PASS Information

Non-interventional PASS Study report

Final Report

Title	**Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study**
Study report Version identifier	Version 1.0
Date of the last version	22 November 2019
EU PAS Register number	EUPAS11081
Active substance	Thiocolchicoside: - ATC code: M03BX05
Medicinal product	TCC-containing medicinal products for systemic use* *All substances will be summarized under the term "systemic thiocolchicoside"
Product reference	Information is detailed in the Study Protocol in Annex 1; §15.1.
Procedure number	EMEA/H/N/PSA/j/0010.1
Marketing authorization holder (MAH) or sponsor company	Consortium of companies. The full list of all MAHs (Companies and/or their Affiliates and licensors) and address is provided in Annex 2; §15.2. Acarpia services farmacêuticos Lda, Alter laboratoire, Angelini, Aristo Pharma GmbH, Arrow Génériques, Biogaran, Cristers, Daiichi Sankyo, Doc Generici, Dompé Farmaceutici SpA, EG labo, EG SpA, Epifarma Srl, I.B.N. SAVIO Srl., Generis Farmacêutica, Korangi, Laboratorio Farmaceutico CT Srl, MDM, Mylan, Sandoz, Sanofi-Aventis Groupe, SF Group Srl, SPA, Teofarma Srl, Union Health Srl, Zentiva
Joint PASS	Yes
Research question and objectives	The aim of this drug utilization study is to characterize prescribing practices of TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription. The study objectives are: • To describe the demographic and clinical characteristics of treated patients (i.e. age and gender, co-medications, pregnancy, contraceptive use, lactation) • To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender)

	• To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration • To compare patient characteristics pre- and post-implementation of risk minimization measure (RMMs)
Countries of study	France and Italy
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TITLE

Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study

1. ABSTRACT

1.1 Title

Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study

Version 1.0: 20 November 2019

Supervised by:

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1.2 Keywords

Thiocolchicoside-containing medicinal products for systemic use, Safety, Direct Healthcare Professional Communication, Educational Materials, Risk minimization measures.

1.3 Rationale and background

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity, used in the management of non-specific low back pain. TCC is indicated as adjuvant treatment of painful muscular contractures in acute spinal pathology, in adults and adolescents from 16 years onwards (see Study Protocol; Annex 1; §15.1).

An Article 31 referral on TCC-containing medicinal products for systemic use was initiated in February 2013. The Committee on Human Medicinal Products (CHMP) had concerns regarding the potential genotoxicity of TCC-containing medicinal products for systemic use.

As per European Commission decision dated 17th January 2014, risk minimization measures (RMMs) were implemented, including a Direct Healthcare Professional Communication (DHPC), changes to the Summary of product characteristics (SmPC) and Package Leaflet and Educational Materials (EM) for Health Care Professionals (HCP) and patients. A Drug Utilization Study (DUS) was also requested to assess the effectiveness of the imposed RMMs and to further characterize the prescribing patterns for TCC-containing medicinal products for systemic use.

1.4 Research question and objectives

The aim of this DUS was to characterize prescribing practices of systemic TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of treated patients (i.e. age and gender, co-medications; pregnancy, contraceptive use, lactation)
- To describe the indication for which TCC is prescribed in routine clinical practice (overall and by age/gender)
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration
- To compare patient's characteristics pre- and post-implementation of RMMs

1.5 Study design

Cross-sectional study based on existing databases in France and Italy.

Study period: The overall study covers three years starting from effective date of implementation (i.e. completion of EM distribution: 08th October 2015 for Italy, 26th April 2016 for France) of RMMs.

In addition, a baseline period spanning over year 2013 was used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of RMMs.

1.6 Setting

Study population:

The study population included patients with at least one prescription of TCC-containing medicinal products for systemic use during the study period, i.e. before (pre-implementation period, baseline: year 2013) or after the implementation (post-implementation period 1 and 2) of the RMMs. The effective date of implementation of RMMs was considered per country (completion of EM distribution: 8th October 2015 for Italy, 26th April 2016 for France).

Prescriber population:

A national representative sample of General Practitioners (GPs) was considered for each country. In addition, and for France only, a panel of specialists (rheumatologists) was considered as well.

1.7 Subjects and study size, including dropouts

During the third analysis period (post-implementation period: April 2018 through April 2019 in France and October 2017 through October 2018 in Italy), 29 600 patients were identified in the French GP database, 1 815 in the French rheumatologist database and 15 349 in the Italian GP database, as having received at least one prescription of TCC.

1.8 Variables and data sources

Variables: Age, gender, treatment indication, dose, duration, route of administration, concomitant treatments, use of appropriate contraceptive measures, pregnancy and lactation, during the study period.

Data Sources: Longitudinal electronic medical records (EMR) databases were used in France and Italy (IQVIA [formerly IMS] Longitudinal Patient Database [LPD]® and Disease Analyzer [DA]). The data are collected routinely from GPs and rheumatologists (for France only) in the outpatient setting.

1.9 Results

A total of 34 460 patients in the French GP database, 1 383 in the French rheumatologists' database and 19 877 in the Italian GP database were included in the analyses during the pre-implementation period. For the third analysis period, 23 079 patients in the French GP database, 1 063 in the French rheumatologists' database and 14 957 in the Italian GP database were included. A total of 81 690 patients in the French GP database, 3 016 in the French rheumatologists' database and 41 061 in the Italian GP database were included for the entire 36-month post-implementation period analysis.

In all periods, French physicians prescribed mainly oral form of systemic TCC (over 95% and over 80% of prescriptions emitted in the GP and rheumatologists' panels respectively). The contrary applied to Italian GPs who prescribed mainly IM form of systemic TCC (over 70% of prescriptions).

The diagnosis associated to prescription of systemic TCC agreed with the authorized indication in 53.3% (French GP panel), 71.3% (French rheumatologists' panel) and 75.6% (Italian GP panel) of prescriptions in the pre-implementation period. In study period 3 there was a slight increase in on-label prescriptions in Italian GP panel (78.3%). In the overall post-implementation period, these proportion were 53.9% (French GP panel), 70.9% (French rheumatologists' panel) and 75.8% (Italian GP panel).

Systemic TCC was prescribed as adjuvant of a concomitant treatment in a large majority of prescriptions, ranging from 86.6% (Italian GP panel), to 88.8% (French rheumatologists' panel) and 93.5% (French GP panel) of prescriptions in the pre-implementation period. In the study period 3, there was a moderate increase in Italian GP panel (89.0%) while value remained stable in French rheumatologists' panel (89.5%) and French GP panel (92.3%). In the overall post-implementation period, values ranged from 88.6% (Italian GP panel), to 88.0% (French rheumatologists' panel) and 92.7% (French GP panel).

In the pre-implementation period, daily dose restriction for oral form was respected in 98.7% (Italian GP panel), 99.7% (French GP panel) and 100% (French rheumatologists' panel) of prescriptions. In study period 3, these proportions ranged from 98.1% in Italian GP panel, 99.8% in French GP panel and 100% for French rheumatologists' panel. In the overall the post-implementation period, the proportions were 98.5% (Italian GP panel), 99.7% (French GP panel) and 100% (French rheumatologists' panel).

Daily dosage restrictions for IM form was respected in 63.6% (French GP panel), 62.9% (French rheumatologists' panel) and 99.9% (Italian GP panel) of prescriptions in the pre-implementation period. During study period 3, there was an improved compliance in French GP panel (89.2%) while values

remained stable in French rheumatologists' panel (58.4%) and Italian GP panel (99.9%). In the overall post-implementation period, these proportions were 81.0% (French GP panel), 67.1% (French rheumatologists' panel) and 99.9% (Italian GP panel).

Restrictions on treatment duration were less followed than restrictions on daily dosage. For oral form, and in the pre-implementation period, restrictions on treatment duration were respected in 40.3% (French rheumatologists' panel), 46.7% (French GP panel) and 52.3% (Italian GP panel) of prescriptions. During study period 3, compliance with treatment duration restrictions for oral form improved in the French rheumatologists' panel (53.4%) and the French GP panel (69.4%) but not in Italian GP panel (48.7%). In the overall post-implementation period, these proportions were 49.2% (French rheumatologists' panel), 66.2% (French GP panel) and 46.6% (Italian GP panel).

Concerning the IM form, restrictions on treatment duration were respected in 32.4% (French rheumatologists' panel), 30.4% (French GP panel) and 12.8% (Italian GP panel) of prescriptions during pre-implementation period. During study period 3, compliance with treatment duration restrictions for IM form improved in the French rheumatologists' panel (49.1%) and the French GP panel (50.7%) but not in Italian GP panel (11.3%). In the overall post-implementation period, these proportions were 43.2% (French rheumatologists' panel), 48.7% (French GP panel) and 11.6% (Italian GP panel).

In the pre-implementation period, restriction to short-term treatment was respected in 92.2% (French rheumatologists' panel), 94.7% (French GP panel) and 98.9% (Italian GP panel) of prescriptions. During study period 3, compliance with restriction to short-term treatment improved in all three panels: the French rheumatologists' panel (96.8%), the French GP panel (96.8%) and Italian GP panel (99.2%). In the overall post-implementation period, these proportions were 96.3% (French rheumatologists' panel), 96.5% (French GP panel) and 99.2% (Italian GP panel).

In the pre-implementation period, minimal age of 16 years was respected in 100% (French rheumatologists' panel), 99% (French GP panel) and 99.8% (Italian GP panel) of prescriptions. During study period 3, compliance with minimal age improved in the Italian GP panel (99.9%), the French GP panel (99.6%). In the overall post-implementation period, these proportions were 100% (French rheumatologists' panel), 99.5% (French GP panel) and 99.9% (Italian GP panel).

No TCC prescriptions were encountered concomitantly to a pregnancy in the French rheumatologists' panel (all periods). TCC prescriptions were encountered concomitantly to a pregnancy in the French GP panel (pre-implementation: 0.6% of total prescriptions; study period 3: 0.7%; overall post-implementation period: 0.4%) and in the Italian GP panel (pre-implementation: 4.0%; study period 3: 4.0%; overall post-implementation period: 4.3%).

Systemic TCC prescription concomitant to a breastfeeding period was not recorded in the French rheumatologists' panel and was encountered in less than 0.1% of prescriptions in the French GP panel and Italian GP panels (all study periods)

In the pre-implementation period, for 86.1% (French GP panel), 92.8% (Italian GP panel) and 100% (French rheumatologists' panel) of prescriptions filled by female patients of child bearing potential (16-49 years old) it was not possible to find a record indicating use of hormonal contraceptives or IUD. In the study period 3 and overall post-implementation period, this proportion was respectively 91.3% and 89.5% (French GP panel), 96.2% and 95.1% (Italian GP panel) and 100% in both periods (French rheumatologists' panel).

1.10 Discussion

This study was conducted to assess the effectiveness of the DHPC and EM implemented as RMM. This final report for the DUS TCC includes results for France and Italy.

The results of the study indicated a substantial prescription of thiocolchicoside in a context of off-label use of any type, especially among French GP panel but with an improvement with the implementation of the RMMs. Admittedly, the lack of information on prescription in the database may have led to an overestimation of this number, but similar results were obtained in the survey (EUPAS11765) conducted as complement to this DUS following the European Referral on thiocolchicoside containing products for systemic use.

A significant improvement in the compliance to treatment duration for oral form in the French GP panel was observed after RMM implementation. Figures on treatment duration in the Italian GP panel have to be considered with caution due to the fact that treatment durations had to be calculated from available information. Compliance to restrictions concerning the use of systemic TCC for long term treatment of chronic conditions was already high in the pre-implementation period and significantly decreased after implementation of the RMM in the French GP and rheumatologist panels. Although a significant reduction of use in an off-label indication occurred immediately after RMM implementation in the French GP panel, compliance to authorized indication remained essentially the same over the pre- and post-implementation period in the two other panels. The proportions of the concomitant medications relevant to TCC indication showed that systemic TCC was prescribed most frequently as an adjuvant treatment, which remained unchanged in post-implementation period in the three panels. Prescriptions to patients under the age of 16 years were sparse in the pre-implementation and were found to have significantly decreased in the post-implementation period in French and Italian GP panels. No change in prescription behavior of physicians after implementation of RMM was observed concerning restrictions of use in women of childbearing potential not taking appropriate contraception, during pregnancy and during lactation. However, databases records on these parameters are not comprehensive and figures concerning these variables have to be taken with caution.

In conclusion, this study brought the RMMs produced positive effects on physicians' knowlegde and prescribing habits for some safety messages only, as a complement to results of the healthcare professionals survey (EUPAS11765). In view of the result of these two studies the Marketing Authorization Holders Consortium proposed to proactively have a new distribution of adjusted risk minimization measures (Direct Healthcare Professionals Communication, HCP Guide) as well as unchanged Patient Card as an unique package, in order to increase the impact of this communication. This was endorsed in October 2018 by AIFA in a national assessment shared with PRAC.

1.11 Marketing Authorization holders (MAHs)

Consortium of companies.

The full list of all MAHs (Companies and/or their Affiliates and licensors) and address is provided in Annex 2; §15.2

1.12 Names and affiliations of principal investigators

Dr. Massoud Toussi

IQVIA, France

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AIFA	Agenzia Italiana del Farmaco: Italian Medicines Agency
ATC	Anatomical Theraputic Classification
CI	Confidence interval
CHMP	Committee on Human Medicinal Products
DA	Disease Analyzer
DHPC	Direct Healthcare Professional Communication
DUS	Drug Utilization Study
EM	Educational Material
EMR	Electronic Medical record
EU	European Union
GP	General practitioner
HCP	Health care professional
IM	Intramuscular
INN	International Non-proprietary Name
IUD	Intrauterine device
LPD	Longitudinal Patient Data
MAH	Marketing Authorization Holder
PASS	Post-authorization safety study
RMM	Risk minimization measure
SAS	Statistical Analysis System
SOP	Standard operating procedure
SmPC	Summary of product characteristics
TCC	Thiocolchicoside

3. INVESTIGATORS

Sponsor:
Marketing Authorization Holders (MAHs) represented by the following companies are involved in the study via a consortium (the full list of all MAHs is provided in Annex 2; §15.2):

Subcontractor acting as contracted principal investigator
IQVIA
Contact person: Dr Massoud Toussi, Principal, Medical Director, IQVIA, France

Project team :
Dr. Massoud Toussi, Principal, Medical Director, IQVIA, France
Dr. Sophie L. Jouaville, Medical Writer, IQVIA, France
Intissar Bourahla, Project Manager, IQVIA, France
Nicolas Coulombel, Statistician, IQVIA, France
Johanna Despres, Data Manager, IQVIA, France

The steering committee comprises representatives of each MAH and of IQVIA.

This committee is chaired by Sanofi-Aventis R&D.

The roles of the scientific committee are to supervise activities and obligations related to the governance of the cooperation of the parties under the agreement, and to ensure an optimal coordination among parties with respect to the scientific part of the study.

4. OTHER RESPONSIBLE PARTIES

NA

5. MILESTONES

Milestone	Planned date
Start of data collection	Oct 2015 for Italy and April 2016 for France
End of data collection	Oct 2018 for Italy and April 2019 for France
Registration in the EU PASS register	Q3 2015
First Interim Report	Q4 2017
Second Interim Report	Q4 2018
Final report of study results	Q4 2019

6. RATIONALE AND BACKGROUND

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain.

The review of TCC was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that TCC was broken down into 3-demethylthiocolchicine (M2 or SL59.0955) that could damage dividing cells, resulting in aneuploidy (an abnormal number or loss of heterozygosity).

As a result, AIFA asked the European Medicines Agency's Committee on Human Medicinal Products (CHMP) to examine the safety profile of this medicine and consider what regulatory action might be appropriate.

The CHMP reviewed the evidence [European Medicines Agency. Assessment Report], including the opinions of experts in the field of medicines safety, and concluded that aneuploidy could occur with M2 at levels not much greater than those seen after recommended doses of TCC taken by mouth. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory, could increase the risk of developing cancer. On 21 November 2013, the CHMP recommended that authorized uses for TCC-containing medicines for use by mouth or injection should be restricted across the European Union (EU) [European Medicines Agency. Article 31 referral]. The CHMP, therefore, recommended measures to ensure TCC-containing medicines are used as safely as possible. These include restricting the maximum dose and number of days of treatment when given by mouth or injection. Use is also contra-indicated in pregnancy and lactation or in women of childbearing potential not using adequate contraception, as well as in children below 16 years of age or for chronic (long-term) conditions. Topical cutaneous preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review. The European Commission implementing decision was issued on 17 January 2014.

Since this date, the modified indication statement for systemic TCC use is as follows:

- Systemic TCC is indicated only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and adolescents from 16 years of age
- Systemic TCC should not be used for long-term treatment of chronic conditions
- Maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than seven consecutive days. When given intramuscular (IM), the maximum dose should be 4 mg every 12 hours, for up to five days
- Medicines containing TCC should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraception

The European Commission's decision included the distribution of Direct Healthcare Professional Communication (DHPC) and educational material (EM) for prescribers and for patients, highlighting the risks and warnings of genotoxicity reactions as additional risk minimization measure (RMMs).

A drug utilization study (DUS) was conducted in France and Italy, and a Health Care Professionals survey (France, Italy, Portugal, Greece) was planned as part of the assessment of effectiveness of RMMs (routine and additional). This is the final DUS report.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 PRIMARY OBJECTIVE

The aim of this DUS was to characterize prescribing practices of TCC-containing medicinal products for systemic use during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives were:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications, pregnancy, use of appropriate contraceptive measures, lactation),
- To describe for which indication TCC was prescribed in routine clinical practice (overall and by age/gender),
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration.

7.2 SECONDARY OBJECTIVE

- Comparison of patient characteristics, pre- and post- implementation of RMMs as a measurement of the efficacy of the RMMs.

8. AMENDMENTS AND UPDATES

Version number and date	Reason(s) for change
Version 3 dated 26 April 2016	Initial version
Version 4 dated 13 October 2016	Removal of French HEAD database Changes in MAH information Changes in IQVIA personal
Version 5 dated 2 March 2017	Replacement of IMS Health LPD® database by IQVIA (formerly IMS) Disease Analyzer® (DA) for France GP Change in company name from IMS to QuintilesIMS

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an international, multicenter, non-interventional, retrospective, cross-sectional study conducted in outpatient settings in two European countries (i.e. France and Italy).

In accordance with the study objectives, the overall study duration was divided into two phases with respect to the implementation of RMMs as follows:

- **A 1-year pre-implementation period/baseline period:** 12 months duration from 01 January 2013 to 31 December 2013, i.e. before implementation of RMMs.
- **A 3-year post-implementation period:** starts after the first day of distribution of approved EM by national competent authorities in the selected countries up to 3-years after the distribution.

The effective date of implementation of RMMs was considered per country (completion of EM distribution: 08 October 2015 for Italy, 26 April 2016 for France).

This analysis was repeated at 12 months (interim analysis 1), 24 months (interim analysis 2), and 36 months (final report) from the implementation of all the RMMs.

9.2 SETTING

The study was conducted in two European countries: France and Italy.

The following study periods were considered:

- **Pre-implementation period, baseline:** January 2013 through December 2013
- **Post-implementation period 1, study period 1:** October 2015 through September 2016 in Italy and May 2016 to April 2017 in France
- **Post-implementation period 2, study period 2:** October 2016 through September 2017 in Italy and May 2017 to April 2018 in France
- **Post-implementation period 3, study period 3:** October 2017 through September 2018 in Italy and April 2018 to April 2019 in France

9.3 SUBJECTS

9.3.1 Inclusion criteria

The study population included all patients with at least one prescription of TCC-containing medicinal products for systemic use in the selected databases during the study periods, i.e. before or after the implementation of the RMMs.

The “prescription index date” for each patient included in the study was defined as first date in each study period when a patient was prescribed systemic TCC.

9.3.2 Exclusion criteria

No age restrictions or exclusion criteria were applied. This allowed the characterization of all users of TCC-containing medicinal products for systemic use according to each indication for which the medication is being used. This included any pediatric population and patients with contraindications (e.g., pregnant woman).

9.3.3 Analysis populations(s)

This analysis was done on all eligible patients with at least one year of enrollment in the database before index date. However, to assess the effect of including patients prescribed systemic TCC but not analyzed because of enrollment less than one year before index date, such patients were counted, and their main characteristics (i.e. age, gender, dose, duration, treatment indication, co-medications) at index date were described together with the characteristics of patients included in the study.

9.4 VARIABLES

9.4.1 Exposures

The exposure of interest was obtained through systemic TCC prescription.

9.4.1.1 Treatment duration

The use of systemic TCC was assessed through the recorded prescriptions (prescriptions "issued" or "written") in databases. Since electronic medical record (EMR) databases report issued prescriptions rather than dispensed medication, there was no information indicating if, or when, a prescription was filled. The study team assumed that all the prescriptions and their associated dates recorded in both databases reflected actual prescription fills, and study patients began exposure at the index date (=date of prescription issue) and were exposed continuously for the number of days indicated by the days-of-supply for that prescription.

Note: If the days-of-supply field for a given prescription was missing or zero, or the values recorded were determined to be implausible based on the quantity dispensed for that prescription, the days-of-supply were calculated by dividing the total quantity dispensed by the daily prescribed dose.

9.4.1.2 Dose

The distribution of daily prescribed dose (for oral form and IM form) at the index date was described for all users of systemic TCC. The dose described was the one associated to the index prescription. The daily dose of medications was recorded in the EMR databases. The dose was ascertained from the numeric daily dose derived from the dosing instructions. The proportion of missing values was described.

However, the degree of completeness is variable across databases. Missing values for doses were expected. The missing information were specified.

9.4.1.3 Treatment indications

Following the Article 31 referral on TCC-containing medicinal products for systemic use, systemic TCC use is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology.

All diagnoses associated to a systemic TCC prescription were recorded and classified according to ICD-10-CM.

An associated diagnosis was recorded with an issued prescription, but not necessarily the clinical indication.

Of note, Table 9.4-1 displays the list of diseases, conditions, and procedures mapped to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for identification of the current approved indication.

Table 9.4-1: List of diagnoses and corresponding ICD-10-CM codes for identification of the current approved indications

ICD-10-CM description	*ICD-10-CM code*	*Use of codes in indication definitions*
O Other deforming dorsopathies including: • Spondylolysis • Spondylolisthesis • Recurrent atlantoaxial dislocation with myelopathy • Other recurrent atlantoaxial dislocation • Other recurrent vertebral dislocation • Torticollis • Other specified deforming dorsopathies • Deforming dorsopathy, unspecified	M 43 • M43.0 • M43.1 • M43.3 • M43.4 • M43.5 • M43.6 • M43.8 • M43.9	Primary code for the broad definition of the clinical indication
D Dorsalgia • Radiculopathy • Cervicalgia • Sciatica • Lumbago with sciatica • Low back pain • Pain in thoracic spine • Other dorsalgia • Dorsalgia, unspecified	M 54 • M 54.1 • M 54.2 • M 54.3 • M.54.4 • M54 .5 • M54 .6 • M54 .8 • M54 .9	Primary code for the broad definition of the clinical indication

9.4.2 Pregnancy, contraceptive use and lactation: for women of child bearing potential

Use of appropriate contraceptive measures during the study period:

In the GP EMR databases, contraceptive use is not well recorded (see Limitations; §11.2). Therefore, it was expected that the recording of prescriptions for contraceptive measures up to a year before, and concomitantly to TCC prescription, was going to underestimate the population using appropriate contraceptive measures.

Pregnancy:

All the diagnoses related to pregnancies were searched in databases according to data availability.

Some of these diagnoses precise the pregnancy trimester or were related to exams specific of a trimester. If the information on trimester or start date or delivery/end of pregnancy date was available, the pregnancy was considered exposed, if at least one TCC prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date was not available in the EMR database, a pregnancy was considered as exposed to TCC if at least one TCC prescription was issued within 90 days before or within 180 days after the first record of a given pregnancy.

Lactation:

Diagnoses related to breastfeeding were searched in databases according to data availability.

Lactation was considered as concomitant to TCC use if at least one TCC prescription was issued in a window of 90 days before and after any breastfeeding record.

9.4.3 Operational variables and definition of off-label

In summary, all variables to be collected for the study and definition of off-label are listed in Table 9.4-2.

Table 9.4-2: Summary of variables

Characteristic	*Variable definition*	*Off-label definition**
Patient Demographics, at initiation of systemic TCC use:	Patient Demographics, at initiation of systemic TCC use:	
• Age categories	• <16, ≥16 years	• Age at prescription <16 years
• Gender	• Male, female	
• Pregnancy	• Pregnancy diagnosis	• At least one TCC prescription issued in the period between assumed dates of pregnancy start and delivery/end of pregnancy, or, –when no information on pregnancy start or end is available-, within 90 days before or within 180 days after the first record of a given pregnancy
• Contraceptive use	• Prescription of contraceptive medications/devices	• No record of contraceptive use before, at initiation of, and during systemic TCC use
• Lactation status	• Lactation	• At least one TCC prescription issued in a window of 90 days before and after any diagnosis of lactation
• Country	• France, Italy	
Concomitant medications and/or health services, medical devices, before, at initiation of and during systemic TCC use:	Medications: • All analgesics (ATC code: N02) and specifically among them: o Salicylic combinations (N02A) o Paracetamol (N02B) o Opioids (N02A) • Tricyclic antidepressants (N06Amitriptyline type) • Benzodiazepine (ATC code: N03A, clonazepam type) • Muscle relaxants (ATC code: M03) • NSAIDs/Cox-2 inhibitors (ATC code: M01A) • Corticosteroids (ATC code: M01B) • Topical products for joint and muscular pain (ATC code: M02A) • Phytotherapy (harpagophyton, ATC code: V03A) Health services/medical devices and others: • Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10)) • Osteo-therapies (V57 (ICD-9), Z50 (ICD-10)) • Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10)) • Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	• No concomitant medications and/or health services, medical devices, before, at initiation of, and during systemic TCC use

Characteristic	*Variable definition*	*Off-label definition**
Systemic TCC daily doses prescribed	• Oral form: ≤16 mg per day, >16 mg per day • IM form: ≤8 mg per day, >8 mg per day	• Oral form: >16 mg per day • IM form: >8 mg per day
Duration of systemic TCC treatment episode	• Oral form: ≤7 consecutive days, >7 consecutive days • IM form: ≤5 consecutive days • >5 consecutive days	• Oral form: >7 consecutive days • IM form: >5 consecutive days • Long-term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
Treatment indication for systemic TCC prescription	• Clinical diagnosis recorded at the time of prescription	• Other than painful muscle contractures associated with acute spinal pathology

ATC: ;ICD: International Classification of Diseases; IM: ; NSAIDS:; TCC: thiocolchicoside

* Off-label definition is defined as any occurrence of the situations listed in Table 9.4-2 (in the last column) in a prescription

9.5 DATA SOURCES AND MEASUREMENTS

Longitudinal Patient Database (LPD): Rheumatologists France and GPs Italy

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in EMRs. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the country.

The panel of contributing physicians was maintained as a representative sample of the primary care physician population according to three criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she was replaced by another one with a similar profile. Additionally, the patient population was representative of the country population according to age and gender distribution, as provided by the national statistic authorities [Istituto di ricerca della SIMG, 2014] (also see Study Protocol in Annex 1; §15.1).

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills was recorded in the database. The database was not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis was always recorded with an issued prescription, but not necessarily the clinical indication.

In France, data from panels of primary care physicians and data from specialist panels are available. Panels of specialists are independent of GP panel; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, it was not possible to link individual patients across the two types of practitioners.

For this study, it was planned to record information gathered by a panel of French rheumatologists for a better coverage of patients prescribed TCC. Both LPD panels have been validated through previous published works. Indeed, French panel of rheumatologists (LPD France rheumatologists) has been used by French National Authority for Health [Has, 2009; HAS, 2010] and Italian LPD (LPD Italy) have been used in peer reviewed publications [Lapi et al, 2012; Coloma et al, 2013].

Disease Analyzer (DA) France: GPs France

The DA provides a national representative sample of about 1,000 primary care physicians (GPs) and includes over 5 million anonymous patient records and 152 million prescriptions in France.

Physicians are contacted among GPs who are using one of the five practice management software selected by IQVIA and according to the needs of representativity of the panel based on national statistics. Physicians included in the panel are those who volunteer to make available anonymized, patient-level information from their practices for clinical research purposes.

The panel of contributing physicians was maintained as a representative sample of the primary care physician population according to three criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she was replaced by another one with a similar profile. Additionally, the patient population was representative of the country population according to age and gender distribution, as provided by national statistic authorities [Becher et al., 2009] (see also Study Protocol in Annex 1; §15.1).

Recently, DA was used in a PASS study involving the attainment of exposure of pregnant women to sodium valproate and related substances [ENCEPP/SDPP/9678].

Characteristics of the databases are summarized in Table 9.5-1 and Table 9.5-2.

Table 9.5-1: Summary of variables available in LPD and DA

Demographic and medical profile		***Treatment and other medical data***	
Gender	*Yes*	*Drug*	*Yes*
Year of Birth	Yes	Diagnosis	Yes
Social-Economics Status	No	Molecule	Yes
Ethnicity	No	Rx in INN	Yes
Death Recording	Partial	Brand Name	Yes
Registration Date	Yes	Dosage	Yes
"Transferred out" date	No	Duration of script	Yes
Diet	Partial	Repeat	Yes
Exercise	Partial	Cost	Partial
Life style (smoking etc.)	Partial		
Height	Yes	Allergies	Yes
Weight	Yes	Immunization	Yes
Blood pressure	Yes	Lab Tests	Yes
Date of events	Yes	Lab Tests Results	Partial
Home visit	Partial	Referrals	Partial
Medical History	Yes	Hospitalization	Partial
Signs and Symptoms	Yes	Reasons for Hospitalization	Partial

Table 9.5-2: Characteristics of data sources

Characteristics	***DA France***	***LPD France Rheumatologist***	***LPD Italy***
Database type	Primary health care electronic medical record database	Electronic medical record database	Primary health care electronic medical record database
Possibility of linkage	None	None	None
Possibility to request additional information	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	None
Physicians population	GPs: 1,000 (of 54,000 in France)	Rheumatologists: 100 (of 1,749 in France)	GPs: 900 (of 46,000 in Italy)

Data availability	Metropolitan France Since 2004	Metropolitan France. Since 2002 for Rheumatologist panel	All Italy Since 2004
Database population	1,160,000 active patients*	115,000 active patients*	1,000,000 active patients*
Approximate proportion of the country physician population covered by the database	1.85%	5.70%	1.96%
Active international principle coding system	Proprietary thesaurus *(mapped to ATC)*	Proprietary thesaurus *(mapped to ATC)*	Proprietary thesaurus *(mapped to ATC)*
Disease classification	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-9)*

ATC: Anatomical Therapeutic Chemical; GP: general practitioner; ICD

*active patients: patients having visited their physician at least once a year

9.6 BIAS

Selection bias

For all EMR data sources, it must be considered that patients who seek care outside the EMR practice setting do not have these data recorded in the database.

As no exclusion criteria were applied, it can be expected that the selection of the study population did not introduce selection bias.

Information bias

In Italy, only prescription data from general practitioners (GPs) are available, while in France, a specialist panel (rheumatologists) was also available. However, patients cannot be tracked across different physician offices.

For these reasons an under-reporting of diagnoses and medication to an unknown extent might be present in the database. Furthermore, the documentation behavior of physicians may lead to incomplete records in the database and consequently under-reporting.

Only restricted information on use of hormonal contraceptives or intrauterine device (IUD) was available, because most prescriptions are issued rather by gynaecologists than by primary care physicians (PCPs) or rheumatologists.

In the EMR databases, information was limited on pregnancies, lactation and contraceptive use. All information recorded was considered in the analysis, but information was incomplete.

To overcome information gaps, the database study was complemented by a prescriber survey (The European Union electronic Register of Post Authorization Studies [EU PAS] Register Number EUPAS/11765).

Misclassification bias

For this study patients were identified via systemic TCC prescription using International Non-proprietary Name (INN) and/or ATC code and not via diagnoses. Therefore, for the identification of study patients no misclassification bias is expected.

All above mentioned biases are expected to persist across all study periods with minor variations only. The impact on the comparative analysis is considered to be of limited extent.

9.7 STUDY SIZE CALCULATION

The aim of this study was to provide a description of real-life treatment patterns. The study size was driven primarily by the uptake of systemic TCC in the populations from which the automated databases obtain data for France and Italy.

The sample size was calculated to ensure that the study obtains meaningful data for descriptive purposes. The primary objectives were mainly descriptive. The primary objective of this study was to assess the distribution of drug patterns in the overall sample and across countries.

Approximately 50,000 patients in France (GPs + rheumatologists) and 17,000 in Italy (GPs) were expected.

9.7.1 Determination of sample size

The sample size calculation was determined by the desired accuracy/precision of the estimation by confidence interval (CI) of the observed proportions. Calculation use the following formula (normal approximation):

With n sample size, p observed percentage, ε_α 1.96 for 95% CI, e Precision.

$1-pn\times\varepsilon\alpha$

Table 9.7-1 shows that to achieve a sufficient accuracy, i.e. within a marge of accuracy <±5%, of the estimation by a two-sided 95% CI for proportions (p) between 10% and 50% (or from 90% to 50% for complementary percentage), a minimum sample size of around 400 patients is required. The precision for an observed percentage with 95% CI was determined by the formula below:

Calculation use the following formula (normal approximation):

$$e = \sqrt{\frac{p(1-p)}{n} \times \varepsilon_\alpha}$$

With n sample size, p observed percentage, ε_α 1.96 for 95% CI, e Precision.

Table 9.7-1: Required number of patients (1) by acceptable precision (95% CI) for proportions (normal approximation)

	Observed percentage (accuracy): p(1-p)				
Precision	10% (90%)	20% (80%)	30% (70%)	40% (60%)	50% (50%)
± 2.0%	864	1 537	2 017	2 305	2 401
± 2.5%	553	983	1 291	1 475	1 537
± 3.0%	384	683	896	1 024	1 067
± 3.5%	282	502	659	753	784
± 4.0%	216	384	504	576	600
± 5.0%	139	246	323	369	384

9.7.2 Sample size for France and Italy

Preliminary analyzes of patient count per country used to inform design development indicated sufficient sample sizes of prescriptions. For France, approximatively 40 000 patients were prescribed TCC in 2012 from GP panel and 2 800 in specialists. In Italy, more than 17 000 patients were prescribed TCC in 2012. Thus, based on a percentage of missing data on age and gender lower than 5%, the maximal expected sample size was to be over 60 000 patients per year from all data sources.

9.8 DATA MANAGEMENT

Data collected by physicians in usual routine practice into the patient EMR were anonymized and transferred daily in accordance with national legislation. The data are hosted on servers located in datacenters belonging to IQVIA, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (Capability Maturity Model Integration (CMMI), International Organization for Standardization (ISO) 27001 and Information Technology Infrastructure Library (ITIL) in European regulations.

9.8.1 Data collection

The following patients' data were collected from the databases:

- Patient demography: age at the time of the visit, gender
- Pregnancy associated diagnoses for women of child bearing potential
- Lactation associated diagnoses for women of child bearing potential
- Date of prescription of TCC: name of the TCC-containing medicinal product for systemic use, posology, duration of treatment
- Diagnosis associated to prescription of the TCC-containing medicinal product for systemic use
- Concomitant medications/products: concomitant medications/devices, including contraceptive medication/devices were collected using list of therapeutic classes or drugs commonly prescribed.

Concerning concomitant medications/products prescribed in population with acute muscle contractures in spinal pathology, the predefined list, as exhaustive as possible, covered the concomitant medications of interest and the main therapeutic classes, i.e. pain management prescription, including: analgesics, tricyclic antidepressants, benzodiazepine, and antiepileptics.

9.9 STATISTICAL METHODS

9.9.1 Main summary measures

Given the objectives, analyzes were mainly descriptive. To evaluate the differences between subgroups by indication, proportions for categorical variables and means for continuous variables were estimated (with 95% CIs) within each subgroup. If appropriate, medians were used instead of means when the variables of interest did not assume a normal distribution.

Besides, because of the likelihood of some degree of allocation bias, comparative statistical testing was performed in a descriptive manner. Comparison were provided for groups of interest, if the number of patients in each subgroup was sufficient (n>30 in each group). Quantitative variables were statistically compared with a Student's t-test (parametric test) or Wilcoxon signed-rank sum test (non-parametric test, when necessary). Qualitative variables were statistically compared with a Pearson Chi^2 or with Fisher's exact test (expected frequency lower or equal to five for one or several cells). Each statistical test was bilateral with a level of risk α of 5% (without adjustment of the threshold regarding the increase of the tests). Adjustments on statistical analyzes modelling were performed limiting the danger of spurious statistically significant findings with the number of people studied and considering the effect of potential confounders.

Continuous variables were described by the usual statistics: number (number of valid cases, number of missing values), mean, standard deviation, median, minimum, maximum, first and third quartiles.

Categorical variables were described for each modality and the associated percentages. The numbers of data entered, and missing values were indicated.

The statistical analyses were conducted using the Statistical Analysis System (SAS)® softwareV9.4 (or latest version) on Windows™ (SAS Institute, North Carolina, USA).

9.9.2 Main statistical methods

9.9.2.1 Primary analyzes

The description of drug use patterns (overall description by country and by age and gender and incident or prevalent patients) were performed for the baseline period (year 2013) and each year over the first year of inclusion after RMM implementation for both the countries.

Analyses were done overall and by subgroup of prevalent and incident patients. Prevalent patients were defined by the total number of treated patients per year for three years, and incident patients were defined as the total number of new treated patients per year.

For each country, a descriptive analysis of TCC utilization and potential off-label use (as defined in Table 9.4-2) was performed:

Indication:

- Dosage
- Duration
- Therapeutic regimen: mono-therapies or adjuvant therapies (use of TCC along with other pre-specified co-medications)

The prescribed daily dose was defined as the average dose prescribed overall and by indications.

In addition, descriptive analyses were performed according to:

- Age and gender
- In the subgroup of women of childbearing potential: in case of pregnancy, use of contraceptive measures, or lactation during the study period. Proportion of pregnancies exposed to TCC (at least one TCC prescription during pregnancy within the defined study periods) were calculated over the total number of pregnancies in patients included in the study within the defined study periods. Proportion of breastfeeding patients exposed to TCC (at least one TCC prescription concomitant to a lactation record within the defined study period) were calculated over the total number of breastfeeding patients included in the study within the defined study periods.

To assess the impact of RMMs on the target population, the main characteristics of patients (demographic and clinical) were compared between pre- and post-implementation of RMMs.

9.9.2.2 Secondary analysis

A comparison of patient characteristics and proportion of off-label use was performed pre- and post-implementation of RMMs, as a measurement of the effectiveness of the RMMs. The off-label proportion at baseline (year 2013) were estimated on both the basis of the post-RMMs Summary of Product Characteristics (SmPC). Off-label proportion for each year post-implementation of RMMs were estimated based on the post-RMMs SmPC. “Off-label use” definition was based on the collected variables on relevant characteristics of use which are presented in §9.4.3.

To estimate RMMs impact on off-label patients’ rate, the overall differences in off-label before and after RMMs were estimated.

Furthermore, the effect of RMMs on off-label incidence was investigated using a segmented regression analysis [Wagner et al., 2002]. In this analysis, off-label rates (proportion of off-label TCC prescriptions among evaluable TCC prescriptions) were computed by month before (pre-implementation period; baseline: 2013) and after RMMs implementation (study period) according to each country. The model included an intercept (mean outcome rate at beginning of the study) and main period (before/after RMMs) effect and separate time trends before and after RMMs.

The segmented regression analysis of interrupted time series data was used to estimate the effect of the intervention on the monthly off-label rates, immediately after intervention period and to identify whether there was a monthly trend in the rate of off-label use in the baseline period and in the post-intervention period (study period 3).

The rate of off-label use during the intervention period (January 2014 to 07 October 2015 in Italy, January 2014 to 25 April 2016 for France) was excluded from the analysis.

The following model was used to estimate the level and the trend in off-label rate before the intervention period and the change in level and trend after the intervention period:

$$\text{Off-label rate}_t = \beta_0+\beta_1*\text{time}_t + \beta_2*\text{intervention}_t + \beta_3*\text{time after intervention}_t+e_t$$

where:

- off-label rate_t is the proportion of off-label TCC prescriptions per month
- β_0 is the baseline off-label rate at the beginning of the baseline period
- β_1 estimates the change in the off-label rate before intervention (baseline linear trend of the monthly off-label rate)
- time_t is the time in months from the beginning of the baseline period
- β_2 estimates the level change in the off-label rate immediately after the intervention (study period)
- β_3 estimates the change in the trend of the off-label rate after intervention (study period) compared to the trend of the off-label rate during baseline period
- e_t is the random error

The stationarity (constant mean on period, constant variance on period and autocorrelation) was tested per period by using the Dicker-Fuller unit root test.

9.9.3 Missing values

Missing values were excluded from the calculation of percentages.

9.9.4 Sensitivity analyzes

Not applicable

9.9.5 Amendments to the statistical analysis plan

Not applicable

9.10 QUALITY CONTROL

9.10.1 Data collection, validation and data quality control at MAH/MAH representative level

The data were hosted on servers located in datacenters belonging to IQVIA, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (CMMI, ISO 27001 and ITIL) and European regulation.

All data transfers were verified by IQVIA according to standard operating procedures (SOPs) for electronic file acquisition and checking practices.

All programmings were independently reviewed by one of the IQVIA statisticians. The study reports underwent quality control review, senior scientific review, and editorial review.

Analysis data sets and program output were checked for accuracy and integrity according to SOPs of IQVIA that include the following steps:

- Checking program logs for errors and warnings
- Checking output for errors and inconsistencies
- Running quality control programs to verify that specifications were implemented correctly and that any output generated accurately reflects the data
- Checking all results tables for accuracy

None of the extracted data sets contain data that allow identification of patients included in the study. Each electronic record was completely anonymized and do not contain any personally identifying data.

9.10.2 Data quality control at site level

Not applicable: Data are collected by physicians in usual routine practice into the patient EMR. Since data are collected directly by physicians and uploaded in an anonymized way, it is not possible to refer to patients' files and perform any site quality control.

Information was recorded by the physicians whenever they deemed it relevant for their clinical practice and some information (e.g. family history, test results) may be partially available.

10. RESULTS

This final report presents results from the entire 12-month pre-implementation period (hereinafter referred to as Baseline Period: January 2013 through December 2013), the third year of the post-implementation period (hereinafter referred to as Study Period 3: October 2017 through September 2018 in Italy and April 2018 to April 2019 in France) and the entire 36-month post-implementation period (hereinafter referred to as Cumulative Study Period: April 2016 through April 2019 in France and October 2015 through October 2018 in Italy).

10.1 PARTICIPANTS

10.1.1 Number

Baseline period

During this period, 52 776 patients were identified in the French GP database, 3 112 patients in the French rheumatologists' database and 20 346 patients in the Italian GP database, as having received at least one prescription of TCC (Table 10.1-1).

Among these patients, 18 316 patients in the French GP database, 1 729 patients in the French rheumatologists' database and 469 patients in the Italian GP database had less than one year of history in the database prior to the first prescription of TCC and were excluded from the analyses.

Therefore, 34 460 patients in the French GP database, 1 383 patients in the French rheumatologists' database and 19 877 patients in the Italian GP database were included in the analyzes during the baseline period.

The study period 3

In the French GP database were identified 29 600 patients, 1 815 patients in the French rheumatologists' database and 15 349 patients in the Italian GP database, as having received at least one prescription of TCC (Table 10.1-1).

Among these patients, 6 521 patients in the French GP database, 752 patients in the French rheumatologists' database and 392 patients in the Italian GP database had less than one year of history in the database prior to the first prescription of TCC and were excluded from the analyzes.

Therefore, 23 079 patients in the French GP database, 1 063 patients in the French rheumatologists' database and 14 957 patients in the Italian GP database were included in the analyzes during the third analysis period.

The cumulative study periods

Over the 36-month post-implementation period, 107 413 patients were identified in the French GP database, 5 782 patients in the French rheumatologists' database and 42 146 patients in the Italian GP database, as having received at least one prescription of TCC (Table 10.1-1).

Among these patients, 25 723 patients in the French GP database, 2 766 patients in the French rheumatologists' database and 1 085 patients in the Italian GP database had less than one year of history in the database prior to the first prescription of TCC during the 24 months post-implementation period and were excluded from the analyses during the cumulative study period.

Therefore, 81 690 patients in the French GP database, 3 016 patients in the French rheumatologists' database and 41 061 patients in the Italian GP database were included in the analyses during the cumulative study period analysis.

Table 10.1-1: Eligible patients

	France		Italy
	GPs (N=153 660)	**Rheumatologists (N=8 600)**	**GPs (N=57 901)**
Eligible patients	153 660 (100.0%)	8 600 (100.0%)	57 901 (100.0%)
Included (at least one year of enrollment in the database[1])			
Baseline period	34 460 (22.4%)	1 383 (16.1%)	19 877 (34.3%)
Study period year 1	37 771 (24.6%)	1247 (14.5%)	16140 (27.9%)
Study period year 2	34 330 (22.3%)	1185 (13.8%)	16201 (28.0%)
Study period year 3	23 079 (15.0%)	1 063 (12.4%)	14 957 (25.8%)
Cumulated study periods (study periods 1 to 3)	81 690 (53.2%)	3 016 (35.1%)	41 061 (70.9%)
Excluded (less than one year of enrollment in the database[1])			
Baseline period	18 316 (11.9%)	1 729 (20.1%)	469 (0.8%)
Study period year 1	11387 (7.4%)	1141 (13.3%)	393 (0.7%)
Study period year 2	10205 (6.6%)	1014 (11.8%)	422 (0.7%)
Study period year 3	6 521 (4.2%)	752 (8.7%)	392 (0.7%)
Cumulated study periods (study periods 1 to 3)	25 723 (16.7%)	2 766 (32.2%)	1 085 (1.9%)

[1]:one year before the date of the first TCC prescription in the period (Baseline period/ study period)

10.1.2 Demographic characteristics

Demographic characteristics of patients in the French GP database, French rheumatologists' database and Italian database are presented, at baseline and during the third study period and for cumulative study periods (Table 10.1-2).

For all the periods of the study, there was a majority of women, which was systematically highest among French rheumatologists' panel (72.3%) and GP Italians panel (63%). The mean age of patients has been stable throughout the study periods, with the oldest mean age found in patients in French rheumatologists' panel (mean age = 62.3 ± 14.54 years), then Italian GPs panel (mean age = 56.6 ± 15.73 years). The population is youngest among French GPs panel with a mean age of 46.9 ± 15.93 years and with 57% of patients under 50 years of age.

Table 10.1-2: Characteristics of patients at index date

	France GPs			France Rheumatologists			Italy GPs		
	Baseline (N=34 460)	**Study Period 3 (N=23 079)**	**Cumulative Study Periods (N=81 690)**	**Baseline (N=1 383)**	**Study Period 3 (N=1 063)**	**Cumulative Study Periods (N=3 016)**	**Baseline (N=19 877)**	**Study Period 3 (N= 14 957)**	**Cumulative Study Periods (N=41 061)**
Age (years)									
N	34 442 (99.9)	23 073 (100.0)	81 668 (100.0)	1 383 (100.0)	1 062 (99.9)	3 014 (99.9)	19 865 (99.9)	14 939 (99.9)	41 021 (99.9)
Missing (N)	18 (0.1)	6 (0.0)	22 (0.0)	0	1 (0.1)	2 (0.1)	12 (0.1)	18 (0.1)	40 (0.1)
Mean (SD)	45.9 (15.89)	48.3 (15.86)	46.9 (15.93)	60.3 (14.41)	62.7 (14.54)	62.3 (14.53)	55.4 (15.93)	57.4 (15.57)	56.6 (15.73)
Median (Q1 - Q3)	46.0 (34.0-57.0)	48.0 (37.0-59.0)	47.0 (35.0-58.0)	61.0 (50.0-72.0)	63.0 (53.0-73.0)	63.0 (53.0-73.0)	55.0 (44.0-67.0)	57.0 (46.0-69.0)	57.0 (46.0-69.0)
Range	(2.0,98.0)	(2.0,97.0)	(2.0,100.0)	(16.0,98.0)	(14.0,98.0)	(14.0,98.0)	(12.0,101.0)	(11.0,103.0)	(11.0,103.0)
Age (years) -classes									
Missing (N)	18	6	22	-	1	2	12	18	40
<16 years	414 (1.2%)	106 (0.5%)	570 (0.7%)	-	1 (0.1%)	1 (0.0%)	34 (0.2%)	9 (0.1%)	30 (0.1%)
[16;30]	5 273 (15.3%)	2 862 (12.4%)	11 877 (14.5%)	21 (1.5%)	17 (1.6%)	41 (1.4%)	1 002 (5.0%)	609 (4.1%)	1 912 (4.7%)
[30;40]	6 517 (18.9%)	4 177 (18.1%)	15 222 (18.6%)	82 (5.9%)	44 (4.1%)	154 (5.1%)	2 263 (11.4%)	1 355 (9.1%)	3 968 (9.7%)
[40;50]	8 321 (24.2%)	5 230 (22.7%)	18 913 (23.2%)	222 (16.1%)	133 (12.5%)	398 (13.2%)	4 156 (20.9%)	2 735 (18.3%)	7 891 (19.2%)
[50;60]	7 088 (20.6%)	5 111 (22.2%)	17 210 (21.1%)	330 (23.9%)	250 (23.5%)	684 (22.7%)	4 388 (22.1%)	3 467 (23.2%)	9 393 (22.9%)
[60;70]	4 140 (12.0%)	3 221 (14.0%)	10 767 (13.2%)	333 (24.1%)	244 (23.0%)	737 (24.5%)	3 752 (18.9%)	3 105 (20.8%)	8 348 (20.4%)
≥70 years	2 689 (7.8%)	2 366 (10.3%)	7 109 (8.7%)	395 (28.6%)	373 (35.1%)	999 (33.1%)	4 270 (21.5%)	3 659 (24.5%)	9 479 (23.1%)
Gender									
Missing (N)	25	1	1	91	43	118	2 894	2 152	5 863
Male	14 907 (43.3%)	10 211 (44.2%)	36 478 (44.7%)	396 (30.7%)	278 (27.3%)	803 (27.7%)	6 081 (35.8%)	4 717 (36.8%)	13 021 (37.0%)
Female	19 528 (56.7%)	12 867 (55.8%)	45 211 (55.3%)	896 (69.3%)	742 (72.7%)	2 095 (72.3%)	10 902 (64.2%)	8 088 (63.2%)	22 177 (63.0%)

Index date: first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period: year 2013
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included: at least one year of enrollment in the database

10.2 DESCRIPTIVE DATA

10.2.1 Number of TCC systemic prescription

The total number of prescriptions as well as the number of prescriptions per patient in each panel is reported in Table 10.2-1.

Prescriptions to women of childbearing potential (aged 16-49 years) amounted approximatively to half (French GP panel), one third (Italian GP panel) and less than a quarter (French rheumatologists' panel) of prescriptions filled by women.

Less prescriptions of systemic TCC were issued post-implementation in study period 3 as compared to the pre-implementation period (baseline) in the French GP panel (29 631 vs 44 108), French rheumatologists' panels (1 281 vs 1 721) and the Italian GP panel (17 364 vs 23 527).

Table 10.2-1: Number of systemic TCC prescriptions per period

		Baseline	Study Period 3		Cumulative Study Periods	
			Overall	Incident	Overall	Incident
		(N=44 108)	(N=29 631)	(N=12 287)	(N=123 429)	(N=50 597)
France GP panel						
Number of patients with a systemic TCC prescription		34 460	23 079	12 278	81 690	50 544
Number of systemic TCC prescriptions per patient	*Mean (SD)*	1.3 (0.86)	1.3 (0.85)	1.0 (0.03)	1.5 (1.49)	1.0 (0.03)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)
	Range	(1.0,20.0)	(1.0,16.0)	(1.0,2.0)	(1.0,48.0)	(1.0,2.0)
Total systemicTCC prescriptions to women		25 260	16 712	6 714	69 690	27 597
Total systemicTCC prescriptions to women 16-49 years		14 269 (56.5%)*	8 272 (49.5%)*	3 645 (54.3%)*	36 548 (52.5%)*	15 952 (57.8%)*
France rheumatologist panel						
Number of patients with a systemic TCC prescription		1 383	1 063	575	3 016	1 915
Number of systemic TCC prescriptions per patient	*Mean (SD)*	1.2 (0.65)	1.2 (0.56)	1.0 (0.07)	1.4 (1.06)	1.0 (0.06)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,10.0)	(1.0,7.0)	(1.0,2.0)	(1.0,21.0)	(1.0,2.0)
Total systemicTCC prescriptions to women		1 099	881	412	2 866	1 358
Total systemicTCC prescriptions to women 16-49 years		262 (23.8%)*	152 (17.3%)*	82 (19.9%)*	512 (17.9%)*	255 (18.8%)*
Italian GP panel						
Number of patients with a systemic TCC prescription		19 877	14 957	6 441	41 061	20 578
Number of systemic TCC prescriptions per patient	*Mean (SD)*	1.2 (0.51)	1.2 (0.46)	1.0 (0.07)	1.3 (0.80)	1.0 (0.07)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,12.0)	(1.0,10.0)	(1.0,2.0)	(1.0,21.0)	(1.0,2.0)
Total systemicTCC prescriptions to women		12 884	9 316	3 466	29 383	11 109
Total systemicTCC prescriptions to women 16-49 years		4 290 (33.3%)*	2 543 (27.3%)*	1 312 (37.9%)*	8 347 (28.4%)*	4 340 (39.1%)*

Baseline period: year 2013

Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018

Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018

Incident case: New TCC prescription in all patient history with at least one year of medical history

*: as a fraction of Total systemicTCC prescriptions to women

10.2.2 Treatment indication for TCC systemic prescription

Systemic TCC should only be prescribed for treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.

Proportions for diagnoses corresponding to the authorized indication as well as those outside of the authorized indication are presented in Table 10.2-2. These diagnoses were either linked to the prescription or were recorded in patient's EMR on the day of the prescription.

Diagnoses of interest were recorded in 53.3% of systemic TCC prescriptions in the pre-implementation (baseline) period and 53.2% and 53.9% in the post-implementation period (study period 3 and cumulative study periods, respectively), for the GP panel in France.

Diagnoses of interest were recorded in 71.3% of systemic TCC prescriptions in the baseline period and 71.9% and 70.9% in the study period 3 and cumulative study periods, respectively, for the rheumatologist panel in France.

Finally, diagnoses of interest were recorded in 75.6% of systemic TCC prescriptions in the baseline period and 78.3% and 77.6% in the study period 3 and cumulative study periods, respectively, for the GP panel in Italy.

Table 10.2-2:Analysis of systemic TCC prescriptions per panel: Indication

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
FRANCE GP PANEL					
N	44 108	29 631	12 287	123 429	50 597
MISSING	6 494	5 114	2 111	18 015	7 246
TOTAL ON-LABEL	20 057 (53.3%)	13 043 (53.2%)	6 204 (61.0%)	56 854 (53.9%)	26 358 (60.8%)
OTHER DEFORMING DORSOPATHIES INCLUDING - M43	1 115 (3.0%)	700 (2.9%)	410 (4.0%)	3 027 (2.9%)	1 797 (4.1%)
Spondylolysis - M43.0	-	1 (0.0%)	-	1 (0.0%)	-
Spondylolisthesis - M43.1	5 (0.0%)	1 (0.0%)	-	14 (0.0%)	1 (0.0%)
Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-
Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-
Other recurrent vertebral dislocation - M43.5	-	17 (0.1%)	3 (0.0%)	34 (0.0%)	8 (0.0%)
Torticollis - M43.6	1 108 (2.9%)	668 (2.7%)	402 (4.0%)	2 945 (2.8%)	1 776 (4.1%)
Other specified deforming dorsopathies - M43.8	-	10 (0.0%)	4 (0.0%)	25 (0.0%)	9 (0.0%)
Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	3 (0.0%)	1 (0.0%)	8 (0.0%)	3 (0.0%)
DORSALGIA - M54	18 942 (50.4%)	12 343 (50.3%)	5 794 (56.9%)	53 827 (51.1%)	24 561 (56.7%)
Radiculopathy - M54.1	144 (0.4%)	187 (0.4%)	74 (0.4%)	476 (0.5%)	194 (0.4%)
Cervicalgia - M54.2	3 536 (9.4%)	4 034 (9.4%)	1 881 (10.6%)	9 734 (9.2%)	4 532 (10.5%)
Sciatica - M54.3	1 124 (3.0%)	1 218 (2.8%)	519 (2.9%)	2 884 (2.7%)	1 236 (2.9%)
Lumbago with sciatica - M.54.4	1 707 (4.5%)	2 067 (4.8%)	857 (4.8%)	5 039 (4.8%)	2 068 (4.8%)
Low back pain - M54.5	9 182 (24.4%)	11 006 (25.6%)	5 038 (28.3%)	27 294 (25.9%)	12 501 (28.8%)
Pain in thoracic spine - M54.6	18 (0.0%)	39 (0.1%)	17 (0.1%)	111 (0.1%)	51 (0.1%)
Other dorsalgia - M54.8	688 (1.8%)	789 (1.8%)	366 (2.1%)	1 860 (1.8%)	901 (2.1%)
Dorsalgia, unspecified - M54.9	2 543 (6.8%)	2 688 (6.3%)	1 254 (7.0%)	6 429 (6.1%)	3 078 (7.1%)
OTHER THAN PAINFUL MUSCLE CONTRACTURES ASSOCIATED WITH ACUTE SPINAL PATHOLOGY*	17 557 (46.7%)	11 474 (46.8%)	3 972 (39.0%)	48 560 (46.1%)	16 993 (39.2%)
Diseases of the nervous system - (G00–G99)	666 (1.8%)	457 (1.9%)	184 (1.8%)	2 048 (1.9%)	871 (2.0%)
Diseases of the circulatory system - (I00–I99)	356 (0.9%)	427 (1.7%)	83 (0.8%)	1 672 (1.6%)	368 (0.8%)
Essential (primary) hypertension - I10.0	302 (0.8%)	364 (1.5%)	66 (0.6%)	1 477 (1.4%)	316 (0.7%)
Diseases of the respiratory system - (J00–J99)	694 (1.8%)	481 (2.0%)	116 (1.1%)	2 024 (1.9%)	573 (1.3%)
Diseases of the musculoskeletal system and connective tissue - (M00–M99)	4 766 (12.7%)	2 957 (12.1%)	1 305 (12.8%)	13 187 (12.5%)	5 703 (13.2%)
Contracture of muscle - M62.4	1 129 (3.0%)	760 (3.1%)	441 (4.3%)	3 159 (3.0%)	1 739 (4.0%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00–R99)	1 255 (3.3%)	866 (3.5%)	348 (3.4%)	3 646 (3.5%)	1 443 (3.3%)

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
Injury, poisoning and certain other consequences of external causes - (S00–T98)	1 279 (3.4%)	661 (2.7%)	356 (3.5%)	3 126 (3.0%)	1 655 (3.8%)
Factors influencing health status and contact with health services - (Z00–Z99)	7 492 (19.9%)	4 650 (19.0%)	1 296 (12.7%)	19 137 (18.2%)	5 266 (12.1%)
Encounter for issue of repeat prescription - Z76.0	4 607 (12.2%)	2 943 (12.0%)	645 (6.3%)	12 084 (11.5%)	2 718 (6.3%)
Persons encountering health services in other specified circumstances - Z76.8	1 747 (4.6%)	851 (3.5%)	354 (3.5%)	3 713 (3.5%)	1 480 (3.4%)
Other	1 049 (2.8%)	975 (4.0%)	284 (2.8%)	3 720 (3.5%)	1 114 (2.6%)
FRANCE RHEUMATOLOGIST PANEL					
N	1 721	1 281	578	4 184	1 923
MISSING		-		-	-
TOTAL ON-LABEL	1 227 (71.3%)	921 (71.9%)	381 (65.9%)	2 966 (70.9%)	1 250 (65.0%)
OTHER DEFORMING DORSOPATHIES INCLUDING - M43	18 (1.0%)	17 (1.3%)	7 (1.2%)	59 (1.4%)	33 (1.7%)
Spondylolysis - M43.0	-	1 (0.1%)	1 (0.2%)	1 (0.0%)	1 (0.1%)
Spondylolisthesis - M43.1	-	-	-	5 (0.1%)	3 (0.2%)
Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-
Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-
Other recurrent vertebral dislocation - M43.5	-	-	-	-	-
Torticollis - M43.6	4 (0.2%)	1 (0.1%)	1 (0.2%)	6 (0.1%)	4 (0.2%)
Other specified deforming dorsopathies - M43.8	-	-	-	-	-
Deforming dorsopathy, unspecified - M43.9	14 (0.8%)	15 (1.2%)	5 (0.9%)	47 (1.1%)	25 (1.3%)
DORSALGIA - M54	1 209 (70.2%)	904 (70.6%)	374 (64.7%)	2 907 (69.5%)	1 217 (63.3%)
Radiculopathy - M54.1	21 (1.2%)	23 (1.8%)	14 (2.4%)	63 (1.5%)	30 (1.6%)
Cervicalgia - M54.2	346 (20.1%)	247 (19.3%)	104 (18.0%)	778 (18.6%)	365 (19.0%)
Sciatica - M54.3	34 (2.0%)	21 (1.6%)	14 (2.4%)	45 (1.1%)	31 (1.6%)
Lumbago with sciatica - M.54.4	188 (10.9%)	118 (9.2%)	35 (6.1%)	437 (10.4%)	156 (8.1%)
Low back pain - M54.5	470 (27.3%)	363 (28.3%)	167 (28.9%)	1 079 (25.8%)	485 (25.2%)
Pain in thoracic spine - M54.6	-	1 (0.1%)	1 (0.2%)	3 (0.1%)	3 (0.2%)
Other dorsalgia - M54.8	2 (0.1%)	1 (0.1%)	1 (0.2%)	12 (0.3%)	5 (0.3%)
Dorsalgia, unspecified - M54.9	148 (8.6%)	130 (10.1%)	38 (6.6%)	490 (11.7%)	142 (7.4%)
OTHER THAN PAINFUL MUSCLE CONTRACTURES ASSOCIATED WITH ACUTE SPINAL PATHOLOGY*	494 (28.7%)	360 (28.1%)	197 (34.1%)	1 218 (29.1%)	673 (35.0%)
Diseases of the musculoskeletal system and connective tissue - (M00–M99)	436 (25.3%)	309 (24.1%)	163 (28.2%)	1 033 (24.7%)	564 (29.3%)
Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	26 (2.0%)	14 (2.4%)	95 (2.3%)	63 (3.3%)
Other specified arthrosis - M19.8	29 (1.7%)	7 (0.5%)	3 (0.5%)	18 (0.6%)	10 (0.8%)
Pain in shoulder - M25.51	21 (1.2%)	32 (2.5%)	15 (2.6%)	78 (1.9%)	39 (2.0%)
Pain in knee - M25.56	24 (1.4%)	20 (1.6%)	8 (1.4%)	79 (1.9%)	36 (1.9%)

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
Other spondylosis - M47.8	44 (2.6%)	40 (3.1%)	20 (3.5%)	78 (1.9%)	38 (2.0%)
Other shoulder lesions - M75.8	41 (2.4%)	2 (0.2%)	2 (0.3%)	28 (0.7%)	16 (0.8%)
Enthesopathy, unspecified - M77.9	18 (1.0%)	3 (0.2%)	2 (0.3%)	18 (0.4%)	10 (0.5%)
Rheumatism, unspecified - M79.0	16 (0.9%)	-	-	18 (0.4%)	6 (0.3%)
Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	8 (0.6%)	3 (0.5%)	69 (1.6%)	36 (1.9%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00–R99)	33 (1.9%)	31 (2.4%)	19 (3.3%)	100 (2.4%)	57 (3.0%)
Pain, unspecified - R52.9	31 (1.8%)	29 (2.3%)	17 (2.9%)	96 (2.3%)	54 (2.8%)
Other	25 (1.5%)	20 (1.6%)	15 (2.6%)	85 (2.0%)	52 (2.7%)
ITALY GP PANEL					
N	23 527	17 364	6 471	54 892	20 674
MISSING	2 063	1 532	601	4 669	1 884
TOTAL ON-LABEL	16 228 (75.6%)	12 392 (78.3%)	4 449 (75.8%)	38 976 (77.6%)	14 228 (75.7%)
OTHER DEFORMING DORSOPATHIES INCLUDING - M43	1 082 (5.0%)	659 (4.2%)	238 (4.1%)	2 164 (4.3%)	825 (4.4%)
Spondylolysis - M43.0	451 (2.1%)	278 (1.8%)	74 (1.3%)	874 (1.7%)	247 (1.3%)
Spondylolisthesis - M43.1	22 (0.1%)	12 (0.1%)	4 (0.1%)	56 (0.1%)	16 (0.1%)
Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-
Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-
Other recurrent vertebral dislocation - M43.5	-	-	-	-	-
Torticollis - M43.6	405 (1.9%)	241 (1.5%)	112 (1.9%)	764 (1.5%)	382 (2.0%)
Other specified deforming dorsopathies - M43.8	123 (0.6%)	75 (0.5%)	25 (0.4%)	289 (0.6%)	98 (0.5%)
Deforming dorsopathy, unspecified - M43.9	81 (0.4%)	53 (0.3%)	23 (0.4%)	181 (0.4%)	82 (0.4%)
DORSALGIA - M54	15 146 (70.6%)	11 733 (74.1%)	4 211 (71.7%)	36 812 (73.3%)	13 403 (71.3%)
Radiculopathy - M54.1	220 (1.0%)	111 (0.7%)	24 (0.4%)	418 (0.8%)	88 (0.5%)
Cervicalgia - M54.2	2 270 (10.6%)	1 544 (9.8%)	644 (11.0%)	4 902 (9.8%)	2 113 (11.2%)
Sciatica - M54.3	627 (2.9%)	496 (3.1%)	198 (3.4%)	1 554 (3.1%)	595 (3.2%)
Lumbago with sciatica - M.54.4	-	-	-	-	-
Low back pain - M54.5	11 393 (53.1%)	9149 (57.8%)	3 187 (54.3%)	28 543 (56.8%)	10 091 (53.7%)
Pain in thoracic spine - M54.6	292 (1.4%)	195 (1.2%)	52 (0.9%)	646 (1.3%)	183 (1.0%)
Other dorsalgia - M54.8	-	-	-	-	-
Dorsalgia, unspecified - M54.9	344 (1.6%)	238 (1.5%)	106 (1.8%)	749 (1.5%)	333 (1.8%)
OTHER THAN PAINFUL MUSCLE CONTRACTURES ASSOCIATED WITH ACUTE SPINAL PATHOLOGY*	5 236 (24.4%)	3 440 (21.7%)	1 421 (24.2%)	11 247 (22.4%)	4 562 (24.3%)
Diseases of The Musculoskeletal System and Connective Tissue (710-739)	3 378 (15.7%)	2 144 (13.5%)	788 (13.4%)	7 136 (14.2%)	2 635 (14.0%)

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
Osteoarthrosis Unspecified Whether Generalized or Localized - 715.9	650 (3.0%)	398 (2.5%)	114 (1.9%)	1 309 (2.6%)	387 (2.1%)
Spasm of Muscle - 728.85	392 (1.8%)	224 (1.4%)	107 (1.8%)	814 (1.6%)	394 (2.1%)
Other Affections of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	182 (1.1%)	71 (1.2%)	639 (1.3%)	245 (1.3%)
Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	386 (2.4%)	196 (3.3%)	1 224 (2.4%)	551 (2.9%)
Injury and Poisoning (800-999)	524 (2.4%)	335 (2.1%)	159 (2.7%)	1 126 (2.2%)	562 (3.0%)
Other	743 (3.5%)	575 (3.6%)	278 (4.7%)	1 761 (3.5%)	814 (4.3%)

Baseline period: year 2013
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case: New CC prescription in all patient history with at least one year of medical history

10.2.3 Cotreatments to TCC systemic prescription

Systemic TCC should only be used as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.

Table 10.2-3 presents the proportions of the concomitant medications relevant to TCC indication recorded in the three panels.

A treatment concomitant to a systemic TCC prescription was found in 93.5% of systemic TCC prescriptions in the baseline (pre-implementation) period and in 92.3% and 92.7% in the study (post-implementation) period 3 and cumulative study periods, respectively, for the GP panel in France.

A treatment concomitant to a systemic TCC prescription was found in 88.8% of systemic TCC prescriptions in the baseline period and in 89.5% and 88.0% in study period 3 and cumulative study periods, respectively, for the rheumatologist panel in France.

A treatment concomitant to a systemic TCC prescription was found in 86.6% of systemic TCC prescriptions in the baseline period and in 89.0% and 88.6% in study period 3 and cumulative study periods, respectively, for the GP panel in Italy.

In study period 3 as well as the cumulative study periods, the most prescribed concomitant medicines were NSAIDs/Cox-2 inhibitors for the rheumatologist panel (54.6%) and Italian GP panel (77.8%). The analgesics were the most common concomintant treatment prescribed by France GPs panel (67.7%), and it was very often prescribed by French rheumatologists (44.3%), but less by Italian GPs (10.8%).

Table 10.2-3: Analysis of systemic TCC prescriptions per panel: Concomitant treatment

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
FRANCE GP PANEL					
N	44 108	29 631	12 287	123 429	50 597
CONCOMITANT TREATMENT					
Yes	41 234 (93.5%)	27 348 (92.3%)	11 185 (91.0%)	114 367 (92.7%)	46 270 (91.4%)
No	2 874 (6.5%)	2 283 (7.7%)	1 102 (9.0%)	9 062 (7.3%)	4 327 (8.6%)
MEDICATIONS:					
Analgesics	31 393 (71.2%)	20 047 (67.7%)	7 777 (63.3%)	85 260 (69.1%)	32 832 (64.9%)
Acetylsalicylic	251 (0.6%)	272 (0.9%)	66 (0.5%)	1 191 (1.0%)	339 (0.7%)
Paracetamol	30 435 (69.0%)	19 195 (64.8%)	7 501 (61.0%)	81 741 (66.2%)	31 751 (62.8%)
Opioids	10 908 (24.7%)	7 031 (23.7%)	2 357 (19.2%)	29 339 (23.8%)	9 849 (19.5%)
Antidepressants	3 781 (8.6%)	2 217 (7.5%)	564 (4.6%)	9 606 (7.8%)	2 359 (4.7%)
Antiepileptics	1 439 (3.3%)	885 (3.0%)	203 (1.7%)	3 780 (3.1%)	847 (1.7%)
Muscle relaxants	3 076 (7.0%)	1 012 (3.4%)	263 (2.1%)	3 816 (3.1%)	994 (2.0%)
NSAIDs/Cox-2 inhibitors	27 801 (63.0%)	17 867 (60.3%)	7 583 (61.7%)	76 008 (61.6%)	31 677 (62.6%)
Corticosteroids for systemic use	2 699 (6.1%)	2 417 (8.2%)	796 (6.5%)	9 584 (7.8%)	3 288 (6.5%)
Topical products for joint and muscular pain	9 988 (22.6%)	7 718 (26.0%)	3 037 (24.7%)	30 743 (24.9%)	12 147 (24.0%)
Phytotherapy	16 (0.0%)	11 (0.0%)	6 (0.0%)	45 (0.0%)	19 (0.0%)
HEALTH SERVICES/MEDICAL DEVICES AND OTHERS:					
Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	727 (1.6%)	236 (0.8%)	106 (0.9%)	1 232 (1.0%)	498 (1.0%)
Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-
FRANCE RHEUMATOLOGIST PANEL					
N	1 721	1 281	578	4 148	1 923
CONCOMITANT TREATMENT					
Yes	1 529 (88.8%)	1 146 (89.5%)	503 (87.0%)	3 681 (88.0%)	1 631 (84.8%)
No	192 (11.2%)	135 (10.5%)	75 (13.0%)	503 (12.0%)	292 (15.2%)
MEDICATIONS:	-	-		-	
Analgesics	879 (51.1%)	567 (44.3%)	218 (37.7%)	1 897 (45.3%)	760 (39.5%)
Acetylsalicylic	43 (2.5%)	3 (0.2%)	1 (0.2%)	7 (0.2%)	4 (0.2%)
Paracetamol	743 (43.2%)	460 (35.9%)	177 (30.6%)	1 589 (38.0%)	638 (33.2%)
Opioids	358 (20.8%)	215 (16.8%)	74 (12.8%)	791 (18.9%)	291 (15.1%)
Antidepressants	59 (3.4%)	51 (4.0%)	12 (2.1%)	176 (4.2%)	43 (2.2%)

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
Antiepileptics	67 (3.9%)	46 (3.6%)	9 (1.6%)	175 (4.2%)	43 (2.2%)
Muscle relaxants	61 (3.5%)	22 (1.7%)	4 (0.7%)	70 (1.7%)	13 (0.7%)
NSAIDs/Cox-2 inhibitors	849 (49.3%)	700 (54.6%)	321 (55.5%)	2 133 (51.0%)	975 (50.7%)
Corticosteroids for systemic use	493 (28.6%)	363 (28.3%)	160 (27.7%)	1 211 (28.9%)	523 (27.2%)
Topical products for joint and muscular pain	174 (10.1%)	107 (8.4%)	31 (5.4%)	395 (9.4%)	123 (6.4%)
Phytotherapy	6 (0.3%)	1 (0.1%)	-	9 (0.2%)	2 (0.1%)
HEALTH SERVICES/MEDICAL DEVICES AND OTHERS:					
Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	1 (0.1%)	-	7 (0.2%)	2 (0.1%)
Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-
ITALY GP PANEL					
N	23 527	17 364	6 471	54 892	20 674
CONCOMITANT TREATMENT					
Yes	20 376 (86.6%)	15 447 (89.0%)	5 651 (87.3%)	48 622 (88.6%)	17 921 (86.7%)
No	3 151 (13.4%)	1 917 (11.0%)	820 (12.7%)	6 270 (11.4%)	2 753 (13.3%)
MEDICATIONS:					
Analgesics	2 949 (12.5%)	1 880 (10.8%)	704 (10.9%)	6 035 (11.0%)	2 197 (10.6%)
Acetylsalicylic	7 (0.0%)	8 (0.0%)	3 (0.0%)	31 (0.1%)	9 (0.0%)
Paracetamol	2 478 (10.5%)	1 457 (8.4%)	573 (8.9%)	4 682 (8.5%)	1 792 (8.7%)
Opioids	1 910 (8.1%)	1 173 (6.8%)	386 (6.0%)	3 784 (6.9%)	1 249 (6.0%)
Antidepressants	895 (3.8%)	737 (4.2%)	201 (3.1%)	2 269 (4.1%)	664 (3.2%)
Antiepileptics	405 (1.7%)	376 (2.2%)	111 (1.7%)	1 142 (2.1%)	317 (1.5%)
Muscle relaxants	152 (0.6%)	129 (0.7%)	44 (0.7%)	458 (0.8%)	155 (0.7%)
NSAIDs/Cox-2 inhibitors	17 641 (75.0%)	13 507 (77.8%)	4 927 (76.1%)	42 611 (77.6%)	15 670 (75.8%)
Corticosteroids for systemic use	2 153 (9.2%)	1 982 (11.4%)	668 (10.3%)	5 954 (10.8%)	1 974 (9.5%)
Topical products for joint and muscular pain	511 (2.2%)	182 (1.0%)	92 (1.4%)	696 (1.3%)	344 (1.7%)
Phytotherapy	5 (0.0%)	6 (0.0%)	3 (0.0%)	15 (0.0%)	4 (0.0%)
HEALTH SERVICES/MEDICAL DEVICES AND OTHERS:					
Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-	-	-
Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10)	-	-	-	-	-

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
Baseline period: year 2013					
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018					
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018					
Incident case: New TCC prescription in all patient history with at least one year of medical history					

10.2.4 Dose and duration of TCC systemic prescription

Doses of systemic TCC should be restricted as follows and the recommended dose and duration should not be exceeded:

- Oral forms: the recommended and maximal dose is 8 mg every 12 hours, i.e. 16 mg per day. The treatment duration was limited to seven consecutive days.

- Intramuscular form: the recommended and maximal dose is 4 mg every 12 hours, i.e. 8 mg per day. The treatment duration was limited to five consecutive days.

It is not to be used for long-term treatment of chronic conditions.

Table 10.2-4 summarizes data about dose and duration of prescriptions of systemic TCC in the three panels for pre-implementation (baseline) period and during post-implementation period (study period 3) as well as cumulative study period.

Overall, the French physisicans prescribed more oral form than IM form. This tendency was inversed in the Italian panel, with over 70% of prescriptions issued for IM form.

French GP panel

Physicians prescribed mainly (96.5%) oral form of systemic TCC, with a mean daily dose of 11.5±3.67 mg (baseline) to 11.7±3.79 mg (study period 3) and prescriptions being ≤16 mg in over 99.7% of prescriptions (for baseline, study period 3, and cumulative study periods). Mean duration of prescription of oral form was 8.9 days (study period 3 and cumulative study periods) to 10.8 days (baseline). Duration of prescription was under ≤7 days in 46.7% (baseline) to 66.2% (cumulative study periods) and 69.4% (study period 3) of prescriptions.

In the case of the oral form of systemic TCC, approximately 99% (baseline and study periods) of prescriptions respected daily dose restrictions, and 46.7% (baseline), 69.4% (study period 3) and 66.2% (cumulative study periods) followed the restrictions of duration.

For the intramuscular (IM) form, a mean daily dose of 9.3 mg (baseline), 7.6 mg (study period 3) and 8.6 mg (cumulative study periods) were observed. Prescribed daily dose was ≤8 mg for 63.6% (baseline) to 89.2% (study period 3) of prescriptions. Mean duration of prescription ranged from 6.1 days (study period 3) to 8.6 days (baseline). Duration of prescription was under ≤5 days in 30.4% (baseline), 50.7% (study period 3) and 48.7% (cumulative study periods) of prescriptions.

Long-term treatment was defined as a duration between the previous and the current prescriptions which was less than 1.5 times the duration of the previous prescription. Long-term treatment, as per this definition, was encountered in 3.2% (study period 3) to 5.3% (baseline) of prescriptions.

French rheumatologists' panel

Physicians prescribed mainly (>82%) oral form of systemic TCC, with a mean daily dose of 10.6±4.45 mg (study period 3) to 11.0±4.35 mg (cumulative study periods), and prescriptions being ≤16 mg for 100% of prescriptions (all study periods). Mean duration of prescription of oral form ranged from 20.9 days (study period 3) to 30.1 days (baseline), being under ≤7 days duration for 40.3% (baseline) to 53.4% (study period 3) and 49.2% (cumulative study periods) of prescriptions. In the case of the oral form of systemic TCC, 100% (baseline and study periods) of prescriptions respected daily dose restrictions, and 40.3% (baseline) to 49.2% (cumulative study periods) followed the restrictions of duration.

For the IM form, a mean daily dose of 10.2± mg (baseline) to 11.1 mg (study period 3) and prescriptions being ≤8 mg from 58.4% (study period 3) to 67.1% (cumulative study periods) of prescriptions. Mean duration of prescription of IM form was 18.9 days (baseline), 11.7 days (study period 3) and 13.1 days (cumulative study periods), duration being under ≤5 days for 32.4% (baseline) to 49.1% (study period 3) of prescriptions. For the IM form, prescribed in less than 20% of prescriptions, 62.9% (baseline), 58.4% (study period 3) and 67.1% (cumulative study periods) of prescriptions respected daily dose restrictions, and 32.4% (baseline) to 49.1% (study period 3) and 43.2% (cumulative study periods) followed the restrictions of duration.

Long-term treatment, as per the definition, was encountered in 7.8% (baseline), 3.2% (study period 3) and 3.7% (cumulative study periods) of prescriptions.

Italian GP panel

Unlike the French panels, Italian GPs prescribed more IM form than oral form of systemic TCC, with 79.1% at period 3 and 72.6% at baseline, with mean daily dose of 4.6 mg (baseline, study period 3, and cumulative study periods), and prescriptions being ≤8 mg for 99.9% of prescriptions (all study periods). Mean duration of prescription of IM form ranged from 5.8 days (study period 3 and cumulative study periods) to 5.9 days (baseline) days, being under ≤5 days duration from 11.3% (study period 3) to 12.8% (baseline) of prescriptions.

For the IM form, prescribed in more than 70% of prescriptions, 99.9% of prescriptions respected daily dose restrictions, and 12.8% (baseline), 11.3% (study period 3) and 11.6% (cumulative study periods) followed the restrictions of duration.

For the oral form, mean daily dose of 11.2 mg (cumulative study periods) to 11.6 mg (baseline) of prescriptions were noted. The oral prescriptions being ≤16 mg ranged from 98.1% (study period 3) of all prescriptions to 98.7% (baseline) of all prescriptions. The mean duration of prescription of oral form ranged from 8.2 (baseline) days to 10.5 days (study period 3). Duration of prescription was under ≤7 days in 52.3% (baseline), 48.7% (study period 3) and 46.6% (cumulative study periods) of prescriptions. In case of the oral form of systemic TCC, prescribed in less than 30% of prescriptions, 98.7% (baseline), 98.1% (study period 3) and 98.5% (cumulative study periods) of prescriptions respected daily dose restrictions, and 52.3% (baseline), 48.7% (study period 3) and 46.6% (cumulative study periods) followed the restrictions of duration.

The long-term treatment was encountered in 1.1% (baseline), 0.8% (both study period 3 and cumulative study periods, respectively) of prescriptions.

Of note: In the French GP panel, there was a high number of missing values concerning the dose and duration of IM form of systemic TCC prescriptions (≥40%).

In the Italian GP panel, there was a high number of missing values concerning the dose and duration of oral form (>60%) and IM form (~75%) of systemic TCC prescriptions. In addition, in the Italian GP panel, only posology (when available) was documented. Daily dose was therefore directly available, while the duration was deduced from the posology and the number of boxes/packs prescribed. For over 98% of cases, the IM form packaging comprised six vials per box. Therefore, a posology of one vial per day associated to a prescription of one box was resulting in a calculated treatment duration of six days.

Table 10.2-4: Analysis of TCC systemic prescriptions per panel: Dose and duration

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
FRANCE GP PANEL					
N	44 108	29 631	12 287	123 429	50 597
Route of systemic prescription					
Intramuscular	1 543 (3.5%)	1 025 (3.5%)	363 (3.0%)	3 501 (2.8%)	1 221 (2.4%)
Oral	42 565 (96.5%)	28 606 (96.5%)	11 924 (97.0%)	119 928 (97.2%)	49 376 (97.6%)
Oral form					
• TCC daily dose					
Missing (N)	2 323 (5.46)	4 118 (14.4)	1 708 (14.3)	110 462 (92.1)	45 354 (91.9)
Mean (SD)	11.5 (3.67)	11.7 (3.79)	11.9 (3.85)	11.6 (3.74)	11.8 (3.79)
Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
Range	(2.0,132.0)	(2.0,36.0)	(2.0,36.0)	(2.0,132.0)	(2.0,48.0)
≤16 mg	40 130 (99.7%)	24 446 (99.8%)	10 196 (99.8%)	110 243 (99.8%)	45 256 (99.8%)
>16 mg	112 (0.3%)	42 (0.2%)	20 (0.2%)	219 (0.2%)	98 (0.2%)
• Duration of systemic TCC treatment (days)					
N	40 830 (95.9)	24 971 (87.3)	10 452 (87.7)	112 699 (94.0)	46 418 (94.0)
Missing (N)	1 735 (4.08)	3 635 (12.7)	1 472 (12.3)	7 229 (6.0)	2 958 (6.0)
Mean (SD)	10.8 (12.32)	8.9 (11.62)	7.7 (9.42)	8.9 (10.79)	7.8 (8.26)
Median (Q1 - Q3)	8.0 (6.0-10.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)
Range	(2.0,132.0)	(1.0,336.0)	(1.0,336.0)	(1.0,336.0)	(1.0,336.0)
≤7 days	19 067 (46.7%)	17 332 (69.4%)	7 710 (73.8%)	74 551 (66.2%)	32 839 (70.7%)
>7 days	21 763 (53.3%)	7 639 (30.6%)	2 742 (26.2%)	38 148 (33.8%)	13 579 (29.3%)
Intramuscular form					
• TCC daily dose					
N	926 (60.0)	379 (37.0)	150 (41.3)	1 595 (45.6)	615 (50.4)
Missing (N)	617 (40.0)	646 (63.0)	213 (58.7)	1 906 (54.4)	606 (49.6)
Mean (SD)	9.3 (4.35)	7.6 (4.04)	7.4 (3.03)	8.6 (4.95)	8.3 (3.97)
Median (Q1 - Q3)	8.0 (6.0-12.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
Range	(4.0,24.0)	(4.0,28.0)	(4.0,16.0)	(4.0,32.0)	(4.0,32.0)
≤8 mg	589 (63.6%)	338 (89.2%)	131 (87.3%)	1 292 (81.0%)	501 (81.5%)
>8 mg	337 (36.4%)	41 (10.8%)	19 (12.7%)	303 (19.0%)	114 (18.5%)
• Duration of systemic TCC treatment (days)					
N	859 (55.7)	422 (41.2)	176 (48.5)	1 784 (51.0)	691 (56.6)
Missing (N)	684 (44.33)	603 (58.8)	187 (51.5)	1 717 (49.0)	530 (43.4)
Mean (SD)	8.6 (11.11)	6.1 (8.48)	5.7 (2.97)	6.8 (8.54)	6.5 (8.09)
Median (Q1 - Q3)	6.0 (5.0-8.0)	5.0 (5.0-6.0)	5.0 (5.0-6.0)	6.0 (5.0-6.0)	5.0 (5.0-6.0)
Range	(1.0,231.0)	(2.0,168.0)	(3.0,28.0)	(1.0,168.0)	(1.0,168.0)
≤5 days	261 (30.4%)	214 (50.7%)	93 (52.8%)	869 (48.7%)	372 (53.8%)
>5 days	598 (69.6%)	208 (49.3%)	83 (47.2%)	915 (51.3%)	319 (46.2%)
Long-Term Treatment					
Missing (N)	512	1 218	-	2 483	-
Yes	2 289 (5.3%)	913 (3.2%)	-	4 280 (3.5%)	-
No	41 307 (94.7%)	27 500 (96.8%)	12 287 (100.0%)	116 666 (96.5%)	50 597 (100.0%)
FRANCE RHEUMATOLOGIST PANEL					
N	1 721	1 281	578	4 184	1 923
Route of systemic prescription					
Intramuscular	282 (16.4%)	214 (16.7%)	123 (21.3%)	738 (17.6%)	432 (22.5%)
Oral	1 439 (83.6%)	1 067 (83.3%)	455 (78.7%)	3 446 (82.4%)	1 491 (77.5%)
Oral form					
• TCC daily dose					
N	1 193 (82.9)	870 (81.5)	362 (79.6)	2 831 (82.2)	1 196 (80.2)

		Baseline	Study Period 3		Cumulative Study Periods	
			Overall	Incident	Overall	Incident
	Missing (N)	246 (17.10)	197 (18.5)	93 (20.4)	615 (17.8)	295 (19.8)
	Mean (SD)	10.7 (4.00)	10.6 (4.45)	10.2 (4.49)	11.0 (4.35)	10.8 (4.47)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(2.0,16.0)	(2.0,16.0)	(2.0,16.0)	(1.3,16.0)	(1.3,16.0)
	≤16 mg	1 193 (100.0%)	870 (100.0%)	362 (100.0%)	2 831 (100.0%)	1 196 (100.0%)
	>16 mg	-	-	-	-	-
• Duration of systemic TCC treatment (days)						
	N	1 185 (82.3)	870 (81.5)	362 (79.6)	2 831 (82.2)	1 196 (80.2)
	Missing (N)	254 (17.65)	197 (18.5)	93 (20.4)	615 (17.8)	295 (19.8)
	Mean (SD)	30.1 (44.54)	20.9 (37.77)	16.3 (31.42)	21.5 (39.09)	14.8 (24.04)
	Median (Q1 - Q3)	12.0 (6.0-30.0)	7.0 (4.0-17.0)	7.0 (4.0-14.0)	9.0 (4.0-15.0)	7.0 (4.0-14.0)
	Range	(1.0,360.0)	(1.0,360.0)	(1.0,360.0)	(1.0,360.0)	(1.0,360.0)
	≤7 days	478 (40.3%)	465 (53.4%)	213 (58.8%)	1 394 (49.2%)	662 (55.4%)
	>7 days	707 (59.7%)	405 (46.6%)	149 (41.2%)	1 437 (50.8%)	534 (44.6%)
Intramuscular form						
• TCC daily dose						
	N	280 (99.3)	214 (100.0)	123 (100.0)	738 (100.0)	432 (100.0)
	Missing (N)	2 (0.71)	0	0	0	0
	Mean (SD)	10.2 (3.91)	11.1 (4.09)	11.0 (4.08)	10.3 (3.92)	10.2 (3.95)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,16.0)	(4.0,16.0)	(4.0,16.0)	(4.0,16.0)
	≤8 mg	176 (62.9%)	125 (58.4%)	72 (58.5%)	495 (67.1%)	288 (66.7%)
	>8 mg	104 (37.1%)	89 (41.6%)	51 (41.5%)	243 (32.9%)	144 (33.3%)
• Duration of systemic TCC treatment (days)						
	N	278 (98.6)	214 (100.0)	123 (100.0)	738 (100.0)	432 (100.0)
	Missing (N)	4 (1.42)	0	0	0	0
	Mean (SD)	18.9 (42.46)	11.7 (21.27)	8.9 (11.82)	13.1 (31.11)	9.9 (22.61)
	Median (Q1 - Q3)	10.0 (5.0-12.0)	6.0 (4.0-12.0)	5.0 (4.0-10.0)	6.0 (4.0-10.0)	6.0 (4.0-10.0)
	Range	(1.0,360.0)	(2.0,180.0)	(2.0,90.0)	(2.0,360.0)	(2.0,360.0)
	≤5 days	90 (32.4%)	105 (49.1%)	65 (52.8%)	319 (43.2%)	207 (47.9%)
	>5 days	188 (67.6%)	109 (50.9%)	58 (47.2%)	419 (56.8%)	225 (52.1%)
Long-Term Treatment						
	Missing (N)	23	25	-	81	-
	Yes	132 (7.8%)	40 (3.2%)	-	152 (3.7%)	-
	No	1 566 (92.2%)	1 216 (96.8%)	578 (100.0%)	3 951 (96.3%)	1 923 (100.0%)
ITALY GP PANEL						
N		23 527	17 364	6 471	54 892	20 674
Route of systemic prescription						
	Intramuscular	17 086 (72.6%)	13 729 (79.1%)	4 746 (73.3%)	43 008 (78.4%)	15 059 (72.8%)
	Oral	6 441 (27.4%)	3 635 (20.9%)	1 725 (26.7%)	11 884 (21.6%)	5 615 (27.2%)
Oral form						
• TCC daily dose						
	N	2 599 (40.4)	1 285 (35.4)	580 (33.6)	4 227 (35.6)	1 859 (33.1)
	Missing (N)	3 842 (59.65)	2 350 (64.6)	1 145 (66.4)	7 657 (64.4)	3 756 (66.9)
	Mean (SD)	11.6 (4.38)	11.5 (4.79)	11.7 (4.82)	11.2 (4.62)	11.2 (4.67)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,32.0)	(4.0,24.0)	(2.0,32.0)	(4.0,24.0)
	≤16 mg	2 565 (98.7%)	1 261 (98.1%)	568 (97.9%)	4 165 (98.5%)	1 831 (98.5%)
	>16 mg	34 (1.3%)	24 (1.9%)	12 (2.1%)	62 (1.5%)	28 (1.5%)
• Duration of systemic TCC treatment (days)						

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
N	2 596 (40.3)	1 284 (35.3)	580 (33.6)	4 225 (35.6)	1 858 (33.1)
Missing (N)	3 845 (59.70)	2 351 (64.7)	1 145 (66.4)	7 659 (64.4)	3 757 (66.9)
Mean (SD)	8.2 (4.30)	10.5 (4.85)	10.3 (4.87)	9.9 (4.94)	9.9 (4.84)
Median (Q1 - Q3)	6.0 (5.0-10.0)	10.0 (7.0-14.0)	7.0 (7.0-14.0)	10.0 (7.0-10.0)	10.0 (7.0-10.0)
Range	(3.0,60.0)	(3.0,30.0)	(4.0,30.0)	(3.0,50.0)	(3.0,30.0)
≤7 days	1 357 (52.3%)	625 (48.7%)	299 (51.6%)	1 967 (46.6%)	890 (47.9%)
>7 days	1 239 (47.7%)	659 (51.3%)	281 (48.4%)	2 258 (53.4%)	968 (52.1%)
Intramuscular form					
• TCC daily dose					
N	4 299 (25.2)	2 960 (21.6)	866 (18.2)	9 568 (22.2)	2 810 (18.7)
Missing (N)	12 787 (74.84)	10 769 (78.4)	3 880 (81.8)	33 440 (77.8)	12 249 (81.3)
Mean (SD)	4.6 (1.47)	4.6 (1.47)	4.6 (1.44)	4.6 (1.45)	4.6 (1.47)
Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
Range	(2.0,16.0)	(2.0,16.0)	(4.0,8.0)	(2.0,16.0)	(4.0,12.0)
≤8 mg	4 295 (99.9%)	2 958 (99.9%)	866 (100.0%)	9 560 (99.9%)	2 808 (99.9%)
>8 mg	4 (0.1%)	2 (0.1%)	-	8 (0.1%)	2 (0.1%)
• Duration of systemic TCC treatment (days)					
N	4 297 (25.1)	2 960 (21.6)	866 (18.2)	9 566 (22.2)	2 809 (18.7)
Missing (N)	12 789 (74.85)	10 769 (78.4)	3 880 (81.8)	33 442 (77.8)	12 250 (81.3)
Mean (SD)	5.9 (1.66)	5.8 (1.35)	5.7 (1.18)	5.8 (1.39)	5.8 (1.29)
Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
Range	(1.0,24.0)	(1.0,12.0)	(3.0,12.0)	(1.0,18.0)	(2.0,12.0)
≤5 days	552 (12.8%)	334 (11.3%)	104 (12.0%)	1 107 (11.6%)	343 (12.2%)
>5 days	3 745 (87.2%)	2 626 (88.7%)	762 (88.0%)	8 459 (88.4%)	2 466 (87.8%)
Long-Term Treatment					
Missing (N)	2 390	1 767	-	5 475	-
Yes	225 (1.1%)	121 (0.8%)	-	380 (0.8%)	-
No	20 912 (98.9%)	15 476 (99.2%)	6 471 (100.0%)	49 037 (99.2%)	20 674 (100.0%)

Baseline period: year 2013
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case: New TCC prescription in all patient history with at least one year of medical history
Long-term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

10.2.5 Special populations in TCC systemic prescription

Patients below the age of 16 years

Systemic TCC should only be used as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and in adolescents from 16 years onwards.

As shown in Table 10.2-5, 0.4% (overall – study period 3) to 1.1% (incident– cumulative study periods) in the French GP panel, one case (overall – study periods 3 and cumulative study periods) in the French rheumatologists' panel and 0.1% (overall and incident – both study periods) to 0.2% (baseline) of prescriptions in the Italian GP panel, were issued to patients aged less than 16 years old. The mean age was very close to 14 years for all panels and any period considered.

Table 10.2-5: : Analysis of TCC systemic prescriptions per panel: Patients under 16 years old

		Baseline	Study Period 3		Cumulative Study Periods	
			Overall	Incident	Overall	Incident
France GP panel	**N**	44 108	29 631	12 287	123 429	50 597
	Missing (N)	20	7	5	27	18
	<16 years	452 (1.0%)	117 (0.4%)	99 (0.8%)	661 (0.5%)	533 (1.1%)
	Mean (SD)	13.8 (1.94)	13.6 (2.57)	13.6 (2.46)	13.9 (2.12)	13.9 (2.07)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	15.0 (13.0-15.0)	15.0 (13.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)
	Range	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)
France Rheumatologist panel	**N**	1 721	1 281	578	4 184	1 923
	Missing (N)	-	1	-	3	2
	<16 years	-	1 (0.1%)	1 (0.2%)	1 (0.0%)	1 (0.1%)
	Mean (SD)	-	14.0 ()	14.0 ()	14.0 ()	14.0 ()
	Median (Q1 - Q3)	-	14.0 (14.0-14.0)	14.0 (14.0-14.0)	14.0 (14.0-14.0)	14.0 (14.0-14.0)
	Range	-	(14.0,14.0)	(14.0,14.0)	(14.0,14.0)	(14.0,14.0)
Italy GP panel	**N**	23 527	17 364	6 471	54 892	20 674
	Missing (N)	14	18	11	54	27
	<16 years	36 (0.2%)	9 (0.1%)	9 (0.1%)	32 (0.1%)	30 (0.1%)
	Mean (SD)	14.2 (0.92)	13.8 (1.39)	13.8 (1.39)	13.9 (1.25)	14.0 (1.16)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)
	Range	(12.0,15.0)	(11.0,15.0)	(11.0,15.0)	(11.0,15.0)	(11.0,15.0)

Baseline period: year 2013
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case: New TCC prescription in all patient history with at least one year of medical history

Female patients of child bearing potential

Systemic TCC should not be used in pregnancy and lactation, nor be used in women of childbearing potential not using adequate contraception.

The results on concomitant use of hormonal contraceptives or IUD, concomitant pregnancy or lactation period in all TCC prescriptions in the baseline and study periods, recorded in the three panels, are displayed in Table 10.2-6.

For percentage calculation, proportion of systemic prescriptions of TCC concomitant to pregnancy were expressed as a fraction of the total number of prescriptions of TCC filled by women presenting a diagnosis of pregnancy during the defined study periods. Proportion of systemic prescriptions of TCC concomitant to breastfeeding were expressed as a fraction of the total number of patients presenting a diagnosis of breastfeeding within the defined study periods. Proportion of systemic prescriptions of TCC non-concomitant use of hormonal contraceptives or IUD was expressed as a fraction of the total number of patients of child bearing potential (16-49 years old) within the defined study periods.

Pregnancy

In the French GP panel, 77 prescriptions during baseline and 176 prescriptions in the cumulative study periods were issued concomitantly to a pregnancy. These prescriptions were delivered to 71 (0.6% of total patients) patients in the baseline, 49 (0.7% of total patients) in the study period 3 and 108 (0.4% of total patients) in cumulative study periods (Table 15**.3-49**, Table 15**.3-52**, and Table 15**.3-55** of Statistical Report in Annex 3; §15.3).

In the rheumatologist panel, no diagnosis signaling a pregnancy was recorded (Table 15**.3-50**, Table 15**.3-53** and Table 15**.3-56** of Statistical Report in Annex 3; §15.3).

In the Italian GP panel, 169, 103 and 349 prescriptions were issued concomitantly to a pregnancy during baseline, study period 3 and cumulative study periods respectively. These prescriptions were issued to 150 (4.0% of total patients) patients in the baseline, 92 (4.0% of total patients) in the study period 3 and 291 (4.3% of total patients) in the cumulative study periods (Table 15**.3-51**, Table 15**.3-54** and Table 15**.3-57** of Statistical Report in Annex 3; §15.3).

Lactation

In the French GP panel, six prescriptions during baseline, one prescription in the study period 3 and seven prescriptions in the cumulative study periods were issued concomitantly to a breastfeeding patient. Four patients were involved in the baseline and three in the study period (<0.01% of total patients) (Table 15**.3-40** of Statistical Report in Annex 3; §15.3).

In the rheumatologist panel, no diagnosis signaling breastfeeding was recorded (Table 15**.3-41** of Statistical Report in Annex 3; §15.3).

In the Italian GP panel, four prescriptions during baseline and three prescriptions in the cumulative study periods were issued concomitantly to breastfeeding patient. Three patients were involved in the baseline and two in the study period (0.1% of total patients) (Table 15**.3-42** of Statistical Report in Annex 3; §15.3).

Contraceptive use

In the French GP panel: Proportion of systemic prescriptions of TCC non-concomitant to the use of hormonal contraceptives or IUD was recorded for 12 290 prescriptions (86.1%) in the baseline period, 7 550 prescriptions (91.3%) and 32721 prescriptions (89.5%) in cumulative study periods (Table 15**.3-49** and Table 15**.3-52** of Statistical Report in Annex 3; §15.3).

In the French rheumatologists' panel: Proportion of systemic prescriptions of TCC non-concomitant to the use of hormonal contraceptives or IUD was recorded for 262 prescriptions (100%) in the baseline, 152 prescriptions (100%) and for 512 prescriptions (100%) in the cumulative study periods (Table 15**.3-50** and Table 15**.3-53** of Statistical Report in Annex 3; §15.3).

In the Italian GP panel: Proportion of systemic prescriptions of TCC non-concomitant to the use of hormonal contraceptives or IUD was recorded for 3 982 prescriptions (92.8%) in the baseline period, 2 447 prescriptions (96.2%) and 7 934 prescriptions (95.1%) in the cumulative study periods (Table 15**.3-51** and Table 15**.3-54** of Statistical Report in Annex 3; §15.3).

Table 10.2-6: Analysis of TCC systemic prescriptions per panel: women of childbearing potential

		Baseline	Study Period 3		Cumulative Study Periods	
			Overall	Incident	Overall	Incident
FRANCE GP PANEL						
	Number of prescriptions: total	44 108 (100.0%)	29 631 (100.0%)	12 287 (100.0%)	123 429 (100.0%)	50 597 (100.0%)
	Number of prescriptions filled by women	25 260 (57.3%)	16 712 (56.4%)	6 714 (54.6%)	69 690 (56.5%)	27 597 (54.5%)
	Number of prescriptions filled by women of child bearing potential (16-49 years old)	14 269 (56.5%)	8 272 (49.5%)	3 645 (54.3%)	36 548 (52.5%)	15 952 (57.8%)
	• Number of prescriptions filled by women presenting a pregnancy during the period	307 (2.2%)	193 (2.3%)	89 (2.4%)	615 (1.7%)	268 (1.7%)
	• Number of TCC prescriptions concomitant to pregnancy	77 (25.1%)	58 (30.1%)	28 (31.5%)	176 (28.6%)	65 (24.3%)
	• Number of prescriptions filled by women presenting a diagnosis of lactation during the period	19 (0.1%)	3 (0.0%)	3 (0.1%)	27 (0.1%)	9 (0.1%)
	• Number of TCC prescriptions concomitant to lactation	6 (31.6%)	1 (33.3%)	1 (33.3%)	7 (25.9%)	3 (33.3%)
	• Number of TCC prescriptions filled by women not having contraception during the period	10 921 (76.5%)	7 805 (94.4%)	3 460 (94.9%)	30 903 (84.6%)	13 728 (86.1%)
FRANCE RHEUMATOLOGIST PANEL	**Number of prescriptions: total**	1 721 (100.0%)	1 281 (100.0%)	578 (100.0%)	4 184 (100.0%)	1 923 (100.0%)
	Number of prescriptions filled by women	1 099 (68.9%)	881 (72.2%)	412 (72.9%)	2 866 (72.1%)	1 358 (72.6%)
	Number of prescriptions filled by women of child bearing potential (16-49 years old)	262 (23.8%)	152 (17.3%)	82 (19.9%)	512 (17.9%)	255 (18.8%)
	• Number of prescriptions filled by women presenting a pregnancy during the period	-	-	-	-	-
	• Number of TCC prescriptions concomitant to pregnancy	-	-	-	-	-
	• Number of prescriptions filled by women presenting a diagnosis of lactation during the period	-	-	-	-	-
	• Number of TCC prescriptions concomitant to lactation		-	-	-	-
	• Number of TCC prescriptions filled by women not having contraception during the period	261 (99.6%)	152 (100.0%)	82 (100.0%)	512 (100.0%)	255 (100.0%)
ITALY GP PANEL	**Number of prescriptions: total**	23 527 (100.0%)	17 364 (100.0%)	6 471 (100.0%)	54 892 (100.0%)	20 674 (100.0%)
	Number of prescriptions filled by women	12 884 (64.0%)	9 316 (62.7%)	3 466 (61.2%)	29 383 (62.6%)	11 109 (61.5%)
	Number of prescriptions filled by women of child bearing potential (16-49 years old)	4 290 (33.3%)	2 543 (27.3%)	1 312 (37.9%)	8 347 (28.4%)	4 340 (39.1%)

	Baseline	Study Period 3		Cumulative Study Periods	
		Overall	Incident	Overall	Incident
• Number of prescriptions filled by women presenting a pregnancy during the period	353 (8.2%)	219 (8.6%)	131 (10.0%)	707 (8.5%)	431 (9.9%)
• Number of TCC prescriptions concomitant to pregnancy	169 (47.9%)	103 (47.0%)	61 (46.6%)	349 (49.4%)	213 (49.4%)
• Number of prescriptions filled by women presenting a diagnosis of lactation during the period	8 (0.2%)	1 (0.0%)	-	9 (0.1%)	7 (0.2%)
• Number of TCC prescriptions concomitant to lactation	4 (50.0%)	-	-	3 (33.3%)	3 (42.9%)
• Number of TCC prescriptions filled by women not having contraception during the period	3 509 (81.8%)	2 236 (87.9%)	1 146 (87.3%)	7 570 (90.7%)	3 934 (90.6%)

Baseline period: year 2013

Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018

Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018

Incident case: New TCC prescription in all patient history with at least one year of medical history

Long-term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

10.3 OUTCOME DATA

Table 10.3-1 shows a summary of off-label use of systemic TCC in the three panels.

Concerning baseline (pre-implementation period), the off-label proportion was estimated based on the post-RMMs SmPC.

Overall prescriptions to patients under the age of 16 years were sparse. Between 0% (panel of French rheumatologists – baseline period) and 1.0% (panel of French GPs – baseline period) of prescriptions were issued to patients being under 16 years old.

Systemic TCC was prescribed as adjuvant of a concomitant treatment in a large majority of prescriptions, ranging from 86.6% in Italian GP panel (baseline period) to 93.5% in French GP panel (baseline period) (Table 10.3-1).

Concerning dose of systemic TCC oral prescriptions, physicians in all panels respected the restrictions of daily dose for the oral form, ranging from 98% in Italian GP panel (all periods) to 100% in the French GP and rheumatologist panels (all periods). The IM form was less frequently prescribed in France (~3% in the GP panel, ~17% in the rheumatologist panel). The French GPs respected the restrictions of daily dose of oral form in 99.7% (baseline) to 99.8% (both study periods) of prescriptions, and French rheumatologists respected the restrictions of daily dose of oral form in 100% (baseline and both study periods) of prescriptions. Italian GPs, whose TCC prescriptions were for IM form in 70% of cases, respected the restrictions of daily dose in 99.9% (all three periods) of prescriptions (Table 10.3-1).

Restrictions of duration were less respected than restrictions on daily dose. For oral form, French GPs respected restrictions of duration for 46.7% (baseline), 69.4% (study period 3) and 66.2% (cumulative study periods) of prescriptions, while Italian GPs respected restrictions of duration for 46.6% (cumulative study periods) to 52.3% (baseline) of prescriptions. French rheumatologists respected restrictions of duration for only 40.3% (baseline), 53.4% (study period 3) and 49.2% (cumulative study periods) of prescriptions. Concerning the IM form, French GPs respected restrictions of duration for 30.4% (baseline) to 50.7% (study period 3) and 48.7% (cumulative study periods) of prescriptions, while French rheumatologists respected restrictions of duration for 32.4% (baseline), 49.1% (study period 3) and 43.2% (cumulative study periods) of prescriptions. Italian GPs respected restrictions of duration for only 12.8% (baseline), 11.3% (study period 3) and 11.6% (cumulative study periods) of prescriptions (Table 10.3-1).

Concerning pregnancy, no TCC prescriptions were encountered concomitantly to a pregnancy in the French rheumatologists' panel. Less TCC prescriptions were encountered concomitantly to a pregnancy in the French GP panel (0.5% for baseline and cumulative study periods of total prescriptions) than in the Italian GP panel (3.9% for baseline to 4.2% for cumulative study periods of total prescriptions). These findings need to be considered carefully. As mentioned in the protocol, the records were not comprehensive and the identification whether a pregnant woman was exposed to TCC or not required certain assumptions to overcome the incompleteness of data.

Systemic TCC prescription concomitant to a breastfeeding period was encountered in ≤0.1% of prescriptions.

Proportion of systemic prescriptions of TCC to female patients for whom it was not possible to find a record indicating use of hormonal contraceptives or IUD was very high as anticipated, exceeding 86% of prescriptions filled by female patients of child bearing potential (16-49 years old).

Table 10.3-1: Contraindications to prescription of TCC-containing medicinal products for systemic use per panel according to period.

		Baseline Period	Study Period 3	Cumulative Study Periods
FRANCE GP PANEL				
	N	44 108	29 631	123 429
	Age at prescription (years) <16 years	452 (1.0%)	117 (0.4%)	661 (0.5%)
	No concomitant medications and/or health services, medical devices during systemic TCC use	2 874 (6.5%)	2 283 (7.7%)	9 062 (7.3%)
	Oral form			
	• daily dose>16 mg per day	112 (0.3%)	42 (0.2%)	219 (0.2%)
	• duration >7 consecutive days	21 763 (53.3%)	7 639 (30.6%)	38 148 (33.8%)
	IM form			
	• daily dose>8 mg per day	337 (36.4%)	41 (10.8%)	303 (19.0%)
	• duration >5 consecutive days	598 (69.6%)	208 (49.3%)	915 (51.3%)
	Long-term treatment	2 289 (5.3%)	913 (3.2%)	4 280 (3.5%)
	Treatment indication: other than painful muscle contractures associated with acute spinal pathology	17 557 (46.7%)	11 474 (46.8%)	48 560 (46.1%)
	In women of child bearing potential: [3]			
	• Pregnancy	77 (0.5%)	58 (0.7%)	176 (0.5%)
	• No contraceptive use	12 290 (86.1%)	7 550 (91.3%)	32 721 (89.5%)
	• Lactation	6 (0.0%)	1 (0.0%)	7 (0.0%)
FRANCE RHEUMATOLOGIST PANEL				
	N	1 721	1 281	4 184
	Age at prescription (years) <16 years	-	1 (0.1%)	1 (0.0%)
	No concomitant medications and/or health services, medical devices during systemic TCC use	192 (11.2%)	135 (10.5%)	503 (12.0%)
	Oral form			
	• daily dose>16 mg per day	-	-	-
	• duration >7 consecutive days	707 (59.7%)	405 (46.6%)	1 437 (50.8%)
	IM form			
	• daily dose>8 mg per day	104 (37.1%)	89 (41.6%)	243 (32.9%)
	• duration >5 consecutive days	188 (67.6%)	109 (50.9%)	419 (56.8%)
	Long-term treatment	132 (7.8%)	40 (3.2%)	152 (3.7%)
	Treatment indication: other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	360 (28.1%)	1 218 (29.1%)
	In women of child bearing potential[3]:			
	• Pregnancy	-	-	-
	• No contraceptive use	262 (100.0%)	152 (100.0%)	512 (100.0%)
	• Lactation	-	-	-
ITALY GP PANEL				
	N	23 527	17 364	54 892
	Age at prescription (years) <16 years	36 (0.2%)	9 (0.1%)	32 (0.1%)
	No concomitant medications and/or health services, medical devices during systemic TCC use	3 151 (13.4%)	1 917 (11.0%)	6 270 (11.4%)
	Oral form			
	• daily dose>16 mg per day	34 (1.3%)	24 (1.9%)	62 (1.5%)
	• duration >7 consecutive days	1 239 (47.7%)	659 (51.3%)	2 258 (53.4%)
	IM form			
	• daily dose>8 mg per day	4 (0.1%)	2 (0.1%)	8 (0.1%)
	• duration >5 consecutive days	3 745 (87.2%)	2 626 (88.7%)	8 459 (88.4%)
	Long-term treatment	225 (1.1%)	121 (0.8%)	380 (0.8%)
	Treatment indication: other than painful muscle contractures associated with acute spinal pathology	5 236 (24.4%)	3 440 (21.7%)	11 247 (22.4%)

	Baseline Period	Study Period 3	Cumulative Study Periods
In women of child bearing potential:			
• Pregnancy	169 (3.9%)	103 (4.1%)	349 (4.2%)
• No contraceptive use	3 982 (92.8%)	2 447 (96.2%)	7 934 (95.1%)
• Lactation	4 (0.1%)	-	3 (0.0%)

Baseline period: year 2013

Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018

Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018

In women of child bearing potential: percentage based on women of child bearing potential

Long-term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

10.4 MAIN RESULTS

To evaluate the effects of an RMM, a comparison of the prescribing patterns of systemic TCC in the baseline and in the study periods under observation was performed using two types of analyzes.

10.4.1 Comparison of off-label use during baseline and study periods

The first analysis involved a comparison of patient's characteristics at TCC prescription and proportion of off-label, pre- (baseline: 2013) and post-implementation (study periods 3 and cumulative study periods) of RMMs as a measurement of the effectiveness of the RMMs was performed. To this end, the off-label proportion at baseline (year 2013) was estimated based on the post-RMMs SmPC.

The results of the comparison between the pre-implementation (baseline and post-implementation [overall and incident] – study periods 3 and cumulative study periods) periods for the three panels are presented in Table 10.4-1.

French GP panel

Prescription to patients under the age of 16 years decreased between the pre- (1% of prescriptions) and post-implementation cumulative study periods (0.5% of prescriptions; p-value <0.001).

For oral form, we observed a significative increase for compliance to maximal recommended dose between the pre- and post-implementation cumulative study periods (99.7% vs 99.8% of prescriptions; p-value <0.05) as well as compliance to recommended duration (46.7% vs 66.2% of prescriptions; p-value <0.001).

For IM form, there was an increase between the pre- and post-implementation cumulative study periods for compliance to maximal recommended dose (63.6% vs 81.0% of prescriptions; p-value <0.001) as well as compliance to recommended duration (30.4% vs 48.7% of prescriptions; p-value <0.001).

Compliance to restriction to short term treatment increased between the pre- and post-implementation period (94.7% vs 96.5% of prescriptions; p-value <0.001).

There was an increase in the prescription to women having no record indicating use of hormonal contraceptives or IUD (91.3% of prescriptions for post-implementation period 3 and 89.5% for cumulative study periods vs 86.1% for pre-implementation period; p-value <0.001).

French rheumatologists' panel

In the French rheumatologists' panel, statistically significant differences could be observed between the pre-implementation period (baseline) and the post-implementation periods (study periods 3 and cumulative study periods) with respect to the compliance to recommended duration of treatment for oral and IM forms (p-value <0.02) and restriction to short term treatment (p-value <0.001), in the study period as compared to the baseline.

Italian GP panel

Prescription to patients under the age of 16 years decreased between the pre- (0.2% of prescriptions) and post-implementation periods (0.1% of prescriptions; p-value=0.01).

Prescription of TCC as adjuvant of a concomitant treatment increased between the pre- and post-implementation periods (88.6% of prescriptions for post-implementation cumulative study periods vs 86.6% for pre-implementation period; p-value <0.001).

For oral form, compliance to maximal recommended dose remained unchanged (p-value >0.05) between pre- and post-implementation period. The compliance to recommended duration decreased significantly from pre- to post-implementation periods (46.6% of prescriptions for post-implementation cumulative study periods vs 52.3% for pre-implementation period; p-value <0.001).

For IM form, compliance to maximal recommended dose remained unchanged (p-value >0.05) between pre- and post-implementation period while compliance to recommended duration decreased after the RMM (11.6% of prescriptions for post-implementation cumulative study periods vs 12.8% for pre-implementation period; p-value <0.05)

However, due to the limitation of the Italian GP panel in term of dose and duration (see Limitations; §11.2) these results should be taken with caution.

Compliance to restriction to short term treatment increased slightly between the pre- and post-implementation period (99.2% of prescriptions for post-implementation vs 98.9% for pre-implementation period; p-value=0.01).

Compliance to treatment indication increased slightly between the pre- and post-implementation period (77.6% of prescriptions for post-implementation cumulative study periods vs 75.8% for pre-implementation period; p-value=0.001).

Table 10.4-1: Comparison of off-label during baseline, overall and incident study period per panel

		Study Period 3				Cumulative Study Periods			
	Baseline period (N= 44 108)	Overall (N=29 631)	Incident (N=12 287)	p-value Baseline vs Overall Study period	p-value Baseline vs Incident Study period	Overall (N=123 429)	Incident (N=50 597)	p-value Baseline vs Overall Study period	p-value Baseline vs Incident Study period
FRANCE GP PANEL									
Age at prescription (years) <16 years	452 (1.0%)	117 (0.4%)	99 (0.8%)	<0.001 [a]	0.496 [a]	661 (0.5%)	533 (1.1%)	<0.001 [a]	0.496 [a]
No concomitant medications and/or health services, medical devices during systemic TCC use	2 874 (6.5%)	2 283 (7.7%)	1 102 (9.0%)	<0.001 [a]	<0.001 [a]	9 062 (7.3%)	4 327 (8.6%)	<0.001 [a]	<0.001 [a]
Oral form									
daily dose>16 mg per day	112 (0.3%)	42 (0.2%)	20 (0.2%)	0.032 [a]	0.249 [a]	219 (0.2%)	98 (0.2%)	0.032 [a]	0.249 [a]
duration >7 consecutive days	21 763 (53.3%)	7 639 (30.6%)	2 742 (26.2%)	<0.001 [a]	<0.001 [a]	38 148 (33.8%)	13 579 (29.3%)	<0.001 [a]	<0.001 [a]
IM form									
daily dose>8 mg per day	337 (36.4%)	41 (10.8%)	19 (12.7%)	<0.001 [a]	<0.001 [a]	303 (19.0%)	114 (18.5%)	<0.001 [a]	<0.001 [a]
duration >5 consecutive days	598 (69.6%)	208 (49.3%)	83 (47.2%)	<0.001 [a]	<0.001 [a]	915 (51.3%)	319 (46.2%)	<0.001 [a]	<0.001 [a]
Long-term treatment	2 289 (5.3%)	913 (3.2%)	-	<0.001 [a]	<0.001 [a]	4 280 (3.5%)	-	<0.001 [a]	<0.001 [a]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology	17 557 (46.7%)	11 474 (46.8%)	3 972 (39.0%)	0.571 [a]	<0.001 [a]	48 560 (46.1%)	16 993 (39.2%)	0.571 [a]	<0.001 [a]
In women of child bearing potential:									
Pregnancy	77 (0.5%)	58 (0.7%)	28 (0.8%)	0.022 [a]	0.006 [a]	176 (0.5%)	65 (0.4%)	0.022 [a]	0.006 [a]
No contraceptive use	12 290 (86.1%)	7 550 (91.3%)	3 383 (92.8%)	<0.001 [a]	<0.001 [a]	32 721 (89.5%)	14 502 (90.9%)	<0.001 [a]	<0.001 [a]
Lactation	6 (0.0%)	1 (0.0%)	1 (0.0%)	0.055 [a]	0.369 [a]	7 (0.0%)	3 (0.0%)	0.055 [a]	0.369 [a]
FRANCE RHEUMATOLOGIST PANEL									
Age at prescription (years) <16 years	-	1 (0.1%)	1 (0.2%)			1 (0.0%)	1 (0.1%)		
No concomitant medications and/or health services, medical devices during systemic TCC use	192 (11.2%)	135 (10.5%)	75 (13.0%)	0.027 [a]	<0.001 [a]	503 (12.0%)	292 (15.2%)	0.027 [a]	<0.001 [a]
Oral form									
daily dose>16 mg per day	-	-	-	N/A [a]	N/A [a]	-	-	N/A [a]	N/A [a]
duration >7 consecutive days	707 (59.7%)	405 (46.6%)	149 (41.2%)	0.016 [a]	<0.001 [a]	1 437 (50.8%)	534 (44.6%)	0.016 [a]	<0.001 [a]
IM form									
daily dose>8 mg per day	104 (37.1%)	89 (41.6%)	51 (41.5%)	0.033 [a]	0.156 [a]	243 (32.9%)	144 (33.3%)	0.033 [a]	0.156 [a]
duration >5 consecutive days	188 (67.6%)	109 (50.9%)	58 (47.2%)	0.019 [a]	<0.001 [a]	419 (56.8%)	225 (52.1%)	0.019 [a]	<0.001 [a]
Long-term treatment	132 (7.8%)	40 (3.2%)	-	<0.001 [a]	<0.001 [a]	152 (3.7%)	-	<0.001 [a]	<0.001 [a]

Treatment indication: other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	360 (28.1%)	197 (34.1%)	0.113 [a]	0.029 [a]	1 218 (29.1%)	673 (35.0%)	0.113 [a]	0.029 [a]
In women of child bearing potential:									
Pregnancy	-	-	-	N/A [a]	N/A [a]	-	-	N/A [a]	N/A [a]
No contraceptive use	262 (100.0%)	152 (100.0%)	82 (100.0%)	N/A [a]	N/A [a]	512 (100.0%)	255 (100.0%)	N/A [a]	N/A [a]
Lactation	-	-	-	N/A [a]	N/A [a]	-	-	N/A [a]	N/A [a]
ITALY GP PANEL									
Age at prescription (years) <16 years	36 (0.2%)	9 (0.1%)	9 (0.1%)	0.010 [b]	0.765 [b]	32 (0.1%)	30 (0.1%)	0.010 [b]	0.765 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use	3 151 (13.4%)	1 917 (11.0%)	820 (12.7%)	<0.001 [b]	0.507 [b]	6 270 (11.4%)	2 753 (13.3%)	<0.001 [b]	0.507 [b]
Oral form									
daily dose>16 mg per day	34 (1.3%)	24 (1.9%)	12 (2.1%)	0.087 [b]	0.391 [b]	62 (1.5%)	28 (1.5%)	0.087 [b]	0.391 [b]
duration >7 consecutive days	1 239 (47.7%)	659 (51.3%)	281 (48.4%)	<0.001 [b]	0.013 [b]	2 258 (53.4%)	968 (52.1%)	<0.001 [b]	0.013 [b]
IM form									
daily dose>8 mg per day	4 (0.1%)	2 (0.1%)	-	0.601 [b]	0.935 [b]	8 (0.1%)	2 (0.1%)	0.601 [b]	0.935 [b]
duration >5 consecutive days	3 745 (87.2%)	2 626 (88.7%)	762 (88.0%)	0.035 [b]	0.097 [b]	8 459 (88.4%)	2 466 (87.8%)	0.035 [b]	0.097 [b]
Long-term treatment	225 (1.1%)	121 (0.8%)	-	0.010 [b]	<0.001 [b]	380 (0.8%)	-	0.010 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology	5 236 (24.4%)	3 440 (21.7%)	1 421 (24.2%)	0.001 [b]	0.101 [b]	11 247 (22.4%)	4 562 (24.3%)	0.001 [b]	0.101 [b]
In women of child bearing potential:									
Pregnancy	169 (3.9%)	103 (4.1%)	61 (4.6%)	0.744 [b]	0.077 [b]	349 (4.2%)	213 (4.9%)	0.744 [b]	0.077 [b]
No contraceptive use	3 982 (92.8%)	2 447 (96.2%)	1 255 (95.7%)	<0.001 [b]	<0.001 [b]	7 934 (95.1%)	4 121 (95.0%)	<0.001 [b]	<0.001 [b]
Lactation	4 (0.1%)	-	-	0.331 [b]	0.750 [b]	3 (0.0%)	3 (0.1%)	0.331 [b]	0.750 [b]

Baseline period: year 2013
Study period year 3: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Cumulative Study Periods: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
In women of child bearing potential: percentage based on women of child bearing potential
[a] Fisher's exact test
[b] Chi-square test

10.4.2 Analysis of RMMs impact on off-label rate in included patients

The final analysis was a segmented regression analysis. In this analysis, incidence rates were computed by months before (baseline: 2013) and after RMMs implementation (according to each country). The model included an intercept (mean outcome rate at beginning of the study) and main period (before/after RMMs) effect and separate time trends before and after RMM.

By treatment indication

The analysis on the French GP panel showed that the intervention was associated with a statistically significant reduction of off-label rate immediately after intervention. However, this effect was not sustained over the post-implementation period as shown by the change in the slope of all-label use after intervention (Figure 1).

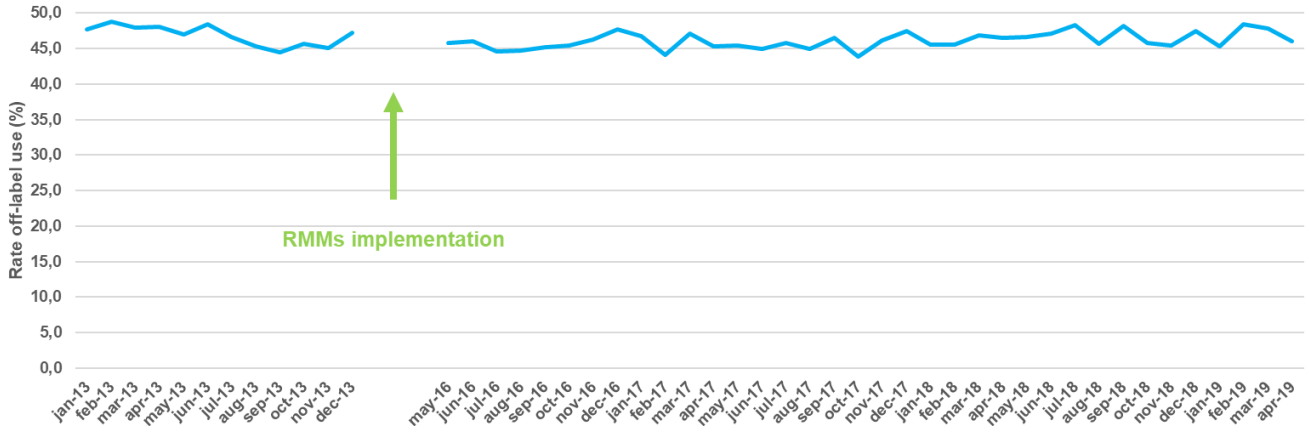
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 48.6%.

A pre-intervention trend was observed: the variable time showed that before the intervention there was a significant reduction of 0.27 percentage point with each month (p-value=0.0038).

There was a significant immediate effect of the intervention on the off-label rate: the "intervention" variable showed a change in the level of the off-label use rate after the intervention period: the off-label use rate decreased immediately after the intervention period by -3.9 percentage points (p-value<0.0001).

The 'time after intervention variable' showed a change in the trend in the off-label use rate following the intervention period compared to the reference period: there was a significant increase of 0.32 percentage points with each month compared to the previous slope (p-value=0.0011) (Table 15**.3-103** of Statistical Report in Annex 3; §15.3).

Figure 1: Evolution of off-label rate- treatment indication - French GP panel



The analysis by French rheumatologists' panel showed that the intervention was not associated with a change in the off-label rate immediately after the intervention, but that there was a change in the slope after the intervention compared to the slope before the intervention. Due to the small number of evaluable prescriptions per month, the interpretation of the results for France rheumatologists' panel must be interpreted with caution. (Figure 2).

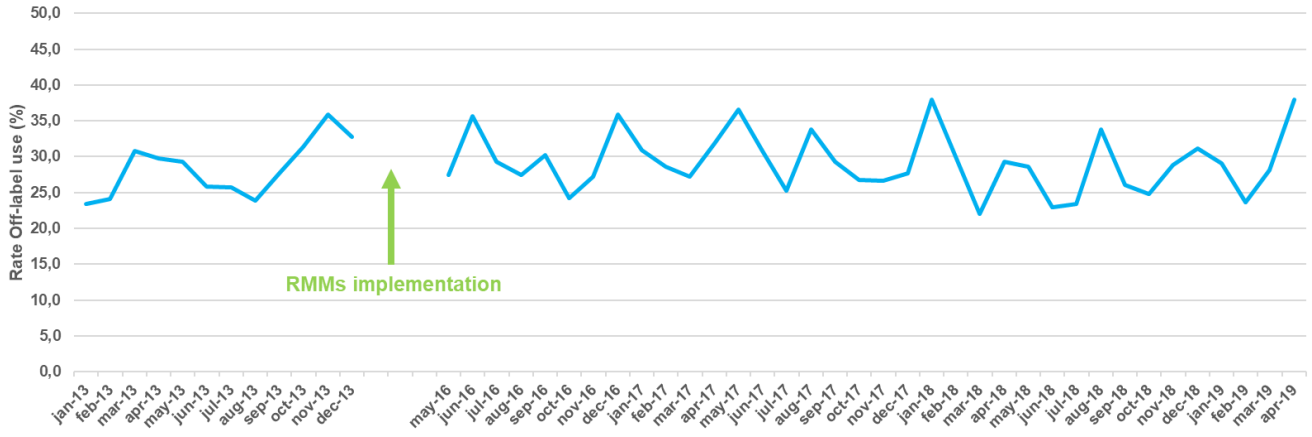
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 24.4%.

A pre-intervention trend was observed: the variable time showed that before the intervention there was a significant increase of 0.8 percentage point with each month (p-value=0.0204).

The ‘time after intervention variable’ showed a change in the trend in the off-label use rate following the intervention period compared to the reference period: there was a significant decrease of 0.86 percentage points with each month compared to the previous reference period. (p-value=0.0160).

The dummy variable was not interpretable but allowed to have stationary data i.e. with a constant mean, variance, and autocorrelation through time (Table 15**.3-104** of Statistical Report in Annex 3; §15.3).

Figure 2: Evolution of off-label rate - treatment indication – French Rheumatologist panel (Cumulative Study Periods)



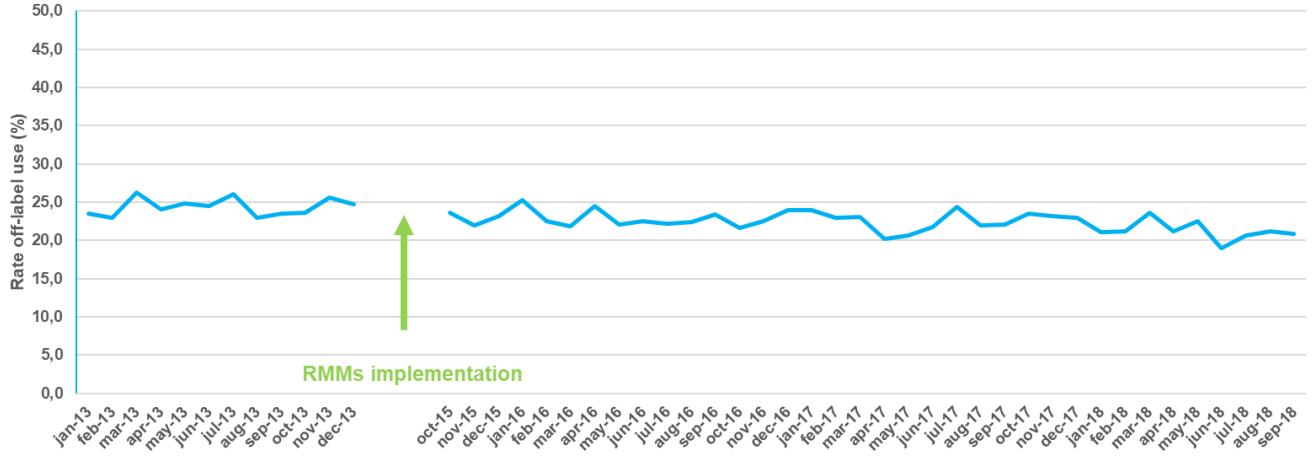
Analysis on the Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 3).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 24.1%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.9491).

There was no significant change in the trend of the rate of off-label use following intervention period compared to the baseline period (p-value=0.3341) (Table 15**.3-105** of Statistical Report in Annex 3; §15.3).

Figure 3: Evolution of off-label rate - treatment indication – Italian GPs panel (Cumulative Study Periods)



By age under 16 years

The analyses of RMMs impact on off-label rate in patients under 16 years of age are presented for French and Italian GP panels in Figure 4 and Figure 5, respectively. There was only one case under 16 years old in French rheumatologist panel and therefore no regression analysis could be performed.

The analysis on the French GP panel showed that the intervention was associated with a statistically significant reduction of off-label rate immediately after intervention. However, this effect was not sustained over the post-implementation period as shown by the change in the slope of all-label use after intervention (Figure 4).

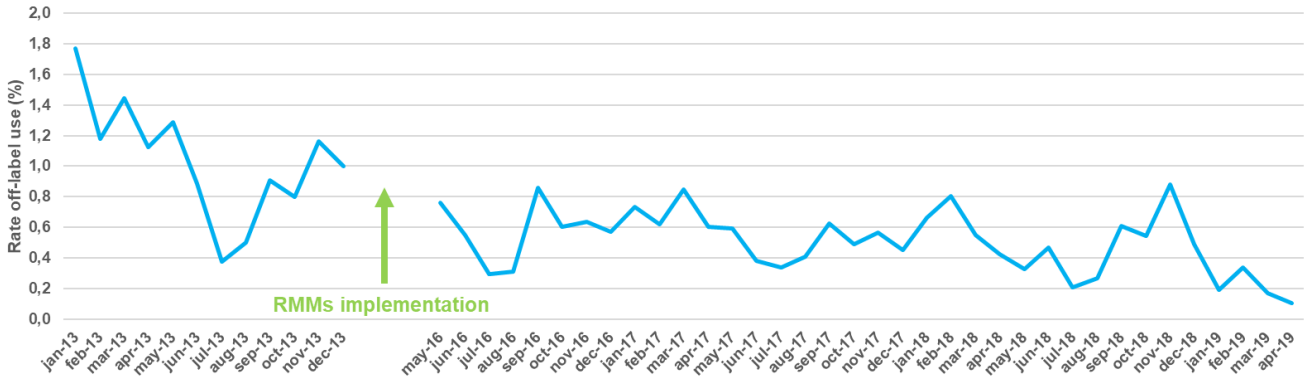
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 1.4%.

A pre-intervention trend was observed: the variable time showed that before the intervention there was a significant reduction of 0.06 percentage point with each month (p-value=0.0031).

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable showed a change on the level of the rate of off-label use following the intervention period: the rate of off-label use decreased immediately after the intervention period by -0.67 percentage points (p-value=0.0007).

The 'time after intervention variable' showed a change in the trend of the rate of off-label use following the intervention period compared to baseline period: there was a significant increase of 0.05 percentage point with each month in comparison with the previous slope (p-value=0.0111) (Table 15**.3-106** of Statistical Report in Annex 3; §15.3).

Figure 4: Evolution of off-label rate- age under 16 years old - French GP panel (Cumulative Study Periods)



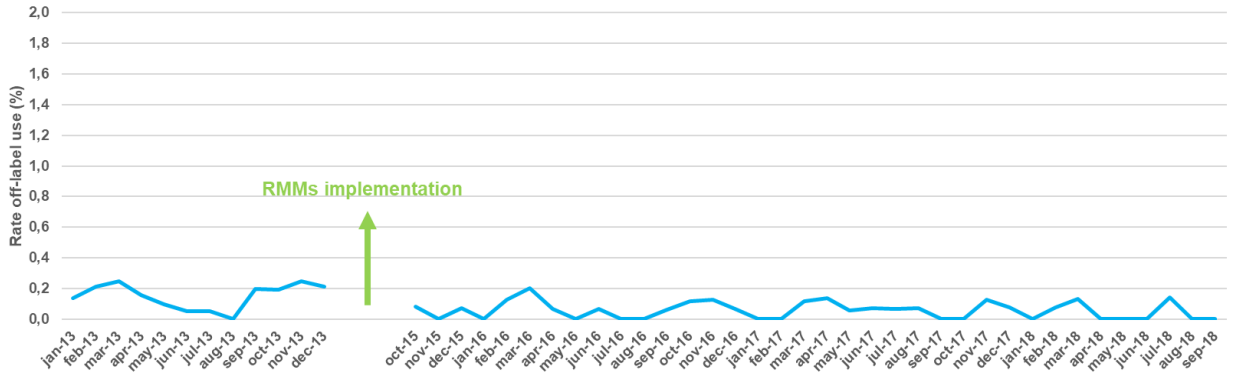
Analysis on the Italian GP panel showed that the intervention was associated with a significant decrease of off-label rate immediately after intervention. No further effect was noted on trend of off-label use in the long-term (Figure 5).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 0.21%.

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable showed a change on the level of the rate of off-label use following the intervention period: the rate of off-label use released immediately after the intervention period by -0.13 percentage points (p-value=0.0120).

There was no significant change in the trend of the rate of off-label use following intervention compared to the baseline period (p-value=0.8633) (Table 15**.3-107** of Statistical Report in Annex 3; §15.3). The dummy variable was not interpretable but allowed to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 5: Evolution of off-label rate – age under 16 years old– Italian GPs panel (Cumulative Study Periods)



By concomitant use status

The analysis on the French GP panel showed that the intervention was associated with a statistically significant reduction of off-label rate immediately after intervention and a change in the slope after intervention compared to the slope before intervention (Figure 6).

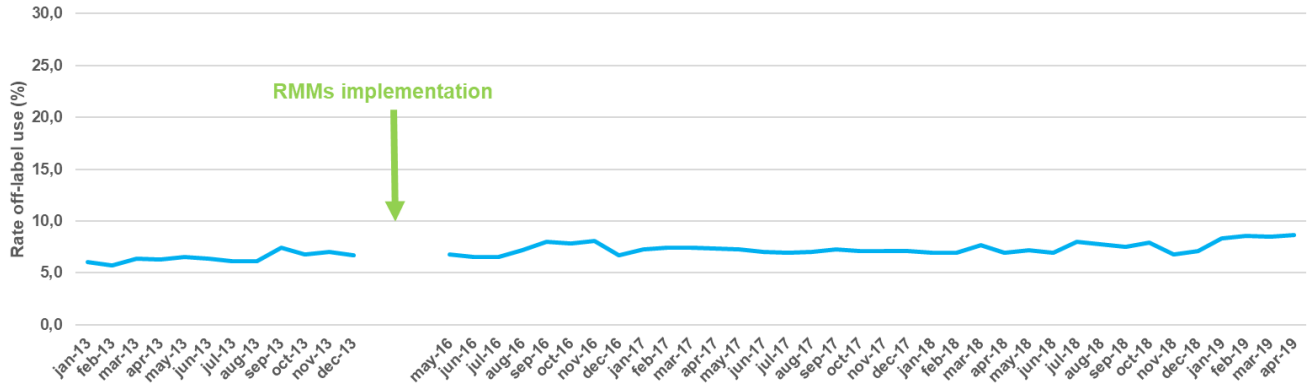
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 5.9%.

A pre-intervention trend was observed: the variable time showed that before the intervention there was a significant increase of 0.09 percentage point with each month (p-value=0.0295).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.0610).

There was no significant change in the trend of the rate of off-label use that following the intervention period compared to the baseline period (p-value=0.1213) (Table 15.**3-108** of Statistical Report in Annex 3; §15.3).

Figure 6: Evolution of off-label rate- no concomitant use - French GP panel (Cumulative Study Periods)



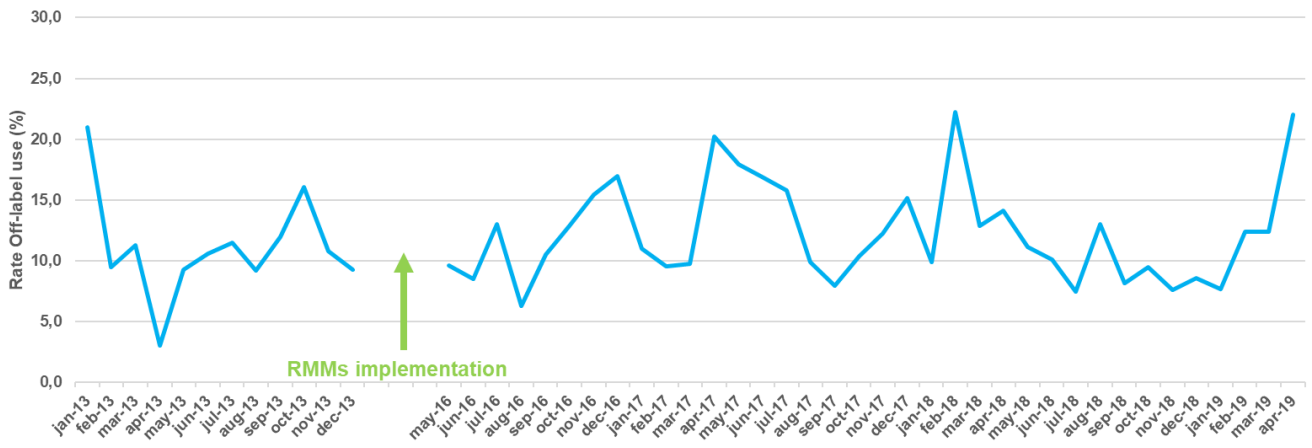
There was no effect of the intervention observed on the monthly off-label rates in the French rheumatologists' panel, immediately after intervention period and in the trend of off-label use after implementation of RMM. Due the low number of evaluable prescriptions per month, interpretation of the results for the French rheumatologists' panel must be interpreted with caution (Figure 7).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 12%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.9127).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.7197) (Table 15.**3-109** of Statistical Report in Annex 3; §15.3).

Figure 7: Evolution of off-label rate - no concomitant use – French Rheumatologist panel (Cumulative Study Periods)



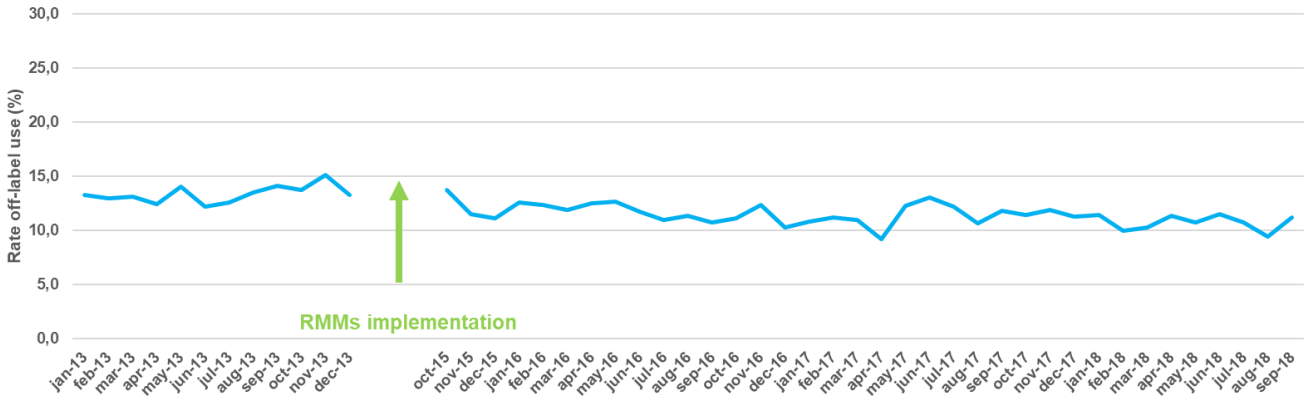
Analysis on the Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 8).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 13%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.6584).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.0800) (Table 15.**3-110** of Statistical Report in Annex 3; §15.3). The dummy variable was not interpretable but allowed to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 8: Evolution of off-label rate - no concomitant use – Italian GPs panel (Cumulative Study Periods)



By IM form dosage >8 mg per day

Due to a high number of missing values in France, the number of observations per months was insufficient (<100 prescriptions) for a segmented regression analysis of off-label rate by IM form dosage for French GP and rheumatologist panels.

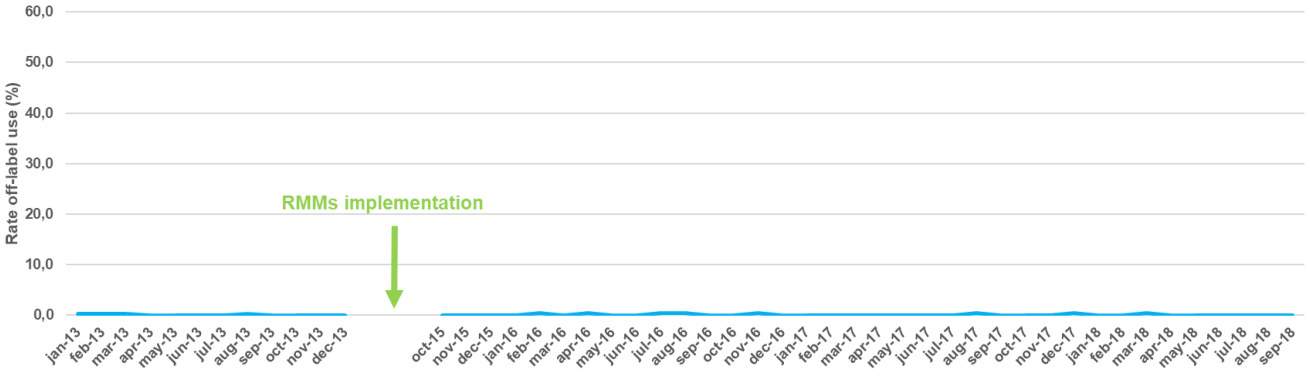
The analysis on Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and the trend continued through post-implementation period (Figure 9).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 0.23%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.4916).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.1596) (Table 15**.3-111** of Statistical Report in Annex 3; §15.3).

Figure 9: Evolution of off-label rate - IM form dosage >8 mg per day – Italian GPs panel (Cumulative Study Periods)



By oral form dosage >16 mg per day

Due to the insufficient number of observations per months (<100 prescriptions) in the France rheumatologist panel, a segmented regression analysis of off-label rates by oral form dosage was not performed.

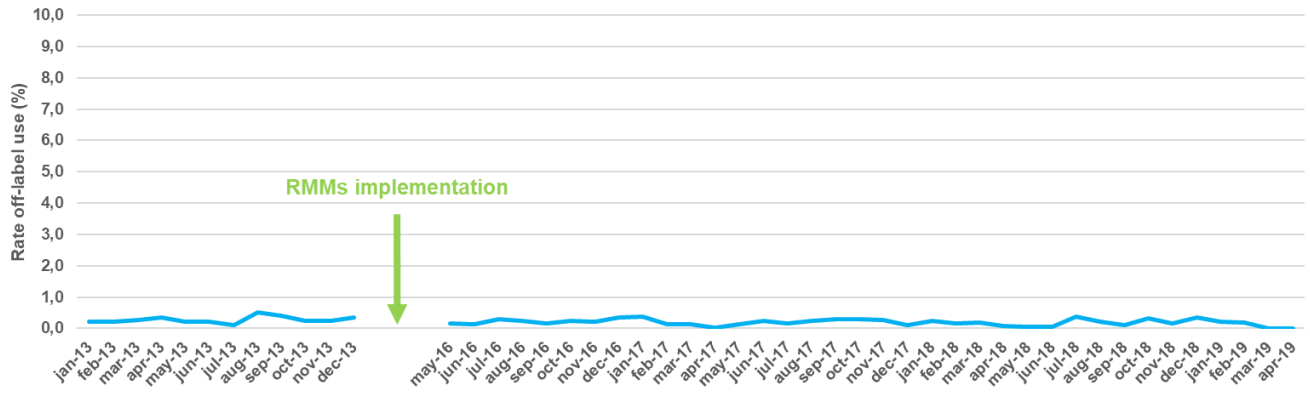
The analysis on the French GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 10).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 0.21%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.6976).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.2114) (Table 15**.3-112** of Statistical Report in Annex 3; §15.3).

Figure 10: Evolution of off-label rate- oral form dosage>16 mg per day - French GP panel (Cumulative Study Periods)



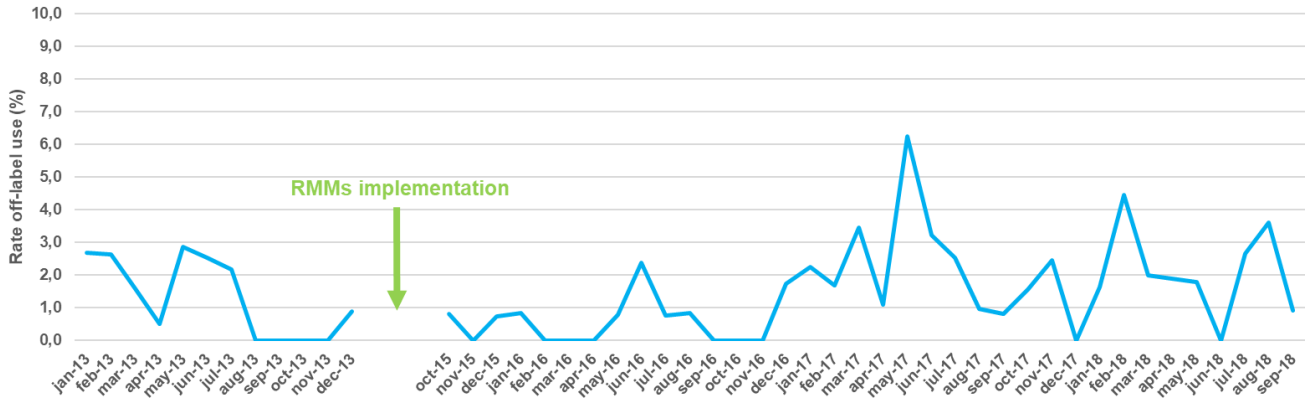
Analysis on the Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and the trend continued through post-implementation period (Figure 11).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 2%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.0562).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.9164) (Table 15.**3-113** of Statistical Report in Annex 3; §15.3). The dummy variable was not interpretable but allowed to have stationary data, i.e. with a constant mean, variance, and autocorrelation through time.

Figure 11: Evolution of off-label rate - oral form dosage>16 mg per day– Italian GPs panel (Cumulative Study Periods)



By IM form >5 consecutive days

Due to a high number of missing values in France, the number of observations per months was insufficient (100 prescriptions) for a segmented regression analysis of off-label rate for IM duration >5 consecutive days for French GP and rheumatologist panels.

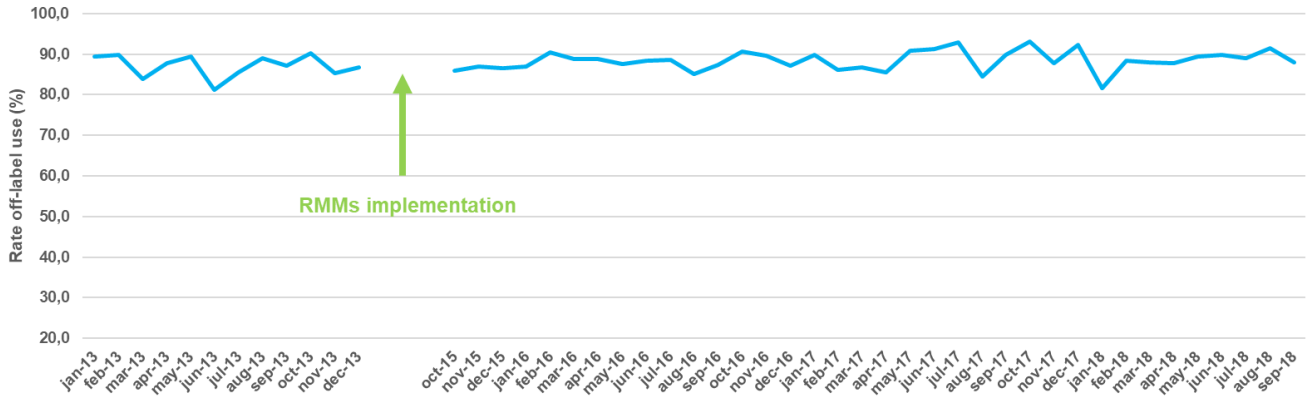
The analysis on Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and this trend continued through post-implementation period (Figure 12).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 87.6%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.7366).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.5414) (Table 15.**3-114** of Statistical Report in Annex 3; §15.3).

Figure 12: Evolution of off-label rate - IM form >5 consecutive days – Italian GPs panel (Cumulative Study Periods)



By oral form >7 consecutive days

The segmented regression analysis for Italian GP panel by oral form >7 consecutive days was not appropriate due to the lower number of prescriptions per month among GPs in Italy.

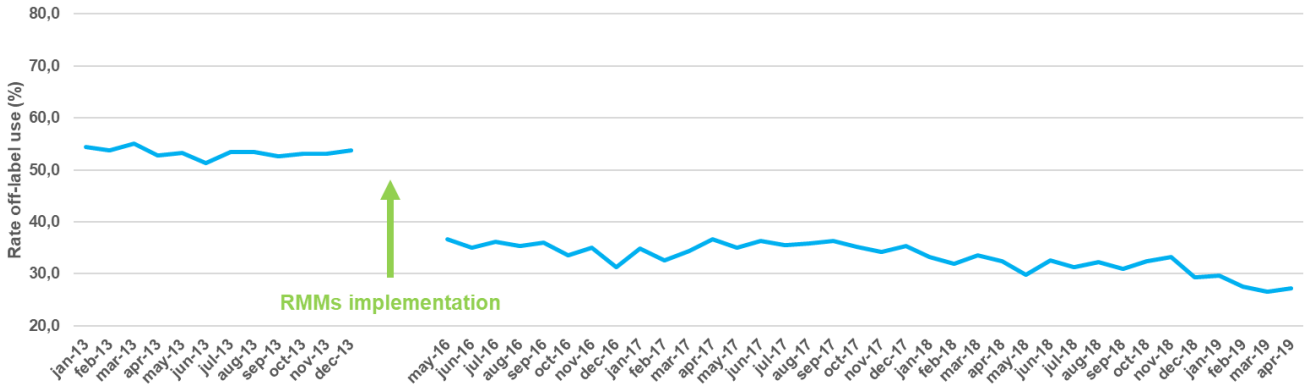
The analysis on the French GP panel showed that the intervention was associated with a significant decrease of off-label rate immediately after intervention. No further effect was found on trend of the rate of off-label use in the long-term (Figure 13).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 53.9%.

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable showed a change on the level of the rate of off-label use following the intervention period: the rate of off-label use released immediately after the intervention period by -14.5 percentage points (p-value<0.0001).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.4192) (Table 15.**3-115** of Statistical Report in Annex 3; §15.3).

Figure 13: Evolution of off-label rate- oral form >7 consecutive days - French GP panel (Cumulative Study Periods)



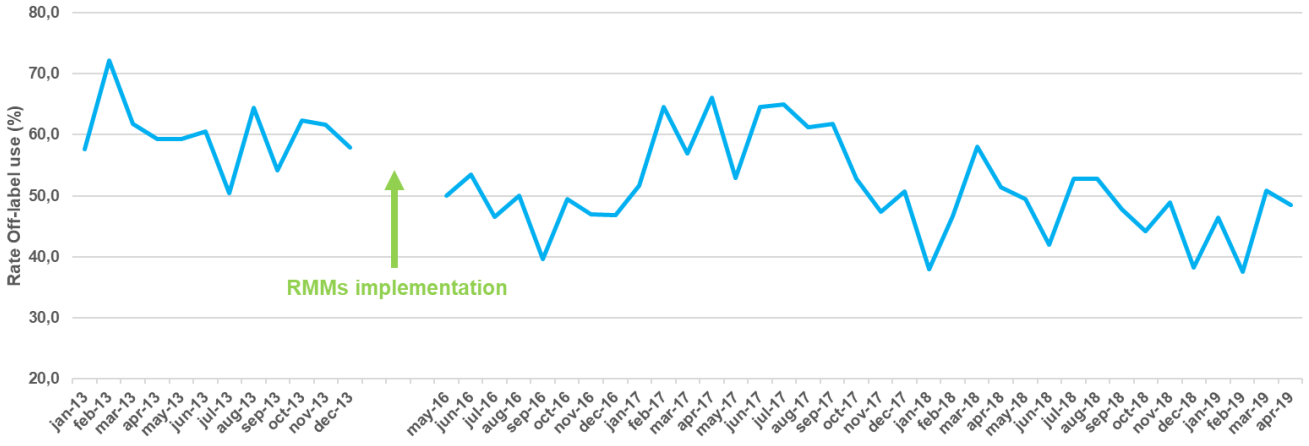
There was no effect of the intervention observed on the monthly off-label rates in the French rheumatologists' panel, immediately after intervention period and in the trend of off-label use through post-implementation period. Due the low number of evaluable prescriptions per month, interpretation of the results for the French rheumatologists' panel were interpreted with caution (Figure 14).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 62.6%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3388).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.7771) (Table 15**.3-116** of Statistical Report in Annex 3; §15.3).

Figure 14: Evolution of off-label rate - oral form >7 consecutive days –France Rheumatologist panel (Cumulative Study Periods)



By long-term treatment

The analysis on the French GP panel showed that the intervention was not associated with a significant decrease of off-label rate immediately after intervention but revealed a significative change in slope towards a reduction of off-label rate after implementation of RMM (Figure 15).

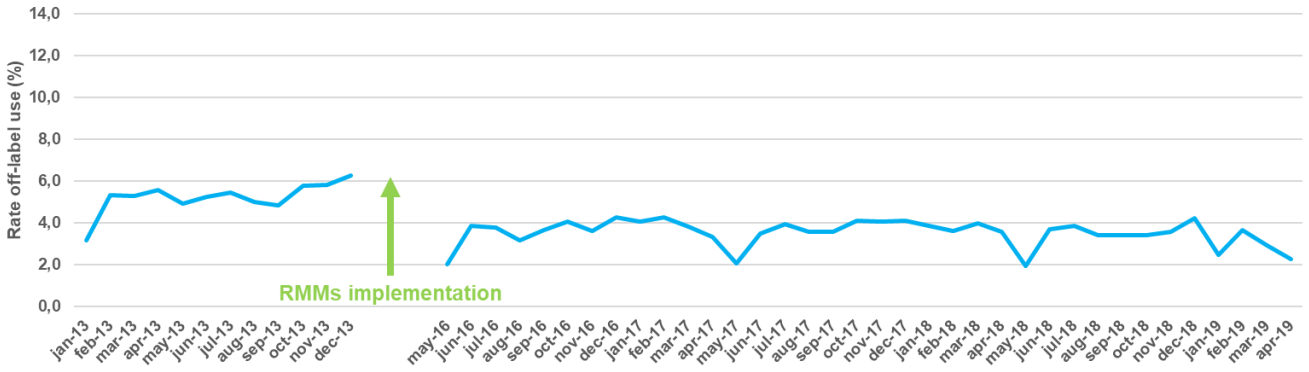
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 4.3%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.14 percentage point with each month (p-value=0.0133).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3420).

The 'time after intervention variable' showed a change in the trend of the rate of off-label use following intervention period compared to the baseline period: there was a significant decrease of 0.15 percentage point with each month in comparison with the previous slope (p-value=0.0090) (Table 15**.3-118** of Statistical Report in Annex 3; §15.3).

Figure 15: Evolution of off-label rate- long-term treatment - French GP panel (Cumulative Study Periods)



There was no effect of the intervention observed on the monthly off-label rates in the French rheumatologists' panel, immediately after intervention period but as in the French GP panel, a sustained effect was observed with a significative change in slope towards a reduction of off-label rate after

implementation of RMM. Due the low number of evaluable prescriptions per month, interpretation of the results for the French rheumatologists'panel were interpreted with caution (Figure 16).

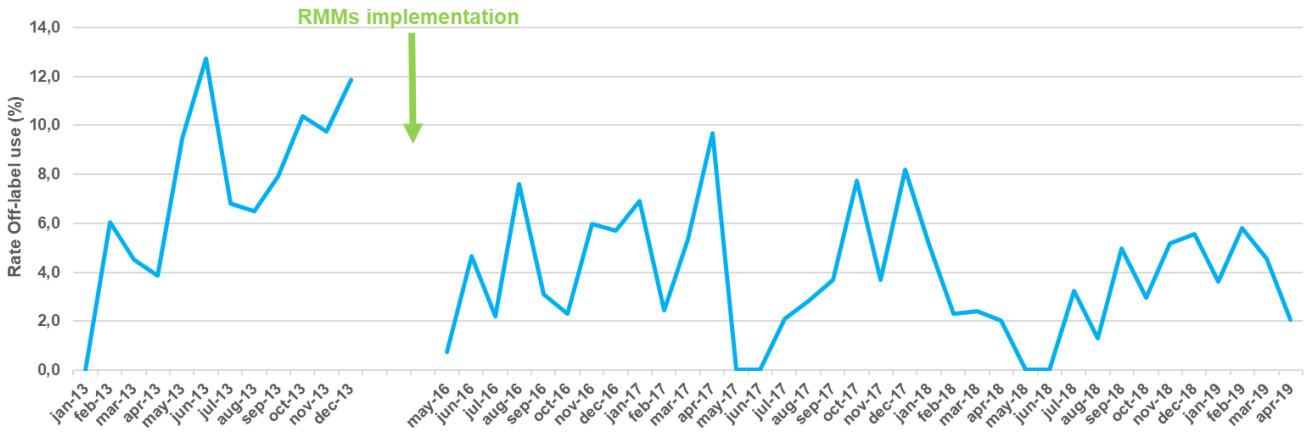
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 2.7%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.74 percentage point with each month (p-value=0.0011).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.4287).

The 'time after intervention variable' shows a change in the trend of the rate of off-label use following the intervention period compared to the baseline period: there was a significant decrease of 0.75 percentage point with each month in comparison with the previous slope (p-value=0.0011) (Table 15**.3-119** of Statistical Report in Annex 3; §15.3).

Figure 16: Evolution of off-label rate - long-term treatment –Rheumatologists France panel (Cumulative Study Periods)



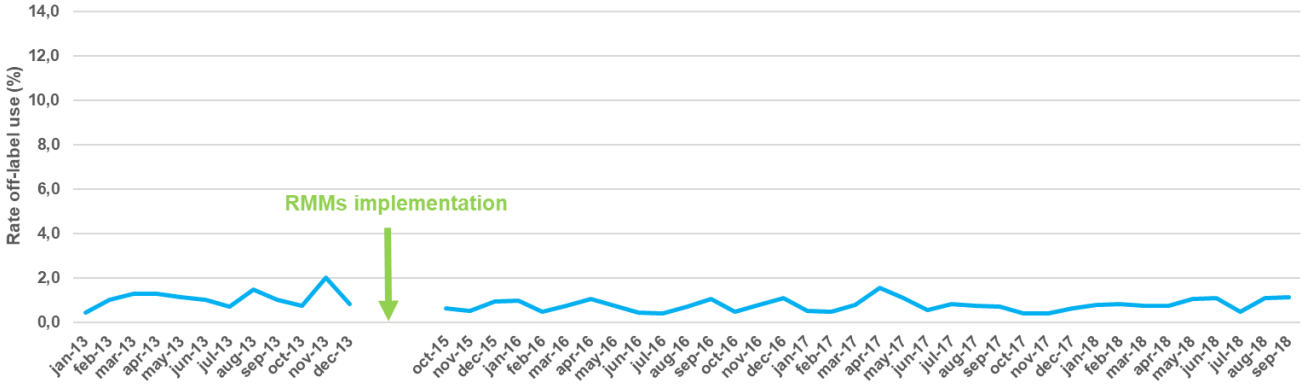
The analysis on GPs in Italy showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 17).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 0.88%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3251).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.3102) (Table 15**.3-120** of Statistical Report in Annex 3; §15.3).

Figure 17: Evolution of off-label rate - long-term treatment –Italy GPs panel (Cumulative Study Periods)



By pregnancy status

The segmented regression analysis results for GPs in France and Italy are presented in Figure 18 and Figure 19, respectively. There were no pregnancies reported in the rheumatologist panel in France.

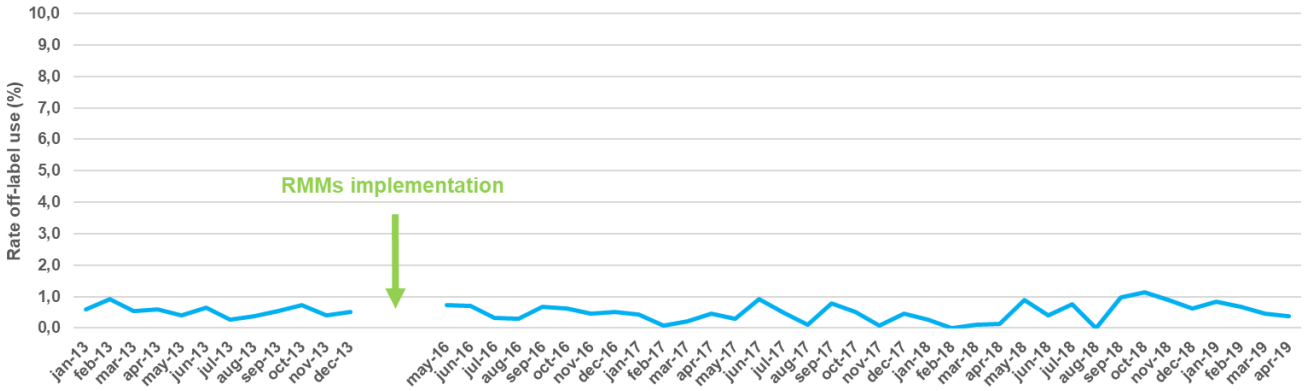
The analysis on the French GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after the intervention period and in the trend of off-label use through post-implementation period (Figure 18).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 0.65%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1765).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.3691) (Table 15**.3-121** of Statistical Report in Annex 3; §15.3).

Figure 18: Evolution of off-label rate- pregnancy - French GP panel (Cumulative Study Periods)



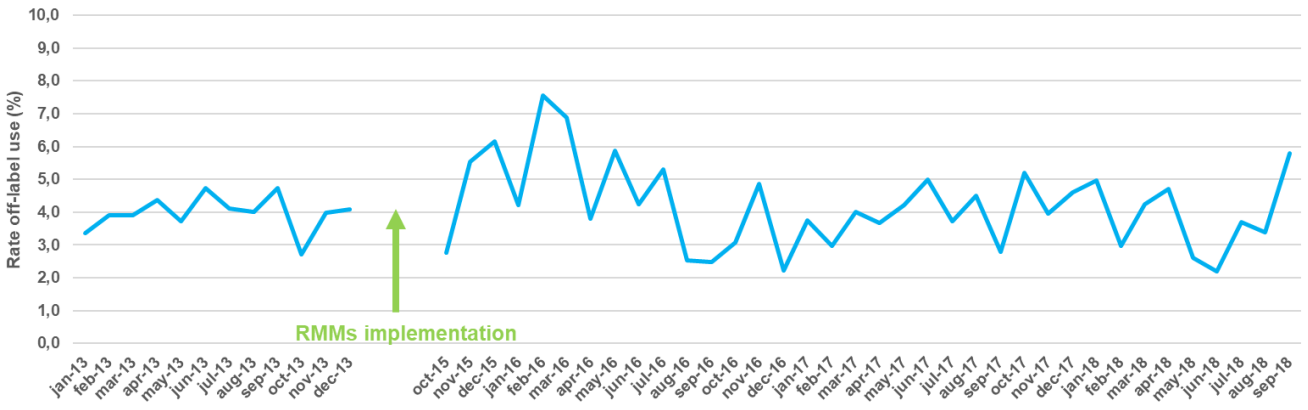
Analysis on the Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 19).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 3.9%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1652).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.6677) (Table 15**.3-122** of Statistical Report in Annex 3; §15.3).

Figure 19: Evolution of off-label rate - pregnancy – Italian GPs panel (Cumulative Study Periods)



By lactation status

The segmented regression analysis results for GPs in France and Italy are presented in Figure 20 and Figure 21, respectively. There were no cases of lactation reported in French rheumatologists' panel.

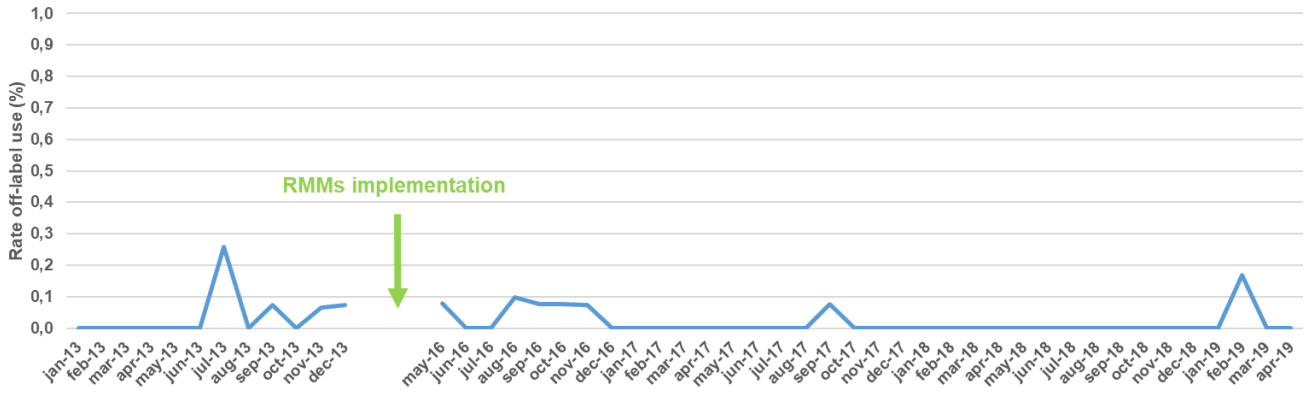
The analysis on the French GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period, or in the trend of off-label use through study period 3 (Figure 20).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was -0.007% (p-value=0.8172).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.2154).

There was no significant change in the trend of the rate of off-label use following the intervention period compared to the baseline period (p-value=0.0659) (Table 15.**3-123** of Statistical Report in Annex 3; §15.3).

Figure 20: Evolution of off-label rate- lactation - French GP panel (Cumulative Study Periods)



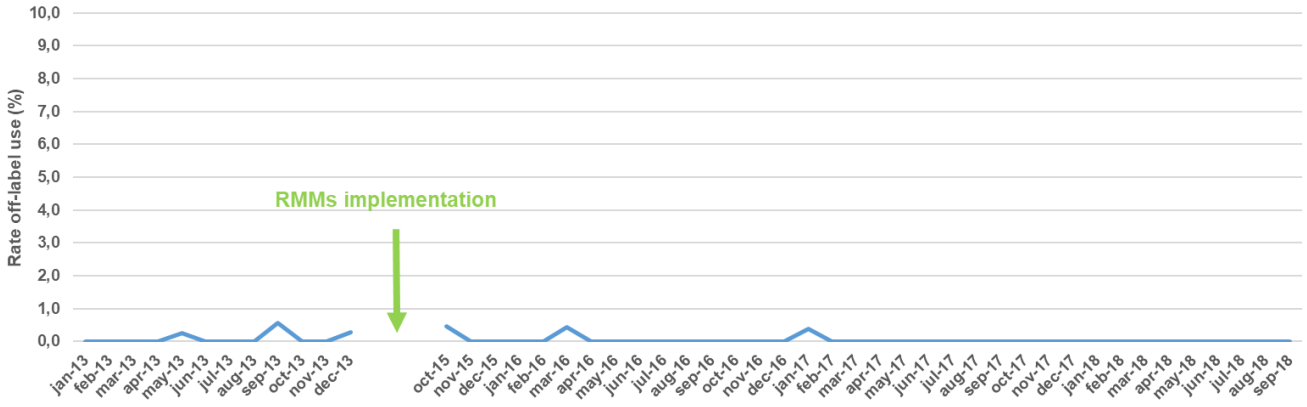
Analysis on the Italian GP panel showed that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and in the trend of off-label use through post-implementation period (Figure 21).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was -0.02% (p-value=0.7874).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1126).

There was no significant change in the trend of the rate of off-label use that follow intervention period compared to the baseline period (p-value=0.0647) (Table 15.**3-124** of Statistical Report in Annex 3; §15.3).

Figure 21: Evolution of off-label rate - lactation – Italian GPs panel (Cumulative Study Periods)



By contraceptive use status

The segmented regression analysis results for GPs in France and Italy are presented in Figure 22 and Figure 23, respectively. The analysis was not adequate for the rheumatologist panel in France since contraception prescription is not usually done by rheumatologists in France.

The analysis on the French GP panel showed that the intervention was associated with a significant increase of off-label rate immediately after intervention but there was no change in the slope after intervention compared to the slope before intervention (Figure 22).

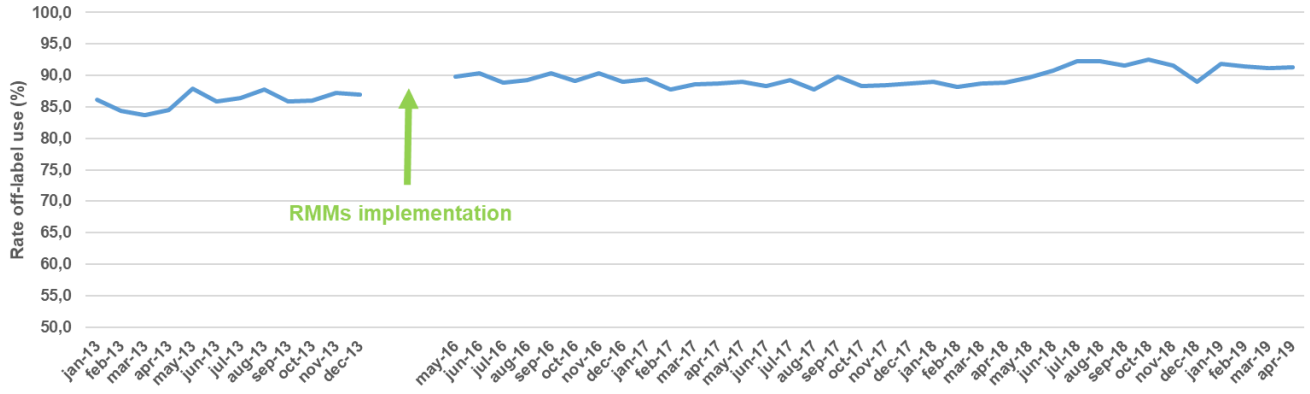
For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 84.8%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.21 percentage point with each month (p-value=0.0449).

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use increased immediately after the intervention period by 2.9 percentage points (p-value=0.0037).

There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.1884) (Table 15.**3-125** of Statistical Report in Annex 3; §15.3).

Figure 22: Evolution of off-label rate- no contraceptive use - French GP panel (Cumulative Study Periods)



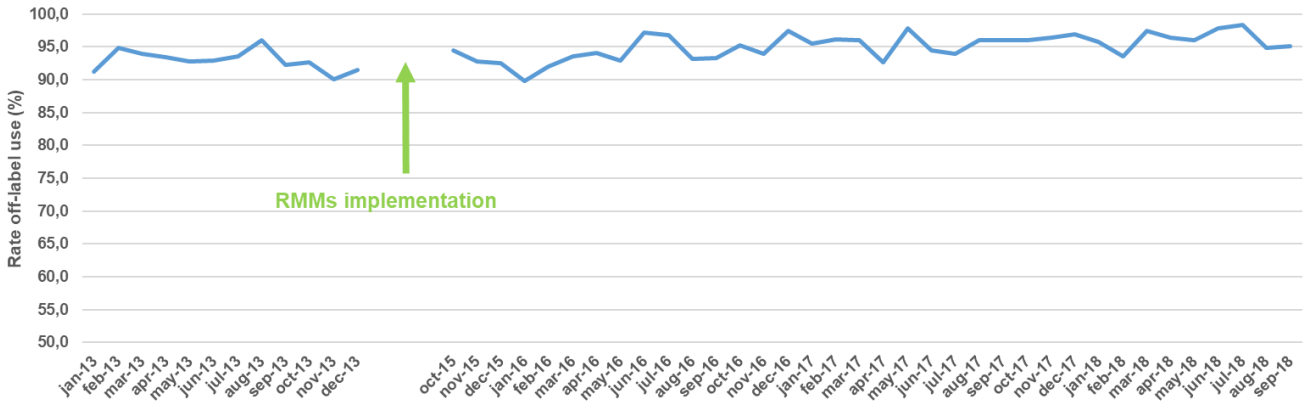
Analysis on the Italian GP panel showed that the intervention was not associated with a change of off-label rate after intervention but a sustained effect was observed with a significative change in slope towards an increase of off-label rate after implementation of RMM (Figure 23).

For the cumulative study periods, the intercept variable showed that the rate of off-label use at the beginning of the baseline period was 93.8%.

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1154).

The 'time after intervention variable' showed a change in the trend of the rate of off-label use following the intervention period compared to the baseline period: there was a significant increase of 0.3 percentage point with each month in comparison with the previous slope (p-value=0.0277) (Table 15**.3-126** of Statistical Report in Annex 3; §15.3). The dummy variable was not interpretable but allowed to have stationary data, i.e. with a constant mean, variance, and autocorrelation through time.

Figure 23: Evolution of off-label rate - no contraceptive use– Italian GPs panel (Cumulative Study Periods)



10.5 OTHER ANALYSES

10.5.1 Comparison of excluded and included populations

Populations that were excluded from analyzes because of a history in the database of less than 12 months (study period 3) and overall cumulative study period of years 1, 2 and 3, were compared to included populations in Table 15**.3-4** through Table 15**.3-6**, Table 15**.3-13** through Table 15**.3-15**, and Table 15**.3-16** through Table 15**.3-18** of Statistical Report in Annex 3; §15.3. Populations excluded were defined as the ones that did not have at least one visit at physician office before the year preceding their inclusion in any period, with the index date being the first prescription of systemic TCC in the considered period.

In the French GP panel:

In the overall cumulative study periods, excluded population amounted to 25 723 patients (23.9%). These patients were younger (mean age=42.0±15.45) than the included population (mean age=46.9±15.93). Population below the age of 16 years was in the same proportion in both populations. The frequency of TCC prescriptions concomitant to a pregnancy in women of childbearing potential were proportional in both populations but there less contraceptive use in the excluded group (no breastfeeding in both groups). About the treatment, the oral form was the most commonly used with the same frequency, the same dosage but with slightly less treatment time over 7 days (24.7% versus 31%) when compared to the included population. Overall, and all the study periods, total off-label was higher in the included population than in the excluded population.

In the French Rheumatologist panel:

In the overall cumulative study periods, excluded population amounted to 2 765 patients (32.2%). These patients were younger (mean age=52.4±16.01) than the included population (mean age= 62.3±14.53). Population below the age of 16 years was in the same proportion in both populations. The frequency of TCC prescriptions concomitant to breastfeeding in women of childbearing potential were proportional in both populations (no pregnancy and contraceptive use in both groups in this panel). About the treatment, the oral form was the most commonly used with the same frequency, the same dosage but with slightly less treatment time over 7 days (38% versus 44.2%) as in the included population. Overall, and all the study periods, total off-label was higher in the included population than in the excluded population.

In the Italian GP panel:

In the overall cumulative study periods, excluded population amounted to 1085 patients (1.9%), which was a very small sample compared to the patients included. These patients were younger (mean age=47.2±16.03) than the included population (mean age=56.6±15.73). Population below the age of 16 years was more frequent in excluded population (1.4% versus 0.1%). The frequency of concomitant pregnancy and non-contraceptive use in women of childbearing potential were proportional in both populations. Overall, and all the study periods, total off-label was similar in the included and excluded populations.

10.6 ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable

11. DISCUSSION

11.1 KEY RESULTS

This study was conducted to assess the effectiveness of the DHPC and EM implemented as RMM. This final report for the DUS TCC includes results for the countries France and Italy for the entire 12-month pre-implementation period, the third year of the post-implementation period and the entire 36-month post-implementation period.

This section provides information on patient and prescription numbers include per country and the key results to characterized prescribing practices off TCC-containing medicinal products for systemic use during typical clinical use (primary objective) and to evaluate efficacity of RMMs (secondary objective) in main study periods.

11.1.1 Number of patients and prescriptions

A total of 34 460 patients in the French GP database, 1 383 in the French rheumatologists' database and 19 877 in the Italian GP database were included in the analyses during the pre-implementation period.

A total of 81 690 patients in the French GP database, 3 016 in the French rheumatologists' database and 41 061 in the Italian GP database were included for the entire 36-month post-implementation period analysis. Overall, the number of patients included in the analysis remains fairly stable over each period of the study. For the first interim period, 37 771 patients in the French GP database, 1 247 in the French rheumatologists' database and 16 140 in the Italian GP database were included. During the second interim period, 34 330 patients in the French GP database, 1 185 in the French rheumatologists' database and 16 201 in the Italian GP database were included in the analyses.

For the third analysis period, 23 079 patients in the French GP database, 1 063 in the French rheumatologists' database and 14 957 in the Italian GP database were included.

For all the periods of the study, there was a majority of women. Patients tended to be older in the rheumatologist panel (mean age over 60 years old) and the Italian GP panel (mean age over 55 years old) than in the French GP panel (mean age under 50 years old).

11.1.2 Prescription for approved indication and safe use

In all periods, French physicians prescribed mainly oral form of systemic TCC (over 95% and over 80% of prescriptions emitted in the GP panel and rheumatologists' panel respectively). The contrary applied to Italian GPs who prescribed mainly IM form of systemic TCC (over 70% of prescriptions).

The diagnosis associated to prescription of systemic TCC agreed with the authorized indication in 53.3% (French GP panel), 71.3% (French rheumatologists' panel) and 75.6% (Italian GP panel) of prescriptions in the pre-implementation period. There had been very few changes between study period 3 and pre-implementation period for French panels, but in Italian GP panel there was a slight increase in on-label prescriptions (78.3%). In the overall post-implementation period, the diagnosis associated to prescription of systemic TCC agreed with the authorized indication in 53.9% (French GP panel), 70.9% (French rheumatologists' panel) and 75.8% (Italian GP panel) of prescriptions.

Systemic TCC was prescribed as adjuvant of a concomitant treatment in a large majority of prescriptions, ranging from 86.6% (Italian GP panel), to 88.8% (French rheumatologists' panel) and 93.5% (French GP panel) of prescriptions in the pre-implementation period. In the study period 3, there was a moderate increase in Italian GP panel (89.0%) while value remained stable in French rheumatologists' panel (89.5%) and

French GP panel (92.3%). In the overall post-implementation period, values ranged from 88.6% (Italian GP panel), to 88.0% (French rheumatologists' panel) and 92.7% (French GP panel).

Physicians were compliant, in all panels and in all periods, with restrictions concerning daily dosage for the oral form. In the pre-implementation period, daily dose restriction for oral form was respected in 98.7% (Italian GP panel), 99.7% (French GP panel) and 100% (French rheumatologists' panel) of prescriptions. Daily dose restrictions compliance for oral form remained stable in study period 3, with 98.1% in Italian GP panel, 99.8% in French GP panel and 100% for French rheumatologists' panel. In the overall the post-implementation period, daily dose restrictions for oral form were respected in 98.5% (Italian GP panel), 99.7% (French GP panel) and 100% (French rheumatologists' panel) of prescriptions.

Daily dosage restrictions for IM form was respected in 63.6% (French GP panel), 62.9% (French rheumatologists' panel) and 99.9% (Italian GP panel) of prescriptions in the pre-implementation period. During study period 3, there was an improved compliance in French GP panel (89.2%) while values remained stable in French rheumatologists' panel (58.4%) and Italian GP panel (99.9%). In the overall post-implementation period, daily dose restrictions for IM form were respected in 81.0% (French GP panel), 67.1% (French rheumatologists' panel) and 99.9% (Italian GP panel) of prescriptions.

Restrictions on treatment duration were less followed than restrictions on daily dosage. For oral form, and in the pre-implementation period, restrictions on treatment duration were respected in 40.3% (French rheumatologists' panel), 46.7% (French GP panel) and 52.3% (Italian GP panel) of prescriptions. During study period 3, compliance with treatment duration restrictions for oral form improved in the French rheumatologists' panel (53.4%) and the French GP panel (69.4%) but not in Italian GP panel (48.7%). In the overall post-implementation period, treatment duration restrictions for oral form were respected in 49.2% (French rheumatologists' panel), 66.2% (French GP panel) and 46.6% (Italian GP panel) of prescriptions.

Concerning the IM form, and in the pre-implementation period, restrictions on treatment duration were respected in 32.4% (French rheumatologists' panel), 30.4% (French GP panel) and 12.8% (Italian GP panel) of prescriptions. During study period 3, compliance with treatment duration restrictions for IM form improved in the French rheumatologists' panel (49.1%) and the French GP panel (50.7%) but not in Italian GP panel (11.3%). In the overall post-implementation period, treatment duration restrictions for IM form were respected in 43.2% (French rheumatologists' panel), 48.7% (French GP panel) and 11.6% (Italian GP panel) of prescriptions.

Physicians in all panels and in all period were majoritarily compliant to the restrictions concerning the use of systemic TCC for long term treatment of chronic conditions. Long-term treatment was defined as a duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription. In the pre-implementation period, restriction to short-term treatment was respected in 92.2% (French rheumatologists' panel), 94.7% (French GP panel) and 98.9% (Italian GP panel) of prescriptions. During study period 3, compliance with restriction to short-term treatment improved in all three panels: the French rheumatologists' panel (96.8%), the French GP panel (96.8%) and Italian GP panel (99.2%). In the overall post-implementation period, compliance with restriction to short-term treatment was respected in 96.3% (French rheumatologists' panel), 96.5% (French GP panel) and 99.2% (Italian GP panel) of prescriptions.

Overall prescriptions to patients under the age of 16 years were sparse in the pre-implementation as well as in the post-implementation period. In the pre-implementation period, minimal age of 16 years was respected in 100% (French rheumatologists' panel), 99% (French GP panel) and 99.8% (Italian GP panel) of prescriptions. During study period 3, compliance with minimal age improved in the Italian GP panel (99.9%), the French GP panel (99.6%). In the overall post-implementation period, compliance with minimal age was respected in 100% (French rheumatologists' panel), 99.5% (French GP panel) and 99.9% (Italian GP panel) of prescriptions.

Concerning pregnancy: no TCC prescriptions were encountered concomitantly to a pregnancy in the French rheumatologists' panel (all periods). TCC prescriptions were encountered concomitantly to a pregnancy in the French GP panel (pre-implementation: 0.6% of total prescriptions; study period 3: 0.7%; overall post-implementation period: 0.4%) and in the Italian GP panel (pre-implementation: 4.0%; study period 3: 4.0%; overall post-implementation period: 4.3%) (Table 15**.3-49**, Table 15**.3-52**, and Table 15**.3-55** of Statistical Report in Annex 3; §15.3).

Systemic TCC prescription concomitant to a breastfeeding period was not recorded in the French rheumatologists' panel and was encountered in less than 0.1% of prescriptions in the French GP panel and Italian GP panels (all study periods) (Table 15**.3-41** and Table 15**.3-42** of Statistical Report in Annex 3; §15.3).

Proportion of systemic prescriptions of TCC to women of childbearing potential for whom it was not possible to find a record indicating use of hormonal contraceptives or IUD was very high, as anticipated. In the pre-implementation period, for 86.1% (French GP panel), 92.8% (Italian GP panel) and 100% (French rheumatologists' panel) of prescriptions filled by female patients of child bearing potential (16-49 years old) it was not possible to find a record indicating use of hormonal contraceptives or IUD. In the study period 3 and overall post-implementation period, this proportion was respectively 91.3% and 89.5% (French GP panel), 96.2% and 95.1% (Italian GP panel) and 100% in both periods (French rheumatologists' panel) (Table 15**.3-49** through Table 15**.3-54** of Statistical Report in Annex 3; §15.3).

11.1.3 Analysis of RMMs impact on off-label rate in included patients

To evaluate the effects of RMM on the prescribing patterns of systemic TCC, two types of analyses were performed.

The first analysis involved a comparison of patient characteristics at TCC prescription and proportion of off-label, pre- (baseline: 2013) and post- implementation (study periods) of RMMs as a measurement of the efficacy of the RMMs was performed. To this end, the off-label proportion at pre-implementation (year 2013) was estimated based on the post-RMMs SmPC.

The results of the comparison between the pre-implementation and post-implementation periods for French GP panel revealed significant improvements in systemic TCC use between the pre-implementation and the study periods concerning: minimal age, maximal dose and duration of treatment (oral and IM form) and use of TCC as a short-term treatment. No impact of RMM was found with regard to compliance to restriction of indication and use of TCC as adjuvant medication. In addition, there was no improvement as to use in women of childbearing potential with a pregnancy, breastfeeding or not using contraception.

In the French rheumatologists' panel, we observed statistically significant improvement in use of systemic TCC between the pre-implementation period and the post-implementation period with regards to maximal dose and duration of treatment for IM form, duration of treatment for oral form, and use of TCC as a short-term treatment. Rheumatologist were already compliant to restrictions concerning oral form dosage and minimal age in the pre-implementation period and no improvement was expected. As for the pregnancy, lactation and contraceptive use, they were not recorded in this panel and were therefore not evaluable.

For Italian GP panel, analysis revealed improvements in systemic TCC use between the pre-implementation and the post-implementation period with respect to prescription to patients under the age of 16 years, prescription of TCC as adjuvant of a concomitant treatment, compliance to restriction to short-term treatment and compliance to treatment indication. Due to the high number of missing values for treatment duration in the panel (see Limitations; §11.2), it was difficult to reach a conclusion regarding this parameter for oral, and particularly IM form. The value of the off-label considering treatment duration in the Italian GP panel should therefore be taken with caution. As in French GP panel, prescriptions in women of childbearing potential with a pregnancy, breastfeeding or not using contraceptive was not impacted by RMM in the Italian GP panel.

The second analysis was a segmented regression analysis. In this analysis, incidence rates were computed by months before (pre-implementation: 2013) and after RMMs (according to each country).

Results from the segmented regression analysis displayed the dynamics of response of off-label to the intervention (RMM implementation). Hence, we observed a statistically significant reduction of off-label rate immediately after intervention for off-label on treatment indication (French GP panel), prescription to under 16 years old patients (French and Italian GP panels) and duration of treatment for oral form (French GP panel). We observed a persistent decrease in off-label trend after the intervention for off-label on treatment indication (French rheumatologist panel), long-term treatment (French GP and rheumatologist panels) and prescription to under 16 years old patients (French GP panel).

11.2 LIMITATIONS

11.2.1 Limitations related to the databases

- EMR databases (DA, LPD) used for the study have limitations consistent with a provider-sourced EMR database. Although the quality of data collection is monitored by database owners, the information provided by the physicians in health records can still be underreported.
- Recording of the indication of each prescribed treatment is mandatory in the physician software, but the physicians are free to enter any diagnosis and can for instance enter the reason of visit (e.g. flu) as indication for all treatments prescribed at the visit. Because precise indication for systemic TCC comprises both a symptom (painful muscle contractures) and a root cause ("associated with acute spinal pathology"), one part or another may be omitted by a busy physician as indication. In the GP panels, we had to reject a significant proportion of these incomplete diagnoses (e.g. "muscular contracture"). Therefore, the proportion of right indication in these panels may be underestimated.
- In the Italian GP panel: dose and durations of prescriptions were missing in half (oral form) to three quarter (IM form) of prescriptions. Therefore, findings related to dose and duration of prescription in this panel should be used with caution. In addition, in the Italian GP panel posology only (when available) was documented. Daily dose was therefore directly available, while duration was deduced from the posology and the number of boxes/packs prescribed. For the IM form packaging was, for over 98% of cases, of six vials per box. Therefore, a posology of one vial per day associated to a prescription of one box was resulting in a calculated duration of treatment of 6 days, hence off-label, per se.
- In the Italian GP panel, children and teenagers are preferably monitored by pediatricians rather than GPs. For this reason, there is an underepresentation of this age group in the Italian GP panel that may lead to an underestimation of the off-label use in this group.
- In the French GP panel, over 40% of dose and duration values for IM form were missing, therefore findings related to dose and duration of prescription related to IM form in French GP panel should be used with caution.
- Pregnancies were estimated by diagnoses codes in the patient's EMR but cannot always be reliably dated. The identification of pregnancies exposed to TCC was based on some assumptions because the start date and/or end date of pregnancy was often not available in the databases. Particularly, concomitancy was established by comparing duration of prescriptions and calculated duration of a pregnancy following documentation of a pregnancy diagnosis in a patient EMR. When no precision of stage (e.g. "first trimester") was available, an arbitrary rule was applied of "3 months before to 6 months after the date of the first diagnosis" to establish the period of pregnancy. This may lead to an overestimation of the concomitancy. This was particularly the case in the Italian GP panel, where the large majority of pregnancy-related diagnoses were bearing no indication on pregnancy stage. In conclusion, all findings related to pregnancies need to be assessed very carefully. The same is true for lactation.
- Contraceptive use through the prescription of contraceptive medications or devices was probably underestimated. The reasons are (i) a substantial number of women may see a gynaecologist for this purpose and the records of prescriptions were not necessarily visible in EMR records of GP and

rheumatologist panels (ii) devices may have been inserted in a time period not encompassed by this study or removed without being recorded in the EMR (iii) contraception may be ensured by other means than a prescribed devices or medications, for example by use of condoms or body temperature/ovulation date. Although the analyses focused on prescriptions for hormonal contraceptives and IUDs, we expect an underestimation of contraceptive use and country-specific patterns must be considered.

- In France, no link between the panel of GPs and rheumatologists is possible. Panels of specialists are independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, the probability is minimal, given the coverage of each panel (1% of practitioners for GP panel and 5.7% for rheumatologist panel).
- Limitations are also related to the use of prescription data. Only data on dispensed or written prescription were available, therefore, it was assumed that any written or dispensed prescription was consumed.

However, all described limitations are true for all study periods and, therefore, do not have an impact on the comparison of the pre-implementation and the post-implementation periods, other than the reduction in effect size.

11.2.2 Limitations related to the segmented regression analyzes

- The seasonality was not controlled per period due to the lack on monthly data points in the analysis (at least 24 monthly points should be required per period to detect seasonality and control for autocorrelation).
- The number of observations at each data point for France rheumatologists' panel was around 100 prescriptions per month for analysis of off-label rate. This is the limit of the number of observations required to get an acceptable level of variability of estimate for each data point [Wagner et al., 2002].
- Due to the exclusion of the intervention period, the pre-implementation and study period are not "continuous" i.e. the last month of the pre-implementation period was December (2013) while the first month of the study period was October (2015) for Italy and May (2016) for France. Ideally, the first month of the post-intervention period should be January, whatever the year involved. In case of seasonality or autocorrelations, the non-calendar continuity of the period could lead to incorrect inference and interpretations of results.

11.3 INTERPRETATION

A difference in the prescribing attitudes was noted between Italian and French physicians, since oral formulations were prescribed in a larger extent than IM formulations in France, while in Italy the opposite applied.

Overall, a positive trend in terms of decreasing percentages of non-compliance with doses and duration of treatment was observed over the study period. A significant improvement in the compliance to treatment duration for oral form in the French GP panel was observed after RMM implementation. Compliance to treatment duration in the Italian GP panel was difficult to assess due to the fact that treatment durations had to be calculated in Italian GP panel leading to an overestimation of off-label (see Limitations; §11.2).

Compliance to restrictions concerning the use of systemic TCC for long term treatment of chronic conditions was already above 90% of prescriptions in the pre-implementation period and significantly decreased after implementation of the RMM in the French GP and rheumatologist panels.

The treatment indication for TCC systemic prescription was available in almost all the prescriptions. More than half (French GP panel) and over 70% (Italian GP panel and French rheumatologist panel) of systemic TCC prescriptions were found to be made in compliance with the authorized indication. Although a

significant reduction occurred immediately after intervention for use in an off-label indication (French GP panel), these proportions remained essentially the same over the pre- and post-implementation period. It is to be noted that they are probably underestimated: some of the recorded indications classified as off-label were classified as such because the indication recorded was insufficiently detailed (see Limitations; §11.2) not because the indication was an obvious case of off-label use.

The proportions of the concomitant medications relevant to TCC indication showed that systemic TCC was prescribed most frequently as an as adjuvant treatment, which remained unchanged in post-implementation period in the 3 panels.

Overall, prescriptions to patients under the age of 16 years were sparse in the pre-implementation and were found to have significantly decreased in the post-implementation period in French and Italian GP panels.

Compliance to restriction of use in women of childbearing potential who are not taking appropriate contraception was low. During both pre- and post-implementation period, concomitant contraception could be detected in about a quarter of TCC prescriptions in the French GP panel and in a fifth of prescriptions in the Italian GP panel. Almost no concomitant contraception could be noted in the French rheumatologists' panel. No clear changes were observed between the two periods in any of the countries or in any panel. As underlined in paragraph 11.2 (Limitations), a large underestimation of contraception in the female population on the three panels was expected and it is, therefore, difficult to draw any conclusion from this analysis. However, this finding is in agreement with results of the healthcare professionals survey (EUPAS11765) showing that only half of physicians were aware that systemic TCC should not be prescribed to WCBP not using an effective method of contraception.

No significant change was found in the number of exposed pregnancies following the intervention. There were fewer TCC prescriptions in the French panel than in the Italian panel concomitant to a pregnancy. Findings with respect to pregnancies need to be considered with caution. As already addressed in paragraph 11.2 (Limitations), the databases records are not comprehensive, especially in the French rheumatologist panel, and the identification whether a pregnant woman is exposed to TCC or not has required certain assumptions to overcome the incompleteness of data. The same applied to prescriptions during lactation period, for which results were also very limited, given database limitations, and no tendency could be highlighted.

11.4 GENERALISABILITY

The selected EMR data sources (DA and LPD) for this study are designed to be representative for the countries (France, Italy). For France, the main prescribing specialties (rheumatologists and GPs) were considered. In Italy, the database includes only GPs. The national coverage of the EMR data sources with respect to physician universe is 1% (French GP panel), 2% (Italian GP panel) and 5.7% (French rheumatologist panel).

In all target countries, all TCC prescriptions issued to patients available in the databases and the study periods were included in the study, no exclusion criteria were applied.

Furthermore, no further restrictions regarding demographic characteristics, insurance status, comorbidities, region, or other, which could affect the external validity of results, were applied.

Taking the known limitations of the databases into consideration, the findings presented in this report, for the pre-implementation period and the first and second post-implementation periods, are generalizable for the target countries France and Italy.

12. OTHER INFORMATION

None

13. CONCLUSION

The results of the drug utilization study, as a complement to results of the healthcare professionals survey (EUPAS11765) showed that RMMs implemented post Referral for products containing thiocolchicoside for systemic use produced positive effects on physicians' knowlegde and prescribing habits for some safety messages only.

In view of the results of this DUS as well as the results of the Healthcare Professionals Survey dated 2017, the Marketing Authorization Holders Consortium proposed to proactively have a new distribution of adjusted risk minimization measures (Direct Healthcare Professionals Communication, HCP Guide) as well as unchanged Patient Card as an unique package, in order to increase the impact of this communication. This was endorsed in October 2018 by AIFA in a national assessement shared with PRAC. The redistributions occurred in December 2018 in Malta and Spain, in January 2019 in Czech Republic, in March 2019 in Italy and Portugal, in April 2019 in France and will occur bu the end of the year 2019 in Greece.

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15. ANNEX

15.1 Annex 1: List of standalone documents

Number	Document reference Number	Date	Title
1- Protocol	Version 5.0	2nd March 2017	Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study
2- Statistical analysis plan	Version 1.0	1st September 2017	Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study Statistical analysis Plan

POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

TITLE: : Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

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COMPOUND: Thiocolchicoside

STUDY NAME: Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

The Study is conducted by QuintilesIMS Health 90-92 route de la Reine, 92773 Boulogne Billancourt, France

Version Number:	5.0		
Date:	2nd March 2017	Total number of pages:	104 (including annexes)

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- PASS Information

Title	Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study
Protocol version identifier	
Date of last version of protocol	2nd March 2017
EU PAS register number	EUPAS11081
Active substance	M03BX05
Medicinal Product	See Annex 3
Product reference	See Annex 3
Procedure number	EMEA/H/N/PSP/j/0030

Marketing authorization holder(s) or Sponsor company	**1. SANOFI AVENTIS GROUPE,** a French company having its registered office at 54 rue La Boétie, 75008 Paris, France; **2. TEOFARMA Srl**, Via F.lli Cervi N° 8, I-27010 valle Salimbene, 27010 Pavia, Italy; **3. MYLAN** SAS with legal address at 117 Allée des Parcs, 69800 St Priest, France; **4. ANGELINI** with legal address at Angelini Farmacêutica Lda, Rua João Chagas, 53 - 3° piso, 1499-040 Cruz Quebrada – Dafundo, Portugal; **5. DOMPE' FARMACEUTICI S.P.A**., with legal address in Via San Martino 12-12/a, 20122 Milan- Italy and Operative office: Via Santa Lucia 6, 20122 Milan, Italy; **6. GENERIS FARMACEUTICA** with legal address in Rua João de Deus, 19, 2700-487 Amadora, Portugal; **7. KORANGI,** with legal address at Produtos Farmacêuticos Lda. Rua da Vinha, 17P 2765-388 Estoril, Portugal; **8. DAIICHI Sankyo France SAS** with legal address at 1, rue Eugène et Armand Peugeot, 92500 Rueil-Malmaison, France;

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Joint PASS	Yes

Research question and objectives	The aim of this drug utilization study is to characterise prescribing practices of TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription. The study objectives are: • To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications, pregnancy, contraceptive use, lactation) • To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender) • To describe the average duration of treatment episodes
Country(-ies) of study	France and Italy
Author	Sophie L. Jouaville – QuintilesIMS 90/92, route de la Reine 92100 Boulogne-Billancourt, France +33(0)147798367
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2 LIST OF ABBREVIATIONS

DREES	Direction de la recherche, des études, de l'évaluation et des
ENCePP	European Network of Centres for Pharmacoepidemiology and

3 RESPONSIBLE PARTIES

The Scientific Committee:

a) The SC shall be composed of one representative of each MAH and one representative of QuintilesIMS. If the nominated representative is not able to attend an SC meeting on a given date, the MAH shall nominate another representative able to participate in the discussions.

b) QuintilesIMS shall participate in meetings of the SC and shall be responsible for organizing and coordinating such meetings and shall not hold any voting rights.

c) During the meetings of the SC, the MAHs undertake their best efforts to agree to any necessary actions or take any necessary decisions regarding the Services.

d) The decisions taken during the SC shall include, without limitation:

i) Preparation and final validation of the Protocol

ii) Submission of documents, communications, such as interim reports and the Final Report by QuintilesIMS to the MAHs, and

iii) Any subject matters in relation to the management of the Study.

4 ABSTRACT Title

Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records databases study.

Version 5.0 dated on 2nd March 2017 by Sophie L. Jouaville

Rationale and background

An Article 31 referral on thiocolchicoside-containing medicinal products for systemic use was initiated in February 2013. The CHMP has concerns with regard to the potential genotoxicity of thiocolchicoside-containing medicinal products for systemic use. Within the context of minimization measures as per European Commission decision dated 17 January 2014, including a Dear Healthcare Professional Communication, changes to the SmPC, Labelling and Package Leaflet, a Joint Drug Utilization Study will be conducted.

Research question and objectives

The aim of this Drug Utilization Study is to characterise prescribing practices of systemic TCC-containing medicinal products during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications; pregnancy, contraceptive use, lactation)
- To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender)
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration
- To compare patients characteristics pre- and post-implementation of RMMs

Study design:

Cross sectional study based on existing databases in France and Italy.

Study period: The study will cover 3 years starting from effective date of implementation (completion of

educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France) of minimization measures.

In addition, a baseline period spanning over year 2013, will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of minimization measures.

Population:

Study population:

The study population will include patients with at least one prescription of TCC-containing medicinal products for systemic use during the study period, i.e. before (baseline: year 2013) or after the implementation of the minimization measures. The effective date of implementation of minimization measures will be considered per country (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

Prescriber population:

A national representative sample of Generalist Practitioners (GPs) will be considered for each country. In addition and for France only, a panel of specialists (Rheumatologists) will be considered as well.

Variables

Age, gender, treatment indication, dose, duration, route of administration, concomitant treatments, use of appropriate contraceptive measures, pregnancy and lactation, during the study period.

Data Sources

Longitudinal electronic medical records (EMR) databases will be used in France and Italy (IMS LPD® and DA). The data are collected routinely from GPs and rheumatologists (for France only) in the outpatient setting.

Study size

Over 50,000 patients in France (GPs + Rheumatologists), 17,000 in Italy (GPs) are expected.

Data analysis

The analysis will be done annually for the 3 years of study and once for the baseline period. The statistical analysis will be mainly descriptive. Patient's demographic and clinical characteristics available from the selected databases will be used to describe the study population.

Distribution of drug patterns will be done considering the overall sample and by country:

- Distribution of the treatment indication by age groups and gender
- Duration of prescription at index date
- Distribution of daily dose and treatment duration at index date
- Distribution of TCC use in the subgroup of women of childbearing age only:
    - Pregnancy

        - Using appropriate contraceptive measures
        - Lactation
    - Distribution of co-medications used along with TCC scripts
    - Description of prevalent and incident patients

In order to better characterize the impact of risk minimization measures (RMMs) on prescribing practices for thiocolchicoside, patient characteristics will be compared between the two study periods.

Milestones*

*Estimated timelines pending approval of the DUS protocol and Educational Material by the respective competent regulatory authorities.

Draft Study protocol: 3 months after contract signature between all MAHs

Study period: 3 years study (covering data collected from Q3 2015 to Q3 2018 for Italy, and from Q2 2016 to Q2 2019 for France)

Two annual interim reports (Q4 2017, Q4 2018) Final report in Q4 2019

5 AMENDMENTS AND UPDATES

5.1 AMENDMENT # 1

This amendment, Version 4.0, dated 13th October 2016, is to reflect changes that have occurred since the last version of the protocol (V3.0 dated 26th April 2016) and in particular the removal of the French RH data base, the changes in MAH information and the changes in QuintilesIMS personal.

a) Removal of RH database

The French HEAD database will not be available anymore for use in this study, due to routine ongoing evaluations that were required following quality control tests.

Therefore the following sections have been amended:

- PASS information / Research question and objectives
- List of abbreviations
- Abstract/ Research question and objectives, Variables, Data sources, data analysis
- 8.1 Primary objective
- 9.3 Variables (9.3.2, 9.3.3)
- 9.4 Data Sources
- 9.6 Data Management
- 9.8 Primary Analysis
- 9.10 Limitations of the research methods
- 13 References

b) Change in MAHs information

Therefore the following section has been amended:

- PASS Information / Marketing authorization holder(s)

c) Change in IMS personal

Therefore the following section has been amended:

- Name and Address of study management

5.2 AMENDMENT # 2

This amendment, Version 5.0, dated 2nd March 2017, is to reflect changes that have occurred since the last version of the protocol (4.0 dated 13th October 2016) as a consequence of the demand of the PRAC to collect data about concomitance of a TCC prescription with pregnancy and lactation as well as the change of company conducting the study's name.

a) Replacement of IMS Health LPD® France GP database by IMS ®Disease Analyzer (DA) France GP

In order to be able to collect data about concomitance of a TCC prescription with pregnancy or with lactation, IMS Health LPD® France GP database will be replaced by IMS ®DA France GP.

Therefore the following section has been amended:

- Pass information
- List of abbreviations
- Abstract/ Research question and objectives, Variables, Data sources, data analysis
- 8.1 Primary objective
- 9.3 Variables (9.3.2, 9.3.3)
- 9.4 Data Sources
- 9.6 Data Management
- 9.8 Primary Analysis
- 9.10 Limitations of the research methods

b) Change of company name

The merge between IMS Health and Quintiles which occurred on May 2016 results with a change in company name from IMS Health to QuintilesIMS. Therefore the change from IMS Health to QuintilesIMS has been implemented thorough the entire protocol.

6 MILESTONES

Milestone	Planned date
Start of data collection	Oct 2015 for Italy and April 2016 for France
End of data collection	Oct 2018 for Italy and April 2019 for France
Registration in the EU PASS register	Q3 2015
Two annual interim reports	Q4 2017, Q4 2018
Final report of study results	Q4 2019

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain. TCC for systemic use is indicated as adjuvant treatment of painful muscle contractures associated with acute spinal pathology. Widely used by prescribers in the concerned Member States (Czech Republic, France, Greece, Italy, Malta, Portugal and Spain.), the benefits of TCC containing medicinal products are recognized in clinical practice.

The review of thiocolchicoside was triggered by the Italian medicines regulatory agency, AIFA, following new experimental evidence which suggested that thiocolchicoside was broken down into 3-demethylthiocolchicine (M2 or SL59.0955) that could damage dividing cells, resulting in aneuploidy (an abnormal number or loss of heterozygosity).

As a result AIFA asked the European Medicines Agency's Committee on Human Medicinal Products (CHMP) to examine the safety profile of this medicine and consider what regulatory action might be appropriate.

The CHMP reviewed the evidence [European Medicines Agency. Assessment Report][1], including the opinions of experts in the field of medicines safety, and concluded that aneuploidy could occur with M2 at levels not much greater than those seen after recommended doses of thiocolchicoside taken by mouth. Aneuploidy is a risk factor for harm to the developing fetus, reduced fertility in men and in theory could increase the risk of developing cancer. On November 21th 2013 the CHMP recommended that the authorized uses for thiocolchicoside-containing medicines for use by mouth or injection should be restricted across the European Union (EU) [European Medicines Agency. Article 31 referral[2]]. The CHMP therefore recommended measures to ensure thiocolchicoside-containing medicines are used as safely as possible. These include restricting the maximum dose and number of days of treatment when given by mouth or injection. Use is also contra-indicated in pregnancy and lactation or in women of childbearing potential not using adequate contraception, as well as in children below 16 years old or for chronic (long-term) conditions. Topical cutaneous preparations for local application to the skin, which do not produce substantial levels of M2 in the body, are not affected by this review. The European Commission implementing decision was issued on January 17, 2014.

Since this date, the modified indication statement for systemic TCC use is as follow:

- Systemic thiocolchicoside is indicated only as adjuvant treatment of painful muscle contractures associated with acute spinal pathology in adults and adolescents from 16 years of age.
- Systemic thiocolchicoside should not be used for long-term treatment of chronic conditions
- The maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than 7 consecutive days. When given intramuscularly, the maximum dose should be 4 mg every 12 hours, for up to 5 days.
- Medicines containing thiocolchicoside should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraception.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Thiocolchicoside-containing_medicines/WC500162337.pdf

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Thiocolchicoside-containing_medicines/human_referral_000356.jsp&mid=WC0b01ac05805c516f

Local modified SmPC and Direct Healthcare Professional Communication (DHPC) are appended in Annex 4.

European Commission decision included the distribution of educational material for prescribers and for patients, highlighting the risks and warnings of genotoxicity reactions.

7.2 RATIONALE

This drug utilization study (DUS) is being conducted, per regulatory request, following the Article 31 referral on thiocolchicoside-containing medicinal products for systemic use. It is to be included in the Risk Management Plan, as part of the assessement of effectiveness of risk minimization measures, including a Dear Healthcare Professional Communication, educational materials distribution to health care professionals and patients, as well as changes to the SmPC, Labelling and Package Leaflet.

This drug utilization study aims to characterize the prescribing practices during typical clinical use of systemic thiocolchicoside in Italy and France.

Epidemiological studies on the use of drugs are essential to evaluate the intended and adverse effects of prescription medications as they are used in clinical practice. Drug use and patient characterisation studies allow for characterisation of users of the medication in terms of age and sex, treatment indication, use of concurrent medications, prior morbidity and other characteristics.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The aim of this drug utilization study is to characterise prescribing practices of TCC-containing medicinal products for systemic use during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age and gender, co-medications, pregnancy, use of appropriate contraceptive measures, lactation),
- To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender),
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration.

8.2 SECONDARY OBJECTIVES

- Comparison of patient characteristics, pre- and post- implementation of RMMs as a measurement of the efficacy of the risk minimization measures

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is

- An international: France and Italy.
- A multicenter:

Data will be collected from Electronic Medical Record (EMR) databases: IMS Longitudinal Patient databases (LPD) Italy and France-Rheumatologists, and Disease Analyzer (DA) France. These databases collect the electronic Medical Record information obtained from the general practice management software utilized during physician office visits. Approximately 1,000 GPs (DA France) and 100 rheumatologists (LPD France-Rheumatologists) in France and 900 GPs (LPD-Italy) in Italy contribute to the databases. Physician panels in each database are designed to be representative of the physician population in each country by age, gender and localization.

- A non-interventional:

Data from EMR is submitted daily to a coordinating center, cleaned, de-identified, and made available for research. Since data is collected in a non-interventional manner, IMS database mirror real life clinical practice.

- A retrospective: Data will be retrospectively collected
- A cross-sectional study: all patients having systemic TCC prescription during study periods (before or after the implementation of the risk minimization measures) will be included

9.2 SETTING

The study will take place in 2 European countries: France and Italy.

9.2.1 Baseline Period

A one-year baseline period spanning over year 2013, will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of risk minimization measures.

9.2.2 Study Follow-up Period

No follow-up period is planned for this study.

9.2.3 Duration of the study

The study will describe the utilization pattern of systemic thiocolchicoside during the first three years after the effective date of implementation of all the risk minimization measures following the CHMP decision in France and Italy. The effective date of implementation of minimization measures will be considered per country (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

This analysis will be repeated at 12 (interim analysis 1), 24 (interim analysis 2) and 36 (Final report) months from the implementation of all the minimization measures.

In addition, a **baseline period** spanning over year 2013 (January 1st to December 31st), will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of minimization measures.

9.2.4 Eligibility criteria

9.2.4.1 Inclusion criteria

The study population will include all patients with at least one prescription of TCC-containing medicinal products for systemic use in the selected databases during the study periods, i.e. before or after the implementation of the risk minimization measures.

The "prescription index date" for each patient included in the study will be defined as first date in each study period a patient is prescribed systemic thiocolchicoside.

9.2.4.2 Exclusion criteria

No age restrictions or exclusion criteria will be applied. This will allow for the characterization of all users of TCC-containing medicinal products for systemic use according to each indication for which the medication is being used. This will include any pediatric population and patients with contraindications (e.g., pregnant woman).

9.2.4.3 Analysis population(s)

Analysis will be done on all eligible patients with at least one year of enrollment in the database before index date. However, in order to assess the effect of including patients prescribed systemic TCC but not analyzed because of enrollment less than one year before index date, these patients will be counted, and their main characteristics (age, gender, dose, duration, treatment indication, co-medications) at index date, will be described together with the characteristics of patients included in the study.

9.2.5 Modalities of recruitment

9.2.5.1 Physician selection

In the selected EMR-databases, a panel of contributing physicians is maintained as a representative sample of the national physician population.

The EMR-databases contain physicians' daily practice automated records. These physicians are software users of the data provider in each country. They are contacted according to the needs of representativity of the panel based on national statistics and according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. In addition for specialist panels, the type (semi-liberal, liberal) of practice is also considered. As compensation for their participation to the panel, preferential rates on their software subscription or subscription to other services that are part of their medical practice are offered.

A larger panel is therefore maintained from which a stable subset of physicians (1,000 GPs in France, 900 GPs in Italy,100 rheumatologists in France) is selected and maintained on the basis of representativity needs and the reliability of their data. This subset is used in epidemiological studies such as this one (more details § 9.4).

9.2.5.2 Patient selection

Not applicable.

9.3 VARIABLES

9.3.1 Exposures

The exposure of interest is obtained through systemic TCC prescription.

9.3.1.1 Treatment duration

Use of systemic TCC will be assessed through the recorded prescriptions (prescriptions "issued" or "written") in databases. Since EMR-databases report issued prescriptions rather than dispensed medication, there is no information indicating if, or, when a prescription was filled. We will assume that all the prescriptions and their associated dates recorded in both databases reflect actual prescription fills, and subjects will begin exposure at the index date (= prescription issued) and be exposed continuously for the number of days indicated by the days of supply for that prescription.

Note: If the days-of-supply field for a given prescription is missing or zero, or the value recorded has been determined to be implausible based on the quantity dispensed for that prescription, the days of supply will be calculated by dividing the total quantity dispensed by the daily prescribed dose.

9.3.1.2 Dose

The distribution of the daily prescribed dose (for oral form and IM form) at the index date will be described for all users of systemic TCC. The dose described will be the one associated to the index prescription. The daily dose of medications is recorded in the EMR-databases. Dose will be ascertained from the numeric daily dose derived from the dosing instructions. The proportion of missing values will be described.

However, the degree of completeness is variable across databases. Missing values for doses are expected. The missing information will be specified.

9.3.1.3 Treatment indications

Following the Article 31 referral on thiocolchicoside-containing medicinal products for systemic use, systemic thiocolchicoside use is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology.

All diagnoses associated to a systemic TCC prescription will be recorded and classified according to ICD-10-CM. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication. Of note, Table 1 displays the lists of diseases, conditions, and procedures mapped to the ICD-10-CM codes for identification of the current approved indication.

Table 1. List of diagnoses and corresponding ICD-10-CM codes for identification of the current approved indications

ICD-10-CM description	***ICD-10-CM code***	***Use of codes in indication definitions***
Other deforming dorsopathies including: • Spondylolysis • Spondylolisthesis • Recurrent atlantoaxial dislocation with myelopathy • Other recurrent atlantoaxial dislocation • Other recurrent vertebral dislocation • Torticollis • Other specified deforming	M 43 M43.0 M43.1 M43.3 M43.4 M43.5 M43.6	Primary code for the broad definition of the clinical indication
Dorsalgia • Radiculopathy • Cervicalgia • Sciatica • Lumbago with sciatica • Low back pain • Pain in thoracic spine	M 54 M 54.1 M 54.2 M 54.2 M 54.3 M.54.4 M54 .5 M54 .6	Primary code for the broad definition of the clinical indication

9.3.2 Pregnancy, contraceptive use and lactation: for women of child bearing potential

Use of appropriate contraceptive measures during the study period:

In the GP EMR databases contraceptive use is not well recorded (see Study limitations, § 9.10). Therefore it is expected that the recording of prescriptions of contraceptive measures up to a year before and concomitantly to TCC prescription is going to underestimate the population that is using appropriate contraceptive measures.

Pregnancy:

All of the diagnoses related to pregnancies will be searched in databases according to data availability.

Some of these diagnoses precise the pregnancy trimester or are related to exams specific of a trimester. If the information on trimester or start date or delivery/end of pregnancy date is available, the pregnancy will be considered exposed if at least one TCC prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date is not available in the EMR-database, a pregnancy will be considered as exposed to TCC if at least one TCC prescription was issued within 90 days before or within 180 days after the first record of a given pregnancy.

Lactation:

Diagnoses related to breastfeeding will be searched in databases according to data availability.

Lactation will be considered as concomitant to TCC use if at least one TCC prescription is issued in a window of 90 days before and after any breast-feeding record.

9.3.3 Operational variables and definition of off-label

In summary, all variables to be collected for the purpose of the study and definition of off-label are the following:

Table 2. Summary of variables

Patient Demographics, at initiation of systemic TCC use:	Patient Demographics, at initiation of systemic TCC use:	
• Age categories	• <16, ≥16 years	• Age at prescription <16 years
• Gender	• Male, female	
• Pregnancy	• Pregnancy diagnosis	• At least one TCC prescription issued in the period between assumed dates of pregnancy start and delivery/end of pregnancy, or, – when no information on pregnancy start or end is available-, within 90 days before or within 180 days after the first record of a given pregnancy
		• No record of contraceptive use

Concomitant medications and /or health services, medical devices, before, at initiation of and during systemic TCC use:	Medications: • All analgesics (ATC code :N02) and specifically among them: o Salicylic combinations (NO2A) o Paracetamol (N02B) o Opioids (N02A) • Tricyclic antidepressants (N06A,mitriptyline type) • Benzodiazepine (ATC code: N03A, clonazepam type) • Muscle relaxants (ATC code : M03) • NSAIDs/Cox-2 inhibitors (ATC code : M01A) • Corticosterioids (ATC code : MO1B) • Topical products for joint and muscular pain (ATC code: M02A)	• No concomitant medications and /or health services, medical devices, before, at initiation of, and during systemic TCC use

Systemic TCC daily doses prescribed	• Oral form: ≤ 16 mg per day, >16 mg per day • IM form: ≤ 8 mg per day, >8 mg per	• Oral form: >16 mg per day • IM form: >8 mg per day
Duration of systemic TCC treatment episode	• Oral form: ≤ 7 consecutive days, >7 consecutive days • IM form: ≤ 5 consecutive days, >5 consecutive days	• Oral form: >7 consecutive days • IM form: >5 consecutive days • Long term treatment: duration between the previous and the current
Treatment indication for systemic TCC prescription	• clinical diagnosis recorded at the time of prescription	• Other than painful muscle contractures associated with

* Off-label definition is defined as any occurrence of the situations listed in the table 2 (in the last column) in a prescription

9.4 DATA SOURCES

- Longitudinal Patient Database (LPD): Rheumatologists France and GPs Italy

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in electronic medical records. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the country.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Istituto di ricerca della SIMG, 2014] (see also Annex 2).

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

In France, data from panels of primary care physicians and data from specialist panels are available. Panels of specialists are independent of GP panel; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, it is not possible to link individual patients across the two types of practitioners.

For this study, it is planned to record information gathered by a panel of French rheumatologists for a better coverage of patients prescribed TCC. Both LPD panels have been validated through previous published works. Indeed, French panel of Rheumatologists (LPD France-rheumatologists) has been used by French National Authority for Health [Has, 2009; HAS, 2010] and Italian LPD (LPD-Italy) have been used in peer reviewed publications [Lapi et al, 2012; Coloma et al, 2013].

- Disease Analyzer (DA) France: GPs France

Disease Analyzer provides a nationally representative sample of about 1,000 primary care physicians (GPs) and includes over 5 million anonymous patient records and 152 million prescriptions in France.

Physicians are contacted among GPs who are using one of the five practice management software selected by IMS and according to the needs of representativity of the panel based on national statistics. Physicians included in the panel are those who volunteer to make available anonymized, patient-level information from their practices for clinical research purposes.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Becher et al., 2009] (see also Annex 2).

DA was recently used in a PASS study involving the attainment of exposure of pregnant women to sodium valproate and related substances [ENCEPP/SDPP/9678]

Characteristics of the three databases are summarized in Table 3 and Table 4.

Table 3. Summary of variables available in LPD and DA

Demographic and Medical Profile		***Treatment and other medical data***	
Gender	Yes	Drug	Yes
Year of Birth	Yes	Diagnosis	Yes
Socia-Economics Status	No	Molecule	Yes
Ethnicity	No	Rx in INN	Yes
Death Recording	Partial	Brand Name	Yes
Registration Date	Yes	Dosage	Yes
"Transferred out" date	No	Duration of script	Yes
Diet	Partial	Repeat	Yes
Exercise	Partial	Cost	Partial
Life style (smoking etc .)	Partial		
Height	Yes	Allergies	Yes
Weight	Yes	Immunization	Yes
Blood pressure	Yes	Lab Tests	Yes
Date of events	Yes	Lab Tests Results	Partial
Home visit	Partial	Referrals	Partial
Medical History	Yes	Hospitalization	Partial
Signs and Symptoms	Yes	Reasons for Hospitalization	Partial

Table 4. Characteristics of data sources.

Characteristics	*DA France*	*LPD France-Rheumatologist*	*LPD Italy*
Database type medical record database	Primary health care electronic	Electronic medical record database	Primary health care electronic medical record database
Possibility of linkage	None	None	None
Possibility to request additional information	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	None
Physicians population	GPs: 1,000 (of 54,000 in France)	Rheumatologists: 100 (of 1,749 in France)	GPs: 900 (of 46,000 in Italy)
Data availability Since 2004	Metropolitan France	Metropolitan France. Since 2002 for Rheumatologist panel	All Italy Since 2004
Database population	1,160,000 active patients*	115,000 active patients*	1,000,000 active patients*

Approximate proportion of the country physician population covered by the database	1.85%	5.7 %	1.96%
Active principle system	international coding	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*
Disease classification	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-9)*

*active patients: patients having visited their physician at least once a year

9.5 STUDY SIZE

The aim of this study is to provide a description of real life treatment patterns. The study size will be driven primarily by the uptake of systemic TCC in the populations from which the automated databases obtain data for France and Italy.

The sample size is calculated in order to ensure that the study obtains meaningful data for descriptive purposes. The primary objectives are mainly descriptive. The primary objective of this study is to assess the distribution of drug patterns in the overall sample and across countries.

Approximately 50,000 patients in France (GPs + Rheumatologists) and 17,000 in Italy (GPs) are expected.

9.5.1 Determination of sample size

The sample size calculation is determined by the desired accuracy/precision of the estimation by confidence interval of the observed proportions. The Table 5 shows that to achieve a sufficient accuracy, i.e. within a marge of accuracy < +/- 5%, of the estimation by a two-sided 95% confidence interval (CI) for proportions (p) between 10 % and 50 % (or from 90 % to 50 % for complementary percentage), a minimum sample size of around 400 patients is required. The precision for an observed percentage with 95%CI will be determined by the formula below:

Calculation use the following formula (normal approximation):

$$ee = \sqrt{\frac{pp(1-pp)}{}} \times \varepsilon\varepsilon_{\alpha\alpha}$$

nn

With n sample size, p observed percentage, ε_α 1.96 for 95% CI, *ee* Precision.

Table 5. Required number of patients (1) by acceptable precision (95% confidence interval) for proportions (normal approximation)

Observed percentage (accuracy): p(1-p)

		(80%)	(70%)	(60%)	(50%)
± 2.0%	864	1537	2017	2305	2401
± 2.5%	553	983	1291	1475	1537
± 3.0%	384	683	896	1024	1067
± 3.5%	282	502	659	753	784
± 4.0%	216	384	504	576	600
± 5.0%	139	246	323	369	384

9.5.2 Sample size for France and Italy

For the study, investigators will register all consecutive TCC patientsvisiting GPs or specialists, whatever the reason. For the study, the analyzed patients' data set will consist of all registered patients, excluding patients for whom year of birth and/or gender are missing. As no published data are available on the practice of such physicians/sites, it was decided to assess the number of followed subjects from LPD and DA feasibility results. No hypothesis was made on the total number of subjects that will be registered. Thus, based on the feasibility results, for France, approximatively 40,000 patients were prescribed TCC in 2012 from GP panel and 2,800 in specialists. Besides, in Italy, more than 17,000 patients were prescribed TCC in 2012. Thus, based on a percentage of missing data on age and gender lower than 5 %, the maximal expected sample size will be over 60,000 patients per year from all data sources.

Table 6. Summary of the available number of users of TCC in each database in 2012 and 2013

	LPD France- DA France Rheumatologists		LPD Italy
Number of GPs (panel size)	-	1,000	900
Number of Rheumatologists (panel size)	100	Not covered	Not covered
Patients on TCC cmp* - 2012- GP's	-	~40,000	>17,000
Patients on TCC cmp* -2012- Rheumatologists	>2,800	Not covered	Not covered
Patients on TCC cmp* - 2013- GP's	-	~50,000	>16,800
Patients on TCC cmp* -2013- Rheumatologists	>3,100	Not covered	Not covered

*: cmp: cumulative measurement period

9.6 DATA MANAGEMENT

Data collected by physicians in usual routine practice into the patient EMR are anonymized and transferred daily in accordance with national legislation. The data will be hosted on servers located in datacenters belonging to IMS, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (CMMI, ISO 27001 and ITIL) and European regulation.

9.6.1 Data collection schedule

Not applicable.

9.6.2 Data collected

The following patients' data will be collected from the databases:

- Patient demography: age at the time of the visit, gender
- Pregnancy associated diagnoses for women of child bearing potential
- Lactation associated diagnoses for women of child bearing potential
- Date of prescription of TCC: name of the TCC-containing medicinal product for systemic use, posology, duration of treatment
- Diagnosis associated to prescription of the TCC-containing medicinal product for systemic use
- Concomitant medications/products: Concomitant medications/devices, including contraceptive medication/devices will be collected using list of therapeutic classes or drugs commonly prescribed.

Concerning concomitant medications/products prescribed in population with acute muscle contractures in spinal pathology, the predefined list, as exhaustive as possible, covers the concomitant medications of interest and the main therapeutic classes i.e. pain management prescription including: analgesics, tricyclic antidepressants, benzodiazepine, antiepileptics.

9.6.3 Site / Physician questionnaire

Not applicable. However, prescribing physicians may be analyzed and compared to panel population in term of age, gender and localization.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Procedure for withdrawal of patients from study follow-up schedule

Not applicable.

9.6.6 Logistic aspects

Not applicable

9.7 DATA ANALYSIS

A Statistical Analysis Plan (SAP) will be developed and validated prior to database extraction. A final version of the SAP will be provided at the end of the study. Statistical analysis will be performed using SAS® software with

SAS enterprise guide 6.1 (SAS Institute, version 6.1, SAS 9.4, North Carolina, USA) and R© R Foundation for Statistical Computing, version 3.0 and later. Analyses will be performed by statistician and quality control by a senior statistician. Statistical analyses will follow the tables shell validated by the client and will be displayed using tables, listings and/or graphs.

Given the objectives, analyses will be mainly descriptive. To evaluate the differences between sub-groups by indication, proportions for categorical variables and means for continuous variables will be estimated (with 95% confidence intervals) within each sub-group. If appropriate, medians will be used instead of means when the variables of interest do not assume a normal distribution.

Besides, because of the likelihood of some degree of allocation bias, comparative statistical testing will be performed in a descriptive manner. Comparison will be provided for groups of interest, as long as the number of patients in each sub-group is sufficient (n>30 in each group). The Fisher's exact test will be used for comparison of categorical data. Continuous data will be compared by Wilcoxon rank-sum test. All tests where two-sided and p-value <0.05 will be considered to indicate significance. Adjustments on statistical analyses modelling will be performed limiting the danger of spurious statistically significant findings with the numbers of people studied and taking into account the effect of potential confounders.

Continuous variables will be described by the usual statistics: number (number of valid cases, number of missing values), mean, standard deviation, median, minimum, maximum, first and third quartiles.

Categorical variables will be described for each modality and the associated percentages. The numbers of data entered and missing values will be indicated. Missing values will be excluded from the calculation of percentages.

9.8 PRIMARY ANALYSIS

The description of drug use patterns (overall description by country and by age and gender and incident or prevalent patients) will be performed for the baseline period (year 2013) and each year over the 3 years of inclusion for both countries.

Analysis will be done overall and by sub-group of prevalent and incident patients. Prevalent patients will be defined by the total number of treated patients per year during 3 years, and incident patients will be defined as the total number of new treated patients per year.

For each country, a descriptive analysis of TCC utilization and potential off-label use (as defined in table 2) will be performed:

- Indication,
- Dosage,
- Duration,
- Therapeutic regimen: mono-therapies or adjuvant therapies (use of TCC along with other pre-specified co-medications).

The prescribed daily dose will be defined as the average dose prescribed overall and by indications. In

addition descriptive analyses will be performed according to:

- Age and gender
- In the subgroup of women of childbearing potential: in case of pregnancy, use of contraceptive measures, or lactation during the study period. Proportion of pregnancies exposed to TCC (at least one TCC prescription during pregnancy within the defined study period) will be calculated over the total number of pregnancies in patients included in the study within the defined study periods. Proportion of breastfeeding patients exposed to TCC (at least one TCC prescription concomitant to a lactation record within the defined study period) will be calculated over the total number of breastfeeding patients included

in the study within the defined study periods.

In order to assess the impact of RMMs on the target population, the main characteristics of patients (demographic and clinical) will be compared between pre- and post-implementation of RMMs.

9.8.1 Secondary analysis

A comparison of patient characteristics and proportion of off-label use, pre- and post- implementation of RMMs as a measurement of the effectiveness of the risk minimization measures will be performed. The off label patients' proportion at baseline (year 2013) will be estimated on both the basis of the 2013 SmPC (A) and the post-RMMs SmPC (B). Off label patients' proportion for each year post-implementation of RMMs will be estimated on the basis of the post-RMMs SmPC (C). "Off-label use" definition will be based on the collected variables on relevant characteristics of use which are presented in Section 9.3.3

To estimate RMMs impact on off-label patients' rate, the overall difference (Δ = C - B) in off-label before and after RMMs will be estimated.

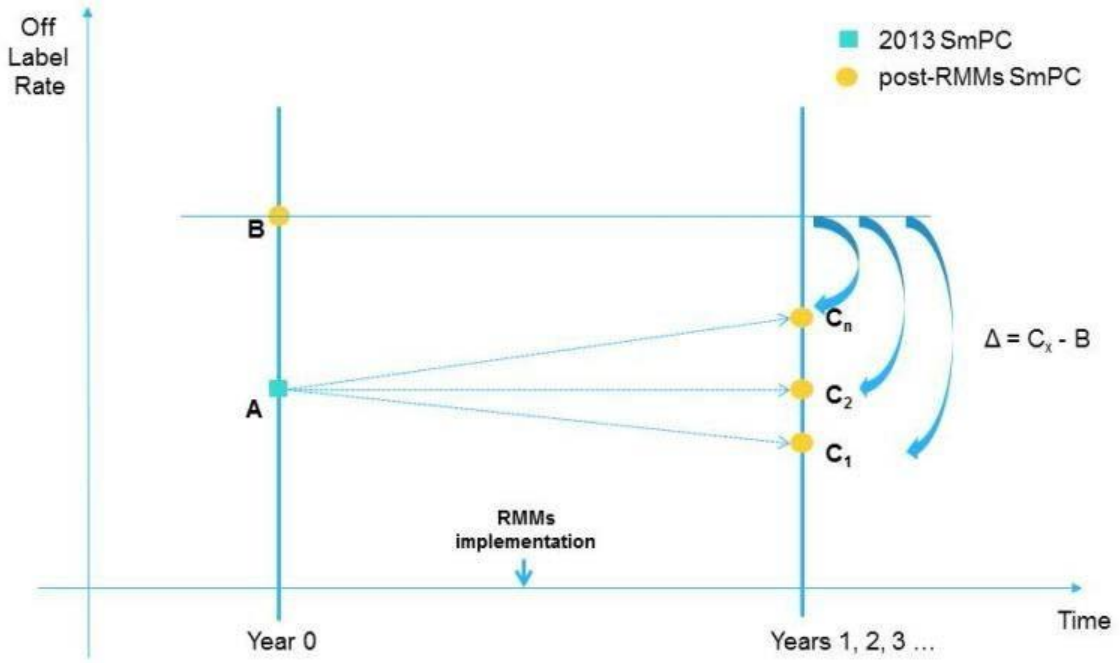

Figure 1: Estimation of RMMs impact on off-label rate

Furthermore, the effect of RMMs on off label incidence will be performed. The analysis will use a segmented regression analysis using a Poisson model [Wagner et al., 2002]. In this analysis, incidence rates will be computed by months before (baseline: 2013) and after RMMs (according to each country). The model will include an intercept (mean outcome rate at beginning of the study) and main period (before / after RMMs) effect and separate time trends before and after RMMs.

9.8.2 Interim analysis

Two annual interim reports are planned for this study.

9.9 QUALITY CONTROL

9.9.1 Data collection, validation and data quality control at MAH/MAH representative level

The data will be hosted on servers located in datacentres belonging to IMS, which ensures a high level of data security and confidentiality in accordance with the methods and good practices currently defined (CMMI, ISO 27001 and ITIL) and European regulation.

All data transfers will be verified by IMS according to SOPs for electronic file acquisition and checking practices. All programming will be independently reviewed by one of the QuintilesIMS statisticians. The study reports will undergo quality-control review, senior scientific review, and editorial review.

Analysis data sets and program output will be checked for accuracy and integrity according to SOPs of QuintilesIMS that include the following steps:

- Checking program logs for errors and warnings
- Checking output for errors and inconsistencies
- Running quality-control programs to verify that specifications were implemented correctly and that any output generated accurately reflects the data
- Checking all results tables for accuracy

None of the extracted data sets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymised and will not contain any personally identifying data.

9.9.2 Data quality control at site level

Not applicable: Data are collected by physicians in usual routine practice into the patient EMR. Since data are collected directly by physicians and uploaded in an anonymized way, it is not possible to refer back to patients' files and perform any site quality control.

Information is recorded by the physicians whenever they deem it relevant for their clinical practice and some information (e.g. family history, test results) may be partially available.

9.10 LIMITATIONS OF THE RESEARCH METHODS

The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to differential reporting of prescriptions or impacts of contacts with patients and health care professionals. Although misclassification of clinical indication is recognized as a potential issue for all these databases, studies evaluating data already collected may be the most efficient way to assess potential off-label use.

However, there are limitations in the conduct of this study

- Potential for missing/incomplete data: No individual patient identifiers will be available. It is therefore impossible to query the physicians providing the data for any missing information. There is no availability of information on death, or date transferred out of the system.

Recording of the indication of each prescribed treatment is mandatory in the physician software, but the physicians are free to enter any diagnosis and can for instance enter the reason of visit (e.g. flu) as indication for

all treatments prescribed at the visit.

Pregnancies are estimated by diagnoses codes in the patient's EMR but cannot always be reliably dated. There is therefore not always a possibility for us to state definitively the concomitance of a TCC prescription with a pregnancy. The same is true for lactation.

Contraceptive use, as researched in women of childbearing potential trough the prescription of contraceptive medications or device, will be underestimated. The reasons are (i) a substantial number of women may see a gynaecologist for this purpose (ii) devices may have been inserted in a time period not encompassed by this study or removed elsewhere (iii) contraception may be insured by other means than a prescribed devices or medications. There is therefore no possibility for us to state definitively the concomitance of a TCC prescription and contraceptive use.

Nevertheless, an accompanying survey performed at the PRAC request (PRACLOQN.8) in the most representative countries for TCC sales (France, Italy, Portugal and Greece) will be an additional source of information on contraception, lactation, and pregnancy for this study.

- Representativity of physicians: while representativeness of EMR-databases used in the present study is established on administrative criteria [Becher et al, 2009; Istituto di ricerca della SIMG, 2014] one

cannot exclude that the voluntary basis of physician's participation to the database leads to a potential bias in physicians' representativity.

- In France: no link between the panel of GPs and Rheumatologists is possible. Panels of specialists are independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, the risk is minimal.

- Bias to be explained:

  - Selection Bias: Health care utilization patterns are best described when they include data from all potential prescribers of a drug. In this instance, the Italian LPD and DA data source will capture patients prescribed TCC only in a GP setting. However this bias will be assessed in France, where a panel of rheumatologists will be available.

  - Misclassification bias can result if study subjects are not categorized correctly with regards to exposure or selected patient characteristics. We expect minimal misclassification with respect to exposure, since this is determined from each database's prescribing records. However, actual adherence to TCC cannot be confirmed. In addition, misclassification bias can occur at the level of associated diagnosis since physician can enter the reason of the visit (e.g. flu) as indication for all treatments prescribed at the visit.

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  - Assessment of representativeness:

    - Representativity assessment of the participating physicians:

Characteristics of participating GPs (gender, age class, region) will be compared to those of the national statistics. In case of discrepancy with national statistics information, weighted analysis could be applied.

    - Representativity assessment of the participating patients:

In order to assess the effect of excluding patients prescribed TCC but for whom there was less than one year of enrolment before the index date, patients exposed to TCC but not meeting this inclusion requirement will be counted and their main characteristics at index date (age, gender) will be described together with the characteristics of patients included in the study.

9.11 OTHER ASPECTS

NA

10 PROTECTION OF HUMAN SUBJECTS

As per Module VIII of the 2013 EMA Guideline on Good Pharmacovigilance Practices (GVP) [EMA GPV, Module VIII, 2016], this study has been included in the EU PASS register (EUPAS11081, ENCePP: Website: encepp.eu/encepp_studies/indexRegister.shtml) prior to the start of data collection.

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments, and the guidelines for Good Epidemiology Practice [2013 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methodological standards for study protocols].

In addition, according to the Guidelines for good Pharmacoepidemiology Practices (GPP) [International Society for Pharmacoepidemiology, 2015] the archive of the study should be maintained for at least five years after final report or first publication of study results, whichever comes later.

10.2.2 Laws and regulations

Approval for use of encrypted and aggregated data from LPD-Italy is granted by the Italian College of General Practitioners, and from LPD-France – rheumatologists and DA France by the CNIL (French National Commission for Data Protection).

10.2.3 Data protection

None of the extracted datasets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymised and will not contain any personally identifying data. QuintilesIMS will ensure a high level of stored data protection according to European regulations.

10.2.4 Insurance

Not applicable.

10.2.5 Secrecy agreement

Not applicable.

10.2.6 Record retention

Not applicable.

10.2.7 Discontinuation of the study

Not applicable.

10.2.8 MAH/MAH representative audits and inspections by competent authorities

Not applicable.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As per the EMA Guideline on Good Pharmacovigilance Practices [Module VI–Management and reporting of adverse reactions to medicinal products (Rev 1) 2014] for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The estimated timelines for the study report, pending approval of the DUS protocol and Educational Material by the respective competent regulatory authorities, are provided below.

The first submitted interim report will analyze data collected within 1 year after starting from effective date of implementation (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

The second interim report will be submitted within 2 years after starting from effective date of implementation (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

The final report will be submitted in Q4 2019. This report will contain all study data of the pre- and post-implementation periods.

The study protocol and final study report will be included in regulatory communications in line with the risk management plan, Periodic Benefit Risk Evaluation Reports (PBRER), and other regulatory milestones and agreed requirements.

Any amendments to the protocol and plans for communication/publication will be made in accordance with procedures outlined in ENCePP guidance.

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH REPRESENTATIVE conducting the study.

12.2 PUBLICATIONS

As per Module VIII of the 2016 EMA Guideline on Good Pharmacovigilance Practices (GVP) [EMA GPV, Module VIII, 2016], this study is included (ENCEPP/SDPP/11081) in the EU PASS register (Website: encepp.eu/encepp_studies/indexRegister.shtml).

Dissemination and communication of findings from this study will be in accordance with the Guidelines for Good Pharmacoepidemiology Practices [GPP,2008] and the EMA Guideline on Good Pharmacovigilance Practices (GVP), Module VIII [EMA GPV, Module VIII, 2013]. Study results will be published following the guidelines of the International Committee of Medical Journal Editors [ICMJE, 2013].

The MAHs will communicate to the EMA and the competent authorities of the Member States in which the product is authorized, the final manuscript of the article within two weeks after first acceptance for publication.

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ANNEXES

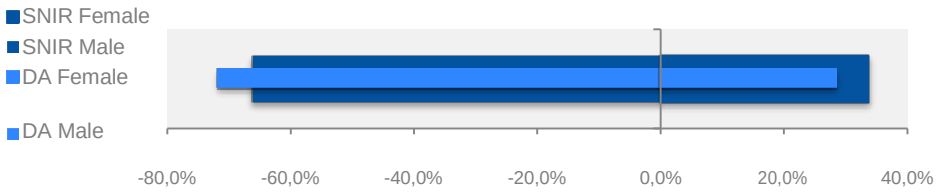
Annex 1 List of stand-alone documents

None

Annex 2 Representativity of physician and patient population for GPs database DA-France and LPD- Italy, and for -LPD-France- Rheumatologist database.

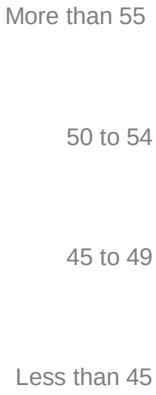
DA-FRANCE: characteristics of physicians and patient population compared to national statistics (SNIR, 2014)

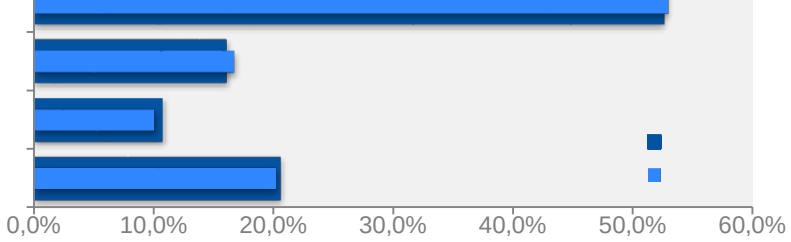
Gender



	DA	SNIR*
Female	28.3%	33.7%
Male	71.7%	66.3%

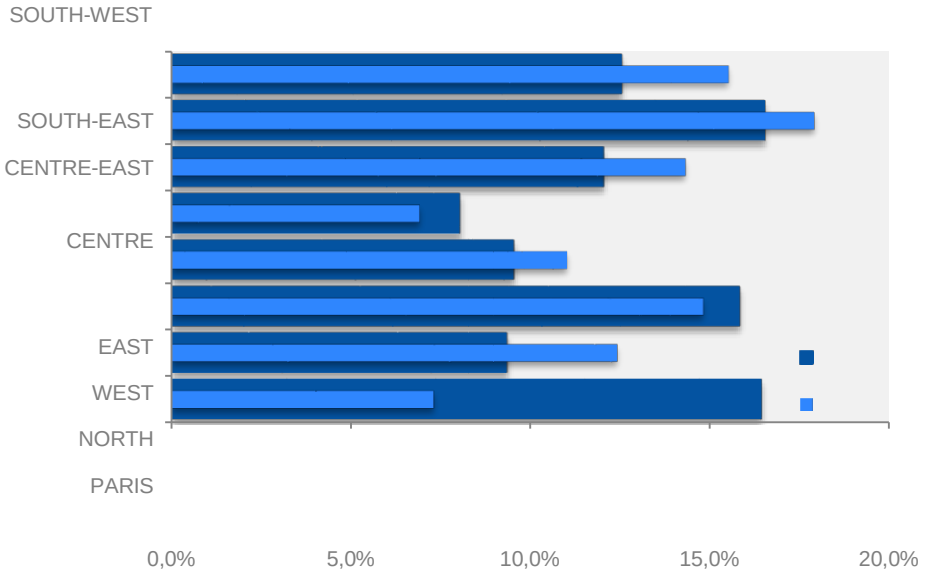
Age distribution





More than 55	52.5%	52.9%
50 to 54	16.0%	16.7%
45 to 49	10.7%	10.1%
Less than 45	20.5%	20,2%

Region



	DA	SNIR*
SOUTH-WEST	15.5%	12.5%
SOUTH-EAST	17.9%	16.5%
CENTRE-EAST	14.3%	12.0%
CENTRE	6.9%	8.0%
EAST	11.0%	9.5%
WEST	14.8%	15.8%
NORTH	12.4%	9.3%
PARIS	7,3%	16.4%

QuintilesIMS™

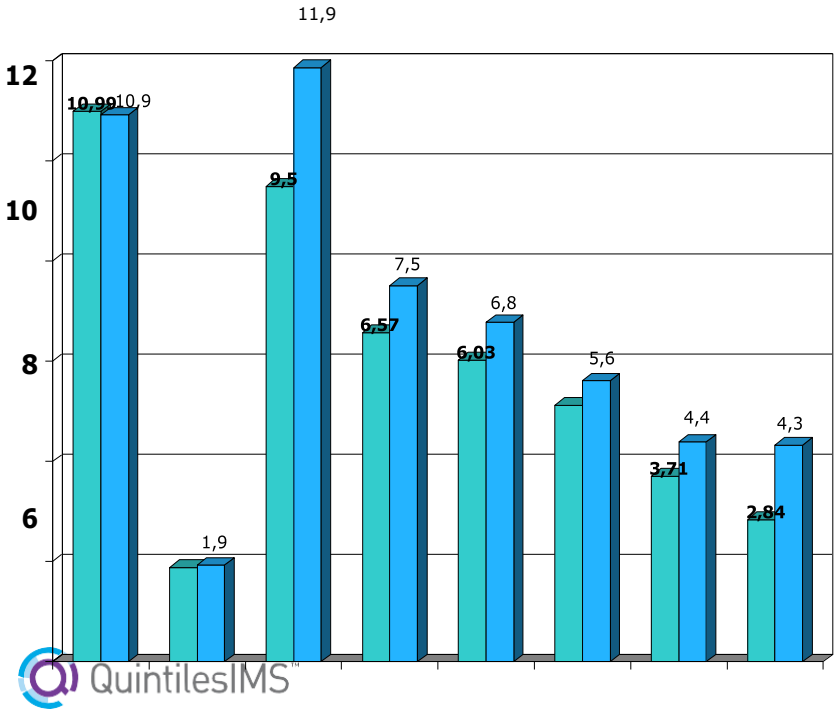
*: Système National Inter-Régimes (SNIR) 2014

DA-FRANCE: Patients distribution by age and gender and comparison to National statistics (EPAS, 2013)

NATIONAL STATISTICS

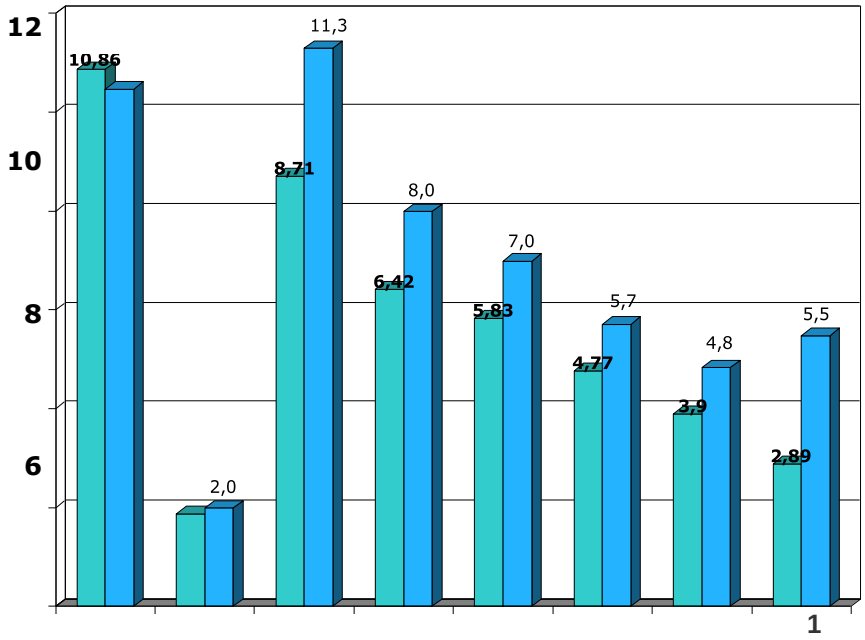
(Echantillon Permanent Assurés Sociaux)

Patientèle EPAS

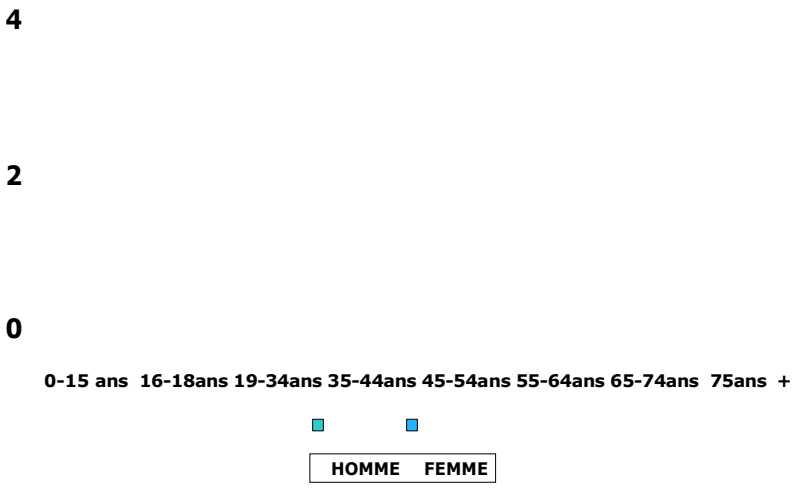


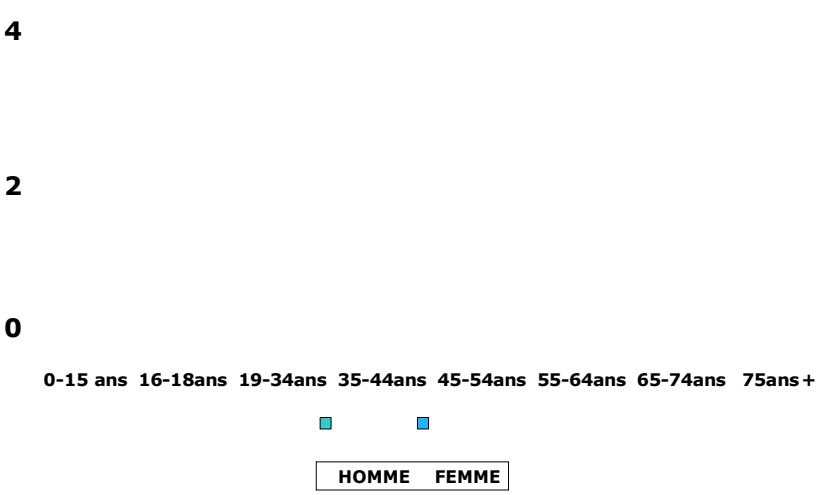
DA-FRANCE

(Patient with at least 1 Gp visit during the year)



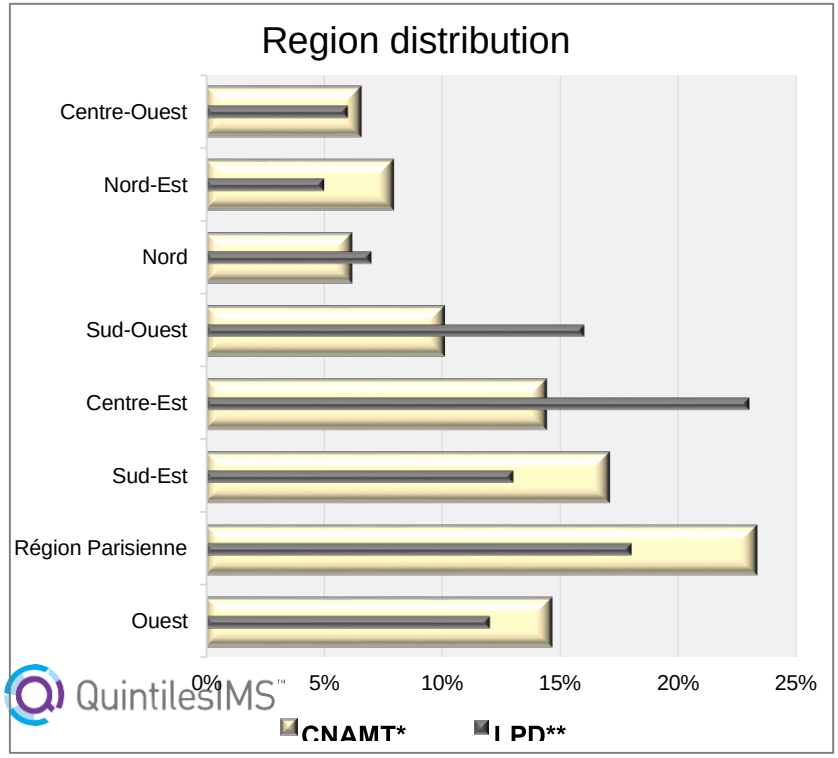
QuintilesIMS





From expert group (Drees, Irdes and Afssaps) : Da France content and methodology assessment

LPD FRANCE-RHEUMATOLOGISTS: Physician demographics and comparison to National Statistics (CNAMTS, 2013)



Gender distribution

CNAMTS* Male	CNAMTS* Female	LPD Male	LPD Female
64,5%	35,5%	59,0%	41,0%

Age distribution

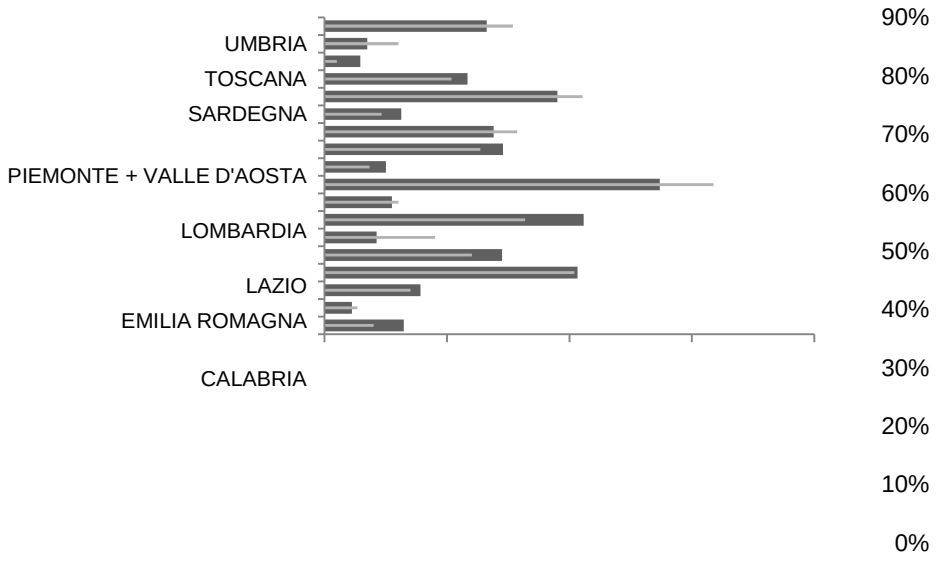
Physician age	CNAMT*	LPD**
Less than 39 years old	6.0%	1.0%
40 to 44 years old	6,5%	8,0%

45 to 49 years old	11,7%	14,0%
50 to 59 years old	41,4%	46,0%
60 years old and over	34,5%	31,0%

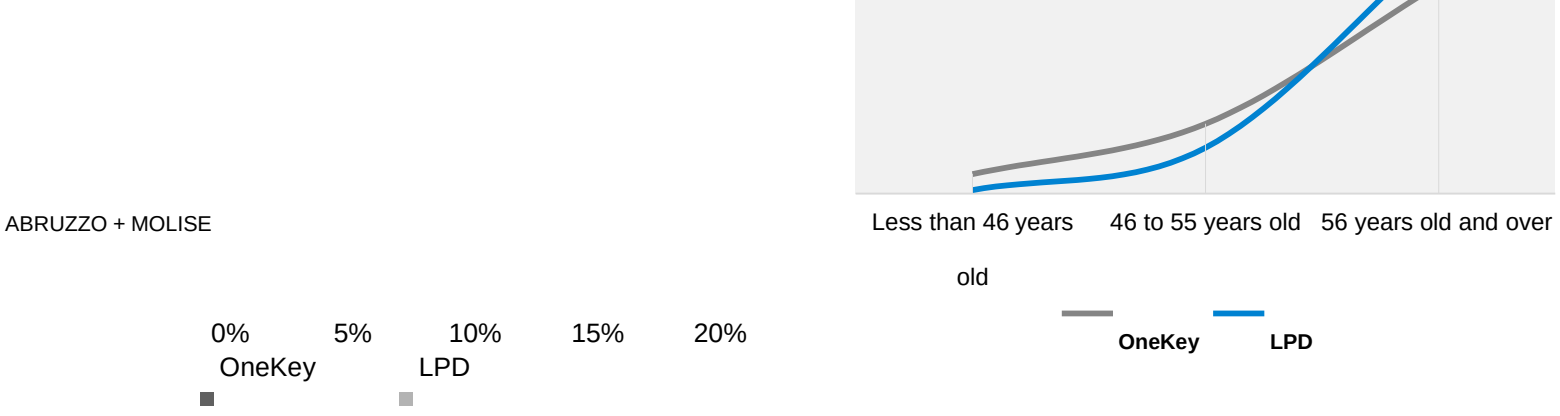
***: CNAMTS, French National Social Security, available at: http://www.ameli.fr/l-assurance-maladie/statistiques-et-publication**

LPD-ITALY: Physician demographics and comparison to National Onekey Physisican Register (2013)

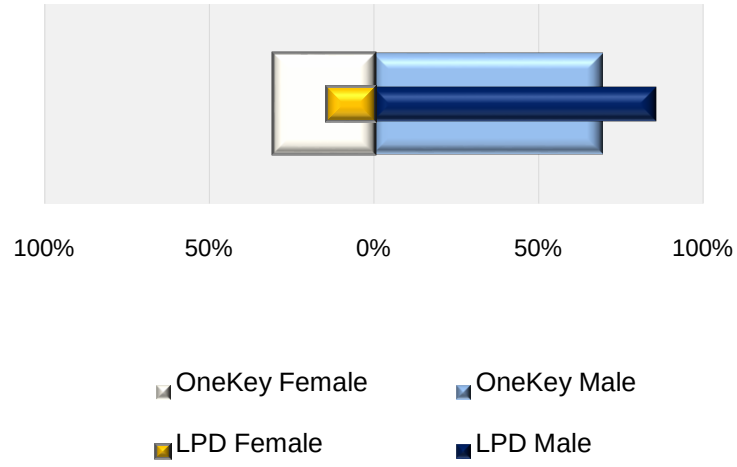
Region distribution



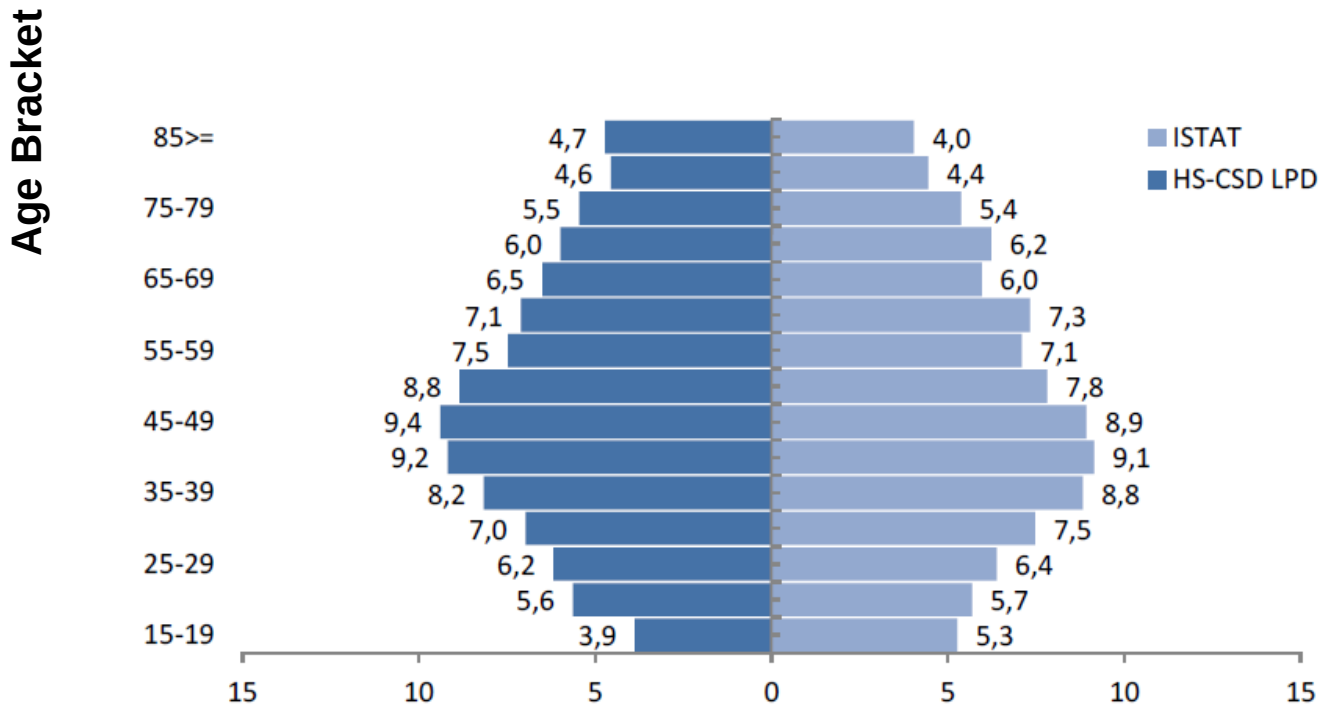
Age distribution



Gender distribution



LPD-ITALY: Comparison of age distribution in the Italian-LPD and national statistics (ISTAT*) (2013)



Percentage (%)

*: Italian National Institute of Statistics

Annex 3 List of Medicinal Products / Products References

Member State	Marketing Authorisation Holder	Invented name Name
France	**Laboratoire Alter** 3, avenue de la Baltique ZA de Courtaboeuf 91140 Villebon Sur Yvette France	THIOCOLCHICOSIDE ALTER
France	**Arrow Generiques** 26, avenue Tony Garnier 69007 Lyon France	THIOCOLCHICOSIDE ARROW
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE ALMUS
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE BIOGARAN
France	**Cristers SAS** 22 quai Gallieni 92150 Suresnes France	THIOCOLCHICOSIDE CRISTERS
France	**DAIICHI SANKYO France SAS** Immeuble le Corosa 1, rue Eugene et Armand Peugeot 92508 Rueil Malmaison	MIOREL
France	**Eg Labo - Laboratoires Eurogenerics** "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex	THIOCOLCHICOSIDE EG

France	**Mylan SAS** 117, allée des Parcs 69800 Saint-Priest France	THIOCOLCHICOSIDE MYLAN
France	**Sandoz** 49, avenue Georges Pompidou 92300 Levallois-Perret France	THIOCOLCHICOSIDE SANDOZ
France	**Sanofi Aventis France** 1-13, boulevard Romain Rolland 75014 Paris France	THIOCOLCHICOSIDE ZENTIVA
Italy	**Mylan S.P.A** Via Vittor Pisani, 20 20124 Milano Italy	THIOCOLCHICOSIDE MYLAN Generics
Italy	**Sandoz S.P.A.** Largo Umberto Boccioni, 1 21040 Origgio (VA) Italy	TIOCOLCHICOSIDE SANDOZ
Italy	**I.B.N. Savio S.r.l**., Via del Mare, 36, 00071 Pomezia (RM) Italy	TIOSIDE
Italy	**Sanofi S.p.A. / Zentiva Italia Srl** Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL TIOCOLCHICOSIDE ZENTIVA
Italy	**ACRAF S.p.A.** Viale Amelia, 70 -00181 Roma, Italy	TIOCOLCHICOSIDE ANGELINI
Italy	**DOC Generici S.R.L.** Via Turati, 40 20121 Milan Italy	TIOCOLCHICOSIDE DOC Generici

Italy	**Dompe' Farmaceutici S.P.A.** Via Campo di Pile S.N.C. 67100 L'Aquila Italy Operative office: Via Santa Lucia 6 20122 Milan Italy	MIOTENS
Italy	**EG S.P.A.** Via Pavia, 6 20136 Milano	TIOCOLCHICOSIDE EG
Italy	**Epifarma S.R.L.** Via San Rocco, 6 85033Episcopia (Potenza)	MUSCOFLEX
Italy	**Laboratorio Farmaceutico C.T.** S.R.L. Strada Solaro 75/77 18038	SCIOMIR
Italy	**MDM S.P.A.** Viale Papiniano, 22/B 20123 Milan Italy	STRIALISIN
Italy	**S.F. Group S.R.L.** Via Beniamino Segre, 59 00134 – Roma Italy	DECONTRIL TERASIDE
Italy	**SPA - Società Prodotti Antibiotici S.p.A.** Via Biella, 8 20143 Milano Italy	MIOREXIL
Italy	**Union Health S.R.L.** Via Adige, 5 66020 San Giovanni Teatino (Chieti) Italy	TIOCOLCHICOSIDE UNION HEALTH

Annex 4 SmPC / DHPC

ANNEXE III

Modifications apportées aux rubriques pertinentes du résumé des caractéristiques du produit, de l'étiquetage et de la notice

RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT

[la formulation ci-dessous doit être insérée]

▼Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Les professionnels de la santé déclarent tout effet indésirable suspecté. Voir rubrique 4.8 pour les modalités de déclaration des effets indésirables.

4. DONNÉES CLINIQUES

4.1 1 Indications thérapeutiques

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Traitement d'appoint des contractures musculaires douloureuses en pathologie rachidienne aiguë chez les adultes et les adolescents à partir de 16 ans.

4.2 2 Posologie et mode d'administration

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Posologie

- *Pour les formes orales dosées à 4 mg et 8 mg :*

La dose recommandée et maximale est de 8 mg toutes les 12 heures (soit 16 mg par jour). La durée du traitement est limitée à 7 jours consécutifs.

- *Pour la forme IM (intramusculaire) :*

La dose recommandée et maximale est de 4 mg toutes les 12 heures (soit 8 mg par jour). La durée du traitement est limitée à 5 jours consécutifs.

o *Pour l'administration orale et IM :*

Des doses supérieures aux doses recommandées ou l'utilisation à long terme doivent être évitées (voir rubrique 4.4).

Population pédiatrique

<Nom de fantaisie> ne doit pas être utilisé chez les enfants et les adolescents âgés de moins de 16 ans pour des raisons de sécurité (voir rubrique 5.3).

Mode d'administration

[À remplir pour chaque pays]

4.3 Contre-indications

[la formulation ci-dessous doit être insérée]

- hypersensibilité à la substance active ou à l'un des excipients (voir rubrique 6.1)
- Grossesse et femmes en âge de procréer n'utilisant pas de contraception (voir rubrique 4.6)
- Allaitement maternel (voir rubrique 4.6)

4.4 Mises en garde spéciales et précautions d'emploi

[la formulation ci-dessous doit être insérée]

[…]

Les études précliniques ont montré que l'un des métabolites du thiocolcoside (SL59.0955) induit de l'aneuploïdie (soit un nombre anormal de chromosomes dans les cellules après division cellulaire) à des concentrations proches de celles observées chez l'homme exposé à des doses de 8 mg deux fois par jour par voie orale (voir rubrique 5.3). L'aneuploïdie est considérée comme un facteur de risque de tératogenèse, d'embryo/fœtotoxicité, d'avortement spontané, et d'altération de la fertilité chez l'homme ainsi qu'un facteur de risque potentiel de cancer. Par mesure de précaution, l'utilisation du produit à des doses supérieures à la dose recommandée ou l'utilisation à long terme doit être évitée (voir rubrique 4.2).

Les patients doivent être soigneusement informés du risque potentiel d'une éventuelle grossesse et des mesures de contraception efficaces à suivre.

4.6 Fertilité, grossesse et allaitement

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

[…]

Grossesse

Les données sur l'utilisation du thiocolchicoside chez la femme enceinte sont limitées. Par conséquent, les risques potentiels pour l'embryon et le fœtus ne sont pas connus.

Les études chez l'animal ont montré des effets tératogènes (voir rubrique 5.3).

<Nom de fantaisie> est contre-indiqué pendant la grossesse et chez les femmes en âge de procréer n'utilisant pas de contraception (voir rubrique 4.3).

Allaitement

Compte tenu du passage du thiocolchicoside dans le lait maternel, son utilisation est contre-indiquée pendant l'allaitement (voir rubrique 4.3).

Fertilité

Dans une étude de toxicité sur la fertilité chez le rat, aucune altération de la fertilité n'a été

observée à des doses allant jusqu'à 12 mg/kg, correspondant à des niveaux de dose n'induisant aucun effet clinique. Le thiocolchicoside et ses métabolites exercent une activité aneugène à différents niveaux de dose, ce qui est un facteur de risque d'altération de la fertilité chez l'homme (voir rubrique 5.3).

4.8 Effets indésirables

[…]

[la formulation ci-dessous doit être insérée]

Déclaration des effets indésirables suspectés

La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration – voir Annexe V*.

*[*Pour le matériel imprimé, veuillez vous référer au guide annoté du modèle QRD.] […]*

5. PROPRIÉTÉS PHARMACOLOGIQUES

5.2 Propriétés pharmacocinétiques

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Absorption

- Après administration intramusculaire (IM), la concentration plasmatique maximale (C_{max}) de thiocolchicoside survient en 30 min et atteint des valeurs de 113 ng/mL après une dose de 4 mg, et de 175 ng/mL après une dose de 8 mg. Les valeurs correspondantes de l'AUC (surface sous la courbe) sont respectivement de 283 et 417 ng.h/mL.

Le métabolite pharmacologiquement actif SL18.0740 est également observé à des concentrations plus faibles avec une C_{max} de 11,7 ng/mL survenant 5 h après administration de thiocolchicoside et une AUC de 83 ng.h/mL.

Il n'existe pas de données concernant le métabolite inactif SL59.0955.

- Après administration orale, le thiocolchicoside n'est pas détecté dans le plasma. Seuls deux métabolites sont observés : le métabolite pharmacologiquement actif SL18.0740 et le métabolite inactif SL59.0955.

Pour ces deux métabolites, les concentrations plasmatiques maximales surviennent 1 heure après administration de thiocolchicoside. Après une dose orale unique de 8 mg de thiocolchicoside, les C_{max} et AUC du SL18.0740 sont respectivement d'environ 60 ng/mL et 130 ng.h/mL. Pour SL59.0955 ces valeurs sont beaucoup plus faibles : C_{max} d'environ 13 ng/mL et AUC allant de 15,5 ng.h/mL (AUC calculée jusqu'à 3 h) à 39,7 ng.h/mL (AUC jusqu'à 24 h).

Distribution

Le volume de distribution apparent du thiocolchicoside est estimé à environ 42,7 Ll après une administration IM de 8 mg. Il n'existe pas de données sur les deux métabolites.

Biotransformation

Après administration orale, le thiocolchicoside est d'abord métabolisé en aglycone 3-déméthyl-thiocolchicine ou SL59.0955. Cette étape se produit principalement par métabolisme intestinal expliquant l'absence de thiocolchicoside inchangé circulant par cette voie d'administration.

SL59.0955 est ensuite glucuro-conjugué en SL18.0740 qui possède une activité pharmacologique équipotente à celle du thiocolchicoside, et contribue donc à l'activité pharmacologique après administration orale de thiocolchicoside. SL59.0955 est également déméthylé en didéméthyl-thiocolchicine.

Élimination

- Après administration IM, la demi-vie apparente d'élimination ($t_{½}$) du thiocolchicoside est de 1,5 h et sa clairance plasmatique de 19,2 L/h.

- Après administration orale de thiocolchicoside radiomarqué, la radioactivité totale est principalement excrétée dans les fèces (79 %) alors que l'excrétion urinaire ne représente que 20 %. Le thiocolchicoside inchangé n'est pas excrété dans l'urine ni dans les fèces. SL18.0740 et SL59.0955 sont retrouvés dans l'urine et les fèces alors que le didéméthyl-thiocolchicine n'est retrouvé que dans les fèces.

Après administration orale de thiocolchicoside, le métabolite SL18.0740 est éliminé avec un $t_{1/2}$ apparent allant de 3,2 à 7 heures, et le métabolite SL59.0955 à un $t_{1/2}$ d'environ 0,8 h.

5.3 Données de sécurité préclinique

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Le profil toxicologique du thiocolchicoside a été évalué *in vitro,* et *in vivo* après administration parentérale et orale.

Le thiocolchicoside est bien toléré après administration orale répétée jusqu'à 6 mois chez le rat et le primate non-humain et ce, à des doses inférieures ou égales à 2 mg/kg/jour chez le rat et 2,5 mg/kg/jour chez le primate non humain, ainsi qu'après administration intramusculaire répétée pendant 4 semaines chez le primate à des doses allant jusqu'à 0,5 mg/kg/jour.

À fortes doses, après administration unique par voie orale, le thiocolchicoside provoque des vomissements chez le chien, des diarrhées chez le rat et des convulsions chez les rongeurs et les non rongeurs..

Après administration répétée, le thiocolchicoside a provoqué des troubles gastro-intestinaux (entérite, vomissements) par voie orale et des vomissements par voie IM.

Le thiocolchicoside lui-même n'induit pas de mutation génique sur bactéries (test d'Ames), d'aberration chromosomique *in vitro* (test d'aberration chromosomique sur lymphocytes humains) ni d'aberration chromosomique *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de souris après administration par voie intrapéritonéale).

Le principal métabolite glucuro-conjugué SL18.0740 n'induit pas de mutation génique sur bactéries (test d'Ames) ; il provoque cependant des aberrations chromosomiques *in vitro* (test du micronoyau *in vitro* sur lymphocyte humain) et des aberrations chromosomiques *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de souris après administration orale). Les micronoyaux résultaient principalement d'une perte de chromosome (présence de centromère dans les micronoyaux révélée par une coloration FISH spécifique du centromère), suggérant des propriétés aneugènes. L'effet aneugène de SL18.0740 a été observé à des concentrations (dans le test *in vitro)* et à des expositions plasmatiques (dans le test *in vivo)* plus élevées (plus de 10 fois sur la base de l'AUC) que celles observées dans le plasma humain à doses thérapeutiques.

Le métabolite aglycone (3-déméthyl-thiocolchicine ou SL59.0955), formé principalement après administration orale, induit des aberrations chromosomiques *in vitro* (test du micronoyau *in vitro* sur lymphocyte humain) et des aberrations chromosomiques *in vivo* (test du micronoyau *in vivo* sur moelle osseuse de rat après administration orale). Les micronoyaux résultaient principalement d'une perte de chromosome (présence de centromère dans les micronoyaux révélée par une coloration FISH ou CREST spécifique du centromère), suggérant des propriétés aneugènes. L'effet aneugène de SL59.0955 a été observé à des concentrations (dans le test *in vitro)* et à des expositions (dans le test *in vivo)* proches de celles observées dans le plasma humain à des doses thérapeutiques de 8 mg deux fois par jour par voie orale. L'effet aneugène dans les cellules en division peut aboutir à des cellules aneuploïdes. L'aneuploïdie est une modification du nombre de chromosomes et une perte d'hétérozygotie, qui est reconnue comme un facteur de risque de tératogenèse, d'embryotoxicité/d'avortement spontané et d'altération de la fertilité masculine, en cas d'effet sur les cellules germinales et comme facteur de risque potentiel de cancer en cas d'effet sur les cellules somatiques. La présence du métabolite aglycone (3 déméthyl-thiocolchicine ou SL59.0955) après administration intramusculaire n'ayant jamais été évaluée, sa formation en utilisant cette voie d'administration ne peut donc être exclue.

Chez le rat, une dose orale de 12 mg/kg/j. de thiocolchicoside a entraîné des malformations majeures ainsi qu'une fœtotoxicité (retard de croissance, mort embryonnaire, altération du taux de distribution par sexe). La dose sans effet toxique était de 3 mg/kg/jour.

Chez le lapin, le thiocolchicoside a montré une toxicité maternelle à partir de 24 mg/kg/jour. En outre, des anomalies mineures ont été observées (côtes surnuméraires, retard d'ossification).

Dans une étude de toxicité sur la fertilité chez le rat, aucune altération de la fertilité n'a été observée à des doses allant jusqu'à 12 mg/kg/jour, soit à des doses n'induisant aucun effet clinique. Le thiocolchicoside et ses métabolites exercent une activité aneugène à différents niveaux de dose, ce qui est reconnu comme un facteur de risque d'altération de la fertilité humaine.

Le potentiel cancérogène n'a pas été évalué.

6.5 Nature et contenu de l'emballage <et équipement spécial pour l'utilisation, l'administration ou l'implantation>

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

30 comprimés/gélules pour la dose de 4 mg et 14 comprimés/gélules pour la dose de 8 mg. 10 flacons / ampoules pour la dose de 4 mg / 2 ml.

ÉTIQUETAGE

MENTIONS DEVANT FIGURER SUR L'EMBALLAGE EXTÉRIEUR

4. FORME PHARMACEUTIQUE ET CONTENU

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

4 mg

[jusqu'à 30] capsules dures [jusqu'à 30] comprimés

8 mg

[jusqu'à 14] capsules dures

[jusqu'à 14] comprimés orodispersibles

4 mg/2 ml

[jusqu'à 10] flacons/ampoules

NOTICE

[la formulation ci-dessous doit être insérée]

▼Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. Vous pouvez y contribuer en signalant tout effet indésirable que vous observez. Voir en fin de rubrique 4 comment déclarer les effets indésirables.

[…]

Notice : Information du patient

1. Qu'est-ce que X et dans quel cas est-il utilisé

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Ce médicament est un relaxant musculaire. Il est utilisé chez les adultes et les adolescents de plus de 16 ans en tant que traitement d'appoint des contractures musculaires douloureuses. Il doit être utilisé pour des affections aiguës liées à la colonne vertébrale.

2. Quelles sont les informations à connaître avant de prendre X

[la formulation ci-dessous doit être insérée]

Ne prenez jamais X:

- si vous êtes allergique au thiocolchicoside ou à l'un des autres composants contenus dans ce médicament (mentionnés dans la rubrique 6)
- si vous êtes enceinte, pourriez tomber enceinte ou pensez que vous pourriez être enceinte
- si vous êtes une femme en âge d'avoir des enfants n'utilisant pas de contraception
- si vous allaitez

Avertissements et précautions

[…]

Respectez rigoureusement les doses et la durée du traitement décrites à la rubrique 3. Vous ne devez pas utiliser ce médicament à une dose plus élevée ou pour une durée dépassant 7 jours *(pour les formes orales)*/5 jours *(pour les formes IM).* Ceci est dû au fait que les produits formés dans votre organisme lorsque vous prenez thiocolchicoside à des doses élevées peuvent provoquer des lésions sur certaines cellules (nombre anormal de chromosomes). Cela a été mis en évidence lors d'études chez l'animal et d'études en laboratoire. Chez l'homme, ce type de lésions cellulaires est un facteur de risque de cancer, d'altération de la fertilité masculine et peut-être dangereux pour un enfant à naître. Parlez-en avec votre médecin si vous avez plus de questions.

Votre médecin vous renseignera sur toutes les mesures relatives à une contraception efficace et sur les risques potentiels d'une grossesse.

Enfants et adolescents

N'administrez pas ce médicament à des enfants ou des adolescents âgés de moins de 16 ans pour des raisons de sécurité.

Grossesse, allaitement et fertilité

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Ne prenez pas ce médicament :

- si vous êtes enceinte, pourriez tomber enceinte ou pensez que vous pourriez être enceinte.
- si vous êtes une femme en âge d'avoir des enfants n'utilisant pas de contraception.

Ce médicament peut mettre en danger votre enfant à naître. Ne prenez pas ce médicament si vous allaitez car ce médicament passe dans le lait maternel.

Ce médicament peut entraîner des problèmes de fertilité masculine par altération potentielle des cellules spermatiques (nombre anormal de chromosomes) ; ceci a été mise en évidence lors d'études en laboratoire (voir en rubrique 2 «Avertissements et précautions»).

3. Comment prendre X

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

Veillez à toujours prendre ce médicament en suivant exactement les instructions de votre médecin ou pharmacien. Vérifiez auprès de votre médecin ou pharmacien en cas de doute.

o *Pour les formes orales dosées à 4 mg et 8 mg :*

La dose recommandée et maximale est de 8 mg toutes les 12 heures (soit 16 mg par jour). La durée du traitement est limitée à 7 jours consécutifs.

o *Pour la forme intramusculaire :*

La dose recommandée et maximale est de 4 mg toutes les 12 heures (soit 8 mg par jour). La durée du traitement est limitée à 5 jours consécutifs.

o *Pour les formes orale et intramusculaire :*

Ne dépassez pas la dose recommandée ni la durée du traitement.

Ce médicament ne doit pas être utilisé pour un traitement à long terme (voir la rubrique 2

«Avertissements et précautions).

Utilisation chez les enfants et les adolescents

N'administrez pas ce médicament à des enfants ou des adolescents âgés de moins de 16 ans pour des raisons de sécurité.

Si vous avez pris plus de X que vous n'auriez dû

Si vous avez pris accidentellement plus de X que vous n'auriez dû, parlez-en à votre médecin, pharmacien ou infirmier/ère.

Si vous oubliez de prendre X

Ne doublez pas une dose pour compenser une dose que vous avez oubliée de prendre.

Si vous avez d'autres questions sur l'utilisation de ce médicament, demandez à votre médecin, à votre pharmacien ou à votre infirmier/ère.

4. Quels sont les effets indésirables éventuels

[la formulation ci-dessous doit être insérée]

Comme tous les médicaments, ce médicament peut provoquer des effets indésirables, mais ils ne surviennent pas systématiquement chez tout le monde.

[…]

[la formulation ci-dessous doit être insérée]

Déclaration des effets secondaires

Si vous ressentez un quelconque effet indésirable, parlez-en à votre médecin, votre pharmacien ou votre infirmier/ère. Ceci s'applique aussi à tout effet indésirable qui ne serait pas mentionné dans cette notice. Vous pouvez également déclarer les effets indésirables directement via le système national de déclaration décrit en Annexe V*. En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament.

*[*Pour le matériel imprimé, veuillez vous référer au guide annoté du modèle QRD.]*

6. Contenu de l'emballage et autres informations

[les formulations actuellement approuvées doivent être supprimées et remplacées par le texte suivant]

30 comprimés/gélules pour la dose de 4 mg et 14 comprimés/gélules pour la dose de 8 mg. 10 flacons / ampoules pour la dose de 4 mg / 2 ml.

ALLEGATO III

Modifiche ai paragrafi rilevanti del riassunto delle caratteristiche del prodotto, etichettatura e foglio illustrativo

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

[il testo sotto riportato deve essere inserito]

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta. Vedere paragrafo 4.8 per informazioni sulle modalità di segnalazione delle reazioni avverse.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

[le indicazioni attualmente autorizzate devono essere eliminate e sostituite con le seguenti]

Trattamento adiuvante di contratture muscolari dolorose nelle patologie acute della colonna vertebrale negli adulti e negli adolescenti dai 16 anni in poi.

4.2 Posologia e modo di somministrazione

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Posologia

- *Per la forma orale di 4 mg e 8 mg*:

La dose raccomandata e massima è di 8 mg ogni 12 ore (16 mg al giorno). La durata del trattamento è limitata a 7 giorni consecutivi.

- *Per la forma intramuscolare*:

La dose raccomandata e massima è di 4 mg ogni 12 ore (8 mg al giorno). La durata del trattamento è limitata a 5 giorni consecutivi.

- *Per entrambe le forme orale e intramuscolare*:

Dosi superiori a quelle raccomandate o l'uso a lungo termine devono essere evitati (vedere paragrafo 4.4).

Popolazione pediatrica

<Nome di fantasia> non deve essere usato nei bambini e negli adolescenti sotto 16 anni di età a causa di problematiche di sicurezza (vedere paragrafo 5.3).

Modo di somministrazione [Completare con i dati nazionali]

4.3 Controindicazioni

[il testo sotto riportato deve essere inserito]

Tiocolchicoside non deve essere utilizzato

- nei pazienti con ipersensibilità al principio attivo o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1
- durante tutto il periodo di gravidanza
- durante l'allattamento
- nelle donne in età fertile che non usano contraccettivi.

4.4 Avvertenze speciali e precauzioni di impiego

[il testo sotto riportato deve essere inserito]

[…]

Studi preclinici hanno dimostrato che uno dei metaboliti della tiocolchicoside (SL59.0955) ha indotto aneuploidia (alterazione del numero dei cromosomi nelle cellule in divisione) a concentrazioni vicine all'esposizione umana osservata con dosi di 8 mg due volte al giorno per os

(vedere paragrafo 5.3). L'aneuploidia viene considerata come un fattore di rischio per teratogenicità, tossicità dell'embrione/feto, aborto spontaneo, alterazione della fertilità maschile e un potenziale fattore di rischio per il cancro. Come misura precauzionale, l'uso del medicinale a dosi superiori alla dose raccomandata o l'uso a lungo termine devono essere evitati (vedere paragrafo 4.2).

I pazienti devono essere accuratamente informati circa il potenziale rischio di una possibile gravidanza e sulle misure di contraccezione efficaci da seguire.

4.6 Fertilità, gravidanza e allattamento

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

[…]

Gravidanza

I dati relativi all'uso di tiocolchicoside in donne in gravidanza sono limitati. Pertanto, i potenziali rischi per l'embrione e il feto sono sconosciuti.

Gli studi su animali hanno mostrato effetti teratogeni (vedere paragrafo 5.3).

<Nome di fantasia> è controindicato durante la gravidanza e nelle donne in età fertile che non usano contraccettivi (vedere paragrafo 4.3).

Allattamento

L'uso di tiocolchicoside è controindicato durante l'allattamento poiché è secreto nel latte materno (vedere paragrafo 4.3).

Fertilità

In uno studio sulla fertilità condotto sui ratti, nessuna alterazione della fertilità è stata osservata a dosi fino a 12 mg/kg, cioè a livelli di dose che non inducono alcun effetto clinico. Tiocolchicoside e i suoi metaboliti esercitano attività aneugenica a diversi livelli di concentrazione, il che è un fattore di rischio di alterazione della fertilità umana (vedere paragrafo 5.3).

4.8 Effetti indesiderati

[...]

[il testo sotto riportato deve essere inserito]

Segnalazione delle reazioni avverse sospette

La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione riportato nell'Allegato V*.

[*For the printed material, please refer to the guidance of the annotated QRD template.] [...]

5. PROPRIETÀ FARMACOLOGICHE

5.2 Proprietà farmacocinetiche

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Assorbimento

- Dopo somministrazione per via intramuscolare, la Cmax di Tiocolchicoside si verifica in 30 minuti e raggiunge i valori di 113 ng/ml dopo una dose di 4 mg, e di 175 ng/ml dopo una dose di 8 mg. I corrispondenti valori di AUC sono rispettivamente 283 e 417 ng.h/ml.

Il metabolita farmacologicamente attivo SL18.0740 si osserva anche a concentrazioni più basse, con una Cmax di 11,7 ng/ml che si ottiene 5 ore dopo la dose e una AUC di 83 ng.h/ml.

Non sono disponibili dati per il metabolita inattivo SL59.0955.

- Dopo somministrazione orale, tiocolchicoside non viene rilevato nel plasma. Si osservano solo due metaboliti: il metabolita farmacologicamente attivo SL18.0740 e un metabolita inattivo SL59.0955. Per entrambi i metaboliti, le concentrazioni plasmatiche massime si verificano 1 ora dopo la somministrazione di tiocolchicoside. Dopo una singola dose orale di 8 mg di tiocolchicoside la Cmax e l'AUC di SL18.0740 sono rispettivamente circa 60 ng/ml e 130 ng.h/ml. Per SL59.0955 questi valori sono molto più bassi: Cmax circa 13 ng/ml e i valori di AUC sono compresi tra 15,5 ng.h/ml (fino a 3h) e 39,7 ng.h/ml (fino a 24h).

Distribuzione

Il volume apparente di distribuzione di tiocolchicoside è stimato intorno a 42,7 L dopo somministrazione intramuscolare di 8 mg. Non sono disponibili dati per entrambi i metaboliti.

Biotrasformazione

Dopo somministrazione orale, tiocolchicoside viene prima metabolizzato in aglicone 3-demetiltiocolchicina o SL59.0955. Questa trasformazione avviene principalmente mediante metabolismo intestinale e spiega la mancanza di tiocolchicoside circolante immodificata con questa via di somministrazione.

Il metabolita SL59.0955 viene poi glucuroconiugato in SL18.0740 che ha attività farmacologica equipotente a tiocolchicoside e supporta quindi l'attività farmacologica dopo somministrazione orale di tiocolchicoside.

Il metabolita SL59.0955 è inoltre demetilato a didemetil-tiocolchicina.

Eliminazione

- Dopo somministrazione intramuscolare il $t_{1/2}$ apparente di tiocolchicoside è 1,5 ore e la clearance plasmatica 19,2 l/h.

- Dopo somministrazione orale, la radioattività totale viene escreta principalmente nelle feci (79%), mentre l'escrezione urinaria rappresenta solo il 20%. Tiocolchicoside immodificato non viene escreto né nelle urine né nelle feci. I metaboliti SL18.0740 e SL59.0955 si trovano nelle urine e nelle feci, mentre il didemetil-tiocolchicina viene recuperato solo nelle feci.

Dopo somministrazione orale di tiocolchicoside, il metabolita SL18.0740 viene eliminato con un $t_{1/2}$ apparente compreso tra 3,2 e 7 ore e il metabolita SL59.0955 ha un $t_{1/2}$ medio di 0.8 ore.

5.3 Dati preclinici di sicurezza

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Il profilo di tiocolchicoside è stato valutato *in vitro* e *in vivo* dopo somministrazione parenterale ed orale.

Tiocolchicoside è stato ben tollerato dopo somministrazione orale per periodi fino a 6 mesi sia nel ratto che nel primate non umano quando somministrato a dosi ripetute inferiori o uguali a 2 mg/kg/die nel ratto e inferiori o uguale a 2,5 mg/kg/die nel primate non umano, e per via

intramuscolare nel primate a dosi ripetute fino a 0,5 mg/kg/die per 4 settimane.

A dosi elevate, dopo somministrazione acuta per via orale, tiocolchicoside ha indotto emesi nel cane, diarrea nel ratto e convulsioni sia nei roditori che nei non roditori.

Dopo somministrazioni ripetute, tiocolchicoside ha indotto disturbi gastro-intestinali (enteriti, emesi) per via orale ed emesi per via intramuscolare.

Thiocolchicoside non ha indotto di per sé mutazione genica nei batteri (Ames test), danno cromosomico *in vitro* (test di aberrazione cromosomica nei linfociti umani) e danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del topo dopo somministrazione intraperitoneale).

Il principale metabolita glucuroconiugato SL18.0740 non ha indotto mutazione genica nei batteri (Ames test), tuttavia ha indotto un danno cromosomico *in vitro* (test del micronucleo sui linfociti umani) e un danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del topo dopo somministrazione orale). I micronuclei provenivano prevalentemente dalla perdita cromosomica (micronuclei centromero positivi dopo colorazione FISH del centromero), suggerendo proprietà aneugeniche. L'effetto aneugenico del metabolita SL18.0740 è stato osservato a concentrazioni nel test *in vitro* e a esposizioni plasmatiche (AUC) nel test *in vivo,* più elevate (maggiori di 10 volte in base alla AUC) rispetto a quelle osservati nel plasma umano a dosi terapeutiche.

Il metabolita aglicone (3-demetilthiocolchicina-SL59.0955), che si forma principalmente dopo somministrazione orale, ha indotto un danno cromosomico *in vitro* (test del micronucleo sui linfociti umani) e un danno cromosomico *in vivo* (test del micronucleo nel midollo osseo del ratto dopo somministrazione orale). I micronuclei provenivano prevalentemente dalla perdita cromosomica (micronuclei centromero positivi dopo colorazione FISH o CREST del centromero), suggerendo

proprietà aneugeniche. L'effetto aneugenico di SL59.0955 è stato osservato a concentrazioni nel test *in vitro* e ad esposizioni nel test *in vivo* vicine a quelle osservate nel plasma umano a dosi terapeutiche di 8 mg due volte al giorno per os. L'effetto aneugenico nelle cellule in divisione può causare cellule aneuploidi. L'aneuploidia è una alterazione nel numero dei cromosomi e perdita della eterozigosi, che è riconosciuta come un fattore di rischio per teratogenicità, tossicità dell'embrione/aborto spontaneo, alterata fertilità maschile, quando riguarda le cellule germinali, e un potenziale fattore di rischio per il tumore quando riguarda le cellule somatiche. La presenza del metabolita aglicone (3-demetilthiocolchicina-SL59.0955) dopo somministrazione intramuscolare non è mai stata valutata, quindi la sua formazione attraverso questa via di somministrazione non può essere esclusa.

Nel ratto, una dose orale di 12 mg/kg/giorno di tiocolchicoside ha provocato malformazioni maggiori insieme a tossicità fetale (ritardo nella crescita, morte dell'embrione, alterazione del tasso di distribuzione del sesso). La dose senza effetto tossico è stata di 3 mg/kg/giorno.

Nel coniglio, tiocolchicoside ha mostrato tossicità materna a partire da 24 mg/kg/giorno. Inoltre, sono state osservate anomalie minori (costole soprannumerarie, ossificazione ritardata).

In uno studio sulla fertilità condotto sui ratti, nessuna alterazione della fertilità è stata osservata a dosi fino a 12 mg/kg/giorno, cioè livelli di dose che non inducono alcun effetto clinico.

Tiocolchicoside e i suoi metaboliti esercitano attività aneugenica a diversi livelli di concentrazione, ciò è riconosciuto come fattore di rischio di alterazione della fertilità umana.

Il potenziale cancerogeno non è stato valutato.

6.5 Natura e contenuto del contenitore < e strumentazione particolare per l'uso, la somministrazione o l'impianto>

[il testo attualmente autorizzato deve essere <u>eliminato e sostituito</u> con il seguente]

30 compresse/capsule per la dose di 4 mg e 14 compresse/capsule per la dose di 8 mg 10 fiale / flaconi per la dose di 4 mg / 2 ml.

ETICHETTATURA

INFORMAZIONI DA APPORRE SUL CONFEZIONAMENTO SECONDARIO

Astuccio per capsule rigide/ compresse / compresse orodispersibili e per la soluzione

4. FORMA FARMACEUTICA E CONTENUTO

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

4 mg[fino a 30] capsule rigide[fino a 30] compresse

8 mg

[fino a 14] capsule rigide

[fino a 14] compresse orodispersibili

4 mg/2 ml

[fino a 10] flaconcini/fiale

FOGLIO ILLUSTRATIVO

[il testo sotto riportato deve essere inserito]

▼Medicinale sottoposto a monitoraggio addizionale. Ciò permetterà la rapida identificazione di nuove informazioni sulla sicurezza. Lei può contribuire segnalando qualsiasi effetto indesiderato riscontrato durante l'assunzione di questo medicinale. Vedere la fine del paragrafo 4 per le informazioni su come segnalare gli effetti indesiderati.

[…]

PL

Foglio illustrativo: informazioni per il paziente

1. Che cos'è X e a cosa serve

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Questo medicinale è un rilassante muscolare. Viene utilizzato negli adulti e negli adolescenti da 16 anni in poi come trattamento adiuvante per le contratture muscolari dolorose. Deve essere utilizzato per condizioni acute legate alla colonna vertebrale.

2. Cosa deve sapere prima prima di prendere X

[il testo sotto riportato deve essere inserito]

Non prenda X se:

- è allergico a tiocolchicoside o ad uno qualsiasi degli eccipienti di questo medicinale (elencati nel paragrafo 6)
- è in gravidanza, sospetta di esserlo o potrebbe andare incontro a gravidanza
- è una donna in età fertile che non usa contraccettivi
- sta allattando al seno

Avvertenze e precauzioni

[...]

Rispetti rigorosamente le dosi e la durata del trattamento riportati al paragrafo 3. Non deve usare questo medicinale a dosi più alte o per più di 7 giorni (*per le forme orali*) /5 giorni (*per le forme* intramuscolari). Questo perché una delle sostanze che si formano nel corpo quando prende tiocolchicoside a dosi elevate potrebbe causare danni ad alcune cellule (numero anomalo di cromosomi). Ciò è stato dimostrato in studi su animali e in studi di laboratorio. Negli esseri umani, questo tipo di danno cellulare è un fattore di rischio per il cancro, danneggia il nascituro, e altera la fertilità maschile. Si rivolga al medico se ha ulteriori domande.

Il medico la informerà su tutte le misure in materia di contraccezione efficace e sul rischio potenziale di una gravidanza .

Bambini e adolescenti

Non somministri questo medicinale a bambini e adolescenti sotto 16 anni a causa di problemi di sicurezza.

Gravidanza, allattamento e fertilità

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Non prenda questo medicinale se:

- è in gravidanza, sospetta di esserlo o potrebbe andare incontro a gravidanza
- è una donna in età fertile che non usa contraccettivi

Infatti questo medicinale può causare danni al nascituro.

Non assuma questo medicinale se sta allattando in quanto il medicinale passa nel latte materno.

Il medicinale può causare problemi alla fertilità maschile a causa di potenziali danni alle cellule spermatiche (numero anormale di cromosomi). Questo si basa su studi di laboratorio (vedere paragrafo 2 "Avvertenze e precauzioni").

3. Come prendere X

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

Prenda questo medicinale seguendo sempre esattamente le istruzioni del medico o del farmacista. Se ha dubbi consulti il medico o il farmacista.

- *Per la forma orale di 4 mg e 8 mg*:

La dose raccomandata e massima è di 8 mg ogni 12 ore (cioè 16 mg al giorno). La durata del trattamento è limitata a 7 giorni consecutivi.

- *Per la forma intramuscolare*:

La dose raccomandata e massima è di 4 mg ogni 12 ore (cioè 8 mg al giorno). La durata del trattamento è limitata a 5 giorni consecutivi.

- *Per entrambe le forme orale e intramuscolare*:

Non superare le dosi raccomandate e la durata del trattamento.

Questo medicinale non deve essere usato per trattamento a lungo termine (vedere paragrafo 2 "Avvertenze e precauzioni").

Uso nei bambini e negli adolescenti

Non somministrare questo medicinale a bambini e adolescenti al di sotto di 16 anni di età a causa di problemi di sicurezza.

Se prende più X di quanto deve

Se accidentalmente prende più X di quanto deve, si rivolga al medico, al farmacista o all'infermiere.

Se dimentica di prendere X

Non prenda una dose doppia per compensare la dimenticanza della dose.

Se ha qualsiasi dubbio sull'uso di questo medicinale, si rivolga al medico, al farmacista o all'infermiere.

4. Possibili effetti indesiderati

[il testo sotto riportato deve essere inserito]

Come tutti i medicinali, questo medicinale può causare effetti indesiderati sebbene non tutte le persone li manifestino.

[...]

[il testo sotto riportato deve essere inserito]

Segnalazione degli effetti indesiderati

Se manifesta un qualsiasi effetto indesiderato, compresi quelli non elencati in questo foglio, si rivolga al medico o al farmacista o all'infermiere. Lei può inoltre segnalare gli effetti indesiderati direttamente tramite il sistema nazionale di segnalazione riportato nell'Allegato V*.

Segnalando gli effetti indesiderati lei può contribuire a fornire maggiori informazioni sulla sicurezza di questo medicinale.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

6. Contenuto della confezione e altre informazioni

[il testo attualmente autorizzato deve essere eliminato e sostituito con il seguente]

30 compresse/capsule per la dose di 4 mg e 14 comprese/capsule per la dose di 8 mg 10 fiale / flaconi per la dose di 4 mg / 2 ml.

INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

L ssionnels de santé

INFORMATIONS
SÉCURITÉ PATIENTS

Avril 2014

Spécialités contenant du thiocolchicoside administrées par voie générale : information importante relative aux indications, aux modalités de traitement, aux contre-indications et aux mises en garde

Information destinée aux rhumatologues, médecins généralistes, médecins du sport et de médecine physique, pharmaciens d'officine et hospitaliers, aux centres de rééducation fonctionnelle.

Madame, Monsieur, Cher confrère,

En accord avec l'Agence Européenne des Médicaments (EMA) et l'Agence nationale de sécurité du médicament et des produits de santé (ANSM), les titulaires des autorisations de mise sur le marché des spécialités contenant du thiocolchicoside administrées par voie générale, souhaitent vous informer des restrictions d'utilisation de ces médicaments, suite aux résultats de nouvelles études précliniques mettant en évidence les effets d'un métabolite du thiocolchicoside sur les chromosomes.

Résumé

Ces nouvelles données précliniques indiquent un risque potentiel de génotoxicité du thiocolchicoside utilisé par voie systémique et ont conduit à des restrictions d'utilisation des médicaments à base de thiocolchicoside administrés par voie orale (PO) ou intramusculaire (IM) :

- le thiocolchicoside doit uniquement être utilisé dans le traitement d'appoint des contractures musculaires douloureuses en cas de pathologies rachidiennes aiguës chez les adultes et les adolescents à partir de 16 ans ;
- Le thiocolchicoside ne doit plus être utilisé au long cours en cas de pathologies chroniques ;
- La posologie et la durée du traitement sont désormais limitées et ne doivent pas être dépassées :
    - La durée du traitement est limitée à 7 jours consécutifs pour la voie orale, avec une dose maximale recommandée de 8 mg toutes les 12 heures, soit 16 mg par jour.
    - La durée du traitement est limitée à 5 jours consécutifs pour la voie injectable (IM), avec une dose maximale recommandée de 4 mg toutes les 12 heures, soit 8 mg au total par jour.
- Le thiocolchicoside est contre-indiqué pendant la grossesse, au cours de l'allaitement, ou chez les femmes en âge de procréer sans contraception efficace.

Informations complémentaires

Le thiocolchicoside est un principe actif avec une action myorelaxante disponible en France sous forme orale et

injectable.

Des études chez l'animal, réalisées à des concentrations proches de celles observées chez l'homme lors de l'administration par voie orale du thiocolchicoside aux doses maximales recommandées de 8 mg deux fois par jour, ont montré que l'un de ses métabolites (SL59.0955 aussi appelé M2 ou 3-déméthylthiocolchicine) induit une aneuploïdie (nombre inégal de chromosomes après division cellulaire).

L'aneuploïdie est reconnue comme un facteur de risque de tératogénicité, d'embryotoxicité, d'avortement spontané et d'altération de la fertilité masculine ainsi que comme un facteur de risque potentiel de cancer. Ce risque est plus important en cas d'exposition de longue durée.

Ces informations ont conduit à la prise de mesures visant à réduire l'exposition au métabolite SL59.0955 du thiocolchicoside administré par voie générale.

Le rapport bénéfice/risque du thiocolchicoside administré par voie générale a été considéré comme favorable dès lors qu'il est utilisé aux doses et durées de traitement désormais recommandées, uniquement dans le traitement d'appoint des contractures musculaires douloureuses en cas de pathologies rachidiennes aiguës chez les adultes et les adolescents à partir de 16 ans et en respectant les contre-indications.

INFORMATION TRANSMISE SOUS L'AUTORITE DE L'ANSM

Lettre aux professionnels de santé

Afin de minimiser les risques, le thiocolchicoside est contre-indiqué en cas de grossesse, d'allaitement et chez les femmes en âge de procréer n'utilisant pas de contraception efficace.

Déclaration des effets indésirables

▼Ce médicament fait l'objet d'une surveillance supplémentaire qui permettra l'identification rapide de nouvelles informations relatives à la sécurité. L'ANSM rappelle que les professionnels de santé doivent déclarer immédiatement tout effet indésirable suspecté d'être dû à un médicament dont ils ont connaissance au centre régional de pharmacovigilance dont ils dépendent géographiquement. Les patients et les associations agréées de patients peuvent également signaler tout effet indésirable à leur centre régional de pharmacovigilance.

Pour plus d'informations, consulter la rubrique « Déclarer un effet indésirable » sur le site Internet de l'ANSM : http://ansm.sante.fr

Information médicale

Pour toute question ou information complémentaire, nous vous remercions de bien vouloir contacter les laboratoires concernés (voir liste ci-dessous)

Dénomination	Titulaire de l'autorisation de mise sur le marché
THIOCOLCHICOSIDE ACTAVIS 4 mg, comprimé	Titulaire ACTAVIS GROUP PTC EHF Exploitant ACTAVIS France Information médicale et Pharmacovigilance
THIOCOLCHICOSIDE ALMUS 4 mg, comprimé	Exploitant ALMUS
THIOCOLCHICOSIDE ALTER 4 mg, comprimé	Titulaire/Exploitant ALTER Information médicale Tél : 01.69.29.83.08 Pharmacovigilance Tel : 01.30.08.72.92
THIOCOLCHICOSIDE ARROW 4 mg, comprimé	Titulaire/Exploitant ARROW GENERIQUES Information médicale et Pharmacovigilance Tel : 04 72 71 63 97
THIOCOLCHICOSIDE BIOGARAN 4 mg, comprimé	Titulaire/Exploitant BIOGARAN Information médicale et Pharmacovigilance
THIOCOLCHICOSIDE CRISTERS 4 mg, comprimé	CRISTERS Information médicale et Pharmacovigilance Tél : 01 42 04 94
MIOREL® 4 mg, gélule MIOREL® 4 mg/2 ml, solution injectable (IM) en ampoule	Titulaire/Exploitant DAIICHI SANKYO France SAS Information médicale et Pharmacovigilance
THIOCOLCHICOSIDE EG 4 mg, comprimé sécable	EG LABO - LABORATOIRES EUROGENERICS Info médicale et pharmacovigilance Tél : 01 46 94 86 96
COLTHIOZID 4 mg/2 ml, solution injectable	Titulaire/Exploitant LABORATOIRE PHARMY II Information médicale et Pharmacovigilance
THIOCOLCHICOSIDE MYLAN 4 mg, comprimé	Titulaire/Exploitant MYLAN SAS Information médicale et Pharmacovigilance Tel : 0810 123 550
THIOCOLCHICOSIDE SANDOZ 4 mg, comprimé	Titulaire/Exploitant SANDOZ Information médicale et Pharmacovigilance

COLTRAMYL 4 mg, comprimé THIOCOLCHICOSIDE ZENTIVA 4 mg, comprimé	SANOFI-AVENTIS FRANCE Information médicale et pharmacovigilance : Numéro vert (métropole) : 0 800 394 000
THIOCOLCHICOSIDE TEVA 4 mg, comprimé	Exploitant TEVA SANTE Information médicale et Pharmacovigilance

NOTA INFORMATIVA IMPORTANTE

CONCORDATA CON L'AGENZIA EUROPEA DEI MEDICINALI (EMA) E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

7 febbraio 2014

MEDICINALI A BASE DI TIOCOLCHICOSIDE PER USO SISTEMICO INFORMAZIONI IMPORTANTI SU INDICAZIONI, REGIME DI TRATTAMENTO, CONTROINDICAZIONI E AVVERTENZE

Gentile Dott.ssa/Egregio Dottore,

l'Agenzia Europea dei Medicinali e l'AIFA in accordo con i titolari dell'autorizzazione all'immissione in commercio desiderano informarla di importanti limitazioni relative all'uso dei medicinali a base di tiocolchicoside per uso sistemico, imposte a seguito dei risultati derivanti dalla revisione di nuovi dati preclinici che hanno sollevato dubbi sull'attività di un metabolita di tiocolchicoside sui cromosomi.

Riassunto

Nuovi dati preclinici indicano un potenziale rischio di genotossicità derivante dall'uso di tiocolchicoside per via orale e intramuscolare (IM).

- Tiocolchicoside per via sistemica deve essere usata solo come trattamento adiuvante delle contratture muscolari dolorose associate a patologie acute della colonna, negli adulti e negli adolescenti di età superiore a 16 anni.
- Tiocolchicoside non deve essere usata per il trattamento a lungo termine di patologie croniche.
- Le seguenti posologie devono essere rispettate; le dosi e la durata raccomandate non devono essere superate:
    - Forme orali: la dose raccomandata, che non deve essere superata, è di 8 mg ogni 12 ore, ossia 16 mg/die. La durata del trattamento non deve superare i 7 giorni consecutivi.
    - Forma IM: la dose raccomandata, che non deve essere superata, è di 4 mg ogni 12 ore, ossia 8 mg/die. La durata del trattamento non deve superare i 5 giorni consecutivi.
- Tiocolchicoside non deve essere usata in gravidanza e durante l'allattamento, né in donne in età fertile che non adottano un adeguato metodo contraccettivo.

Ulteriori informazioni

Tiocolchicoside è un miorilassante disponibile in formulazione orale, iniettabile e topica. Studi preclinici hanno evidenziato che uno dei metaboliti della tiocolchicoside (SL59.0955, noto anche come M2 o 3-demetiltiocolchicina) induce aneuploidia (formazione di un numero anomalo di cromosomi durante la divisione cellulare) a concentrazioni vicine a quelle osservate nell'uomo con l'assunzione della dose orale massima raccomandata di 8 mg due volte al giorno. L'aneuploidia è stata evidenziata come fattore di rischio di teratogenicità, embriofetotossicità/aborto spontaneo, compromissione della fertilità maschile e come potenziale fattore di rischio di cancro. Il rischio è maggiore con l'esposizione a lungo termine.

Pertanto è necessario adottare misure precauzionali per ridurre l'esposizione al metabolita SL59.0955 delle formulazioni sistemiche (le formulazioni topiche non producono

concentrazioni sistemiche significative del metabolita e non sono interessate da queste raccomandazioni).

Tiocolchicoside per via sistemica non deve essere usata per il trattamento a lungo termine di condizioni croniche e il trattamento deve essere limitato a 7 giorni, per le formulazioni orali, e a 5 giorni, per quelle iniettabili. Inoltre la posologia non deve superare la dose di 8 mg ogni 12 ore, per le formulazioni orali, e di 4 mg ogni 12 ore per quelle iniettabili.

Il beneficio delle formulazioni orali a base di tiocolchicoside è considerato superiore ai rischi solo se l'uso avviene secondo questi regimi terapeutici, come adiuvante nel trattamento delle contratture muscolari dolorose nelle patologie acute della colonna vertebrale, in pazienti adulti e adolescenti di età da 16 anni in su.

Per poter minimizzare e gestire il rischio per il feto, tiocolchicoside non deve essere usata in gravidanza e durante l'allattamento, né da donne in età fertile che non adottano un adeguato metodo contraccettivo.

I testi delle modifiche ed integrazioni al riassunto delle caratteristiche del prodotto (RCP) e al foglio illustrativo (FI) dei farmaci a base di tiocolchicoside per uso sistemico sono allegati alla presente Nota.

Richiamo alla segnalazione

I medici e gli altri operatori sanitari sono tenuti a segnalare qualsiasi sospetta reazione avversa associata a medicinali.

I medici e gli altri operatori sanitari devono, a norma di legge, trasmettere le segnalazioni di sospette reazioni avverse, tramite l'apposita scheda cartacea (reperibile sul sito http://www.agenziafarmaco.gov.it/sites/default/files/tipo_filecb84.pdf) o compilando on- line la scheda elettronica (http://www.agenziafarmaco.gov.it/sites/default/files/Scheda_elettronica_AIFA_operatore_sanitario_25.09.2013.doc) tempestivamente, al Responsabile di Farmacovigilanza della struttura sanitaria di appartenenza o, qualora operanti in strutture sanitarie private, tramite la Direzione sanitaria, al responsabile di farmacovigilanza della ASL competente per territorio.

L'AIFA coglie l'occasione per ricordare a tutti gli Operatori Sanitari l'importanza della segnalazione delle reazioni avverse da farmaci, quale strumento indispensabile per confermare un rapporto beneficio rischio favorevole nelle reali condizioni di impiego.

Le Segnalazioni di Sospetta Reazione Avversa da Farmaci devono essere inviate al Responsabile di Farmacovigilanza della Struttura di appartenenza dell'Operatore stesso.

Annex 5 ENCePP checklist for study protocol

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

Study reference number:
EUPAS11081

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]				17
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)				
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.				17
	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

The study will cover 3 years starting from effective implementation of minimization measures

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?				12, 20
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12, 21
2.1.4 Which hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	

Comments:

This is a drug utilization study focused on potential off-label use; therefore, formal hypothesis testing is not applicable.

Section 3: Study design	**Yes** ☐	**No** ☐	**N/A** ☒	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	21, 22
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	21
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	42

Comments:

This is a cross-sectional drug utilisation study; therefore, no endpoint will be measured. Also, as a descriptive cross-sectional study, we will not measure any effects.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	21, 22
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	22
4.2.2 Age and sex?	☒	☐	☐	22

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin? 4.2.4 Disease/indication? 4.2.5 Duration of follow-up?	☒	☐	☐	21 22
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒ ☒ ☐	☐ ☐ ☐	☐ ☐ ☒	22

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	23
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows?	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

This is a cross-sectional drug utilisation study. Users of systemic TCC will be described at the time of TCC prescription; therefore, 5.3 to 5.4 are not applicable.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	38
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	38
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	38
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	22, 29-31
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates?	☒	☐	☐	22, 29-31
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	22, 26-31
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	24, 26-31
9.3 Is a coding system described for:				

9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	25-28
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☒	☐	☐	25-28

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Endpoint do not apply

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☐	☐	☒	
10.2 Are descriptive analyses included?	☒	☐	☐	36-39
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	36-39
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	32

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	34, 37
11.2 Are methods of quality assurance described?	☒	☐	☐	37
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?				
12.1.2 Information bias?				38-39
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☒	

12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a	☒	☐	☐	33

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	40
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	40

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	15-16

Comments:

Deviation is not applicable in this protocol.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	43
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	43

Comments:

Name of the main author of the _____

Date: 02 / March /2017

Signature:

Annex 6 Bibliography

Drug Saf (2013) 36:13–23

DOI 10.1007/s40264-012-0002-x

SHORT COMMUNICATION

A Reference Standard for Evaluation of Methods for Drug Safety Signal Detection Using Electronic Healthcare Record Databases

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Published online: 23 November 2012

Abstract

Background The growing interest in using electronic healthcare record (EHR) databases for drug safety surveillance has spurred development of new methodologies for signal detection. Although several drugs have been withdrawn postmarketing by regulatory authorities after scientific evaluation of harms and benefits, there is no definitive list of confirmed signals (i.e. list of all known adverse reactions and which drugs can cause them). As there is no true gold standard, prospective evaluation of signal detection methods remains a challenge.

Objective Within the context of methods development and evaluation in the EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge), we propose a surrogate reference standard of drug-adverse event associations based on existing scientific literature and expert opinion.

Methods The reference standard was constructed for ten top-ranked events judged as important in pharmacovigi- lance. A stepwise approach was employed to identify which, among a list of drug-event associations, are well recognized (known positive associations) or highly unlikely ('negative controls') based on MEDLINE-indexed publications, drug product labels, spontaneous reports

On behalf of the EU-ADR Consortium.

Electronic supplementary material The online version of thisarticle (doi:10.1007/s40264-012-0002-x) contains supplementarymaterial, which is available to authorized users.

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made to the WHO's pharmacovigilance database, and expert opinion. Only drugs with adequate exposure in the

EU-ADR database network (comprising &60 million person-years of healthcare data) to allow detection of an association were considered. Manual verification of positive associations and negative controls was independently performed by two experts proficient in clinical medicine, pharmacoepidemiology and pharmacovigilance. A third expert adjudicated equivocal cases and arbitrated any disagreement between evaluators.

Results Overall, 94 drug-event associations comprised the reference standard, which included 44 positive associations and 50 negative controls for the ten events of interest: bullous eruptions; acute renal failure; anaphylactic shock; acute myocardial infarction; rhabdomyolysis; aplastic anaemia/pancytopenia; neutropenia/agranulocy- tosis; cardiac valve fibrosis; acute liver injury; and upper gastrointestinal bleeding. For cardiac valve fibrosis, there was no drug with adequate exposure in the database network that satisfied the criteria for a positive association.
Conclusion A strategy for the construction of a reference standard to evaluate signal detection methods that use EHR has been proposed. The resulting reference standard is by no means definitive, however, and should be seen as dynamic. As knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be re-evaluated.

1 Background

The growing interest in the utility of electronic healthcare records (EHRs) for drug safety surveillance has spurred the development of new methodologies for quantitative and automated signal detection. Timely detection of safety signals remains a challenge because no single technique ensures identification of *all* drug-related adverse events, whether signal detection is done using spontaneous reports [1] or using healthcare records [2]. Generation of false alarms similarly constitutes a public health hazard, not only overwhelming regulatory agencies and diverting already scarce resources, but also triggering unwarranted warnings or even drug market withdrawals [3]. Thus, proper evaluation of signal detection methodologies calls for the creation of a reference standard, the purpose of which is to better define the predictive value of these new techniques, as well as their added value to the current pharmacovigi- lance armamentarium.

2 Signal Detection in the Context of Pharmacovigilance

The WHO has defined ‘signal’ as ‘‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely

documented'' [4]. An updated and more encompassing definition has been proposed recently based on a systematic review of how the term is being applied in current pharmacovigilance: a signal represents information that arises from one or multiple sources which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, and is judged to be of sufficient likelihood to justify verificatory and remedial actions [5]. Although a 'gold standard' of confirmed signals, i.e. *causal* drug-adverse event associations, does not exist, a reference standard of recognized associations based on existing published scientific literature, regulatory actions (e.g. labelling changes or withdrawal of marketing authorization), as well as expert opinion, may serve as a suitable surrogate. In this study we describe a reference standard that was put together in the context of methods development within the EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge'; http://www.euadr-project.org), which aims to exploit information from various EHR databases in Europe to produce a computerized integrated system for the early detection of drug safety signals [6]. This reference standard was developed for the primary purpose of evaluating performance of methods for signal detection using EHR.

3 Methodology

The EU-ADR network currently comprises anonymous healthcare data from eight established European databases located in four countries (Denmark, Italy, The Netherlands and the UK) [7]. Clinical and drug dispensing/prescription data used for this paper represent data from 19,647,445 individuals with 59,929,690 person-years (PYs) of follow-up.

4 Adverse Events

In the EU-ADR Project we have chosen an event-based approach to active drug safety surveillance, focusing on events considered to be important from a pharmacovigilance and public health perspective. For the construction of this reference standard, we considered the following top ten events which have been selected from a list of 23 events ranked on the basis of importance in pharmacovigilance using predefined criteria: (i) bullous eruptions; (ii) acute renal failure; (iii) anaphylactic shock; (iv) acute myocardial infarction; (v) rhabdomyolysis; (vi) aplastic anaemia/pancytopenia; (vii) neutropenia/agranulocytosis; (viii) cardiac valve fibrosis; (ix) acute liver injury; and (x) upper gastrointestinal bleeding [8].

5 Drug Selection

The procedure employed in the construction of the reference standard is outlined in Fig. 1. It was first necessary to ensure that the drug-event associations to be included in the reference standard are identifiable in clinical practice and could be investigated in the EU-ADR network. That is, there should be adequate exposure to the drugs to permit detection of an association with the adverse event of interest, if present. In another publication we described the sample size calculations used to derive the total amount of PYs of drug exposure required to detect an association between a drug and a particular event over varying magnitudes of relative risk (RR), using one-sided significance level $\alpha = 0.05$ and power of 80 %, given pooled population-based incidence rates (IR) estimated directly within the EU-ADR network [2]. For this reference standard we employed in the calculations an RR of at least two for all events except for rhabdomyolysis, bullous eruptions and anaphylactic shock, where we used an RR of at least 4. The latter was done to account for the very low background IR of these events in the population (2.5/100,000 PYs for rhabdomyolysis, 5.7/100,000 PYs for anaphylactic shock and 5.9/100,000 PYs for bullous eruptions). A series of steps was subsequently employed to select the positive drug-event associations and 'negative controls' among those potentially eligible (i.e. drugs with an adequate amount of exposure to detect the association of interest) [see Fig. 1].

6 Information Retrieval from Published Literature

To streamline the scientific literature search, we utilized a tool developed within the EU-ADR Project that automatically searches MEDLINE-indexed publications concerning adverse drug reactions (ADRs) [9]. A subset of MEDLINE was downloaded (via PubMed) and imported into a database including all the citations from December 1952 to February 2010 with the 'adverse effects' Medical Subject Heading (MeSH) subheading. For each citation, the PubMed identification (PMID), MeSH descriptors, major/ minor subheadings, substances, date of creation of the citation, as well as publication type, were obtained. Co- occurrence of the drug (from 'substances' OR 'MeSH heading' fields) and the event (under the subheading 'adverse effects') in a citation were noted. Drug codes in the WHO Anatomical Therapeutic Chemical (ATC) clas- sification were first mapped to MeSH headings or supple- mentary concept records using standardized concept unique identifiers from the Unified Medical Language System (UMLS) [10]. Drugs from the 'substances' field were taken into account only if their pharmacological action was qualified by the subheading 'adverse effects'.

Taking the pharmacological action as an additional element for consideration was an attempt to establish a link between the adverse event of interest and the drug in the context of drug safety and not just a co-occurrence in a MEDLINE citation. This becomes particularly important when more than one drug is mentioned in the citation [10].

7 Selection of Known Positive Drug-Event Associations

The drug-event associations were ranked according to the number of MEDLINE citations with co-occurrence of the drug and the adverse event of interest. For the pool of positive drug-event associations, we considered those with the highest number of citations. This meant that more published evidence was available on these associations. Citations may refer to case reports, observational studies, clinical trials, reviews or meta-analyses. The type of publication was taken into account in the evaluation of the evidence regarding each drug-adverse event association, as subsequently described. Supplementary information was obtained from the Summary of Product Characteristics or product labels [11–16]. The aim was to select five drugs that are positively associated with each event of interest. Whenever possible, drugs belonging to different classes were included in the pool. However, the need for minimizing ambiguity (i.e. by selecting strong and well substantiated drug-adverse event associations) took precedence over the need for diversity in terms of drug class. Except for fixed-dose combinations, drug preparations with more than one active substance were excluded from the pool.

8 Selection of 'Negative Controls'

A drug-event association was considered for the pool of 'negative controls' if there were no MEDLINE citations with co-occurrence of the drug and the event of interest and if there was no explicit mention of such adverse event in the drug product label. The pool of 'negative controls' was further evaluated using the WHO spontaneous reporting database (VigiBase™) to exclude associations flagged as a potential signal using standard data mining methodology. The list of potential signals from VigiBase™ (including data up to the fourth quarter of 2010) was generated using the Oracle Health Sciences Empirica™ Signal tool (courtesy of Astellas Pharmaceuticals, Deerfield, IL, USA). Bayesian disproportionality analysis was performed using preferred terms mapped to the events of interest [17]. A value greater than 2 for the lower bound of the 90 % confidence interval (CI) of the Empirical Bayes Geometric Mean (EB_{05}) and the presence of at least one report were used as the criteria for flagging a signal [18]. The aim was to likewise obtain five drug-event associations as 'negative controls' per event of interest.

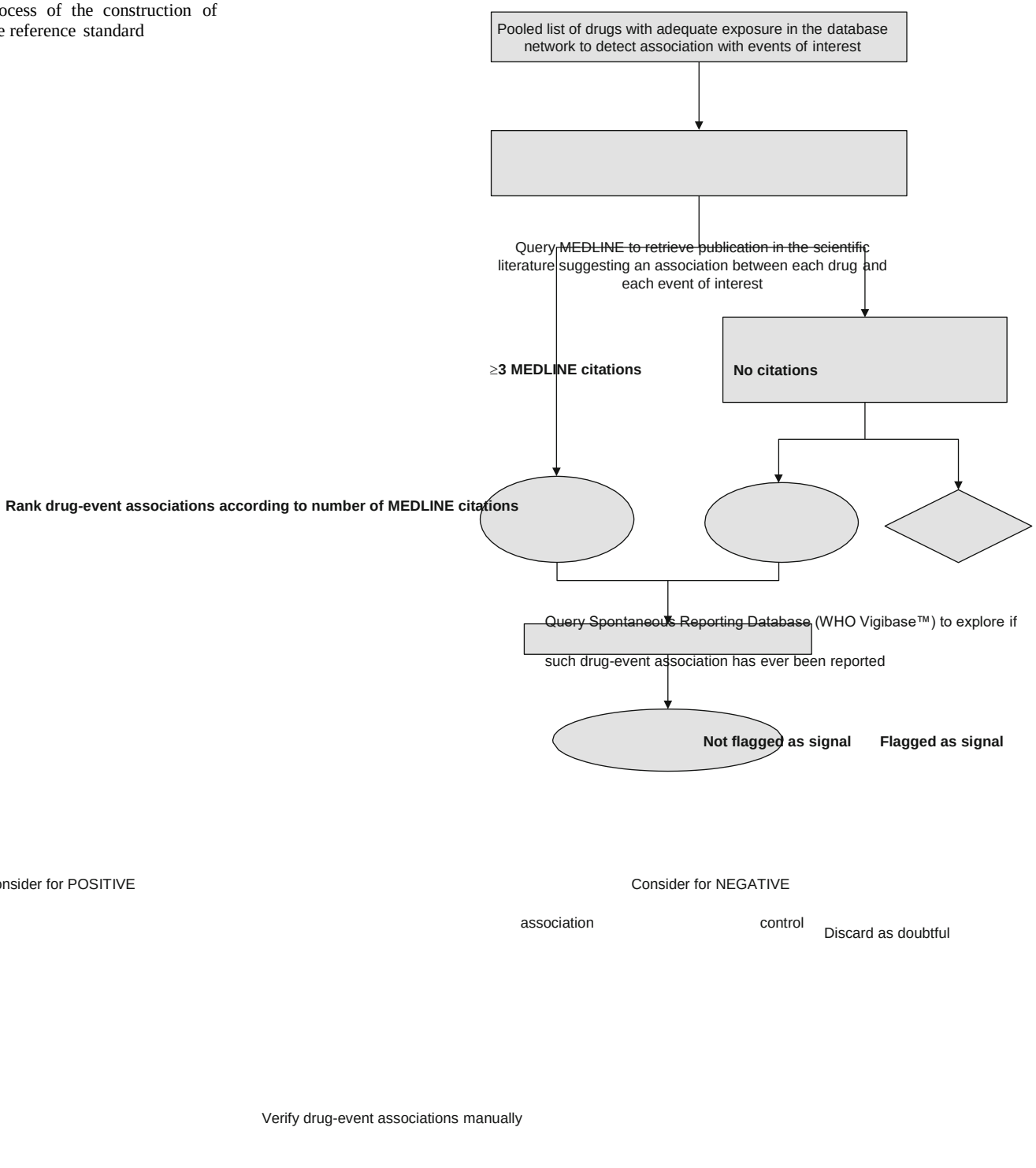

Fig. 1 Flowchart showing the process of the construction of the reference standard

9 Evaluation of the Evidence from Literature

Table 1 shows the scheme that was used as a guide to evaluate evidence from the literature. Manual verification of the positive associations and 'negative controls' was conducted by two physicians with proficiency in clinical medicine, epidemiology and pharmacovigilance. A third expert arbitrated any disagreement between evaluators. The following indices of agreement between evaluators were assessed:

(i) proportion of overall agreement; (ii) proportion of specific agreement; and (iii) kappa statistic, κ, for chance-corrected agreement. The earliest date of MEDLINE citation was also noted for each drug-event association.

10 Results

The amount of drug exposure required to detect a potential signal in the EU-ADR database network for each of the events of interest is shown in Table 2. Overall, there were 893 drugs (i.e. unique ATC codes, 5th level chemical substance) with enough exposure to permit detection of an association with at least one of the ten events of interest. Out of the 893 drugs, the following are the number (i.e. count) of drugs for which there were at least three MEDLINE citations with co-occurrence of the drug and the corresponding event: acute liver injury, 21; acute myocardial infarction, 52; acute renal failure, 51; anaphylactic shock, 26; bullous eruptions, 47; cardiac valve fibrosis, 2; neutropenia/agranulocytosis, 30; aplastic anaemia/pancytopenia, 21; rhabdomyolysis, 8; upper gastrointestinal bleeding, 54. Close to 1,200 abstracts and, when necessary, the full-text journal articles pertaining to all ten events were reviewed to arrive at a shortlist of potential positive associations and 'negative controls'. Specific citations in drug product labels concerning 'undesirable effects', 'warnings', and 'adverse reactions' were used to further restrict the shortlist of associations. Table 3 shows how the manual evaluation of a positive association for acute liver injury with valproic acid and for upper gastrointestinal bleeding with indometacin were done. The complete evaluation for all the positive drug-adverse event associations of interest can be found in Appendix 1 (Online Resource 1).

Table 1 Levels of evidence used in the evaluation of drug safety information from the literature

Level of evidence	Description
I	Evidence from at least one (properly designed) randomized controlled trial or meta-analysis
II	Evidence from at least one observational study (e.g. cohort, case-control, case-crossover, self-controlled case series) OR from at least three published case reports from different sources and concerning different patients
III	Evidence from not more than two published case reports OR from unpublished reports in pharmacovigilance databases and no further substantiation in the literature
IV	Included in drug label (SPC) but no case reports or published studies
V	No evidence from published literature or from WHO spontaneous reporting database and not mentioned in the SPC

Recommendations: Levels I and II ? positive association; Levels III and IV ? cannot be determined ? disregard as doubtful; Level V ? 'negative control'

SPC summary of product characteristics

Table 2 Amount of drug exposure required to detect a potential signal in the EU-ADR database network for the events of interest

Event	Required exposure (person-years)	No. of drugs with sufficient exposure to detect association and with MEDLINE citations
Acute liver injury	32,769	21
Acute myocardial infarction	4,706	52
Acute renal failure	30,397	51
Anaphylactic shock	21,733	26
Bullous eruptions	20,823	47
Cardiac valve fibrosis	13,604	2
Neutropenia/agranulocytosis	82,697	30
Aplastic anaemia/ pancytopenia	77,192	21
Rhabdomyolysis	49,593	8
Upper gastrointestinal bleeding	12,028	54

Only four drugs having sufficient exposure in the database network satisfied the criteria for a positive association with

rhabdomyolysis, all of them being HMG-CoA reductase inhibitors (statins). Fibrates, as a class (ATC 4th level, chemical subgroup), comprised enough exposure to detect an association with rhabdomyolysis, but the individual drugs did not. For cardiac valve fibrosis, no drug with adequate exposure met the criteria for a positive associa- tion after review of the literature.

11 Inter-Evaluator Agreement

The indices for agreement were computed across all drug-event pairs evaluated (179 drug-event pairs), including those that eventually did not get included in the final reference standard. The proportion of overall agreement (the proportion of cases for which both evaluators agreed across all evaluation categories) was 0.93 (95 % CI 0.89, 0.97). The proportions of specific agreement were as follows: (i) 'positive' agreement 0.96 (95 % CI 0.93, 0.98); and (ii) 'negative' agreement 0.90 (95 % CI 0.89, 0.90). There were three instances where one evaluator considered a drug-event association 'undetermined' while the other considered it a positive association (paracetamol [acetaminophen]-anaphylactic shock, bromocriptine-acute myocardial infarction and aspirin [acetylsalicylic acid]-bullous eruptions). Of these three instances only one was eventually included in the reference standard after arbitration (paracetamol-anaphylactic shock). There was a single case where one evaluator marked the association 'undetermined' while the other marked it as 'negative control' (prednisone-neutropenia/agranulocytosis). Arbitration was done by a third expert. There was no disagreement between evaluators in the final list of 'negative control' associations. The chance-corrected agreement kappa coefficient, κ, was 0.83 (unweighted, 95 % CI 0.74, 0.92).

The final reference standard consisted of 94 drug-event associations, which included 44 positive associations and 50 'negative controls' related to the ten events of interest. Table 4 lists the positive associations, including the corresponding level of evidence. The majority of positive associations were based on Level II evidence. The associations for which there was Level I evidence included that of NSAIDs and of heparin with upper gastrointestinal bleeding, the association of the statins with rhabdomyolysis, and the association of coxibs and rosiglitazone with acute myocardial infarction. All 'negative controls', by definition, have Level V evidence and are listed in Table 5. Both positive and 'negative control' associations comprised 68 unique drugs (i.e. ATC 5th level) belonging to 42 different pharmacological subgroups (i.e. ATC 3rd level).

Table 3 Example summary of manual evaluation of positive drug-event associations for valproic acid and indometacin

ATC code	Drug name	Event type	No. of MEDLINE notices	Labelled as AE in SPC [Yes/No]? (Source and label section)
N03AG01	Valproic acid	Acute liver injury	*Total no. of citations = 31* Review[a] = 1 Clinical trial = 1 (RCT) Epidemiological study = 1 (cohort study) Case reports[b] = 28 (1 citation involving 3 cases, 1 citation involving 5 cases, 1 citation reviewing 31 cases, 2 other citations with literature review)	Yes DailyMed[c] (boxed warning, adverse reactions) eMC[d] (special warnings and precautions for use, undesirable effects) Micromedex[e] (adverse reactions)
M01AB01	Indometacin	Upper gastrointestinal bleeding	*Total no. of citations = 45* Review = 13 Clinical trial = 16 (9 RCTs) Epidemiological study = 5 (1 case control and 4 cohort studies) Case reports = 11	Yes eMC[d] (undesirable effects) Micromedex (adverse reactions)

AE adverse event, *ATC* Anatomical Therapeutic Chemical, *eMC* electronic medicines compendium, *RCT* randomized controlled trial, *SPC* summary of product characteristics

[a] Review refers to both systematic and narrative reviews

[b] Case reports involve only one case pertinent to the drug of interest, unless specified

[c] Website for drugs currently marketed and approved by the US FDA (http://dailymed.nlm.nih.gov/)

[d] For drugs licensed in the UK (http://www.medicines.org.uk)

[e] The Micromedex family of international databases provides full-text drug and substance information (http://www.thomsonhc.com/micromedex2/)

Table 4 Positive drug-event associations

Event	Positive associations		
ATC code		Name	Level of evidence
Acute liver injury	N03AF01	Carbamazepine	II
N03AG01		Valproic acid	II
M01AX17		Nimesulide	II
J01CR02		Amoxicillin and clavulanic acid	II
A07EC01		Sulfasalazine	II
Acute myocardial infarction	M01AH02	Rofecoxib	I
A10BG02		Rosiglitazone	I
G03AA07		Levonorgestrel and estrogen	II
N02CC01		Sumatriptan	II
M01AH03		Valdecoxib	I
Acute renal failure	C09AA01	Captopril	II
M01AE01		Ibuprofen	II
N02BE01		Paracetamol (acetaminophen)	II
J01MA02		Ciprofloxacin	II
N05AN01		Lithium	II
Anaphylactic shock	B01AC06	Aspirin (acetylsalicylic acid)	II
N02BE01		Paracetamol (acetaminophen)	II
J01CA04		Amoxicillin	II
J01MA02		Ciprofloxacin	II
M01AB05		Diclofenac	II
Bullous eruptions	N03AF01	Carbamazepine	II

ATC Anatomical Therapeutic Chemical

J01EE01		Sulfamethoxazole and trimethoprim	II
N03AX09		Lamotrigine	II
M04AA01		Allopurinol	II
C03CA01		Furosemide	II
Cardiac valve fibrosis	No drug with sufficient exposure that satisfies criteria for True		Positive
Neutropenia/agranulocytosis	H03BB02	Thiamazole	II
B01AC05		Ticlopidine	II
C09AA01		Captopril	II
N03AF01		Carbamazepine	II
N03AG01		Valproic acid	II
Aplastic anaemia/pancytopenia	B01AC05	Ticlopidine	II
N03AF01		Carbamazepine	II
H03BB02		Thiamazole	II
M04AA01		Allopurinol	II
C09AA01		Captopril	II
Rhabdomyolysis	C10AA07	Rosuvastatin	I
C10AA05		Atorvastatin	I
C10AA03		Pravastatin	I
C10AA01		Simvastatin	I
Upper gastrointestinal bleeding	N02BA01/B01AC06	Aspirin	I
M01AB01		Indometacin	I
B01AB01		Heparin	I
H02AB06		Prednisolone	II
M01AE01		Ibuprofen	I

ATC Anatomical Therapeutic Chemical

Event	ATC code	Name
Acute liver injury	R03AC13	Formoterol
	S01ED05	Carteolol
	G04CA03	Terazosin
	N04BA02	Levodopa and decarboxylase inhibitor
	C01DA02	Glyceryl trinitrate
Acute myocardial infarction	A10AD01	Insulin (human)
	B03AA07	Ferrous sulfate
	J01CR02	Amoxicillin and clavulanic acid
	J05AB11	Valaciclovir
	C10AB04	Gemfibrozil
Acute renal failure	R01AD09	Mometasone
	H03AA01	Levothyroxine sodium
	R06AX26	Fexofenadine
	N04BA02	Levodopa and decarboxylase inhibitor
	B03AA07	Ferrous sulfate
Anaphylactic shock	N06AX11	Mirtazapine
	H03AA01	Levothyroxine sodium
	C02AC01	Clonidine
	C02CA04	Doxazosin
	N05BA04	Oxazepam
Bullous eruptions	C01BC03	Propafenone
	C07AB03	Atenolol
	R03BB01	Ipratropium bromide
	R03BB04	Tiotropium bromide
	C08CA02	Felodipine
Cardiac valve fibrosis	N06AB08	Fluvoxamine
	L04AX03	Methotrexate
	C09CA04	Irbesartan
	C03CA01	Furosemide
	G03CA03	Estradiol
Neutropenia/agranulocytosis	C07AA07	Sotalol
	H03AA01	Levothyroxine sodium
	C10AA05	Atorvastatin
	C01DA14	Isosorbide mononitrate
	G04CA02	Tamsulosin
Aplastic anaemia/pancytopenia	C09CA04	Irbesartan
	C10AA04	Fluvastatin
	S01EE01	Latanoprost
	S01ED01	Timolol
	R06AX27	Desloratadine
Rhabdomyolysis	G03CA03	Estradiol
	C02CA04	Doxazosin
	A10BB12	Glimepiride
	S01ED01	Timolol
	C01DA02	Glyceryl trinitrate
Upper gastrointestinal bleeding	R06AX26	Fexofenadine
	C10AA01	Simvastatin
	S01EC03	Dorzolamide

ATC Anatomical Therapeutic Chemical

L02AE03	Goserelin
N05CF01	Zopiclone

ATC Anatomical Therapeutic Chemical

12 Discussion

In this study we present a novel approach to identify a surrogate 'gold standard' for drug safety signal detection using a systematic and rigorous methodology, applied across various data sources and which could be extended to examine other drug-event associations. We put together a list of drug-adverse event associations known to be true and drug-event associations considered to be unlikely based on current published scientific literature, drug product labels, spontaneous ADR reports and expert opinion. Although the rationale for creating this reference standard is to have one single index against which signal detection methods (as applied to EHR data) can be tested, this reference standard can be re-evaluated and adapted to different settings as needed.

In evaluating the evidence from the literature we only considered associations that were reported with use of the drug in therapeutic doses, which is consistent with the definition of an ADR [19]. For aspirin, citations referring to both cardiovascular prophylactic (low dose) and analgesic doses were considered. We considered, aside from case reports that described the clinical characteristics leading to suspicion of an ADR, publications that proposed (or elucidated) biological mechanisms for the associations. Such publications came in the form of both narrative reviews and systematic reviews. We likewise considered associations that were described in the context of drug-drug interactions (e.g. aplastic anaemia resulting from the synergistic interaction between azathioprine and allopurinol) [20]. For the event acute renal failure, we disregarded associations that arose from rhabdomyolysis leading to renal failure, but considered the reverse situation (i.e. associations for rhabdomyolysis that resulted in renal failure). While randomized controlled trials (RCTS) and meta-analyses are considered supreme with respect to level of evidence, this is more true for evidence regarding efficacy, not so much safety, of interventions [21–24]. This is apparent in Table 4, where most of the evidence pertaining to the positive associations came from observational studies and case reports (or reviews). The associations with Level I evidence are those that are well known (e.g. association of the NSAIDs and heparin with upper gastrointestinal bleeding) or well investigated, either because of contro- versy or public health impact (e.g. the association of the statins with rhabdomyolysis, and the association of coxibs and rosiglitazone with acute myocardial infarction). Interestingly, but perhaps not surprisingly, the most widely-investigated association was that between aspirin and upper gastrointestinal bleeding (259 MEDLINE citations overall, see Appendix [Online Resource 1]). Most of the publications related to this association, including clinical trials, described the drug as a comparator to other drugs that are presumed (and proven) to confer a lower risk of the event. There have been previous attempts to develop a reference standard with which data mining methods for safety signal detection can be evaluated, 'rules of evidence' being devised ad hoc [25–27]. In the creation of this reference standard we employed a systematic approach incorporating various sources of drug safety information, the process designed to be transparent and reproducible, thus also making it easier to update. Different sources have varying comprehensiveness and accuracy with regards to documenting drug-adverse event associations. Because RCTs may be restricted to specific populations and lack statistical power to detect rare events, they must be supplemented by non-experimental studies and other types of evidence, including case reports [21–24]. Rare or idiosyncratic events (e.g. bullous eruption such as Stevens-Johnson syndrome) and events occurring after chronic exposure (e.g. cardiac valvulopathy) are unlikely to be identified in clinical trials, but rather in case reports or observational studies.

There was only one disagreement between evaluators in the final list of positive associations ('undetermined' vs 'positive' for the association paracetamol-anaphylactic shock; arbitration resulted in positive association). There was no disagreement between evaluators in the final list of 'negative control' associations. Although this high overall agreement between evaluators indicates that the resulting reference standard fulfills the pre-determined criteria, as the definitions of positive associations and 'negative con- trols' are based on existing knowledge at the time of this review, these associations (especially the 'negative controls') may be refuted as new data come along [28]. Hence, this reference standard should be considered dynamic and will need periodic re-evaluation. Adoption of this reference standard for use by other investigators can validate its applicability in other settings and will facilitate its further improvement.

While a reference standard, however rigorously constructed, may be able to permit evaluation and comparison of methods for signal detection, a method shown to successfully detect known drug-adverse events associations is not a guarantee that such method will also be able to detect signals, i.e. new, currently unknown drug-event associations (problem of contemporary comparison) [29].

13 Limitations

Since the selection of drugs for the reference standard was

dependent on the presence of adequate exposure to detect an association within the EU-ADR network (i.e. drugs that are more frequently used in the population were more

likely to be chosen), this reference standard may not be as useful for evaluation in situations where the drug use patterns are expected to be different. In particular, the EU-ADR database network is unable to capture information on drugs that are primarily used in hospitals or specialist centres (e.g. anti-cancer drugs), and for this reason such drugs have not been included in the reference standard. This criterion also precluded the inclusion of known associations with drugs that have been withdrawn from the market for a long time before the accrual of healthcare data in the databases. Because of this there was no drug that could be used as a positive reference for the event cardiac valve fibrosis; the use of the appetite suppressants fen- fluramine and phentermine, as well as the dopamine ago- nists pergolide and cabergoline, were inadequately documented or no longer captured in the databases because of the decline in use (or eradication in practice) of these drugs [30]. The choice as to which drug-event pairs can be considered for the positive associations was primarily established on the basis of the number of publications (i.e. number of MEDLINE citations with co-occurrence of the drug and the event of interest). This meant that drugs that have been on the market longer—or were involved in high-profile or controversial issues—had a higher chance of being included in the reference standard.

Finally, the availability of a surrogate 'gold standard' is only one component of the evaluation process for signal detection methodologies [3, 31]. Other issues that need to be considered in performance evaluation of these methods include standardization of event definitions, establishment of reliable and consistent criteria for adjudicating causality and expectedness of adverse events, as well as understanding variations in database content and quality.

14 Conclusions

A unique strategy for the construction of a reference standard to evaluate drug safety signal detection methodologies using EHR has been proposed. This reference standard should be considered dynamic, and as knowledge on drug safety evolves over time and new issues in drug safety arise, this reference standard can be periodically re-evaluated. Our proposed strategy represents a novel contribution to pharmacovigilance, with opportunities for adaptation to evaluate harms and benefits for other suspected ADRs.

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ages ranged from 0.83% to 2% respectively. All-cause healthcare Per Patient Per Year costs were approximately $13,200 in each database. **cOnclusiOns:** Creation of a database using a CDM approach allows for simultaneous examination of standardized claims across databases, thus broadening the efficiency and generalizability of retrospective claims analyses.The diverseness of comorbidities among HCV patients combined with the evolving treatment landscape makes it an ideal candidate for this type of research.

PRM45

big data in eMeRgenCy dePaRtMent CaRe deLiveRy: benefits of Radio fReQUenCy identifiCation

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Objectives: Lack of a coordinated primary care system is forcing individuals to seek emergency departments (EDs) as gateway into the health system. As volumes increase and cases become more complex, combined with inadequate downstream capacity lead to boarding, bottlenecks and wait times. The goal was to review benefits of Radio Frequency identification (RFID) demonstrated in the literature in the ED. **Meth0ds:** Article searches were conducted and they were categorized based on benefits in three areas: patients, staff, assets. **Results:** Evidence of use of RFID in ED went as far back as 2006 with both domestic and international applications mostly using active technology. Majority of the articles demonstrated reducing wait times in the ED. One of the articles in turn demonstrated impact on patient satisfaction. Reduction in wait times were demonstrated when admitting patients into ICU from the emergency setting. In case of staff, use of RFID demonstrated increased satisfaction in a pediatric emergency setting. Evidence also exists in better tracking of assets and equipment in the ED. Very little evidence of use of RFID in simulation and analytical models exist. Most of the studies were retrospective in nature. Wait times and asset tracking are tangible benefits with direct impact on return-on-investment. **cOnclusi0ns:** RFID has been used is various settings in healthcare and quality benefits have been demonstrated. Lesser evidence of RFID use in the ED exists. RFID benefits have primarily been demonstrated with regard to wait times and asset tracking and management. Patient and staff satisfaction are more intangible benefits. As EDs start to reap benefits with wait times, use in simulation and advanced analytical models could potentially inform workload, team configuration and team dynamics studies. As healthcare moves into the era of big data, live streaming RFID data can be tapped for real-time decision making.

PRM46

WHy PeeR-RevieW JoURnaLs ReJeCt ReaL-WoRLd and HeaLtH-eConoMiC PaPeRs

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Objectives: To evaluate the most common reasons provided by peer-reviewed journals to reject manuscripts describing data derived from real-world or health-economic (RW/HE) studies. **MethOds:** Our company project administration records from the last 10 years were reviewed for manuscripts describing HE studies, RW/observational studies (including retrospective database analyses), and patient or disease registries. Reasons for rejection were collected and stratified into "categories". If more than one reason was provided by the journal, then all reasons were counted. Our analysis was based on industry-sponsored manuscripts for which a complete submission history was available. **Results:** Rejection letters were collected for 78 manuscripts. Of these, 12 did not specify a reason for rejection. The remaining records revealed a total of 100 rejection counts. The most common reasons were 'priority rating not high enough' (33%), 'concerns about the methodology' (18%), and 'information not sufficiently novel' (15%). Other reasons for rejection included 'topic not appropriate for the journal' (7%), 'manuscript is biased/conclusions are too strong' (5%), 'industry involvement not sufficiently disclosed' (2%), and referral to a sister journal instead (2%). **cOnclusiOns:** These common reasons for rejection could provide authors with some guidance on which factors are particularly important to focus on during the development of a RW/HE manuscript to help improve the chances of acceptance by peer-reviewed journals.

PRM47

UtiLizing eLeCtRoniC MediCaL ReCoRd netWoRks foR identifying Patients foR CLiniCaL tRiaL ReCRUitMent

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Objectives: Much of the increase in health-care expenses in the U.S. can be traced to the development of new drug therapies; with the average discovery and development process costing over $1.4 billion per drug. This motivates the need to reduce drug costs through more efficient drug development and testing, specifically, by streamlining clinical trials. The current study aims to implement and evaluate a process, using a data driven approach, to recruit patients for a clinical trial for an asthma treatment. Our hypothesis is that recruitment could be improved and accelerated with the support of an EMR network to identify once candidates were identified, all recruitment efforts could be directly targeted to specific patients as opposed to advertising to a large, undefined population or relying on physician referral. This resulted in improved patient response rates, which could conceivably be improved further with the creation of more targeted recruitment materials developed by patient demographic profiles generated from EMR data.

PRM48

CoMPaRative LandsCaPe assessMent of Us HeaLtHCaRe databases foR Use in HeaLtH eConoMiCs ModeLing

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Objectives: Real world evidence (RWE)-based tools are important to fill data gaps and capture real world cost and treatment patterns in economic modeling. The objective of this study was to assess the capabilities of US-based longitudinal, retrospective data assets to inform health economic models in diabetes and oncology. **Meth0ds:** To illustrate the availability of RWE data for modeling, several IMS data assets were compared in a landscape assessment, including Pharmetrics Plus (PMTX+), Oncology Electronic Medical Record (EMR), Ambulatory EMR, Charge Data Master (CDM), Pharmacy (LRx), Office Based Medical Claims Data (Dx), and Laboratory Data (Labs). Diabetes and oncology were chosen to illustrate the range of needed inputs across commonly modeled diseases. Data availability was assessed in a matrix framework across core categories of model inputs including: treatment patterns, epidemiology, adverse events (AEs), patient health metrics (i.e., BMI), costs, resource use, and disease status. **Results:** For oncology, inputs for treatment patterns (PMTX+, Oncology EMR), epidemiology (PMTX+, Oncology EMR, CDM), AEs (PMTX+, Oncology EMR, CDM), and resource use (PMTX+, Oncology EMR) are available in several data assets but information on patient health metrics and disease status may require leveraging the Oncology EMR database to capture sufficient detail. For diabetes, availability of data for populating models is more robust increasing information on treatment patterns (PMTX+, LRx linked to Dx), epidemiology (PMTX+, Ambulatory EMR, CDM), resource use (PMTX+, Labs, Dx), AEs (PMTX+, Ambulatory EMR, CDM, Dx), and patient health metrics (Ambulatory EMR, CDM). While several databases report cost outcomes, the most relevant costs for modeling are found in PMTX+. **cOnclusiOns:** Core concepts for economic modeling can be populated with RWE assets in the US though no single database is likely to cover all inputs. The choice of data should be informed by the research question, patient counts and the ability to link databases.

PRM49

vaLidity and LiMitations of tHe LongitUdinaL Patient

database fRanCe foR Use in PHaRMaCoePideMioLogiCaL and

PHaRMaCoeConoMiCs stUdies

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Objectives: Longitudinal Patients Database (LPD) is a primary care database of anonymized electronic medical records (EMR) from about 4 % of the French population. Diagnosis and prescription data are routinely collected from proprietary practice management software used by physicians (primary care and specialists) to maintain EMR of their patients. Although LPD has been extensively validated by numerous publications and its use by French National Health Authorities, this is the first time that its representativeness and validity is systematically examined. **MethOds:** The distribution of several variables were analyzed and compared to available literature. Part of these variables refers to physician's practices participating to the database while others refer to patients in these practices. Data about prevalence, treatments, and patients profile were retrieved from published French Health Authorities studies based on LPD data and compared to other published sources. **ResuLts:** The sampling methods for the physician's selection practices were shown to provide a good representativeness of the physician panel. Analyze of the patients population showed that LPD included all the subsets of the French general population, although pediatrics were underrepresented. Prevalences of several illnesses (diabetes, asthma, atrial fibrillation, aortic aneurism), treatments (dyslipidemia, diabetes), patients' profiles (dyslipidemia, atrial fibrillation, venous disease) were in agreement to those encountered in literature. However, smoking status, hospitalizations, referral to specialists were only partially reported and no information was available about sociodemographic status or death of patients. The availability of missing information through the use of questionnaires/pop up screens for physicians and patients, and the linkage of the EMR database to a claims database (HEAD) is also documented. **cOnclusiOns:** We found no indications of lack of representativeness or validity of the LPD. While presenting some flaws associated with its naturalistic nature, LPD is a good support for pharmacoepidemiological and pharmacoeconomics studies.

PRM50

LaCk of adHeRenCe to iMMUnosUPPRessive tReatMent in kidney tRansPLant Patients: CoMPUteR assisted QUaLitative data anaLysis (CaQdas) of an exPeRt PaneL

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Objectives: To investigate the risk of Chronic Humoral Rejection (CHR) due to Lack of Adherence to Immunosuppressive Treatment (LAIT) in Kidney Transplant (KT) patients using Computer Assisted Qualitative Data Analysis (CAQDAS). **MethOds:** A systematic literature review was conducted using Medline, Psycinfo and BVS to identify studies published between 2009 and 2013 on CHR due to LAIT in KT patients. Based on this review a questionnaire was developed focussing on the information gaps identified. Six physicians from major Spanish Transplant centres then com-

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Original Full Length Article

Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care

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abstract

Purpose: To assess the gender and age-related 5-year incidence rates of osteoporotic fractures, and their related predictors, in a primary care setting.

Methods: We obtained information from the Health Search-CSD Longitudinal Patients Database (HSD).

This is an Italian General Practice data repository which comprises information given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs).

We selected all patients aged 50 to 85 years, who were actively included into the PCP's list at the beginning of the enrolment period (1st January 2002–31st December 2003). We excluded individuals who were registered in the PCPs' list for less than 1 year before the entry date (Index date) into the cohort, as well as those who were diagnosed with Paget disease or malignant neoplasm. Participants were followed up until the occurrence of osteoporotic fracture, one of the exclusion criteria, or the end of the study period.

Results: The 5-year rates (per 1000 person-years) of any osteoporotic fracture were 11.56 (95% C.I. 11.33 to 11.77) among females, and 4.91 (95% C.I. 4.75 to 5.07) among males. For hip fractures, the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) among females and 1.21 (95% C.I. 1.12 to 1.28) among males, respectively. Advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMI$\leq$20, presence of osteoporosis, gastrointestinal and chronic hepatic disease, depression, chronic obstructive pulmonary disease, use of anticonvulsants and a higher number of co-medications, increased the risk of any osteoporotic fractures.

Conclusions: The use of primary care data confirms a higher incidence of osteoporotic fractures among females vs. males as well as in older individuals. Predictors of osteoporotic fractures were consistent with FRAX® algorithm. Given the clinical utility of a simple score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool.

Introduction

Osteoporosis is a systemic condition characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and, consequently, an increased risk of fracture. Osteoporotic fractures represent an increasing cause of morbidity in the older populations and a considerable burden to health services in many regions of the world [1–4].

Hence, there is the need to improve methods for accurate identification of individuals at high risk of fractures, who might benefit from a preventive or therapeutic intervention. Indeed, although Bone Mass Density (BMD) measurement at the femoral neck with Dual energy X-ray Absorptiometry (DXA) is a strong predictor of the osteoporotic fracture risk [5], there have been several issues associated with its use as a clinical diagnostic test, because of its relevant cost and low sensitivity [6]. Several fractures occur in women with normal BMD [7], and the evidence suggests that risk prediction algorithms that do not include BMD, seem to possess an equal effectiveness [8]. Along this line, less expensive and more practical methods for identifying those individuals at high risk of osteoporotic fractures is a healthcare requirement. These methods should ideally be based on models which have developed similar questions in diverse populations, which are representative of the specific healthcare setting.

Recently, computer-based algorithms (FRAX®) have been devel- oped (www.shef.ac.uk/FRAX®) under the auspices of the World Health Organization (WHO). This algorithm provides 10-year probabilities of hip fracture and other major osteoporotic fractures (i.e., spine and

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forearm). This prediction tool seems to possess a higher sensitivity to detect those at high risk of fracture [9], besides suggesting which intervention threshold should be developed [10]. However, a necessary prerequisite for the implementation of prediction score are data on the epidemiology of fragility fractures and the potential risk factors which underlie this risk. To this purpose, little is known on the general practice setting.

Furthermore, since the incidence of fracture and the prevalence of associated risk factors will change over time, the methods to derive the risk prediction algorithms need to be dynamic, so that they can be modeled over time. Longitudinal primary care databases have the advantage of having large and broadly representative populations with historical data, constantly updated and retrospectively traced to a decade in the majority of practices. In this context, they have been demonstrated to provide complete and reliable information aimed at developing and validating clinical risk score of fractures [11].

Thus, the aim of this study was to assess – in a primary care setting –

the 5-year gender and age specific absolute risk of osteoporotic fractures (hip, vertebral and others) taken as a whole, only those of hip, and the related predictors.

Methods

Data source

We obtained information from the Health Search-CSD Longitudinal Patients Database (HSD), an Italian General Practice (GP) database that comprises data given by computer-based patient records of a selected group of over 900 Primary Care Physicians (PCPs). PCPs voluntarily agreed to collect patient information and to attend specific training courses for data entry. The HSD contains patients' demographic details that are linked through the use of an encrypted code with clinical records (diagnoses, referrals, and tests results), drug prescriptions (drug name, date of the filled prescription, and number of days' supply), prevention records, hospital admissions, and the date of death. To be considered for participation in epidemiological studies, PCPs should meet "up-to-standard" quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, years of recording and the evaluation of missing values [12].

A number of studies have been published confirming the research validity of the HSD information in conducting epidemiological research [13–15].

When this study was initiated, 500 PCPs homogeneously distributed across all Italian areas, covering a patient population of 1,088,229 individuals, fitted the up-to-standard quality criteria.

Study cohort

We enrolled all patients who were actively included into the PCPs list at the beginning of the enrolment period (1st January 2002–31st December 2003). To be eligible patients had to be registered with one of the participating PCPs for at least 1 year before the entry (Index date) into the study cohort, and to be aged between 50 and85 years.

To estimate the osteoporotic-related fractures, we excluded patients who had been diagnosed with alternative causes of bone fragility, such as Paget disease (International Classification Disease, 9th revision, Clinical Modification-ICD9CM-code: 731.x) or malignant neoplasm (ICD9CM: 140–208.x), before the Index date. Subjects were followed up from the Index date until the occurrence of these events, whichever came first: osteoporotic fracture, diagnosis of tumor and/or Paget disease, death, PCP's change, and end of the study period.

According to data availability, participants' mean age (major than 60 years), and medical literature [4,16–18] patients were followed up to 5 years.

Outcomes

Osteoporotic fractures were ascertained through the physician's coded diagnosis [4,16,17,19] during follow-up and were defined as an incident event of hip (ICD9CM: 733.14, 820.x, 821.0 and 821.2), vertebral (733.13, 805.x) and other fractures such as humerus (733.11, 812.x), radius and ulna (733.12, 813.x), shinbone and fibula (733.16, 823.x), and pelvis (808.x).

Covariates

In our analysis we examined a series of explanatory variables. All of them are known to affect the risk of fracture [6,9,20] according to FRAX® score. They comprise history osteoporotic fractures, chronic use of corticosteroids (ATC H02* and at least 120 Defined Daily Dose (DDD) within one year before the Index date), rheumatoid arthritis (ICD9CM 714.x and 720.0 or at least two prescriptions of antirheumatic drugs [ATC M01C*, L04AA*, L01BA01] six months before the Index date), Body Mass Index (BMI) and current smoking.

We have also included additional features potentially associated with fracture risk, such as doctor-diagnosis of osteoporosis (733.0x), hypogonadism (257.2x), neurologic diseases (340.x, 335.2x, 356.x, 359.x, 271.x, 358.x and 740 through 759.x), organ transplant (V42.x), type 1 diabetes (250.x1 and 250x3), hyperthyroidism (242.0, 242.1,

242.8 and 242.9), gastrointestinal diseases (530.x through 534.x), chronic hepatic diseases (571.x), Chronic Pulmonary Obstructive Disease (COPD: 491.2x and 496.x), asthma (493.x) and depression (311.x, 296.2x and 296.3x) [2,11,18,21–26].

Finally, we have also included certain medications as covariates likely related to fracture risk: they comprised use of anticonvulsants (N03A*) and the number of distinct drugs being prescribed six months before the Index date.

Data analysis

On the basis of the study outcomes, we adopted two different cohorts.

In the first one, we also excluded patients with previous osteoporotic fractures before the Index date from the aforementioned "*Study cohort*". Herein, we provided age and sex-specific incidence rates of 5-year overall osteoporotic fractures, and solely those of hip, as cases per 1000 person-years.

In the second one, to investigate the possible risk factors, we maintained the overall "*Study cohort*".

The prevalence of any predictor and the demographic characteristics of the study cohort were then evaluated according to a descriptive analysis for man and women, separately. We used the chi-square test to evaluate the potentially significant differences in baseline characteristics between genders.

Multivariable Poisson regression models, adjusting for selected baseline factors, were constructed to derive continuous hazard functions. Separate models have been carried out for women and men. The outputs were the estimated 5-year risk of fractures combination (vertebral, hip and others) and only for hip fractures. Any covariate was selected according to statistical and/or clinical meaning as shown by univariate analysis and current medical literature, respectively. In particular, any feature apt to identify patient's chronic status at baseline was investigated. Hence, the final models retained age categories, history of fracture, BMI (b=20 vs. higher), rheumatoid arthritis, current smoking (as per FRAX® score), osteoporosis diagnosis, neurologic disease, hyperthyroidism, gastrointestinal and chronic hepatic disease, depression, asthma, COPD, number of co-medications and use of anticonvulsants. We performed a goodness-of-fit test to assess the appropriateness of the Poisson regression.

Statistical significance was defined as a 2-tailed value of $p \leq 0.05$. Estimates of incidence rate ratio, 95% Confidence Intervals (CIs), and

probability values were generated with STATA software, version 10.1 (STATA Corp, College Station, Tex).

Results

Characteristics of the study cohort

After applying the inclusion and exclusion criteria, 271,121 sub- jects (122,553 males and 148,568 females) entered the analysis.

Baseline demographic and clinical features of the study population are shown in Table 1. Significant differences have been observed between males and females with regard to several characteristics. Among females, a significantly higher prevalence of previous fractures was reported when compared with males (2.42% vs. 1.21%; p b 0.0001).

Consistently, females showed a higher prevalence for all other FRAX® items, except for current smoking (males: 6.62% vs. females: 3.86%; %; pb 0.0001).

Concerning the other potential risk factors, presence of osteoporosis, hyperthyroidism, depression, asthma, as well as the use of anticonvulsants showed a greater prevalence among females than males. No significant differences between males and females have been observed about the prevalence of neurologic disease and type 1 diabetes.

Incidence rates

The 5-year incidence rates (per 1000 person-years) of any osteoporotic fracture stratified by age group and gender are depicted in Fig. 1. Overall, we have found estimates ranging from 4.91 (95% C.I. 4.75 to 5.07) among males to 11.56 (95% C.I. 11.33 to 11.77) among females. Although the incidence appeared higher among women across all age groups, an increased gap has been observed from the age group 65–69 years and forward.

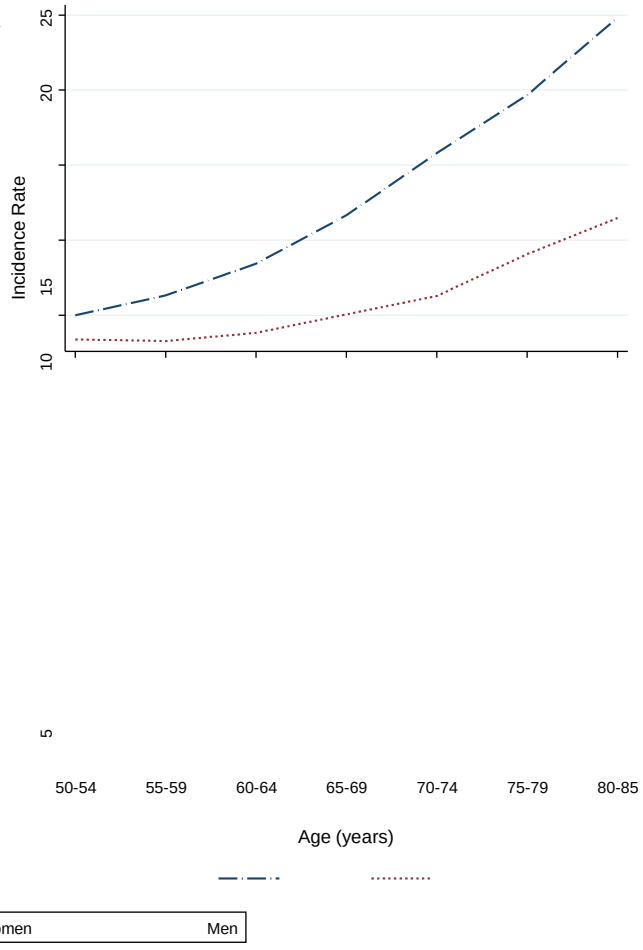

Fig. 1. Age and gender-specific 5-year incidence rates of any osteoporotic fracture (per 1000 person-years).

Concerning hip fractures (Fig. 2), the overall incidence rates were 3.23 (95% C.I. 3.11 to 3.34) and 1.21 (95% C.I. 1.12 to 1.28) among females and males, respectively. We have observed similar incidence up to 60 years between genders, whereas a sharp increase among older females was revealed until the age group 80–85.

Risk factors

The result of the multivariate Poisson regression analysis, in terms

Table 1

Baseline characteristics of the study cohort according to gender.

	Men	Women	P value		
	N = 122,553	N = 148,568			
Demographic characteristics					
Mean age (year)	63.4 (9.74)	65.2 (9.22)	b 0.0001	Age strata	b 0.0001

b=60	48,948 (39.94%)	50,482 (33.98%)	
65–69	39,727 (32.42%)	45,325 (30.51%)	
N=70	33,878 (27.64%)	52,761 (35.51%)	
FRAX® factors			
Fracture history	1489 (1.21%)	3592 (2.42%)	b 0.0001
Hip fracture	318 (0.26%)	951 (0.64%)	b0.0001
Vertebral fracture	429 (0.35%)	784 (0.53%)	b0.0001
Other fractures	772 (0.63%)	1965 (1.32%)	b0.0001
Use of corticosteroids	627 (0.51%)	936 (0.63%)	b0.0001
Rheumatoid arthritis	556 (0.45%)	1595 (1.07%)	b0.0001
BMI b=20[a]	483 (0.39%)	1770 (1.19%)	b0.0001
Current smoking	8115 (6.62%)	5739 (3.86%)	b0.0001
Osteoporotic diagnosis	1009 (0.82%)	17,382 (11.70%)	b0.0001
Hypogonadism	10 (0.01%)	0 (0%)	-
Neurologic disease	1176 (0.96%)	1455 (0.98%)	=0.601
Organ transplant	178 (0.15%)	101 (0.07%)	b0.0001
Type 1 diabetes	135 (0.11%)	153 (0.10%)	=0.568
Hyperthyroidism	377 (0.31%)	1344 (0.90%)	b0.0001
Gastrointestinal disease	9750 (7.96%)	10,087 (6.79%)	b0.0001
Chronic hepatic disease	3796 (3.10%)	3277 (2.21%)	b0.0001
Depression	2225 (1.82%)	6160 (4.15%)	b0.0001
Asthma	2268 (1.85%)	4177 (2.81%)	b0.0001
COPD	6457 (5.27%)	3785 (2.55%)	b0.0001
Pharmacotherapy			
Anticonvulsants	1608 (1.31%)	2108 (1.42%)	=0.017
Number of concurrent medications			b0.0001
0	47,670 (38.90%)	46,804 (31.50%)	
1	36,800 (30.03%)	52,833 (35.56%)	
2+	38,083 (31.07%)	48,931 (32.94%)	

Each feature is reported as n (%).

COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.

[a] BMI: patients with a BMI measurement within 3 years before the Index date.

of 5-year absolute risk for any osteoporotic fracture and only for hip fractures, is shown in Table 2. As a whole, 14,225 osteoporotic fractures occurred in the study cohort, 10,542 (74.1%) among females and 3683 (25.9%) among males.

For female gender, advanced age, history of fracture, use of corticosteroids, rheumatoid arthritis, BMIb= 20, a diagnosis of osteoporosis, gastrointestinal and chronic hepatic diseases, depression, COPD, use of anticonvulsants and a higher number of medications, significantly increased the risk of any osteoporotic fractures. Concerning hip fractures, we gathered a 13.27-fold higher risk among patients

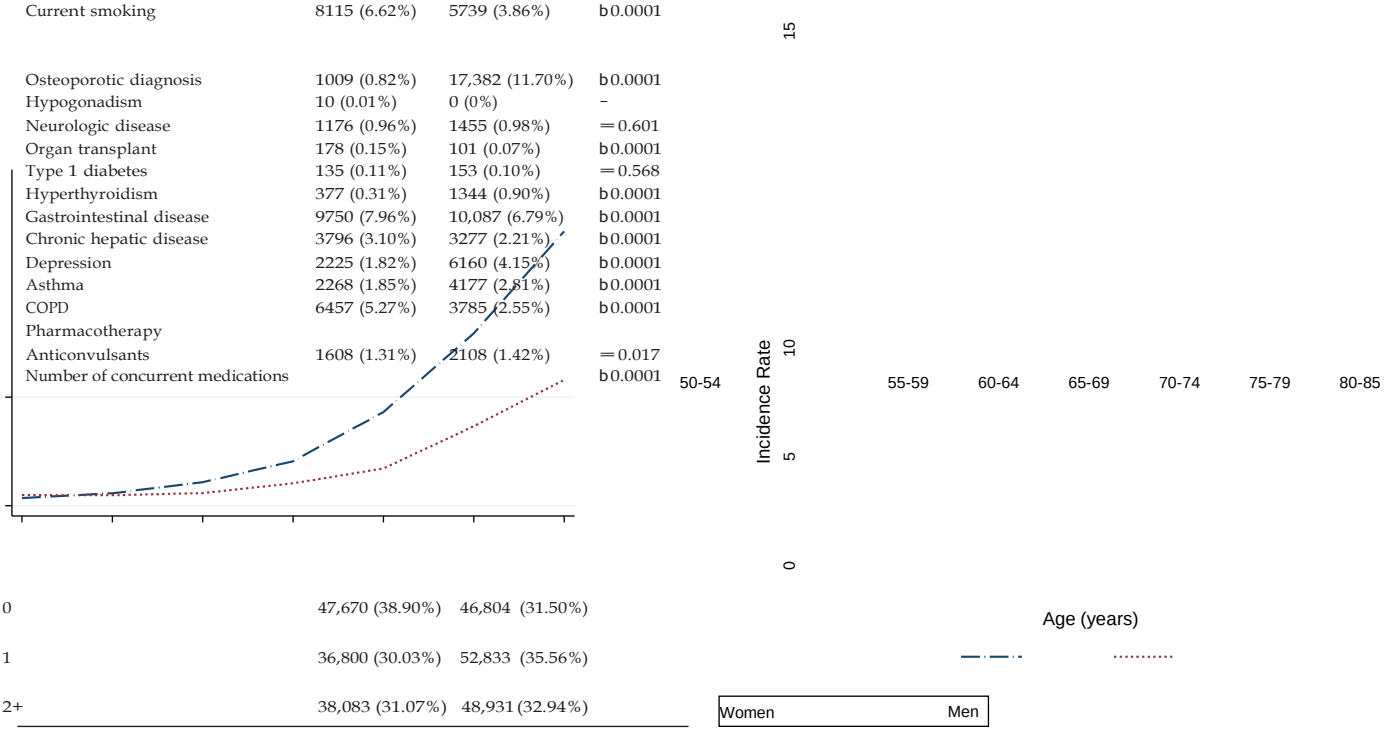

Fig. 2. Age and gender-specific 5-year incidence rates of hip osteoporotic fracture(per 1000 person-years).

Table 2

Multivariable Poisson regression of the association[a] between baseline clinical characteristics and 5-year fracture risk.

	All fractures (N = 14,225)		Hip fractures (N = 3929)	
	Males (N=3683)	Females (N=10,542)	Males (N=914)	Females (N=3015)
Demographic characteristics				
Age strata b=60 65–69 N=70	1	1	1	1
FRAX® factors History of fracture	1.26 (1.16–1.38)	1.68 (1.58–1.78)	2.06 (1.64–2.6)	2.77 (2.32–3.30)
Use of corticosteroids	2.31 (2.13–2.50)	3.19 (3.02–3.37)	8.06 (6.58–9.87)	13.27 (11.37–15.5)
BMI b=20[b]	1.69 (1.18–2.43)	1.42 (1.23–1.63)	1.67 (0.86–3.25)	2.01 (1.61–2.50)
Current smoking	1.06 (0.93–1.20)	1.08 (0.97–1.20)	1.13 (0.87–1.47)	1.13 (0.91–1.39)
Other possible risk factors				
Osteoporotic diagnosis	1.57 (1.23–2.00)	1.42 (1.35–1.49)	2.09 (1.43–3.05)	1.30 (1.19–1.43)
Neurologic disease	1.33 (1.02–1.74)	1.15 (0.97–1.37)	1.66 (1.04–2.66)	1.23 (0.91–1.67)
Hyperthyroidism	1.00 (0.58–1.72)	0.89 (0.72–1.10)	1.69 (0.76–3.78)	1.21 (0.87–1.69)
Gastrointestinal disease	1.13 (1.02–1.27)	1.17 (1.10–1.25)	1.11 (0.89–1.38)	1.13 (1.00–1.29)
Chronic hepatic disease	1.49 (1.27–1.73)	1.33 (1.19–1.48)	1.92 (1.45–2.54)	1.38 (1.13–1.68)
Depression	1.17 (0.95–1.44)	1.24 (1.14–1.35)	1.51 (1.05–2.16)	1.36 (1.17–1.57)
Asthma	1.09 (0.87–1.37)	1.08 (0.96–1.20)	0.82 (0.48–1.39)	1.13 (0.92–1.39)
COPD	1.24 (1.09–1.40)	1.22 (1.10–1.34)	1.19 (0.96–1.49)	1.24 (1.04–1.46)
Pharmacotherapy				
Anticonvulsants	1.57 (1.27–1.95)	1.49 (1.32–1.70)	2.07 (1.45–2.96)	1.61 (1.28–2.01)
Number of concurrent medications				
0	1	1	1	1
1	1.22 (1.12–1.33)	1.22 (1.16–1.29)	1.12 (0.94–1.33)	1.09 (0.99–1.21)
2+	1.23 (1.13–1.33)	1.18 (1.12–1.25)	1.25 (1.06–1.47)	1.15 (1.04–1.26)

COPD: Chronic Obstructive Pulmonary Diseases, BMI: Body Mass Index.

[a] Incidence rate ratio and 95% CI.

[b] BMI: patients with a BMI measurement within 3 years before the Index date.

aged 70 years than lower sixties. Furthermore, a significant increased risk was here reported for the same characteristics related to the overall fractures, with some exceptions. In fact, rheumatoid arthritis, a diagnosis of osteoporosis, depression and COPD did not show any association with hip fracture occurrence.

Instead, among men, the predictors significantly associated with any osteoporotic fracture comprised advanced age, history of fracture, BMIb= 20, a diagnosis of osteoporosis, chronic hepatic disease and COPD as well as the use of anticonvulsants and the increasing number of coexistent medications. Increased age, previous fractures (FRAX® component), a diagnosis of osteoporosis, chronic hepatic disease, use of anticonvulsants and the increasing number of concurrent medications were significantly associated with the risk of hip fracture.

The concurrent prevalence of one or more risk factors significantly affected the results (Fig. 3). The risk of either overall or hip fracture ranged from 8.2 (95% C.I. 8.03 to 8.31) to 2.2 (95% C.I. 2.10. to 2.25)

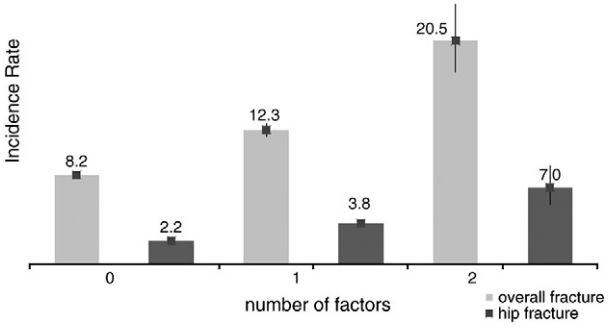

Fig. 3. Incidence rates of fracture (per 1000 person-years) according to the number of risk factors.

per 1000 person years among patients with no risk factor to 20.5(95% C.I. 17.61 to 23.77) and 7.0 among patients (95% C.I. 5.47 to 9.03) with 2 or more risk factors, respectively.

Discussion

The present study provides the basis for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data, derived from the HSD, has allowed the examinations of the general relationship whit each predictor of osteoporotic fractures by gender and duration of follow-up. In general, a higher incidence of osteoporotic fractures was observed among females when compared with males, as well as in the older population strata. This result was confirmed when analysis was restricted to hip fractures. Additionally, we identified predictors which were those expected by FRAX® algorithm and identified in some previous surveys.

In keeping with current medical literature, females showed a higher incidence of osteoporotic fractures than males. When compared with ours, Hippisley-Cox and coworkers [11] reported analogue rates for both genders; Barrett-Connor et al. [27] retrieved a similar incidence of approximately 4 cases per 1000 person-years among male elders; Cooper and Cheng [28,29] showed secular and geographical trends of osteoporotic fractures, whose estimates were coherent with ours.

As expected, an increasing trend of fractures occurrence was positively related to the increasing patients' age. The rate appeared higher among females across all age groups, and a wider gap has been observed from the 65-69 years group and forward. Yet, our findings agree with other surveys [2,4,16,27-32], where the more evident difference was estimated after 60-65 years. As per Cummings [2], Hippisley-Cox [11] and Piscitelli et al. [4], hip and vertebral fractures should be mainly responsible of this trend.

Consistently, our estimates were reproducible with previous findings when the analysis was focused on the hip site [2,4,11]. A sharp increase was achieved among older males and females until the age group of 80–85 years. Between genders, as also reported by Piscitelli et al. [4], no relevant differences has been recorded up to 60–65 years of age, while they strictly diverge moving towards the older age groups. The plausible explanation to these results could be due to bone loss associated with menopause, which is generally more common after 55–60 years of age [2,28,29,31,32].

Also the other determinants of osteoporotic fractures here reported were somewhat in line with other studies [2,4,16,27,30]. Nevertheless, smoking habits and asthma were not supported by our results. Some explanations could address the differences. The fact that a 10-year cohort was adopted by some previous surveys [11,30] implies a higher number of cases, and an increased cumulative effect of risk factors over time [18]. Herein, some clinical features could be missed by our analysis. Furthermore, a study from UK [11] enrolled patients at 30 years of age, whereas we selected patients aged 50+ years to preserve a clinical plausibility between fractures and osteoporosis. Along this line, while asthma is a risk factor in previous investigations [11], the presence of COPD in our predictors could be suggestive of a related respiratory impairment which is more common among elderly than in younger asthmatic patients. Concerning smoking habits, although it was proportionally coherent with the participants' age and selection (oncologic patients were excluded) when compared with the general Italian population [33], its lacking association with fracture occurrence could be due to social desirable answers [34].

Rheumatoid arthritis did not result a risk factor as well. Such an explanation, it could be due to the fact that this disorder is self-reported by patients, who generally misclassify rheumatoid arthritis, osteoarthritis or arthralgia [18].

Concerning both overall and hip fractures, Hippisley-Cox et al. [11] reported the use of tricyclic antidepressants as a predictor. Partly in keeping with them but fully in agreement with other surveys [30], our data report depression as a risk factor. We examined the disease instead of its pharmacological treatment to overcome the possibility of confounding by indication [35]. On the contrary, anticonvulsants were expectedly associated to fracture occurrence also taking into account their indication of use [23,24,36].

In any case, although not-significant, most of the patient's features (e.g. use of steroids among males) inspected by us, were not so far to exclude unit from their CIs.

From a clinical perspective, the history and combination of one or more risk factors could be profitably adopted by the PCP to evaluate the predictability of osteoporotic fractures. FRAX® score is currently proposed by WHO and its use could be part of clinical activity to overcome BMD insensitivity. To this purpose, each predictor here discussed is part of FRAX® [37,38], so demonstrating its or certain variants usefulness for the PCPs [18].

This study has some limitations. Firstly, no validation study has been formally carried out to test the accuracy of the fractures diagnosis. However, the incidence rates here reported are consistently in line with current literature, either between genders or among age categories [2,4,11,16,17,19,27,31,32].

Secondly, absence of information on certain features (e.g. history of falls, alcohol intake, fracture family history [9,37]) could have missed other possible risk factors. Indeed, HSD database does not supply with accurate measures of some covariates. For instance, alcohol abuse it is difficult to measure because of social desirable answers albeit its causal association with osteoporotic fractures is not still exhaustively demonstrated [18]. In the same way, history of falls might be inaccurately recorded in the database, because the PCP does not collect radiographs for most patients [18]. Thus, it appears difficult to record severe falls that are plausibly related to fractures. Consistently, the fracture family history appeared

not analytically usable when the PCPs' standard quality require-ments [12] were verified.

Finally, the possibility of competing rates with mortality could partly explain the lacking association between some covariates, such as smoking habits, and the risk of fracture. Nevertheless, it is more plausible that a relatively short follow-up (5 years instead of 10)could not have permitted an exhaustive analysis of certain variables.

Conclusions

This survey provides a model for the assessment of 5-year probability fracture risk in men and women in a large specific Italian population. The use of primary care data confirms, in fact, a higher incidence of osteoporotic fractures among females when compared with males, as well as in the older population strata. In addition, predictors of osteoporotic fractures were those expected to be identified by the FRAX® algorithm in a general practice setting as well.

In the light of the clinical utility of a simple risk score for the assessment of absolute fracture risk among osteoporotic patients, its assessment and validation in the Italian HSD could potentially provide an applicable prediction tool in primary care.

Conflict ofinterest

No disclosures.

Acknowledgments

We are very grateful to all PCPs who continue to collect data and updateHSD.

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Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

France-Italy

- **COMPOUNDS: Thiocolchicoside**

Statistical Analysis Plan

Version 1.0 dated on 1st September 2017 (final) Protocol version 5.0 dated on 2nd March 2017 Confidential

Version	Date	Description
1.0	01 Sep 2017	SAP

- **SAP approval**

QuintilesIMS

Name	Signature	Date

Sanofi (on behalf of all other MAHs part of the consortium)

Name	Signature	Date

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AESI	Adverse Event of Special Interest
AIFA	Italian Medicines Agency
CI	Confidence Interval
CHMP	Committee on Human Medicinal Products
eCRF	Electronic Case Report Form
DA	Disease Analyzer
DHPC	Direct Healthcare Professional Communication
DREES	Direction de la recherche, des études, de l'évaluation et des statistiques (French National Statistical Institute)
DUS	Drug Utilization Study
EC	European Community
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUQPPV	European Qualified Person for Pharmacovigilance
EMA	European Medicines Agency
EMR	Electronic Medical Record
GP	General Practitioners
HAS	Haute Autorité de Santé (French Health Authority)
LPD	Longitudinal Patient Databases
RMMs	Risk Minimization Measures
SC	Scientific Committee
SmPc	Summary of Product Characteristics
TCC	Thiocolchicoside

LIST OF TABLES AND FIGURES

1 INTRODUCTION

This drug utilization study (DUS) is being conducted, per regulatory request, following the Article 31 referral on thiocolchicoside (TCC)-containing medicinal products for systemic use. It is part of current TCC Risk Management Plan (version 1.2), as part of the pharmacovigilance plan described for the product.

The drug utilization study aims to characterize the prescribing practices during typical clinical use of systemic thiocolchicoside in Europe.

2 STUDY OBJECTIVES

2.1 Primary objectives:

The aim of this drug utilization study is to characterise prescribing practices of TCC-containing medicinal products for systemic use during typical clinical use in representative groups of prescribers and assess main reasons for prescription.

The study objectives are:

- To describe the demographic and clinical characteristics of the treated patients (i.e. age, gender, co-medications, pregnancy, use of appropriate contraceptive measures, lactation).
- To describe for which indication TCC is prescribed in routine clinical practice (overall and by age/gender)
- To describe the average duration of treatment episodes and the daily doses prescribed according to the route of administration.

2.2 Secondary objectives:

Comparison of patient characteristics, pre- and post- implementation of RMMs as a measurement of the efficacy of the risk minimization measures.

3 STUDY DESIGN

This is a retrospective multicenter, non-interventional, drug utilization study, using longitudinal electronic medical records (EMR) databases in primary care setting in France and Italy, obtained from the general practice management software utilized during physician office visits: QuintilesIMS Longitudinal Patient databases (LPD) Italy and France-Rheumatologists, and Disease Analyzer (DA) France.

Approximately 1,000 GPs (DA France) and 100 rheumatologists in France (LPD France-Rheumatologists) and 900 GPs in Italy contribute to the database. Physician panels in each database are designed to be representative of the physician population in each country by age, sex and localization.

Data from EMR is submitted daily to a coordinating center, cleaned, de-identified, and made available for research. Since data is collected in a non-interventional manner, IMS Health database mirror real life practice.

3.1 Study Population

The study population will be patients treated with systemic TCC and who meet the inclusion and exclusion criteria noted below. It will be conducted using GP's and Rheumatologists (only for France) primary care data extracted from the IMS Real World Evidence Electronic Medical Records (IMS RWE EMR) databases of France and Italy.

3.1.1 Eligibility criteria

Inclusion criteria:

The study population will include all patients with at least one prescription of TCC-containing medicinal products for systemic use in the selected databases during the study period, i.e. before or after the implementation of the risk minimization measures.

Exclusion criteria

No age restrictions or exclusion criteria will be applied. This will allow for the characterization of all users of TCC-containing medicinal products for systemic use according to each potential indication for which the medication is being used. This will include any pediatric population and patients with contraindications (e.g., pregnant woman).

The **index date,** "**prescription index date"** for each patient included in the study will be defined as the first date in each study period a patient is prescribed systemic thiocolchicoside (See study period, § 3.1.3). There will be one index date for baseline period and one index date for study period.

3.1.2 Populations of interest

Analysis will be done on all eligible patients with at least one year of enrolment in the database before index date. However, in order to assess the effect of including patients prescribed systemic TCC but not analyzed because of enrolment less than one year before index date, these patients will be counted, and their main characteristics (age, gender, dose, duration, treatment indication, co-medications) at index date, will be described together with the characteristics of patients included in the study. This analysis will be presented in Table 9

Note: a patient could be eligible on study period and not eligible on baseline period.

3.1.3 Study period

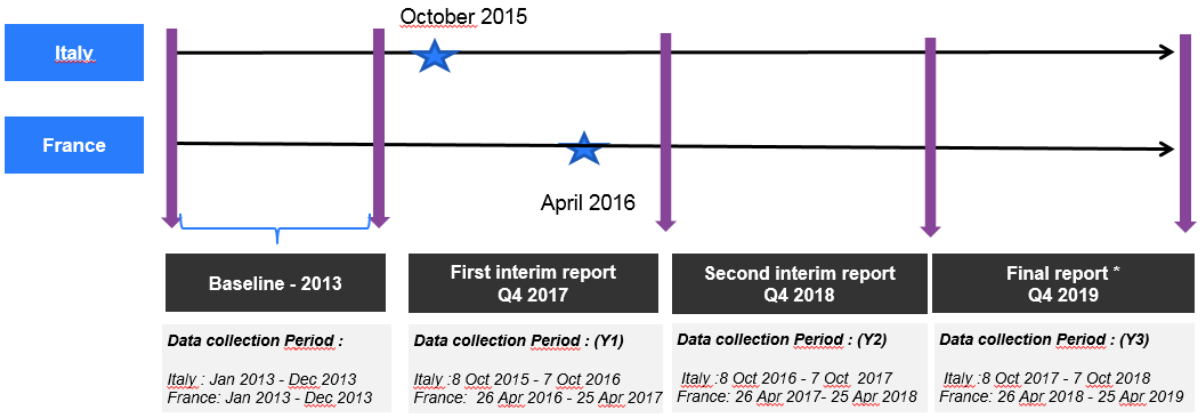
The study will describe the utilization pattern of systemic thiocolchicoside during the first three years after the effective date of implementation of all the risk minimization measures following the CHMP

decision in France and Italy. The effective date of implementation of minimization measures will be considered per country (completion of educational material distribution: October 8th 2015 for Italy, April 26th 2016 for France).

This analysis will be repeated at 12 (interim analysis 1), 24 (interim analysis 2) and 36 (Final report) months from the implementation of all the minimization measures.

In addition, a baseline period spanning over year 2013 (January 1st to December 31st), will be used to describe prescribing practices of systemic TCC-containing medicinal products before implementation of minimization measures.

Figure 1: Study periods



* Final report will present separately results from baseline, Y1, Y2 and Y3

3.2 Sample size

The sample size calculation is determined by the desired accuracy/precision of the estimation by confidence interval of the observed proportions. The Table 1 shows that to achieve a sufficient accuracy,

i.e. within a marge of accuracy < +/- 5%, of the estimation by a two-sided 95% confidence interval (CI) for proportions (p) between 10 % and 50 % (or from 90 % to 50 % for complementary percentage), a minimum sample size of around 400 patients is required. The precision for an observed percentage with 95%CI will be determined by the formula below:

Calculation use the following formula (normal approximation):

$$e = \sqrt{\frac{p(1-p)}{n}} \times \varepsilon_\alpha$$

With n sample size, p observed percentage, ε_α 1.96 for 95% CI, e Precision.

Table 1: Required number of patients by acceptable precision (95% confidence interval) for proportions (normal approximation)

Precision	10% (90%)	20% (80%)	30% (70%)	40% (60%)	50% (50%)
±2.0%	864	1537	2017	2305	2401
±2.5%	553	983	1291	1475	1537
±3.0%	384	683	896	1024	1067
±3.5%	282	502	659	753	784
±4.0%	216	384	504	576	600
±5.0%	139	246	323	369	384

3.3 Sample size for France and Italy

For the study, investigators will register all consecutive TCC patients visiting GPs or specialists, whatever the reason. The analyzed patients' data set will consist of all registered patients, excluding patients for whom year of birth and/or gender are missing. As no published data are available on the practice of such physicians/sites, it was decided to assess the number of followed subjects from LPD and DA feasibility results. No hypothesis was made on the total number of subjects that will be registered. Thus, based on the feasibility results, for France, approximatively 40,000 patients were prescribed TCC in 2012 from GP panel and 2,800 in specialists. Besides, in Italy, more than 17,000 patients were prescribed TCC in 2012. Thus, based on a percentage of missing data on age and gender lower than 5 %, the maximal expected sample size will be over 60,000 patients per year from all data sources.

Table 2: Summary of the available number of users of TCC in each database in 2012 and 2013

	LPD France-	***DA France***	***LPD Italy***
Number of GPs (panel size)	-	1,000	900
Number of Rheumatologists (panel size)	100	Not covered	Not covered
Patients on TCC cmp* - 2012- GP's	-	~40,000	>17,000
Patients on TCC cmp* -2012- Rheumatologists	>2,800	Not covered	Not covered
Patients on TCC cmp* - 2013- GP's	-	~50,000	>16,800
Patients on TCC cmp* -2013- Rheumatologists	>3,100	Not covered	Not covered

*: cmp: cumulative measurement period

4 METHODS

4.1 Data Sources

- Longitudinal Patient Database (LPD): Rheumatologists France and GPs Italy

The LPDs collect medical information from proprietary practice management software used by the physician during patients' office visits for recording their daily patient interactions in electronic medical records. A panel of physicians using this software volunteers to make available anonymized, patient-level information from their practices for clinical research purposes. Since these data are being collected in a non-interventional way, they reflect routine clinical practice in the country.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Istituto di ricerca della SIMG, 2014].

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

In France, data from panels of primary care physicians and data from specialist panels are available. Panels of specialists are independent of GP panel; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, it is not possible to link individual patients across the two types of practitioners.

For this study, it is planned to record information gathered by a panel of French rheumatologists for a better coverage of patients prescribed TCC. Both LPD panels have been validated through previous published works. Indeed, French panel of Rheumatologists (LPD France-rheumatologists) has been used by French National Authority for Health [Has, 2009; HAS, 2010] and Italian LPD (LPD-Italy) have been used in peer reviewed publications [Lapi et al, 2012; Coloma et al, 2013].

- Disease Analyzer (DA) France: GPs France

Disease Analyzer provides a nationally representative sample of about 1,000 primary care physicians (GPs) and includes over 5 million anonymous patient records and 152 million prescriptions in France.

Physicians are contacted among GPs who are using one of the five practice management software

selected by IMS and according to the needs of representativity of the panel based on national statistics. Physicians included in the panel are those who volunteer to make available anonymized, patient-level information from their practices for clinical research purposes.

The panel of contributing physicians is maintained as a representative sample of the primary care physician population according to 3 criteria known to influence prescribing: age, sex, and geographical distribution. Whenever a physician leaves the panel, he/she is replaced by another one with a similar profile. Additionally, the patient population is representative of the country population according to age and gender distribution, as provided by national statistic authorities [Becher et al., 2009].

DA was recently used in a PASS study involving the attainment of exposure of pregnant women to sodium valproate and related substances [ENCEPP/SDPP/9678]

Characteristics of both databases are summarized in Table 3.

Table 3: Characteristics of data sources

Characteristics	***DA France***	***LPD France-***	***LPD Italy***
Database type	Primary health care electronic medical record database	Electronic medical record database	Primary health care electronic medical record database
Possibility of linkage	None	None	None
Possibility to request additional information	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or physicians	• Possibility of pop-up screens filled by physician • Possibility of questionnaires filled by patients and/or	None
Physicians population	GPs: 1,000 (of 54,000 in France)	Rheumatologists: 100 (of 1,749 in France)	GPs: 900 (of 46,000 in Italy)
Data availability	Metropolitan France Since 2004	Metropolitan France. Since 2002 for Rheumatologist panel	All Italy Since 2004
Database population	1,160,000 active patients*	115,000 active patients*	1,000,000 active patients*
Approximate proportion of the country physician population covered by the database	1.85%	5.7 %	1.96%
Active international principle coding system	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*	Proprietary thesaurus (*mapped to ATC)*
Disease classification	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-10)*	Proprietary thesaurus *(mapped to ICD-9)*

*: active patients: patients having visited their physician at least once a year

4.2 Data collected

The following patients' data will be collected from the databases:

- Patient demography: age at the time of the visit, gender,
- Pregnancy and lactation associated diagnoses for women of child bearing potential
- Date of prescription of TCC: name of the TCC-containing medicinal product for systemic use, posology, duration of treatment
- Diagnosis associated to prescription of the TCC-containing medicinal product for systemic use
- Concomitant medications/products: Concomitant medications/devices, including contraceptive medication/devices will be collected using list of therapeutic classes or drugs commonly prescribed.

Concerning concomitant medications/products prescribed in population with acute muscle contractures in spinal pathology, the predefined list, as exhaustive as possible, covers the concomitant medications of interest and the main therapeutic classes i.e. pain management prescription including: analgesics, tricyclic antidepressants, benzodiazepines, antiepileptic drugs.

4.3 Variables

4.3.1 Exposures

The exposure of interest is systemic TCC.

4.3.1.1 Treatment duration

Use of systemic TCC will be assessed by the prescriptions recorded (prescriptions "issued" or "written") in LPD and DA. Since LPD and DA data report issued prescriptions rather than dispensed medication, there is no information indicating if, or, when a prescription was filled. We will assume that all the prescriptions and their associated dates recorded in the two databases reflect actual prescription fills, and subjects will begin exposure at the index date (= prescription issued) and be exposed continuously for the number of days indicated by the days of supply for that prescription.

Note: If the days-of-supply field for a given prescription is missing or zero, or the value recorded has been determined to be implausible based on the quantity dispensed for that prescription, the days of supply will be calculated by dividing the total quantity dispensed by the daily prescribed dose.

4.3.1.2 Dose

The distribution of the daily prescribed dose (for oral form and IM form) will be described for all users of systemic TCC. The daily dose of medications is recorded in both LPD and DA in France, and LPD for Italy. Dose will be ascertained from the numeric daily dose derived from the dosing instructions. The proportion of missing values will be described.

However, the degree of completeness is variable across databases. Missing values for doses are expected. The missing information will be specified.

4.3.1.3 Treatment indications

Following the Article 31 referral on thiocolchicoside-containing medicinal products for systemic use, systemic thiocolchicoside use is recommended only as adjuvant treatment for acute muscle contractures in spinal pathology.

All diagnoses associated to a systemic TCC prescription will be recorded and classified according to ICD-10-CM.

An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication. All diagnoses recorded at the same day of the TCC prescription will be taken into account for the identification of the current approved indication.

Of note, Table 4 displays the lists of diseases, conditions, and procedures mapped to the ICD-10-CM codes for identification of the current approved indication.

Table 4: List of diagnoses and corresponding ICD-10-CM codes for identification of the current approved indications

ICD-10-CM description	***ICD-10-CM code***	***Use of codes in indication definitions***
Other deforming dorsopathies including: • Spondylolysis • Spondylolisthesis • Recurrent atlantoaxial dislocation with myelopathy • Other recurrent atlantoaxial dislocation • Other recurrent vertebral dislocation • Torticollis • Other specified deforming	M 43 M43.0 M43.1 M43.3 M43.4 M43.5 M43.6 M43.8	Primary code for the broad definition of the clinical indication
Dorsalgia • Radiculopathy • Cervicalgia • Sciatica • Lumbago with sciatica • Low back pain	M 54 M 54.1 M 54.2 M 54.3 M.54.4 M54 .5 M54 .6	Primary code for the broad definition of the clinical indication

4.3.2 Pregnancy, contraceptive use and lactation: for women of child bearing potential

Use of appropriate contraceptive measures during the study period:

In the GP EMR databases contraceptive use is not well recorded (see Study limitations, § 9.10). Therefore it is expected that the recording of prescriptions of contraceptive measures up to a year before and concomitantly to TCC prescription is going to underestimate the population that is using appropriate contraceptive measures.

Pregnancy:

All of the diagnoses related to pregnancies will be searched in databases according to data availability.

Some of these diagnoses precise the pregnancy trimester or are related to exams specific of a trimester. If the information on trimester or start date or delivery/end of pregnancy date is available, the pregnancy will be considered exposed if at least one TCC prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date is not available in the EMR-database, a pregnancy will be considered as exposed to TCC if at least one TCC prescription was issued within 90 days before or within 180 days after the first record of a given pregnancy.

Lactation:

Diagnoses related to breastfeeding will be searched in databases according to data availability.

Lactation will be considered as concomitant to TCC use if at least one TCC prescription is issued in a window of 90 days before and after any breast-feeding record.

4.3.3 Operational variables and definition of off-label

In summary, all variables to be collected for the purpose of the study and definition of off-label are the following:

Table 5 : Summary of variables

Patient Demographics, at initiation of systemic TCC	Patient Demographics, at initiation of systemic TCC use

• Age categories	• <16, ≥16 years	• Age at prescription <16 years
• Gender	• Male, female	
• Pregnancy	• Pregnancy diagnosis	• At least one TCC prescription issued in the period between assumed dates of pregnancy start and delivery/end of pregnancy, or, – when no information on pregnancy start or end is available-, within 90

• Contraceptive use	• Prescription of contraceptive medications/devices	• No record of contraceptive use
• Lactation status	• Lactation	• At least one TCC prescription issued in a window of 90 days before and after any diagnosis of lactation
• Country	• France, Italy	
Concomitant medications and /or health services, medical devices, before, at initiation of and during	Medications: • All analgesics (ATC code :N02) and specifically among them: o Salicylic combinations (N02A) o Paracetamol (N02B) o Opioids (N02A) • Tricyclic antidepressants (N06A,amitriptyline type) • Benzodiazepine (ATC code: N03A, clonazepam type) • Muscle relaxants (ATC code : M03)	• No concomitant medications and /or health services, medical devices, before, at initiation of, and during systemic TCC use

Health services/medical devices and others :

	• Functionnal rehabilitation (V57 (ICD-9), Z50 (ICD-10))	
	• Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	
	• Neck braces/Belts / lumbar corsets	
Systemic TCC daily doses prescribed	• Oral form: ≤ 16 mg per day, >16 mg per day	• Oral form: >16 mg per day
Duration of systemic TCC treatment episode	• Oral form: ≤ 7 consecutive days, >7 consecutive days • IM form: ≤ 5 consecutive days,	• Oral form: >7 consecutive days • IM form: >5 consecutive
	• >5 consecutive days	Long term treatment: duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
Treatment indication for systemic TCC	• approved clinical diagnosis recorded at the day of prescription	• Other than painful muscle contractures associated with acute spinal pathology

(*) Off-label is defined as any occurrence of the situations listed in the table 5 (in the last column) in a prescription i.e: age at prescription <16 years, non-concomitant medication and/or health service, TCC daily dose >16mg per day (oral form) or >8 mg per day (IM form), >7 consecutive days of TCC treatment (oral form) or >5 consecutive days (IM form), treatment indication other than painful muscle contractures associated with acute spinal pathology and pregnancy or lactation or contraceptive use in women of child bearing potential

4.3.4 Definition of concomitant medication and/or health services

The definition of concomitant medication and/or health services will be defined for each systemic TCC prescription according to the following algorithms in the table 6:

Table 6: Algorithms for the definition of concomitant medication and/or health services

Treatment	Concomitant definition
Medications :	
Analgesics (N02)	Overlap between medication and systemic TCC prescription
Tricyclic antidepressants (N06A,amitriptyline type)	Overlap between medication and systemic TCC prescription
Benzodiazepine (N03A,clonazepam type)	Overlap between medication and systemic TCC prescription
Muscle relaxants (M03)	Overlap between medication and systemic TCC prescription
NSAIDs/Cox-2 inhibitors (M01A)	Overlap between medication and systemic TCC prescription
Corticosteroids (M01B)	Overlap between medication and systemic TCC prescription
Topical products for joint and muscular pain (M02A)	Overlap between medication and systemic TCC prescription
Phytotherapy (harpagophyton, V03A),	Overlap between medication and systemic TCC prescription
Health services/medical devices and others (LPD only):	
Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	Health service prescribed in the three months before systemic TCC prescription or during TCC treatment
Osteo-therapies (V57 (ICD-9), Z50 (ICD- 10))	Health service prescribed in the three months before systemic TCC prescription or during TCC treatment
Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	Health service prescribed in the three months before systemic TCC prescription or during TCC treatment
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	Health service prescribed in the three months before systemic TCC prescription or during TCC treatment

4.3.5 Derived variables

In summary, all derived variables and algorithms used are the following: Table 7: Summary of variables

Variable	algorithm
Age	Age at the prescription will be calculated according to the following algorithm:
Duration of TCC prescription	Duration will be the duration filled by physician. In case when the duration of the prescription is filled with a number of packs, duration will be calculated according to the daily dose, the number of packs prescribed (including renewal) and the number of pills available in one pack.
Dosage of TCC prescription	Dosage will be calculated according to the posology filled by physician multiplied by the strength of the TCC prescription
Contraceptive use	Any contraceptive use in the year before start date of the TCC prescription and/or during TCC treatment (between start date of TCC prescription until end of prescription)
Pregnancy	If the information on trimester or start date or delivery/end of pregnancy date is available, the pregnancy will be considered exposed if at least one TCC prescription was recorded in the period between assumed dates of pregnancy start and delivery/end of pregnancy. In case information on pregnancy trimester or start date or delivery/end of pregnancy date is not available in the EMR-database, a pregnancy will be considered as exposed to TCC if at least one
Lactation	Any TCC prescription issued in a window of 90 days before and after any breast-feeding record.
Concomitant medication	Any overlap between medication and systemic TCC prescription: The medication should be prescribed during the current TCC treatment (between start date of TCC prescription until end of TCC prescription) OR the medication should start before the TCC prescription and must be ongoing at the start date of the TCC prescription
Concomitant health service	Any health service prescribed in the three months before systemic TCC prescription or during TCC treatment (Between start date of the TCC prescription until end of TCC prescription)

5 STATISTICAL ANALYSIS

5.1 General considerations

All statistical analyses will be performed using SAS® software with SAS enterprise guide 6.1 (SAS Institute, version 6.1, SAS 9.4, North Carolina, USA) and/or R© R Foundation for Statistical Computing, version 3.0 and later.

According to the objectives of the study, the analyses will be mainly descriptive. The statistical results will be displayed using tables, listings and/or graphs. Figures can be performed with SAS® or R (R© R Foundation for Statistical Computing, version 3.0 or later).

Continuous variables (e.g., age) will be summarized by mean, standard deviation (SD), median, Q1-Q3, minimum, and maximum values. Categorical variables will be summarized in terms of the number and percentage of patients in each category. Missing and invalid observations will be tabulated as a separate category. The calculation of proportions will not include the missing/invalid category in the denominators.

Quantitative variables will be statistically compared with a Student's t-test (parametric test) or Wilcoxon signed-rank sum test (non-parametric test, when necessary). Qualitative variables will be statistically compared with a Pearson Chi2 or with Fisher's exact test (expected frequency lower or equal to 5 for one or several cells). Each statistical test will be bilateral with a level of risk α of 5% (without adjustment of the threshold regarding the increase of the tests). If relevant, Confidence Intervals at 95% will also be calculated.

Programming notes:

Decimal places will be defined as follows:

- For continuous variables:
    - 1 for the mean, SD, range, median, and quartiles
- For categorical variables:
    - 1 for the percentage.

For categorical variables percentages will be based on the number of patients with non-missing data.

5.2 Primary analysis

The description of drug use patterns (overall description by country and by age and gender and incident or prevalent cases) will be performed for the baseline period (year 2013) and each year over the 3 years of inclusion for both countries.

Analysis will be done overall and by sub-group of prevalent and incident cases. Prevalent cases will be defined as the total number of treated patients per year during 3 years, and incident cases will be defined as the total number of newly treated patients per year (Newly treated patients regarding all patient history with at least one year of medical history).

For each country: a descriptive analysis of TCC utilization and off-label will be performed:

- Indication,
- Dosage,
- Duration,
- Therapeutic regimen: mono-therapies or adjuvant therapies (use of TCC along with other pre-specified co-medications).

The prescribed daily dose will be defined as the average dose prescribed overall and by route of administration (oral form, IM form)

In addition descriptive analyses will be performed in number of TCC users according to:

- age and gender
- In the subgroup of women of childbearing potential: by pregnancy and use of contraceptive measures during the study period

In addition a descriptive analysis of TCC utilization and off-label will be performed in number of TCC prescribers according to:

- age and gender
- In the subgroup of women of childbearing potential: by pregnancy and use of contraceptive measures during the study period

5.2.1 Secondary analysis

A comparison of patient characteristics and proportion of off-label, pre- and post- implementation of RMMs as a measurement of the efficacy of the risk minimization measures will be performed. The off

label proportion at baseline (year 2013) (B) will be estimated on the basis of the RMMs implementation. Off label proportion for each year post-implementation of RMMs (C_1, C_2,…) will be estimated on the basis of the RMMs implementation. “Off-label use” definition will be based on the collected variables on relevant characteristics of use including dose, duration and indication which are presented in Section 9.3.3

To estimate RMMs impact on off-label rate, the overall difference ($\Delta = C_x - B$) in off-label before and after RMMs will be estimated.

Furthermore, the effect of RMMs on off label incidence will be performed. The analysis will use a segmented regression analysis [Wagner et al., 2002]. In this analysis, incidence rates will be computed by months before (baseline: 2013) and after RMMs implementation (according to each country). The model will include an intercept (mean outcome rate at beginning of the study) and main period (before / after RMMs) effect and separate time trends before and after RMMs.

5.2.2 Interim analysis

Two annual interim reports and a final report are planned for this study

- First interim report will present results from baseline and Y1.
- Secondary interim report will present results from baseline, Y1 and Y2 separately
- Final report will present results from baseline, Y1, Y2 and Y3 separately

5.2.3 Strengths of the research methods

Studies evaluating data already collected may be the most efficient way to assess potential off-label use.

- All physicians participating to the panels use an Electronic Medical Records (EMR) software to manage their patients and record the information during their daily patient visits including the entire prescription writing. The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to recall and to differential reporting of prescriptions or impacts of contacts with patients and health care professionals.
- The tool directly captures data from patients EMRs, no intervention being made to recollect or complete the data. Since data are collected in a non-interventional way, data reflect routine clinical practice and real life settings.[1]
- The panels of physicians are maintained representative of the physicians' population[2,3]
- The patient population is representative of the country population according to age and sex distribution, as provided by national statistic authorities.

5.2.4 Limitations of the research methods

However, there are limitations in the conduct of this study

- Potential for missing/incomplete data: No individual patient identifiers will be available. It is therefore impossible to query the physicians providing the data for any missing information. There is no availability of information on death, or date of patient transfer out of the system.

[1] Sabouret P, Discrepancy between guidelines for stroke prevention in atrial fibrillation and practice patterns in primary care. The nationwide French AFIGP survey. 2015. Archives of Cardiovascular Disease 108, 544—553

[2] Jouaville SL, Miotti H, Coffin G, Sarfati B, Meilhoc A. Validity and limitations of the Longitudinal Patient Database France for use in pharmacoepidemiological and pharmacoeconomics studies. Value in Health. 2015; 18 (3) A18.

[3] Becher H, Kostev K, Schröder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmacoepidemiological and pharmacoeconomic studies. Int J Clin Pharmacol Ther. 2009 Oct;47(10):617-26.

Recording of the indication of each prescribed treatment is mandatory in the physician software, but the physicians are free to enter any diagnosis and can for instance enter the reason of visit (e.g. flu) as indication for all treatments prescribed at the visit.

Pregnancies are estimated by diagnoses codes in the patient's EMR but cannot always be reliably dated. There is therefore not always a possibility for us to state definitively the concomitance of a TCC prescription with a pregnancy. The same is true for lactation.

Contraceptive use, as researched in women of childbearing potential through the prescription of contraceptive medications or device, will be underestimated. The reasons are (i) a substantial number of women may see a gynaecologist for this purpose

(ii) devices may have been inserted in a time period not encompassed by this study or removed elsewhere (iii) contraception may be insured by other means than a prescribed devices or medications. There is therefore no possibility for us to state definitively the concomitance of a TCC prescription and contraceptive use.

Nevertheless, an accompanying survey performed at the PRAC request (PRACLOQN.8) in the most representative countries for TCC sales (France, Italy, Portugal and Greece) will be an additional source of information on contraception, lactation, and pregnancy for this study.

- Representativity of physicians: while representativeness of EMR-databases used in the present study is established on administrative criteria [1,4] one cannot exclude that the voluntary basis of physician's participation to the database leads to a potential bias in physicians' representativity.

- In France: no link between the panel of GPs and Rheumatologists is possible. Panels of specialists are independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur. However, the risk is minimal.

- Bias to be explained:

- Selection Bias: Health care utilization patterns are best described when they include data from all potential prescribers of a drug. In this instance, the Italian LPD and DA data source will capture patients prescribed TCC only in a GP setting. However this bias will be assessed in France, where a panel of rheumatologists will be available.

- Misclassification bias can result if study subjects are not categorized correctly with regards to exposure or selected patient characteristics. We expect minimal misclassification with respect to exposure, since this is determined from each database's prescribing records. However, actual adherence to TCC cannot be confirmed. In addition, misclassification bias can occur at the level of associated diagnosis since physician can enter the reason of the visit (e.g. flu) as indication for all treatments prescribed at the visit.

- Assessment of representativeness:

  - Representativity assessment of the participating physicians:

Characteristics of participating GPs (gender, age class, region) will be compared to those of the national statistics. In case of discrepancy with national statistics information, weighted analysis could be applied.

  - Representativity assessment of the participating patients:

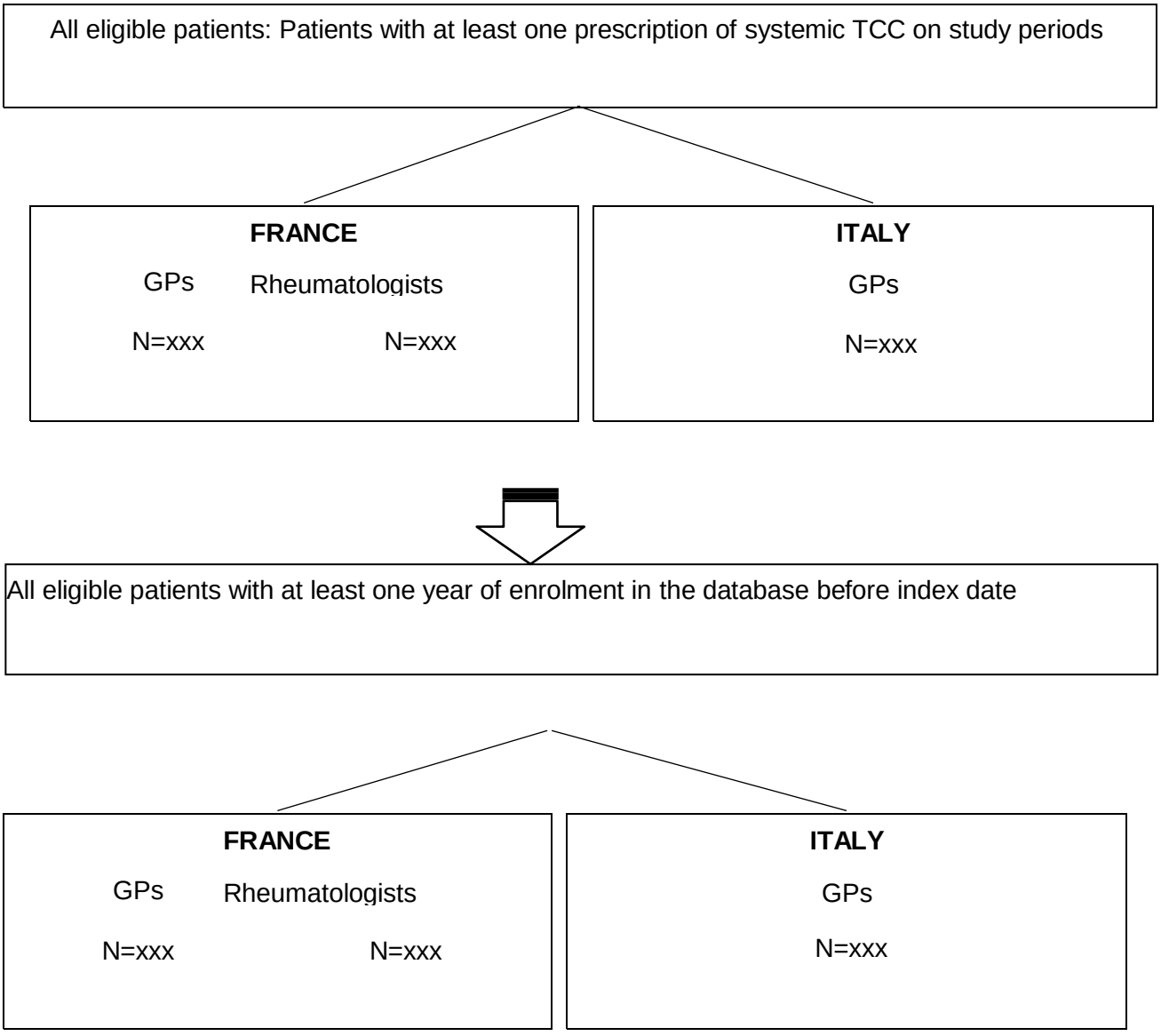
4 Istituto di ricerca della SIMG. VII report Health Search: 2013-2014. Società Italiana di Medicina Generale e delle Cure Primarie. 2014. Available at: http://healthsearch.it/documenti/Archivio/Report/VIIIReport_2013-2014/index.html#p=1

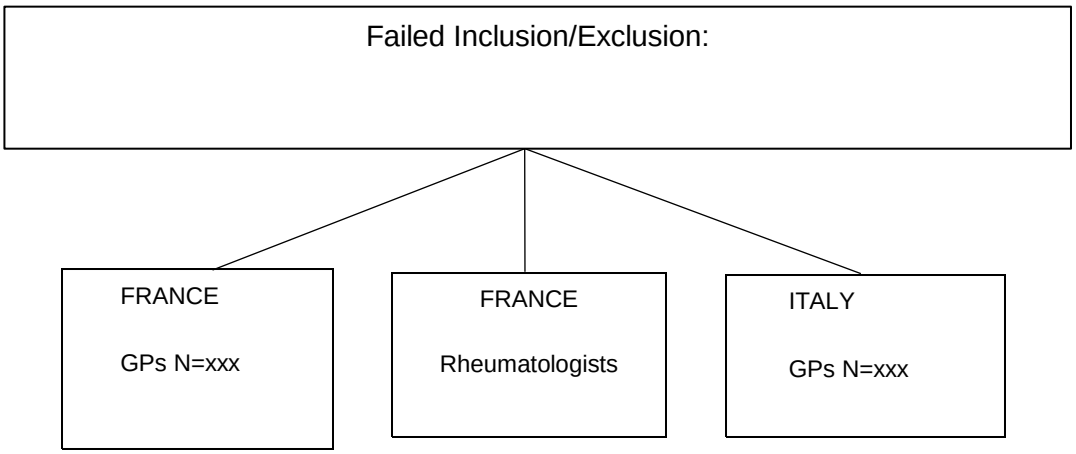
In order to assess the effect of excluding patients prescribed TCC but for whom there was less than one year of enrolment before the index date, patients exposed to TCC but not meeting this inclusion requirement will be counted and their main characteristics at index date (age, gender) will be described together with the characteristics of patients included in the study.

5.3 Missing data

No imputation on missing data will be done. Missing data will be presented in the tables.

6 DIAGRAMS


All eligible patients: Patients with at least one prescription of systemic TCC on study periods
FRANCE
GPs
N=xxx
Rheumatologists
N=xxx
ITALY
GPs
N=xxx
All eligible patients with at least one year of enrolment in the database before index date
FRANCE
GPs
N=xxx
Rheumatologists
N=xxx
ITALY
GPs
N=xxx


Failed Inclusion/Exclusion:
FRANCE
GPs N=xxx
FRANCE
Rheumatologists
ITALY
GPs N=xxx

7 MOCK TABLES

7.1 RESULTS FRANCE

7.1.1 Eligibility criteria - France

Table 8: Total eligible patients - France

	GPs (N=XXX)	Rheumatologists (N=XXX)
Eligible patients	XX (XX.X%)	XX (XX.X%)
Included (at least one year of enrollment in the database[1])	XX (XX.X%)	XX (XX.X%)
Baseline period	XX (XX.X%)	XX (XX.X%)
Study period	XX (XX.X%)	XX (XX.X%)
Excluded (less than one year of enrollment in the database[1])		
Baseline period		
Study period		

[1] :one year before the date of the first TCC prescription in the period (Baseline period/ study period)

7.2 Analysis of included and excluded populations – France

Table 9: Patient's characteristics at index date[1] in France – Baseline period[2]– GPs – eligible patients

		Included[3] Patients (N=XXX)	Excluded[4] Patients (N=XXX)
Age at index date (years)	N	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
	[16;49]	XX (XX.X%)	XX (XX.X%)
	≥50 years	XX (XX.X%)	XX (XX.X%)
	Missing (N)	XX	XX
	Female	XX (XX.X%)	XX (XX.X%)
	Missing (N)	XX	XX
TCC daily dose prescribed at index date (mg)	N	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
Treatment indication for TCC prescription at index date (ICD10)			
	Spondylolysis (M43.0)	XX (XX.X%)	XX (XX.X%)
	Spondylolisthesis (M43.1)	XX (XX.X%)	XX (XX.X%)
	….		
	Dorsalgia (M54) :	XX (XX.X%)	XX (XX.X%)
	Radiculopathy (M54.1)	XX (XX.X%)	XX (XX.X%)
	….		
	Other than painful muscle contractures associated with acute spinal pathology		
Co-medication	Analgesics (N02)	XX (XX.X%)	XX (XX.X%)
	Salicylic combinations (N02A)	XX (XX.X%)	XX (XX.X%)
	Paracetamol (N02B)	XX (XX.X%)	XX (XX.X%)
	….		

Program: pathway & date

Index date[1]: first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2] : year 2013

Patients included[3] : at least one year of enrollment in the database

Table 10: Patient's characteristics at index date[1] in France – Study period[2]– GPs – eligible patients

		Included[3] Patients (N=XXX)	Excluded[4] Patients (N=XXX)
Age at index date (years)	N	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
	[16;49]	XX (XX.X%)	XX (XX.X%)
	≥50 years	XX (XX.X%)	XX (XX.X%)
	Missing (N)	XX	XX
	Female	XX (XX.X%)	XX (XX.X%)
	Missing (N)	XX	XX
TCC daily dose prescribed at index date (mg)	N	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	XX – XX]
	Missing (N)	XX	XX
Treatment indication for TCC prescription at index date (ICD10)			
	Spondylolysis (M43.0)	XX (XX.X%)	XX (XX.X%)
	Spondylolisthesis (M43.1)	XX (XX.X%)	XX (XX.X%)
	….		
	Dorsalgia (M54) :	XX (XX.X%)	XX (XX.X%)
	Radiculopathy (M54.1)	XX (XX.X%)	XX (XX.X%)
	….		
	Other than painful muscle contractures associated with acute spinal pathology		
Co-medication	Analgesics (N02)	XX (XX.X%)	XX (XX.X%)
	Salicylic combinations (N02A)	XX (XX.X%)	XX (XX.X%)
	Paracetamol (N02B)	XX (XX.X%)	XX (XX.X%)
	….		

Program: pathway & date

Index date[1]: first date in the study period a patient is prescribed systemic thiocolchicoside

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

Patients included[3] : at least one year of enrollment in the database

7.3 Primary analysis

7.3.1 Analysis of systemic TCC use patterns

Table 11: Analysis of systemic TCC prescriptions - France – GPs – included patients

		Baseline period[1]	Study period[2] Overall (N=XXX)	Incident[3] (N=XXX)
Total systemic TCC prescriptions	N	XX	XX	XX
Number of patients with a systemic TCC prescription				
	N	XX	XX	XX
Number of systemic TTC prescriptions per patient				
	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
Treatment indication for systemic TCC	Other deforming dorsopathies			
	Spondylolysis (M43.0)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Spondylolisthesis (M43.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Dorsalgia (M54) :	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Radiculopathy (M54.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….			
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
Age at prescription (years)	<16 years	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[16;30[	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[30;40[	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[40;50[	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[50;60[	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	[60;70[	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	≥70 years	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing (N)	XX	XX	XX
	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
Gender	Male	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Female	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
Route of systemic TCC prescription	Oral form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	IM form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX

		Baseline period[1]	Study period[2] Overall (N=XXX)	Incident[3] (N=XXX)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX
	≤16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
TCC daily dose – IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX
	≤8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
Duration of TCC treatment (days)– Oral form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
Duration of TCC treatment (days)– IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX
Long term treatment[4]				
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history

		Baseline period[1]	Study period[2] Overall (N=XXX)	Incident[3] (N=XXX)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If yes, detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:	Analgesics (N02), including:	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Salicylic combinations (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Paracetamol (N02B)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Opioids (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Tricyclic antidepressants (N06A,amitriptyline type)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Benzodiazepine (N03A, clonazepam type)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Muscle relaxants (M03)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	NSAIDs/Cox-2 inhibitors (M01A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Corticosteroids (M01B)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Topical products for joint and muscular pain (M02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Phytotherapy (harpagophyton V03A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Health services/medical devices and others:				
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history

Table 12: Analysis of systemic TCC prescriptions according to age in men - France – GPs – included patients

		Baseline period[1]		Study period[2]	
		Male <16 years (N=XX)	**Male ≥16 years (N=XX)**	**Male <16 years (N=XX)**	**Male ≥16 years (N=XX)**
Total systemic TCC prescriptions	N	XX	XX	XX	XX
Number of patients with a systemic TCC prescription					
Number of systemic TTC prescriptions per patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
Treatment indication for systemic					
	Spondylolysis (M43.0)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Spondylolisthesis (M43.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Dorsalgia (M54) :	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Radiculopathy (M54.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
….					
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX
Route of systemic TCC prescription	Oral form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	IM form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX
TCC daily dose – Oral form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX
	≤16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

		Baseline period[1]		Study period[2]	
		Male <16 years (N=XX)	**Male ≥16 years (N=XX)**	**Male <16 years (N=XX)**	**Male ≥16 years (N=XX)**
TCC daily dose – IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX
	≤8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX
Duration of systemic TCC treatment (days)– Oral form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Duration of systemic TCC treatment (days)– IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX
Long term treatment	Yes	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Concomitant medications and/or health services, medical devices during systemic TCC use					
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If yes, detail of the concomitant medications and/or health services, medical devices during systemic TCC use:					
Medications:	Analgesics (N02), including:	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Salicylic combinations (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Paracetamol (N02B)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Opioids (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

		Baseline period[1]		Study period[2]	
		Male <16 years (N=XX)	**Male ≥16 years (N=XX)**	**Male <16 years (N=XX)**	**Male ≥16 years (N=XX)**
Health services/medical devices and others:					
	Functionnal rehabilitation (V57 (ICD-9), Z50 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

Table 13: **analysis of systemic TCC prescriptions according to age in women - France – GPs – included patients**

		Baseline period[1]			Study period[2]		
		Female <16 years (N=XX)	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**	**Female <16 years (N=XX)**	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**
Total systemic TCC prescriptions	N	XX	XX	XX	XX	XX	XX
Number of patients with a systemic TCC prescription							
Number of systemic TTC prescriptions per patient	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
Treatment indication for systemic ….	Other deforming dorsopathies including Spondylolysis (M43.0)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Spondylolisthesis (M43.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	….	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Dorsalgia (M54) :	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Radiculopathy (M54.1)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Other	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

		Baseline period[1]			Study period[2]		
		Female <16 years (N=XX)	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**	**Female <16 years (N=XX)**	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**
Pregnancy	Yes	na	XX (XX.X%)	na	na	XX (XX.X%)	na
	No	na	XX.X (XX.X)	na	na	XX.X (XX.X)	na
Contraceptive use	Yes	na	XX (XX.X%)	na	na	XX (XX.X%)	na
	No	na	XX.X (XX.X)	na	na	XX.X (XX.X)	na
Lactation	Yes	na	XX (XX.X%)	na	na	XX (XX.X%)	na
	No	na	XX.X (XX.X)	na	na	XX.X (XX.X)	na
Route of systemic TCC prescription	Oral form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	IM form	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX
TCC daily dose – Oral form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX	XX	XX
	≤16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>16 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

		Baseline period[1]			Study period[2]		
		Female <16 years (N=XX)	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**	**Female <16 years (N=XX)**	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**
TCC daily dose – IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX	XX	XX
	≤8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>8 mg per day	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX
Duration of systemic TCC treatment (days)– Oral form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

		Baseline period[1]			Study period[2]		
		Female <16 years (N=XX)	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**	**Female <16 years (N=XX)**	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**
Duration of systemic TCC treatment (days)– IM form	N	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]	XX [XX-XX]
	(Range)	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]	[XX – XX]
	Missing	XX	XX	XX	XX	XX	XX
	≤7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	>7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Missing	XX	XX	XX	XX	XX	XX
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Concomitant medications and/or health services, medical devices	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
If yes, detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
Medications:	Analgesics (N02), including:	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Salicylic combinations (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Paracetamol (N02B)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Opioids (N02A)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
…							

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th april 2017 / Italy: 8th October 2015-7th October 2016

Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or non contraceptive

		Baseline period[1]			Study period[2]		
		Female <16 years (N=XX)	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**	**Female <16 years (N=XX)**	**Female 16-49 years (N=XX**	**Female ≥50 years (N=XX)**
Health services/medical devices and others:							
	Functionnal rehabilitation (V57 (ICD-9), Z50 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Osteo-therapies (V57 (ICD-9), Z50 (ICD- 10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016

Table 14: **Summary of off label use of systemic TCC (patients) - France – GPs – included patients**

		Baseline period[1] (N=XXX)	Study period[2] (N=XXX)	p-value
Off label use[3]	Yes	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	No	XX (XX.X%)	XX (XX.X%)	
	Age <16 years old	XX (XX.X%)	XX (XX.X%)	
	No concomitant medications/ and or health health services, medical devices			
	Oral form: daily dose>16 mg per day	XX (XX.X%)	XX (XX.X%)	
	IM form: daily dose>8 mg per day	XX (XX.X%)	XX (XX.X%)	
	Oral form: >7 consecutive days	XX (XX.X%)	XX (XX.X%)	
	IM form: >5 consecutive days	XX (XX.X%)	XX (XX.X%)	
	Long term treatment	XX (XX.X%)	XX (XX.X%)	
	Indication: other than painful muscle contractures associated with acute spinal pathology			
	Pregnancy[4]	XX (XX.X%)	XX (XX.X%)	
	Lactation[4]	XX (XX.X%)	XX (XX.X%)	
	No contraceptive use[4]	XX (XX.X%)	XX (XX.X%)	

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016

Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, concomitant medication and pregnancy or non contraceptive use or lactation for women of childbearing potential

[4]: percentage based on women of child bearing potential

Table 15: **Summary of off label use of systemic TCC in TCC prescribers - France – GPs – included patients**

		Baseline period[1] (N=XXX)	Study period[2] (N=XXX)	p-value
Off label use[3] (at least one TCC prescription)	Yes	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	No	XX (XX.X%)	XX (XX.X%)	
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	
	(Range)	[XX – XX]	[XX – XX]	
	[10%-20%[	XX (XX.X%)	XX (XX.X%)	
	[20%-30%[	XX (XX.X%)	XX (XX.X%)	
	[30%-40%[	XX (XX.X%)	XX (XX.X%)	
	[50%-60%[	XX (XX.X%)	XX (XX.X%)	
	[60%-70%[	XX (XX.X%)	XX (XX.X%)	
	[70%-80%[	XX (XX.X%)	XX (XX.X%)	
	[80%-90%[	XX (XX.X%)	XX (XX.X%)	
	90% and more	XX (XX.X%)	XX (XX.X%)	
Correlation between proportion of off label use and number of TCC	N	XX (XX.X%)	XX (XX.X%)	
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	
	(Range)	[XX – XX]	[XX – XX]	
detail of off label use (at least one TCC prescription) :				
	Age <16 years old	XX (XX.X%)	XX (XX.X%)	
	No concomitant medications/ and or health health services, medical devices			
	Oral form: daily dose>16 mg per day	XX (XX.X%)	XX (XX.X%)	
	IM form: daily dose>8 mg per day	XX (XX.X%)	XX (XX.X%)	
	Oral form: >7 consecutive days	XX (XX.X%)	XX (XX.X%)	
	IM form: >5 consecutive days	XX (XX.X%)	XX (XX.X%)	
	Long term treatment	XX (XX.X%)	XX (XX.X%)	
	Indication: other than painful muscle contractures associated with acute spinal pathology			
in women of child bearing potential (at				
	Pregnancy[4]	XX (XX.X%)	XX (XX.X%)	
	Lactation[4]	XX (XX.X%)	XX (XX.X%)	
	No contraceptive use[4]	XX (XX.X%)	XX (XX.X%)	

Baseline period[1] (N=XXX)	Study period[2] (N=XXX)	p-value

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016

Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, concomitant medication and pregnancy or non contraceptive use or lactation for women of childbearing potential
[4:] percentage based on women of child bearing potential

7.4 Secondary analysis

Table 16: Comparison of patients' characteristics between pre- and post-implementation of RMMs - France – GPs – included patients

		Baseline period[1] (N=XXX)	Study period[2] (N=XXX)	p-value
Age (years)	N	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	
	Median [Q1 – Q3]	XX [XX-XX]	XX [XX-XX]	
	(Range)	[XX – XX]	XX – XX]	
	Missing (N)	XX	XX	
	[16;30[	XX (XX.X%)	XX (XX.X%)	
	[30;40[	XX (XX.X%)	XX (XX.X%)	
	[40;50[	XX (XX.X%)	XX (XX.X%)	
	[50;60[	XX (XX.X%)	XX (XX.X%)	
	[60;70[	XX (XX.X%)	XX (XX.X%)	
	≥70 years	XX (XX.X%)	XX (XX.X%)	
	Missing (N)	XX	XX	
	Female	XX (XX.X%)	XX (XX.X%)	
	Missing (N)	XX	XX	
Off label use[3]				
	No	XX (XX.X%)	XX (XX.X%)	
	Age <16 years old	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	No concomitant medications/ and or health health services, medical devices	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Oral form: daily dose>16 mg per day	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	IM form: daily dose>8 mg per day	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Oral form: >7 consecutive days	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	IM form: >5 consecutive days	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Indication: other than painful muscle contractures associated with acute spinal pathology	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Pregnancy[4]	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	Lactation[4]	XX (XX.X%)	XX (XX.X%)	XX.X [-]*
	No contraceptive use[4]	XX (XX.X%)	XX (XX.X%)	XX.X [-]*

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016

Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, concomitant medication and pregnancy or non contraceptive use or lactation for women of childbearing potential

4: percentage based on women of child bearing potential

Table 17: Analysis of pregnancies exposed to TCC - France – GPs – included patients

Total female patients			
		Baseline period[1] (N=XXX)	**Study period[2] (N=XXX)**
	No	XX (XX.X%)	XX (XX.X%)

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016
Pregnancies exposed[3] At least one TCC prescription during pregnancy within the defined study period

Table 18: Analysis of breastfeeding patients exposed to TCC - France – GPs – included patients

		Total female patients	
		Baseline period[1] (N=XXX)	**Study period[2] (N=XXX)**
Breastfeeding patients exposed to	No	XX (XX.X%)	XX (XX.X%)

Program: pathway & date
Baseline period[1] : year 2013

Study period[2] : France: 26th April 2016 – 25th April 2017 / Italy: 8th October 2015-7th October 2016

Breastfeeding patients exposed[3] At least one TCC prescription concomitant to a lactation record within the defined study period

Table 19: Analysis of the effect of RMMs on off label rate[1] (prescriptions) - France – GPs – included patients

	Off label proportion
Off label rate on baseline period[2] (B)	XX.X%
Off label rate on study period[3] (C)	XX.X%
Overall difference (Δ=C-B)	XX.X%

Off label use[1] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, concomitant medication and pregnancy or non contraceptive use or lactation for women of childbearing potential

Baseline period[2] : year 2013

Table 20: Analysis of the effect of RMMs on off label incidence[1]- France – GPs – included patients

Intercept	XX.X	XX.X	XX.X
Baseline[2] trend	XX.X	XX.X	XX.X
Level change after RMMs[3]	XX.X	XX.X	XX.X
Trend change after RMMs[3]	XX.X	XX.X	XX.X

Off label use[1] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication

Baseline period[2] : year 2013

7.5 RESULTS FRANCE RHEUMATOLOGISTS

Same tables as for France in GPs

7.6 RESULTS ITALY GPs

Same tables as for France in GPs

15.2 Annex 2: List of represented MAHs contact details and Product References

Marketing authorization holder(s) or Sponsor Company	**1.** **SANOFI-AVENTIS GROUPE,** a French company having its registered office at 54 rue La Boétie, 75008 Paris, France; **2.** **TEOFARMA Srl**, Via F.lli Cervi N° 8, I-27010 valle Salimbene, 27010 Pavia, Italy; **3.** **MYLAN** SAS with legal address at 117 Allée des Parcs, 69800 St Priest, France; **4.** **ANGELINI** with legal address at Angelini Farmacêutica Lda, Rua João Chagas, 53 - 3° piso, 1499-040 Cruz Quebrada – Dafundo, Portugal; **5.** **DOMPÉ' FARMACEUTICI S.P.A**., with legal address in Via San Martino 12-12/a, 20122 Milan- Italy and Operative office: Via Santa Lucia 6, 20122 Milan, Italy; **6.** **GENERIS FARMACÊUTICA** with legal address in Rua João de Deus, 19, 2700-487 Amadora, Portugal; **7.** **KORANGI,** with legal address at Produtos Farmacêuticos Lda. Rua da Vinha, 17P 2765-388 Estoril, Portugal **8.** **DAIICHI Sankyo France SAS** with legal address at 1, rue Eugène et Armand Peugeot, 92500 Rueil-Malmaison, France; **9.** **BIOGARAN SAS** with legal address 15, Boulevard Charles de Gaulle, 92707 Colombes Cedex, France; **10.** **SANDOZ SAS** with legal address 49, avenue Georges Pompidou, 92593 Levallois-Perret, France,; **11.** **CRISTERS SAS**, with legal address 22, Quai Gallieni, 92150 Suresnes, France; **12.** **EG Labo** with legal address at Quintet Bât. A, 12 Rue Barthelemy Danjou, 92100 Boulogne-Billancourt, France; **13.** **Zentiva with legal address at** 35 Rue du Val de Marne 5013 Paris, France **14.** **EG S.p.A.** with legal address at Milan- Via Pavia, 6- 20136 Milan, Italy; **15.** **ARROW génériques SAS** with legal address 26 avenue Tony Garnier 69007 Lyon, France; **16.** **DOC Generici** with legal address via Turati 40, 20121 Milano, Italy; **17.** **MDM** with legal address Via Volturno, 29/b, 20900 Monza, **Italy**; **18.** **Aristo Pharma GmbH** with legal address Wallenroder Straße 8 – 10, 13435 Berlin; **19.** **UNION HEALTH S.r.l** with legal address in Via Adige 5 – 66020 San Giovanni Teatino – Chieti, Italy; **20.** **SF GROUP S.r.l** with legal address in Via Beniamino Segre 59 - 00134 Roma, Italy; **21.** **Laboratoire ALTER**, 3 Avenue de la Baltique ZA de Courtaboeuf - 91140 Villebon-sur-Yvette, France; ***22.*** **EPIFARMA S.r.l**. with legal address via San Rocco 6, 85033 Episcopia, Italy; **23.** **ACARPIA SERVIÇOS FARMACÊUTICOS LDA,** a Portuguese company having its registered office at 88 Rua dos Murcas, 9000 Funchal, Portugal; **24.** **SPA - SOCIETÀ' PRODOTTI ANTIBIOTICI** S.p.A., an Italian company having its registered office at via Biella 8, 20143 Milano, Italy; **25.** **I.B.N. Savio S.r.l.,** Via del Mare, 36, 00071 Pomezia (RM), Italy; **26.** **LABORATORIO FARMACEUTICO CT Srl** with legal address in Strada Solaro, 75/77 – 18038 Sanremo (IM), Italy;

Product references:

Member State (in EEA)	Marketing Authorisation Holder	Invented Name Name
France	**Laboratoire Alter** 3, avenue de la Baltique ZA de Courtaboeuf 91140 Villebon-Sur-Yvette France	THIOCOLCHICOSIDE ALTER
France	**Arrow Génériques** 26, avenue Tony Garnier 69007 Lyon France	THIOCOLCHICOSIDE ARROW
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE ALMUS
France	**Biogaran** 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE BIOGARAN
France	**Cristers SAS** 22 quai Gallieni 92150 Suresnes France	THIOCOLCHICOSIDE CRISTERS
France	**DAIICHI SANKYO France SAS** Immeuble le Corosa 1, rue Eugène et Armand Peugeot 92508 Rueil-Malmaison France	MIOREL
France	**Eg Labo - Laboratoires Eurogenerics** "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne-Billancourt Cedex France	THIOCOLCHICOSIDE EG
France	**Mylan SAS** **117, allée des Parcs** **69800 Saint-Priest** **France**	THIOCOLCHICOSIDE MYLAN
France	**Sandoz** **49, avenue Georges Pompidou** **92300 Levallois-Perret** **France**	THIOCOLCHICOSIDE SANDOZ
France	**Sanofi-Aventis France** **82 avenue Raspail,** **94250 Gentilly** **France**	COLTRAMYL
France	**ZENTIVA FRANCE** **35 Rue du Val de Marne** **75013 Paris** **France**	THIOCOLCHICOSIDE ZENTIVA
Italy	**Mylan S.P.A** **Via Vittor Pisani, 20** **20124 Milano** **Italy**	THIOCOLCHICOSIDE MYLAN Generics
Italy	**Sandoz S.P.A.**	TIOCOLCHICOSIDE SANDOZ

Member State (in EEA)	Marketing Authorisation Holder	Invented Name Name
	Largo Umberto Boccioni, 1 21040 Origgio (VA) Italy	
Italy	**I.B.N. Savio S.r.l. Via del Mare, 36, 00071 Pomezia (RM) Italy**	TIOSIDE
Italy	**Sanofi S.p.A. Viale Luigi Bodio, 37/B 20158 Milan Italy**	MUSCORIL
Italy	**Zentiva Italia, S.r.l. Viale Bodio 37/b 201 58 Milano Italy**	TIOCOLCHICOSIDE ZENTIVA
Italy	**Aristo Pharma GmbH Wallenroder Str. 8-10 13435 Berlin Germany**	TIOCOLCHICOSIDE ARISTO
Italy	**DOC Generici S.R.L. Via Turati, 40 20121 Milan Italy**	TIOCOLCHICOSIDE DOC Generici
Italy	**Dompé' Farmaceutici S.P.A. Via San Martino 12-12/a 20122 Milan Italy Operative office: Via Santa Lucia 6 20122 Milan Italy**	MIOTENS
Italy	**EG S.P.A. Via Pavia, 6 20136 Milano Italy**	TIOCOLCHICOSIDE EG
Italy	**Epifarma S.R.L. Via San Rocco, 6 85033 Episcopia (Potenza) Italy**	MUSCOFLEX
Italy	**Laboratorio Farmaceutico C.T. S.R.L. Strada Solaro 75/77 18038 Sanremo (IM) Italy**	SCIOMIR
Italy	**MDM S.P.A. Via Volturno 29/b,20900 Monza, Italy**	STRIALISIN
Italy	**S.F. Group S.R.L. Via Beniamino Segre, 59 00134 Roma Italy**	DECONTRIL TERASIDE
Italy	**SPA - Società Prodotti Antibiotici S.p.A. Via Biella, 8 20143 Milano Italy**	MIOREXIL
Italy	**Union Health S.R.L. Via Adige, 5 66020 San Giovanni Teatino (Chieti) Italy**	TIOCOLCHICOSIDE UNION HEALTH

15.3 Annex 3: Statistical report

Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic use in France and Italy: an electronic medical records database study

France-Italy

COMPOUNDS: Thiocolchicoside

Statistical report

Version 1.0 dated on 21th August 2019

Protocol version 5.0 dated on 2nd March 2017

Confidential

Version	Date	Description
0.1	06 September 2019	Tables – final report
1.0	10 September 2019	Final report (tables and figures)

IQVIA PROJET TEAM

Fonction	Name
Project Manager	**Intissar Bourahla**
Medical Writer	**Sophie Jouaville**
Statistician	**Aurélie Lampuré**

Sponsor

Fonction	Name
Sponsor	

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	06/09/2019	Aurélie Lampuré	Not applicable – first draft
1.0	10/09/2019	Aurélie Lampuré	Addition of figures and results of interrupted time series models

SIGNATURES

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Aurélie Lampuré _____ _____

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Name Signature Date

Data Manager

Johanna Despres _____ _____

Name Signature Date

Principal in charge

Massoud Toussi _____ _____

Name Signature Date

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RESULTS

Selection

Table 15.3-1**: Total eligible patients – GPs France**

DUS TCC	Page 1 of 1
	GPs (N=153660)
Eligible patients	153660 (100.0%)
Included (at least one year of enrollment in the database[1])	
Baseline period	34460 (22.4%)
Study period year 1	37771 (24.6%)
Study period year 2	34330 (22.3%)
Study period year 3	23079 (15.0%)
Cumulated study periods (year 1+year 2+year 3)	81690 (53.2%)
Excluded (less than one year of enrollment in the database[1])	
Baseline period	18316 (11.9%)
Study period year 1	11387 (7.4%)
Study period year 2	10205 (6.6%)
Study period year 3	6521 (4.2%)
Cumulated study periods (year 1+year 2+year 3)	25723 (16.7%)

[1]: one year before the date of the first TCC prescription in the period (baseline period/study period)

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_01.sas; By: Alampure; Date & time: 31JUL19 09:09;

Table 15.3-2**: Total eligible patients – Rheumatologists France**

DUS TCC	Page 1 of 1
	Rheumatologists (N=8600)
Eligible patients	8600 (100.0%)
Included (at least one year of enrollment in the database[1])	
Baseline period	1383 (16.1%)
Study period year 1	1247 (14.5%)
Study period year 2	1185 (13.8%)
Study period year 3	1063 (12.4%)
Cumulated study periods (year 1+year 2+year 3)	3016 (35.1%)
Excluded (less than one year of enrollment in the database[1])	
Baseline period	1729 (20.1%)
Study period year 1	1141 (13.3%)
Study period year 2	1014 (11.8%)
Study period year 3	752 (8.7%)
Cumulated study periods (year 1+year 2+year 3)	2766 (32.2%)

[1]: one year before the date of the first TCC prescription in the period (baseline period/study period)

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_01.sas; By: Alampure; Date & time: 19AUG19 09:36;

Table 15.3-3**: Total eligible patients – GPs Italy**

DUS TCC	Page 1 of 1
	GPs (N=57901)
Eligible patients	57901 (100.0%)
Included (at least one year of enrollment in the database[1])	
Baseline period	19877 (34.3%)
Study period year 1	16140 (27.9%)
Study period year 2	16201 (28.0%)
Study period year 3	14957 (25.8%)
Cumulated study periods (year 1+year 2+year 3)	41061 (70.9%)
Excluded (less than one year of enrollment in the database[1])	
Baseline period	469 (0.8%)
Study period year 1	393 (0.7%)
Study period year 2	422 (0.7%)
Study period year 3	392 (0.7%)
Cumulated study periods (year 1+year 2+year 3)	1085 (1.9%)

[1]: one year before the date of the first TCC prescription in the period (baseline period/study period)

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_01.sas; By: Alampure; Date & time: 19AUG19 09:36;

Analysis of included and excluded populations

Table 15.3-4: Patient's characteristics at index date[1] – Baseline period[2] – GPs France – eligible patients

		Included[3] Patients (N=34460)	Excluded[4] Patients (N=18316)
Age (years)	N	34442 (99.9)	18277 (99.8)
	Missing (N)	18 (0.1)	39 (0.2)
	Mean (SD)	45.9 (15.89)	42.8 (15.80)
	Median (Q1 - Q3)	46.0 (34.0-57.0)	42.0 (30.0-54.0)
	Range	(2.0,98.0)	(0.0,95.0)
Age (years) -classes	Missing (N)	18	39
	<16 years	414 (1.2%)	222 (1.2%)
	[16;30[	5273 (15.3%)	4003 (21.9%)
	[30;40[	6517 (18.9%)	3932 (21.5%)
	[40;50[	8321 (24.2%)	4093 (22.4%)
	[50;60[	7088 (20.6%)	3210 (17.6%)
	[60;70[	4140 (12.0%)	1755 (9.6%)
	≥70 years	2689 (7.8%)	1062 (5.8%)
Gender	Missing (N)	25	42
	Male	14907 (43.3%)	8505 (46.5%)
	Female	19528 (56.7%)	9769 (53.5%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
By: Ncoulombel; Date & time: 04OCT18 12:13;

			Included[3] Patients (N=34460)	Excluded[4] Patients (N=18316)
Oral form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	1806	1133
		≤16 mg	31367 (99.7%)	16348 (99.6%)
		>16 mg	96 (0.3%)	61 (0.4%)
	Duration of TCC treatment at index date (days)	Missing (N)	1347	803
		≤7 days	15780 (49.4%)	10031 (59.9%)
		>7 days	16142 (50.6%)	6708 (40.1%)
IM form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	489	420
		≤8 mg	452 (61.2%)	243 (65.0%)
		>8 mg	286 (38.8%)	131 (35.0%)
	Duration of TCC treatment at index date (days)	Missing (N)	542	381
		≤5 days	196 (28.6%)	197 (47.7%)
		>5 days	489 (71.4%)	216 (52.3%)
Treatment indication for TCC prescription at index date (ICD10)		Missing	4957	4277
		Other deforming dorsopathies including - M43	1035 (3.5%)	545 (3.9%)
		Spondylolysis - M43.0	-	-
		Spondylolisthesis - M43.1	4 (0.0%)	-
		Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
		Other recurrent atlantoaxial dislocation - M43.4	-	-
		Other recurrent vertebral dislocation - M43.5	-	-
		Torticollis - M43.6	1031 (3.5%)	545 (3.9%)
		Other specified deforming dorsopathies - M43.8	-	-
		Deforming dorsopathy, unspecified - M43.9	-	-
		Dorsalgia - M54	15805 (53.6%)	7550 (53.8%)
		Radiculopathy - M54.1	116 (0.4%)	52 (0.4%)
		Cervicalgia - M54.2	2952 (10.0%)	1323 (9.4%)
		Sciatica - M54.3	891 (3.0%)	396 (2.8%)
		Lumbago with sciatica - M.54.4	1342 (4.5%)	655 (4.7%)
		Low back pain - M54.5	7737 (26.2%)	3824 (27.2%)
		Pain in thoracic spine - M54.6	16 (0.1%)	6 (0.0%)
		Other dorsalgia - M54.8	578 (2.0%)	317 (2.3%)
		Dorsalgia, unspecified - M54.9	2173 (7.4%)	977 (7.0%)
		Other than painful muscle contractures associated with acute spinal pathology	12663 (42.9%)	5944 (42.3%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
By: Ncoulombel; Date & time: 04OCT18 12:13;

		Included[3] Patients (N=34460)	Excluded[4] Patients (N=18316)
Medications			
	Analgesics (N02)	24030 (69.7%)	12833 (70.1%)
	Acetylsalicylic	174 (0.5%)	62 (0.3%)
	Paracetamol	23429 (68.0%)	12514 (68.3%)
	Opioids (N02A)	7714 (22.4%)	4004 (21.9%)
	Antidepressants (N06A)	2229 (6.5%)	758 (4.1%)
	Antiepileptics (N03A)	779 (2.3%)	242 (1.3%)
	Muscle relaxants (M03)	2269 (6.6%)	1362 (7.4%)
	NSAIDs/Cox-2 inhibitors (M01A)	21990 (63.8%)	12106 (66.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1914 (5.6%)	882 (4.8%)
	Topical products for joint and muscular pain (M02A)	7664 (22.2%)	4237 (23.1%)
	Phytotherapy (V03A)	14 (0.0%)	5 (0.0%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	517 (1.5%)	189 (1.0%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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			Included[3] Patients (N=34460)	Excluded[4] Patients (N=18316)
Women of childbearing potential				
		Pregnancy	71 (0.6%)	29 (0.5%)
		No contraceptive use	9831 (86.9%)	5845 (92.5%)
		Lactation	4 (0.0%)	-
Off label use[5]	Missing (N)		7106	5627
	Yes		20008 (73.1%)	8581 (67.6%)
	No		7346 (26.9%)	4108 (32.4%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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Table 15.3-5: Patient's characteristics at index date[1] – Baseline period[2] – Rheumatologists France – eligible patients

		Included[3] Patients (N=1383)	Excluded[4] Patients (N=1729)
Age (years)	N	1383 (100.0)	1728 (99.9)
	Missing (N)	0	1 (0.1)
	Mean (SD)	60.3 (14.41)	52.5 (16.64)
	Median (Q1 - Q3)	61.0 (50.0-72.0)	52.0 (41.0-64.0)
	Range	(16.0,98.0)	(14.0,94.0)
Age (years) -classes	Missing (N)	-	1
	<16 years	-	3 (0.2%)
	[16;30[	21 (1.5%)	151 (8.7%)
	[30;40[	82 (5.9%)	240 (13.9%)
	[40;50[	222 (16.1%)	372 (21.5%)
	[50;60[	330 (23.9%)	397 (23.0%)
	[60;70[	333 (24.1%)	275 (15.9%)
	≥70 years	395 (28.6%)	290 (16.8%)
Gender	Missing (N)	91	1
	Male	396 (30.7%)	646 (37.4%)
	Female	896 (69.3%)	1082 (62.6%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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		Included[3] Patients (N=1383)	Excluded[4] Patients (N=1729)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	223	209
	≤16 mg	914 (100.0%)	1233 (100.0%)
	>16 mg	-	-
Duration of TCC treatment at index date (days)	Missing (N)	231	219
	≤7 days	407 (44.9%)	638 (52.2%)
	>7 days	499 (55.1%)	585 (47.8%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	2	-
	≤8 mg	154 (61.8%)	163 (56.2%)
	>8 mg	95 (38.2%)	127 (43.8%)
Duration of TCC treatment at index date (days)	Missing (N)	4	2
	≤5 days	83 (33.6%)	145 (50.3%)
	>5 days	164 (66.4%)	143 (49.7%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-
	Other deforming dorsopathies including - M43	17 (1.2%)	7 (0.4%)
	Spondylolysis - M43.0	-	-
	Spondylolisthesis - M43.1	-	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	3 (0.2%)	1 (0.1%)
	Other specified deforming dorsopathies - M43.8	-	-
	Deforming dorsopathy, unspecified - M43.9	14 (1.0%)	6 (0.3%)
	Dorsalgia - M54	970 (70.1%)	1234 (71.4%)
	Radiculopathy - M54.1	14 (1.0%)	22 (1.3%)
	Cervicalgia - M54.2	283 (20.5%)	391 (22.6%)
	Sciatica - M54.3	28 (2.0%)	30 (1.7%)
	Lumbago with sciatica - M.54.4	134 (9.7%)	209 (12.1%)
	Low back pain - M54.5	389 (28.1%)	441 (25.5%)
	Pain in thoracic spine - M54.6	-	-
	Other dorsalgia - M54.8	2 (0.1%)	3 (0.2%)
	Dorsalgia, unspecified - M54.9	120 (8.7%)	138 (8.0%)
	Other than painful muscle contractures associated with acute spinal pathology	396 (28.6%)	488 (28.2%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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		Included[3] Patients (N=1383)	Excluded[4] Patients (N=1729)
Medications			
	Analgesics (N02)	661 (47.8%)	755 (43.7%)
	Acetylsalicylic	42 (3.0%)	58 (3.4%)
	Paracetamol	560 (40.5%)	645 (37.3%)
	Opioids (N02A)	255 (18.4%)	344 (19.9%)
	Antidepressants (N06A)	34 (2.5%)	25 (1.4%)
	Antiepileptics (N03A)	40 (2.9%)	71 (4.1%)
	Muscle relaxants (M03)	50 (3.6%)	45 (2.6%)
	NSAIDs/Cox-2 inhibitors (M01A)	672 (48.6%)	733 (42.4%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	400 (28.9%)	508 (29.4%)
	Topical products for joint and muscular pain (M02A)	131 (9.5%)	81 (4.7%)
	Phytotherapy (V03A)	4 (0.3%)	1 (0.1%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	4 (0.2%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
By: Ncoulombel; Date & time: 04OCT18 12:20;

			Included[3] Patients (N=1383)	Excluded[4] Patients (N=1729)
Women of childbearing potential				
		Pregnancy	-	-
		No contraceptive use	202 (100.0%)	445 (100.0%)
		Lactation	-	-
Off label use[5]	Missing (N)		312	226
	Yes		784 (73.2%)	1061 (70.6%)
	No		287 (26.8%)	442 (29.4%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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Table 15.3-6: Patient's characteristics at index date[1] – Baseline period[2] – GPs Italy – eligible patients

DUS TCC **Page 1 of 4**

		Included[3] Patients (N=19877)	Excluded[4] Patients (N=469)
Age (years)	N	19865 (99.9)	469 (100.0)
	Missing (N)	12 (0.1)	0
	Mean (SD)	55.4 (15.93)	44.4 (16.00)
	Median (Q1 - Q3)	55.0 (44.0-67.0)	43.0 (33.0-53.0)
	Range	(12.0,101.0)	(7.0,91.0)
Age (years) -classes	Missing (N)	12	-
	<16 years	34 (0.2%)	7 (1.5%)
	[16;30[	1002 (5.0%)	72 (15.4%)
	[30;40[	2263 (11.4%)	116 (24.7%)
	[40;50[	4156 (20.9%)	127 (27.1%)
	[50;60[	4388 (22.1%)	71 (15.1%)
	[60;70[	3752 (18.9%)	33 (7.0%)
	≥70 years	4270 (21.5%)	43 (9.2%)
Gender	Missing (N)	2894	2
	Male	6081 (35.8%)	243 (52.0%)
	Female	10902 (64.2%)	224 (48.0%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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		Included[3] Patients (N=19877)	Excluded[4] Patients (N=469)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	3342	124
	≤16 mg	2260 (98.8%)	63 (100.0%)
	>16 mg	27 (1.2%)	-
Duration of TCC treatment at index date (days)	Missing (N)	3345	124
	≤7 days	1194 (52.3%)	34 (54.0%)
	>7 days	1090 (47.7%)	29 (46.0%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	10867	235
	≤8 mg	3511 (99.9%)	53 (100.0%)
	>8 mg	4 (0.1%)	-
Duration of TCC treatment at index date (days)	Missing (N)	10869	235
	≤5 days	463 (13.2%)	7 (13.2%)
	>5 days	3050 (86.8%)	46 (86.8%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	1787	50
	Other deforming dorsopathies including - M43	924 (5.1%)	18 (4.3%)
	Spondylolysis - M43.0	374 (2.1%)	3 (0.7%)
	Spondylolisthesis - M43.1	19 (0.1%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	366 (2.0%)	12 (2.9%)
	Other specified deforming dorsopathies - M43.8	103 (0.6%)	2 (0.5%)
	Deforming dorsopathy, unspecified - M43.9	62 (0.3%)	1 (0.2%)
	Dorsalgia - M54	12727 (70.4%)	302 (72.1%)
	Radiculopathy - M54.1	182 (1.0%)	-
	Cervicalgia - M54.2	1953 (10.8%)	56 (13.4%)
	Sciatica - M54.3	529 (2.9%)	13 (3.1%)
	Lumbago with sciatica - M.54.4	-	-
	Low back pain - M54.5	9515 (52.6%)	213 (50.8%)
	Pain in thoracic spine - M54.6	239 (1.3%)	8 (1.9%)
	Other dorsalgia - M54.8	-	-
	Dorsalgia, unspecified - M54.9	309 (1.7%)	12 (2.9%)
	Other than painful muscle contractures associated with acute spinal pathology	4439 (24.5%)	99 (23.6%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Included[3] Patients (N=19877)	Excluded[4] Patients (N=469)
Medications			
	Analgesics (N02)	2404 (12.1%)	45 (9.6%)
	Acetylsalicylic	6 (0.0%)	-
	Paracetamol	2034 (10.2%)	42 (9.0%)
	Opioids (N02A)	1516 (7.6%)	21 (4.5%)
	Antidepressants (N06A)	711 (3.6%)	9 (1.9%)
	Antiepileptics (N03A)	299 (1.5%)	11 (2.3%)
	Muscle relaxants (M03)	122 (0.6%)	-
	NSAIDs/Cox-2 inhibitors (M01A)	14967 (75.3%)	339 (72.3%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1661 (8.4%)	43 (9.2%)
	Topical products for joint and muscular pain (M02A)	458 (2.3%)	19 (4.1%)
	Phytotherapy (V03A)	4 (0.0%)	-
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
By: Ncoulombel; Date & time: 04OCT18 12:24;

		Included[3] Patients (N=19877)	Excluded[4] Patients (N=469)
Women of childbearing potential			
	Pregnancy	150 (4.0%)	2 (1.4%)
	No contraceptive use	3513 (92.9%)	140 (95.2%)
	Lactation	3 (0.1%)	-
Off label use[5]	Missing (N)	15241	361
	Yes	3885 (83.8%)	82 (75.9%)
	No	751 (16.2%)	26 (24.1%)

Index date[1] : first date in the Baseline period a patient is prescribed systemic thiocolchicoside
Baseline period[2]: year 2013
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_02.sas;
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Table 15.3-7: Patient's characteristics at index date[1] – Study period year 1[2] – GPs France – eligible patients

DUS TCC		Page 1 of 4	
		Included[3] Patients (N=37771)	**Excluded[4] Patients (N=11387)**
Age (years)	N	37766 (100.0)	11376 (99.9)
	Missing (N)	5 (0.0)	11 (0.1)
	Mean (SD)	46.8 (15.69)	41.7 (15.07)
	Median (Q1 - Q3)	46.0 (35.0-57.0)	40.0 (30.0-52.0)
	Range	(2.0,100.0)	(0.0,95.0)
Age (years) -classes	Missing (N)	5	11
	<16 years	264 (0.7%)	74 (0.7%)
	[16;30[	5381 (14.2%)	2699 (23.7%)
	[30;40[	7006 (18.6%)	2709 (23.8%)
	[40;50[	8931 (23.6%)	2499 (22.0%)
	[50;60[	8092 (21.4%)	1920 (16.9%)
	[60;70[	5006 (13.3%)	965 (8.5%)
	≥70 years	3086 (8.2%)	510 (4.5%)
Gender	Male	16743 (44.3%)	5558 (48.8%)
	Female	21028 (55.7%)	5829 (51.2%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

		Included[3] Patients (N=37771)	Excluded[4] Patients (N=11387)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	2081	635
	≤16 mg	34620 (99.8%)	10452 (99.7%)
	>16 mg	73 (0.2%)	29 (0.3%)
Duration of TCC treatment at index date (days)	Missing (N)	1285	340
	≤7 days	24037 (67.7%)	7866 (73.0%)
	>7 days	11452 (32.3%)	2910 (27.0%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	528	162
	≤8 mg	388 (76.1%)	109 (88.6%)
	>8 mg	122 (23.9%)	14 (11.4%)
Duration of TCC treatment at index date (days)	Missing (N)	470	146
	≤5 days	311 (54.8%)	91 (65.5%)
	>5 days	257 (45.2%)	48 (34.5%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	4658	2164
	Other deforming dorsopathies including - M43	1130 (3.4%)	333 (3.6%)
	Spondylolysis - M43.0	-	-
	Spondylolisthesis - M43.1	7 (0.0%)	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	1122 (3.4%)	332 (3.6%)
	Other specified deforming dorsopathies - M43.8	-	-
	Deforming dorsopathy, unspecified - M43.9	1 (0.0%)	-
	Dorsalgia - M54	18264 (55.2%)	5521 (59.9%)
	Radiculopathy - M54.1	152 (0.5%)	35 (0.4%)
	Cervicalgia - M54.2	3349 (10.1%)	880 (9.5%)
	Sciatica - M54.3	962 (2.9%)	331 (3.6%)
	Lumbago with sciatica - M.54.4	1619 (4.9%)	484 (5.2%)
	Low back pain - M54.5	9207 (27.8%)	2838 (30.8%)
	Pain in thoracic spine - M54.6	31 (0.1%)	11 (0.1%)
	Other dorsalgia - M54.8	673 (2.0%)	242 (2.6%)
	Dorsalgia, unspecified - M54.9	2271 (6.9%)	700 (7.6%)
	Other than painful muscle contractures associated with acute spinal pathology	13719 (41.4%)	3369 (36.5%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

		Included[3] Patients (N=37771)	Excluded[4] Patients (N=11387)
Medications			
	Analgesics (N02)	25714 (68.1%)	7973 (70.0%)
	Acetylsalicylic	307 (0.8%)	59 (0.5%)
	Paracetamol	24847 (65.8%)	7732 (67.9%)
	Opioids (N02A)	8070 (21.4%)	2480 (21.8%)
	Antidepressants (N06A)	2245 (5.9%)	373 (3.3%)
	Antiepileptics (N03A)	841 (2.2%)	150 (1.3%)
	Muscle relaxants (M03)	941 (2.5%)	320 (2.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	23947 (63.4%)	7698 (67.6%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	2563 (6.8%)	647 (5.7%)
	Topical products for joint and muscular pain (M02A)	8832 (23.4%)	2599 (22.8%)
	Phytotherapy (V03A)	13 (0.0%)	-
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	397 (1.1%)	141 (1.2%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

		Included[3] Patients (N=37771)	Excluded[4] Patients (N=11387)
Women of childbearing potential			
	Pregnancy	52 (0.4%)	13 (0.3%)
	No contraceptive use	10597 (90.0%)	3729 (95.2%)
	Lactation	3 (0.0%)	-
Off label use[5]	Missing (N)	6954	2855
	Yes	18920 (61.4%)	4655 (54.6%)
	No	11897 (38.6%)	3877 (45.4%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-8: Patient's characteristics at index date[1] – Study period year 1[2] – Rheumatologists France – eligible patients

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		Included[3] Patients (N=1247)	Excluded[4] Patients (N=1141)
Age (years)	N	1246 (99.9)	1141 (100.0)
	Missing (N)	1 (0.1)	0
	Mean (SD)	62.1 (14.30)	52.4 (15.81)
	Median (Q1 - Q3)	62.0 (52.0-72.0)	52.0 (42.0-63.0)
	Range	(19.0,94.0)	(15.0,93.0)
Age (years) -classes	Missing (N)	1	-
	<16 years	-	1 (0.1%)
	[16;30[	12 (1.0%)	86 (7.5%)
	[30;40[	69 (5.5%)	158 (13.8%)
	[40;50[	164 (13.2%)	250 (21.9%)
	[50;60[	288 (23.1%)	288 (25.2%)
	[60;70[	330 (26.5%)	181 (15.9%)
	≥70 years	383 (30.7%)	177 (15.5%)
Gender	Missing (N)	60	-
	Male	352 (29.7%)	409 (35.8%)
	Female	835 (70.3%)	732 (64.2%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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			Included[3] Patients (N=1247)	Excluded[4] Patients (N=1141)
Oral form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	182	130
		≤16 mg	847 (100.0%)	811 (99.8%)
		>16 mg	-	2 (0.2%)
	Duration of TCC treatment at index date (days)	Missing (N)	182	131
		≤7 days	458 (54.1%)	489 (60.2%)
		>7 days	389 (45.9%)	323 (39.8%)
IM form				
	TCC daily dose prescribed at index date (mg)	≤8 mg	160 (72.7%)	140 (70.4%)
		>8 mg	60 (27.3%)	59 (29.6%)
	Duration of TCC treatment at index date (days)	≤5 days	87 (39.5%)	111 (55.8%)
		>5 days	133 (60.5%)	88 (44.2%)
Treatment indication for TCC prescription at index date (ICD10)		Missing	-	-
		Other deforming dorsopathies including - M43	15 (1.2%)	4 (0.4%)
		Spondylolysis - M43.0	-	-
		Spondylolisthesis - M43.1	1 (0.1%)	2 (0.2%)
		Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
		Other recurrent atlantoaxial dislocation - M43.4	-	-
		Other recurrent vertebral dislocation - M43.5	-	-
		Torticollis - M43.6	3 (0.2%)	-
		Other specified deforming dorsopathies - M43.8	-	-
		Deforming dorsopathy, unspecified - M43.9	11 (0.9%)	2 (0.2%)
		Dorsalgia - M54	848 (68.0%)	852 (74.7%)
		Radiculopathy - M54.1	16 (1.3%)	11 (1.0%)
		Cervicalgia - M54.2	233 (18.7%)	281 (24.6%)
		Sciatica - M54.3	9 (0.7%)	18 (1.6%)
		Lumbago with sciatica - M.54.4	141 (11.3%)	126 (11.0%)
		Low back pain - M54.5	289 (23.2%)	266 (23.3%)
		Pain in thoracic spine - M54.6	-	-
		Other dorsalgia - M54.8	2 (0.2%)	3 (0.3%)
		Dorsalgia, unspecified - M54.9	158 (12.7%)	147 (12.9%)
		Other than painful muscle contractures associated with acute spinal pathology	384 (30.8%)	285 (25.0%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=1247)	Excluded[4] Patients (N=1141)
Medications			
	Analgesics (N02)	557 (44.7%)	407 (35.7%)
	Acetylsalicylic	2 (0.2%)	1 (0.1%)
	Paracetamol	466 (37.4%)	345 (30.2%)
	Opioids (N02A)	228 (18.3%)	173 (15.2%)
	Antidepressants (N06A)	45 (3.6%)	28 (2.5%)
	Antiepileptics (N03A)	41 (3.3%)	48 (4.2%)
	Muscle relaxants (M03)	13 (1.0%)	11 (1.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	611 (49.0%)	576 (50.5%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	375 (30.1%)	330 (28.9%)
	Topical products for joint and muscular pain (M02A)	112 (9.0%)	40 (3.5%)
	Phytotherapy (V03A)	4 (0.3%)	3 (0.3%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.2%)	1 (0.1%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:20;

		Included[3] Patients (N=1247)	Excluded[4] Patients (N=1141)
Women of childbearing potential			
	Pregnancy	-	-
	No contraceptive use	159 (100.0%)	316 (100.0%)
	Lactation	-	-
Off label use[5]	Missing (N)	234	131
	Yes	717 (70.8%)	634 (62.8%)
	No	296 (29.2%)	376 (37.2%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:20;

Table 15.3-9: Patient's characteristics at index date[1] – Study period year 1[2] – GPs Italy – eligible patients

DUS TCC		Page 1 of 4	
		Included[3] Patients (N=16140)	**Excluded[4] Patients (N=393)**
Age (years)	N	16128 (99.9)	393 (100.0)
	Missing (N)	12 (0.1)	0
	Mean (SD)	56.7 (15.49)	48.2 (15.61)
	Median (Q1 - Q3)	56.0 (46.0-68.0)	47.0 (37.0-57.0)
	Range	(11.0,101.0)	(13.0,93.0)
Age (years) -classes	Missing (N)	12	-
	<16 years	9 (0.1%)	5 (1.3%)
	[16;30[	683 (4.2%)	43 (10.9%)
	[30;40[	1543 (9.6%)	72 (18.3%)
	[40;50[	3130 (19.4%)	102 (26.0%)
	[50;60[	3811 (23.6%)	85 (21.6%)
	[60;70[	3298 (20.4%)	45 (11.5%)
	≥70 years	3654 (22.7%)	41 (10.4%)
Gender	Missing (N)	2297	-
	Male	5185 (37.5%)	198 (50.4%)
	Female	8658 (62.5%)	195 (49.6%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

			Included[3] Patients (N=16140)	Excluded[4] Patients (N=393)
Oral form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	2574	73
		≤16 mg	1340 (99.3%)	30 (100.0%)
		>16 mg	9 (0.7%)	-
	Duration of TCC treatment at index date (days)	Missing (N)	2575	73
		≤7 days	598 (44.4%)	11 (36.7%)
		>7 days	750 (55.6%)	19 (63.3%)
IM form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	9536	244
		≤8 mg	2761 (99.9%)	46 (97.9%)
		>8 mg	4 (0.1%)	1 (2.1%)
	Duration of TCC treatment at index date (days)	Missing (N)	9536	244
		≤5 days	348 (12.6%)	6 (12.8%)
		>5 days	2417 (87.4%)	41 (87.2%)
Treatment indication for TCC prescription at index date (ICD10)		Missing	1367	36
		Other deforming dorsopathies including - M43	659 (4.5%)	8 (2.2%)
		Spondylolysis - M43.0	248 (1.7%)	2 (0.6%)
		Spondylolisthesis - M43.1	22 (0.1%)	-
		Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
		Other recurrent atlantoaxial dislocation - M43.4	-	-
		Other recurrent vertebral dislocation - M43.5	-	-
		Torticollis - M43.6	251 (1.7%)	3 (0.8%)
		Other specified deforming dorsopathies - M43.8	92 (0.6%)	2 (0.6%)
		Deforming dorsopathy, unspecified - M43.9	46 (0.3%)	1 (0.3%)
		Dorsalgia - M54	10682 (72.3%)	271 (75.9%)
		Radiculopathy - M54.1	122 (0.8%)	-
		Cervicalgia - M54.2	1529 (10.3%)	43 (12.0%)
		Sciatica - M54.3	432 (2.9%)	11 (3.1%)
		Lumbago with sciatica - M.54.4	-	-
		Low back pain - M54.5	8188 (55.4%)	209 (58.5%)
		Pain in thoracic spine - M54.6	192 (1.3%)	4 (1.1%)
		Other dorsalgia - M54.8	-	-
		Dorsalgia, unspecified - M54.9	219 (1.5%)	4 (1.1%)
		Other than painful muscle contractures associated with acute spinal pathology	3432 (23.2%)	78 (21.8%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=16140)	Excluded[4] Patients (N=393)
Medications			
	Analgesics (N02)	1752 (10.9%)	38 (9.7%)
	Acetylsalicylic	9 (0.1%)	-
	Paracetamol	1405 (8.7%)	30 (7.6%)
	Opioids (N02A)	1106 (6.9%)	28 (7.1%)
	Antidepressants (N06A)	650 (4.0%)	13 (3.3%)
	Antiepileptics (N03A)	294 (1.8%)	13 (3.3%)
	Muscle relaxants (M03)	140 (0.9%)	1 (0.3%)
	NSAIDs/Cox-2 inhibitors (M01A)	12569 (77.9%)	293 (74.6%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1530 (9.5%)	44 (11.2%)
	Topical products for joint and muscular pain (M02A)	227 (1.4%)	11 (2.8%)
	Phytotherapy (V03A)	3 (0.0%)	1 (0.3%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

			Included[3] Patients (N=16140)	Excluded[4] Patients (N=393)
Women of childbearing potential				
		Pregnancy	121 (4.6%)	2 (2.0%)
		No contraceptive use	2440 (93.2%)	95 (96.9%)
		Lactation	2 (0.1%)	-
Off label use[5]	Missing (N)		12780	320
	Yes		2909 (86.6%)	65 (89.0%)
	No		451 (13.4%)	8 (11.0%)

Index date[1] : first date in the study period year 1 a patient is prescribed systemic thiocolchicoside
Study period year 1[2] : France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

Table 15.3-10: Patient's characteristics at index date[1] – Study period year 2[2] – GPs France – eligible patients

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		Included[3] Patients (N=34330)	Excluded[4] Patients (N=10205)
Age (years)	N	34317 (100.0)	10198 (99.9)
	Missing (N)	13 (0.0)	7 (0.1)
	Mean (SD)	47.1 (15.69)	42.3 (15.40)
	Median (Q1 - Q3)	47.0 (36.0-58.0)	41.0 (30.0-53.0)
	Range	(3.0,98.0)	(0.0,103.0)
Age (years) -classes	Missing (N)	13	7
	<16 years	212 (0.6%)	55 (0.5%)
	[16;30[	4704 (13.7%)	2386 (23.4%)
	[30;40[	6378 (18.6%)	2320 (22.7%)
	[40;50[	8080 (23.5%)	2224 (21.8%)
	[50;60[	7461 (21.7%)	1700 (16.7%)
	[60;70[	4592 (13.4%)	996 (9.8%)
	≥70 years	2890 (8.4%)	517 (5.1%)
Gender	Missing (N)	-	1
	Male	15200 (44.3%)	5013 (49.1%)
	Female	19130 (55.7%)	5191 (50.9%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

		Included[3] Patients (N=34330)	Excluded[4] Patients (N=10205)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	1849	589
	≤16 mg	31576 (99.8%)	9357 (99.8%)
	>16 mg	67 (0.2%)	21 (0.2%)
Duration of TCC treatment at index date (days)	Missing (N)	1316	357
	≤7 days	21703 (67.5%)	7215 (75.1%)
	>7 days	10473 (32.5%)	2395 (24.9%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	407	159
	≤8 mg	365 (81.5%)	73 (84.9%)
	>8 mg	83 (18.5%)	13 (15.1%)
Duration of TCC treatment at index date (days)	Missing (N)	350	143
	≤5 days	229 (45.3%)	54 (52.9%)
	>5 days	276 (54.7%)	48 (47.1%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	4966	2188
	Other deforming dorsopathies including - M43	992 (3.4%)	327 (4.1%)
	Spondylolysis - M43.0	-	-
	Spondylolisthesis - M43.1	-	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	13 (0.0%)	4 (0.0%)
	Torticollis - M43.6	970 (3.3%)	315 (3.9%)
	Other specified deforming dorsopathies - M43.8	7 (0.0%)	7 (0.1%)
	Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	1 (0.0%)
	Dorsalgia - M54	16276 (55.4%)	4768 (59.5%)
	Radiculopathy - M54.1	153 (0.5%)	35 (0.4%)
	Cervicalgia - M54.2	2932 (10.0%)	793 (9.9%)
	Sciatica - M54.3	829 (2.8%)	219 (2.7%)
	Lumbago with sciatica - M.54.4	1401 (4.8%)	431 (5.4%)
	Low back pain - M54.5	8373 (28.5%)	2538 (31.7%)
	Pain in thoracic spine - M54.6	28 (0.1%)	6 (0.1%)
	Other dorsalgia - M54.8	577 (2.0%)	161 (2.0%)
	Dorsalgia, unspecified - M54.9	1983 (6.8%)	585 (7.3%)
	Other than painful muscle contractures associated with acute spinal pathology	12096 (41.2%)	2922 (36.4%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
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		Included[3] Patients (N=34330)	Excluded[4] Patients (N=10205)
Medications			
	Analgesics (N02)	23102 (67.3%)	6969 (68.3%)
	Acetylsalicylic	291 (0.8%)	45 (0.4%)
	Paracetamol	22220 (64.7%)	6756 (66.2%)
	Opioids (N02A)	7388 (21.5%)	2270 (22.2%)
	Antidepressants (N06A)	2129 (6.2%)	329 (3.2%)
	Antiepileptics (N03A)	809 (2.4%)	130 (1.3%)
	Muscle relaxants (M03)	934 (2.7%)	304 (3.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	21454 (62.5%)	6782 (66.5%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	2510 (7.3%)	586 (5.7%)
	Topical products for joint and muscular pain (M02A)	8660 (25.2%)	2370 (23.2%)
	Phytotherapy (V03A)	10 (0.0%)	-
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	329 (1.0%)	128 (1.3%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

			Included[3] Patients (N=34330)	Excluded[4] Patients (N=10205)
Women of childbearing potential				
		Pregnancy	32 (0.3%)	10 (0.3%)
		No contraceptive use	9516 (89.6%)	3186 (93.7%)
		Lactation	1 (0.0%)	-
Off label use[5]	Missing (N)		6919	2798
	Yes		16752 (61.1%)	3929 (53.0%)
	No		10659 (38.9%)	3478 (47.0%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas;
By: Ncoulombel; Date & time: 04OCT18 12:13;

Table 15.3-11: Patient's characteristics at index date[1] – Study period year 2[2] – Rheumatologists France – eligible patients

		Included[3] Patients (N=1185)	Excluded[4] Patients (N=1014)
Age (years)	N	1184 (99.9)	1014 (100.0)
	Missing (N)	1 (0.1)	0
	Mean (SD)	62.8 (14.37)	53.1 (16.00)
	Median (Q1 - Q3)	63.0 (53.0-73.5)	53.0 (42.0-64.0)
	Range	(17.0,97.0)	(15.0,94.0)
Age (years) -classes	Missing (N)	1	-
	<16 years	-	1 (0.1%)
	[16;30[	13 (1.1%)	78 (7.7%)
	[30;40[	57 (4.8%)	123 (12.1%)
	[40;50[	149 (12.6%)	222 (21.9%)
	[50;60[	270 (22.8%)	252 (24.9%)
	[60;70[	279 (23.6%)	169 (16.7%)
	≥70 years	416 (35.1%)	169 (16.7%)
Gender	Missing (N)	56	-
	Male	295 (26.1%)	331 (32.6%)
	Female	834 (73.9%)	683 (67.4%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=1185)	Excluded[4] Patients (N=1014)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	178	122
	≤16 mg	756 (100.0%)	725 (100.0%)
	>16 mg	-	-
Duration of TCC treatment at index date (days)	Missing (N)	178	122
	≤7 days	367 (48.5%)	400 (55.2%)
	>7 days	389 (51.5%)	325 (44.8%)
IM form			
TCC daily dose prescribed at index date (mg)	≤8 mg	183 (71.8%)	115 (68.9%)
	>8 mg	72 (28.2%)	52 (31.1%)
Duration of TCC treatment at index date (days)	≤5 days	108 (42.4%)	97 (58.1%)
	>5 days	147 (57.6%)	70 (41.9%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-
	Other deforming dorsopathies including - M43	20 (1.7%)	2 (0.2%)
	Spondylolysis - M43.0	-	-
	Spondylolisthesis - M43.1	2 (0.2%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	1 (0.1%)	-
	Other specified deforming dorsopathies - M43.8	-	-
	Deforming dorsopathy, unspecified - M43.9	17 (1.4%)	2 (0.2%)
	Dorsalgia - M54	811 (68.4%)	756 (74.6%)
	Radiculopathy - M54.1	16 (1.4%)	13 (1.3%)
	Cervicalgia - M54.2	217 (18.3%)	246 (24.3%)
	Sciatica - M54.3	13 (1.1%)	15 (1.5%)
	Lumbago with sciatica - M.54.4	118 (10.0%)	150 (14.8%)
	Low back pain - M54.5	301 (25.4%)	196 (19.3%)
	Pain in thoracic spine - M54.6	2 (0.2%)	1 (0.1%)
	Other dorsalgia - M54.8	6 (0.5%)	3 (0.3%)
	Dorsalgia, unspecified - M54.9	138 (11.6%)	132 (13.0%)
	Other than painful muscle contractures associated with acute spinal pathology	354 (29.9%)	256 (25.2%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=1185)	Excluded[4] Patients (N=1014)
Medications			
	Analgesics (N02)	493 (41.6%)	345 (34.0%)
	Acetylsalicylic	2 (0.2%)	-
	Paracetamol	418 (35.3%)	315 (31.1%)
	Opioids (N02A)	208 (17.6%)	160 (15.8%)
	Antidepressants (N06A)	40 (3.4%)	16 (1.6%)
	Antiepileptics (N03A)	43 (3.6%)	35 (3.5%)
	Muscle relaxants (M03)	14 (1.2%)	9 (0.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	586 (49.5%)	457 (45.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	329 (27.8%)	296 (29.2%)
	Topical products for joint and muscular pain (M02A)	95 (8.0%)	30 (3.0%)
	Phytotherapy (V03A)	3 (0.3%)	4 (0.4%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	3 (0.3%)	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=1185)	Excluded[4] Patients (N=1014)
Women of childbearing potential			
	Pregnancy	-	-
	No contraceptive use	149 (100.0%)	279 (100.0%)
	Lactation	-	-
Off label use[5]	Missing (N)	220	123
	Yes	719 (74.5%)	596 (66.9%)
	No	246 (25.5%)	295 (33.1%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-12: Patient's characteristics at index date[1] – Study period year 2[2] – GPs Italy – eligible patients

DUS TCC		Page 1 of 4	
		Included[3] Patients (N=16201)	**Excluded[4] Patients (N=422)**
Age (years)	N	16184 (99.9)	422 (100.0)
	Missing (N)	17 (0.1)	0
	Mean (SD)	56.9 (15.62)	46.7 (15.90)
	Median (Q1 - Q3)	57.0 (46.0-69.0)	46.0 (35.0-56.0)
	Range	(12.0,103.0)	(13.0,93.0)
Age (years) -classes	Missing (N)	17	-
	<16 years	13 (0.1%)	6 (1.4%)
	[16;30[	729 (4.5%)	50 (11.8%)
	[30;40[	1493 (9.2%)	88 (20.9%)
	[40;50[	3076 (19.0%)	119 (28.2%)
	[50;60[	3734 (23.1%)	73 (17.3%)
	[60;70[	3330 (20.6%)	45 (10.7%)
	≥70 years	3809 (23.5%)	41 (9.7%)
Gender	Missing (N)	2360	-
	Male	5075 (36.7%)	219 (51.9%)
	Female	8766 (63.3%)	203 (48.1%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Included[3] Patients (N=16201)	Excluded[4] Patients (N=422)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	2187	72
	≤16 mg	1287 (98.1%)	36 (100.0%)
	>16 mg	25 (1.9%)	-
Duration of TCC treatment at index date (days)	Missing (N)	2187	72
	≤7 days	614 (46.8%)	11 (30.6%)
	>7 days	698 (53.2%)	25 (69.4%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	9958	262
	≤8 mg	2806 (99.9%)	54 (100.0%)
	>8 mg	2 (0.1%)	-
Duration of TCC treatment at index date (days)	Missing (N)	9960	262
	≤5 days	322 (11.5%)	5 (9.3%)
	>5 days	2484 (88.5%)	49 (90.7%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	1424	41
	Other deforming dorsopathies including - M43	642 (4.3%)	9 (2.4%)
	Spondylolysis - M43.0	251 (1.7%)	1 (0.3%)
	Spondylolisthesis - M43.1	15 (0.1%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	224 (1.5%)	7 (1.8%)
	Other specified deforming dorsopathies - M43.8	89 (0.6%)	-
	Deforming dorsopathy, unspecified - M43.9	63 (0.4%)	1 (0.3%)
	Dorsalgia - M54	10761 (72.8%)	294 (77.2%)
	Radiculopathy - M54.1	129 (0.9%)	-
	Cervicalgia - M54.2	1452 (9.8%)	43 (11.3%)
	Sciatica - M54.3	467 (3.2%)	14 (3.7%)
	Lumbago with sciatica - M.54.4	-	-
	Low back pain - M54.5	8289 (56.1%)	226 (59.3%)
	Pain in thoracic spine - M54.6	195 (1.3%)	4 (1.0%)
	Other dorsalgia - M54.8	-	-
	Dorsalgia, unspecified - M54.9	229 (1.5%)	7 (1.8%)
	Other than painful muscle contractures associated with acute spinal pathology	3374 (22.8%)	78 (20.5%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Included[3] Patients (N=16201)	Excluded[4] Patients (N=422)
Medications			
	Analgesics (N02)	1755 (10.8%)	58 (13.7%)
	Acetylsalicylic	9 (0.1%)	-
	Paracetamol	1376 (8.5%)	48 (11.4%)
	Opioids (N02A)	1054 (6.5%)	33 (7.8%)
	Antidepressants (N06A)	645 (4.0%)	15 (3.6%)
	Antiepileptics (N03A)	294 (1.8%)	7 (1.7%)
	Muscle relaxants (M03)	136 (0.8%)	5 (1.2%)
	NSAIDs/Cox-2 inhibitors (M01A)	12623 (77.9%)	323 (76.5%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1638 (10.1%)	39 (9.2%)
	Topical products for joint and muscular pain (M02A)	228 (1.4%)	8 (1.9%)
	Phytotherapy (V03A)	4 (0.0%)	1 (0.2%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Included[3] Patients (N=16201)	Excluded[4] Patients (N=422)
Women of childbearing potential			
	Pregnancy	104 (4.0%)	-
	No contraceptive use	2501 (95.6%)	112 (97.4%)
	Lactation	1 (0.0%)	-
Off label use[5]	Missing (N)	12870	333
	Yes	2865 (86.0%)	82 (92.1%)
	No	466 (14.0%)	7 (7.9%)

Index date[1] : first date in the study period year 2 a patient is prescribed systemic thiocolchicoside
Study period year 2[2] : France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_03_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

Table 15.3-13: Patient's characteristics at index date[1] – Study period year 3[2] – GPs France – eligible patients

DUS TCC		Page 1 of 4	
		Included[3] Patients (N=23079)	**Excluded[4] Patients (N=6521)**
Age (years)	N	23073 (100.0)	6519 (100.0)
	Missing (N)	6 (0.0)	2 (0.0)
	Mean (SD)	48.3 (15.86)	42.8 (15.64)
	Median (Q1 - Q3)	48.0 (37.0-59.0)	41.0 (30.0-53.0)
	Range	(2.0,97.0)	(0.0,94.0)
Age (years) - classes	Missing (N)	6	2
	<16 years	106 (0.5%)	26 (0.4%)
	[16;30[	2862 (12.4%)	1496 (22.9%)
	[30;40[	4177 (18.1%)	1504 (23.1%)
	[40;50[	5230 (22.7%)	1389 (21.3%)
	[50;60[	5111 (22.2%)	1065 (16.3%)
	[60;70[	3221 (14.0%)	666 (10.2%)
	≥70 years	2366 (10.3%)	373 (5.7%)
Gender	Missing (N)	1	-
	Male	10211 (44.2%)	3333 (51.1%)
	Female	12867 (55.8%)	3188 (48.9%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_03_03.sas; By: Alampure; Date & time: 31JUL19 09:09;

		Included[3] Patients (N=23079)	Excluded[4] Patients (N=6521)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	2997	750
	≤16 mg	19288 (99.8%)	5506 (99.7%)
	>16 mg	34 (0.2%)	19 (0.3%)
Duration of TCC treatment at index date (days)	Missing (N)	2579	644
	≤7 days	14041 (71.1%)	4340 (77.1%)
	>7 days	5699 (28.9%)	1291 (22.9%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	474	176
	≤8 mg	268 (89.9%)	61 (83.6%)
	>8 mg	30 (10.1%)	12 (16.4%)
Duration of TCC treatment at index date (days)	Missing (N)	434	168
	≤5 days	170 (50.3%)	50 (61.7%)
	>5 days	168 (49.7%)	31 (38.3%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	3966	1487
	Other deforming dorsopathies including - M43	647 (3.4%)	214 (4.3%)
	Spondylolysis - M43.0	1 (0.0%)	-
	Spondylolisthesis - M43.1	1 (0.0%)	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	13 (0.1%)	2 (0.0%)
	Torticollis - M43.6	624 (3.3%)	206 (4.1%)
	Other specified deforming dorsopathies - M43.8	7 (0.0%)	2 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	1 (0.0%)	3 (0.1%)
	Dorsalgia - M54	10470 (54.8%)	3026 (60.1%)
	Radiculopathy - M54.1	83 (0.4%)	29 (0.6%)
	Cervicalgia - M54.2	1849 (9.7%)	458 (9.1%)
	Sciatica - M54.3	517 (2.7%)	138 (2.7%)
	Lumbago with sciatica - M.54.4	958 (5.0%)	287 (5.7%)
	Low back pain - M54.5	5428 (28.4%)	1643 (32.6%)
	Pain in thoracic spine - M54.6	32 (0.2%)	3 (0.1%)
	Other dorsalgia - M54.8	346 (1.8%)	103 (2.0%)
	Dorsalgia, unspecified - M54.9	1257 (6.6%)	365 (7.3%)
	Other than painful muscle contractures associated with acute spinal pathology	7996 (41.8%)	1794 (35.6%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=23079)	Excluded[4] Patients (N=6521)
Medications			
	Analgesics (N02)	15177 (65.8%)	4330 (66.4%)
	Acetylsalicylic	189 (0.8%)	23 (0.4%)
	Paracetamol	14577 (63.2%)	4173 (64.0%)
	Opioids (N02A)	4949 (21.4%)	1370 (21.0%)
	Antidepressants (N06A)	1329 (5.8%)	205 (3.1%)
	Antiepileptics (N03A)	515 (2.2%)	75 (1.2%)
	Muscle relaxants (M03)	698 (3.0%)	204 (3.1%)
	NSAIDs/Cox-2 inhibitors (M01A)	14145 (61.3%)	4273 (65.5%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1727 (7.5%)	350 (5.4%)
	Topical products for joint and muscular pain (M02A)	5854 (25.4%)	1741 (26.7%)
	Phytotherapy (V03A)	7 (0.0%)	2 (0.0%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	192 (0.8%)	91 (1.4%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_03_03.sas; By: Alampure; Date & time: 31JUL19 09:09;

			Included[3] Patients (N=23079)	Excluded[4] Patients (N=6521)
Women of childbearing potential				
		Pregnancy	49 (0.7%)	11 (0.5%)
		No contraceptive use	6154 (92.0%)	1992 (96.6%)
		Lactation	1 (0.0%)	1 (0.0%)
Off label use[5]	Missing (N)		6668	2165
	Yes		9879 (60.2%)	2245 (51.5%)
	No		6532 (39.8%)	2111 (48.5%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_03_03.sas; By: Alampure; Date & time: 31JUL19 09:09;

Table 15.3-14: Patient's characteristics at index date[1] – Study period year 3[2] – Rheumatologists France – eligible patients

		Included[3] Patients (N=1063)	Excluded[4] Patients (N=752)
Age (years)	N	1062 (99.9)	751 (99.9)
	Missing (N)	1 (0.1)	1 (0.1)
	Mean (SD)	62.7 (14.54)	51.9 (16.22)
	Median (Q1 - Q3)	63.0 (53.0-73.0)	51.0 (39.0-64.0)
	Range	(14.0,98.0)	(15.0,93.0)
Age (years) - classes	Missing (N)	1	1
	<16 years	1 (0.1%)	1 (0.1%)
	[16;30[	17 (1.6%)	64 (8.5%)
	[30;40[	44 (4.1%)	124 (16.5%)
	[40;50[	133 (12.5%)	160 (21.3%)
	[50;60[	250 (23.5%)	151 (20.1%)
	[60;70[	244 (23.0%)	132 (17.6%)
	≥70 years	373 (35.1%)	119 (15.8%)
Gender	Missing (N)	43	1
	Male	278 (27.3%)	269 (35.8%)
	Female	742 (72.7%)	482 (64.2%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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			Included[3] Patients (N=1063)	Excluded[4] Patients (N=752)
Oral form				
	TCC daily dose prescribed at index date (mg)	Missing (N)	170	162
		≤16 mg	713 (100.0%)	484 (100.0%)
		>16 mg	-	-
	Duration of TCC treatment at index date (days)	Missing (N)	170	162
		≤7 days	397 (55.7%)	346 (71.5%)
		>7 days	316 (44.3%)	138 (28.5%)
IM form				
	TCC daily dose prescribed at index date (mg)	≤8 mg	110 (59.1%)	69 (65.1%)
		>8 mg	76 (40.9%)	37 (34.9%)
	Duration of TCC treatment at index date (days)	≤5 days	96 (51.6%)	63 (59.4%)
		>5 days	90 (48.4%)	43 (40.6%)
Treatment indication for TCC prescription at index date (ICD10)		Missing	-	-
		Other deforming dorsopathies including - M43	12 (1.1%)	2 (0.3%)
		Spondylolysis - M43.0	1 (0.1%)	-
		Spondylolisthesis - M43.1	-	-
		Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
		Other recurrent atlantoaxial dislocation - M43.4	-	-
		Other recurrent vertebral dislocation - M43.5	-	-
		Torticollis - M43.6	1 (0.1%)	1 (0.1%)
		Other specified deforming dorsopathies - M43.8	-	-
		Deforming dorsopathy, unspecified - M43.9	10 (0.9%)	1 (0.1%)
		Dorsalgia - M54	741 (69.7%)	523 (69.5%)
		Radiculopathy - M54.1	21 (2.0%)	9 (1.2%)
		Cervicalgia - M54.2	199 (18.7%)	172 (22.9%)
		Sciatica - M54.3	19 (1.8%)	15 (2.0%)
		Lumbago with sciatica - M.54.4	98 (9.2%)	103 (13.7%)
		Low back pain - M54.5	303 (28.5%)	165 (21.9%)
		Pain in thoracic spine - M54.6	1 (0.1%)	2 (0.3%)
		Other dorsalgia - M54.8	1 (0.1%)	2 (0.3%)
		Dorsalgia, unspecified - M54.9	99 (9.3%)	55 (7.3%)
		Other than painful muscle contractures associated with acute spinal pathology	310 (29.2%)	227 (30.2%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

		Included[3] Patients (N=1063)	Excluded[4] Patients (N=752)
Medications			
	Analgesics (N02)	425 (40.0%)	242 (32.2%)
	Acetylsalicylic	2 (0.2%)	-
	Paracetamol	352 (33.1%)	206 (27.4%)
	Opioids (N02A)	153 (14.4%)	111 (14.8%)
	Antidepressants (N06A)	39 (3.7%)	21 (2.8%)
	Antiepileptics (N03A)	28 (2.6%)	20 (2.7%)
	Muscle relaxants (M03)	13 (1.2%)	3 (0.4%)
	NSAIDs/Cox-2 inhibitors (M01A)	587 (55.2%)	398 (52.9%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	301 (28.3%)	196 (26.1%)
	Topical products for joint and muscular pain (M02A)	81 (7.6%)	19 (2.5%)
	Phytotherapy (V03A)	1 (0.1%)	1 (0.1%)
Health services/medical devices and others:			
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	1 (0.1%)	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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			Included[3] Patients (N=1063)	Excluded[4] Patients (N=752)
Women of childbearing potential				
		Pregnancy	-	-
		No contraceptive use	136 (100.0%)	225 (100.0%)
		Lactation	-	-
Off label use[5]	Missing (N)		207	163
	Yes		587 (68.6%)	353 (59.9%)
	No		269 (31.4%)	236 (40.1%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-15: Patient's characteristics at index date[1] – Study period year 3[2] – GPs Italy – eligible patients

		Included[3] Patients (N=14957)	Excluded[4] Patients (N=392)
Age (years)	N	14939 (99.9)	392 (100.0)
	Missing (N)	18 (0.1)	0
	Mean (SD)	57.4 (15.57)	47.6 (16.10)
	Median (Q1 - Q3)	57.0 (46.0-69.0)	46.0 (35.5-57.5)
	Range	(11.0,103.0)	(11.0,97.0)
Age (years) - classes	Missing (N)	18	-
	<16 years	9 (0.1%)	4 (1.0%)
	[16;30[	609 (4.1%)	46 (11.7%)
	[30;40[	1355 (9.1%)	77 (19.6%)
	[40;50[	2735 (18.3%)	96 (24.5%)
	[50;60[	3467 (23.2%)	78 (19.9%)
	[60;70[	3105 (20.8%)	54 (13.8%)
	≥70 years	3659 (24.5%)	37 (9.4%)
Gender	Missing (N)	2152	-
	Male	4717 (36.8%)	209 (53.3%)
	Female	8088 (63.2%)	183 (46.7%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=14957)	Excluded[4] Patients (N=392)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	2140	75
	≤16 mg	1139 (98.2%)	27 (96.4%)
	>16 mg	21 (1.8%)	1 (3.6%)
Duration of TCC treatment at index date (days)	Missing (N)	2140	75
	≤7 days	568 (49.0%)	14 (50.0%)
	>7 days	592 (51.0%)	14 (50.0%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	9207	234
	≤8 mg	2503 (99.9%)	55 (100.0%)
	>8 mg	2 (0.1%)	-
Duration of TCC treatment at index date (days)	Missing (N)	9207	234
	≤5 days	290 (11.6%)	11 (20.0%)
	>5 days	2215 (88.4%)	44 (80.0%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	1354	36
	Other deforming dorsopathies including - M43	577 (4.2%)	14 (3.9%)
	Spondylolysis - M43.0	238 (1.7%)	-
	Spondylolisthesis - M43.1	10 (0.1%)	1 (0.3%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	214 (1.6%)	12 (3.4%)
	Other specified deforming dorsopathies - M43.8	70 (0.5%)	-
	Deforming dorsopathy, unspecified - M43.9	45 (0.3%)	1 (0.3%)
	Dorsalgia - M54	10017 (73.6%)	274 (77.0%)
	Radiculopathy - M54.1	97 (0.7%)	-
	Cervicalgia - M54.2	1350 (9.9%)	38 (10.7%)
	Sciatica - M54.3	418 (3.1%)	10 (2.8%)
	Lumbago with sciatica - M.54.4	-	-
	Low back pain - M54.5	7771 (57.1%)	218 (61.2%)
	Pain in thoracic spine - M54.6	159 (1.2%)	2 (0.6%)
	Other dorsalgia - M54.8	-	-
	Dorsalgia, unspecified - M54.9	222 (1.6%)	6 (1.7%)
	Other than painful muscle contractures associated with acute spinal pathology	3009 (22.1%)	68 (19.1%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

		Included[3] Patients (N=14957)	Excluded[4] Patients (N=392)
Medications			
	Analgesics (N02)	1602 (10.7%)	42 (10.7%)
	Acetylsalicylic	5 (0.0%)	-
	Paracetamol	1262 (8.4%)	39 (9.9%)
	Opioids (N02A)	976 (6.5%)	21 (5.4%)
	Antidepressants (N06A)	617 (4.1%)	7 (1.8%)
	Antiepileptics (N03A)	300 (2.0%)	6 (1.5%)
	Muscle relaxants (M03)	114 (0.8%)	4 (1.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	11667 (78.0%)	295 (75.3%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	1590 (10.6%)	45 (11.5%)
	Topical products for joint and muscular pain (M02A)	173 (1.2%)	10 (2.6%)
	Phytotherapy (V03A)	5 (0.0%)	-
Health services/medical devices and others:			
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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			Included[3] Patients (N=14957)	Excluded[4] Patients (N=392)
Women of childbearing potential				
		Pregnancy	92 (4.0%)	4 (4.7%)
		No contraceptive use	2186 (96.1%)	81 (94.2%)
		Lactation	-	-
Off label use[5]	Missing (N)		12011	311
	Yes		2515 (85.4%)	63 (77.8%)
	No		431 (14.6%)	18 (22.2%)

Index date[1] : first date in the study period year 3 a patient is prescribed systemic thiocolchicoside
Study period year 3[2] : France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_03_03.sas; By: Alampure; Date & time: 19AUG19 09:36;

Table 15.3-16: Patient's characteristics at index date[1] – Cumulated study periods (years 1, 2 and 3)[2] – GPs France – eligible patients

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		Included[3] Patients (N=81690)	Excluded[4] Patients (N=25723)
Age (years)	N	81668 (100.0)	25705 (99.9)
	Missing (N)	22 (0.0)	18 (0.1)
	Mean (SD)	46.9 (15.93)	42.0 (15.45)
	Median (Q1 - Q3)	47.0 (35.0-58.0)	40.0 (30.0-53.0)
	Range	(2.0,100.0)	(0.0,103.0)
Age (years) - classes	Missing (N)	22	18
	<16 years	570 (0.7%)	151 (0.6%)
	[16;30[	11877 (14.5%)	6233 (24.2%)
	[30;40[	15222 (18.6%)	5945 (23.1%)
	[40;50[	18913 (23.2%)	5471 (21.3%)
	[50;60[	17210 (21.1%)	4215 (16.4%)
	[60;70[	10767 (13.2%)	2395 (9.3%)
	≥70 years	7109 (8.7%)	1295 (5.0%)
Gender	Missing (N)	1	1
	Male	36478 (44.7%)	12803 (49.8%)
	Female	45211 (55.3%)	12919 (50.2%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=81690)	Excluded[4] Patients (N=25723)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	5735	1842
	≤16 mg	73625 (99.8%)	23127 (99.7%)
	>16 mg	159 (0.2%)	67 (0.3%)
Duration of TCC treatment at index date (days)	Missing (N)	4179	1263
	≤7 days	51983 (69.0%)	17894 (75.3%)
	>7 days	23357 (31.0%)	5879 (24.7%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	1142	448
	≤8 mg	883 (80.8%)	229 (87.4%)
	>8 mg	210 (19.2%)	33 (12.6%)
Duration of TCC treatment at index date (days)	Missing (N)	1011	411
	≤5 days	630 (51.5%)	184 (61.5%)
	>5 days	594 (48.5%)	115 (38.5%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	11572	5454
	Other deforming dorsopathies including - M43	2519 (3.6%)	808 (4.0%)
	Spondylolysis - M43.0	-	-
	Spondylolisthesis - M43.1	8 (0.0%)	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	12 (0.0%)	4 (0.0%)
	Torticollis - M43.6	2483 (3.5%)	793 (3.9%)
	Other specified deforming dorsopathies - M43.8	12 (0.0%)	7 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	4 (0.0%)	3 (0.0%)
	Dorsalgia - M54	39483 (56.3%)	12233 (60.4%)
	Radiculopathy - M54.1	336 (0.5%)	93 (0.5%)
	Cervicalgia - M54.2	7166 (10.2%)	1979 (9.8%)
	Sciatica - M54.3	2008 (2.9%)	624 (3.1%)
	Lumbago with sciatica - M.54.4	3471 (5.0%)	1084 (5.3%)
	Low back pain - M54.5	20130 (28.7%)	6446 (31.8%)
	Pain in thoracic spine - M54.6	76 (0.1%)	20 (0.1%)
	Other dorsalgia - M54.8	1421 (2.0%)	462 (2.3%)
	Dorsalgia, unspecified - M54.9	4875 (7.0%)	1525 (7.5%)
	Other than painful muscle contractures associated with acute spinal pathology	28116 (40.1%)	7228 (35.7%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=81690)	Excluded[4] Patients (N=25723)
Medications			
	Analgesics (N02)	54493 (66.7%)	17580 (68.3%)
	Acetylsalicylic	610 (0.7%)	116 (0.5%)
	Paracetamol	52613 (64.4%)	17033 (66.2%)
	Opioids (N02A)	16927 (20.7%)	5514 (21.4%)
	Antidepressants (N06A)	4506 (5.5%)	757 (2.9%)
	Antiepileptics (N03A)	1694 (2.1%)	284 (1.1%)
	Muscle relaxants (M03)	2014 (2.5%)	743 (2.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	51370 (62.9%)	17232 (67.0%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	5624 (6.9%)	1404 (5.5%)
	Topical products for joint and muscular pain (M02A)	19745 (24.2%)	6097 (23.7%)
	Phytotherapy (V03A)	27 (0.0%)	2 (0.0%)
Health services/medical devices and others:			
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	812 (1.0%)	332 (1.3%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_03_04.sas; By: Alampure; Date & time: 01AUG19 09:55;

			Included[3] Patients (N=81690)	Excluded[4] Patients (N=25723)
Women of childbearing potential				
		Pregnancy	108 (0.4%)	27 (0.3%)
		No contraceptive use	22854 (90.6%)	8159 (95.3%)
		Lactation	5 (0.0%)	1 (0.0%)
Off label use[5]	Missing (N)		17332	7274
	Yes		38651 (60.1%)	9723 (52.7%)
	No		25707 (39.9%)	8726 (47.3%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-17: Patient's characteristics at index date[1] – Cumulated study periods (years 1, 2 and 3)[2] – Rheumatologists France – eligible patients

		Included[3] Patients (N=3016)	Excluded[4] Patients (N=2766)
Age (years)	N	3014 (99.9)	2765 (100.0)
	Missing (N)	2 (0.1)	1 (0.0)
	Mean (SD)	62.3 (14.53)	52.4 (16.01)
	Median (Q1 - Q3)	63.0 (53.0-73.0)	52.0 (41.0-63.0)
	Range	(14.0,98.0)	(15.0,94.0)
Age (years) - classes	Missing (N)	2	1
	<16 years	1 (0.0%)	3 (0.1%)
	[16;30[	41 (1.4%)	223 (8.1%)
	[30;40[	154 (5.1%)	389 (14.1%)
	[40;50[	398 (13.2%)	597 (21.6%)
	[50;60[	684 (22.7%)	657 (23.8%)
	[60;70[	737 (24.5%)	456 (16.5%)
	≥70 years	999 (33.1%)	440 (15.9%)
Gender	Missing (N)	118	1
	Male	803 (27.7%)	967 (35.0%)
	Female	2095 (72.3%)	1798 (65.0%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=3016)	Excluded[4] Patients (N=2766)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	446	393
	≤16 mg	1967 (100.0%)	1922 (99.9%)
	>16 mg	-	2 (0.1%)
Duration of TCC treatment at index date (days)	Missing (N)	446	394
	≤7 days	1097 (55.8%)	1192 (62.0%)
	>7 days	870 (44.2%)	731 (38.0%)
IM form			
TCC daily dose prescribed at index date (mg)	≤8 mg	424 (69.2%)	307 (68.2%)
	>8 mg	189 (30.8%)	143 (31.8%)
Duration of TCC treatment at index date (days)	≤5 days	270 (44.0%)	257 (57.1%)
	>5 days	343 (56.0%)	193 (42.9%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-
	Other deforming dorsopathies including - M43	40 (1.3%)	8 (0.3%)
	Spondylolysis - M43.0	1 (0.0%)	-
	Spondylolisthesis - M43.1	3 (0.1%)	2 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	5 (0.2%)	1 (0.0%)
	Other specified deforming dorsopathies - M43.8	-	-
	Deforming dorsopathy, unspecified - M43.9	31 (1.0%)	5 (0.2%)
	Dorsalgia - M54	2036 (67.5%)	2028 (73.3%)
	Radiculopathy - M54.1	45 (1.5%)	32 (1.2%)
	Cervicalgia - M54.2	573 (19.0%)	663 (24.0%)
	Sciatica - M54.3	36 (1.2%)	48 (1.7%)
	Lumbago with sciatica - M.54.4	302 (10.0%)	360 (13.0%)
	Low back pain - M54.5	753 (25.0%)	596 (21.5%)
	Pain in thoracic spine - M54.6	3 (0.1%)	3 (0.1%)
	Other dorsalgia - M54.8	8 (0.3%)	8 (0.3%)
	Dorsalgia, unspecified - M54.9	316 (10.5%)	318 (11.5%)
	Other than painful muscle contractures associated with acute spinal pathology	940 (31.2%)	730 (26.4%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

		Included[3] Patients (N=3016)	Excluded[4] Patients (N=2766)
Medications			
	Analgesics (N02)	1223 (40.6%)	934 (33.8%)
	Acetylsalicylic	4 (0.1%)	1 (0.0%)
	Paracetamol	1036 (34.4%)	810 (29.3%)
	Opioids (N02A)	474 (15.7%)	416 (15.0%)
	Antidepressants (N06A)	77 (2.6%)	62 (2.2%)
	Antiepileptics (N03A)	88 (2.9%)	96 (3.5%)
	Muscle relaxants (M03)	29 (1.0%)	22 (0.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	1528 (50.7%)	1349 (48.8%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	856 (28.4%)	791 (28.6%)
	Topical products for joint and muscular pain (M02A)	220 (7.3%)	85 (3.1%)
	Phytotherapy (V03A)	5 (0.2%)	8 (0.3%)
Health services/medical devices and others:			
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	5 (0.2%)	1 (0.0%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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		Included[3] Patients (N=3016)	Excluded[4] Patients (N=2766)
Women of childbearing potential			
	Pregnancy	-	-
	No contraceptive use	401 (100.0%)	779 (100.0%)
	Lactation	-	-
Off label use[5]	Missing (N)	547	396
	Yes	1737 (70.4%)	1503 (63.4%)
	No	732 (29.6%)	867 (36.6%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-18: Patient's characteristics at index date[1] – Cumulated study periods (years 1, 2 and 3)[2] – GPs Italy – eligible patients

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		Included[3] Patients (N=41061)	Excluded[4] Patients (N=1085)
Age (years)	N	41021 (99.9)	1085 (100.0)
	Missing (N)	40 (0.1)	0
	Mean (SD)	56.6 (15.73)	47.2 (16.03)
	Median (Q1 - Q3)	57.0 (46.0-69.0)	46.0 (36.0-57.0)
	Range	(11.0,103.0)	(11.0,97.0)
Age (years) - classes	Missing (N)	40	-
	<16 years	30 (0.1%)	15 (1.4%)
	[16;30[	1912 (4.7%)	130 (12.0%)
	[30;40[	3968 (9.7%)	216 (19.9%)
	[40;50[	7891 (19.2%)	288 (26.5%)
	[50;60[	9393 (22.9%)	200 (18.4%)
	[60;70[	8348 (20.4%)	128 (11.8%)
	≥70 years	9479 (23.1%)	108 (10.0%)
Gender	Missing (N)	5863	-
	Male	13021 (37.0%)	557 (51.3%)
	Female	22177 (63.0%)	528 (48.7%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
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		Included[3] Patients (N=41061)	Excluded[4] Patients (N=1085)
Oral form			
TCC daily dose prescribed at index date (mg)	Missing (N)	6255	202
	≤16 mg	3412 (98.6%)	90 (98.9%)
	>16 mg	48 (1.4%)	1 (1.1%)
Duration of TCC treatment at index date (days)	Missing (N)	6256	202
	≤7 days	1633 (47.2%)	34 (37.4%)
	>7 days	1826 (52.8%)	57 (62.6%)
IM form			
TCC daily dose prescribed at index date (mg)	Missing (N)	24645	657
	≤8 mg	6871 (99.9%)	135 (99.3%)
	>8 mg	7 (0.1%)	1 (0.7%)
Duration of TCC treatment at index date (days)	Missing (N)	24647	657
	≤5 days	843 (12.3%)	20 (14.7%)
	>5 days	6033 (87.7%)	116 (85.3%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	3617	105
	Other deforming dorsopathies including - M43	1648 (4.4%)	27 (2.8%)
	Spondylolysis - M43.0	625 (1.7%)	3 (0.3%)
	Spondylolisthesis - M43.1	40 (0.1%)	1 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-
	Other recurrent vertebral dislocation - M43.5	-	-
	Torticollis - M43.6	633 (1.7%)	19 (1.9%)
	Other specified deforming dorsopathies - M43.8	218 (0.6%)	1 (0.1%)
	Deforming dorsopathy, unspecified - M43.9	132 (0.4%)	3 (0.3%)
	Dorsalgia - M54	27142 (72.5%)	749 (76.4%)
	Radiculopathy - M54.1	283 (0.8%)	-
	Cervicalgia - M54.2	3853 (10.3%)	114 (11.6%)
	Sciatica - M54.3	1177 (3.1%)	31 (3.2%)
	Lumbago with sciatica - M.54.4	-	-
	Low back pain - M54.5	20786 (55.5%)	580 (59.2%)
	Pain in thoracic spine - M54.6	453 (1.2%)	7 (0.7%)
	Other dorsalgia - M54.8	-	-
	Dorsalgia, unspecified - M54.9	590 (1.6%)	17 (1.7%)
	Other than painful muscle contractures associated with acute spinal pathology	8654 (23.1%)	204 (20.8%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
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Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

		Included[3] Patients (N=41061)	Excluded[4] Patients (N=1085)
Medications			
	Analgesics (N02)	4474 (10.9%)	129 (11.9%)
	Acetylsalicylic	20 (0.0%)	-
	Paracetamol	3583 (8.7%)	110 (10.1%)
	Opioids (N02A)	2719 (6.6%)	74 (6.8%)
	Antidepressants (N06A)	1623 (4.0%)	27 (2.5%)
	Antiepileptics (N03A)	739 (1.8%)	23 (2.1%)
	Muscle relaxants (M03)	338 (0.8%)	10 (0.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	31846 (77.6%)	813 (74.9%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-
	Corticosteroids for systemic use (H02A)	4094 (10.0%)	113 (10.4%)
	Topical products for joint and muscular pain (M02A)	576 (1.4%)	27 (2.5%)
	Phytotherapy (V03A)	10 (0.0%)	2 (0.2%)
Health services/medical devices and others:			
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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			Included[3] Patients (N=41061)	Excluded[4] Patients (N=1085)
Women of childbearing potential				
		Pregnancy	291 (4.3%)	6 (2.1%)
		No contraceptive use	6439 (94.9%)	270 (96.1%)
		Lactation	3 (0.0%)	-
Off label use[5]	Missing (N)		32664	865
	Yes		7183 (85.5%)	190 (86.4%)
	No		1214 (14.5%)	30 (13.6%)

Index date[1] : first date in the study period a patient is prescribed systemic thiocolchicoside
Study period years 1, 2 and 3[2] : France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Patients included[3]: at least one year of enrollment in the database
Patients excluded[4]: less than one year of enrollment in the database
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Analysis of systemic TCC prescriptions in included patients

Table 15.3-19: Analysis of systemic TCC prescriptions – Baseline and study period year 1 – GPs France – included patients

			Study period year 1[2]	
		Baseline period[1] (N=44108)	Overall (N=49100)	Incident[3] (N=20356)
Total systemic TCC prescriptions		44108 (100.0%)	49100 (100.0%)	20356 (100.0%)
Number of patients with a systemic TCC prescription		34460	37771	20327
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	37771 (100.0)	20327 (100.0)
	Mean (SD)	1.3 (0.86)	1.3 (0.86)	1.0 (0.04)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,20.0)	(1.0,24.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	6140	2568
	Other deforming dorsopathies including - M43	1115 (3.0%)	1229 (2.9%)	747 (4.2%)
	Spondylolysis - M43.0	-	-	-
	Spondylolisthesis - M43.1	5 (0.0%)	9 (0.0%)	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	1108 (2.9%)	1219 (2.8%)	745 (4.2%)
	Other specified deforming dorsopathies - M43.8	-	-	-
	Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	1 (0.0%)	1 (0.0%)
	Dorsalgia - M54	18942 (50.4%)	22028 (51.3%)	10006 (56.3%)
	Radiculopathy - M54.1	144 (0.4%)	187 (0.4%)	74 (0.4%)
	Cervicalgia - M54.2	3536 (9.4%)	4034 (9.4%)	1881 (10.6%)
	Sciatica - M54.3	1124 (3.0%)	1218 (2.8%)	519 (2.9%)
	Lumbago with sciatica - M.54.4	1707 (4.5%)	2067 (4.8%)	857 (4.8%)
	Low back pain - M54.5	9182 (24.4%)	11006 (25.6%)	5038 (28.3%)
	Pain in thoracic spine - M54.6	18 (0.0%)	39 (0.1%)	17 (0.1%)
	Other dorsalgia - M54.8	688 (1.8%)	789 (1.8%)	366 (2.1%)
	Dorsalgia, unspecified - M54.9	2543 (6.8%)	2688 (6.3%)	1254 (7.0%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	19703 (45.9%)	7035 (39.5%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	875 (2.0%)	380 (2.1%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	685 (1.6%)	160 (0.9%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	624 (1.5%)	144 (0.8%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	812 (1.9%)	263 (1.5%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	5547 (12.9%)	2403 (13.5%)
	Contracture of muscle - M62.4	1129 (3.0%)	1226 (2.9%)	680 (3.8%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	1380 (3.2%)	555 (3.1%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	1354 (3.2%)	725 (4.1%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	7659 (17.8%)	2131 (12.0%)

	Baseline period[1] (N=44108)	Study period year 1[2] Overall (N=49100)	Incident[3] (N=20356)
Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	4882 (11.4%)	1128 (6.3%)
Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	1523 (3.5%)	621 (3.5%)
Other	1049 (2.8%)	1391 (3.2%)	418 (2.3%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=44108)	Study period year 1[2] Overall (N=49100)	Study period year 1[2] Incident[3] (N=20356)
Age at prescription (years)	Missing (N)	20	5	3
	<16 years	452 (1.0%)	306 (0.6%)	239 (1.2%)
	[16;30[	6208 (14.1%)	6269 (12.8%)	3682 (18.1%)
	[30;40[	8075 (18.3%)	8786 (17.9%)	3840 (18.9%)
	[40;50[	10817 (24.5%)	11599 (23.6%)	4484 (22.0%)
	[50;60[	9475 (21.5%)	10961 (22.3%)	3780 (18.6%)
	[60;70[	5453 (12.4%)	6872 (14.0%)	2576 (12.7%)
	≥70 years	3608 (8.2%)	4302 (8.8%)	1752 (8.6%)
Age at prescription (years)	N	44088 (100.0)	49095 (100.0)	20353 (100.0)
	Missing (N)	20 (0.0)	5 (0.0)	3 (0.0)
	Mean (SD)	46.6 (15.74)	47.7 (15.61)	45.5 (16.62)
	Median (Q1 - Q3)	46.0 (35.0-57.0)	47.0 (36.0-58.0)	45.0 (33.0-57.0)
	Range	(2.0,98.0)	(2.0,100.0)	(2.0,99.0)
Gender	Missing (N)	35	-	-
	Male	18813 (42.7%)	21508 (43.8%)	9254 (45.5%)
	Female	25260 (57.3%)	27592 (56.2%)	11102 (54.5%)
Route of systemic TCC prescription	Intramuscular	1543 (3.5%)	1355 (2.8%)	472 (2.3%)
	Oral	42565 (96.5%)	47745 (97.2%)	19884 (97.7%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=44108)	Study period year 1[2] Overall (N=49100)	Incident[3] (N=20356)
Oral form				
TCC daily dose	N	40242 (94.5)	44905 (94.1)	18666 (93.9)
	Missing (N)	2323 (5.5)	2840 (5.9)	1218 (6.1)
	Mean (SD)	11.5 (3.67)	11.5 (3.71)	11.8 (3.77)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(2.0,132.0)	(2.0,48.0)	(2.0,48.0)
	Missing (N)	2323	2840	1218
	≤16 mg	40130 (99.7%)	44812 (99.8%)	18625 (99.8%)
	>16 mg	112 (0.3%)	93 (0.2%)	41 (0.2%)
Duration of systemic TCC treatment (days)	N	40830 (95.9)	45957 (96.3)	19160 (96.4)
	Missing (N)	1735 (4.1)	1788 (3.7)	724 (3.6)
	Mean (SD)	10.8 (12.32)	8.8 (10.48)	7.7 (7.66)
	Median (Q1 - Q3)	8.0 (6.0-10.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)
	Range	(1.0,364.0)	(1.0,336.0)	(1.0,336.0)
	Missing (N)	1735	1788	724
	≤7 days	19067 (46.7%)	29997 (65.3%)	13447 (70.2%)
	>7 days	21763 (53.3%)	15960 (34.7%)	5713 (29.8%)
Intramuscular				
TCC daily dose	N	926 (60.0)	641 (47.3)	248 (52.5)
	Missing (N)	617 (40.0)	714 (52.7)	224 (47.5)
	Mean (SD)	9.3 (4.35)	9.2 (5.16)	8.8 (3.99)
	Median (Q1 - Q3)	8.0 (6.0-12.0)	8.0 (8.0-8.0)	8.0 (8.0-8.0)
	Range	(4.0,24.0)	(4.0,28.0)	(4.0,16.0)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=44108)	Study period year 1[2] Overall (N=49100)	Incident[3] (N=20356)
	Missing (N)	617	714	224
	≤8 mg	589 (63.6%)	489 (76.3%)	190 (76.6%)
	>8 mg	337 (36.4%)	152 (23.7%)	58 (23.4%)
Duration of systemic TCC treatment (days)	N	859 (55.7)	719 (53.1)	277 (58.7)
	Missing (N)	684 (44.3)	636 (46.9)	195 (41.3)
	Mean (SD)	8.6 (11.11)	6.3 (7.59)	6.0 (5.28)
	Median (Q1 - Q3)	6.0 (5.0-8.0)	5.0 (5.0-6.0)	5.0 (4.0-6.0)
	Range	(1.0,231.0)	(1.0,168.0)	(1.0,49.0)
	Missing (N)	684	636	195
	≤5 days	261 (30.4%)	381 (53.0%)	163 (58.8%)
	>5 days	598 (69.6%)	338 (47.0%)	114 (41.2%)
Long term treatment[4]	Missing (N)	512	656	-
	Yes	2289 (5.3%)	1765 (3.6%)	-
	No	41307 (94.7%)	46679 (96.4%)	20356 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	41234 (93.5%)	45514 (92.7%)	18625 (91.5%)
	No	2874 (6.5%)	3586 (7.3%)	1731 (8.5%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medication				
	Analgesics (N02)	31393 (71.2%)	34298 (69.9%)	13437 (66.0%)
	Acetylsalicylic	251 (0.6%)	484 (1.0%)	143 (0.7%)
	Paracetamol	30435 (69.0%)	32936 (67.1%)	13017 (63.9%)
	Opioids (N02A)	10908 (24.7%)	11690 (23.8%)	4028 (19.8%)
	Antidepressants (N06A)	3781 (8.6%)	3816 (7.8%)	953 (4.7%)
	Antiepileptics (N03A)	1439 (3.3%)	1490 (3.0%)	319 (1.6%)
	Muscle relaxants (M03)	3076 (7.0%)	1408 (2.9%)	363 (1.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	27801 (63.0%)	30663 (62.5%)	12835 (63.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2699 (6.1%)	3647 (7.4%)	1318 (6.5%)
	Topical products for joint and muscular pain (M02A)	9988 (22.6%)	11519 (23.5%)	4698 (23.1%)
	Phytotherapy (V03A)	16 (0.0%)	16 (0.0%)	9 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	727 (1.6%)	535 (1.1%)	210 (1.0%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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Table 15.3-20: Analysis of systemic TCC prescriptions – Baseline and study period year 1 – Rheumatologists France – included patients

			Study period year 1[2]	
		Baseline period[1] (N=1721)	Overall (N=1494)	Incident[3] (N=685)
Total systemic TCC prescriptions		1721 (100.0%)	1494 (100.0%)	685 (100.0%)
Number of patients with a systemic TCC prescription		1383	1247	684
Number of systemic TCC prescriptions per patient	N	1383 (100.0)	1247 (100.0)	684 (100.0)
	Mean (SD)	1.2 (0.65)	1.2 (0.58)	1.0 (0.04)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,10.0)	(1.0,7.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	18 (1.2%)	11 (1.6%)
	Spondylolysis - M43.0	-	-	-
	Spondylolisthesis - M43.1	-	1 (0.1%)	1 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	4 (0.2%)	4 (0.3%)	3 (0.4%)
	Other specified deforming dorsopathies - M43.8	-	-	-
	Deforming dorsopathy, unspecified - M43.9	14 (0.8%)	13 (0.9%)	7 (1.0%)
	Dorsalgia - M54	1209 (70.2%)	1033 (69.1%)	429 (62.6%)
	Radiculopathy - M54.1	21 (1.2%)	20 (1.3%)	9 (1.3%)
	Cervicalgia - M54.2	346 (20.1%)	272 (18.2%)	129 (18.8%)
	Sciatica - M54.3	34 (2.0%)	10 (0.7%)	8 (1.2%)
	Lumbago with sciatica - M.54.4	188 (10.9%)	183 (12.2%)	70 (10.2%)
	Low back pain - M54.5	470 (27.3%)	351 (23.5%)	153 (22.3%)
	Pain in thoracic spine - M54.6	-	-	-
	Other dorsalgia - M54.8	2 (0.1%)	3 (0.2%)	1 (0.1%)
	Dorsalgia, unspecified - M54.9	148 (8.6%)	194 (13.0%)	59 (8.6%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	443 (29.7%)	245 (35.8%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	369 (24.7%)	205 (29.9%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	38 (2.5%)	29 (4.2%)
	Other specified arthrosis - M19.8	29 (1.7%)	11 (0.7%)	7 (1.0%)
	Pain in shoulder - M25.51	21 (1.2%)	21 (1.4%)	12 (1.8%)
	Pain in knee - M25.56	24 (1.4%)	17 (1.1%)	7 (1.0%)
	Other spondylosis - M47.8	44 (2.6%)	38 (2.5%)	18 (2.6%)
	Other shoulder lesions - M75.8	41 (2.4%)	26 (1.7%)	14 (2.0%)
	Enthesopathy, unspecified - M77.9	18 (1.0%)	12 (0.8%)	7 (1.0%)
	Rheumatism, unspecified - M79.0	16 (0.9%)	18 (1.2%)	6 (0.9%)
	Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	50 (3.3%)	27 (3.9%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	31 (2.1%)	16 (2.3%)
	Pain, unspecified - R52.9	31 (1.8%)	30 (2.0%)	15 (2.2%)
	Other	25 (1.5%)	43 (2.9%)	24 (3.5%)

	Baseline period[1] (N=1721)	Study period year 1[2] Overall (N=1494)	Incident[3] (N=685)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription

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		Baseline period[1] (N=1721)	Study period year 1[2] Overall (N=1494)	Study period year 1[2] Incident[3] (N=685)
Age at prescription (years)	Missing (N)	-	1	1
	<16 years	-	-	-
	[16;30[	26 (1.5%)	13 (0.9%)	9 (1.3%)
	[30;40[	98 (5.7%)	76 (5.1%)	39 (5.7%)
	[40;50[	288 (16.7%)	202 (13.5%)	76 (11.1%)
	[50;60[	420 (24.4%)	361 (24.2%)	155 (22.7%)
	[60;70[	414 (24.1%)	393 (26.3%)	182 (26.6%)
	≥70 years	475 (27.6%)	448 (30.0%)	223 (32.6%)
Age at prescription (years)	N	1721 (100.0)	1493 (99.9)	684 (99.9)
	Missing (N)	0	1 (0.1)	1 (0.1)
	Mean (SD)	60.1 (14.29)	61.9 (14.05)	62.4 (14.34)
	Median (Q1 - Q3)	60.0 (50.0-71.0)	61.0 (52.0-72.0)	63.0 (53.0-73.0)
	Range	(16.0,98.0)	(19.0,94.0)	(19.0,94.0)
Gender	Missing (N)	125	80	18
	Male	497 (31.1%)	416 (29.4%)	200 (30.0%)
	Female	1099 (68.9%)	998 (70.6%)	467 (70.0%)
Route of systemic TCC prescription	Intramuscular	282 (16.4%)	245 (16.4%)	136 (19.9%)
	Oral	1439 (83.6%)	1249 (83.6%)	549 (80.1%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

			Study period year 1[2]	
		Baseline period[1] (N=1721)	Overall (N=1494)	Incident[3] (N=685)
Oral form				
TCC daily dose	N	1193 (82.9)	1039 (83.2)	443 (80.7)
	Missing (N)	246 (17.1)	210 (16.8)	106 (19.3)
	Mean (SD)	10.7 (4.00)	11.1 (4.30)	11.1 (4.46)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(2.0,16.0)	(2.0,16.0)	(2.0,16.0)
	Missing (N)	246	210	106
	≤16 mg	1193 (100.0%)	1039 (100.0%)	443 (100.0%)
	>16 mg	-	-	-
Duration of systemic TCC treatment (days)	N	1185 (82.3)	1039 (83.2)	443 (80.7)
	Missing (N)	254 (17.7)	210 (16.8)	106 (19.3)
	Mean (SD)	30.1 (44.54)	22.7 (41.63)	14.4 (20.37)
	Median (Q1 - Q3)	12.0 (6.0-30.0)	8.0 (4.0-18.0)	7.0 (4.0-15.0)
	Range	(1.0,360.0)	(2.0,360.0)	(3.0,180.0)
	Missing (N)	254	210	106
	≤7 days	478 (40.3%)	509 (49.0%)	244 (55.1%)
	>7 days	707 (59.7%)	530 (51.0%)	199 (44.9%)
Intramuscular				
TCC daily dose	N	280 (99.3)	245 (100.0)	136 (100.0)
	Missing (N)	2 (0.7)	0	0
	Mean (SD)	10.2 (3.91)	9.9 (3.92)	9.8 (3.88)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-14.0)
	Range	(4.0,24.0)	(4.0,16.0)	(4.0,16.0)
	Missing (N)	2	-	-
	≤8 mg	176 (62.9%)	171 (69.8%)	96 (70.6%)
	>8 mg	104 (37.1%)	74 (30.2%)	40 (29.4%)
Duration of systemic TCC treatment (days)	N	278 (98.6)	245 (100.0)	136 (100.0)
	Missing (N)	4 (1.4)	0	0
	Mean (SD)	18.9 (42.46)	14.0 (36.92)	11.0 (31.91)
	Median (Q1 - Q3)	10.0 (5.0-12.0)	6.0 (4.0-10.0)	6.0 (4.0-10.0)
	Range	(1.0,360.0)	(2.0,360.0)	(2.0,360.0)
	Missing (N)	4	-	-
	≤5 days	90 (32.4%)	97 (39.6%)	59 (43.4%)
	>5 days	188 (67.6%)	148 (60.4%)	77 (56.6%)
Long term treatment[4]	Missing (N)	23	27	-
	Yes	132 (7.8%)	66 (4.5%)	-
	No	1566 (92.2%)	1401 (95.5%)	685 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	1529 (88.8%)	1320 (88.4%)	580 (84.7%)
	No	192 (11.2%)	174 (11.6%)	105 (15.3%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medication				
	Analgesics (N02)	879 (51.1%)	710 (47.5%)	292 (42.6%)
	Acetylsalicylic	43 (2.5%)	2 (0.1%)	2 (0.3%)
	Paracetamol	743 (43.2%)	600 (40.2%)	245 (35.8%)
	Opioids (N02A)	358 (20.8%)	302 (20.2%)	122 (17.8%)
	Antidepressants (N06A)	59 (3.4%)	67 (4.5%)	17 (2.5%)

		Baseline period[1] (N=1721)	Study period year 1[2] Overall (N=1494)	Study period year 1[2] Incident[3] (N=685)
	Antiepileptics (N03A)	67 (3.9%)	70 (4.7%)	16 (2.3%)
	Muscle relaxants (M03)	61 (3.5%)	24 (1.6%)	3 (0.4%)
	NSAIDs/Cox-2 inhibitors (M01A)	849 (49.3%)	743 (49.7%)	338 (49.3%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	493 (28.6%)	451 (30.2%)	195 (28.5%)
	Topical products for joint and muscular pain (M02A)	174 (10.1%)	160 (10.7%)	50 (7.3%)
	Phytotherapy (V03A)	6 (0.3%)	5 (0.3%)	2 (0.3%)
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	3 (0.2%)	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-21: Analysis of systemic TCC prescriptions – Baseline and study period year 1 – GPs Italy – included patients

			Study period year 1[2]	
		Baseline period[1] (N=23527)	Overall (N=18695)	Incident[3] (N=7105)
Total systemic TCC prescriptions		23527 (100.0%)	18695 (100.0%)	7105 (100.0%)
Number of patients with a systemic TCC prescription		19877	16140	7064
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	16140 (100.0)	7064 (100.0)
	Mean (SD)	1.2 (0.51)	1.2 (0.46)	1.0 (0.08)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,12.0)	(1.0,9.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	2063	1549	616
	Other deforming dorsopathies including - M43	1082 (5.0%)	757 (4.4%)	295 (4.5%)
	Spondylolysis - M43.0	451 (2.1%)	294 (1.7%)	91 (1.4%)
	Spondylolisthesis - M43.1	22 (0.1%)	26 (0.2%)	8 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	405 (1.9%)	274 (1.6%)	134 (2.1%)
	Other specified deforming dorsopathies - M43.8	123 (0.6%)	111 (0.6%)	35 (0.5%)
	Deforming dorsopathy, unspecified - M43.9	81 (0.4%)	52 (0.3%)	27 (0.4%)
	Dorsalgia - M54	15146 (70.6%)	12466 (72.7%)	4592 (70.8%)
	Radiculopathy - M54.1	220 (1.0%)	148 (0.9%)	25 (0.4%)
	Cervicalgia - M54.2	2270 (10.6%)	1716 (10.0%)	737 (11.4%)
	Sciatica - M54.3	627 (2.9%)	517 (3.0%)	189 (2.9%)
	Lumbago with sciatica - M.54.4	-	-	-
	Low back pain - M54.5	11393 (53.1%)	9604 (56.0%)	3476 (53.6%)
	Pain in thoracic spine - M54.6	292 (1.4%)	227 (1.3%)	64 (1.0%)
	Other dorsalgia - M54.8	-	-	-
	Dorsalgia, unspecified - M54.9	344 (1.6%)	254 (1.5%)	101 (1.6%)
	Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	3923 (22.9%)	1602 (24.7%)
	Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	2499 (14.6%)	932 (14.4%)
	Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	475 (2.8%)	133 (2.0%)
	Spasm Of Muscle - 728.85	392 (1.8%)	291 (1.7%)	142 (2.2%)
	Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	233 (1.4%)	80 (1.2%)
	Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	418 (2.4%)	186 (2.9%)
	Injury And Poisoning (800-999)	524 (2.4%)	425 (2.5%)	214 (3.3%)
	Other	743 (3.5%)	581 (3.4%)	270 (4.2%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=23527)	Study period year 1[2] Overall (N=18695)	Incident[3] (N=7105)
Age at prescription (years)	Missing (N)	14	15	6
	<16 years	36 (0.2%)	10 (0.1%)	9 (0.1%)
	[16;30[	1083 (4.6%)	729 (3.9%)	531 (7.5%)
	[30;40[	2573 (10.9%)	1708 (9.1%)	898 (12.6%)
	[40;50[	4851 (20.6%)	3577 (19.1%)	1490 (21.0%)
	[50;60[	5180 (22.0%)	4418 (23.7%)	1495 (21.1%)
	[60;70[	4496 (19.1%)	3825 (20.5%)	1242 (17.5%)
	≥70 years	5294 (22.5%)	4413 (23.6%)	1434 (20.2%)
Age at prescription (years)	N	23513 (99.9)	18680 (99.9)	7099 (99.9)
	Missing (N)	14 (0.1)	15 (0.1)	6 (0.1)
	Mean (SD)	56.0 (15.89)	57.2 (15.46)	54.0 (16.58)
	Median (Q1 - Q3)	56.0 (44.0-68.0)	57.0 (46.0-69.0)	53.0 (42.0-67.0)
	Range	(12.0,101.0)	(11.0,101.0)	(13.0,101.0)
Gender	Missing (N)	3395	2654	883
	Male	7248 (36.0%)	6084 (37.9%)	2419 (38.9%)
	Female	12884 (64.0%)	9957 (62.1%)	3803 (61.1%)
Route of systemic TCC prescription	Intramuscular	17086 (72.6%)	14334 (76.7%)	5048 (71.0%)
	Oral	6441 (27.4%)	4361 (23.3%)	2057 (29.0%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=23527)	Study period year 1[2] Overall (N=18695)	Incident[3] (N=7105)
Oral form				
TCC daily dose	N	2599 (40.4)	1505 (34.5)	658 (32.0)
	Missing (N)	3842 (59.6)	2856 (65.5)	1399 (68.0)
	Mean (SD)	11.6 (4.38)	10.7 (4.25)	10.8 (4.33)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,24.0)	(4.0,24.0)
	Missing (N)	3842	2856	1399
	≤16 mg	2565 (98.7%)	1496 (99.4%)	653 (99.2%)
	>16 mg	34 (1.3%)	9 (0.6%)	5 (0.8%)
Duration of systemic TCC treatment (days)	N	2596 (40.3)	1504 (34.5)	657 (31.9)
	Missing (N)	3845 (59.7)	2857 (65.5)	1400 (68.1)
	Mean (SD)	8.2 (4.30)	8.9 (4.46)	9.0 (4.54)
	Median (Q1 - Q3)	6.0 (5.0-10.0)	10.0 (5.0-10.0)	10.0 (5.0-10.0)
	Range	(3.0,60.0)	(3.0,40.0)	(3.0,20.0)
	Missing (N)	3845	2857	1400
	≤7 days	1357 (52.3%)	672 (44.7%)	301 (45.8%)
	>7 days	1239 (47.7%)	832 (55.3%)	356 (54.2%)
Intramuscular				
TCC daily dose	N	4299 (25.2)	3258 (22.7)	964 (19.1)
	Missing (N)	12787 (74.8)	11076 (77.3)	4084 (80.9)
	Mean (SD)	4.6 (1.47)	4.6 (1.46)	4.7 (1.51)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(2.0,16.0)	(2.0,12.0)	(4.0,12.0)
	Missing (N)	12787	11076	4084
	≤8 mg	4295 (99.9%)	3254 (99.9%)	963 (99.9%)
	>8 mg	4 (0.1%)	4 (0.1%)	1 (0.1%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=23527)	Study period year 1[2] Overall (N=18695)	Incident[3] (N=7105)
Duration of systemic TCC treatment (days)	N	4297 (25.1)	3258 (22.7)	964 (19.1)
	Missing (N)	12789 (74.9)	11076 (77.3)	4084 (80.9)
	Mean (SD)	5.9 (1.66)	5.8 (1.38)	5.8 (1.37)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(1.0,24.0)	(2.0,12.0)	(3.0,12.0)
	Missing (N)	12789	11076	4084
	≤5 days	552 (12.8%)	396 (12.2%)	132 (13.7%)
	>5 days	3745 (87.2%)	2862 (87.8%)	832 (86.3%)
Long term treatment[4]	Missing (N)	2390	1816	-
	Yes	225 (1.1%)	122 (0.7%)	-
	No	20912 (98.9%)	16757 (99.3%)	7105 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	20376 (86.6%)	16459 (88.0%)	6101 (85.9%)
	No	3151 (13.4%)	2236 (12.0%)	1004 (14.1%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medication				
	Analgesics (N02)	2949 (12.5%)	2074 (11.1%)	756 (10.6%)
	Acetylsalicylic	7 (0.0%)	11 (0.1%)	3 (0.0%)
	Paracetamol	2478 (10.5%)	1624 (8.7%)	624 (8.8%)
	Opioids (N02A)	1910 (8.1%)	1327 (7.1%)	448 (6.3%)
	Antidepressants (N06A)	895 (3.8%)	766 (4.1%)	235 (3.3%)
	Antiepileptics (N03A)	405 (1.7%)	381 (2.0%)	107 (1.5%)
	Muscle relaxants (M03)	152 (0.6%)	172 (0.9%)	53 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	17641 (75.0%)	14504 (77.6%)	5343 (75.2%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2153 (9.2%)	1910 (10.2%)	625 (8.8%)
	Topical products for joint and muscular pain (M02A)	511 (2.2%)	261 (1.4%)	124 (1.7%)
	Phytotherapy (V03A)	5 (0.0%)	3 (0.0%)	-
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-22: Analysis of systemic TCC prescriptions – Baseline and study period year 2 – GPs France – included patients

			Study period year 2[2]	
		Baseline period[1] (N=44108)	Overall (N=44691)	Incident[3] (N=17954)
Total systemic TCC prescriptions		44108 (100.0%)	44691 (100.0%)	17954 (100.0%)
Number of patients with a systemic TCC prescription		34460	34330	17939
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	34330 (100.0)	17939 (100.0)
	Mean (SD)	1.3 (0.86)	1.3 (0.89)	1.0 (0.03)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,20.0)	(1.0,21.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	6760	2567
	Other deforming dorsopathies including - M43	1115 (3.0%)	1098 (2.9%)	640 (4.2%)
	Spondylolysis - M43.0	-	-	-
	Spondylolisthesis - M43.1	5 (0.0%)	4 (0.0%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	17 (0.0%)	5 (0.0%)
	Torticollis - M43.6	1108 (2.9%)	1058 (2.8%)	629 (4.1%)
	Other specified deforming dorsopathies - M43.8	-	15 (0.0%)	5 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	4 (0.0%)	1 (0.0%)
	Dorsalgia - M54	18942 (50.4%)	19455 (51.3%)	8761 (56.9%)
	Radiculopathy - M54.1	144 (0.4%)	185 (0.5%)	69 (0.4%)
	Cervicalgia - M54.2	3536 (9.4%)	3500 (9.2%)	1623 (10.5%)
	Sciatica - M54.3	1124 (3.0%)	1045 (2.8%)	430 (2.8%)
	Lumbago with sciatica - M.54.4	1707 (4.5%)	1801 (4.7%)	697 (4.5%)
	Low back pain - M54.5	9182 (24.4%)	9930 (26.2%)	4463 (29.0%)
	Pain in thoracic spine - M54.6	18 (0.0%)	36 (0.1%)	16 (0.1%)
	Other dorsalgia - M54.8	688 (1.8%)	661 (1.7%)	341 (2.2%)
	Dorsalgia, unspecified - M54.9	2543 (6.8%)	2297 (6.1%)	1122 (7.3%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	17378 (45.8%)	5986 (38.9%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	716 (1.9%)	307 (2.0%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	560 (1.5%)	125 (0.8%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	489 (1.3%)	106 (0.7%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	731 (1.9%)	194 (1.3%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	4680 (12.3%)	1995 (13.0%)
	Contracture of muscle - M62.4	1129 (3.0%)	1172 (3.1%)	618 (4.0%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	1399 (3.7%)	540 (3.5%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	1111 (2.9%)	574 (3.7%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	6827 (18.0%)	1839 (12.0%)
	Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	4259 (11.2%)	945 (6.1%)
	Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	1338 (3.5%)	505 (3.3%)
	Other	1049 (2.8%)	1354 (3.6%)	412 (2.7%)

		Study period year 2[2]	
	Baseline period[1] (N=44108)	Overall (N=44691)	Incident[3] (N=17954)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period year 2[2]	
		Baseline period[1] (N=44108)	Overall (N=44691)	Incident[3] (N=17954)
Age at prescription (years)	Missing (N)	20	15	10
	<16 years	452 (1.0%)	238 (0.5%)	195 (1.1%)
	[16;30[	6208 (14.1%)	5529 (12.4%)	3208 (17.9%)
	[30;40[	8075 (18.3%)	8014 (17.9%)	3440 (19.2%)
	[40;50[	10817 (24.5%)	10417 (23.3%)	3816 (21.3%)
	[50;60[	9475 (21.5%)	10181 (22.8%)	3452 (19.2%)
	[60;70[	5453 (12.4%)	6234 (14.0%)	2253 (12.6%)
	≥70 years	3608 (8.2%)	4063 (9.1%)	1580 (8.8%)
Age at prescription (years)	N	44088 (100.0)	44676 (100.0)	17944 (99.9)
	Missing (N)	20 (0.0)	15 (0.0)	10 (0.1)
	Mean (SD)	46.6 (15.74)	48.0 (15.59)	45.7 (16.69)
	Median (Q1 - Q3)	46.0 (35.0-57.0)	48.0 (37.0-58.0)	45.0 (33.0-57.0)
	Range	(2.0,98.0)	(3.0,98.0)	(3.0,98.0)
Gender	Missing (N)	35	-	-
	Male	18813 (42.7%)	19309 (43.2%)	8173 (45.5%)
	Female	25260 (57.3%)	25382 (56.8%)	9781 (54.5%)
Route of systemic TCC prescription	Intramuscular	1543 (3.5%)	1121 (2.5%)	386 (2.1%)
	Oral	42565 (96.5%)	43570 (97.5%)	17568 (97.9%)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=44108)	Study period year 2[2] Overall (N=44691)	Incident[3] (N=17954)
Oral form				
TCC daily dose	N	40242 (94.5)	41062 (94.2)	16472 (93.8)
	Missing (N)	2323 (5.5)	2508 (5.8)	1096 (6.2)
	Mean (SD)	11.5 (3.67)	11.6 (3.74)	11.9 (3.78)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(2.0,132.0)	(2.0,32.0)	(2.0,28.0)
	Missing (N)	2323	2508	1096
	≤16 mg	40130 (99.7%)	40978 (99.8%)	16435 (99.8%)
	>16 mg	112 (0.3%)	84 (0.2%)	37 (0.2%)
Duration of systemic TCC treatment (days)	N	40830 (95.9)	41764 (95.9)	16806 (95.7)
	Missing (N)	1735 (4.1)	1806 (4.1)	762 (4.3)
	Mean (SD)	10.8 (12.32)	9.0 (10.60)	7.9 (8.15)
	Median (Q1 - Q3)	8.0 (6.0-10.0)	7.0 (6.0-8.0)	7.0 (5.0-8.0)
	Range	(1.0,364.0)	(1.0,196.0)	(1.0,196.0)
	Missing (N)	1735	1806	762
	≤7 days	19067 (46.7%)	27218 (65.2%)	11682 (69.5%)
	>7 days	21763 (53.3%)	14546 (34.8%)	5124 (30.5%)
Intramuscular				
TCC daily dose	N	926 (60.0)	575 (51.3)	217 (56.2)
	Missing (N)	617 (40.0)	546 (48.7)	169 (43.8)
	Mean (SD)	9.3 (4.35)	8.7 (5.14)	8.4 (4.39)
	Median (Q1 - Q3)	8.0 (6.0-12.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
	Range	(4.0,24.0)	(4.0,32.0)	(4.0,32.0)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period year 2[2]	
		Baseline period[1] (N=44108)	Overall (N=44691)	Incident[3] (N=17954)
	Missing (N)	617	546	169
	≤8 mg	589 (63.6%)	465 (80.9%)	180 (82.9%)
	>8 mg	337 (36.4%)	110 (19.1%)	37 (17.1%)
Duration of systemic TCC treatment (days)	N	859 (55.7)	643 (57.4)	238 (61.7)
	Missing (N)	684 (44.3)	478 (42.6)	148 (38.3)
	Mean (SD)	8.6 (11.11)	7.7 (9.44)	7.8 (12.22)
	Median (Q1 - Q3)	6.0 (5.0-8.0)	6.0 (5.0-6.0)	6.0 (5.0-6.0)
	Range	(1.0,231.0)	(2.0,168.0)	(2.0,168.0)
	Missing (N)	684	478	148
	≤5 days	261 (30.4%)	274 (42.6%)	116 (48.7%)
	>5 days	598 (69.6%)	369 (57.4%)	122 (51.3%)
Long term treatment[4]	Missing (N)	512	609	-
	Yes	2289 (5.3%)	1602 (3.6%)	-
	No	41307 (94.7%)	42480 (96.4%)	17954 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	41234 (93.5%)	41498 (92.9%)	16460 (91.7%)
	No	2874 (6.5%)	3193 (7.1%)	1494 (8.3%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use: medication				
	Analgesics (N02)	31393 (71.2%)	30910 (69.2%)	11618 (64.7%)
	Acetylsalicylic	251 (0.6%)	435 (1.0%)	130 (0.7%)
	Paracetamol	30435 (69.0%)	29605 (66.2%)	11233 (62.6%)
	Opioids (N02A)	10908 (24.7%)	10613 (23.7%)	3464 (19.3%)
	Antidepressants (N06A)	3781 (8.6%)	3573 (8.0%)	842 (4.7%)
	Antiepileptics (N03A)	1439 (3.3%)	1405 (3.1%)	325 (1.8%)
	Muscle relaxants (M03)	3076 (7.0%)	1396 (3.1%)	368 (2.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	27801 (63.0%)	27475 (61.5%)	11259 (62.7%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2699 (6.1%)	3520 (7.9%)	1174 (6.5%)
	Topical products for joint and muscular pain (M02A)	9988 (22.6%)	11505 (25.7%)	4412 (24.6%)
	Phytotherapy (V03A)	16 (0.0%)	18 (0.0%)	4 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	727 (1.6%)	461 (1.0%)	182 (1.0%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

		Study period year 2[2]	
	Baseline period[1] (N=44108)	Overall (N=44691)	Incident[3] (N=17954)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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Table 15.3-23: Analysis of systemic TCC prescriptions – Baseline and study period year 2 – Rheumatologists France – included patients

			Study period year 2[2]	
		Baseline period[1] (N=1721)	Overall (N=1409)	Incident[3] (N=660)
Total systemic TCC prescriptions		1721 (100.0%)	1409 (100.0%)	660 (100.0%)
Number of patients with a systemic TCC prescription		1383	1185	656
Number of systemic TCC prescriptions per patient	N	1383 (100.0)	1185 (100.0)	656 (100.0)
	Mean (SD)	1.2 (0.65)	1.2 (0.53)	1.0 (0.08)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,10.0)	(1.0,7.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	24 (1.7%)	15 (2.3%)
	Spondylolysis - M43.0	-	-	-
	Spondylolisthesis - M43.1	-	4 (0.3%)	2 (0.3%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	4 (0.2%)	1 (0.1%)	-
	Other specified deforming dorsopathies - M43.8	-	-	-
	Deforming dorsopathy, unspecified - M43.9	14 (0.8%)	19 (1.3%)	13 (2.0%)
	Dorsalgia - M54	1209 (70.2%)	970 (68.8%)	414 (62.7%)
	Radiculopathy - M54.1	21 (1.2%)	20 (1.4%)	7 (1.1%)
	Cervicalgia - M54.2	346 (20.1%)	259 (18.4%)	132 (20.0%)
	Sciatica - M54.3	34 (2.0%)	14 (1.0%)	9 (1.4%)
	Lumbago with sciatica - M.54.4	188 (10.9%)	136 (9.7%)	51 (7.7%)
	Low back pain - M54.5	470 (27.3%)	365 (25.9%)	165 (25.0%)
	Pain in thoracic spine - M54.6	-	2 (0.1%)	2 (0.3%)
	Other dorsalgia - M54.8	2 (0.1%)	8 (0.6%)	3 (0.5%)
	Dorsalgia, unspecified - M54.9	148 (8.6%)	166 (11.8%)	45 (6.8%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	415 (29.5%)	231 (35.0%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	355 (25.2%)	196 (29.7%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	31 (2.2%)	20 (3.0%)
	Other specified arthrosis - M19.8	-	6 (0.4%)	4 (0.6%)
	Pain in shoulder - M25.51	21 (1.2%)	25 (1.8%)	12 (1.8%)
	Pain in knee - M25.56	24 (1.4%)	42 (3.0%)	21 (3.2%)
	Other spondylosis - M47.8	-	37 (2.6%)	16 (2.4%)
	Other shoulder lesions - M75.8	41 (2.4%)	-	-
	Enthesopathy, unspecified - M77.9	18 (1.0%)	3 (0.2%)	1 (0.2%)
	Rheumatism, unspecified - M79.0	16 (0.9%)	-	-
	Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	11 (0.8%)	6 (0.9%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	38 (2.7%)	22 (3.3%)
	Pain, unspecified - R52.9	31 (1.8%)	37 (2.6%)	22 (3.3%)
	Other	25 (1.5%)	22 (1.6%)	13 (2.0%)

	Baseline period[1] (N=1721)	Study period year 2[2] Overall (N=1409)	Incident[3] (N=660)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th april 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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			Study period year 2[2]	
		Baseline period[1] (N=1721)	Overall (N=1409)	Incident[3] (N=660)
Age at prescription (years)	Missing (N)	-	1	1
	<16 years	-	-	-
	[16;30[	26 (1.5%)	13 (0.9%)	10 (1.5%)
	[30;40[	98 (5.7%)	68 (4.8%)	34 (5.2%)
	[40;50[	288 (16.7%)	187 (13.3%)	82 (12.4%)
	[50;60[	420 (24.4%)	323 (22.9%)	140 (21.2%)
	[60;70[	414 (24.1%)	328 (23.3%)	150 (22.8%)
	≥70 years	475 (27.6%)	489 (34.7%)	243 (36.9%)
Age at prescription (years)	N	1721 (100.0)	1408 (99.9)	659 (99.8)
	Missing (N)	0	1 (0.1)	1 (0.2)
	Mean (SD)	60.1 (14.29)	62.7 (14.33)	62.8 (14.69)
	Median (Q1 - Q3)	60.0 (50.0-71.0)	62.0 (52.0-73.0)	64.0 (53.0-74.0)
	Range	(16.0,98.0)	(17.0,97.0)	(17.0,97.0)
Gender	Missing (N)	125	70	21
	Male	497 (31.1%)	352 (26.3%)	160 (25.0%)
	Female	1099 (68.9%)	987 (73.7%)	479 (75.0%)
Route of systemic TCC prescription	Intramuscular	282 (16.4%)	279 (19.8%)	173 (26.2%)
	Oral	1439 (83.6%)	1130 (80.2%)	487 (73.8%)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th april 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=1721)	Study period year 2[2] Overall (N=1409)	Incident[3] (N=660)
Oral form				
TCC daily dose	N	1193 (82.9)	922 (81.6)	391 (80.3)
	Missing (N)	246 (17.1)	208 (18.4)	96 (19.7)
	Mean (SD)	10.7 (4.00)	11.1 (4.32)	11.2 (4.42)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(2.0,16.0)	(1.3,16.0)	(1.3,16.0)
	Missing (N)	246	208	96
	≤16 mg	1193 (100.0%)	922 (100.0%)	391 (100.0%)
	>16 mg	-	-	-
Duration of systemic TCC treatment (days)	N	1185 (82.3)	922 (81.6)	391 (80.3)
	Missing (N)	254 (17.7)	208 (18.4)	96 (19.7)
	Mean (SD)	30.1 (44.54)	20.9 (37.33)	13.7 (19.57)
	Median (Q1 - Q3)	12.0 (6.0-30.0)	10.0 (5.0-15.0)	7.0 (4.0-14.0)
	Range	(1.0,360.0)	(1.0,360.0)	(2.0,180.0)
	Missing (N)	254	208	96
	≤7 days	478 (40.3%)	420 (45.6%)	205 (52.4%)
	>7 days	707 (59.7%)	502 (54.4%)	186 (47.6%)
Intramuscular				
TCC daily dose	N	280 (99.3)	279 (100.0)	173 (100.0)
	Missing (N)	2 (0.7)	0	0
	Mean (SD)	10.2 (3.91)	9.9 (3.71)	10.0 (3.85)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,16.0)	(4.0,16.0)
	Missing (N)	2	-	-
	≤8 mg	176 (62.9%)	199 (71.3%)	120 (69.4%)
	>8 mg	104 (37.1%)	80 (28.7%)	53 (30.6%)
Duration of systemic TCC treatment (days)	N	278 (98.6)	279 (100.0)	173 (100.0)
	Missing (N)	4 (1.4)	0	0
	Mean (SD)	18.9 (42.46)	13.3 (31.95)	9.7 (19.50)
	Median (Q1 - Q3)	10.0 (5.0-12.0)	6.0 (5.0-10.0)	6.0 (5.0-7.0)
	Range	(1.0,360.0)	(2.0,360.0)	(2.0,195.0)
	Missing (N)	4	-	-
	≤5 days	90 (32.4%)	117 (41.9%)	83 (48.0%)
	>5 days	188 (67.6%)	162 (58.1%)	90 (52.0%)
Long term treatment[4]	Missing (N)	23	29	-
	Yes	132 (7.8%)	46 (3.3%)	-
	No	1566 (92.2%)	1334 (96.7%)	660 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	1529 (88.8%)	1215 (86.2%)	548 (83.0%)
	No	192 (11.2%)	194 (13.8%)	112 (17.0%)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th april 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=1721)	Study period year 2[2] Overall (N=1409)	Incident[3] (N=660)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medication				
	Analgesics (N02)	879 (51.1%)	620 (44.0%)	250 (37.9%)
	Acetylsalicylic	43 (2.5%)	2 (0.1%)	1 (0.2%)
	Paracetamol	743 (43.2%)	529 (37.5%)	216 (32.7%)
	Opioids (N02A)	358 (20.8%)	274 (19.4%)	95 (14.4%)
	Antidepressants (N06A)	59 (3.4%)	58 (4.1%)	14 (2.1%)
	Antiepileptics (N03A)	67 (3.9%)	59 (4.2%)	18 (2.7%)
	Muscle relaxants (M03)	61 (3.5%)	24 (1.7%)	6 (0.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	849 (49.3%)	690 (49.0%)	316 (47.9%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	493 (28.6%)	397 (28.2%)	168 (25.5%)
	Topical products for joint and muscular pain (M02A)	174 (10.1%)	128 (9.1%)	42 (6.4%)
	Phytotherapy (V03A)	6 (0.3%)	3 (0.2%)	-
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	3 (0.2%)	2 (0.3%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th april 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-24: Analysis of systemic TCC prescriptions – Baseline and study period year 2 – GPs Italy – included patients

			Study period year 2[2]	
		Baseline period[1] (N=23527)	Overall (N=18833)	Incident[3] (N=7098)
Total systemic TCC prescriptions		23527 (100.0%)	18833 (100.0%)	7098 (100.0%)
Number of patients with a systemic TCC prescription		19877	16201	7073
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	16201 (100.0)	7073 (100.0)
	Mean (SD)	1.2 (0.51)	1.2 (0.49)	1.0 (0.06)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,12.0)	(1.0,18.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	2063	1588	667
	Other deforming dorsopathies including - M43	1082 (5.0%)	748 (4.3%)	292 (4.5%)
	Spondylolysis - M43.0	451 (2.1%)	302 (1.8%)	82 (1.3%)
	Spondylolisthesis - M43.1	22 (0.1%)	18 (0.1%)	4 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	405 (1.9%)	249 (1.4%)	136 (2.1%)
	Other specified deforming dorsopathies - M43.8	123 (0.6%)	103 (0.6%)	38 (0.6%)
	Deforming dorsopathy, unspecified - M43.9	81 (0.4%)	76 (0.4%)	32 (0.5%)
	Dorsalgia - M54	15146 (70.6%)	12613 (73.1%)	4600 (71.5%)
	Radiculopathy - M54.1	220 (1.0%)	159 (0.9%)	39 (0.6%)
	Cervicalgia - M54.2	2270 (10.6%)	1642 (9.5%)	732 (11.4%)
	Sciatica - M54.3	627 (2.9%)	541 (3.1%)	208 (3.2%)
	Lumbago with sciatica - M.54.4	-	-	-
	Low back pain - M54.5	11393 (53.1%)	9790 (56.8%)	3428 (53.3%)
	Pain in thoracic spine - M54.6	292 (1.4%)	224 (1.3%)	67 (1.0%)
	Other dorsalgia - M54.8	-	-	-
	Dorsalgia, unspecified - M54.9	344 (1.6%)	257 (1.5%)	126 (2.0%)
	Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	3884 (22.5%)	1539 (23.9%)
	Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	2493 (14.5%)	915 (14.2%)
	Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	436 (2.5%)	140 (2.2%)
	Spasm Of Muscle - 728.85	392 (1.8%)	299 (1.7%)	145 (2.3%)
	Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	224 (1.3%)	94 (1.5%)
	Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	420 (2.4%)	169 (2.6%)
	Injury And Poisoning (800-999)	524 (2.4%)	366 (2.1%)	189 (2.9%)
	Other	743 (3.5%)	605 (3.5%)	266 (4.1%)

	Baseline period[1] (N=23527)	Study period year 2[2] Overall (N=18833)	Incident[3] (N=7098)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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			Study period year 2[2]	
		Baseline period[1] (N=23527)	**Overall (N=18833)**	**Incident[3] (N=7098)**
Age at prescription (years)	Missing (N)	14	21	10
	<16 years	36 (0.2%)	13 (0.1%)	12 (0.2%)
	[16;30[	1083 (4.6%)	777 (4.1%)	589 (8.3%)
	[30;40[	2573 (10.9%)	1664 (8.8%)	898 (12.7%)
	[40;50[	4851 (20.6%)	3517 (18.7%)	1459 (20.6%)
	[50;60[	5180 (22.0%)	4335 (23.0%)	1454 (20.5%)
	[60;70[	4496 (19.1%)	3904 (20.8%)	1229 (17.3%)
	≥70 years	5294 (22.5%)	4602 (24.5%)	1447 (20.4%)
Age at prescription (years)	N	23513 (99.9)	18812 (99.9)	7088 (99.9)
	Missing (N)	14 (0.1)	21 (0.1)	10 (0.1)
	Mean (SD)	56.0 (15.89)	57.4 (15.58)	53.9 (16.89)
	Median (Q1 - Q3)	56.0 (44.0-68.0)	57.0 (46.0-69.0)	53.0 (42.0-67.0)
	Range	(12.0,101.0)	(12.0,103.0)	(12.0,96.0)
Gender	Missing (N)	3395	2781	927
	Male	7248 (36.0%)	5942 (37.0%)	2331 (37.8%)
	Female	12884 (64.0%)	10110 (63.0%)	3840 (62.2%)
Route of systemic TCC prescription	Intramuscular	17086 (72.6%)	14945 (79.4%)	5265 (74.2%)
	Oral	6441 (27.4%)	3888 (20.6%)	1833 (25.8%)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period year 2[2]	
		Baseline period[1] (N=23527)	Overall (N=18833)	Incident[3] (N=7098)
Oral form				
TCC daily dose	N	2599 (40.4)	1437 (37.0)	621 (33.9)
	Missing (N)	3842 (59.6)	2451 (63.0)	1212 (66.1)
	Mean (SD)	11.6 (4.38)	11.3 (4.80)	11.3 (4.84)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(2.0,32.0)	(4.0,24.0)
	Missing (N)	3842	2451	1212
	≤16 mg	2565 (98.7%)	1408 (98.0%)	610 (98.2%)
	>16 mg	34 (1.3%)	29 (2.0%)	11 (1.8%)
Duration of systemic TCC treatment (days)	N	2596 (40.3)	1437 (37.0)	621 (33.9)
	Missing (N)	3845 (59.7)	2451 (63.0)	1212 (66.1)
	Mean (SD)	8.2 (4.30)	10.4 (5.33)	10.4 (4.99)
	Median (Q1 - Q3)	6.0 (5.0-10.0)	10.0 (7.0-14.0)	10.0 (7.0-14.0)
	Range	(3.0,60.0)	(3.0,50.0)	(4.0,30.0)
	Missing (N)	3845	2451	1212
	≤7 days	1357 (52.3%)	670 (46.6%)	290 (46.7%)
	>7 days	1239 (47.7%)	767 (53.4%)	331 (53.3%)
Intramuscular				
TCC daily dose	N	4299 (25.2)	3350 (22.4)	980 (18.6)
	Missing (N)	12787 (74.8)	11595 (77.6)	4285 (81.4)
	Mean (SD)	4.6 (1.47)	4.6 (1.43)	4.6 (1.47)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(2.0,16.0)	(2.0,12.0)	(4.0,12.0)
	Missing (N)	12787	11595	4285
	≤8 mg	4295 (99.9%)	3348 (99.9%)	979 (99.9%)
	>8 mg	4 (0.1%)	2 (0.1%)	1 (0.1%)

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=23527)	Study period year 2[2] Overall (N=18833)	Incident[3] (N=7098)
Duration of systemic TCC treatment (days)	N	4297 (25.1)	3348 (22.4)	979 (18.6)
	Missing (N)	12789 (74.9)	11597 (77.6)	4286 (81.4)
	Mean (SD)	5.9 (1.66)	5.9 (1.44)	5.9 (1.31)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(1.0,24.0)	(2.0,18.0)	(2.0,12.0)
	Missing (N)	12789	11597	4286
	≤5 days	552 (12.8%)	377 (11.3%)	107 (10.9%)
	>5 days	3745 (87.2%)	2971 (88.7%)	872 (89.1%)
Long term treatment[4]	Missing (N)	2390	1892	-
	Yes	225 (1.1%)	137 (0.8%)	-
	No	20912 (98.9%)	16804 (99.2%)	7098 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	20376 (86.6%)	16716 (88.8%)	6169 (86.9%)
	No	3151 (13.4%)	2117 (11.2%)	929 (13.1%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medication				
	Analgesics (N02)	2949 (12.5%)	2081 (11.0%)	737 (10.4%)
	Acetylsalicylic	7 (0.0%)	12 (0.1%)	3 (0.0%)
	Paracetamol	2478 (10.5%)	1601 (8.5%)	595 (8.4%)
	Opioids (N02A)	1910 (8.1%)	1284 (6.8%)	415 (5.8%)
	Antidepressants (N06A)	895 (3.8%)	766 (4.1%)	228 (3.2%)
	Antiepileptics (N03A)	405 (1.7%)	385 (2.0%)	99 (1.4%)
	Muscle relaxants (M03)	152 (0.6%)	157 (0.8%)	58 (0.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	17641 (75.0%)	14600 (77.5%)	5400 (76.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2153 (9.2%)	2062 (10.9%)	681 (9.6%)
	Topical products for joint and muscular pain (M02A)	511 (2.2%)	253 (1.3%)	128 (1.8%)
	Phytotherapy (V03A)	5 (0.0%)	6 (0.0%)	1 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

Table 15.3-25: Analysis of systemic TCC prescriptions – Baseline and study period year 3 – GPs France – included patients

			Study period year 3[2]	
		Baseline period[1] (N=44108)	Overall (N=29631)	Incident[3] (N=12287)
Total systemic TCC prescriptions		44108 (100.0%)	29631 (100.0%)	12287 (100.0%)
Number of patients with a systemic TCC prescription		34460	23079	12278
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	23079 (100.0)	12278 (100.0)
	Mean (SD)	1.3 (0.86)	1.3 (0.85)	1.0 (0.03)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,20.0)	(1.0,16.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	5114	2111
	Other deforming dorsopathies including - M43	1115 (3.0%)	700 (2.9%)	410 (4.0%)
	Spondylolysis - M43.0	-	1 (0.0%)	-
	Spondylolisthesis - M43.1	5 (0.0%)	1 (0.0%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	17 (0.1%)	3 (0.0%)
	Torticollis - M43.6	1108 (2.9%)	668 (2.7%)	402 (4.0%)
	Other specified deforming dorsopathies - M43.8	-	10 (0.0%)	4 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	3 (0.0%)	1 (0.0%)
	Dorsalgia - M54	18942 (50.4%)	12343 (50.3%)	5794 (56.9%)
	Radiculopathy - M54.1	144 (0.4%)	104 (0.4%)	51 (0.5%)
	Cervicalgia - M54.2	3536 (9.4%)	2200 (9.0%)	1028 (10.1%)
	Sciatica - M54.3	1124 (3.0%)	621 (2.5%)	287 (2.8%)
	Lumbago with sciatica - M.54.4	1707 (4.5%)	1170 (4.8%)	514 (5.1%)
	Low back pain - M54.5	9182 (24.4%)	6358 (25.9%)	3000 (29.5%)
	Pain in thoracic spine - M54.6	18 (0.0%)	36 (0.1%)	18 (0.2%)
	Other dorsalgia - M54.8	688 (1.8%)	410 (1.7%)	194 (1.9%)
	Dorsalgia, unspecified - M54.9	2543 (6.8%)	1444 (5.9%)	702 (6.9%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	11474 (46.8%)	3972 (39.0%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	457 (1.9%)	184 (1.8%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	427 (1.7%)	83 (0.8%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	364 (1.5%)	66 (0.6%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	481 (2.0%)	116 (1.1%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	2957 (12.1%)	1305 (12.8%)
	Contracture of muscle - M62.4	1129 (3.0%)	760 (3.1%)	441 (4.3%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	866 (3.5%)	348 (3.4%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	661 (2.7%)	356 (3.5%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	4650 (19.0%)	1296 (12.7%)
	Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	2943 (12.0%)	645 (6.3%)
	Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	851 (3.5%)	354 (3.5%)
	Other	1049 (2.8%)	975 (4.0%)	284 (2.8%)

	Baseline period[1] (N=44108)	Study period year 3[2] Overall (N=29631)	Incident[3] (N=12287)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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		Baseline period[1] (N=44108)	Study period year 3[2] Overall (N=29631)	Study period year 3[2] Incident[3] (N=12287)
Age at prescription (years)	Missing (N)	20	7	5
	<16 years	452 (1.0%)	117 (0.4%)	99 (0.8%)
	[16;30[	6208 (14.1%)	3322 (11.2%)	1943 (15.8%)
	[30;40[	8075 (18.3%)	5085 (17.2%)	2258 (18.4%)
	[40;50[	10817 (24.5%)	6719 (22.7%)	2591 (21.1%)
	[50;60[	9475 (21.5%)	6735 (22.7%)	2421 (19.7%)
	[60;70[	5453 (12.4%)	4385 (14.8%)	1633 (13.3%)
	≥70 years	3608 (8.2%)	3261 (11.0%)	1337 (10.9%)
Age at prescription (years)	N	44088 (100.0)	29624 (100.0)	12282 (100.0)
	Missing (N)	20 (0.0)	7 (0.0)	5 (0.0)
	Mean (SD)	46.6 (15.74)	49.1 (15.78)	47.2 (16.86)
	Median (Q1 - Q3)	46.0 (35.0-57.0)	49.0 (38.0-60.0)	47.0 (35.0-59.0)
	Range	(2.0,98.0)	(2.0,97.0)	(2.0,97.0)
Gender	Missing (N)	35	1	1
	Male	18813 (42.7%)	12918 (43.6%)	5572 (45.4%)
	Female	25260 (57.3%)	16712 (56.4%)	6714 (54.6%)
Route of systemic TCC prescription	Intramuscular	1543 (3.5%)	1025 (3.5%)	363 (3.0%)
	Oral	42565 (96.5%)	28606 (96.5%)	11924 (97.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period year 3[2]	
		Baseline period[1] (N=44108)	Overall (N=29631)	Incident[3] (N=12287)
Oral form				
TCC daily dose	N	40242 (94.5)	24488 (85.6)	10216 (85.7)
	Missing (N)	2323 (5.5)	4118 (14.4)	1708 (14.3)
	Mean (SD)	11.5 (3.67)	11.7 (3.79)	11.9 (3.85)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(2.0,132.0)	(2.0,36.0)	(2.0,36.0)
	Missing (N)	2323	4118	1708
	≤16 mg	40130 (99.7%)	24446 (99.8%)	10196 (99.8%)
	>16 mg	112 (0.3%)	42 (0.2%)	20 (0.2%)
Duration of systemic TCC treatment (days)	N	40830 (95.9)	24971 (87.3)	10452 (87.7)
	Missing (N)	1735 (4.1)	3635 (12.7)	1472 (12.3)
	Mean (SD)	10.8 (12.32)	8.9 (11.62)	7.7 (9.42)
	Median (Q1 - Q3)	8.0 (6.0-10.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)
	Range	(1.0,364.0)	(1.0,336.0)	(1.0,336.0)
	Missing (N)	1735	3635	1472
	≤7 days	19067 (46.7%)	17332 (69.4%)	7710 (73.8%)
	>7 days	21763 (53.3%)	7639 (30.6%)	2742 (26.2%)
Intramuscular				
TCC daily dose	N	926 (60.0)	379 (37.0)	150 (41.3)
	Missing (N)	617 (40.0)	646 (63.0)	213 (58.7)
	Mean (SD)	9.3 (4.35)	7.6 (4.04)	7.4 (3.03)
	Median (Q1 - Q3)	8.0 (6.0-12.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
	Range	(4.0,24.0)	(4.0,28.0)	(4.0,16.0)
	Missing (N)	617	646	213
	≤8 mg	589 (63.6%)	338 (89.2%)	131 (87.3%)
	>8 mg	337 (36.4%)	41 (10.8%)	19 (12.7%)
Duration of systemic TCC treatment (days)	N	859 (55.7)	422 (41.2)	176 (48.5)
	Missing (N)	684 (44.3)	603 (58.8)	187 (51.5)
	Mean (SD)	8.6 (11.11)	6.1 (8.48)	5.7 (2.97)
	Median (Q1 - Q3)	6.0 (5.0-8.0)	5.0 (5.0-6.0)	5.0 (5.0-6.0)
	Range	(1.0,231.0)	(2.0,168.0)	(3.0,28.0)
	Missing (N)	684	603	187
	≤5 days	261 (30.4%)	214 (50.7%)	93 (52.8%)
	>5 days	598 (69.6%)	208 (49.3%)	83 (47.2%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=44108)	Study period year 3[2] Overall (N=29631)	Incident[3] (N=12287)
Long term treatment[4]	Missing (N)	512	1218	-
	Yes	2289 (5.3%)	913 (3.2%)	-
	No	41307 (94.7%)	27500 (96.8%)	12287 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	41234 (93.5%)	27348 (92.3%)	11185 (91.0%)
	No	2874 (6.5%)	2283 (7.7%)	1102 (9.0%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	31393 (71.2%)	20047 (67.7%)	7777 (63.3%)
	Acetylsalicylic	251 (0.6%)	272 (0.9%)	66 (0.5%)
	Paracetamol	30435 (69.0%)	19195 (64.8%)	7501 (61.0%)
	Opioids (N02A)	10908 (24.7%)	7031 (23.7%)	2357 (19.2%)
	Antidepressants (N06A)	3781 (8.6%)	2217 (7.5%)	564 (4.6%)
	Antiepileptics (N03A)	1439 (3.3%)	885 (3.0%)	203 (1.7%)
	Muscle relaxants (M03)	3076 (7.0%)	1012 (3.4%)	263 (2.1%)
	NSAIDs/Cox-2 inhibitors (M01A)	27801 (63.0%)	17867 (60.3%)	7583 (61.7%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2699 (6.1%)	2417 (8.2%)	796 (6.5%)
	Topical products for joint and muscular pain (M02A)	9988 (22.6%)	7718 (26.0%)	3037 (24.7%)
	Phytotherapy (V03A)	16 (0.0%)	11 (0.0%)	6 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	727 (1.6%)	236 (0.8%)	106 (0.9%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-26: Analysis of systemic TCC prescriptions – Baseline and study period year 3 – Rheumatologists France – included patients

		Study period year 3[2]		
		Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)
Total systemic TCC prescriptions		1721 (100.0%)	1281 (100.0%)	578 (100.0%)
Number of patients with a systemic TCC prescription		1383	1063	575
Number of systemic TCC prescriptions per patient	N	1383 (100.0)	1063 (100.0)	575 (100.0)
	Mean (SD)	1.2 (0.65)	1.2 (0.56)	1.0 (0.07)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,10.0)	(1.0,7.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	17 (1.3%)	7 (1.2%)
	Spondylolysis - M43.0	-	1 (0.1%)	1 (0.2%)
	Spondylolisthesis - M43.1	-	-	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	4 (0.2%)	1 (0.1%)	1 (0.2%)
	Other specified deforming dorsopathies - M43.8	-	-	-
	Deforming dorsopathy, unspecified - M43.9	14 (0.8%)	15 (1.2%)	5 (0.9%)
	Dorsalgia - M54	1209 (70.2%)	904 (70.6%)	374 (64.7%)
	Radiculopathy - M54.1	21 (1.2%)	23 (1.8%)	14 (2.4%)
	Cervicalgia - M54.2	346 (20.1%)	247 (19.3%)	104 (18.0%)
	Sciatica - M54.3	34 (2.0%)	21 (1.6%)	14 (2.4%)
	Lumbago with sciatica - M.54.4	188 (10.9%)	118 (9.2%)	35 (6.1%)
	Low back pain - M54.5	470 (27.3%)	363 (28.3%)	167 (28.9%)
	Pain in thoracic spine - M54.6	-	1 (0.1%)	1 (0.2%)
	Other dorsalgia - M54.8	2 (0.1%)	1 (0.1%)	1 (0.2%)
	Dorsalgia, unspecified - M54.9	148 (8.6%)	130 (10.1%)	38 (6.6%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	360 (28.1%)	197 (34.1%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	309 (24.1%)	163 (28.2%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	26 (2.0%)	14 (2.4%)
	Other specified arthrosis - M19.8	29 (1.7%)	7 (0.5%)	3 (0.5%)
	Pain in shoulder - M25.51	21 (1.2%)	32 (2.5%)	15 (2.6%)
	Pain in knee - M25.56	24 (1.4%)	20 (1.6%)	8 (1.4%)
	Other spondylosis - M47.8	44 (2.6%)	40 (3.1%)	20 (3.5%)
	Other shoulder lesions - M75.8	41 (2.4%)	2 (0.2%)	2 (0.3%)
	Enthesopathy, unspecified - M77.9	18 (1.0%)	3 (0.2%)	2 (0.3%)
	Rheumatism, unspecified - M79.0	16 (0.9%)	-	-
	Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	8 (0.6%)	3 (0.5%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	31 (2.4%)	19 (3.3%)
	Pain, unspecified - R52.9	31 (1.8%)	29 (2.3%)	17 (2.9%)
	Other	25 (1.5%)	20 (1.6%)	15 (2.6%)

	Study period year 3[2]		
	Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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		Study period year 3[2] Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)
Age at prescription (years)	Missing (N)	-	1	-
	<16 years	-	1 (0.1%)	1 (0.2%)
	[16;30[	26 (1.5%)	18 (1.4%)	12 (2.1%)
	[30;40[	98 (5.7%)	52 (4.1%)	26 (4.5%)
	[40;50[	288 (16.7%)	153 (12.0%)	74 (12.8%)
	[50;60[	420 (24.4%)	312 (24.4%)	122 (21.1%)
	[60;70[	414 (24.1%)	296 (23.1%)	139 (24.0%)
	≥70 years	475 (27.6%)	448 (35.0%)	204 (35.3%)
Age at prescription (years)	N	1721 (100.0)	1280 (99.9)	578 (100.0)
	Missing (N)	0	1 (0.1)	0
	Mean (SD)	60.1 (14.29)	62.8 (14.37)	62.5 (14.77)
	Median (Q1 - Q3)	60.0 (50.0-71.0)	63.0 (53.0-73.0)	63.0 (53.0-73.0)
	Range	(16.0,98.0)	(14.0,98.0)	(14.0,98.0)
Gender	Missing (N)	125	61	13
	Male	497 (31.1%)	339 (27.8%)	153 (27.1%)
	Female	1099 (68.9%)	881 (72.2%)	412 (72.9%)
Route of systemic TCC prescription	Intramuscular	282 (16.4%)	214 (16.7%)	123 (21.3%)
	Oral	1439 (83.6%)	1067 (83.3%)	455 (78.7%)
Oral form				
TCC daily dose	N	1193 (82.9)	870 (81.5)	362 (79.6)
	Missing (N)	246 (17.1)	197 (18.5)	93 (20.4)
	Mean (SD)	10.7 (4.00)	10.6 (4.45)	10.2 (4.49)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(2.0,16.0)	(2.0,16.0)	(2.0,16.0)
	Missing (N)	246	197	93
	≤16 mg	1193 (100.0%)	870 (100.0%)	362 (100.0%)
	>16 mg	-	-	-

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Study period year 3[2]		
		Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)
Duration of systemic TCC treatment (days)	N	1185 (82.3)	870 (81.5)	362 (79.6)
	Missing (N)	254 (17.7)	197 (18.5)	93 (20.4)
	Mean (SD)	30.1 (44.54)	20.9 (37.77)	16.3 (31.42)
	Median (Q1 - Q3)	12.0 (6.0-30.0)	7.0 (4.0-17.0)	7.0 (4.0-14.0)
	Range	(1.0,360.0)	(1.0,360.0)	(1.0,360.0)
	Missing (N)	254	197	93
	≤7 days	478 (40.3%)	465 (53.4%)	213 (58.8%)
	>7 days	707 (59.7%)	405 (46.6%)	149 (41.2%)
Intramuscular				
TCC daily dose	N	280 (99.3)	214 (100.0)	123 (100.0)
	Missing (N)	2 (0.7)	0	0
	Mean (SD)	10.2 (3.91)	11.1 (4.09)	11.0 (4.08)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,16.0)	(4.0,16.0)
	Missing (N)	2	-	-
	≤8 mg	176 (62.9%)	125 (58.4%)	72 (58.5%)
	>8 mg	104 (37.1%)	89 (41.6%)	51 (41.5%)
Duration of systemic TCC treatment (days)	N	278 (98.6)	214 (100.0)	123 (100.0)
	Missing (N)	4 (1.4)	0	0
	Mean (SD)	18.9 (42.46)	11.7 (21.27)	8.9 (11.82)
	Median (Q1 - Q3)	10.0 (5.0-12.0)	6.0 (4.0-12.0)	5.0 (4.0-10.0)
	Range	(1.0,360.0)	(2.0,180.0)	(2.0,90.0)
	Missing (N)	4	-	-
	≤5 days	90 (32.4%)	105 (49.1%)	65 (52.8%)
	>5 days	188 (67.6%)	109 (50.9%)	58 (47.2%)
Long term treatment[4]	Missing (N)	23	25	-
	Yes	132 (7.8%)	40 (3.2%)	-
	No	1566 (92.2%)	1216 (96.8%)	578 (100.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Study period year 3[2] Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	1529 (88.8%)	1146 (89.5%)	503 (87.0%)
	No	192 (11.2%)	135 (10.5%)	75 (13.0%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	879 (51.1%)	567 (44.3%)	218 (37.7%)
	Acetylsalicylic	43 (2.5%)	3 (0.2%)	1 (0.2%)
	Paracetamol	743 (43.2%)	460 (35.9%)	177 (30.6%)
	Opioids (N02A)	358 (20.8%)	215 (16.8%)	74 (12.8%)
	Antidepressants (N06A)	59 (3.4%)	51 (4.0%)	12 (2.1%)
	Antiepileptics (N03A)	67 (3.9%)	46 (3.6%)	9 (1.6%)
	Muscle relaxants (M03)	61 (3.5%)	22 (1.7%)	4 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	849 (49.3%)	700 (54.6%)	321 (55.5%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	493 (28.6%)	363 (28.3%)	160 (27.7%)
	Topical products for joint and muscular pain (M02A)	174 (10.1%)	107 (8.4%)	31 (5.4%)
	Phytotherapy (V03A)	6 (0.3%)	1 (0.1%)	-
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	1 (0.1%)	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-27: Analysis of systemic TCC prescriptions – Baseline and study period year 3 – GPs Italy – included patients

			Study period year 3[2]	
		Baseline period[1] (N=23527)	Overall (N=17364)	Incident[3] (N=6471)
Total systemic TCC prescriptions		23527 (100.0%)	17364 (100.0%)	6471 (100.0%)
Number of patients with a systemic TCC prescription		19877	14957	6441
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	14957 (100.0)	6441 (100.0)
	Mean (SD)	1.2 (0.51)	1.2 (0.46)	1.0 (0.07)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,12.0)	(1.0,10.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	2063	1532	601
	Other deforming dorsopathies including - M43	1082 (5.0%)	659 (4.2%)	238 (4.1%)
	Spondylolysis - M43.0	451 (2.1%)	278 (1.8%)	74 (1.3%)
	Spondylolisthesis - M43.1	22 (0.1%)	12 (0.1%)	4 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	405 (1.9%)	241 (1.5%)	112 (1.9%)
	Other specified deforming dorsopathies - M43.8	123 (0.6%)	75 (0.5%)	25 (0.4%)
	Deforming dorsopathy, unspecified - M43.9	81 (0.4%)	53 (0.3%)	23 (0.4%)
	Dorsalgia - M54	15146 (70.6%)	11733 (74.1%)	4211 (71.7%)
	Radiculopathy - M54.1	220 (1.0%)	111 (0.7%)	24 (0.4%)
	Cervicalgia - M54.2	2270 (10.6%)	1544 (9.8%)	644 (11.0%)
	Sciatica - M54.3	627 (2.9%)	496 (3.1%)	198 (3.4%)
	Lumbago with sciatica - M.54.4	-	-	-
	Low back pain - M54.5	11393 (53.1%)	9149 (57.8%)	3187 (54.3%)
	Pain in thoracic spine - M54.6	292 (1.4%)	195 (1.2%)	52 (0.9%)
	Other dorsalgia - M54.8	-	-	-
	Dorsalgia, unspecified - M54.9	344 (1.6%)	238 (1.5%)	106 (1.8%)
	Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	3440 (21.7%)	1421 (24.2%)
	Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	2144 (13.5%)	788 (13.4%)
	Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	398 (2.5%)	114 (1.9%)
	Spasm Of Muscle - 728.85	392 (1.8%)	224 (1.4%)	107 (1.8%)
	Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	182 (1.1%)	71 (1.2%)
	Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	386 (2.4%)	196 (3.3%)
	Injury And Poisoning (800-999)	524 (2.4%)	335 (2.1%)	159 (2.7%)
	Other	743 (3.5%)	575 (3.6%)	278 (4.7%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

			Study period year 3[2]	
		Baseline period[1] (N=23527)	Overall (N=17364)	Incident[3] (N=6471)
Age at prescription (years)	Missing (N)	14	18	11
	<16 years	36 (0.2%)	9 (0.1%)	9 (0.1%)
	[16;30[	1083 (4.6%)	649 (3.7%)	487 (7.5%)
	[30;40[	2573 (10.9%)	1539 (8.9%)	821 (12.7%)
	[40;50[	4851 (20.6%)	3124 (18.0%)	1329 (20.6%)
	[50;60[	5180 (22.0%)	4043 (23.3%)	1306 (20.2%)
	[60;70[	4496 (19.1%)	3632 (20.9%)	1192 (18.5%)
	≥70 years	5294 (22.5%)	4350 (25.1%)	1316 (20.4%)
Age at prescription (years)	N	23513 (99.9)	17346 (99.9)	6460 (99.8)
	Missing (N)	14 (0.1)	18 (0.1)	11 (0.2)
	Mean (SD)	56.0 (15.89)	57.7 (15.45)	54.1 (16.74)
	Median (Q1 - Q3)	56.0 (44.0-68.0)	58.0 (47.0-70.0)	54.0 (42.0-67.0)
	Range	(12.0,101.0)	(11.0,103.0)	(11.0,99.0)
Gender	Missing (N)	3395	2516	805
	Male	7248 (36.0%)	5532 (37.3%)	2200 (38.8%)
	Female	12884 (64.0%)	9316 (62.7%)	3466 (61.2%)
Route of systemic TCC prescription	Intramuscular	17086 (72.6%)	13729 (79.1%)	4746 (73.3%)
	Oral	6441 (27.4%)	3635 (20.9%)	1725 (26.7%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period year 3[2]	
		Baseline period[1] (N=23527)	Overall (N=17364)	Incident[3] (N=6471)
Oral form				
TCC daily dose	N	2599 (40.4)	1285 (35.4)	580 (33.6)
	Missing (N)	3842 (59.6)	2350 (64.6)	1145 (66.4)
	Mean (SD)	11.6 (4.38)	11.5 (4.79)	11.7 (4.82)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,32.0)	(4.0,24.0)
	Missing (N)	3842	2350	1145
	≤16 mg	2565 (98.7%)	1261 (98.1%)	568 (97.9%)
	>16 mg	34 (1.3%)	24 (1.9%)	12 (2.1%)
Duration of systemic TCC treatment (days)	N	2596 (40.3)	1284 (35.3)	580 (33.6)
	Missing (N)	3845 (59.7)	2351 (64.7)	1145 (66.4)
	Mean (SD)	8.2 (4.30)	10.5 (4.85)	10.3 (4.87)
	Median (Q1 - Q3)	6.0 (5.0-10.0)	10.0 (7.0-14.0)	7.0 (7.0-14.0)
	Range	(3.0,60.0)	(3.0,30.0)	(4.0,30.0)
	Missing (N)	3845	2351	1145
	≤7 days	1357 (52.3%)	625 (48.7%)	299 (51.6%)
	>7 days	1239 (47.7%)	659 (51.3%)	281 (48.4%)
Intramuscular				
TCC daily dose	N	4299 (25.2)	2960 (21.6)	866 (18.2)
	Missing (N)	12787 (74.8)	10769 (78.4)	3880 (81.8)
	Mean (SD)	4.6 (1.47)	4.6 (1.47)	4.6 (1.44)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(2.0,16.0)	(2.0,16.0)	(4.0,8.0)
	Missing (N)	12787	10769	3880
	≤8 mg	4295 (99.9%)	2958 (99.9%)	866 (100.0%)
	>8 mg	4 (0.1%)	2 (0.1%)	-
Duration of systemic TCC treatment (days)	N	4297 (25.1)	2960 (21.6)	866 (18.2)
	Missing (N)	12789 (74.9)	10769 (78.4)	3880 (81.8)
	Mean (SD)	5.9 (1.66)	5.8 (1.35)	5.7 (1.18)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(1.0,24.0)	(1.0,12.0)	(3.0,12.0)
	Missing (N)	12789	10769	3880
	≤5 days	552 (12.8%)	334 (11.3%)	104 (12.0%)
	>5 days	3745 (87.2%)	2626 (88.7%)	762 (88.0%)
Long term treatment[4]	Missing (N)	2390	1767	-
	Yes	225 (1.1%)	121 (0.8%)	-
	No	20912 (98.9%)	15476 (99.2%)	6471 (100.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=23527)	Study period year 3[2] Overall (N=17364)	Study period year 3[2] Incident[3] (N=6471)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	20376 (86.6%)	15447 (89.0%)	5651 (87.3%)
	No	3151 (13.4%)	1917 (11.0%)	820 (12.7%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	2949 (12.5%)	1880 (10.8%)	704 (10.9%)
	Acetylsalicylic	7 (0.0%)	8 (0.0%)	3 (0.0%)
	Paracetamol	2478 (10.5%)	1457 (8.4%)	573 (8.9%)
	Opioids (N02A)	1910 (8.1%)	1173 (6.8%)	386 (6.0%)
	Antidepressants (N06A)	895 (3.8%)	737 (4.2%)	201 (3.1%)
	Antiepileptics (N03A)	405 (1.7%)	376 (2.2%)	111 (1.7%)
	Muscle relaxants (M03)	152 (0.6%)	129 (0.7%)	44 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	17641 (75.0%)	13507 (77.8%)	4927 (76.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2153 (9.2%)	1982 (11.4%)	668 (10.3%)
	Topical products for joint and muscular pain (M02A)	511 (2.2%)	182 (1.0%)	92 (1.4%)
	Phytotherapy (V03A)	5 (0.0%)	6 (0.0%)	3 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-28: Analysis of systemic TCC prescriptions – Baseline and cumulated study period years 1, 2 and 3 – GPs France – included patients

		Baseline period[1] (N=44108)	Study period years 1, 2 and 3[2] Overall (N=123429)	Incident[3] (N=50597)
Total systemic TCC prescriptions		44108 (100.0%)	123429 (100.0%)	50597 (100.0%)
Number of patients with a systemic TCC prescription		34460	81690	50544
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	81690 (100.0)	50544 (100.0)
	Mean (SD)	1.3 (0.86)	1.5 (1.49)	1.0 (0.03)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)
	Range	(1.0,20.0)	(1.0,48.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	18015	7246
	Other deforming dorsopathies including - M43	1115 (3.0%)	3027 (2.9%)	1797 (4.1%)
	Spondylolysis - M43.0	-	1 (0.0%)	-
	Spondylolisthesis - M43.1	5 (0.0%)	14 (0.0%)	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	34 (0.0%)	8 (0.0%)
	Torticollis - M43.6	1108 (2.9%)	2945 (2.8%)	1776 (4.1%)
	Other specified deforming dorsopathies - M43.8	-	25 (0.0%)	9 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	2 (0.0%)	8 (0.0%)	3 (0.0%)
	Dorsalgia - M54	18942 (50.4%)	53827 (51.1%)	24561 (56.7%)
	Radiculopathy - M54.1	144 (0.4%)	476 (0.5%)	194 (0.4%)
	Cervicalgia - M54.2	3536 (9.4%)	9734 (9.2%)	4532 (10.5%)
	Sciatica - M54.3	1124 (3.0%)	2884 (2.7%)	1236 (2.9%)
	Lumbago with sciatica - M.54.4	1707 (4.5%)	5039 (4.8%)	2068 (4.8%)
	Low back pain - M54.5	9182 (24.4%)	27294 (25.9%)	12501 (28.8%)
	Pain in thoracic spine - M54.6	18 (0.0%)	111 (0.1%)	51 (0.1%)
	Other dorsalgia - M54.8	688 (1.8%)	1860 (1.8%)	901 (2.1%)
	Dorsalgia, unspecified - M54.9	2543 (6.8%)	6429 (6.1%)	3078 (7.1%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	48560 (46.1%)	16993 (39.2%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	2048 (1.9%)	871 (2.0%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	1672 (1.6%)	368 (0.8%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	1477 (1.4%)	316 (0.7%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	2024 (1.9%)	573 (1.3%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	13187 (12.5%)	5703 (13.2%)
	Contracture of muscle - M62.4	1129 (3.0%)	3159 (3.0%)	1739 (4.0%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	3646 (3.5%)	1443 (3.3%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	3126 (3.0%)	1655 (3.8%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	19137 (18.2%)	5266 (12.1%)
	Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	12084 (11.5%)	2718 (6.3%)
	Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	3713 (3.5%)	1480 (3.4%)
	Other	1049 (2.8%)	3720 (3.5%)	1114 (2.6%)

	Baseline period[1] (N=44108)	Study period years 1, 2 and 3[2] Overall (N=123429)	Incident[3] (N=50597)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription
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		Baseline period[1] (N=44108)	Study period years 1, 2 and 3[2] Overall (N=123429)	Incident[3] (N=50597)
Age at prescription (years)	Missing (N)	20	27	18
	<16 years	452 (1.0%)	661 (0.5%)	533 (1.1%)
	[16;30[	6208 (14.1%)	15120 (12.3%)	8833 (17.5%)
	[30;40[	8075 (18.3%)	21889 (17.7%)	9538 (18.9%)
	[40;50[	10817 (24.5%)	28736 (23.3%)	10891 (21.5%)
	[50;60[	9475 (21.5%)	27879 (22.6%)	9653 (19.1%)
	[60;70[	5453 (12.4%)	17491 (14.2%)	6462 (12.8%)
	≥70 years	3608 (8.2%)	11626 (9.4%)	4669 (9.2%)
Age at prescription (years)	N	44088 (100.0)	123402 (100.0)	50579 (100.0)
	Missing (N)	20 (0.0)	27 (0.0)	18 (0.0)
	Mean (SD)	46.6 (15.74)	48.1 (15.65)	46.0 (16.72)
	Median (Q1 - Q3)	46.0 (35.0-57.0)	48.0 (37.0-59.0)	45.0 (33.0-58.0)
	Range	(2.0,98.0)	(2.0,100.0)	(2.0,99.0)
Gender	Missing (N)	35	1	1
	Male	18813 (42.7%)	53738 (43.5%)	22999 (45.5%)
	Female	25260 (57.3%)	69690 (56.5%)	27597 (54.5%)
Route of systemic TCC prescription	Intramuscular	1543 (3.5%)	3501 (2.8%)	1221 (2.4%)
	Oral	42565 (96.5%)	119928 (97.2%)	49376 (97.6%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=44108)	Overall (N=123429)	Incident[3] (N=50597)
Oral form				
TCC daily dose	N	40242 (94.5)	110462 (92.1)	45354 (91.9)
	Missing (N)	2323 (5.5)	9466 (7.9)	4022 (8.1)
	Mean (SD)	11.5 (3.67)	11.6 (3.74)	11.8 (3.79)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(2.0,132.0)	(2.0,48.0)	(2.0,48.0)
	Missing (N)	2323	9466	4022
	≤16 mg	40130 (99.7%)	110243 (99.8%)	45256 (99.8%)
	>16 mg	112 (0.3%)	219 (0.2%)	98 (0.2%)
Duration of systemic TCC treatment (days)	N	40830 (95.9)	112699 (94.0)	46418 (94.0)
	Missing (N)	1735 (4.1)	7229 (6.0)	2958 (6.0)
	Mean (SD)	10.8 (12.32)	8.9 (10.79)	7.8 (8.26)
	Median (Q1 - Q3)	8.0 (6.0-10.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)
	Range	(1.0,364.0)	(1.0,336.0)	(1.0,336.0)
	Missing (N)	1735	7229	2958
	≤7 days	19067 (46.7%)	74551 (66.2%)	32839 (70.7%)
	>7 days	21763 (53.3%)	38148 (33.8%)	13579 (29.3%)
Intramuscular				
TCC daily dose	N	926 (60.0)	1595 (45.6)	615 (50.4)
	Missing (N)	617 (40.0)	1906 (54.4)	606 (49.6)
	Mean (SD)	9.3 (4.35)	8.6 (4.95)	8.3 (3.97)
	Median (Q1 - Q3)	8.0 (6.0-12.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
	Range	(4.0,24.0)	(4.0,32.0)	(4.0,32.0)
	Missing (N)	617	1906	606
	≤8 mg	589 (63.6%)	1292 (81.0%)	501 (81.5%)
	>8 mg	337 (36.4%)	303 (19.0%)	114 (18.5%)
Duration of systemic TCC treatment (days)	N	859 (55.7)	1784 (51.0)	691 (56.6)
	Missing (N)	684 (44.3)	1717 (49.0)	530 (43.4)
	Mean (SD)	8.6 (11.11)	6.8 (8.54)	6.5 (8.09)
	Median (Q1 - Q3)	6.0 (5.0-8.0)	6.0 (5.0-6.0)	5.0 (5.0-6.0)
	Range	(1.0,231.0)	(1.0,168.0)	(1.0,168.0)
	Missing (N)	684	1717	530
	≤5 days	261 (30.4%)	869 (48.7%)	372 (53.8%)
	>5 days	598 (69.6%)	915 (51.3%)	319 (46.2%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=44108)	Study period years 1, 2 and 3[2] Overall (N=123429)	Incident[3] (N=50597)
Long term treatment[4]	Missing (N)	512	2483	-
	Yes	2289 (5.3%)	4280 (3.5%)	-
	No	41307 (94.7%)	116666 (96.5%)	50597 (100.0%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	41234 (93.5%)	114367 (92.7%)	46270 (91.4%)
	No	2874 (6.5%)	9062 (7.3%)	4327 (8.6%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	31393 (71.2%)	85260 (69.1%)	32832 (64.9%)
	Acetylsalicylic	251 (0.6%)	1191 (1.0%)	339 (0.7%)
	Paracetamol	30435 (69.0%)	81741 (66.2%)	31751 (62.8%)
	Opioids (N02A)	10908 (24.7%)	29339 (23.8%)	9849 (19.5%)
	Antidepressants (N06A)	3781 (8.6%)	9606 (7.8%)	2359 (4.7%)
	Antiepileptics (N03A)	1439 (3.3%)	3780 (3.1%)	847 (1.7%)
	Muscle relaxants (M03)	3076 (7.0%)	3816 (3.1%)	994 (2.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	27801 (63.0%)	76008 (61.6%)	31677 (62.6%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2699 (6.1%)	9584 (7.8%)	3288 (6.5%)
	Topical products for joint and muscular pain (M02A)	9988 (22.6%)	30743 (24.9%)	12147 (24.0%)
	Phytotherapy (V03A)	16 (0.0%)	45 (0.0%)	19 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	727 (1.6%)	1232 (1.0%)	498 (1.0%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-29: Analysis of systemic TCC prescriptions – Baseline and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

			Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=1721)	Overall (N=4184)	Incident[3] (N=1923)
Total systemic TCC prescriptions		1721 (100.0%)	4184 (100.0%)	1923 (100.0%)
Number of patients with a systemic TCC prescription		1383	3016	1915
Number of systemic TCC prescriptions per patient	N	1383 (100.0)	3016 (100.0)	1915 (100.0)
	Mean (SD)	1.2 (0.65)	1.4 (1.06)	1.0 (0.06)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,10.0)	(1.0,21.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	59 (1.4%)	33 (1.7%)
	Spondylolysis - M43.0	-	1 (0.0%)	1 (0.1%)
	Spondylolisthesis - M43.1	-	5 (0.1%)	3 (0.2%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	4 (0.2%)	6 (0.1%)	4 (0.2%)
	Other specified deforming dorsopathies - M43.8	-	-	-
	Deforming dorsopathy, unspecified - M43.9	14 (0.8%)	47 (1.1%)	25 (1.3%)
	Dorsalgia - M54	1209 (70.2%)	2907 (69.5%)	1217 (63.3%)
	Radiculopathy - M54.1	21 (1.2%)	63 (1.5%)	30 (1.6%)
	Cervicalgia - M54.2	346 (20.1%)	778 (18.6%)	365 (19.0%)
	Sciatica - M54.3	34 (2.0%)	45 (1.1%)	31 (1.6%)
	Lumbago with sciatica - M.54.4	188 (10.9%)	437 (10.4%)	156 (8.1%)
	Low back pain - M54.5	470 (27.3%)	1079 (25.8%)	485 (25.2%)
	Pain in thoracic spine - M54.6	-	3 (0.1%)	3 (0.2%)
	Other dorsalgia - M54.8	2 (0.1%)	12 (0.3%)	5 (0.3%)
	Dorsalgia, unspecified - M54.9	148 (8.6%)	490 (11.7%)	142 (7.4%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	1218 (29.1%)	673 (35.0%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	1033 (24.7%)	564 (29.3%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	95 (2.3%)	63 (3.3%)
	Other specified arthrosis - M19.8	29 (1.7%)	18 (0.6%)	10 (0.8%)
	Pain in shoulder - M25.51	21 (1.2%)	78 (1.9%)	39 (2.0%)
	Pain in knee - M25.56	24 (1.4%)	79 (1.9%)	36 (1.9%)
	Other spondylosis - M47.8	44 (2.6%)	78 (1.9%)	38 (2.0%)
	Other shoulder lesions - M75.8	41 (2.4%)	28 (0.7%)	16 (0.8%)
	Enthesopathy, unspecified - M77.9	18 (1.0%)	18 (0.4%)	10 (0.5%)
	Rheumatism, unspecified - M79.0	16 (0.9%)	18 (0.4%)	6 (0.3%)
	Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	69 (1.6%)	36 (1.9%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	100 (2.4%)	57 (3.0%)
	Pain, unspecified - R52.9	31 (1.8%)	96 (2.3%)	54 (2.8%)
	Other	25 (1.5%)	85 (2.0%)	52 (2.7%)

	Baseline period[1] (N=1721)	Study period years 1, 2 and 3[2] Overall (N=4184)	Incident[3] (N=1923)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=1721)	Study period years 1, 2 and 3[2] Overall (N=4184)	Incident[3] (N=1923)
Age at prescription (years)	Missing (N)	-	3	2
	<16 years	-	1 (0.0%)	1 (0.1%)
	[16;30[	26 (1.5%)	44 (1.1%)	31 (1.6%)
	[30;40[	98 (5.7%)	196 (4.7%)	99 (5.2%)
	[40;50[	288 (16.7%)	542 (13.0%)	232 (12.1%)
	[50;60[	420 (24.4%)	996 (23.8%)	417 (21.7%)
	[60;70[	414 (24.1%)	1017 (24.3%)	471 (24.5%)
	≥70 years	475 (27.6%)	1385 (33.1%)	670 (34.9%)
Age at prescription (years)	N	1721 (100.0)	4181 (99.9)	1921 (99.9)
	Missing (N)	0	3 (0.1)	2 (0.1)
	Mean (SD)	60.1 (14.29)	62.4 (14.24)	62.6 (14.58)
	Median (Q1 - Q3)	60.0 (50.0-71.0)	62.0 (52.0-73.0)	63.0 (53.0-73.0)
	Range	(16.0,98.0)	(14.0,98.0)	(14.0,98.0)
Gender	Missing (N)	125	211	52
	Male	497 (31.1%)	1107 (27.9%)	513 (27.4%)
	Female	1099 (68.9%)	2866 (72.1%)	1358 (72.6%)
Route of systemic TCC prescription	Intramuscular	282 (16.4%)	738 (17.6%)	432 (22.5%)
	Oral	1439 (83.6%)	3446 (82.4%)	1491 (77.5%)
Oral form				
TCC daily dose	N	1193 (82.9)	2831 (82.2)	1196 (80.2)
	Missing (N)	246 (17.1)	615 (17.8)	295 (19.8)
	Mean (SD)	10.7 (4.00)	11.0 (4.35)	10.8 (4.47)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(2.0,16.0)	(1.3,16.0)	(1.3,16.0)
	Missing (N)	246	615	295
	≤16 mg	1193 (100.0%)	2831 (100.0%)	1196 (100.0%)
	>16 mg	-	-	-

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=1721)	Overall (N=4184)	Incident[3] (N=1923)
Duration of systemic TCC treatment (days)	N	1185 (82.3)	2831 (82.2)	1196 (80.2)
	Missing (N)	254 (17.7)	615 (17.8)	295 (19.8)
	Mean (SD)	30.1 (44.54)	21.5 (39.09)	14.8 (24.04)
	Median (Q1 - Q3)	12.0 (6.0-30.0)	9.0 (4.0-15.0)	7.0 (4.0-14.0)
	Range	(1.0,360.0)	(1.0,360.0)	(1.0,360.0)
	Missing (N)	254	615	295
	≤7 days	478 (40.3%)	1394 (49.2%)	662 (55.4%)
	>7 days	707 (59.7%)	1437 (50.8%)	534 (44.6%)
Intramuscular				
TCC daily dose	N	280 (99.3)	738 (100.0)	432 (100.0)
	Missing (N)	2 (0.7)	0	0
	Mean (SD)	10.2 (3.91)	10.3 (3.92)	10.2 (3.95)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,16.0)	(4.0,16.0)
	Missing (N)	2	-	-
	≤8 mg	176 (62.9%)	495 (67.1%)	288 (66.7%)
	>8 mg	104 (37.1%)	243 (32.9%)	144 (33.3%)
Duration of systemic TCC treatment (days)	N	278 (98.6)	738 (100.0)	432 (100.0)
	Missing (N)	4 (1.4)	0	0
	Mean (SD)	18.9 (42.46)	13.1 (31.11)	9.9 (22.61)
	Median (Q1 - Q3)	10.0 (5.0-12.0)	6.0 (4.0-10.0)	6.0 (4.0-10.0)
	Range	(1.0,360.0)	(2.0,360.0)	(2.0,360.0)
	Missing (N)	4	-	-
	≤5 days	90 (32.4%)	319 (43.2%)	207 (47.9%)
	>5 days	188 (67.6%)	419 (56.8%)	225 (52.1%)
Long term treatment[4]	Missing (N)	23	81	-
	Yes	132 (7.8%)	152 (3.7%)	-
	No	1566 (92.2%)	3951 (96.3%)	1923 (100.0%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline period[1] (N=1721)	Study period years 1, 2 and 3[2] Overall (N=4184)	Incident[3] (N=1923)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	1529 (88.8%)	3681 (88.0%)	1631 (84.8%)
	No	192 (11.2%)	503 (12.0%)	292 (15.2%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	879 (51.1%)	1897 (45.3%)	760 (39.5%)
	Acetylsalicylic	43 (2.5%)	7 (0.2%)	4 (0.2%)
	Paracetamol	743 (43.2%)	1589 (38.0%)	638 (33.2%)
	Opioids (N02A)	358 (20.8%)	791 (18.9%)	291 (15.1%)
	Antidepressants (N06A)	59 (3.4%)	176 (4.2%)	43 (2.2%)
	Antiepileptics (N03A)	67 (3.9%)	175 (4.2%)	43 (2.2%)
	Muscle relaxants (M03)	61 (3.5%)	70 (1.7%)	13 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	849 (49.3%)	2133 (51.0%)	975 (50.7%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	493 (28.6%)	1211 (28.9%)	523 (27.2%)
	Topical products for joint and muscular pain (M02A)	174 (10.1%)	395 (9.4%)	123 (6.4%)
	Phytotherapy (V03A)	6 (0.3%)	9 (0.2%)	2 (0.1%)
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	2 (0.1%)	7 (0.2%)	2 (0.1%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-30: Analysis of systemic TCC prescriptions – Baseline and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

			Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=23527)	Overall (N=54892)	Incident[3] (N=20674)
Total systemic TCC prescriptions		23527 (100.0%)	54892 (100.0%)	20674 (100.0%)
Number of patients with a systemic TCC prescription		19877	41061	20578
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	41061 (100.0)	20578 (100.0)
	Mean (SD)	1.2 (0.51)	1.3 (0.80)	1.0 (0.07)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,12.0)	(1.0,21.0)	(1.0,2.0)
Treatment indication for TCC prescription at index date (ICD10)	Missing	2063	4669	1884
	Other deforming dorsopathies including - M43	1082 (5.0%)	2164 (4.3%)	825 (4.4%)
	Spondylolysis - M43.0	451 (2.1%)	874 (1.7%)	247 (1.3%)
	Spondylolisthesis - M43.1	22 (0.1%)	56 (0.1%)	16 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-
	Torticollis - M43.6	405 (1.9%)	764 (1.5%)	382 (2.0%)
	Other specified deforming dorsopathies - M43.8	123 (0.6%)	289 (0.6%)	98 (0.5%)
	Deforming dorsopathy, unspecified - M43.9	81 (0.4%)	181 (0.4%)	82 (0.4%)
	Dorsalgia - M54	15146 (70.6%)	36812 (73.3%)	13403 (71.3%)
	Radiculopathy - M54.1	220 (1.0%)	418 (0.8%)	88 (0.5%)
	Cervicalgia - M54.2	2270 (10.6%)	4902 (9.8%)	2113 (11.2%)
	Sciatica - M54.3	627 (2.9%)	1554 (3.1%)	595 (3.2%)
	Lumbago with sciatica - M.54.4	-	-	-
	Low back pain - M54.5	11393 (53.1%)	28543 (56.8%)	10091 (53.7%)
	Pain in thoracic spine - M54.6	292 (1.4%)	646 (1.3%)	183 (1.0%)
	Other dorsalgia - M54.8	-	-	-
	Dorsalgia, unspecified - M54.9	344 (1.6%)	749 (1.5%)	333 (1.8%)
	Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	11247 (22.4%)	4562 (24.3%)
	Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	7136 (14.2%)	2635 (14.0%)
	Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	1309 (2.6%)	387 (2.1%)
	Spasm Of Muscle - 728.85	392 (1.8%)	814 (1.6%)	394 (2.1%)
	Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	639 (1.3%)	245 (1.3%)
	Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	1224 (2.4%)	551 (2.9%)
	Injury And Poisoning (800-999)	524 (2.4%)	1126 (2.2%)	562 (3.0%)
	Other	743 (3.5%)	1761 (3.5%)	814 (4.3%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=23527)	Study period years 1, 2 and 3[2] Overall (N=54892)	Incident[3] (N=20674)
Age at prescription (years)	Missing (N)	14	54	27
	<16 years	36 (0.2%)	32 (0.1%)	30 (0.1%)
	[16;30[	1083 (4.6%)	2155 (3.9%)	1607 (7.8%)
	[30;40[	2573 (10.9%)	4911 (9.0%)	2617 (12.7%)
	[40;50[	4851 (20.6%)	10218 (18.6%)	4278 (20.7%)
	[50;60[	5180 (22.0%)	12796 (23.3%)	4255 (20.6%)
	[60;70[	4496 (19.1%)	11361 (20.7%)	3663 (17.7%)
	≥70 years	5294 (22.5%)	13365 (24.4%)	4197 (20.3%)
Age at prescription (years)	N	23513 (99.9)	54838 (99.9)	20647 (99.9)
	Missing (N)	14 (0.1)	54 (0.1)	27 (0.1)
	Mean (SD)	56.0 (15.89)	57.4 (15.50)	54.0 (16.74)
	Median (Q1 - Q3)	56.0 (44.0-68.0)	57.0 (46.0-69.0)	53.0 (42.0-67.0)
	Range	(12.0,101.0)	(11.0,103.0)	(11.0,101.0)
Gender	Missing (N)	3395	7951	2615
	Male	7248 (36.0%)	17558 (37.4%)	6950 (38.5%)
	Female	12884 (64.0%)	29383 (62.6%)	11109 (61.5%)
Route of systemic TCC prescription	Intramuscular	17086 (72.6%)	43008 (78.4%)	15059 (72.8%)
	Oral	6441 (27.4%)	11884 (21.6%)	5615 (27.2%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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			Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=23527)	Overall (N=54892)	Incident[3] (N=20674)
Oral form				
TCC daily dose	N	2599 (40.4)	4227 (35.6)	1859 (33.1)
	Missing (N)	3842 (59.6)	7657 (64.4)	3756 (66.9)
	Mean (SD)	11.6 (4.38)	11.2 (4.62)	11.2 (4.67)
	Median (Q1 - Q3)	12.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(4.0,24.0)	(2.0,32.0)	(4.0,24.0)
	Missing (N)	3842	7657	3756
	≤16 mg	2565 (98.7%)	4165 (98.5%)	1831 (98.5%)
	>16 mg	34 (1.3%)	62 (1.5%)	28 (1.5%)
Duration of systemic TCC treatment (days)	N	2596 (40.3)	4225 (35.6)	1858 (33.1)
	Missing (N)	3845 (59.7)	7659 (64.4)	3757 (66.9)
	Mean (SD)	8.2 (4.30)	9.9 (4.94)	9.9 (4.84)
	Median (Q1 - Q3)	6.0 (5.0-10.0)	10.0 (7.0-10.0)	10.0 (7.0-10.0)
	Range	(3.0,60.0)	(3.0,50.0)	(3.0,30.0)
	Missing (N)	3845	7659	3757
	≤7 days	1357 (52.3%)	1967 (46.6%)	890 (47.9%)
	>7 days	1239 (47.7%)	2258 (53.4%)	968 (52.1%)
Intramuscular				
TCC daily dose	N	4299 (25.2)	9568 (22.2)	2810 (18.7)
	Missing (N)	12787 (74.8)	33440 (77.8)	12249 (81.3)
	Mean (SD)	4.6 (1.47)	4.6 (1.45)	4.6 (1.47)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(2.0,16.0)	(2.0,16.0)	(4.0,12.0)
	Missing (N)	12787	33440	12249
	≤8 mg	4295 (99.9%)	9560 (99.9%)	2808 (99.9%)
	>8 mg	4 (0.1%)	8 (0.1%)	2 (0.1%)
Duration of systemic TCC treatment (days)	N	4297 (25.1)	9566 (22.2)	2809 (18.7)
	Missing (N)	12789 (74.9)	33442 (77.8)	12250 (81.3)
	Mean (SD)	5.9 (1.66)	5.8 (1.39)	5.8 (1.29)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(1.0,24.0)	(1.0,18.0)	(2.0,12.0)
	Missing (N)	12789	33442	12250
	≤5 days	552 (12.8%)	1107 (11.6%)	343 (12.2%)
	>5 days	3745 (87.2%)	8459 (88.4%)	2466 (87.8%)
Long term treatment[4]	Missing (N)	2390	5475	-
	Yes	225 (1.1%)	380 (0.8%)	-
	No	20912 (98.9%)	49037 (99.2%)	20674 (100.0%)

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline period[1] (N=23527)	Study period years 1, 2 and 3[2] Overall (N=54892)	Incident[3] (N=20674)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	20376 (86.6%)	48622 (88.6%)	17921 (86.7%)
	No	3151 (13.4%)	6270 (11.4%)	2753 (13.3%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:				
Medications:				
	Analgesics (N02)	2949 (12.5%)	6035 (11.0%)	2197 (10.6%)
	Acetylsalicylic	7 (0.0%)	31 (0.1%)	9 (0.0%)
	Paracetamol	2478 (10.5%)	4682 (8.5%)	1792 (8.7%)
	Opioids (N02A)	1910 (8.1%)	3784 (6.9%)	1249 (6.0%)
	Antidepressants (N06A)	895 (3.8%)	2269 (4.1%)	664 (3.2%)
	Antiepileptics (N03A)	405 (1.7%)	1142 (2.1%)	317 (1.5%)
	Muscle relaxants (M03)	152 (0.6%)	458 (0.8%)	155 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	17641 (75.0%)	42611 (77.6%)	15670 (75.8%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-
	Corticosteroids for systemic use (H02A)	2153 (9.2%)	5954 (10.8%)	1974 (9.5%)
	Topical products for joint and muscular pain (M02A)	511 (2.2%)	696 (1.3%)	344 (1.7%)
	Phytotherapy (V03A)	5 (0.0%)	15 (0.0%)	4 (0.0%)
Health services/medical devices and others:				
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-31: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period years 1 and 2 – GPs France – included patients

		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Total systemic TCC prescriptions		195 (100.0%)	18605 (100.0%)	144 (100.0%)	21363 (100.0%)	108 (100.0%)	19193 (100.0%)
Number of patients with a systemic TCC prescription		176	14722	130	16613 (100.0%)	99 (100.0%)	15095 (100.0%)
Number of systemic TCC prescriptions per patient	N	176 (100.0)	14722 (100.0)	130 (100.0)	16613 (100.0)	99 (100.0)	15095 (100.0)
	Mean (SD)	1.1 (0.78)	1.3 (0.80)	1.1 (0.55)	1.3 (0.80)	1.1 (0.38)	1.3 (0.80)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,11.0)	(1.0,14.0)	(1.0,6.0)	(1.0,14.0)	(1.0,4.0)	(1.0,13.0)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Treatment indication for TCC prescription at index date (ICD10)	Missing	31	2666	17	2647	12	2857
	Other deforming dorsopathies including - M43	22 (13.4%)	398 (2.5%)	13 (10.2%)	461 (2.5%)	13 (13.5%)	417 (2.6%)
	Spondylolysis - M43.0	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	1 (0.0%)	-	5 (0.0%)	-	1 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	10 (0.1%)
	Torticollis - M43.6	22 (13.4%)	397 (2.5%)	13 (10.2%)	456 (2.4%)	13 (13.5%)	397 (2.4%)
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	7 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	-	-	-	-	-	2 (0.0%)
	Dorsalgia - M54	64 (39.0%)	8634 (54.2%)	56 (44.1%)	10144 (54.2%)	35 (36.5%)	8938 (54.7%)
	Radiculopathy - M54.1	-	56 (0.4%)	-	69 (0.4%)	-	83 (0.5%)
	Cervicalgia - M54.2	8 (4.9%)	1247 (7.8%)	8 (6.3%)	1432 (7.7%)	6 (6.3%)	1180 (7.2%)
	Sciatica - M54.3	1 (0.6%)	500 (3.1%)	-	543 (2.9%)	1 (1.0%)	458 (2.8%)
	Lumbago with sciatica - M.54.4	-	778 (4.9%)	2 (1.6%)	1009 (5.4%)	-	856 (5.2%)
	Low back pain - M54.5	30 (18.3%)	4655 (29.2%)	21 (16.5%)	5575 (29.8%)	17 (17.7%)	5041 (30.9%)
	Pain in thoracic spine - M54.6	-	11 (0.1%)	1 (0.8%)	17 (0.1%)	-	17 (0.1%)
	Other dorsalgia - M54.8	5 (3.0%)	274 (1.7%)	3 (2.4%)	338 (1.8%)	2 (2.1%)	278 (1.7%)
	Dorsalgia, unspecified - M54.9	20 (12.2%)	1113 (7.0%)	21 (16.5%)	1161 (6.2%)	9 (9.4%)	1025 (6.3%)
	Other than painful muscle contractures associated with acute spinal pathology	78 (47.6%)	6907 (43.3%)	58 (45.7%)	8111 (43.3%)	48 (50.0%)	6981 (42.7%)

Baseline period[1]: year 2013
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Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Age at prescription (years)	<16 years	195 (100.0%)	-	144 (100.0%)	-	108 (100.0%)	-
	[16;30[	-	2771 (14.9%)	-	2853 (13.4%)	-	2456 (12.8%)
	[30;40[	-	3516 (18.9%)	-	3969 (18.6%)	-	3498 (18.2%)
	[40;50[	-	4526 (24.3%)	-	5050 (23.6%)	-	4515 (23.5%)
	[50;60[	-	4041 (21.7%)	-	4819 (22.6%)	-	4406 (23.0%)
	[60;70[	-	2338 (12.6%)	-	2949 (13.8%)	-	2656 (13.8%)
	≥70 years	-	1413 (7.6%)	-	1723 (8.1%)	-	1662 (8.7%)
Age at prescription (years)	N	195 (100.0)	18605 (100.0)	144 (100.0)	21363 (100.0)	108 (100.0)	19193 (100.0)
	Mean (SD)	13.8 (2.11)	46.6 (15.35)	13.7 (2.61)	47.4 (15.29)	14.1 (2.00)	47.8 (15.30)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	46.0 (35.0-57.0)	15.0 (14.0-15.0)	47.0 (36.0-58.0)	15.0 (14.0-15.0)	48.0 (37.0-58.0)
	Range	(2.0,15.0)	(16.0,95.0)	(2.0,15.0)	(16.0,98.0)	(3.0,15.0)	(16.0,97.0)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Oral TCC daily dose › Oral form	N	181 (95.3)	17066 (94.6)	138 (96.5)	19695 (94.5)	99 (93.4)	17808 (95.0)
	Missing (N)	9 (4.7)	966 (5.4)	5 (3.5)	1154 (5.5)	7 (6.6)	945 (5.0)
	Mean (SD)	10.9 (3.43)	11.6 (3.67)	10.3 (3.63)	11.6 (3.70)	11.4 (3.95)	11.7 (3.73)
	Median (Q1 - Q3)	12.0 (8.0-12.0)	12.0 (8.0-16.0)	8.8 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(4.0,16.0)	(4.0,132.0)	(2.0,16.0)	(4.0,24.0)	(4.0,24.0)	(4.0,32.0)
	Missing (N)	9	966	5	1154	7	945
	≤16 mg	181 (100.0%)	17028 (99.8%)	138 (100.0%)	19648 (99.8%)	98 (99.0%)	17771 (99.8%)
	>16 mg	-	38 (0.2%)	-	47 (0.2%)	1 (1.0%)	37 (0.2%)
Duration of TCC treatment (days)› Oral form	N	182 (95.8)	17304 (96.0)	141 (98.6)	20131 (96.6)	102 (96.2)	18069 (96.4)
	Missing (N)	8 (4.2)	728 (4.0)	2 (1.4)	718 (3.4)	4 (3.8)	684 (3.6)
	Mean (SD)	8.4 (9.00)	10.2 (11.49)	7.6 (7.47)	8.7 (10.54)	8.7 (11.15)	8.9 (10.48)
	Median (Q1 - Q3)	6.0 (6.0-8.0)	8.0 (6.0-10.0)	6.0 (5.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)
	Range	(2.0,84.0)	(1.0,364.0)	(2.0,84.0)	(1.0,196.0)	(2.0,84.0)	(1.0,196.0)
	Missing (N)	8	728	2	718	4	684
	≤7 days	129 (70.9%)	8395 (48.5%)	96 (68.1%)	13291 (66.0%)	65 (63.7%)	11999 (66.4%)
	>7 days	53 (29.1%)	8909 (51.5%)	45 (31.9%)	6840 (34.0%)	37 (36.3%)	6070 (33.6%)

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Intramuscular							
TCC daily dose › IM form	N	2 (40.0)	363 (63.4)	()	257 (50.0)	1 (50.0)	246 (55.9)
	Missing (N)	3 (60.0)	210 (36.6)	1 ()	257 (50.0)	1 (50.0)	194 (44.1)
	Mean (SD)	8.0 (0.00)	9.5 (4.29)	()	9.5 (5.21)	16.0 ()	8.9 (5.17)
	Median (Q1 - Q3)	8.0 (8.0-8.0)	8.0 (8.0-12.0)	(-)	8.0 (8.0-16.0)	16.0 (16.0-16.0)	8.0 (4.0-8.0)
	Range	(8.0,8.0)	(4.0,16.0)	(,)	(4.0,28.0)	(16.0,16.0)	(4.0,32.0)
	Missing (N)	3	210	1	257	1	194
	≤8 mg	2 (100.0%)	230 (63.4%)	-	188 (73.2%)	-	197 (80.1%)
	>8 mg	-	133 (36.6%)	-	69 (26.8%)	1 (100.0%)	49 (19.9%)
Duration of TCC treatment (days)› IM form	N	2 (40.0)	333 (58.1)	()	286 (55.6)	1 (50.0)	273 (62.0)
	Missing (N)	3 (60.0)	240 (41.9)	1 ()	228 (44.4)	1 (50.0)	167 (38.0)
	Mean (SD)	19.0 (12.73)	8.7 (8.96)	()	6.3 (5.73)	5.0 ()	7.7 (7.95)
	Median (Q1 - Q3)	19.0 (10.0-28.0)	6.0 (5.0-8.0)	(-)	5.0 (5.0-6.0)	5.0 (5.0-5.0)	6.0 (5.0-7.0)
	Range	(10.0,28.0)	(1.0,84.0)	(,)	(1.0,49.0)	(5.0,5.0)	(2.0,84.0)
	Missing (N)	3	240	1	228	1	167
	≤5 days	-	89 (26.7%)	-	165 (57.7%)	1 (100.0%)	120 (44.0%)
	>5 days	2 (100.0%)	244 (73.3%)	-	121 (42.3%)	-	153 (56.0%)
Long term treatment[4]	Missing (N)	1	212	-	241	-	190
	Yes	5 (2.6%)	915 (5.0%)	3 (2.1%)	737 (3.5%)	1 (0.9%)	653 (3.4%)
	No	189 (97.4%)	17478 (95.0%)	141 (97.9%)	20385 (96.5%)	107 (99.1%)	18350 (96.6%)

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	179 (91.8%)	17449 (93.8%)	131 (91.0%)	19897 (93.1%)	97 (89.8%)	17920 (93.4%)
	No	16 (8.2%)	1156 (6.2%)	13 (9.0%)	1466 (6.9%)	11 (10.2%)	1273 (6.6%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
medication							
	Analgesics (N02)	108 (55.4%)	13437 (72.2%)	78 (54.2%)	15117 (70.8%)	66 (61.1%)	13448 (70.1%)
	Acetylsalicylic	-	115 (0.6%)	-	243 (1.1%)	1 (0.9%)	218 (1.1%)
	Paracetamol	108 (55.4%)	13042 (70.1%)	78 (54.2%)	14497 (67.9%)	63 (58.3%)	12837 (66.9%)
	Opioids (N02A)	8 (4.1%)	5024 (27.0%)	10 (6.9%)	5348 (25.0%)	8 (7.4%)	4790 (25.0%)
	Antidepressants (N06A)	-	975 (5.2%)	-	1021 (4.8%)	1 (0.9%)	992 (5.2%)
	Antiepileptics (N03A)	-	513 (2.8%)	-	602 (2.8%)	-	586 (3.1%)
	Muscle relaxants (M03)	3 (1.5%)	1277 (6.9%)	4 (2.8%)	620 (2.9%)	1 (0.9%)	602 (3.1%)
	NSAIDs/Cox-2 inhibitors (M01A)	119 (61.0%)	12029 (64.7%)	95 (66.0%)	13704 (64.1%)	55 (50.9%)	12131 (63.2%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	4 (2.1%)	1188 (6.4%)	4 (2.8%)	1566 (7.3%)	5 (4.6%)	1497 (7.8%)
	Topical products for joint and muscular pain (M02A)	67 (34.4%)	4447 (23.9%)	37 (25.7%)	5093 (23.8%)	38 (35.2%)	5138 (26.8%)
	Phytotherapy (V03A)	-	7 (0.0%)	-	3 (0.0%)	-	10 (0.1%)

Baseline period[1]: year 2013
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=144)	Male ≥16 years (N=21363)	Male <16 years (N=108)	Male ≥16 years (N=19193)
Health services/medical devices and others:							
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	1 (0.5%)	277 (1.5%)	3 (2.1%)	227 (1.1%)	1 (0.9%)	172 (0.9%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	Yes	-	-	-	-	-	-
	No	195 (100.0%)	18605 (100.0%)	144 (100.0%)	21363 (100.0%)	108 (100.0%)	19193 (100.0%)
Off label use	Missing (N)	41	3740	21	3892	19	3832
	Yes	154 (100.0%)	10922 (73.5%)	123 (100.0%)	10999 (63.0%)	89 (100.0%)	9548 (62.2%)
	No	-	3943 (26.5%)	-	6472 (37.0%)	-	5813 (37.8%)

Baseline period[1]: year 2013
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Table 15.3-32: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period years 1 and 2 – Rheumatologists France – included patients

		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Total systemic TCC prescriptions		-	497 (100.0%)	-	416 (100.0%)	-	352 (100.0%)
Number of patients with a systemic TCC prescription		-	396	-	352 (100.0%)	-	295 (100.0%)
Number of systemic TCC prescriptions per patient	N		396 (100.0)		352 (100.0)		295 (100.0)
	Mean (SD)		1.3 (0.70)		1.2 (0.61)		1.2 (0.60)
	Median (Q1 - Q3)		1.0 (1.0-1.0)		1.0 (1.0-1.0)		1.0 (1.0-1.0)
	Range		(1.0,10.0)		(1.0,7.0)		(1.0,7.0)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Treatment indication for TCC prescription at index date (ICD10)							
	Missing	-	-	-	-	-	-
	Other deforming dorsopathies including - M43	-	9 (1.8%)	-	2 (0.5%)	-	5 (1.4%)
	Spondylolysis - M43.0	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	-	-	-	-	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-
	Torticollis - M43.6	-	2 (0.4%)	-	-	-	-
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	-
	Deforming dorsopathy, unspecified - M43.9	-	7 (1.4%)	-	2 (0.5%)	-	5 (1.4%)
	Dorsalgia - M54	-	353 (71.0%)	-	317 (76.2%)	-	257 (73.0%)
	Radiculopathy - M54.1	-	8 (1.6%)	-	6 (1.4%)	-	6 (1.7%)
	Cervicalgia - M54.2	-	77 (15.5%)	-	70 (16.8%)	-	59 (16.8%)
	Sciatica - M54.3	-	12 (2.4%)	-	3 (0.7%)	-	3 (0.9%)
	Lumbago with sciatica - M.54.4	-	62 (12.5%)	-	71 (17.1%)	-	36 (10.2%)
	Low back pain - M54.5	-	154 (31.0%)	-	121 (29.1%)	-	97 (27.6%)
	Pain in thoracic spine - M54.6	-	-	-	-	-	1 (0.3%)
	Other dorsalgia - M54.8	-	1 (0.2%)	-	1 (0.2%)	-	3 (0.9%)
	Dorsalgia, unspecified - M54.9	-	39 (7.8%)	-	45 (10.8%)	-	52 (14.8%)
	Other than painful muscle contractures associated with acute spinal pathology	-	135 (27.2%)	-	97 (23.3%)	-	90 (25.6%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Age at prescription (years)	<16 years	-	-	-	-	-	-
	[16;30[	-	9 (1.8%)	-	7 (1.7%)	-	5 (1.4%)
	[30;40[	-	39 (7.8%)	-	25 (6.0%)	-	14 (4.0%)
	[40;50[	-	87 (17.5%)	-	71 (17.1%)	-	74 (21.0%)
	[50;60[	-	128 (25.8%)	-	96 (23.1%)	-	67 (19.0%)
	[60;70[	-	113 (22.7%)	-	109 (26.2%)	-	77 (21.9%)
	≥70 years	-	121 (24.3%)	-	108 (26.0%)	-	115 (32.7%)
Age at prescription (years)	N		497 (100.0)		416 (100.0)		352 (100.0)
	Mean (SD)		58.3 (14.50)		60.1 (14.59)		61.1 (14.50)
	Median (Q1 - Q3)		59.0 (48.0-69.0)		60.0 (50.0-70.0)		61.5 (48.0-72.5)
	Range		(16.0,92.0)		(19.0,94.0)		(17.0,92.0)

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Oral TCC daily dose › Oral form	N		364 (86.5)		297 (84.1)		253 (84.6)
	Missing (N)		57 (13.5)		56 (15.9)		46 (15.4)
	Mean (SD)		10.6 (3.84)		11.6 (4.23)		11.4 (4.30)
	Median (Q1 - Q3)		8.0 (8.0-16.0)		12.0 (8.0-16.0)		8.0 (8.0-16.0)
	Range		(4.0,16.0)		(2.0,16.0)		(1.3,16.0)
	Missing (N)	-	57	-	56	-	46
	≤16 mg	-	364 (100.0%)	-	297 (100.0%)	-	253 (100.0%)
	>16 mg	-	-	-	-	-	-
Duration of TCC treatment (days)› Oral form	N		361 (85.7)		297 (84.1)		253 (84.6)
	Missing (N)		60 (14.3)		56 (15.9)		46 (15.4)
	Mean (SD)		25.8 (38.95)		16.5 (24.31)		17.5 (26.47)
	Median (Q1 - Q3)		10.0 (6.0-30.0)		7.0 (4.0-15.0)		10.0 (6.0-15.0)
	Range		(1.0,180.0)		(2.0,180.0)		(1.0,180.0)
	Missing (N)	-	60	-	56	-	46
	≤7 days	-	170 (47.1%)	-	159 (53.5%)	-	120 (47.4%)
	>7 days	-	191 (52.9%)	-	138 (46.5%)	-	133 (52.6%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Intramuscular TCC daily dose › IM form	N		76 (100.0)		63 (100.0)		53 (100.0)
	Mean (SD)		10.7 (4.51)		10.0 (3.65)		10.5 (3.90)
	Median (Q1 - Q3)		8.0 (8.0-16.0)		8.0 (8.0-16.0)		8.0 (8.0-16.0)
	Range		(4.0,24.0)		(4.0,16.0)		(4.0,16.0)
	≤8 mg	-	44 (57.9%)	-	46 (73.0%)	-	34 (64.2%)
	>8 mg	-	32 (42.1%)	-	17 (27.0%)	-	19 (35.8%)
Duration of TCC treatment (days)› IM form	N		75 (98.7)		63 (100.0)		53 (100.0)
	Missing (N)		1 (1.3)		0		0
	Mean (SD)		11.7 (28.52)		9.0 (13.11)		8.3 (12.20)
	Median (Q1 - Q3)		7.0 (2.0-12.0)		5.0 (4.0-10.0)		6.0 (4.0-7.0)
	Range		(1.0,180.0)		(2.0,90.0)		(3.0,90.0)
	Missing (N)	-	1	-	-	-	-
	≤5 days	-	33 (44.0%)	-	35 (55.6%)	-	26 (49.1%)
	>5 days	-	42 (56.0%)	-	28 (44.4%)	-	27 (50.9%)
Long term treatment[4]	Missing (N)	-	2	-	10	-	8
	Yes	-	31 (6.3%)	-	11 (2.7%)	-	8 (2.3%)
	No	-	464 (93.7%)	-	395 (97.3%)	-	336 (97.7%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	-	441 (88.7%)	-	370 (88.9%)	-	312 (88.6%)
	No	-	56 (11.3%)	-	46 (11.1%)	-	40 (11.4%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
medication							
	Analgesics (N02)	-	226 (45.5%)	-	182 (43.8%)	-	153 (43.5%)
	Acetylsalicylic	-	11 (2.2%)	-	1 (0.2%)	-	-
	Paracetamol	-	182 (36.6%)	-	153 (36.8%)	-	132 (37.5%)
	Opioids (N02A)	-	115 (23.1%)	-	97 (23.3%)	-	79 (22.4%)
	Antidepressants (N06A)	-	13 (2.6%)	-	11 (2.6%)	-	10 (2.8%)
	Antiepileptics (N03A)	-	25 (5.0%)	-	24 (5.8%)	-	17 (4.8%)
	Muscle relaxants (M03)	-	9 (1.8%)	-	12 (2.9%)	-	14 (4.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	-	253 (50.9%)	-	203 (48.8%)	-	172 (48.9%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	152 (30.6%)	-	120 (28.8%)	-	109 (31.0%)
	Topical products for joint and muscular pain (M02A)	-	40 (8.0%)	-	37 (8.9%)	-	39 (11.1%)
	Phytotherapy (V03A)	-	-	-	1 (0.2%)	-	1 (0.3%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=0)	Male ≥16 years (N=416)	Male <16 years (N=0)	Male ≥16 years (N=352)
Health services/medical devices and others:							
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	1 (0.2%)	-	1 (0.2%)	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	Yes	-	-	-	-	-	-
	No	-	497 (100.0%)	-	416 (100.0%)	-	352 (100.0%)
Off label use	Missing (N)	-	61	-	56	-	46
	Yes	-	304 (69.7%)	-	236 (65.6%)	-	216 (70.6%)
	No	-	132 (30.3%)	-	124 (34.4%)	-	90 (29.4%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
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Table 15.3-33: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period years 1 and 2 – GPs Italy – included patients

		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Total systemic TCC prescriptions		14 (100.0%)	7234 (100.0%)	3 (100.0%)	6081 (100.0%)	8 (100.0%)	5934 (100.0%)
Number of patients with a systemic TCC prescription		14	6067	3	5182 (100.0%)	8 (100.0%)	5067 (100.0%)
Number of systemic TCC prescriptions per patient	N	14 (100.0)	6067 (100.0)	3 (100.0)	5182 (100.0)	8 (100.0)	5067 (100.0)
	Mean (SD)	1.0 (0.00)	1.2 (0.51)	1.0 (0.00)	1.2 (0.49)	1.0 (0.00)	1.2 (0.49)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,1.0)	(1.0,7.0)	(1.0,1.0)	(1.0,7.0)	(1.0,1.0)	(1.0,6.0)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	647	-	505	1	499
	Other deforming dorsopathies including - M43	5 (35.7%)	289 (4.4%)	-	202 (3.6%)	1 (14.3%)	185 (3.4%)
	Spondylolysis - M43.0	-	112 (1.7%)	-	61 (1.1%)	-	65 (1.2%)
	Spondylolisthesis - M43.1	-	8 (0.1%)	-	11 (0.2%)	-	5 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-
	Torticollis - M43.6	5 (35.7%)	106 (1.6%)	-	92 (1.6%)	1 (14.3%)	71 (1.3%)
	Other specified deforming dorsopathies - M43.8	-	40 (0.6%)	-	26 (0.5%)	-	28 (0.5%)
	Deforming dorsopathy, unspecified - M43.9	-	23 (0.3%)	-	12 (0.2%)	-	16 (0.3%)
	Dorsalgia - M54	3 (21.4%)	4940 (75.0%)	1 (33.3%)	4346 (77.9%)	3 (42.9%)	4233 (77.9%)
	Radiculopathy - M54.1	-	59 (0.9%)	-	34 (0.6%)	-	42 (0.8%)
	Cervicalgia - M54.2	2 (14.3%)	524 (8.0%)	1 (33.3%)	443 (7.9%)	1 (14.3%)	403 (7.4%)
	Sciatica - M54.3	-	204 (3.1%)	-	174 (3.1%)	-	183 (3.4%)
	Lumbago with sciatica - M.54.4	-	-	-	-	-	-
	Low back pain - M54.5	1 (7.1%)	3971 (60.3%)	-	3538 (63.5%)	2 (28.6%)	3456 (63.6%)
	Pain in thoracic spine - M54.6	-	78 (1.2%)	-	73 (1.3%)	-	62 (1.1%)
	Other dorsalgia - M54.8	-	-	-	-	-	-
	Dorsalgia, unspecified - M54.9	-	104 (1.6%)	-	84 (1.5%)	-	87 (1.6%)
	Other than painful muscle contractures associated with acute spinal pathology	6 (42.9%)	1358 (20.6%)	2 (66.7%)	1028 (18.4%)	3 (42.9%)	1017 (18.7%)

Baseline period[1]: year 2013
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Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Age at prescription (years)	<16 years	14 (100.0%)	-	3 (100.0%)	-	8 (100.0%)	-
	[16;30[	-	382 (5.3%)	-	272 (4.5%)	-	284 (4.8%)
	[30;40[	-	980 (13.5%)	-	687 (11.3%)	-	669 (11.3%)
	[40;50[	-	1576 (21.8%)	-	1290 (21.2%)	-	1220 (20.6%)
	[50;60[	-	1585 (21.9%)	-	1439 (23.7%)	-	1398 (23.6%)
	[60;70[	-	1319 (18.2%)	-	1126 (18.5%)	-	1129 (19.0%)
	≥70 years	-	1392 (19.2%)	-	1267 (20.8%)	-	1234 (20.8%)
Age at prescription (years)	N	14 (100.0)	7234 (100.0)	3 (100.0)	6081 (100.0)	8 (100.0)	5934 (100.0)
	Mean (SD)	14.2 (0.89)	54.3 (15.77)	14.0 (1.00)	55.5 (15.57)	14.0 (1.07)	55.5 (15.55)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	54.0 (42.0-66.0)	14.0 (13.0-15.0)	55.0 (44.0-67.0)	14.0 (13.5-15.0)	55.0 (44.0-67.0)
	Range	(12.0,15.0)	(16.0,97.0)	(13.0,15.0)	(16.0,98.0)	(12.0,15.0)	(16.0,101.0)

Baseline period[1]: year 2013
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Oral TCC daily dose › Oral form	N	7 (58.3)	744 (40.8)	()	465 (34.2)	4 (50.0)	428 (37.2)
	Missing (N)	5 (41.7)	1079 (59.2)	3 ()	896 (65.8)	4 (50.0)	722 (62.8)
	Mean (SD)	10.3 (3.90)	12.1 (4.37)	()	11.1 (4.27)	7.0 (2.00)	11.5 (4.69)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	12.0 (8.0-16.0)	(-)	8.0 (8.0-16.0)	8.0 (6.0-8.0)	8.0 (8.0-16.0)
	Range	(8.0,16.0)	(4.0,24.0)	(,)	(4.0,24.0)	(4.0,8.0)	(2.0,24.0)
	Missing (N)	5	1079	3	896	4	722
	≤16 mg	7 (100.0%)	733 (98.5%)	-	462 (99.4%)	4 (100.0%)	422 (98.6%)
	>16 mg	-	11 (1.5%)	-	3 (0.6%)	-	6 (1.4%)
Duration of TCC treatment (days)› Oral form	N	7 (58.3)	742 (40.7)	()	465 (34.2)	4 (50.0)	428 (37.2)
	Missing (N)	5 (41.7)	1081 (59.3)	3 ()	896 (65.8)	4 (50.0)	722 (62.8)
	Mean (SD)	8.6 (2.44)	7.8 (3.92)	()	8.6 (4.26)	13.5 (4.73)	10.1 (5.18)
	Median (Q1 - Q3)	10.0 (5.0-10.0)	6.0 (5.0-10.0)	(-)	10.0 (5.0-10.0)	12.0 (10.0-17.0)	10.0 (7.0-10.0)
	Range	(5.0,10.0)	(3.0,20.0)	(,)	(3.0,20.0)	(10.0,20.0)	(4.0,50.0)
	Missing (N)	5	1081	3	896	4	722
	≤7 days	2 (28.6%)	428 (57.7%)	-	224 (48.2%)	-	207 (48.4%)
	>7 days	5 (71.4%)	314 (42.3%)	-	241 (51.8%)	4 (100.0%)	221 (51.6%)

Baseline period[1]: year 2013
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Intramuscular TCC daily dose › IM form	N	()	1294 (23.9)		1002 (21.2)		1018 (21.3)
	Missing (N)	2 ()	4117 (76.1)		3718 (78.8)		3766 (78.7)
	Mean (SD)	()	4.6 (1.43)		4.6 (1.42)		4.5 (1.38)
	Median (Q1 - Q3)	(-)	4.0 (4.0-4.0)		4.0 (4.0-4.0)		4.0 (4.0-4.0)
	Range	(,)	(4.0,8.0)		(2.0,12.0)		(2.0,8.0)
	Missing (N)	2	4117	-	3718	-	3766
	≤8 mg	-	1294 (100.0%)	-	1001 (99.9%)	-	1018 (100.0%)
	>8 mg	-	-	-	1 (0.1%)	-	-
Duration of TCC treatment (days)› IM form	N	()	1294 (23.9)		1002 (21.2)		1017 (21.3)
	Missing (N)	2 ()	4117 (76.1)		3718 (78.8)		3767 (78.7)
	Mean (SD)	()	6.0 (1.78)		5.8 (1.28)		5.9 (1.36)
	Median (Q1 - Q3)	(-)	6.0 (6.0-6.0)		6.0 (6.0-6.0)		6.0 (6.0-6.0)
	Range	(,)	(3.0,18.0)		(2.0,12.0)		(3.0,18.0)
	Missing (N)	2	4117	-	3718	-	3767
	≤5 days	-	162 (12.5%)	-	113 (11.3%)	-	108 (10.6%)
	>5 days	-	1132 (87.5%)	-	889 (88.7%)	-	909 (89.4%)
Long term treatment[4]	Missing (N)	-	754	-	662	-	633
	Yes	-	77 (1.2%)	-	44 (0.8%)	-	48 (0.9%)
	No	14 (100.0%)	6403 (98.8%)	3 (100.0%)	5375 (99.2%)	8 (100.0%)	5253 (99.1%)

Baseline period[1]: year 2013
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	9 (64.3%)	6372 (88.1%)	2 (66.7%)	5430 (89.3%)	4 (50.0%)	5348 (90.1%)
	No	5 (35.7%)	862 (11.9%)	1 (33.3%)	651 (10.7%)	4 (50.0%)	586 (9.9%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
medication							
	Analgesics (N02)	2 (14.3%)	869 (12.0%)	-	661 (10.9%)	2 (25.0%)	631 (10.6%)
	Acetylsalicylic	-	4 (0.1%)	-	3 (0.0%)	-	2 (0.0%)
	Paracetamol	2 (14.3%)	759 (10.5%)	-	542 (8.9%)	2 (25.0%)	515 (8.7%)
	Opioids (N02A)	-	561 (7.8%)	-	423 (7.0%)	-	391 (6.6%)
	Antidepressants (N06A)	-	169 (2.3%)	-	130 (2.1%)	-	120 (2.0%)
	Antiepileptics (N03A)	-	112 (1.5%)	-	122 (2.0%)	-	107 (1.8%)
	Muscle relaxants (M03)	-	42 (0.6%)	-	42 (0.7%)	-	51 (0.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	5 (35.7%)	5603 (77.5%)	2 (66.7%)	4839 (79.6%)	1 (12.5%)	4689 (79.0%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	660 (9.1%)	-	609 (10.0%)	-	685 (11.5%)
	Topical products for joint and muscular pain (M02A)	2 (14.3%)	156 (2.2%)	-	88 (1.4%)	1 (12.5%)	76 (1.3%)
	Phytotherapy (V03A)	-	4 (0.1%)	-	-	-	-

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 1[1]		Study period year 2[2]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=3)	Male ≥16 years (N=6081)	Male <16 years (N=8)	Male ≥16 years (N=5934)
Health services/medical devices and others:							
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	Yes	-	-	-	-	-	-
	No	14 (100.0%)	7234 (100.0%)	3 (100.0%)	6081 (100.0%)	8 (100.0%)	5934 (100.0%)
Off label use	Missing (N)	7	5273	3	4650	5	4529
	Yes	7 (100.0%)	1620 (82.6%)	-	1221 (85.3%)	3 (100.0%)	1196 (85.1%)
	No	-	341 (17.4%)	-	210 (14.7%)	-	209 (14.9%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-34: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs France – included patients

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Total systemic TCC prescriptions		195 (100.0%)	18605 (100.0%)	55 (100.0%)	12861 (100.0%)	307 (100.0%)	53420 (100.0%)
Number of patients with a systemic TCC prescription		176	14722	48	10162 (100.0%)	268 (100.0%)	36212 (100.0%)
Number of systemic TCC prescriptions per patient	N	176 (100.0)	14722 (100.0)	48 (100.0)	10162 (100.0)	268 (100.0)	36212 (100.0)
	Mean (SD)	1.1 (0.78)	1.3 (0.80)	1.1 (0.50)	1.3 (0.79)	1.1 (0.73)	1.5 (1.36)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,11.0)	(1.0,14.0)	(1.0,4.0)	(1.0,13.0)	(1.0,8.0)	(1.0,36.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Treatment indication for TCC prescription at index date (ICD10)	Missing	31	2666	12	2178	41	7683
	Other deforming dorsopathies including - M43	22 (13.4%)	398 (2.5%)	6 (14.0%)	277 (2.6%)	32 (12.0%)	1155 (2.5%)
	Spondylolysis - M43.0	-	-	-	1 (0.0%)	-	1 (0.0%)
	Spondylolisthesis - M43.1	-	1 (0.0%)	-	1 (0.0%)	-	7 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	7 (0.1%)	-	17 (0.0%)
	Torticollis - M43.6	22 (13.4%)	397 (2.5%)	6 (14.0%)	263 (2.5%)	32 (12.0%)	1116 (2.4%)
	Other specified deforming dorsopathies - M43.8	-	-	-	3 (0.0%)	-	10 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	-	-	-	2 (0.0%)	-	4 (0.0%)
	Dorsalgia - M54	64 (39.0%)	8634 (54.2%)	18 (41.9%)	5778 (54.1%)	109 (41.0%)	24860 (54.4%)
	Radiculopathy - M54.1	-	56 (0.4%)	-	37 (0.3%)	-	189 (0.4%)
	Cervicalgia - M54.2	8 (4.9%)	1247 (7.8%)	1 (2.3%)	784 (7.3%)	15 (5.6%)	3396 (7.4%)
	Sciatica - M54.3	1 (0.6%)	500 (3.1%)	-	301 (2.8%)	1 (0.4%)	1302 (2.8%)
	Lumbago with sciatica - M.54.4	-	778 (4.9%)	-	585 (5.5%)	2 (0.8%)	2450 (5.4%)
	Low back pain - M54.5	30 (18.3%)	4655 (29.2%)	12 (27.9%)	3285 (30.7%)	50 (18.8%)	13901 (30.4%)
	Pain in thoracic spine - M54.6	-	11 (0.1%)	-	14 (0.1%)	1 (0.4%)	48 (0.1%)
	Other dorsalgia - M54.8	5 (3.0%)	274 (1.7%)	1 (2.3%)	180 (1.7%)	6 (2.3%)	796 (1.7%)
	Dorsalgia, unspecified - M54.9	20 (12.2%)	1113 (7.0%)	4 (9.3%)	592 (5.5%)	34 (12.8%)	2778 (6.1%)
	Other than painful muscle contractures associated with acute spinal pathology	78 (47.6%)	6907 (43.3%)	19 (44.2%)	4628 (43.3%)	125 (47.0%)	19722 (43.1%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_05_01.sas; By: Alampure; Date & time: 07AUG19 16:09;

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Age at prescription (years)	<16 years	195 (100.0%)	-	55 (100.0%)	-	307 (100.0%)	-
	[16;30[	-	2771 (14.9%)	-	1482 (11.5%)	-	6791 (12.7%)
	[30;40[	-	3516 (18.9%)	-	2327 (18.1%)	-	9795 (18.3%)
	[40;50[	-	4526 (24.3%)	-	3044 (23.7%)	-	12610 (23.6%)
	[50;60[	-	4041 (21.7%)	-	2894 (22.5%)	-	12120 (22.7%)
	[60;70[	-	2338 (12.6%)	-	1817 (14.1%)	-	7422 (13.9%)
	≥70 years	-	1413 (7.6%)	-	1297 (10.1%)	-	4682 (8.8%)
Age at prescription (years)	N	195 (100.0)	18605 (100.0)	55 (100.0)	12861 (100.0)	307 (100.0)	53420 (100.0)
	Mean (SD)	13.8 (2.11)	46.6 (15.35)	13.7 (2.90)	48.6 (15.46)	13.9 (2.47)	47.9 (15.34)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	46.0 (35.0-57.0)	15.0 (14.0-15.0)	48.0 (37.0-59.0)	15.0 (14.0-15.0)	48.0 (37.0-58.0)
	Range	(2.0,15.0)	(16.0,95.0)	(3.0,15.0)	(16.0,94.0)	(2.0,15.0)	(16.0,98.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_05_01.sas; By: Alampure; Date & time: 07AUG19 16:09;

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Oral							
TCC daily dose › Oral form	N	181 (95.3)	17066 (94.6)	43 (84.3)	10655 (85.7)	280 (93.3)	48161 (92.6)
	Missing (N)	9 (4.7)	966 (5.4)	8 (15.7)	1774 (14.3)	20 (6.7)	3873 (7.4)
	Mean (SD)	10.9 (3.43)	11.6 (3.67)	10.1 (3.07)	11.8 (3.79)	10.6 (3.70)	11.7 (3.73)
	Median (Q1 - Q3)	12.0 (8.0-12.0)	12.0 (8.0-16.0)	8.0 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-12.0)	12.0 (8.0-16.0)
	Range	(4.0,16.0)	(4.0,132.0)	(4.0,16.0)	(2.0,24.0)	(2.0,24.0)	(2.0,32.0)
	Missing (N)	9	966	8	1774	20	3873
	≤16 mg	181 (100.0%)	17028 (99.8%)	43 (100.0%)	10637 (99.8%)	279 (99.6%)	48059 (99.8%)
	>16 mg	-	38 (0.2%)	-	18 (0.2%)	1 (0.4%)	102 (0.2%)
Duration of TCC treatment (days)› Oral form	N	182 (95.8)	17304 (96.0)	45 (88.2)	10868 (87.4)	288 (96.0)	49071 (94.3)
	Missing (N)	8 (4.2)	728 (4.0)	6 (11.8)	1561 (12.6)	12 (4.0)	2963 (5.7)
	Mean (SD)	8.4 (9.00)	10.2 (11.49)	6.7 (3.52)	8.6 (10.97)	7.9 (8.57)	8.8 (10.62)
	Median (Q1 - Q3)	6.0 (6.0-8.0)	8.0 (6.0-10.0)	6.0 (6.0-7.0)	7.0 (6.0-8.0)	6.0 (6.0-8.0)	7.0 (6.0-8.0)
	Range	(2.0,84.0)	(1.0,364.0)	(3.0,28.0)	(1.0,280.0)	(2.0,84.0)	(1.0,280.0)
	Missing (N)	8	728	6	1561	12	2963
	≤7 days	129 (70.9%)	8395 (48.5%)	39 (86.7%)	7622 (70.1%)	200 (69.4%)	32914 (67.1%)
	>7 days	53 (29.1%)	8909 (51.5%)	6 (13.3%)	3246 (29.9%)	88 (30.6%)	16157 (32.9%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Intramuscular							
TCC daily dose › IM form	N	2 (40.0)	363 (63.4)	1 (25.0)	188 (43.5)	2 (28.6)	691 (49.9)
	Missing (N)	3 (60.0)	210 (36.6)	3 (75.0)	244 (56.5)	5 (71.4)	695 (50.1)
	Mean (SD)	8.0 (0.00)	9.5 (4.29)	16.0 ()	7.2 (2.82)	16.0 (0.00)	8.6 (4.75)
	Median (Q1 - Q3)	8.0 (8.0-8.0)	8.0 (8.0-12.0)	16.0 (16.0-16.0)	8.0 (4.0-8.0)	16.0 (16.0-16.0)	8.0 (4.0-8.0)
	Range	(8.0,8.0)	(4.0,16.0)	(16.0,16.0)	(4.0,16.0)	(16.0,16.0)	(4.0,32.0)
	Missing (N)	3	210	3	244	5	695
	≤8 mg	2 (100.0%)	230 (63.4%)	-	167 (88.8%)	-	552 (79.9%)
	>8 mg	-	133 (36.6%)	1 (100.0%)	21 (11.2%)	2 (100.0%)	139 (20.1%)
Duration of TCC treatment (days)› IM form	N	2 (40.0)	333 (58.1)	1 (25.0)	209 (48.4)	2 (28.6)	768 (55.4)
	Missing (N)	3 (60.0)	240 (41.9)	3 (75.0)	223 (51.6)	5 (71.4)	618 (44.6)
	Mean (SD)	19.0 (12.73)	8.7 (8.96)	5.0 ()	5.7 (2.92)	5.0 (0.00)	6.7 (6.14)
	Median (Q1 - Q3)	19.0 (10.0-28.0)	6.0 (5.0-8.0)	5.0 (5.0-5.0)	5.0 (5.0-6.0)	5.0 (5.0-5.0)	5.0 (5.0-6.0)
	Range	(10.0,28.0)	(1.0,84.0)	(5.0,5.0)	(3.0,28.0)	(5.0,5.0)	(1.0,84.0)
	Missing (N)	3	240	3	223	5	618
	≤5 days	-	89 (26.7%)	1 (100.0%)	109 (52.2%)	2 (100.0%)	394 (51.3%)
	>5 days	2 (100.0%)	244 (73.3%)	-	100 (47.8%)	-	374 (48.7%)
Long term treatment[4]	Missing (N)	1	212	1	492	1	923
	Yes	5 (2.6%)	915 (5.0%)	-	388 (3.1%)	4 (1.3%)	1778 (3.4%)
	No	189 (97.4%)	17478 (95.0%)	54 (100.0%)	11981 (96.9%)	302 (98.7%)	50719 (96.6%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	179 (91.8%)	17449 (93.8%)	52 (94.5%)	11960 (93.0%)	280 (91.2%)	49780 (93.2%)
	No	16 (8.2%)	1156 (6.2%)	3 (5.5%)	901 (7.0%)	27 (8.8%)	3640 (6.8%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
Medication							
	Analgesics (N02)	108 (55.4%)	13437 (72.2%)	25 (45.5%)	8804 (68.5%)	169 (55.0%)	37371 (70.0%)
	Acetylsalicylic	-	115 (0.6%)	-	130 (1.0%)	1 (0.3%)	591 (1.1%)
	Paracetamol	108 (55.4%)	13042 (70.1%)	25 (45.5%)	8411 (65.4%)	166 (54.1%)	35747 (66.9%)
	Opioids (N02A)	8 (4.1%)	5024 (27.0%)	4 (7.3%)	3245 (25.2%)	22 (7.2%)	13385 (25.1%)
	Antidepressants (N06A)	-	975 (5.2%)	-	636 (4.9%)	1 (0.3%)	2649 (5.0%)
	Antiepileptics (N03A)	-	513 (2.8%)	1 (1.8%)	359 (2.8%)	1 (0.3%)	1547 (2.9%)
	Muscle relaxants (M03)	3 (1.5%)	1277 (6.9%)	4 (7.3%)	442 (3.4%)	9 (2.9%)	1664 (3.1%)
	NSAIDs/Cox-2 inhibitors (M01A)	119 (61.0%)	12029 (64.7%)	40 (72.7%)	8039 (62.5%)	190 (61.9%)	33876 (63.4%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	4 (2.1%)	1188 (6.4%)	1 (1.8%)	1031 (8.0%)	10 (3.3%)	4094 (7.7%)
	Topical products for joint and muscular pain (M02A)	67 (34.4%)	4447 (23.9%)	18 (32.7%)	3490 (27.1%)	93 (30.3%)	13721 (25.7%)
	Phytotherapy (V03A)	-	7 (0.0%)	-	6 (0.0%)	-	19 (0.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=195)	Male ≥16 years (N=18605)	Male <16 years (N=55)	Male ≥16 years (N=12861)	Male <16 years (N=307)	Male ≥16 years (N=53420)
Health services/medical devices and others:							
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	1 (0.5%)	277 (1.5%)	-	78 (0.6%)	4 (1.3%)	477 (0.9%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-
Off label use	Missing (N)	41	3740	18	3773	58	11498
	Yes	154 (100.0%)	10922 (73.5%)	37 (100.0%)	5620 (61.8%)	249 (100.0%)	26169 (62.4%)
	No	-	3943 (26.5%)	-	3468 (38.2%)	-	15753 (37.6%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_05_01.sas; By: Alampure; Date & time: 07AUG19 16:09;

Table 15.3-35: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Total systemic TCC prescriptions		-	497 (100.0%)	1 (100.0%)	338 (100.0%)	1 (100.0%)	1106 (100.0%)
Number of patients with a systemic TCC prescription		-	396	1	277 (100.0%)	1 (100.0%)	802 (100.0%)
Number of systemic TCC prescriptions per patient	N		396 (100.0)	1 (100.0)	277 (100.0)	1 (100.0)	802 (100.0)
	Mean (SD)		1.3 (0.70)	1.0 ()	1.2 (0.62)	1.0 ()	1.4 (1.13)
	Median (Q1 - Q3)		1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range		(1.0,10.0)	(1.0,1.0)	(1.0,7.0)	(1.0,1.0)	(1.0,21.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Treatment indication for TCC prescription at index date (ICD10)							
	Missing	-	-	-	-	-	-
	Other deforming dorsopathies including - M43	-	9 (1.8%)	-	5 (1.5%)	-	12 (1.1%)
	Spondylolysis - M43.0	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	-	-	-	-	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-
	Torticollis - M43.6	-	2 (0.4%)	-	-	-	-
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	-
	Deforming dorsopathy, unspecified - M43.9	-	7 (1.4%)	-	5 (1.5%)	-	12 (1.1%)
	Dorsalgia - M54	-	353 (71.0%)	1 (100.0%)	255 (75.4%)	1 (100.0%)	829 (75.0%)
	Radiculopathy - M54.1	-	8 (1.6%)	-	5 (1.5%)	-	17 (1.5%)
	Cervicalgia - M54.2	-	77 (15.5%)	-	68 (20.1%)	-	197 (17.8%)
	Sciatica - M54.3	-	12 (2.4%)	-	6 (1.8%)	-	12 (1.1%)
	Lumbago with sciatica - M.54.4	-	62 (12.5%)	-	32 (9.5%)	-	139 (12.6%)
	Low back pain - M54.5	-	154 (31.0%)	1 (100.0%)	117 (34.6%)	1 (100.0%)	335 (30.3%)
	Pain in thoracic spine - M54.6	-	-	-	-	-	1 (0.1%)
	Other dorsalgia - M54.8	-	1 (0.2%)	-	-	-	4 (0.4%)
	Dorsalgia, unspecified - M54.9	-	39 (7.8%)	-	27 (8.0%)	-	124 (11.2%)
	Other than painful muscle contractures associated with acute spinal pathology	-	135 (27.2%)	-	78 (23.1%)	-	265 (24.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Age at prescription (years)	<16 years	-	-	1 (100.0%)	-	1 (100.0%)	-
	[16;30[	-	9 (1.8%)	-	7 (2.1%)	-	19 (1.7%)
	[30;40[	-	39 (7.8%)	-	19 (5.6%)	-	58 (5.2%)
	[40;50[	-	87 (17.5%)	-	45 (13.3%)	-	190 (17.2%)
	[50;60[	-	128 (25.8%)	-	83 (24.6%)	-	246 (22.2%)
	[60;70[	-	113 (22.7%)	-	75 (22.2%)	-	261 (23.6%)
	≥70 years	-	121 (24.3%)	-	109 (32.2%)	-	332 (30.0%)
Age at prescription (years)	N		497 (100.0)	1 (100.0)	338 (100.0)	1 (100.0)	1106 (100.0)
	Mean (SD)		58.3 (14.50)	14.0 ()	61.2 (14.72)	14.0 ()	60.7 (14.60)
	Median (Q1 - Q3)		59.0 (48.0-69.0)	14.0 (14.0-14.0)	62.0 (51.0-72.0)	14.0 (14.0-14.0)	61.0 (50.0-72.0)
	Range		(16.0,92.0)	(14.0,14.0)	(22.0,98.0)	(14.0,14.0)	(17.0,98.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Oral							
TCC daily dose › Oral form	N		364 (86.5)	1 (100.0)	228 (82.3)	1 (100.0)	778 (83.7)
	Missing (N)		57 (13.5)	0	49 (17.7)	0	151 (16.3)
	Mean (SD)		10.6 (3.84)	16.0 ()	11.1 (4.37)	16.0 ()	11.4 (4.30)
	Median (Q1 - Q3)		8.0 (8.0-16.0)	16.0 (16.0-16.0)	8.0 (8.0-16.0)	16.0 (16.0-16.0)	8.0 (8.0-16.0)
	Range		(4.0,16.0)	(16.0,16.0)	(2.0,16.0)	(16.0,16.0)	(1.3,16.0)
	Missing (N)	-	57	-	49	-	151
	≤16 mg	-	364 (100.0%)	1 (100.0%)	228 (100.0%)	1 (100.0%)	778 (100.0%)
	>16 mg	-	-	-	-	-	-
Duration of TCC treatment (days)› Oral form	N		361 (85.7)	1 (100.0)	228 (82.3)	1 (100.0)	778 (83.7)
	Missing (N)		60 (14.3)	0	49 (17.7)	0	151 (16.3)
	Mean (SD)		25.8 (38.95)	4.0 ()	15.6 (27.26)	4.0 ()	16.6 (25.89)
	Median (Q1 - Q3)		10.0 (6.0-30.0)	4.0 (4.0-4.0)	7.0 (4.0-12.0)	4.0 (4.0-4.0)	7.0 (4.0-15.0)
	Range		(1.0,180.0)	(4.0,4.0)	(1.0,180.0)	(4.0,4.0)	(1.0,180.0)
	Missing (N)	-	60	-	49	-	151
	≤7 days	-	170 (47.1%)	1 (100.0%)	140 (61.4%)	1 (100.0%)	419 (53.9%)
	>7 days	-	191 (52.9%)	-	88 (38.6%)	-	359 (46.1%)

Baseline period[1]: year 2013
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Intramuscular							
TCC daily dose › IM form	N		76 (100.0)		61 (100.0)		177 (100.0)
	Mean (SD)		10.7 (4.51)		12.2 (4.07)		10.9 (3.97)
	Median (Q1 - Q3)		8.0 (8.0-16.0)		16.0 (8.0-16.0)		8.0 (8.0-16.0)
	Range		(4.0,24.0)		(4.0,16.0)		(4.0,16.0)
	≤8 mg	-	44 (57.9%)	-	27 (44.3%)	-	107 (60.5%)
	>8 mg	-	32 (42.1%)	-	34 (55.7%)	-	70 (39.5%)
Duration of TCC treatment (days)› IM form	N		75 (98.7)		61 (100.0)		177 (100.0)
	Missing (N)		1 (1.3)		0		0
	Mean (SD)		11.7 (28.52)		7.5 (6.29)		8.3 (10.88)
	Median (Q1 - Q3)		7.0 (2.0-12.0)		5.0 (4.0-10.0)		5.0 (4.0-10.0)
	Range		(1.0,180.0)		(2.0,30.0)		(2.0,90.0)
	Missing (N)	-	1	-	-	-	-
	≤5 days	-	33 (44.0%)	-	35 (57.4%)	-	96 (54.2%)
	>5 days	-	42 (56.0%)	-	26 (42.6%)	-	81 (45.8%)
Long term treatment[4]	Missing (N)	-	2	-	6	-	24
	Yes	-	31 (6.3%)	-	7 (2.1%)	-	26 (2.4%)
	No	-	464 (93.7%)	1 (100.0%)	325 (97.9%)	1 (100.0%)	1056 (97.6%)

Baseline period[1]: year 2013
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	-	441 (88.7%)	1 (100.0%)	314 (92.9%)	1 (100.0%)	996 (90.1%)
	No	-	56 (11.3%)	-	24 (7.1%)	-	110 (9.9%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
Medications:							
	Analgesics (N02)	-	226 (45.5%)	1 (100.0%)	134 (39.6%)	1 (100.0%)	469 (42.4%)
	Acetylsalicylic	-	11 (2.2%)	-	-	-	1 (0.1%)
	Paracetamol	-	182 (36.6%)	1 (100.0%)	103 (30.5%)	1 (100.0%)	388 (35.1%)
	Opioids (N02A)	-	115 (23.1%)	-	69 (20.4%)	-	245 (22.2%)
	Antidepressants (N06A)	-	13 (2.6%)	-	5 (1.5%)	-	26 (2.4%)
	Antiepileptics (N03A)	-	25 (5.0%)	-	16 (4.7%)	-	57 (5.2%)
	Muscle relaxants (M03)	-	9 (1.8%)	-	12 (3.6%)	-	38 (3.4%)
	NSAIDs/Cox-2 inhibitors (M01A)	-	253 (50.9%)	-	192 (56.8%)	-	567 (51.3%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	152 (30.6%)	-	106 (31.4%)	-	335 (30.3%)
	Topical products for joint and muscular pain (M02A)	-	40 (8.0%)	-	23 (6.8%)	-	99 (9.0%)
	Phytotherapy (V03A)	-	-	-	-	-	2 (0.2%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=0)	Male ≥16 years (N=497)	Male <16 years (N=1)	Male ≥16 years (N=338)	Male <16 years (N=1)	Male ≥16 years (N=1106)
Health services/medical devices and others:							
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	1 (0.2%)	-	-	-	1 (0.1%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-
Off label use	Missing (N)	-	61	-	49	-	151
	Yes	-	304 (69.7%)	1 (100.0%)	178 (61.6%)	1 (100.0%)	630 (66.0%)
	No	-	132 (30.3%)	-	111 (38.4%)	-	325 (34.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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Table 15.3-36: Analysis of systemic TCC prescriptions according to age in men – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Total systemic TCC prescriptions		14 (100.0%)	7234 (100.0%)	2 (100.0%)	5530 (100.0%)	13 (100.0%)	17545 (100.0%)
Number of patients with a systemic TCC prescription		14	6067	2	4715 (100.0%)	12 (100.0%)	13009 (100.0%)
Number of systemic TCC prescriptions per patient	N	14 (100.0)	6067 (100.0)	2 (100.0)	4715 (100.0)	12 (100.0)	13009 (100.0)
	Mean (SD)	1.0 (0.00)	1.2 (0.51)	1.0 (0.00)	1.2 (0.47)	1.1 (0.29)	1.3 (0.83)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,1.0)	(1.0,7.0)	(1.0,1.0)	(1.0,7.0)	(1.0,2.0)	(1.0,14.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	647	-	460	1	1464
	Other deforming dorsopathies including - M43	5 (35.7%)	289 (4.4%)	-	158 (3.1%)	1 (8.3%)	545 (3.4%)
	Spondylolysis - M43.0	-	112 (1.7%)	-	53 (1.0%)	-	179 (1.1%)
	Spondylolisthesis - M43.1	-	8 (0.1%)	-	4 (0.1%)	-	20 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-
	Torticollis - M43.6	5 (35.7%)	106 (1.6%)	-	61 (1.2%)	1 (8.3%)	224 (1.4%)
	Other specified deforming dorsopathies - M43.8	-	40 (0.6%)	-	24 (0.5%)	-	78 (0.5%)
	Deforming dorsopathy, unspecified - M43.9	-	23 (0.3%)	-	16 (0.3%)	-	44 (0.3%)
	Dorsalgia - M54	3 (21.4%)	4940 (75.0%)	1 (50.0%)	3994 (78.8%)	5 (41.7%)	12573 (78.2%)
	Radiculopathy - M54.1	-	59 (0.9%)	-	42 (0.8%)	-	118 (0.7%)
	Cervicalgia - M54.2	2 (14.3%)	524 (8.0%)	-	391 (7.7%)	2 (16.7%)	1237 (7.7%)
	Sciatica - M54.3	-	204 (3.1%)	-	145 (2.9%)	-	502 (3.1%)
	Lumbago with sciatica - M.54.4	-	-	-	-	-	-
	Low back pain - M54.5	1 (7.1%)	3971 (60.3%)	-	3275 (64.6%)	2 (16.7%)	10269 (63.9%)
	Pain in thoracic spine - M54.6	-	78 (1.2%)	-	72 (1.4%)	-	207 (1.3%)
	Other dorsalgia - M54.8	-	-	-	-	-	-
	Dorsalgia, unspecified - M54.9	-	104 (1.6%)	1 (50.0%)	69 (1.4%)	1 (8.3%)	240 (1.5%)
	Other than painful muscle contractures associated with acute spinal pathology	6 (42.9%)	1358 (20.6%)	1 (50.0%)	918 (18.1%)	6 (50.0%)	2963 (18.4%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Age at prescription (years)	<16 years	14 (100.0%)	-	2 (100.0%)	-	13 (100.0%)	-
	[16;30[	-	382 (5.3%)	-	256 (4.6%)	-	812 (4.6%)
	[30;40[	-	980 (13.5%)	-	652 (11.8%)	-	2008 (11.4%)
	[40;50[	-	1576 (21.8%)	-	1124 (20.3%)	-	3634 (20.7%)
	[50;60[	-	1585 (21.9%)	-	1334 (24.1%)	-	4171 (23.8%)
	[60;70[	-	1319 (18.2%)	-	1045 (18.9%)	-	3300 (18.8%)
	≥70 years	-	1392 (19.2%)	-	1119 (20.2%)	-	3620 (20.6%)
Age at prescription (years)	N	14 (100.0)	7234 (100.0)	2 (100.0)	5530 (100.0)	13 (100.0)	17545 (100.0)
	Mean (SD)	14.2 (0.89)	54.3 (15.77)	12.0 (1.41)	55.3 (15.32)	13.7 (1.25)	55.4 (15.48)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	54.0 (42.0-66.0)	12.0 (11.0-13.0)	55.0 (44.0-67.0)	14.0 (13.0-15.0)	55.0 (44.0-67.0)
	Range	(12.0,15.0)	(16.0,97.0)	(11.0,13.0)	(16.0,96.0)	(11.0,15.0)	(16.0,101.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Oral							
TCC daily dose › Oral form	N	7 (58.3)	744 (40.8)	1 (50.0)	365 (33.7)	5 (38.5)	1258 (35.0)
	Missing (N)	5 (41.7)	1079 (59.2)	1 (50.0)	719 (66.3)	8 (61.5)	2337 (65.0)
	Mean (SD)	10.3 (3.90)	12.1 (4.37)	8.0 ()	11.8 (5.02)	7.2 (1.79)	11.4 (4.65)
	Median (Q1 - Q3)	8.0 (8.0-16.0)	12.0 (8.0-16.0)	8.0 (8.0-8.0)	12.0 (8.0-16.0)	8.0 (8.0-8.0)	8.0 (8.0-16.0)
	Range	(8.0,16.0)	(4.0,24.0)	(8.0,8.0)	(4.0,24.0)	(4.0,8.0)	(2.0,24.0)
	Missing (N)	5	1079	1	719	8	2337
	≤16 mg	7 (100.0%)	733 (98.5%)	1 (100.0%)	353 (96.7%)	5 (100.0%)	1237 (98.3%)
	>16 mg	-	11 (1.5%)	-	12 (3.3%)	-	21 (1.7%)
Duration of TCC treatment (days)› Oral form	N	7 (58.3)	742 (40.7)	1 (50.0)	364 (33.6)	5 (38.5)	1257 (35.0)
	Missing (N)	5 (41.7)	1081 (59.3)	1 (50.0)	720 (66.4)	8 (61.5)	2338 (65.0)
	Mean (SD)	8.6 (2.44)	7.8 (3.92)	10.0 ()	10.1 (4.49)	12.8 (4.38)	9.6 (4.71)
	Median (Q1 - Q3)	10.0 (5.0-10.0)	6.0 (5.0-10.0)	10.0 (10.0-10.0)	7.0 (7.0-14.0)	10.0 (10.0-14.0)	10.0 (7.0-10.0)
	Range	(5.0,10.0)	(3.0,20.0)	(10.0,10.0)	(4.0,20.0)	(10.0,20.0)	(3.0,50.0)
	Missing (N)	5	1081	1	720	8	2338
	≤7 days	2 (28.6%)	428 (57.7%)	-	186 (51.1%)	-	617 (49.1%)
	>7 days	5 (71.4%)	314 (42.3%)	1 (100.0%)	178 (48.9%)	5 (100.0%)	640 (50.9%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Intramuscular							
TCC daily dose › IM form	N	()	1294 (23.9)		921 (20.7)		2941 (21.1)
	Missing (N)	2 ()	4117 (76.1)		3525 (79.3)		11009 (78.9)
	Mean (SD)	()	4.6 (1.43)		4.6 (1.44)		4.6 (1.41)
	Median (Q1 - Q3)	(-)	4.0 (4.0-4.0)		4.0 (4.0-4.0)		4.0 (4.0-4.0)
	Range	(,)	(4.0,8.0)		(2.0,8.0)		(2.0,12.0)
	Missing (N)	2	4117	-	3525	-	11009
	≤8 mg	-	1294 (100.0%)	-	921 (100.0%)	-	2940 (100.0%)
	>8 mg	-	-	-	-	-	1 (0.0%)
Duration of TCC treatment (days)› IM form	N	()	1294 (23.9)		921 (20.7)		2940 (21.1)
	Missing (N)	2 ()	4117 (76.1)		3525 (79.3)		11010 (78.9)
	Mean (SD)	()	6.0 (1.78)		5.8 (1.35)		5.8 (1.33)
	Median (Q1 - Q3)	(-)	6.0 (6.0-6.0)		6.0 (6.0-6.0)		6.0 (6.0-6.0)
	Range	(,)	(3.0,18.0)		(3.0,12.0)		(2.0,18.0)
	Missing (N)	2	4117	-	3525	-	11010
	≤5 days	-	162 (12.5%)	-	112 (12.2%)	-	333 (11.3%)
	>5 days	-	1132 (87.5%)	-	809 (87.8%)	-	2607 (88.7%)
Long term treatment[4]	Missing (N)	-	754	-	608	-	1903
	Yes	-	77 (1.2%)	-	36 (0.7%)	-	128 (0.8%)
	No	14 (100.0%)	6403 (98.8%)	2 (100.0%)	4886 (99.3%)	13 (100.0%)	15514 (99.2%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	9 (64.3%)	6372 (88.1%)	2 (100.0%)	4978 (90.0%)	8 (61.5%)	15756 (89.8%)
	No	5 (35.7%)	862 (11.9%)	-	552 (10.0%)	5 (38.5%)	1789 (10.2%)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:							
Medications:							
	Analgesics (N02)	2 (14.3%)	869 (12.0%)	1 (50.0%)	517 (9.3%)	3 (23.1%)	1809 (10.3%)
	Acetylsalicylic	-	4 (0.1%)	-	-	-	5 (0.0%)
	Paracetamol	2 (14.3%)	759 (10.5%)	1 (50.0%)	418 (7.6%)	3 (23.1%)	1475 (8.4%)
	Opioids (N02A)	-	561 (7.8%)	-	341 (6.2%)	-	1155 (6.6%)
	Antidepressants (N06A)	-	169 (2.3%)	-	135 (2.4%)	-	385 (2.2%)
	Antiepileptics (N03A)	-	112 (1.5%)	-	91 (1.6%)	-	320 (1.8%)
	Muscle relaxants (M03)	-	42 (0.6%)	-	43 (0.8%)	-	136 (0.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	5 (35.7%)	5603 (77.5%)	1 (50.0%)	4365 (78.9%)	4 (30.8%)	13893 (79.2%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	660 (9.1%)	-	676 (12.2%)	-	1970 (11.2%)
	Topical products for joint and muscular pain (M02A)	2 (14.3%)	156 (2.2%)	-	54 (1.0%)	1 (7.7%)	218 (1.2%)
	Phytotherapy (V03A)	-	4 (0.1%)	-	1 (0.0%)	-	1 (0.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]		Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Male <16 years (N=14)	Male ≥16 years (N=7234)	Male <16 years (N=2)	Male ≥16 years (N=5530)	Male <16 years (N=13)	Male ≥16 years (N=17545)
Health services/medical devices and others:							
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-
Off label use	Missing (N)	7	5273	1	4270	9	13449
	Yes	7 (100.0%)	1620 (82.6%)	1 (100.0%)	1055 (83.7%)	4 (100.0%)	3472 (84.8%)
	No	-	341 (17.4%)	-	205 (16.3%)	-	624 (15.2%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication and no concomitant medication
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Table 15.3-37: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period years 1 and 2 – GPs France – included patients

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Total systemic TCC prescriptions		256 (100.0%)	14269 (100.0%)	10728 (100.0%)	162 (100.0%)	14782 (100.0%)	12644 (100.0%)	130 (100.0%)	13491 (100.0%)	11754 (100.0%)
Number of patients with a systemic TCC prescription		237	11321	7992	134 (100.0%)	11780 (100.0%)	9137 (100.0%)	113 (100.0%)	10618 (100.0%)	8436 (100.0%)
Number of systemic TCC prescriptions per patient	N	237 (100.0)	11321 (100.0)	7992 (100.0)	134 (100.0)	11780 (100.0)	9137 (100.0)	113 (100.0)	10618 (100.0)	8436 (100.0)
	Mean (SD)	1.1 (0.30)	1.3 (0.81)	1.3 (1.02)	1.2 (0.74)	1.3 (0.74)	1.4 (1.07)	1.2 (0.79)	1.3 (0.81)	1.4 (1.08)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,3.0)	(1.0,19.0)	(1.0,20.0)	(1.0,7.0)	(1.0,16.0)	(1.0,24.0)	(1.0,9.0)	(1.0,21.0)	(1.0,19.0)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Treatment indication for TCC prescription at index date (ICD10)	Missing	44	2128	1604	13	1864	1597	18	2045	1822
	Other deforming dorsopathies including - M43	20 (9.4%)	508 (4.2%)	165 (1.8%)	20 (13.4%)	522 (4.0%)	212 (1.9%)	17 (15.2%)	460 (4.0%)	191 (1.9%)
	Spondylolysis - M43.0	-	-	-	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	1 (0.0%)	3 (0.0%)	-	2 (0.0%)	2 (0.0%)	-	3 (0.0%)	-
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-	-	3 (0.0%)	4 (0.0%)
	Torticollis - M43.6	20 (9.4%)	506 (4.2%)	161 (1.8%)	20 (13.4%)	519 (4.0%)	210 (1.9%)	17 (15.2%)	447 (3.9%)	184 (1.9%)
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	-	-	6 (0.1%)	2 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	-	1 (0.0%)	1 (0.0%)	-	1 (0.0%)	-	-	1 (0.0%)	1 (0.0%)
	Dorsalgia - M54	86 (40.6%)	6172 (50.8%)	3968 (43.5%)	52 (34.9%)	6889 (53.3%)	4885 (44.2%)	41 (36.6%)	5986 (52.3%)	4450 (44.8%)
	Radiculopathy - M54.1	2 (0.9%)	37 (0.3%)	49 (0.5%)	-	47 (0.4%)	71 (0.6%)	-	42 (0.4%)	60 (0.6%)
	Cervicalgia - M54.2	15 (7.1%)	1510 (12.4%)	752 (8.2%)	9 (6.0%)	1667 (12.9%)	918 (8.3%)	10 (8.9%)	1485 (13.0%)	819 (8.2%)
	Sciatica - M54.3	2 (0.9%)	305 (2.5%)	314 (3.4%)	-	297 (2.3%)	378 (3.4%)	-	255 (2.2%)	331 (3.3%)
	Lumbago with sciatica - M.54.4	1 (0.5%)	505 (4.2%)	422 (4.6%)	-	572 (4.4%)	484 (4.4%)	-	497 (4.3%)	447 (4.5%)
	Low back pain - M54.5	31 (14.6%)	2604 (21.4%)	1856 (20.3%)	25 (16.8%)	3040 (23.5%)	2344 (21.2%)	15 (13.4%)	2659 (23.2%)	2195 (22.1%)
	Pain in thoracic spine - M54.6	-	4 (0.0%)	3 (0.0%)	-	13 (0.1%)	8 (0.1%)	-	11 (0.1%)	8 (0.1%)
	Other dorsalgia - M54.8	10 (4.7%)	287 (2.4%)	111 (1.2%)	3 (2.0%)	282 (2.2%)	163 (1.5%)	4 (3.6%)	244 (2.1%)	133 (1.3%)
	Dorsalgia, unspecified - M54.9	25 (11.8%)	920 (7.6%)	461 (5.1%)	15 (10.1%)	971 (7.5%)	519 (4.7%)	12 (10.7%)	793 (6.9%)	457 (4.6%)
	Other than painful muscle contractures associated with acute spinal pathology	106 (50.0%)	5461 (45.0%)	4991 (54.7%)	77 (51.7%)	5507 (42.6%)	5950 (53.9%)	54 (48.2%)	5000 (43.7%)	5291 (53.3%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Age at prescription (years)	<16 years	256 (100.0%)	-	-	162 (100.0%)	-	-	130 (100.0%)	-	-
	[16;30[	-	3433 (24.1%)	-	-	3416 (23.1%)	-	-	3073 (22.8%)	-
	[30;40[	-	4555 (31.9%)	-	-	4817 (32.6%)	-	-	4516 (33.5%)	-
	[40;50[	-	6281 (44.0%)	-	-	6549 (44.3%)	-	-	5902 (43.7%)	-
	[50;60[	-	-	5431 (50.6%)	-	-	6142 (48.6%)	-	-	5775 (49.1%)
	[60;70[	-	-	3112 (29.0%)	-	-	3923 (31.0%)	-	-	3578 (30.4%)
	≥70 years	-	-	2185 (20.4%)	-	-	2579 (20.4%)	-	-	2401 (20.4%)
Age at prescription (years)	N	256 (100.0)	14269 (100.0)	10728 (100.0)	162 (100.0)	14782 (100.0)	12644 (100.0)	130 (100.0)	13491 (100.0)	11754 (100.0)
	Mean (SD)	13.9 (1.80)	36.3 (8.92)	61.7 (9.42)	14.0 (1.62)	36.6 (8.79)	61.9 (9.29)	13.9 (1.64)	36.6 (8.81)	61.9 (9.29)
	Median (Q1 - Q3)	14.0 (13.0-15.0)	38.0 (30.0-44.0)	59.0 (54.0-67.0)	15.0 (13.0-15.0)	38.0 (30.0-44.0)	60.0 (54.0-68.0)	14.0 (13.0-15.0)	38.0 (30.0-44.0)	60.0 (54.0-68.0)
	Range	(2.0,15.0)	(16.0,49.0)	(50.0,98.0)	(2.0,15.0)	(16.0,49.0)	(50.0,100.0)	(3.0,15.0)	(16.0,49.0)	(50.0,98.0)
Pregnancy	Yes	-	77 (0.5%)	3 (0.0%)	-	70 (0.5%)	7 (0.1%)	-	48 (0.4%)	8 (0.1%)
	No	256 (100.0%)	14192 (99.5%)	10725 (100.0%)	162 (100.0%)	14712 (99.5%)	12637 (99.9%)	130 (100.0%)	13443 (99.6%)	11746 (99.9%)
Contraception	Yes	15 (5.9%)	1979 (13.9%)	100 (0.9%)	6 (3.7%)	1575 (10.7%)	125 (1.0%)	4 (3.1%)	1527 (11.3%)	102 (0.9%)
	No	241 (94.1%)	12290 (86.1%)	10628 (99.1%)	156 (96.3%)	13207 (89.3%)	12519 (99.0%)	126 (96.9%)	11964 (88.7%)	11652 (99.1%)
Lactation	Yes	-	6 (0.0%)	-	-	5 (0.0%)	-	-	1 (0.0%)	-
	No	256 (100.0%)	14263 (100.0%)	10728 (100.0%)	162 (100.0%)	14777 (100.0%)	12644 (100.0%)	130 (100.0%)	13490 (100.0%)	11754 (100.0%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Route of systemic TCC prescription	Intramuscular	4 (1.6%)	377 (2.6%)	579 (5.4%)	1 (0.6%)	258 (1.7%)	580 (4.6%)	1 (0.8%)	214 (1.6%)	464 (3.9%)
	Oral	252 (98.4%)	13892 (97.4%)	10149 (94.6%)	161 (99.4%)	14524 (98.3%)	12064 (95.4%)	129 (99.2%)	13277 (98.4%)	11290 (96.1%)
Oral form	TCC daily dose › Oral									
	N	237 (94.0)	13136 (94.6)	9573 (94.3)	155 (96.3)	13711 (94.4)	11203 (92.9)	122 (94.6)	12522 (94.3)	10496 (93.0)
	Missing (N)	15 (6.0)	756 (5.4)	576 (5.7)	6 (3.7)	813 (5.6)	861 (7.1)	7 (5.4)	755 (5.7)	794 (7.0)
	Mean (SD)	10.6 (3.44)	11.6 (3.68)	11.1 (3.64)	10.5 (3.67)	11.6 (3.71)	11.3 (3.74)	11.0 (3.60)	11.7 (3.74)	11.4 (3.73)
	Median (Q1 - Q3)	9.6 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-12.0)	12.0 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,48.0)	(2.0,48.0)	(4.0,24.0)	(4.0,48.0)	(4.0,48.0)	(2.0,16.0)	(4.0,28.0)	(4.0,24.0)
	Missing (N)	15	756	576	6	813	861	7	755	794
	≤16 mg	236 (99.6%)	13084 (99.6%)	9552 (99.8%)	154 (99.4%)	13681 (99.8%)	11188 (99.9%)	122 (100.0%)	12498 (99.8%)	10474 (99.8%)
	>16 mg	1 (0.4%)	52 (0.4%)	21 (0.2%)	1 (0.6%)	30 (0.2%)	15 (0.1%)	-	24 (0.2%)	22 (0.2%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Duration of TCC treatment (days)› Oral form	N	240 (95.2)	13330 (96.0)	9724 (95.8)	156 (96.9)	14035 (96.6)	11490 (95.2)	122 (94.6)	12766 (96.2)	10690 (94.7)
	Missing (N)	12 (4.8)	562 (4.0)	425 (4.2)	5 (3.1)	489 (3.4)	574 (4.8)	7 (5.4)	511 (3.8)	600 (5.3)
	Mean (SD)	8.7 (7.13)	9.9 (9.75)	13.0 (16.18)	7.7 (5.81)	7.9 (7.73)	10.2 (12.95)	7.8 (5.25)	8.1 (8.32)	10.2 (12.92)
	Median (Q1 - Q3)	7.0 (6.0-8.0)	8.0 (6.0-10.0)	8.0 (6.0-14.0)	6.0 (5.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-9.0)	7.0 (5.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-10.0)
	Range	(2.0,84.0)	(1.0,252.0)	(2.0,364.0)	(2.0,36.0)	(1.0,336.0)	(1.0,252.0)	(2.0,30.0)	(1.0,196.0)	(1.0,196.0)
	Missing (N)	12	562	425	5	489	574	7	511	600
	≤7 days	132 (55.0%)	6440 (48.3%)	3946 (40.6%)	111 (71.2%)	9603 (68.4%)	6894 (60.0%)	76 (62.3%)	8607 (67.4%)	6460 (60.4%)
	>7 days	108 (45.0%)	6890 (51.7%)	5778 (59.4%)	45 (28.8%)	4432 (31.6%)	4596 (40.0%)	46 (37.7%)	4159 (32.6%)	4230 (39.6%)
Intramuscular TCC daily dose › IM form	N	4 (100.0)	245 (65.0)	307 (53.0)	()	133 (51.6)	250 (43.1)	()	131 (61.2)	197 (42.5)
	Missing (N)	0	132 (35.0)	272 (47.0)	1 ()	125 (48.4)	330 (56.9)	1 ()	83 (38.8)	267 (57.5)
	Mean (SD)	9.0 (2.00)	10.4 (4.33)	8.4 (4.28)	()	8.3 (4.24)	9.3 (5.52)	()	8.4 (4.18)	8.7 (5.66)
	Median (Q1 - Q3)	8.0 (8.0-10.0)	8.0 (8.0-16.0)	8.0 (4.0-12.0)	(-)	8.0 (4.0-8.0)	8.0 (8.0-8.0)	(-)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
	Range	(8.0,12.0)	(4.0,24.0)	(4.0,24.0)	(,)	(4.0,28.0)	(4.0,28.0)	(,)	(4.0,28.0)	(4.0,28.0)
	Missing (N)	-	132	272	1	125	330	1	83	267
	≤8 mg	3 (75.0%)	124 (50.6%)	226 (73.6%)	-	111 (83.5%)	189 (75.6%)	-	109 (83.2%)	159 (80.7%)
	>8 mg	1 (25.0%)	121 (49.4%)	81 (26.4%)	-	22 (16.5%)	61 (24.4%)	-	22 (16.8%)	38 (19.3%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Duration of TCC treatment (days)› IM form	N	4 (100.0)	217 (57.6)	299 (51.6)	()	130 (50.4)	303 (52.2)	()	134 (62.6)	235 (50.6)
	Missing (N)	0	160 (42.4)	280 (48.4)	1 ()	128 (49.6)	277 (47.8)	1 ()	80 (37.4)	229 (49.4)
	Mean (SD)	7.0 (2.45)	7.7 (5.73)	9.2 (15.48)	()	5.9 (4.98)	6.4 (9.77)	()	8.7 (15.49)	7.2 (5.83)
	Median (Q1 - Q3)	6.5 (5.0-9.0)	6.0 (5.0-8.0)	6.0 (5.0-10.0)	(-)	5.0 (5.0-6.0)	6.0 (5.0-6.0)	(-)	6.0 (5.0-6.0)	6.0 (5.0-7.0)
	Range	(5.0,10.0)	(2.0,56.0)	(2.0,231.0)	(,)	(2.0,49.0)	(2.0,168.0)	(,)	(2.0,168.0)	(2.0,28.0)
	Missing (N)	-	160	280	1	128	277	1	80	229
	≤5 days	2 (50.0%)	68 (31.3%)	99 (33.1%)	-	71 (54.6%)	145 (47.9%)	-	63 (47.0%)	90 (38.3%)
	>5 days	2 (50.0%)	149 (68.7%)	200 (66.9%)	-	59 (45.4%)	158 (52.1%)	-	71 (53.0%)	145 (61.7%)
Long term treatment[4]	Missing (N)	1	143	155	2	134	279	1	143	275
	Yes	1 (0.4%)	621 (4.4%)	738 (7.0%)	3 (1.9%)	417 (2.8%)	605 (4.9%)	-	397 (3.0%)	551 (4.8%)
	No	254 (99.6%)	13505 (95.6%)	9835 (93.0%)	157 (98.1%)	14231 (97.2%)	11760 (95.1%)	129 (100.0%)	12951 (97.0%)	10928 (95.2%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	233 (91.0%)	13326 (93.4%)	9995 (93.2%)	147 (90.7%)	13654 (92.4%)	11680 (92.4%)	113 (86.9%)	12468 (92.4%)	10890 (92.6%)
	No	23 (9.0%)	943 (6.6%)	733 (6.8%)	15 (9.3%)	1128 (7.6%)	964 (7.6%)	17 (13.1%)	1023 (7.6%)	864 (7.4%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
Medication										
	Analgesics (N02)	146 (57.0%)	9952 (69.7%)	7707 (71.8%)	92 (56.8%)	10141 (68.6%)	8865 (70.1%)	78 (60.0%)	9141 (67.8%)	8171 (69.5%)
	Acetylsalicylic	2 (0.8%)	70 (0.5%)	64 (0.6%)	2 (1.2%)	101 (0.7%)	138 (1.1%)	-	68 (0.5%)	148 (1.3%)
	Paracetamol	144 (56.3%)	9700 (68.0%)	7399 (69.0%)	90 (55.6%)	9800 (66.3%)	8466 (67.0%)	78 (60.0%)	8808 (65.3%)	7813 (66.5%)
	Opioids (N02A)	14 (5.5%)	3199 (22.4%)	2650 (24.7%)	8 (4.9%)	3221 (21.8%)	3101 (24.5%)	11 (8.5%)	2940 (21.8%)	2862 (24.3%)
	Antidepressants (N06A)	-	1211 (8.5%)	1588 (14.8%)	1 (0.6%)	1003 (6.8%)	1791 (14.2%)	-	951 (7.0%)	1629 (13.9%)
	Antiepileptics (N03A)	-	417 (2.9%)	508 (4.7%)	-	300 (2.0%)	588 (4.7%)	-	298 (2.2%)	521 (4.4%)
	Muscle relaxants (M03)	6 (2.3%)	1074 (7.5%)	712 (6.6%)	-	404 (2.7%)	380 (3.0%)	3 (2.3%)	415 (3.1%)	375 (3.2%)
	NSAIDs/Cox-2 inhibitors (M01A)	164 (64.1%)	9246 (64.8%)	6206 (57.8%)	109 (67.3%)	9556 (64.6%)	7195 (56.9%)	79 (60.8%)	8715 (64.6%)	6488 (55.2%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	4 (1.6%)	751 (5.3%)	751 (7.0%)	7 (4.3%)	1054 (7.1%)	1015 (8.0%)	5 (3.8%)	1059 (7.8%)	953 (8.1%)
	Topical products for joint and muscular pain (M02A)	74 (28.9%)	3142 (22.0%)	2249 (21.0%)	45 (27.8%)	3405 (23.0%)	2938 (23.2%)	37 (28.5%)	3339 (24.7%)	2949 (25.1%)
	Phytotherapy (V03A)	1 (0.4%)	-	8 (0.1%)	-	-	13 (0.1%)	-	-	8 (0.1%)
Health services/medical devices and others:										
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	11 (4.3%)	273 (1.9%)	164 (1.5%)	3 (1.9%)	199 (1.3%)	102 (0.8%)	2 (1.5%)	180 (1.3%)	106 (0.9%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-

Baseline period[1]: year 2013

Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016

Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=162)	Female 16-49 years (N=14782)	Female ≥50 years (N=12644)	Female <16 years (N=130)	Female 16-49 years (N=13491)	Female ≥50 years (N=11754)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	58	2939	2379	20	2684	2641	24	2764	2730
	Yes	198 (100.0%)	8507 (75.1%)	6780 (81.2%)	142 (100.0%)	7575 (62.6%)	7160 (71.6%)	106 (100.0%)	6848 (63.8%)	6380 (70.7%)
	No	-	2823 (24.9%)	1569 (18.8%)	-	4523 (37.4%)	2843 (28.4%)	-	3879 (36.2%)	2644 (29.3%)

Baseline period[1]: year 2013
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Table 15.3-38: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period years 1 and 2 – Rheumatologists France – included patients

DUS TCC

		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	**Female 16-49 years (N=262)**	**Female ≥50 years (N=837)**	**Female <16 years (N=0)**	**Female 16-49 years (N=186)**	**Female ≥50 years (N=812)**	**Female <16 years (N=0)**	**Female 16-49 years (N=174)**	**Female ≥50 years (N=813)**
Total systemic TCC prescriptions		-	262 (100.0%)	837 (100.0%)	-	186 (100.0%)	812 (100.0%)	-	174 (100.0%)	813 (100.0%)
Number of patients with a systemic TCC prescription		-	202	694	-	159 (100.0%)	679 (100.0%)	-	149 (100.0%)	687 (100.0%)
Number of systemic TCC prescriptions per patient	N		202 (100.0)	694 (100.0)		159 (100.0)	679 (100.0)		149 (100.0)	687 (100.0)
	Mean (SD)		1.3 (0.67)	1.2 (0.59)		1.2 (0.49)	1.2 (0.56)		1.2 (0.43)	1.2 (0.52)
	Median (Q1 - Q3)		1.0 (1.0-1.0)	1.0 (1.0-1.0)		1.0 (1.0-1.0)	1.0 (1.0-1.0)		1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range		(1.0,5.0)	(1.0,9.0)		(1.0,4.0)	(1.0,6.0)		(1.0,3.0)	(1.0,5.0)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Treatment indication for TCC prescription at index date (ICD10)										
	Missing	-	-	-	-	-	-	-	-	-
	Other deforming dorsopathies including - M43	-	3 (1.1%)	5 (0.6%)	-	6 (3.2%)	7 (0.9%)	-	8 (4.6%)	9 (1.1%)
	Spondylolysis - M43.0	-	-	-	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	-	-	-	-	1 (0.1%)	-	-	4 (0.5%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-	-	-	-
	Torticollis - M43.6	-	-	2 (0.2%)	-	2 (1.1%)	2 (0.2%)	-	1 (0.6%)	-
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	-	-	-	-
	Deforming dorsopathy, unspecified - M43.9	-	3 (1.1%)	3 (0.4%)	-	4 (2.2%)	4 (0.5%)	-	7 (4.0%)	5 (0.6%)
	Dorsalgia - M54	-	194 (74.0%)	577 (68.9%)	-	129 (69.4%)	534 (65.8%)	-	124 (71.3%)	541 (66.5%)
	Radiculopathy - M54.1	-	-	12 (1.4%)	-	-	13 (1.6%)	-	-	14 (1.7%)
	Cervicalgia - M54.2	-	76 (29.0%)	168 (20.1%)	-	35 (18.8%)	152 (18.7%)	-	48 (27.6%)	143 (17.6%)
	Sciatica - M54.3	-	5 (1.9%)	17 (2.0%)	-	3 (1.6%)	4 (0.5%)	-	2 (1.1%)	9 (1.1%)
	Lumbago with sciatica - M.54.4	-	25 (9.5%)	90 (10.8%)	-	22 (11.8%)	83 (10.2%)	-	19 (10.9%)	76 (9.3%)
	Low back pain - M54.5	-	70 (26.7%)	225 (26.9%)	-	37 (19.9%)	178 (21.9%)	-	36 (20.7%)	212 (26.1%)
	Pain in thoracic spine - M54.6	-	-	-	-	-	-	-	-	1 (0.1%)
	Other dorsalgia - M54.8	-	-	1 (0.1%)	-	1 (0.5%)	1 (0.1%)	-	-	5 (0.6%)
	Dorsalgia, unspecified - M54.9	-	18 (6.9%)	64 (7.6%)	-	31 (16.7%)	103 (12.7%)	-	19 (10.9%)	81 (10.0%)
	Other than painful muscle contractures associated with acute spinal pathology	-	65 (24.8%)	255 (30.5%)	-	51 (27.4%)	271 (33.4%)	-	42 (24.1%)	263 (32.3%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Age at prescription (years)	<16 years	-	-	-	-	-	-	-	-	-
	[16;30[	-	15 (5.7%)	-	-	6 (3.2%)	-	-	8 (4.6%)	-
	[30;40[	-	59 (22.5%)	-	-	51 (27.4%)	-	-	54 (31.0%)	-
	[40;50[	-	188 (71.8%)	-	-	129 (69.4%)	-	-	112 (64.4%)	-
	[50;60[	-	-	263 (31.4%)	-	-	245 (30.2%)	-	-	241 (29.6%)
	[60;70[	-	-	266 (31.8%)	-	-	256 (31.5%)	-	-	231 (28.4%)
	≥70 years	-	-	308 (36.8%)	-	-	311 (38.3%)	-	-	341 (41.9%)
Age at prescription (years)	N		262 (100.0)	837 (100.0)		186 (100.0)	812 (100.0)		174 (100.0)	813 (100.0)
	Mean (SD)		41.9 (6.35)	66.1 (10.54)		42.4 (6.18)	66.8 (10.90)		41.5 (5.99)	67.4 (11.14)
	Median (Q1 - Q3)		43.5 (39.0-47.0)	65.0 (58.0-75.0)		44.0 (38.0-48.0)	66.0 (58.0-76.0)		43.0 (38.0-47.0)	67.0 (58.0-76.0)
	Range		(21.0,49.0)	(50.0,98.0)		(21.0,49.0)	(50.0,94.0)		(19.0,49.0)	(50.0,97.0)
Pregnancy	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	186 (100.0%)	812 (100.0%)	-	174 (100.0%)	813 (100.0%)
Contraception	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	186 (100.0%)	812 (100.0%)	-	174 (100.0%)	813 (100.0%)
Lactation	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	186 (100.0%)	812 (100.0%)	-	174 (100.0%)	813 (100.0%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Route of systemic TCC prescription	Intramuscular	-	50 (19.1%)	145 (17.3%)	-	33 (17.7%)	142 (17.5%)	-	37 (21.3%)	186 (22.9%)
	Oral	-	212 (80.9%)	692 (82.7%)	-	153 (82.3%)	670 (82.5%)	-	137 (78.7%)	627 (77.1%)
Oral TCC daily dose › Oral form	N		188 (88.7)	548 (79.2)		137 (89.5)	542 (80.9)		115 (83.9)	504 (80.4)
	Missing (N)		24 (11.3)	144 (20.8)		16 (10.5)	128 (19.1)		22 (16.1)	123 (19.6)
	Mean (SD)		11.0 (3.96)	10.6 (3.96)		11.1 (4.10)	11.0 (4.39)		11.5 (4.25)	11.0 (4.38)
	Median (Q1 - Q3)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range		(4.0,16.0)	(2.0,16.0)		(4.0,16.0)	(2.0,16.0)		(2.0,16.0)	(2.0,16.0)
	Missing (N)	-	24	144	-	16	128	-	22	123
	≤16 mg	-	188 (100.0%)	548 (100.0%)	-	137 (100.0%)	542 (100.0%)	-	115 (100.0%)	504 (100.0%)
	>16 mg	-	-	-	-	-	-	-	-	-

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Duration of TCC treatment (days)› Oral form	N		188 (88.7)	544 (78.6)		137 (89.5)	542 (80.9)		115 (83.9)	504 (80.4)
	Missing (N)		24 (11.3)	148 (21.4)		16 (10.5)	128 (19.1)		22 (16.1)	123 (19.6)
	Mean (SD)		26.4 (38.34)	31.6 (47.74)		22.9 (47.62)	21.3 (37.58)		16.7 (31.93)	21.3 (36.32)
	Median (Q1 - Q3)		10.0 (6.0-30.0)	12.0 (6.0-30.0)		6.0 (4.0-12.0)	10.0 (5.0-18.0)		8.0 (4.0-12.0)	10.0 (5.0-15.0)
	Range		(2.0,180.0)	(2.0,360.0)		(3.0,360.0)	(3.0,360.0)		(3.0,195.0)	(1.0,360.0)
	Missing (N)	-	24	148	-	16	128	-	22	123
	≤7 days	-	89 (47.3%)	201 (36.9%)	-	84 (61.3%)	246 (45.4%)	-	57 (49.6%)	220 (43.7%)
	>7 days	-	99 (52.7%)	343 (63.1%)	-	53 (38.7%)	296 (54.6%)	-	58 (50.4%)	284 (56.3%)
Intramuscular TCC daily dose › IM form	N		49 (98.0)	144 (99.3)		33 (100.0)	142 (100.0)		37 (100.0)	186 (100.0)
	Missing (N)		1 (2.0)	1 (0.7)		0	0		0	0
	Mean (SD)		9.8 (3.31)	10.1 (3.62)		9.8 (4.41)	9.9 (3.83)		11.1 (3.96)	9.4 (3.50)
	Median (Q1 - Q3)		8.0 (8.0-12.0)	8.0 (8.0-12.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-8.0)
	Range		(4.0,16.0)	(4.0,16.0)		(4.0,16.0)	(4.0,16.0)		(6.0,16.0)	(4.0,16.0)
	Missing (N)	-	1	1	-	-	-	-	-	-
	≤8 mg	-	35 (71.4%)	92 (63.9%)	-	23 (69.7%)	100 (70.4%)	-	22 (59.5%)	143 (76.9%)
	>8 mg	-	14 (28.6%)	52 (36.1%)	-	10 (30.3%)	42 (29.6%)	-	15 (40.5%)	43 (23.1%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Duration of TCC treatment (days)› IM form	N		49 (98.0)	143 (98.6)		33 (100.0)	142 (100.0)		37 (100.0)	186 (100.0)
	Missing (N)		1 (2.0)	2 (1.4)		0	0		0	0
	Mean (SD)		23.9 (46.37)	19.1 (44.10)		7.7 (5.28)	16.7 (46.50)		9.4 (6.82)	15.2 (37.97)
	Median (Q1 - Q3)		10.0 (5.0-12.0)	12.0 (5.0-12.0)		6.0 (4.0-10.0)	6.0 (5.0-10.0)		7.0 (4.0-12.0)	6.0 (5.0-10.0)
	Range		(1.0,180.0)	(1.0,360.0)		(4.0,30.0)	(2.0,360.0)		(2.0,30.0)	(2.0,360.0)
	Missing (N)	-	1	2	-	-	-	-	-	-
	≤5 days	-	16 (32.7%)	36 (25.2%)	-	15 (45.5%)	45 (31.7%)	-	16 (43.2%)	74 (39.8%)
	>5 days	-	33 (67.3%)	107 (74.8%)	-	18 (54.5%)	97 (68.3%)	-	21 (56.8%)	112 (60.2%)
Long term treatment[4]	Missing (N)	-	1	12	-	2	14	-	5	14
	Yes	-	27 (10.3%)	58 (7.0%)	-	7 (3.8%)	41 (5.1%)	-	3 (1.8%)	29 (3.6%)
	No	-	234 (89.7%)	767 (93.0%)	-	177 (96.2%)	757 (94.9%)	-	166 (98.2%)	770 (96.4%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	-	238 (90.8%)	737 (88.1%)	-	165 (88.7%)	707 (87.1%)	-	154 (88.5%)	685 (84.3%)
	No	-	24 (9.2%)	100 (11.9%)	-	21 (11.3%)	105 (12.9%)	-	20 (11.5%)	128 (15.7%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
medication										
	Analgesics (N02)	-	121 (46.2%)	439 (52.4%)	-	87 (46.8%)	383 (47.2%)	-	70 (40.2%)	352 (43.3%)
	Acetylsalicylic	-	4 (1.5%)	27 (3.2%)	-	1 (0.5%)	-	-	1 (0.6%)	-
	Paracetamol	-	110 (42.0%)	364 (43.5%)	-	78 (41.9%)	319 (39.3%)	-	64 (36.8%)	296 (36.4%)
	Opioids (N02A)	-	51 (19.5%)	165 (19.7%)	-	33 (17.7%)	151 (18.6%)	-	34 (19.5%)	141 (17.3%)
	Antidepressants (N06A)	-	6 (2.3%)	29 (3.5%)	-	10 (5.4%)	36 (4.4%)	-	9 (5.2%)	31 (3.8%)
	Antiepileptics (N03A)	-	4 (1.5%)	29 (3.5%)	-	12 (6.5%)	24 (3.0%)	-	10 (5.7%)	24 (3.0%)
	Muscle relaxants (M03)	-	18 (6.9%)	22 (2.6%)	-	4 (2.2%)	8 (1.0%)	-	2 (1.1%)	8 (1.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	-	150 (57.3%)	378 (45.2%)	-	94 (50.5%)	404 (49.8%)	-	93 (53.4%)	391 (48.1%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	72 (27.5%)	244 (29.2%)	-	50 (26.9%)	249 (30.7%)	-	44 (25.3%)	219 (26.9%)
	Topical products for joint and muscular pain (M02A)	-	19 (7.3%)	91 (10.9%)	-	14 (7.5%)	81 (10.0%)	-	3 (1.7%)	80 (9.8%)
	Phytotherapy (V03A)	-	-	6 (0.7%)	-	1 (0.5%)	2 (0.2%)	-	1 (0.6%)	-
Health services/medical devices and others:										
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	1 (0.4%)	-	-	2 (1.1%)	-	-	1 (0.6%)	2 (0.2%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=186)	Female ≥50 years (N=812)	Female <16 years (N=0)	Female 16-49 years (N=174)	Female ≥50 years (N=813)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	-	25	150	-	16	128	-	22	123
	Yes	-	175 (73.8%)	542 (78.9%)	-	107 (62.9%)	538 (78.7%)	-	109 (71.7%)	542 (78.6%)
	No	-	62 (26.2%)	145 (21.1%)	-	63 (37.1%)	146 (21.3%)	-	43 (28.3%)	148 (21.4%)

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Table 15.3-39: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period years 1 and 2 – GPs Italy – included patients

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Total systemic TCC prescriptions		17 (100.0%)	4290 (100.0%)	8577 (100.0%)	7 (100.0%)	2900 (100.0%)	7050 (100.0%)	4 (100.0%)	2904 (100.0%)	7202 (100.0%)
Number of patients with a systemic TCC prescription		15	3782	7105	6 (100.0%)	2617 (100.0%)	6040 (100.0%)	4 (100.0%)	2616 (100.0%)	6151 (100.0%)
Number of systemic TCC prescriptions per patient	N	15 (100.0)	3782 (100.0)	7105 (100.0)	6 (100.0)	2617 (100.0)	6040 (100.0)	4 (100.0)	2616 (100.0)	6151 (100.0)
	Mean (SD)	1.1 (0.35)	1.1 (0.41)	1.2 (0.58)	1.2 (0.41)	1.1 (0.36)	1.2 (0.48)	1.0 (0.00)	1.1 (0.40)	1.2 (0.52)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,2.0)	(1.0,7.0)	(1.0,12.0)	(1.0,2.0)	(1.0,5.0)	(1.0,9.0)	(1.0,1.0)	(1.0,6.0)	(1.0,18.0)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	394	791	-	233	638	-	261	630
	Other deforming dorsopathies including - M43	2 (11.8%)	212 (5.4%)	418 (5.4%)	2 (28.6%)	144 (5.4%)	311 (4.9%)	1 (25.0%)	133 (5.0%)	325 (4.9%)
	Spondylolysis - M43.0	-	39 (1.0%)	243 (3.1%)	-	27 (1.0%)	170 (2.7%)	-	21 (0.8%)	170 (2.6%)
	Spondylolisthesis - M43.1	-	2 (0.1%)	7 (0.1%)	-	2 (0.1%)	11 (0.2%)	-	1 (0.0%)	8 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-	-	-	-
	Torticollis - M43.6	2 (11.8%)	129 (3.3%)	102 (1.3%)	-	78 (2.9%)	62 (1.0%)	-	61 (2.3%)	87 (1.3%)
	Other specified deforming dorsopathies - M43.8	-	12 (0.3%)	43 (0.6%)	-	19 (0.7%)	50 (0.8%)	-	17 (0.6%)	38 (0.6%)
	Deforming dorsopathy, unspecified - M43.9	-	30 (0.8%)	23 (0.3%)	2 (28.6%)	18 (0.7%)	18 (0.3%)	1 (25.0%)	33 (1.2%)	22 (0.3%)
	Dorsalgia - M54	5 (29.4%)	2846 (73.0%)	4996 (64.2%)	1 (14.3%)	1932 (72.4%)	4271 (66.6%)	1 (25.0%)	1951 (73.8%)	4387 (66.8%)
	Radiculopathy - M54.1	-	14 (0.4%)	104 (1.3%)	-	11 (0.4%)	71 (1.1%)	-	15 (0.6%)	74 (1.1%)
	Cervicalgia - M54.2	1 (5.9%)	718 (18.4%)	762 (9.8%)	-	476 (17.8%)	626 (9.8%)	1 (25.0%)	404 (15.3%)	607 (9.2%)
	Sciatica - M54.3	-	82 (2.1%)	259 (3.3%)	-	64 (2.4%)	219 (3.4%)	-	50 (1.9%)	234 (3.6%)
	Lumbago with sciatica - M.54.4	-	-	-	-	-	-	-	-	-
	Low back pain - M54.5	2 (11.8%)	1890 (48.5%)	3681 (47.3%)	-	1294 (48.5%)	3187 (49.7%)	-	1388 (52.5%)	3300 (50.2%)
	Pain in thoracic spine - M54.6	-	57 (1.5%)	91 (1.2%)	-	30 (1.1%)	81 (1.3%)	-	38 (1.4%)	90 (1.4%)
	Other dorsalgia - M54.8	-	-	-	-	-	-	-	-	-
	Dorsalgia, unspecified - M54.9	2 (11.8%)	85 (2.2%)	99 (1.3%)	1 (14.3%)	57 (2.1%)	87 (1.4%)	-	56 (2.1%)	82 (1.2%)
	Other than painful muscle contractures associated with acute spinal pathology	10 (58.8%)	838 (21.5%)	2372 (30.5%)	4 (57.1%)	591 (22.2%)	1830 (28.5%)	2 (50.0%)	559 (21.2%)	1860 (28.3%)

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Age at prescription (years)	<16 years	17 (100.0%)	-	-	7 (100.0%)	-	-	4 (100.0%)	-	-
	[16;30[	-	535 (12.5%)	-	-	367 (12.7%)	-	-	377 (13.0%)	-
	[30;40[	-	1188 (27.7%)	-	-	784 (27.0%)	-	-	737 (25.4%)	-
	[40;50[	-	2567 (59.8%)	-	-	1749 (60.3%)	-	-	1790 (61.6%)	-
	[50;60[	-	-	2781 (32.4%)	-	-	2311 (32.8%)	-	-	2268 (31.5%)
	[60;70[	-	-	2531 (29.5%)	-	-	2127 (30.2%)	-	-	2188 (30.4%)
	≥70 years	-	-	3265 (38.1%)	-	-	2612 (37.0%)	-	-	2746 (38.1%)
Age at prescription (years)	N	17 (100.0)	4290 (100.0)	8577 (100.0)	7 (100.0)	2900 (100.0)	7050 (100.0)	4 (100.0)	2904 (100.0)	7202 (100.0)
	Mean (SD)	14.1 (1.05)	39.6 (7.77)	66.2 (10.59)	14.1 (1.46)	39.7 (7.73)	66.0 (10.49)	14.0 (1.41)	39.9 (7.80)	66.4 (10.54)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	41.0 (35.0-46.0)	65.0 (57.0-74.0)	15.0 (14.0-15.0)	42.0 (35.0-46.0)	65.0 (57.0-74.0)	14.5 (13.0-15.0)	42.0 (35.0-46.0)	66.0 (57.0-74.0)
	Range	(12.0,15.0)	(16.0,49.0)	(50.0,99.0)	(11.0,15.0)	(16.0,49.0)	(50.0,101.0)	(12.0,15.0)	(16.0,49.0)	(50.0,103.0)
Pregnancy	Yes	-	169 (3.9%)	7 (0.1%)	-	136 (4.7%)	10 (0.1%)	-	110 (3.8%)	9 (0.1%)
	No	17 (100.0%)	4121 (96.1%)	8570 (99.9%)	7 (100.0%)	2764 (95.3%)	7040 (99.9%)	4 (100.0%)	2794 (96.2%)	7193 (99.9%)
Contraception	Yes	-	308 (7.2%)	43 (0.5%)	-	190 (6.6%)	27 (0.4%)	-	127 (4.4%)	25 (0.3%)
	No	17 (100.0%)	3982 (92.8%)	8534 (99.5%)	7 (100.0%)	2710 (93.4%)	7023 (99.6%)	4 (100.0%)	2777 (95.6%)	7177 (99.7%)
Lactation	Yes	-	4 (0.1%)	-	-	2 (0.1%)	-	-	1 (0.0%)	-
	No	17 (100.0%)	4286 (99.9%)	8577 (100.0%)	7 (100.0%)	2898 (99.9%)	7050 (100.0%)	4 (100.0%)	2903 (100.0%)	7202 (100.0%)

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Route of systemic TCC prescription	Intramuscular	1 (5.9%)	2644 (61.6%)	6516 (76.0%)	1 (14.3%)	1879 (64.8%)	5636 (79.9%)	1 (25.0%)	2038 (70.2%)	5841 (81.1%)
	Oral	16 (94.1%)	1646 (38.4%)	2061 (24.0%)	6 (85.7%)	1021 (35.2%)	1414 (20.1%)	3 (75.0%)	866 (29.8%)	1361 (18.9%)
Oral TCC daily dose › Oral form	N	8 (50.0)	670 (40.7)	793 (38.5)	2 (33.3)	333 (32.6)	501 (35.4)	2 (66.7)	310 (35.8)	480 (35.3)
	Missing (N)	8 (50.0)	976 (59.3)	1268 (61.5)	4 (66.7)	688 (67.4)	913 (64.6)	1 (33.3)	556 (64.2)	881 (64.7)
	Mean (SD)	10.0 (3.02)	11.3 (4.44)	11.6 (4.48)	10.0 (2.83)	10.7 (4.42)	10.1 (4.15)	6.0 (2.83)	11.6 (5.10)	10.9 (4.77)
	Median (Q1 - Q3)	8.0 (8.0-12.0)	11.0 (8.0-16.0)	12.0 (8.0-16.0)	10.0 (8.0-12.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)	6.0 (4.0-8.0)	11.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(8.0,16.0)	(4.0,24.0)	(4.0,24.0)	(8.0,12.0)	(4.0,24.0)	(4.0,24.0)	(4.0,8.0)	(4.0,32.0)	(4.0,24.0)
	Missing (N)	8	976	1268	4	688	913	1	556	881
	≤16 mg	8 (100.0%)	661 (98.7%)	780 (98.4%)	2 (100.0%)	330 (99.1%)	499 (99.6%)	2 (100.0%)	299 (96.5%)	473 (98.5%)
	>16 mg	-	9 (1.3%)	13 (1.6%)	-	3 (0.9%)	2 (0.4%)	-	11 (3.5%)	7 (1.5%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Duration of TCC treatment (days)› Oral form	N	8 (50.0)	669 (40.6)	793 (38.5)	2 (33.3)	333 (32.6)	500 (35.4)	2 (66.7)	310 (35.8)	480 (35.3)
	Missing (N)	8 (50.0)	977 (59.4)	1268 (61.5)	4 (66.7)	688 (67.4)	914 (64.6)	1 (33.3)	556 (64.2)	881 (64.7)
	Mean (SD)	8.4 (2.26)	8.6 (4.79)	8.3 (4.39)	8.0 (2.83)	9.1 (4.56)	9.5 (4.59)	17.0 (4.24)	10.4 (5.53)	11.0 (5.68)
	Median (Q1 - Q3)	10.0 (6.0-10.0)	10.0 (5.0-10.0)	6.0 (5.0-10.0)	8.0 (6.0-10.0)	10.0 (5.0-10.0)	10.0 (5.0-10.0)	17.0 (14.0-20.0)	10.0 (7.0-14.0)	10.0 (7.0-14.0)
	Range	(5.0,10.0)	(3.0,60.0)	(3.0,50.0)	(6.0,10.0)	(3.0,20.0)	(3.0,20.0)	(14.0,20.0)	(3.0,50.0)	(4.0,50.0)
	Missing (N)	8	977	1268	4	688	914	1	556	881
	≤7 days	3 (37.5%)	332 (49.6%)	405 (51.1%)	1 (50.0%)	142 (42.6%)	191 (38.2%)	-	149 (48.1%)	201 (41.9%)
	>7 days	5 (62.5%)	337 (50.4%)	388 (48.9%)	1 (50.0%)	191 (57.4%)	309 (61.8%)	2 (100.0%)	161 (51.9%)	279 (58.1%)
Intramuscular TCC daily dose › IM form	N	1 (100.0)	622 (23.5)	1685 (25.9)	()	403 (21.4)	1302 (23.1)	1 (100.0)	420 (20.6)	1327 (22.7)
	Missing (N)	0	2022 (76.5)	4831 (74.1)	1 ()	1476 (78.6)	4334 (76.9)	0	1618 (79.4)	4514 (77.3)
	Mean (SD)	4.0 ()	4.6 (1.53)	4.6 (1.48)	()	4.6 (1.44)	4.6 (1.48)	4.0 ()	4.7 (1.51)	4.6 (1.39)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	(-)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(4.0,4.0)	(4.0,16.0)	(4.0,12.0)	(,)	(4.0,8.0)	(2.0,12.0)	(4.0,4.0)	(4.0,12.0)	(4.0,12.0)
	Missing (N)	-	2022	4831	1	1476	4334	-	1618	4514
	≤8 mg	1 (100.0%)	619 (99.5%)	1684 (99.9%)	-	403 (100.0%)	1299 (99.8%)	1 (100.0%)	419 (99.8%)	1326 (99.9%)
	>8 mg	-	3 (0.5%)	1 (0.1%)	-	-	3 (0.2%)	-	1 (0.2%)	1 (0.1%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label

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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Duration of TCC treatment (days)› IM form	N	1 (100.0)	622 (23.5)	1683 (25.8)	()	403 (21.4)	1302 (23.1)	1 (100.0)	420 (20.6)	1326 (22.7)
	Missing (N)	0	2022 (76.5)	4833 (74.2)	1 ()	1476 (78.6)	4334 (76.9)	0	1618 (79.4)	4515 (77.3)
	Mean (SD)	6.0 ()	5.9 (1.59)	5.9 (1.66)	()	5.7 (1.18)	5.8 (1.45)	6.0 ()	5.9 (1.53)	5.9 (1.47)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	(-)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(6.0,6.0)	(1.0,12.0)	(2.0,24.0)	(,)	(3.0,12.0)	(2.0,12.0)	(6.0,6.0)	(2.0,12.0)	(3.0,12.0)
	Missing (N)	-	2022	4833	1	1476	4334	-	1618	4515
	≤5 days	-	76 (12.2%)	222 (13.2%)	-	50 (12.4%)	164 (12.6%)	-	55 (13.1%)	138 (10.4%)
	>5 days	1 (100.0%)	546 (87.8%)	1461 (86.8%)	-	353 (87.6%)	1138 (87.4%)	1 (100.0%)	365 (86.9%)	1188 (89.6%)
Long term treatment[4]	Missing (N)	1	310	989	-	192	724	-	192	772
	Yes	-	33 (0.8%)	85 (1.1%)	-	9 (0.3%)	49 (0.8%)	-	16 (0.6%)	49 (0.8%)
	No	16 (100.0%)	3947 (99.2%)	7503 (98.9%)	7 (100.0%)	2699 (99.7%)	6277 (99.2%)	4 (100.0%)	2696 (99.4%)	6381 (99.2%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	9 (52.9%)	3558 (82.9%)	7430 (86.6%)	2 (28.6%)	2420 (83.4%)	6212 (88.1%)	3 (75.0%)	2495 (85.9%)	6369 (88.4%)
	No	8 (47.1%)	732 (17.1%)	1147 (13.4%)	5 (71.4%)	480 (16.6%)	838 (11.9%)	1 (25.0%)	409 (14.1%)	833 (11.6%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
medication										
	Analgesics (N02)	-	547 (12.8%)	1158 (13.5%)	1 (14.3%)	310 (10.7%)	831 (11.8%)	1 (25.0%)	317 (10.9%)	878 (12.2%)
	Acetylsalicylic	-	-	2 (0.0%)	-	2 (0.1%)	4 (0.1%)	-	1 (0.0%)	6 (0.1%)
	Paracetamol	-	466 (10.9%)	946 (11.0%)	1 (14.3%)	254 (8.8%)	615 (8.7%)	1 (25.0%)	254 (8.7%)	634 (8.8%)
	Opioids (N02A)	-	276 (6.4%)	829 (9.7%)	-	169 (5.8%)	575 (8.2%)	-	144 (5.0%)	596 (8.3%)
	Antidepressants (N06A)	-	123 (2.9%)	535 (6.2%)	1 (14.3%)	100 (3.4%)	480 (6.8%)	-	97 (3.3%)	470 (6.5%)
	Antiepileptics (N03A)	-	69 (1.6%)	177 (2.1%)	-	34 (1.2%)	189 (2.7%)	-	37 (1.3%)	190 (2.6%)
	Muscle relaxants (M03)	-	37 (0.9%)	47 (0.5%)	-	33 (1.1%)	78 (1.1%)	-	34 (1.2%)	53 (0.7%)
	NSAIDs/Cox-2 inhibitors (M01A)	7 (41.2%)	3008 (70.1%)	6395 (74.6%)	1 (14.3%)	2121 (73.1%)	5457 (77.4%)	2 (50.0%)	2149 (74.0%)	5542 (77.0%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	412 (9.6%)	756 (8.8%)	-	272 (9.4%)	709 (10.1%)	-	333 (11.5%)	728 (10.1%)
	Topical products for joint and muscular pain (M02A)	3 (17.6%)	126 (2.9%)	160 (1.9%)	-	65 (2.2%)	87 (1.2%)	-	59 (2.0%)	89 (1.2%)
	Phytotherapy (V03A)	-	-	1 (0.0%)	-	1 (0.0%)	1 (0.0%)	-	2 (0.1%)	2 (0.0%)
Health services/medical devices and others:										
	Neck braces/Belts / lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-	-	-	-	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label
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		Baseline[1]			Study period year 1[1]			Study period year 2[2]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2900)	Female ≥50 years (N=7050)	Female <16 years (N=4)	Female 16-49 years (N=2904)	Female ≥50 years (N=7202)
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	8	3047	6173	5	2178	5289	1	2197	5431
	Yes	9 (100.0%)	1025 (82.5%)	2093 (87.1%)	2 (100.0%)	629 (87.1%)	1565 (88.9%)	3 (100.0%)	588 (83.2%)	1570 (88.7%)
	No	-	218 (17.5%)	311 (12.9%)	-	93 (12.9%)	196 (11.1%)	-	119 (16.8%)	201 (11.3%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label

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Table 15.3-40: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs France – included patients

		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Total systemic TCC prescriptions		256 (100.0%)	14269 (100.0%)	10728 (100.0%)	62 (100.0%)	8272 (100.0%)	8373 (100.0%)	354 (100.0%)	36548 (100.0%)	32772 (100.0%)
Number of patients with a systemic TCC prescription		237	11321	7992	58 (100.0%)	6691 (100.0%)	6149 (100.0%)	298 (100.0%)	25209 (100.0%)	20039 (100.0%)
Number of systemic TCC prescriptions per patient	N	237 (100.0)	11321 (100.0)	7992 (100.0)	58 (100.0)	6691 (100.0)	6149 (100.0)	298 (100.0)	25209 (100.0)	20039 (100.0)
	Mean (SD)	1.1 (0.30)	1.3 (0.81)	1.3 (1.02)	1.1 (0.32)	1.2 (0.74)	1.4 (1.02)	1.2 (1.08)	1.4 (1.25)	1.6 (1.90)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-2.0)
	Range	(1.0,3.0)	(1.0,19.0)	(1.0,20.0)	(1.0,3.0)	(1.0,16.0)	(1.0,16.0)	(1.0,17.0)	(1.0,34.0)	(1.0,48.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Treatment indication for TCC prescription at index date (ICD10)	Missing	44	2128	1604	14	1437	1469	45	5346	4888
	Other deforming dorsopathies including - M43	20 (9.4%)	508 (4.2%)	165 (1.8%)	5 (10.4%)	281 (4.1%)	131 (1.9%)	42 (13.6%)	1263 (4.0%)	534 (1.9%)
	Spondylolysis - M43.0	-	-	-	-	-	-	-	-	-
	Spondylolisthesis - M43.1	-	1 (0.0%)	3 (0.0%)	-	-	-	-	5 (0.0%)	2 (0.0%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	4 (0.1%)	6 (0.1%)	-	7 (0.0%)	10 (0.0%)
	Torticollis - M43.6	20 (9.4%)	506 (4.2%)	161 (1.8%)	5 (10.4%)	270 (4.0%)	124 (1.8%)	42 (13.6%)	1236 (4.0%)	518 (1.9%)
	Other specified deforming dorsopathies - M43.8	-	-	-	-	7 (0.1%)	-	-	13 (0.0%)	2 (0.0%)
	Deforming dorsopathy, unspecified - M43.9	-	1 (0.0%)	1 (0.0%)	-	-	1 (0.0%)	-	2 (0.0%)	2 (0.0%)
	Dorsalgia - M54	86 (40.6%)	6172 (50.8%)	3968 (43.5%)	24 (50.0%)	3471 (50.8%)	3051 (44.2%)	117 (37.9%)	16347 (52.4%)	12386 (44.4%)
	Radiculopathy - M54.1	2 (0.9%)	37 (0.3%)	49 (0.5%)	-	24 (0.4%)	43 (0.6%)	-	113 (0.4%)	174 (0.6%)
	Cervicalgia - M54.2	15 (7.1%)	1510 (12.4%)	752 (8.2%)	-	874 (12.8%)	541 (7.8%)	19 (6.1%)	4026 (12.9%)	2278 (8.2%)
	Sciatica - M54.3	2 (0.9%)	305 (2.5%)	314 (3.4%)	-	126 (1.8%)	194 (2.8%)	-	678 (2.2%)	903 (3.2%)
	Lumbago with sciatica - M.54.4	1 (0.5%)	505 (4.2%)	422 (4.6%)	-	292 (4.3%)	293 (4.2%)	-	1362 (4.4%)	1224 (4.4%)
	Low back pain - M54.5	31 (14.6%)	2604 (21.4%)	1856 (20.3%)	14 (29.2%)	1532 (22.4%)	1514 (21.9%)	54 (17.5%)	7231 (23.2%)	6053 (21.7%)
	Pain in thoracic spine - M54.6	-	4 (0.0%)	3 (0.0%)	-	16 (0.2%)	6 (0.1%)	-	40 (0.1%)	22 (0.1%)
	Other dorsalgia - M54.8	10 (4.7%)	287 (2.4%)	111 (1.2%)	4 (8.3%)	130 (1.9%)	95 (1.4%)	11 (3.6%)	656 (2.1%)	391 (1.4%)
	Dorsalgia, unspecified - M54.9	25 (11.8%)	920 (7.6%)	461 (5.1%)	6 (12.5%)	477 (7.0%)	365 (5.3%)	33 (10.7%)	2241 (7.2%)	1341 (4.8%)
	Other than painful muscle contractures associated with acute spinal pathology	106 (50.0%)	5461 (45.0%)	4991 (54.7%)	19 (39.6%)	3083 (45.1%)	3722 (53.9%)	150 (48.5%)	13592 (43.6%)	14964 (53.7%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Age at prescription (years)	<16 years	256 (100.0%)	-	-	62 (100.0%)	-	-	354 (100.0%)	-	-
	[16;30[	-	3433 (24.1%)	-	-	1840 (22.2%)	-	-	8329 (22.8%)	-
	[30;40[	-	4555 (31.9%)	-	-	2758 (33.3%)	-	-	12094 (33.1%)	-
	[40;50[	-	6281 (44.0%)	-	-	3674 (44.4%)	-	-	16125 (44.1%)	-
	[50;60[	-	-	5431 (50.6%)	-	-	3841 (45.9%)	-	-	15759 (48.1%)
	[60;70[	-	-	3112 (29.0%)	-	-	2568 (30.7%)	-	-	10069 (30.7%)
	≥70 years	-	-	2185 (20.4%)	-	-	1964 (23.5%)	-	-	6944 (21.2%)
Age at prescription (years)	N	256 (100.0)	14269 (100.0)	10728 (100.0)	62 (100.0)	8272 (100.0)	8373 (100.0)	354 (100.0)	36548 (100.0)	32772 (100.0)
	Mean (SD)	13.9 (1.80)	36.3 (8.92)	61.7 (9.42)	13.5 (2.25)	36.9 (8.72)	62.6 (9.55)	13.9 (1.76)	36.6 (8.78)	62.1 (9.36)
	Median (Q1 - Q3)	14.0 (13.0-15.0)	38.0 (30.0-44.0)	59.0 (54.0-67.0)	14.0 (13.0-15.0)	38.0 (31.0-44.0)	60.0 (55.0-69.0)	14.0 (13.0-15.0)	38.0 (30.0-44.0)	60.0 (54.0-68.0)
	Range	(2.0,15.0)	(16.0,49.0)	(50.0,98.0)	(2.0,15.0)	(16.0,49.0)	(50.0,97.0)	(2.0,15.0)	(16.0,49.0)	(50.0,100.0)
Pregnancy	Yes	-	77 (0.5%)	3 (0.0%)	1 (1.6%)	58 (0.7%)	17 (0.2%)	1 (0.3%)	176 (0.5%)	32 (0.1%)
	No	256 (100.0%)	14192 (99.5%)	10725 (100.0%)	61 (98.4%)	8214 (99.3%)	8356 (99.8%)	353 (99.7%)	36372 (99.5%)	32740 (99.9%)
Contraception	Yes	15 (5.9%)	1979 (13.9%)	100 (0.9%)	-	722 (8.7%)	73 (0.9%)	10 (2.8%)	3827 (10.5%)	300 (0.9%)
	No	241 (94.1%)	12290 (86.1%)	10628 (99.1%)	62 (100.0%)	7550 (91.3%)	8300 (99.1%)	344 (97.2%)	32721 (89.5%)	32472 (99.1%)
Lactation	Yes	-	6 (0.0%)	-	-	1 (0.0%)	-	-	7 (0.0%)	-
	No	256 (100.0%)	14263 (100.0%)	10728 (100.0%)	62 (100.0%)	8271 (100.0%)	8373 (100.0%)	354 (100.0%)	36541 (100.0%)	32772 (100.0%)

Baseline period[1]: year 2013
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Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Route of systemic TCC prescription	Intramuscular	4 (1.6%)	377 (2.6%)	579 (5.4%)	8 (12.9%)	154 (1.9%)	427 (5.1%)	10 (2.8%)	626 (1.7%)	1471 (4.5%)
	Oral	252 (98.4%)	13892 (97.4%)	10149 (94.6%)	54 (87.1%)	8118 (98.1%)	7946 (94.9%)	344 (97.2%)	35922 (98.3%)	31301 (95.5%)
Oral										
TCC daily dose › Oral form	N	237 (94.0)	13136 (94.6)	9573 (94.3)	47 (87.0)	6942 (85.5)	6793 (85.5)	324 (94.2)	33178 (92.4)	28493 (91.0)
	Missing (N)	15 (6.0)	756 (5.4)	576 (5.7)	7 (13.0)	1176 (14.5)	1153 (14.5)	20 (5.8)	2744 (7.6)	2808 (9.0)
	Mean (SD)	10.6 (3.44)	11.6 (3.68)	11.1 (3.64)	10.4 (3.60)	11.9 (3.82)	11.5 (3.76)	10.7 (3.63)	11.7 (3.74)	11.4 (3.74)
	Median (Q1 - Q3)	9.6 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-12.0)	8.0 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)	12.0 (8.0-12.0)	12.0 (8.0-16.0)	12.0 (8.0-16.0)
	Range	(4.0,24.0)	(4.0,48.0)	(2.0,48.0)	(4.0,16.0)	(2.0,36.0)	(2.0,24.0)	(2.0,24.0)	(2.0,48.0)	(2.0,48.0)
	Missing (N)	15	756	576	7	1176	1153	20	2744	2808
	≤16 mg	236 (99.6%)	13084 (99.6%)	9552 (99.8%)	47 (100.0%)	6931 (99.8%)	6780 (99.8%)	323 (99.7%)	33113 (99.8%)	28443 (99.8%)
	>16 mg	1 (0.4%)	52 (0.4%)	21 (0.2%)	-	11 (0.2%)	13 (0.2%)	1 (0.3%)	65 (0.2%)	50 (0.2%)

Baseline period[1]: year 2013
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Duration of TCC treatment (days)›										
Oral form	N	240 (95.2)	13330 (96.0)	9724 (95.8)	48 (88.9)	7081 (87.2)	6921 (87.1)	326 (94.8)	33885 (94.3)	29102 (93.0)
	Missing (N)	12 (4.8)	562 (4.0)	425 (4.2)	6 (11.1)	1037 (12.8)	1025 (12.9)	18 (5.2)	2037 (5.7)	2199 (7.0)
	Mean (SD)	8.7 (7.13)	9.9 (9.75)	13.0 (16.18)	10.0 (16.07)	8.0 (9.57)	10.1 (14.17)	8.1 (8.02)	8.0 (8.37)	10.1 (13.24)
	Median (Q1 - Q3)	7.0 (6.0-8.0)	8.0 (6.0-10.0)	8.0 (6.0-14.0)	6.0 (5.0-7.0)	7.0 (6.0-8.0)	7.0 (6.0-8.0)	6.0 (5.0-8.0)	7.0 (6.0-8.0)	7.0 (6.0-9.0)
	Range	(2.0,84.0)	(1.0,252.0)	(2.0,364.0)	(3.0,84.0)	(1.0,168.0)	(1.0,336.0)	(2.0,84.0)	(1.0,336.0)	(1.0,336.0)
	Missing (N)	12	562	425	6	1037	1025	18	2037	2199
	≤7 days	132 (55.0%)	6440 (48.3%)	3946 (40.6%)	37 (77.1%)	5185 (73.2%)	4443 (64.2%)	224 (68.7%)	23397 (69.0%)	17797 (61.2%)
	>7 days	108 (45.0%)	6890 (51.7%)	5778 (59.4%)	11 (22.9%)	1896 (26.8%)	2478 (35.8%)	102 (31.3%)	10488 (31.0%)	11305 (38.8%)
Intramuscular										
TCC daily dose › IM form	N	4 (100.0)	245 (65.0)	307 (53.0)	1 (12.5)	64 (41.6)	125 (29.3)	1 (10.0)	328 (52.4)	572 (38.9)
	Missing (N)	0	132 (35.0)	272 (47.0)	7 (87.5)	90 (58.4)	302 (70.7)	9 (90.0)	298 (47.6)	899 (61.1)
	Mean (SD)	9.0 (2.00)	10.4 (4.33)	8.4 (4.28)	16.0 ()	7.3 (2.62)	8.4 (5.68)	16.0 ()	8.2 (3.96)	8.9 (5.61)
	Median (Q1 - Q3)	8.0 (8.0-10.0)	8.0 (8.0-16.0)	8.0 (4.0-12.0)	16.0 (16.0-16.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)	16.0 (16.0-16.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
	Range	(8.0,12.0)	(4.0,24.0)	(4.0,24.0)	(16.0,16.0)	(4.0,16.0)	(4.0,28.0)	(16.0,16.0)	(4.0,28.0)	(4.0,28.0)
	Missing (N)	-	132	272	7	90	302	9	298	899
	≤8 mg	3 (75.0%)	124 (50.6%)	226 (73.6%)	-	61 (95.3%)	110 (88.0%)	-	281 (85.7%)	458 (80.1%)
	>8 mg	1 (25.0%)	121 (49.4%)	81 (26.4%)	1 (100.0%)	3 (4.7%)	15 (12.0%)	1 (100.0%)	47 (14.3%)	114 (19.9%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Duration of TCC treatment (days)› IM form	N	4 (100.0)	217 (57.6)	299 (51.6)	1 (12.5)	69 (44.8)	142 (33.3)	1 (10.0)	333 (53.2)	680 (46.2)
	Missing (N)	0	160 (42.4)	280 (48.4)	7 (87.5)	85 (55.2)	285 (66.7)	9 (90.0)	293 (46.8)	791 (53.8)
	Mean (SD)	7.0 (2.45)	7.7 (5.73)	9.2 (15.48)	28.0 ()	8.1 (19.81)	5.7 (2.71)	28.0 ()	7.5 (13.70)	6.5 (7.48)
	Median (Q1 - Q3)	6.5 (5.0-9.0)	6.0 (5.0-8.0)	6.0 (5.0-10.0)	28.0 (28.0-28.0)	5.0 (5.0-6.0)	6.0 (5.0-6.0)	28.0 (28.0-28.0)	5.0 (5.0-6.0)	6.0 (5.0-6.0)
	Range	(5.0,10.0)	(2.0,56.0)	(2.0,231.0)	(28.0,28.0)	(2.0,168.0)	(3.0,28.0)	(28.0,28.0)	(2.0,168.0)	(2.0,168.0)
	Missing (N)	-	160	280	7	85	285	9	293	791
	≤5 days	2 (50.0%)	68 (31.3%)	99 (33.1%)	-	39 (56.5%)	65 (45.8%)	-	173 (52.0%)	300 (44.1%)
	>5 days	2 (50.0%)	149 (68.7%)	200 (66.9%)	1 (100.0%)	30 (43.5%)	77 (54.2%)	1 (100.0%)	160 (48.0%)	380 (55.9%)
Long term treatment[4]	Missing (N)	1	143	155	1	267	457	4	544	1011
	Yes	1 (0.4%)	621 (4.4%)	738 (7.0%)	-	208 (2.6%)	317 (4.0%)	3 (0.9%)	1022 (2.8%)	1473 (4.6%)
	No	254 (99.6%)	13505 (95.6%)	9835 (93.0%)	61 (100.0%)	7797 (97.4%)	7599 (96.0%)	347 (99.1%)	34982 (97.2%)	30288 (95.4%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	233 (91.0%)	13326 (93.4%)	9995 (93.2%)	58 (93.5%)	7587 (91.7%)	7683 (91.8%)	318 (89.8%)	33712 (92.2%)	30254 (92.3%)
	No	23 (9.0%)	943 (6.6%)	733 (6.8%)	4 (6.5%)	685 (8.3%)	690 (8.2%)	36 (10.2%)	2836 (7.8%)	2518 (7.7%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
Medications:										
	Analgesics (N02)	146 (57.0%)	9952 (69.7%)	7707 (71.8%)	30 (48.4%)	5456 (66.0%)	5726 (68.4%)	200 (56.5%)	24740 (67.7%)	22763 (69.5%)
	Acetylsalicylic	2 (0.8%)	70 (0.5%)	64 (0.6%)	-	36 (0.4%)	106 (1.3%)	2 (0.6%)	205 (0.6%)	392 (1.2%)
	Paracetamol	144 (56.3%)	9700 (68.0%)	7399 (69.0%)	30 (48.4%)	5277 (63.8%)	5446 (65.0%)	198 (55.9%)	23887 (65.4%)	21726 (66.3%)
	Opioids (N02A)	14 (5.5%)	3199 (22.4%)	2650 (24.7%)	2 (3.2%)	1801 (21.8%)	1977 (23.6%)	21 (5.9%)	7964 (21.8%)	7941 (24.2%)
	Antidepressants (N06A)	-	1211 (8.5%)	1588 (14.8%)	-	537 (6.5%)	1043 (12.5%)	1 (0.3%)	2491 (6.8%)	4463 (13.6%)
	Antiepileptics (N03A)	-	417 (2.9%)	508 (4.7%)	-	188 (2.3%)	337 (4.0%)	-	786 (2.2%)	1446 (4.4%)
	Muscle relaxants (M03)	6 (2.3%)	1074 (7.5%)	712 (6.6%)	3 (4.8%)	324 (3.9%)	239 (2.9%)	6 (1.7%)	1143 (3.1%)	994 (3.0%)
	NSAIDs/Cox-2 inhibitors (M01A)	164 (64.1%)	9246 (64.8%)	6206 (57.8%)	52 (83.9%)	5264 (63.6%)	4468 (53.4%)	240 (67.8%)	23536 (64.4%)	18151 (55.4%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	4 (1.6%)	751 (5.3%)	751 (7.0%)	1 (1.6%)	631 (7.6%)	751 (9.0%)	13 (3.7%)	2744 (7.5%)	2719 (8.3%)
	Topical products for joint and muscular pain (M02A)	74 (28.9%)	3142 (22.0%)	2249 (21.0%)	16 (25.8%)	2184 (26.4%)	2006 (24.0%)	98 (27.7%)	8929 (24.4%)	7893 (24.1%)
	Phytotherapy (V03A)	1 (0.4%)	-	8 (0.1%)	-	4 (0.0%)	1 (0.0%)	-	4 (0.0%)	22 (0.1%)
Health services/medical devices and others:										
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	11 (4.3%)	273 (1.9%)	164 (1.5%)	1 (1.6%)	104 (1.3%)	53 (0.6%)	6 (1.7%)	483 (1.3%)	261 (0.8%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=256)	Female 16-49 years (N=14269)	Female ≥50 years (N=10728)	Female <16 years (N=62)	Female 16-49 years (N=8272)	Female ≥50 years (N=8373)	Female <16 years (N=354)	Female 16-49 years (N=36548)	Female ≥50 years (N=32772)
Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))		-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	58	2939	2379	20	2402	2640	64	7850	8011
	Yes	198 (100.0%)	8507 (75.1%)	6780 (81.2%)	42 (100.0%)	3657 (62.3%)	4031 (70.3%)	290 (100.0%)	18082 (63.0%)	17572 (71.0%)
	No	-	2823 (24.9%)	1569 (18.8%)	-	2213 (37.7%)	1702 (29.7%)	-	10616 (37.0%)	7189 (29.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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Table 15.3-41: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Total systemic TCC prescriptions		-	262 (100.0%)	837 (100.0%)	-	152 (100.0%)	729 (100.0%)	-	512 (100.0%)	2354 (100.0%)
Number of patients with a systemic TCC prescription		-	202	694	-	136 (100.0%)	608 (100.0%)	-	401 (100.0%)	1712 (100.0%)
Number of systemic TCC prescriptions per patient	N		202 (100.0)	694 (100.0)		136 (100.0)	608 (100.0)		401 (100.0)	1712 (100.0)
	Mean (SD)		1.3 (0.67)	1.2 (0.59)		1.1 (0.39)	1.2 (0.55)		1.3 (0.73)	1.4 (1.01)
	Median (Q1 - Q3)		1.0 (1.0-1.0)	1.0 (1.0-1.0)		1.0 (1.0-1.0)	1.0 (1.0-1.0)		1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range		(1.0,5.0)	(1.0,9.0)		(1.0,4.0)	(1.0,6.0)		(1.0,6.0)	(1.0,14.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-	-	-	-	-	-	-
	Other deforming dorsopathies including - M43	-	3 (1.1%)	5 (0.6%)	-	6 (3.9%)	5 (0.7%)	-	20 (3.9%)	21 (0.9%)
	Spondylolysis - M43.0	-	-	-	-	1 (0.7%)	-	-	1 (0.2%)	-
	Spondylolisthesis - M43.1	-	-	-	-	-	-	-	-	5 (0.2%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-	-	-	-
	Torticollis - M43.6	-	-	2 (0.2%)	-	-	1 (0.1%)	-	3 (0.6%)	3 (0.1%)
	Other specified deforming dorsopathies - M43.8	-	-	-	-	-	-	-	-	-
	Deforming dorsopathy, unspecified - M43.9	-	3 (1.1%)	3 (0.4%)	-	5 (3.3%)	4 (0.5%)	-	16 (3.1%)	13 (0.6%)
	Dorsalgia - M54	-	194 (74.0%)	577 (68.9%)	-	105 (69.1%)	493 (67.6%)	-	358 (69.9%)	1568 (66.6%)
	Radiculopathy - M54.1	-	-	12 (1.4%)	-	2 (1.3%)	16 (2.2%)	-	2 (0.4%)	43 (1.8%)
	Cervicalgia - M54.2	-	76 (29.0%)	168 (20.1%)	-	39 (25.7%)	126 (17.3%)	-	122 (23.8%)	421 (17.9%)
	Sciatica - M54.3	-	5 (1.9%)	17 (2.0%)	-	3 (2.0%)	11 (1.5%)	-	8 (1.6%)	24 (1.0%)
	Lumbago with sciatica - M.54.4	-	25 (9.5%)	90 (10.8%)	-	7 (4.6%)	71 (9.7%)	-	48 (9.4%)	230 (9.8%)
	Low back pain - M54.5	-	70 (26.7%)	225 (26.9%)	-	28 (18.4%)	206 (28.3%)	-	101 (19.7%)	596 (25.3%)
	Pain in thoracic spine - M54.6	-	-	-	-	-	1 (0.1%)	-	-	2 (0.1%)
	Other dorsalgia - M54.8	-	-	1 (0.1%)	-	1 (0.7%)	-	-	2 (0.4%)	6 (0.3%)
	Dorsalgia, unspecified - M54.9	-	18 (6.9%)	64 (7.6%)	-	25 (16.4%)	62 (8.5%)	-	75 (14.6%)	246 (10.5%)
	Other than painful muscle contractures associated with acute spinal pathology	-	65 (24.8%)	255 (30.5%)	-	41 (27.0%)	231 (31.7%)	-	134 (26.2%)	765 (32.5%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Age at prescription (years)	<16 years	-	-	-	-	-	-	-	-	-
	[16;30[	-	15 (5.7%)	-	-	11 (7.2%)	-	-	25 (4.9%)	-
	[30;40[	-	59 (22.5%)	-	-	33 (21.7%)	-	-	138 (27.0%)	-
	[40;50[	-	188 (71.8%)	-	-	108 (71.1%)	-	-	349 (68.2%)	-
	[50;60[	-	-	263 (31.4%)	-	-	215 (29.5%)	-	-	701 (29.8%)
	[60;70[	-	-	266 (31.8%)	-	-	198 (27.2%)	-	-	685 (29.1%)
	≥70 years	-	-	308 (36.8%)	-	-	316 (43.3%)	-	-	968 (41.1%)
Age at prescription (years)	N		262 (100.0)	837 (100.0)		152 (100.0)	729 (100.0)		512 (100.0)	2354 (100.0)
	Mean (SD)		41.9 (6.35)	66.1 (10.54)		41.9 (6.78)	67.5 (11.18)		41.9 (6.30)	67.3 (11.07)
	Median (Q1 - Q3)		43.5 (39.0-47.0)	65.0 (58.0-75.0)		44.0 (38.5-47.0)	67.0 (58.0-75.0)		43.0 (38.0-47.0)	67.0 (58.0-76.0)
	Range		(21.0,49.0)	(50.0,98.0)		(19.0,49.0)	(50.0,96.0)		(19.0,49.0)	(50.0,97.0)
Pregnancy	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	152 (100.0%)	729 (100.0%)	-	512 (100.0%)	2354 (100.0%)
Contraception	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	152 (100.0%)	729 (100.0%)	-	512 (100.0%)	2354 (100.0%)
Lactation	Yes	-	-	-	-	-	-	-	-	-
	No	-	262 (100.0%)	837 (100.0%)	-	152 (100.0%)	729 (100.0%)	-	512 (100.0%)	2354 (100.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Route of systemic TCC prescription	Intramuscular	-	50 (19.1%)	145 (17.3%)	-	31 (20.4%)	119 (16.3%)	-	101 (19.7%)	447 (19.0%)
	Oral	-	212 (80.9%)	692 (82.7%)	-	121 (79.6%)	610 (83.7%)	-	411 (80.3%)	1907 (81.0%)
Oral										
TCC daily dose› Oral form	N		188 (88.7)	548 (79.2)		93 (76.9)	498 (81.6)		345 (83.9)	1544 (81.0)
	Missing (N)		24 (11.3)	144 (20.8)		28 (23.1)	112 (18.4)		66 (16.1)	363 (19.0)
	Mean (SD)		11.0 (3.96)	10.6 (3.96)		11.4 (4.29)	10.3 (4.48)		11.3 (4.19)	10.8 (4.42)
	Median (Q1 - Q3)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range		(4.0,16.0)	(2.0,16.0)		(4.0,16.0)	(2.0,16.0)		(2.0,16.0)	(2.0,16.0)
	Missing (N)	-	24	144	-	28	112	-	66	363
	≤16 mg	-	188 (100.0%)	548 (100.0%)	-	93 (100.0%)	498 (100.0%)	-	345 (100.0%)	1544 (100.0%)
	>16 mg	-	-	-	-	-	-	-	-	-

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Duration of TCC treatment (days)› Oral form	N		188 (88.7)	544 (78.6)		93 (76.9)	498 (81.6)		345 (83.9)	1544 (81.0)
	Missing (N)		24 (11.3)	148 (21.4)		28 (23.1)	112 (18.4)		66 (16.1)	363 (19.0)
	Mean (SD)		26.4 (38.34)	31.6 (47.74)		17.4 (44.63)	21.9 (37.23)		19.3 (42.14)	21.5 (37.04)
	Median (Q1 - Q3)		10.0 (6.0-30.0)	12.0 (6.0-30.0)		6.0 (4.0-12.0)	10.0 (4.0-24.0)		6.0 (4.0-12.0)	10.0 (4.0-18.0)
	Range		(2.0,180.0)	(2.0,360.0)		(1.0,360.0)	(2.0,360.0)		(1.0,360.0)	(1.0,360.0)
	Missing (N)	-	24	148	-	28	112	-	66	363
	≤7 days	-	89 (47.3%)	201 (36.9%)	-	65 (69.9%)	234 (47.0%)	-	206 (59.7%)	700 (45.3%)
	>7 days	-	99 (52.7%)	343 (63.1%)	-	28 (30.1%)	264 (53.0%)	-	139 (40.3%)	844 (54.7%)
Intramuscular TCC daily dose› IM form	N		49 (98.0)	144 (99.3)		31 (100.0)	119 (100.0)		101 (100.0)	447 (100.0)
	Missing (N)		1 (2.0)	1 (0.7)		0	0		0	0
	Mean (SD)		9.8 (3.31)	10.1 (3.62)		11.4 (4.42)	10.4 (3.89)		10.8 (4.27)	9.8 (3.72)
	Median (Q1 - Q3)		8.0 (8.0-12.0)	8.0 (8.0-12.0)		8.0 (8.0-16.0)	8.0 (8.0-16.0)		8.0 (8.0-16.0)	8.0 (8.0-12.0)
	Range		(4.0,16.0)	(4.0,16.0)		(4.0,16.0)	(4.0,16.0)		(4.0,16.0)	(4.0,16.0)
	Missing (N)	-	1	1	-	-	-	-	-	-
	≤8 mg	-	35 (71.4%)	92 (63.9%)	-	16 (51.6%)	81 (68.1%)	-	61 (60.4%)	324 (72.5%)
	>8 mg	-	14 (28.6%)	52 (36.1%)	-	15 (48.4%)	38 (31.9%)	-	40 (39.6%)	123 (27.5%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Duration of TCC treatment (days)› IM form	N		49 (98.0)	143 (98.6)		31 (100.0)	119 (100.0)		101 (100.0)	447 (100.0)
	Missing (N)		1 (2.0)	2 (1.4)		0	0		0	0
	Mean (SD)		23.9 (46.37)	19.1 (44.10)		12.0 (16.00)	12.5 (24.84)		9.6 (10.27)	15.0 (38.05)
	Median (Q1 - Q3)		10.0 (5.0-12.0)	12.0 (5.0-12.0)		7.0 (5.0-14.0)	6.0 (4.0-12.0)		6.0 (4.0-12.0)	6.0 (5.0-10.0)
	Range		(1.0,180.0)	(1.0,360.0)		(2.0,90.0)	(2.0,180.0)		(2.0,90.0)	(2.0,360.0)
	Missing (N)	-	1	2	-	-	-	-	-	-
	≤5 days	-	16 (32.7%)	36 (25.2%)	-	13 (41.9%)	56 (47.1%)	-	44 (43.6%)	175 (39.1%)
	>5 days	-	33 (67.3%)	107 (74.8%)	-	18 (58.1%)	63 (52.9%)	-	57 (56.4%)	272 (60.9%)
Long term treatment[4]	Missing (N)	-	1	12	-	3	14	-	10	42
	Yes	-	27 (10.3%)	58 (7.0%)	-	1 (0.7%)	26 (3.6%)	-	11 (2.2%)	96 (4.2%)
	No	-	234 (89.7%)	767 (93.0%)	-	148 (99.3%)	689 (96.4%)	-	491 (97.8%)	2216 (95.8%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	-	238 (90.8%)	737 (88.1%)	-	137 (90.1%)	636 (87.2%)	-	456 (89.1%)	2028 (86.2%)
	No	-	24 (9.2%)	100 (11.9%)	-	15 (9.9%)	93 (12.8%)	-	56 (10.9%)	326 (13.8%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
Medications:										
	Analgesics (N02)	-	121 (46.2%)	439 (52.4%)	-	52 (34.2%)	337 (46.2%)	-	209 (40.8%)	1072 (45.5%)
	Acetylsalicylic	-	4 (1.5%)	27 (3.2%)	-	-	3 (0.4%)	-	2 (0.4%)	3 (0.1%)
	Paracetamol	-	110 (42.0%)	364 (43.5%)	-	43 (28.3%)	276 (37.9%)	-	185 (36.1%)	891 (37.9%)
	Opioids (N02A)	-	51 (19.5%)	165 (19.7%)	-	19 (12.5%)	113 (15.5%)	-	86 (16.8%)	405 (17.2%)
	Antidepressants (N06A)	-	6 (2.3%)	29 (3.5%)	-	3 (2.0%)	30 (4.1%)	-	22 (4.3%)	97 (4.1%)
	Antiepileptics (N03A)	-	4 (1.5%)	29 (3.5%)	-	7 (4.6%)	18 (2.5%)	-	29 (5.7%)	66 (2.8%)
	Muscle relaxants (M03)	-	18 (6.9%)	22 (2.6%)	-	2 (1.3%)	5 (0.7%)	-	8 (1.6%)	21 (0.9%)
	NSAIDs/Cox-2 inhibitors (M01A)	-	150 (57.3%)	378 (45.2%)	-	91 (59.9%)	386 (52.9%)	-	278 (54.3%)	1181 (50.2%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	72 (27.5%)	244 (29.2%)	-	32 (21.1%)	209 (28.7%)	-	126 (24.6%)	677 (28.8%)
	Topical products for joint and muscular pain (M02A)	-	19 (7.3%)	91 (10.9%)	-	10 (6.6%)	65 (8.9%)	-	27 (5.3%)	226 (9.6%)
	Phytotherapy (V03A)	-	-	6 (0.7%)	-	-	-	-	2 (0.4%)	2 (0.1%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=0)	Female 16-49 years (N=262)	Female ≥50 years (N=837)	Female <16 years (N=0)	Female 16-49 years (N=152)	Female ≥50 years (N=729)	Female <16 years (N=0)	Female 16-49 years (N=512)	Female ≥50 years (N=2354)
Health services/medical devices and others:										
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	1 (0.4%)	-	-	1 (0.7%)	-	-	4 (0.8%)	2 (0.1%)
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	-	25	150	-	28	112	-	66	363
	Yes	-	175 (73.8%)	542 (78.9%)	-	75 (60.5%)	459 (74.4%)	-	291 (65.2%)	1539 (77.3%)
	No	-	62 (26.2%)	145 (21.1%)	-	49 (39.5%)	158 (25.6%)	-	155 (34.8%)	452 (22.7%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
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Table 15.3-42: Analysis of systemic TCC prescriptions according to age in women – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Total systemic TCC prescriptions		17 (100.0%)	4290 (100.0%)	8577 (100.0%)	7 (100.0%)	2543 (100.0%)	6766 (100.0%)	18 (100.0%)	8347 (100.0%)	21018 (100.0%)
Number of patients with a systemic TCC prescription		15	3782	7105	7 (100.0%)	2275 (100.0%)	5812 (100.0%)	17 (100.0%)	6786 (100.0%)	15475 (100.0%)
Number of systemic TCC prescriptions per patient	N	15 (100.0)	3782 (100.0)	7105 (100.0)	7 (100.0)	2275 (100.0)	5812 (100.0)	17 (100.0)	6786 (100.0)	15475 (100.0)
	Mean (SD)	1.1 (0.35)	1.1 (0.41)	1.2 (0.58)	1.0 (0.00)	1.1 (0.38)	1.2 (0.47)	1.1 (0.24)	1.2 (0.61)	1.4 (0.83)
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
	Range	(1.0,2.0)	(1.0,7.0)	(1.0,12.0)	(1.0,1.0)	(1.0,5.0)	(1.0,10.0)	(1.0,2.0)	(1.0,8.0)	(1.0,21.0)

Baseline period[1]: year 2013
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Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	394	791	-	274	624	-	768	1892
	Other deforming dorsopathies including - M43	2 (11.8%)	212 (5.4%)	418 (5.4%)	1 (14.3%)	111 (4.9%)	289 (4.7%)	4 (22.2%)	388 (5.1%)	925 (4.8%)
	Spondylolysis - M43.0	-	39 (1.0%)	243 (3.1%)	-	21 (0.9%)	156 (2.5%)	-	69 (0.9%)	496 (2.6%)
	Spondylolisthesis - M43.1	-	2 (0.1%)	7 (0.1%)	-	1 (0.0%)	7 (0.1%)	-	4 (0.1%)	26 (0.1%)
	Recurrent atlantoaxial dislocation with myelopathy - M43.3	-	-	-	-	-	-	-	-	-
	Other recurrent atlantoaxial dislocation - M43.4	-	-	-	-	-	-	-	-	-
	Other recurrent vertebral dislocation - M43.5	-	-	-	-	-	-	-	-	-
	Torticollis - M43.6	2 (11.8%)	129 (3.3%)	102 (1.3%)	-	60 (2.6%)	84 (1.4%)	-	199 (2.6%)	233 (1.2%)
	Other specified deforming dorsopathies - M43.8	-	12 (0.3%)	43 (0.6%)	-	10 (0.4%)	28 (0.5%)	-	46 (0.6%)	116 (0.6%)
	Deforming dorsopathy, unspecified - M43.9	-	30 (0.8%)	23 (0.3%)	1 (14.3%)	19 (0.8%)	14 (0.2%)	4 (22.2%)	70 (0.9%)	54 (0.3%)
	Dorsalgia - M54	5 (29.4%)	2846 (73.0%)	4996 (64.2%)	2 (28.6%)	1661 (73.2%)	4246 (69.1%)	4 (22.2%)	5544 (73.1%)	12904 (67.5%)
	Radiculopathy - M54.1	-	14 (0.4%)	104 (1.3%)	-	6 (0.3%)	43 (0.7%)	-	32 (0.4%)	188 (1.0%)
	Cervicalgia - M54.2	1 (5.9%)	718 (18.4%)	762 (9.8%)	1 (14.3%)	367 (16.2%)	600 (9.8%)	2 (11.1%)	1247 (16.5%)	1833 (9.6%)
	Sciatica - M54.3	-	82 (2.1%)	259 (3.3%)	-	63 (2.8%)	220 (3.6%)	-	177 (2.3%)	673 (3.5%)
	Lumbago with sciatica - M.54.4	-	-	-	-	-	-	-	-	-
	Low back pain - M54.5	2 (11.8%)	1890 (48.5%)	3681 (47.3%)	1 (14.3%)	1161 (51.2%)	3226 (52.5%)	1 (5.6%)	3843 (50.7%)	9713 (50.8%)
	Pain in thoracic spine - M54.6	-	57 (1.5%)	91 (1.2%)	-	24 (1.1%)	65 (1.1%)	-	92 (1.2%)	236 (1.2%)
	Other dorsalgia - M54.8	-	-	-	-	-	-	-	-	-
	Dorsalgia, unspecified - M54.9	2 (11.8%)	85 (2.2%)	99 (1.3%)	-	40 (1.8%)	92 (1.5%)	1 (5.6%)	153 (2.0%)	261 (1.4%)
	Other than painful muscle contractures associated with acute spinal pathology	10 (58.8%)	838 (21.5%)	2372 (30.5%)	4 (57.1%)	497 (21.9%)	1607 (26.2%)	10 (55.6%)	1647 (21.7%)	5297 (27.7%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Age at prescription (years)	<16 years	17 (100.0%)	-	-	7 (100.0%)	-	-	18 (100.0%)	-	-
	[16;30[	-	535 (12.5%)	-	-	309 (12.2%)	-	-	1053 (12.6%)	-
	[30;40[	-	1188 (27.7%)	-	-	674 (26.5%)	-	-	2195 (26.3%)	-
	[40;50[	-	2567 (59.8%)	-	-	1560 (61.3%)	-	-	5099 (61.1%)	-
	[50;60[	-	-	2781 (32.4%)	-	-	2082 (30.8%)	-	-	6661 (31.7%)
	[60;70[	-	-	2531 (29.5%)	-	-	2013 (29.8%)	-	-	6328 (30.1%)
	≥70 years	-	-	3265 (38.1%)	-	-	2671 (39.5%)	-	-	8029 (38.2%)
Age at prescription (years)	N	17 (100.0)	4290 (100.0)	8577 (100.0)	7 (100.0)	2543 (100.0)	6766 (100.0)	18 (100.0)	8347 (100.0)	21018 (100.0)
	Mean (SD)	14.1 (1.05)	39.6 (7.77)	66.2 (10.59)	14.3 (0.95)	39.8 (7.81)	66.6 (10.56)	14.2 (1.20)	39.8 (7.78)	66.3 (10.53)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	41.0 (35.0-46.0)	65.0 (57.0-74.0)	15.0 (13.0-15.0)	42.0 (35.0-46.0)	66.0 (58.0-74.0)	15.0 (14.0-15.0)	42.0 (35.0-46.0)	66.0 (57.0-74.0)
	Range	(12.0,15.0)	(16.0,49.0)	(50.0,99.0)	(13.0,15.0)	(16.0,49.0)	(50.0,103.0)	(11.0,15.0)	(16.0,49.0)	(50.0,103.0)
Pregnancy	Yes	-	169 (3.9%)	7 (0.1%)	1 (14.3%)	103 (4.1%)	9 (0.1%)	1 (5.6%)	349 (4.2%)	28 (0.1%)
	No	17 (100.0%)	4121 (96.1%)	8570 (99.9%)	6 (85.7%)	2440 (95.9%)	6757 (99.9%)	17 (94.4%)	7998 (95.8%)	20990 (99.9%)
Contraception	Yes	-	308 (7.2%)	43 (0.5%)	-	96 (3.8%)	16 (0.2%)	-	413 (4.9%)	68 (0.3%)
	No	17 (100.0%)	3982 (92.8%)	8534 (99.5%)	7 (100.0%)	2447 (96.2%)	6750 (99.8%)	18 (100.0%)	7934 (95.1%)	20950 (99.7%)
Lactation	Yes	-	4 (0.1%)	-	-	-	-	-	3 (0.0%)	-
	No	17 (100.0%)	4286 (99.9%)	8577 (100.0%)	7 (100.0%)	2543 (100.0%)	6766 (100.0%)	18 (100.0%)	8344 (100.0%)	21018 (100.0%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Route of systemic TCC prescription	Intramuscular	1 (5.9%)	2644 (61.6%)	6516 (76.0%)	2 (28.6%)	1753 (68.9%)	5492 (81.2%)	4 (22.2%)	5670 (67.9%)	16969 (80.7%)
	Oral	16 (94.1%)	1646 (38.4%)	2061 (24.0%)	5 (71.4%)	790 (31.1%)	1274 (18.8%)	14 (77.8%)	2677 (32.1%)	4049 (19.3%)
Oral										
TCC daily dose› Oral form	N	8 (50.0)	670 (40.7)	793 (38.5)	3 (60.0)	274 (34.7)	437 (34.3)	7 (50.0)	917 (34.3)	1418 (35.0)
	Missing (N)	8 (50.0)	976 (59.3)	1268 (61.5)	2 (40.0)	516 (65.3)	837 (65.7)	7 (50.0)	1760 (65.7)	2631 (65.0)
	Mean (SD)	10.0 (3.02)	11.3 (4.44)	11.6 (4.48)	6.7 (2.31)	11.7 (4.69)	11.1 (4.76)	7.4 (2.76)	11.3 (4.76)	10.7 (4.58)
	Median (Q1 - Q3)	8.0 (8.0-12.0)	11.0 (8.0-16.0)	12.0 (8.0-16.0)	8.0 (4.0-8.0)	12.0 (8.0-16.0)	8.0 (8.0-16.0)	8.0 (4.0-8.0)	8.0 (8.0-16.0)	8.0 (8.0-16.0)
	Range	(8.0,16.0)	(4.0,24.0)	(4.0,24.0)	(4.0,8.0)	(4.0,32.0)	(4.0,24.0)	(4.0,12.0)	(4.0,32.0)	(4.0,24.0)
	Missing (N)	8	976	1268	2	516	837	7	1760	2631
	≤16 mg	8 (100.0%)	661 (98.7%)	780 (98.4%)	3 (100.0%)	271 (98.9%)	430 (98.4%)	7 (100.0%)	900 (98.1%)	1402 (98.9%)
	>16 mg	-	9 (1.3%)	13 (1.6%)	-	3 (1.1%)	7 (1.6%)	-	17 (1.9%)	16 (1.1%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Duration of TCC treatment (days)› Oral form	N	8 (50.0)	669 (40.6)	793 (38.5)	3 (60.0)	274 (34.7)	437 (34.3)	7 (50.0)	917 (34.3)	1417 (35.0)
	Missing (N)	8 (50.0)	977 (59.4)	1268 (61.5)	2 (40.0)	516 (65.3)	837 (65.7)	7 (50.0)	1760 (65.7)	2632 (65.0)
	Mean (SD)	8.4 (2.26)	8.6 (4.79)	8.3 (4.39)	13.3 (5.77)	10.5 (4.78)	10.8 (5.01)	12.9 (5.40)	9.9 (5.01)	10.4 (5.15)
	Median (Q1 - Q3)	10.0 (6.0-10.0)	10.0 (5.0-10.0)	6.0 (5.0-10.0)	10.0 (10.0-20.0)	10.0 (7.0-14.0)	10.0 (7.0-14.0)	10.0 (10.0-20.0)	10.0 (7.0-10.0)	10.0 (7.0-14.0)
	Range	(5.0,10.0)	(3.0,60.0)	(3.0,50.0)	(10.0,20.0)	(3.0,30.0)	(4.0,30.0)	(6.0,20.0)	(3.0,50.0)	(3.0,50.0)
	Missing (N)	8	977	1268	2	516	837	7	1760	2632
	≤7 days	3 (37.5%)	332 (49.6%)	405 (51.1%)	-	135 (49.3%)	199 (45.5%)	1 (14.3%)	426 (46.5%)	591 (41.7%)
	>7 days	5 (62.5%)	337 (50.4%)	388 (48.9%)	3 (100.0%)	139 (50.7%)	238 (54.5%)	6 (85.7%)	491 (53.5%)	826 (58.3%)
Intramuscular TCC daily dose› IM form	N	1 (100.0)	622 (23.5)	1685 (25.9)	1 (50.0)	313 (17.9)	1192 (21.7)	2 (50.0)	1136 (20.0)	3821 (22.5)
	Missing (N)	0	2022 (76.5)	4831 (74.1)	1 (50.0)	1440 (82.1)	4300 (78.3)	2 (50.0)	4534 (80.0)	13148 (77.5)
	Mean (SD)	4.0 ()	4.6 (1.53)	4.6 (1.48)	8.0 ()	4.8 (1.58)	4.6 (1.46)	6.0 (2.83)	4.7 (1.51)	4.6 (1.45)
	Median (Q1 - Q3)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	8.0 (8.0-8.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	6.0 (4.0-8.0)	4.0 (4.0-4.0)	4.0 (4.0-4.0)
	Range	(4.0,4.0)	(4.0,16.0)	(4.0,12.0)	(8.0,8.0)	(4.0,8.0)	(2.0,16.0)	(4.0,8.0)	(4.0,12.0)	(2.0,16.0)
	Missing (N)	-	2022	4831	1	1440	4300	2	4534	13148
	≤8 mg	1 (100.0%)	619 (99.5%)	1684 (99.9%)	1 (100.0%)	313 (100.0%)	1190 (99.8%)	2 (100.0%)	1135 (99.9%)	3815 (99.8%)
	>8 mg	-	3 (0.5%)	1 (0.1%)	-	-	2 (0.2%)	-	1 (0.1%)	6 (0.2%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=0)	Female 16-49 years (N=638)	Female ≥50 years (N=2546)	Female <16 years (N=11)	Female 16-49 years (N=6442)	Female ≥50 years (N=16798)
Duration of TCC treatment (days)› IM form	N	1 (100.0)	622 (23.5)	1683 (25.8)		90 (19.1)	461 (21.3)	1 (50.0)	913 (20.8)	3089 (22.6)
	Missing (N)	0	2022 (76.5)	4833 (74.2)		381 (80.9)	1701 (78.7)	1 (50.0)	3475 (79.2)	10550 (77.4)
	Mean (SD)	6.0 ()	5.9 (1.59)	5.9 (1.66)		5.8 (1.24)	6.0 (1.52)	6.0 ()	5.8 (1.36)	5.9 (1.47)
	Median (Q1 - Q3)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)		6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)	6.0 (6.0-6.0)
	Range	(6.0,6.0)	(1.0,12.0)	(2.0,24.0)		(3.0,12.0)	(1.0,12.0)	(6.0,6.0)	(2.0,12.0)	(1.0,12.0)
	Missing (N)	-	2022	4833	-	381	1701	1	3475	10550
	≤5 days	-	76 (12.2%)	222 (13.2%)	-	10 (11.1%)	47 (10.2%)	-	115 (12.6%)	349 (11.3%)
	>5 days	1 (100.0%)	546 (87.8%)	1461 (86.8%)	-	80 (88.9%)	414 (89.8%)	1 (100.0%)	798 (87.4%)	2740 (88.7%)
Long term treatment[4]	Missing (N)	1	310	989	-	77	392	-	461	1888
	Yes	-	33 (0.8%)	85 (1.1%)	-	7 (1.2%)	17 (0.8%)	-	32 (0.5%)	115 (0.8%)
	No	16 (100.0%)	3947 (99.2%)	7503 (98.9%)	-	554 (98.8%)	2137 (99.2%)	11 (100.0%)	5949 (99.5%)	14795 (99.2%)
Concomitant medications and/or health services, medical devices during systemic TCC use	Yes	9 (52.9%)	3558 (82.9%)	7430 (86.6%)	-	561 (87.9%)	2256 (88.6%)	5 (45.5%)	5476 (85.0%)	14837 (88.3%)
	No	8 (47.1%)	732 (17.1%)	1147 (13.4%)	-	77 (12.1%)	290 (11.4%)	6 (54.5%)	966 (15.0%)	1961 (11.7%)

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Detail of the concomitant medications and/or health services, medical devices during systemic TCC use:										
Medications:										
	Analgesics (N02)	-	547 (12.8%)	1158 (13.5%)	1 (14.3%)	268 (10.5%)	826 (12.2%)	3 (16.7%)	895 (10.7%)	2535 (12.1%)
	Acetylsalicylic	-	-	2 (0.0%)	-	3 (0.1%)	3 (0.0%)	-	6 (0.1%)	13 (0.1%)
	Paracetamol	-	466 (10.9%)	946 (11.0%)	1 (14.3%)	200 (7.9%)	624 (9.2%)	3 (16.7%)	708 (8.5%)	1873 (8.9%)
	Opioids (N02A)	-	276 (6.4%)	829 (9.7%)	-	124 (4.9%)	554 (8.2%)	-	437 (5.2%)	1725 (8.2%)
	Antidepressants (N06A)	-	123 (2.9%)	535 (6.2%)	-	89 (3.5%)	448 (6.6%)	1 (5.6%)	286 (3.4%)	1398 (6.7%)
	Antiepileptics (N03A)	-	69 (1.6%)	177 (2.1%)	-	52 (2.0%)	192 (2.8%)	-	123 (1.5%)	571 (2.7%)
	Muscle relaxants (M03)	-	37 (0.9%)	47 (0.5%)	-	22 (0.9%)	44 (0.7%)	-	89 (1.1%)	175 (0.8%)
	NSAIDs/Cox-2 inhibitors (M01A)	7 (41.2%)	3008 (70.1%)	6395 (74.6%)	3 (42.9%)	1862 (73.2%)	5265 (77.8%)	6 (33.3%)	6132 (73.5%)	16264 (77.4%)
	Antiinflammatory/antirheumatic agents in combination with corticosteroids (M01B)	-	-	-	-	-	-	-	-	-
	Corticosteroids for systemic use (H02A)	-	412 (9.6%)	756 (8.8%)	-	288 (11.3%)	718 (10.6%)	-	893 (10.7%)	2155 (10.3%)
	Topical products for joint and muscular pain (M02A)	3 (17.6%)	126 (2.9%)	160 (1.9%)	-	33 (1.3%)	71 (1.0%)	-	157 (1.9%)	247 (1.2%)
	Phytotherapy (V03A)	-	-	1 (0.0%)	-	1 (0.0%)	4 (0.1%)	-	4 (0.0%)	7 (0.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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		Baseline[1]			Study period year 3[2]			Study period years 1, 2 and 3[3]		
		Female <16 years (N=17)	Female 16-49 years (N=4290)	Female ≥50 years (N=8577)	Female <16 years (N=7)	Female 16-49 years (N=2543)	Female ≥50 years (N=6766)	Female <16 years (N=18)	Female 16-49 years (N=8347)	Female ≥50 years (N=21018)
Health services/medical devices and others:										
	Neck braces/Belts/lumbar corsets (V53.7 (ICD-9), Z46.89 (ICD-10))	-	-	-	-	-	-	-	-	-
	Functional rehabilitation (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Osteo-therapies (V57 (ICD-9), Z50 (ICD-10))	-	-	-	-	-	-	-	-	-
	Infiltrations (81.92 (ICD-9), 3EOU3NZ (ICD-10))	-	-	-	-	-	-	-	-	-
Off label use	Missing (N)	8	3047	6173	3	1979	5177	9	6354	15897
	Yes	9 (100.0%)	1025 (82.5%)	2093 (87.1%)	4 (100.0%)	472 (83.7%)	1404 (88.4%)	9 (100.0%)	1689 (84.7%)	4539 (88.6%)
	No	-	218 (17.5%)	311 (12.9%)	-	92 (16.3%)	185 (11.6%)	-	304 (15.3%)	582 (11.4%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential/ Contraceptive use was not taking into account in definition of off label
Long term treatment[4]:duration between the previous and the current prescription being less than 1.5 times the duration of the previous prescription

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Table 15.3-43: Summary of off label use of systemic TCC prescriptions – Study period year 1 vs. baseline – GPs France – included patients

			Study period year 1[2]			
		Baseline period[1] (N= 44108)	Overall (N=49100)	Incident[3] (N= 20356)	p-value Baseline vs Overall Study period year 1	p-value Baseline vs Incident Study period year 1
Age at prescription (years) <16 years		452 (1.0%)	306 (0.6%)	239 (1.2%)	<0.001 [b]	0.090 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		2874 (6.5%)	3586 (7.3%)	1731 (8.5%)	<0.001 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		112 (0.3%)	93 (0.2%)	41 (0.2%)	0.034 [b]	0.186 [b]
duration >7 consecutive days		21763 (53.3%)	15960 (34.7%)	5713 (29.8%)	<0.001 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		337 (36.4%)	152 (23.7%)	58 (23.4%)	<0.001 [b]	<0.001 [b]
duration >5 consecutive days		598 (69.6%)	338 (47.0%)	114 (41.2%)	<0.001 [b]	<0.001 [b]
Long term treatment		2289 (5.3%)	1765 (3.6%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		17557 (46.7%)	19703 (45.9%)	7035 (39.5%)	0.383 [b]	<0.001 [b]
In women of child bearing potential:						
Pregnancy		77 (0.5%)	70 (0.5%)	22 (0.3%)	0.427 [b]	0.038 [b]
No contraceptive use		12290 (86.1%)	13207 (89.3%)	5957 (90.5%)	<0.001 [b]	<0.001 [b]
Lactation		6 (0.0%)	5 (0.0%)	1 (0.0%)	0.719 [b]	0.291 [b]
Off label use	Missing (N)	9212	9263	3829	<0.001 [b]	<0.001 [b]
	Yes	26561 (76.1%)	25999 (65.3%)	9897 (59.9%)		
	No	8335 (23.9%)	13838 (34.7%)	6630 (40.1%)		

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

Table 15.3-44: Summary of off label use of systemic TCC prescriptions – Study period year 1 vs. baseline – Rheumatologists France – included patients

			Study period year 1[2]			
		Baseline period[1] (N= 1721)	Overall (N=1494)	Incident[3] (N= 685)	p-value Baseline vs Overall Study period year 1	p-value Baseline vs Incident Study period year 1
Age at prescription (years) <16 years		-	-	-		
No concomitant medications and/or health services, medical devices during systemic TCC use		192 (11.2%)	174 (11.6%)	105 (15.3%)	0.663 [b]	0.006 [b]
Oral form						
daily dose>16 mg per day		-	-	-	N/A [b]	N/A [b]
duration >7 consecutive days		707 (59.7%)	530 (51.0%)	199 (44.9%)	<0.001 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		104 (37.1%)	74 (30.2%)	40 (29.4%)	0.093 [b]	0.117 [b]
duration >5 consecutive days		188 (67.6%)	148 (60.4%)	77 (56.6%)	0.086 [b]	0.029 [b]
Long term treatment		132 (7.8%)	66 (4.5%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		494 (28.7%)	443 (29.7%)	245 (35.8%)	0.670 [b]	0.269 [b]
In women of child bearing potential:						
Pregnancy		-	-	-	N/A [b]	N/A [b]
No contraceptive use		262 (100.0%)	186 (100.0%)	86 (100.0%)	N/A [b]	N/A [b]
Lactation		-	-	-	N/A [b]	N/A [b]
Off label use	Missing (N)	361	280	123	0.149 [b]	0.876 [b]
	Yes	1021 (75.1%)	881 (72.6%)	420 (74.7%)		
	No	339 (24.9%)	333 (27.4%)	142 (25.3%)		

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

Table 15.3-45: Summary of off label use of systemic TCC prescriptions – Study period year 1 vs. baseline – GPs Italy – included patients

			Study period year 1[2]			
		Baseline period[1] (N= 23527)	Overall (N=18695)	Incident[3] (N= 7105)	p-value Baseline vs Overall Study period year 1	p-value Baseline vs Incident Study period year 1
Age at prescription (years) <16 years		36 (0.2%)	10 (0.1%)	9 (0.1%)	0.001 [b]	0.606 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		3151 (13.4%)	2236 (12.0%)	1004 (14.1%)	<0.001 [b]	0.113 [b]
Oral form						
daily dose>16 mg per day		34 (1.3%)	9 (0.6%)	5 (0.8%)	0.025 [b]	0.223 [b]
duration >7 consecutive days		1239 (47.7%)	832 (55.3%)	356 (54.2%)	<0.001 [b]	0.003 [b]
IM form						
daily dose>8 mg per day		4 (0.1%)	4 (0.1%)	1 (0.1%)	0.695 [b]	0.923 [b]
duration >5 consecutive days		3745 (87.2%)	2862 (87.8%)	832 (86.3%)	0.368 [b]	0.482 [b]
Long term treatment		225 (1.1%)	122 (0.7%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		5236 (24.4%)	3923 (22.9%)	1602 (24.7%)	0.004 [b]	0.103 [b]
In women of child bearing potential:						
Pregnancy		169 (3.9%)	136 (4.7%)	76 (5.0%)	0.123 [b]	0.078 [b]
No contraceptive use		3982 (92.8%)	2710 (93.4%)	1421 (93.8%)	0.302 [b]	0.194 [b]
Lactation		4 (0.1%)	2 (0.1%)	2 (0.1%)	0.724 [b]	0.694 [b]
Off label use	Missing (N)	17903	14779	5743	<0.001 [b]	0.428 [b]
	Yes	4754 (84.5%)	3417 (87.3%)	1163 (85.4%)		
	No	870 (15.5%)	499 (12.7%)	199 (14.6%)		

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

Table 15.3-46: Summary of off label use of systemic TCC prescriptions – Study period year 2 vs. baseline – GPs France – included patients

		Baseline period[1] (N= 44108)	Study period year 2[2] Overall (N=44691)	Study period year 2[2] Incident[3] (N= 17954)	p-value Baseline vs Overall Study period year 2	p-value Baseline vs Incident Study period year 2
Age at prescription (years) <16 years		452 (1.0%)	238 (0.5%)	195 (1.1%)	<0.001 [b]	0.496 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		2874 (6.5%)	3193 (7.1%)	1494 (8.3%)	<0.001 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		112 (0.3%)	84 (0.2%)	37 (0.2%)	0.032 [b]	0.249 [b]
duration >7 consecutive days		21763 (53.3%)	14546 (34.8%)	5124 (30.5%)	<0.001 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		337 (36.4%)	110 (19.1%)	37 (17.1%)	<0.001 [b]	<0.001 [b]
duration >5 consecutive days		598 (69.6%)	369 (57.4%)	122 (51.3%)	<0.001 [b]	<0.001 [b]
Long term treatment		2289 (5.3%)	1602 (3.6%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		17557 (46.7%)	17378 (45.8%)	5986 (38.9%)	0.571 [b]	<0.001 [b]
In women of child bearing potential:						
Pregnancy		77 (0.5%)	48 (0.4%)	15 (0.3%)	0.022 [b]	0.006 [b]
No contraceptive use		12290 (86.1%)	11964 (88.7%)	5162 (90.2%)	<0.001 [b]	<0.001 [b]
Lactation		6 (0.0%)	1 (0.0%)	1 (0.0%)	0.055 [b]	0.369 [b]
Off label use	Missing (N)	9212	9384	3669	<0.001 [b]	<0.001 [b]
	Yes	26561 (76.1%)	22971 (65.1%)	8496 (59.5%)		
	No	8335 (23.9%)	12336 (34.9%)	5789 (40.5%)		

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

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Table 15.3-47: Summary of off label use of systemic TCC prescriptions – Study period year 2 vs. baseline – Rheumatologists France – included patients

			Study period year 2[2]			
		Baseline period[1] (N= 1721)	Overall (N=1409)	Incident[3] (N= 660)	p-value Baseline vs Overall Study period year 2	p-value Baseline vs Incident Study period year 2
Age at prescription (years) <16 years		-	-	-		
No concomitant medications and/or health services, medical devices during systemic TCC use		192 (11.2%)	194 (13.8%)	112 (17.0%)	0.027 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		-	-	-	N/A [b]	N/A [b]
duration >7 consecutive days		707 (59.7%)	502 (54.4%)	186 (47.6%)	0.016 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		104 (37.1%)	80 (28.7%)	53 (30.6%)	0.033 [b]	0.156 [b]
duration >5 consecutive days		188 (67.6%)	162 (58.1%)	90 (52.0%)	0.019 [b]	<0.001 [b]
Long term treatment		132 (7.8%)	46 (3.3%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		494 (28.7%)	415 (29.5%)	231 (35.0%)	0.113 [b]	0.029 [b]
In women of child bearing potential:						
Pregnancy		-	-	-	N/A [b]	N/A [b]
No contraceptive use		262 (100.0%)	174 (100.0%)	87 (100.0%)	N/A [b]	N/A [b]
Lactation		-	-	-	N/A [b]	N/A [b]
Off label use	Missing (N)	361	261	112	0.795 [b]	0.973 [b]
	Yes	1021 (75.1%)	867 (75.5%)	411 (75.0%)		
	No	339 (24.9%)	281 (24.5%)	137 (25.0%)		

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

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Table 15.3-48: Summary of off label use of systemic TCC prescriptions – Study period year 2 vs. baseline – GPs Italy – included patients

			Study period year 2[2]			
		Baseline period[1] (N= 23527)	Overall (N=18833)	Incident[3] (N= 7098)	p-value Baseline vs Overall Study period year 2	p-value Baseline vs Incident Study period year 2
Age at prescription (years) <16 years		36 (0.2%)	13 (0.1%)	12 (0.2%)	0.010 [b]	0.765 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		3151 (13.4%)	2117 (11.2%)	929 (13.1%)	<0.001 [b]	0.507 [b]
Oral form						
daily dose>16 mg per day		34 (1.3%)	29 (2.0%)	11 (1.8%)	0.087 [b]	0.391 [b]
duration >7 consecutive days		1239 (47.7%)	767 (53.4%)	331 (53.3%)	<0.001 [b]	0.013 [b]
IM form						
daily dose>8 mg per day		4 (0.1%)	2 (0.1%)	1 (0.1%)	0.601 [b]	0.935 [b]
duration >5 consecutive days		3745 (87.2%)	2971 (88.7%)	872 (89.1%)	0.035 [b]	0.097 [b]
Long term treatment		225 (1.1%)	137 (0.8%)	-	0.010 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		5236 (24.4%)	3884 (22.5%)	1539 (23.9%)	0.001 [b]	0.101 [b]
In women of child bearing potential:						
Pregnancy		169 (3.9%)	110 (3.8%)	76 (5.0%)	0.744 [b]	0.077 [b]
No contraceptive use		3982 (92.8%)	2777 (95.6%)	1445 (95.5%)	<0.001 [b]	<0.001 [b]
Lactation		4 (0.1%)	1 (0.0%)	1 (0.1%)	0.331 [b]	0.750 [b]
Off label use	Missing (N)	17903	14944	5772	0.011 [b]	0.184 [b]
	Yes	4754 (84.5%)	3360 (86.4%)	1140 (86.0%)		
	No	870 (15.5%)	529 (13.6%)	186 (14.0%)		

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential

Table 15.3-49: Summary of off label use of systemic TCC prescriptions – Study period year 3 vs. baseline – GPs France – included patients

			Study period year 3[2]			
		Baseline period[1] (N=44108)	Overall (N=29631)	Incident[3] (N=12287)	p-value Baseline vs Overall Study period year 3	p-value Baseline vs Incident Study period year 3
Age at prescription (years) <16 years		452 (1.0%)	117 (0.4%)	99 (0.8%)	<0.001 [b]	0.496 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		2874 (6.5%)	2283 (7.7%)	1102 (9.0%)	<0.001 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		112 (0.3%)	42 (0.2%)	20 (0.2%)	0.032 [b]	0.249 [b]
duration >7 consecutive days		21763 (53.3%)	7639 (30.6%)	2742 (26.2%)	<0.001 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		337 (36.4%)	41 (10.8%)	19 (12.7%)	<0.001 [b]	<0.001 [b]
duration >5 consecutive days		598 (69.6%)	208 (49.3%)	83 (47.2%)	<0.001 [b]	<0.001 [b]
Long term treatment		2289 (5.3%)	913 (3.2%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		17557 (46.7%)	11474 (46.8%)	3972 (39.0%)	0.571 [b]	<0.001 [b]
In women of child bearing potential:						
Pregnancy[4]		77 (0.5%)	58 (0.7%)	28 (0.8%)	0.022 [b]	0.006 [b]
No contraceptive use[4]		12290 (86.1%)	7550 (91.3%)	3383 (92.8%)	<0.001 [b]	<0.001 [b]
Lactation[4]		6 (0.0%)	1 (0.0%)	1 (0.0%)	0.055 [b]	0.369 [b]
Off label use[5]	Missing (N)	9212	8861	3604	<0.001 [b]	<0.001 [b]
	Yes	26561 (76.1%)	13387 (64.5%)	5004 (57.6%)		
	No	8335 (23.9%)	7383 (35.5%)	3679 (42.4%)		

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
[3]: percentage based on women of child bearing potential
Off label use[4] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-50: Summary of off label use of systemic TCC prescriptions – Study period year 3 vs. baseline – Rheumatologists France – included patients

			Study period year 3[2]			
		Baseline period[1] (N=1721)	Overall (N=1281)	Incident[3] (N=578)	p-value Baseline vs Overall Study period year 3	p-value Baseline vs Incident Study period year 3
Age at prescription (years) <16 years		-	1 (0.1%)	1 (0.2%)		
No concomitant medications and/or health services, medical devices during systemic TCC use		192 (11.2%)	135 (10.5%)	75 (13.0%)	0.027 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		-	-	-	N/A [b]	N/A [b]
duration >7 consecutive days		707 (59.7%)	405 (46.6%)	149 (41.2%)	0.016 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		104 (37.1%)	89 (41.6%)	51 (41.5%)	0.033 [b]	0.156 [b]
duration >5 consecutive days		188 (67.6%)	109 (50.9%)	58 (47.2%)	0.019 [b]	<0.001 [b]
Long term treatment		132 (7.8%)	40 (3.2%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		494 (28.7%)	360 (28.1%)	197 (34.1%)	0.113 [b]	0.029 [b]
In women of child bearing potential:						
Pregnancy[4]		-	-	-	N/A [b]	N/A [b]
No contraceptive use[4]		262 (100.0%)	152 (100.0%)	82 (100.0%)	N/A [b]	N/A [b]
Lactation[4]		-	-	-	N/A [b]	N/A [b]
Off label use[5]	Missing (N)	361	250	106	0.795 [b]	0.973 [b]
	Yes	1021 (75.1%)	713 (69.2%)	336 (71.2%)		
	No	339 (24.9%)	318 (30.8%)	136 (28.8%)		

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
[3]: percentage based on women of child bearing potential
Off label use[4] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-51: Summary of off label use of systemic TCC prescriptions – Study period year 3 vs. baseline – GPs Italy – included patients

			Study period year 3[2]			
		Baseline period[1] (N=23527)	Overall (N=17364)	Incident[3] (N=6471)	p-value Baseline vs Overall Study period year 3	p-value Baseline vs Incident Study period year 3
Age at prescription (years) <16 years		36 (0.2%)	9 (0.1%)	9 (0.1%)	0.010 [b]	0.765 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		3151 (13.4%)	1917 (11.0%)	820 (12.7%)	<0.001 [b]	0.507 [b]
Oral form						
daily dose>16 mg per day		34 (1.3%)	24 (1.9%)	12 (2.1%)	0.087 [b]	0.391 [b]
duration >7 consecutive days		1239 (47.7%)	659 (51.3%)	281 (48.4%)	<0.001 [b]	0.013 [b]
IM form						
daily dose>8 mg per day		4 (0.1%)	2 (0.1%)	-	0.601 [b]	0.935 [b]
duration >5 consecutive days		3745 (87.2%)	2626 (88.7%)	762 (88.0%)	0.035 [b]	0.097 [b]
Long term treatment		225 (1.1%)	121 (0.8%)	-	0.010 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		5236 (24.4%)	3440 (21.7%)	1421 (24.2%)	0.001 [b]	0.101 [b]
In women of child bearing potential:						
Pregnancy[4]		169 (3.9%)	103 (4.1%)	61 (4.6%)	0.744 [b]	0.077 [b]
No contraceptive use[4]		3982 (92.8%)	2447 (96.2%)	1255 (95.7%)	<0.001 [b]	<0.001 [b]
Lactation[4]		4 (0.1%)	-	-	0.331 [b]	0.750 [b]
Off label use[5]	Missing (N)	17903	13946	5268	0.011 [b]	0.184 [b]
	Yes	4754 (84.5%)	2936 (85.9%)	1007 (83.7%)		
	No	870 (15.5%)	482 (14.1%)	196 (16.3%)		

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
[3]: percentage based on women of child bearing potential
Off label use[4] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-52: Summary of off label use of systemic TCC prescriptions – Cumulated study period years 1, 2 and 3 vs. baseline – GPs France – included patients

			Study period years 1, 2 and 3[2]			
		Baseline period[1] (N=44108)	Overall (N=123429)	Incident[3] (N=50597)	p-value Baseline vs Overall Study period years 1, 2 and 3	p-value Baseline vs Incident Study period years 1, 2 and 3
Age at prescription (years) <16 years		452 (1.0%)	661 (0.5%)	533 (1.1%)	<0.001 [b]	0.496 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		2874 (6.5%)	9062 (7.3%)	4327 (8.6%)	<0.001 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		112 (0.3%)	219 (0.2%)	98 (0.2%)	0.032 [b]	0.249 [b]
duration >7 consecutive days		21763 (53.3%)	38148 (33.8%)	13579 (29.3%)	<0.001 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		337 (36.4%)	303 (19.0%)	114 (18.5%)	<0.001 [b]	<0.001 [b]
duration >5 consecutive days		598 (69.6%)	915 (51.3%)	319 (46.2%)	<0.001 [b]	<0.001 [b]
Long term treatment		2289 (5.3%)	4280 (3.5%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		17557 (46.7%)	48560 (46.1%)	16993 (39.2%)	0.571 [b]	<0.001 [b]
In women of child bearing potential:						
Pregnancy[4]		77 (0.5%)	176 (0.5%)	65 (0.4%)	0.022 [b]	0.006 [b]
No contraceptive use[4]		12290 (86.1%)	32721 (89.5%)	14502 (90.9%)	<0.001 [b]	<0.001 [b]
Lactation[4]		6 (0.0%)	7 (0.0%)	3 (0.0%)	0.055 [b]	0.369 [b]
Off label use[5]	Missing (N)	9212	27509	11102	<0.001 [b]	<0.001 [b]
	Yes	26561 (76.1%)	62362 (65.0%)	23397 (59.2%)		
	No	8335 (23.9%)	33558 (35.0%)	16098 (40.8%)		

Baseline period[1]: year 2013
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
[4]: percentage based on women of child bearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-53: Summary of off label use of systemic TCC prescriptions – Cumulated study period years 1, 2 and 3 vs. baseline – Rheumatologists France – included patients

			Study period years 1, 2 and 3[2]			
		Baseline period[1] (N=1721)	Overall (N=4184)	Incident[3] (N=1923)	p-value Baseline vs Overall Study period years 1, 2 and 3	p-value Baseline vs Incident Study period years 1, 2 and 3
Age at prescription (years) <16 years		-	1 (0.0%)	1 (0.1%)		
No concomitant medications and/or health services, medical devices during systemic TCC use		192 (11.2%)	503 (12.0%)	292 (15.2%)	0.027 [b]	<0.001 [b]
Oral form						
daily dose>16 mg per day		-	-	-	N/A [b]	N/A [b]
duration >7 consecutive days		707 (59.7%)	1437 (50.8%)	534 (44.6%)	0.016 [b]	<0.001 [b]
IM form						
daily dose>8 mg per day		104 (37.1%)	243 (32.9%)	144 (33.3%)	0.033 [b]	0.156 [b]
duration >5 consecutive days		188 (67.6%)	419 (56.8%)	225 (52.1%)	0.019 [b]	<0.001 [b]
Long term treatment		132 (7.8%)	152 (3.7%)	-	<0.001 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		494 (28.7%)	1218 (29.1%)	673 (35.0%)	0.113 [b]	0.029 [b]
In women of child bearing potential:						
Pregnancy[4]		-	-	-	N/A [b]	N/A [b]
No contraceptive use[4]		262 (100.0%)	512 (100.0%)	255 (100.0%)	N/A [b]	N/A [b]
Lactation[4]		-	-	-	N/A [b]	N/A [b]
Off label use[5]	Missing (N)	361	791	341	0.795 [b]	0.973 [b]
	Yes	1021 (75.1%)	2461 (72.5%)	1167 (73.8%)		
	No	339 (24.9%)	932 (27.5%)	415 (26.2%)		

Baseline period[1]: year 2013
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
[4]: percentage based on women of child bearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-54: Summary of off label use of systemic TCC prescriptions – Cumulated study period years 1, 2 and 3 vs. baseline – GPs Italy – included patients

			Study period years 1, 2 and 3[2]			
		Baseline period[1] (N=23527)	Overall (N=54892)	Incident[3] (N=20674)	p-value Baseline vs Overall Study period years 1, 2 and 3	p-value Baseline vs Incident Study period years 1, 2 and 3
Age at prescription (years) <16 years		36 (0.2%)	32 (0.1%)	30 (0.1%)	0.010 [b]	0.765 [b]
No concomitant medications and/or health services, medical devices during systemic TCC use		3151 (13.4%)	6270 (11.4%)	2753 (13.3%)	<0.001 [b]	0.507 [b]
Oral form						
daily dose>16 mg per day		34 (1.3%)	62 (1.5%)	28 (1.5%)	0.087 [b]	0.391 [b]
duration >7 consecutive days		1239 (47.7%)	2258 (53.4%)	968 (52.1%)	<0.001 [b]	0.013 [b]
IM form						
daily dose>8 mg per day		4 (0.1%)	8 (0.1%)	2 (0.1%)	0.601 [b]	0.935 [b]
duration >5 consecutive days		3745 (87.2%)	8459 (88.4%)	2466 (87.8%)	0.035 [b]	0.097 [b]
Long term treatment		225 (1.1%)	380 (0.8%)	-	0.010 [b]	<0.001 [b]
Treatment indication: other than painful muscle contractures associated with acute spinal pathology		5236 (24.4%)	11247 (22.4%)	4562 (24.3%)	0.001 [b]	0.101 [b]
In women of child bearing potential:						
Pregnancy[4]		169 (3.9%)	349 (4.2%)	213 (4.9%)	0.744 [b]	0.077 [b]
No contraceptive use[4]		3982 (92.8%)	7934 (95.1%)	4121 (95.0%)	<0.001 [b]	<0.001 [b]
Lactation[4]		4 (0.1%)	3 (0.0%)	3 (0.1%)	0.331 [b]	0.750 [b]
Off label use[5]	Missing (N)	17903	43669	16783	0.011 [b]	0.184 [b]
	Yes	4754 (84.5%)	9713 (86.5%)	3310 (85.1%)		
	No	870 (15.5%)	1510 (13.5%)	581 (14.9%)		

Baseline period[1]: year 2013
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[3]: New TCC prescription in all patient history with at least one year of medical history
[4]: percentage based on women of child bearing potential
Off label use[5] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-55: Summary of off label use of systemic TCC (patients) at index date – GPs France – included patients

DUS TCC

		Baseline period[1] (N=34460)	Study period year 1[2] (N=37771)	Study period year 2[3] (N=34330)	Study period year 3[4] (N=23079)	Study period years 1, 2 and 3[5] (N=81690)
Detail of off label use[6]:						
	Age <16 years old	414 (1.2%)	264 (0.7%)	212 (0.6%)	106 (0.5%)	570 (0.7%)
	No concomitant medications and/or health services, medical devices	2347 (6.8%)	2905 (7.7%)	2597 (7.6%)	1885 (8.2%)	6485 (7.9%)
	Oral form: daily dose>16 mg per day	96 (0.3%)	73 (0.2%)	67 (0.2%)	34 (0.2%)	159 (0.2%)
	Oral form: >7 consecutive days	16142 (50.6%)	11452 (32.3%)	10473 (32.5%)	5699 (28.9%)	23357 (31.0%)
	IM form: daily dose>8 mg per day	286 (38.8%)	122 (23.9%)	83 (18.5%)	30 (10.1%)	210 (19.2%)
	IM form: >5 consecutive days	489 (71.4%)	257 (45.2%)	276 (54.7%)	168 (49.7%)	594 (48.5%)
	Long term treatment	-	-	-	-	-
	Indication: other than painful muscle contractures associated with acute spinal pathology	12663 (42.9%)	13719 (41.4%)	12096 (41.2%)	7996 (41.8%)	28116 (40.1%)
In women of child bearing potential:						
	N	11319 (100.0%)	11779 (100.0%)	10616 (100.0%)	6689 (100.0%)	25231 (100.0%)
	Pregnancy	71 (0.6%)	52 (0.4%)	32 (0.3%)	49 (0.7%)	108 (0.4%)
	Lactation	4 (0.0%)	3 (0.0%)	1 (0.0%)	1 (0.0%)	5 (0.0%)
	No contraceptive use	9831 (86.9%)	10597 (90.0%)	9516 (89.6%)	6154 (92.0%)	22854 (90.6%)
Off label use[6]	Missing (N)	7106	6954	6919	6668	17332
	Yes	20008 (73.1%)	18920 (61.4%)	16752 (61.1%)	9879 (60.2%)	38651 (60.1%)
	No	7346 (26.9%)	11897 (38.6%)	10659 (38.9%)	6532 (39.8%)	25707 (39.9%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-56: Summary of off label use of systemic TCC (patients) at index date – Rheumatologists France – included patients

DUS TCC

		Baseline period[1] (N=1383)	Study period year 1[2] (N=1247)	Study period year 2[3] (N=1185)	Study period year 3[4] (N=1063)	Study period years 1, 2 and 3[5] (N=3016)
Detail of off label use[6]:						
	Age <16 years old	-	-	-	1 (0.1%)	1 (0.0%)
	No concomitant medications and/or health services, medical devices	171 (12.4%)	160 (12.8%)	173 (14.6%)	123 (11.6%)	409 (13.6%)
	Oral form: daily dose>16 mg per day	-	-	-	-	-
	Oral form: >7 consecutive days	499 (55.1%)	389 (45.9%)	389 (51.5%)	316 (44.3%)	870 (44.2%)
	IM form: daily dose>8 mg per day	95 (38.2%)	60 (27.3%)	72 (28.2%)	76 (40.9%)	189 (30.8%)
	IM form: >5 consecutive days	164 (66.4%)	133 (60.5%)	147 (57.6%)	90 (48.4%)	343 (56.0%)
	Long term treatment	-	-	-	-	-
	Indication: other than painful muscle contractures associated with acute spinal pathology	396 (28.6%)	384 (30.8%)	354 (29.9%)	310 (29.2%)	940 (31.2%)
In women of child bearing potential:						
	N	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)
	Pregnancy	-	-	-	-	-
	Lactation	-	-	-	-	-
	No contraceptive use	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)
Off label use[6]	Missing (N)	312	234	220	207	547
	Yes	784 (73.2%)	717 (70.8%)	719 (74.5%)	587 (68.6%)	1737 (70.4%)
	No	287 (26.8%)	296 (29.2%)	246 (25.5%)	269 (31.4%)	732 (29.6%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-57: Summary of off label use of systemic TCC (patients) at index date – GPs Italy – included patients

DUS TCC **Page 1 of 1**

		Baseline period[1] (N=19877)	Study period year 1[2] (N=16140)	Study period year 2[3] (N=16201)	Study period year 3[4] (N=14957)	Study period years 1, 2 and 3[5] (N=41061)
Detail of off label use[6]:						
	Age <16 years old	34 (0.2%)	9 (0.1%)	13 (0.1%)	9 (0.1%)	30 (0.1%)
	No concomitant medications and/or health services, medical devices	2698 (13.6%)	1957 (12.1%)	1848 (11.4%)	1666 (11.1%)	4874 (11.9%)
	Oral form: daily dose>16 mg per day	27 (1.2%)	9 (0.7%)	25 (1.9%)	21 (1.8%)	48 (1.4%)
	Oral form: >7 consecutive days	1090 (47.7%)	750 (55.6%)	698 (53.2%)	592 (51.0%)	1826 (52.8%)
	IM form: daily dose>8 mg per day	4 (0.1%)	4 (0.1%)	2 (0.1%)	2 (0.1%)	7 (0.1%)
	IM form: >5 consecutive days	3050 (86.8%)	2417 (87.4%)	2484 (88.5%)	2215 (88.4%)	6033 (87.7%)
	Long term treatment	-	-	-	-	-
	Indication: other than painful muscle contractures associated with acute spinal pathology	4439 (24.5%)	3432 (23.2%)	3375 (22.8%)	3009 (22.1%)	8655 (23.1%)
In women of child bearing potential:						
	N	3782 (100.0%)	2617 (100.0%)	2616 (100.0%)	2275 (100.0%)	6788 (100.0%)
	Pregnancy	150 (4.0%)	121 (4.6%)	104 (4.0%)	92 (4.0%)	291 (4.3%)
	Lactation	3 (0.1%)	2 (0.1%)	1 (0.0%)	-	3 (0.0%)
	No contraceptive use	3513 (92.9%)	2440 (93.2%)	2501 (95.6%)	2186 (96.1%)	6439 (94.9%)
Off label use[6]	Missing (N)	15241	12780	12870	12011	32664
	Yes	3885 (83.8%)	2909 (86.6%)	2865 (86.0%)	2515 (85.4%)	7183 (85.5%)
	No	751 (16.2%)	451 (13.4%)	466 (14.0%)	431 (14.6%)	1214 (14.5%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-58: Summary of off label use of systemic TCC (patients) – GPs France – included patients

DUS TCC

		Baseline period[1] (N=34460)	Study period year 1[2] (N=37771)	Study period year 2[3] (N=34330)	Study period year 3[4] (N=23079)	Study period years 1, 2 and 3[5] (N=81690)
Detail of off label use[6]:						
	Age <16 years old	414 (1.2%)	264 (0.7%)	212 (0.6%)	106 (0.5%)	570 (0.7%)
	No concomitant medications and/or health services, medical devices	2637 (7.7%)	3260 (8.6%)	2903 (8.5%)	2065 (8.9%)	7971 (9.8%)
	Oral form: daily dose>16 mg per day	105 (0.3%)	78 (0.2%)	73 (0.2%)	36 (0.2%)	184 (0.2%)
	Oral form: >7 consecutive days	16741 (48.6%)	11987 (31.7%)	10904 (31.8%)	5939 (25.7%)	25310 (31.0%)
	IM form: daily dose>8 mg per day	300 (0.9%)	124 (0.3%)	86 (0.3%)	31 (0.1%)	229 (0.3%)
	IM form: >5 consecutive days	532 (1.5%)	289 (0.8%)	304 (0.9%)	177 (0.8%)	709 (0.9%)
	Long term treatment	1448 (4.2%)	1178 (3.1%)	1030 (3.0%)	627 (2.7%)	2655 (3.3%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	13960 (40.5%)	15305 (40.5%)	13448 (39.2%)	8834 (38.3%)	33535 (41.1%)
In women of child bearing potential:						
	N	11319 (100.0%)	11779 (100.0%)	10616 (100.0%)	6689 (100.0%)	25231 (100.0%)
	Pregnancy	73 (0.6%)	57 (0.5%)	35 (0.3%)	53 (0.8%)	146 (0.6%)
	Lactation	6 (0.1%)	3 (0.0%)	1 (0.0%)	1 (0.0%)	5 (0.0%)
	No contraceptive use	9897 (87.4%)	10654 (90.4%)	9565 (90.1%)	6174 (92.3%)	23180 (91.9%)
Off label use[6]	Missing (N)	7944	7854	7746	7396	21175
	Yes	19878 (75.0%)	19193 (64.2%)	16929 (63.7%)	9776 (62.3%)	38928 (64.3%)
	No	6638 (25.0%)	10724 (35.8%)	9655 (36.3%)	5907 (37.7%)	21587 (35.7%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-59: Summary of off label use of systemic TCC (patients) – Rheumatologists France – included patients

DUS TCC

		Baseline period[1] (N=1383)	Study period year 1[2] (N=1247)	Study period year 2[3] (N=1185)	Study period year 3[4] (N=1063)	Study period years 1, 2 and 3[5] (N=3016)
Detail of off label use[6]:						
	Age <16 years old	-	-	-	1 (0.1%)	1 (0.0%)
	No concomitant medications and/or health services, medical devices	181 (13.1%)	170 (13.6%)	182 (15.4%)	129 (12.1%)	462 (15.3%)
	Oral form: daily dose>16 mg per day	-	-	-	-	-
	Oral form: >7 consecutive days	520 (37.6%)	403 (32.3%)	397 (33.5%)	324 (30.5%)	930 (30.8%)
	IM form: daily dose>8 mg per day	98 (7.1%)	64 (5.1%)	75 (6.3%)	78 (7.3%)	206 (6.8%)
	IM form: >5 consecutive days	172 (12.4%)	133 (10.7%)	149 (12.6%)	93 (8.7%)	357 (11.8%)
	Long term treatment	94 (6.8%)	46 (3.7%)	29 (2.4%)	28 (2.6%)	85 (2.8%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	405 (29.3%)	390 (31.3%)	359 (30.3%)	315 (29.6%)	980 (32.5%)
In women of child bearing potential:						
	N	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)
	Pregnancy	-	-	-	-	-
	Lactation	-	-	-	-	-
	No contraceptive use	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)
Off label use[6]	Missing (N)	313	236	222	211	564
	Yes	801 (74.9%)	726 (71.8%)	724 (75.2%)	594 (69.7%)	1769 (72.1%)
	No	269 (25.1%)	285 (28.2%)	239 (24.8%)	258 (30.3%)	683 (27.9%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_09.sas; By: Alampure; Date & time: 29AUG19 09:31;

Table 15.3-60: Summary of off label use of systemic TCC (patients) – GPs Italy – included patients

DUS TCC **Page 1 of 1**

		Baseline period[1] (N=19877)	Study period year 1[2] (N=16140)	Study period year 2[3] (N=16201)	Study period year 3[4] (N=14957)	Study period years 1, 2 and 3[5] (N=41061)
Detail of off label use[6]:						
	Age <16 years old	34 (0.2%)	9 (0.1%)	13 (0.1%)	9 (0.1%)	30 (0.1%)
	No concomitant medications and/or health services, medical devices	2957 (14.9%)	2140 (13.3%)	2034 (12.6%)	1817 (12.1%)	5757 (14.0%)
	Oral form: daily dose>16 mg per day	30 (0.2%)	9 (0.1%)	26 (0.2%)	22 (0.1%)	54 (0.1%)
	Oral form: >7 consecutive days	1148 (5.8%)	784 (4.9%)	732 (4.5%)	620 (4.1%)	2018 (4.9%)
	IM form: daily dose>8 mg per day	4 (0.0%)	4 (0.0%)	2 (0.0%)	2 (0.0%)	7 (0.0%)
	IM form: >5 consecutive days	3160 (15.9%)	2465 (15.3%)	2539 (15.7%)	2264 (15.1%)	6340 (15.4%)
	Long term treatment	208 (1.0%)	117 (0.7%)	124 (0.8%)	112 (0.7%)	348 (0.8%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	4604 (23.2%)	3545 (22.0%)	3492 (21.6%)	3107 (20.8%)	9411 (22.9%)
In women of child bearing potential:						
	N	3782 (100.0%)	2617 (100.0%)	2616 (100.0%)	2275 (100.0%)	6788 (100.0%)
	Pregnancy	156 (4.1%)	125 (4.8%)	108 (4.1%)	95 (4.2%)	317 (4.7%)
	Lactation	3 (0.1%)	2 (0.1%)	1 (0.0%)	-	3 (0.0%)
	No contraceptive use	3522 (93.1%)	2448 (93.5%)	2501 (95.6%)	2189 (96.2%)	6474 (95.4%)
Off label use[6]	Missing (N)	15325	12834	12928	12051	32999
	Yes	3860 (84.8%)	2876 (87.0%)	2838 (86.7%)	2500 (86.0%)	6975 (86.5%)
	No	692 (15.2%)	430 (13.0%)	435 (13.3%)	406 (14.0%)	1087 (13.5%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-61: Summary of off label use of systemic TCC in TCC prescribers – GPs France – included patients

		Baseline period[1] (N=1002)	Study period year 1[2] (N=1026)	Study period year 2[3] (N=972)	Study period year 3[4] (N=896)	Study period years 1, 2 and 3[5] (N=1143)
Detail of off label use (at least one off-label use):						
	Age <16 years old	319 (31.8%)	185 (18.0%)	166 (17.1%)	91 (10.2%)	317 (27.7%)
	No concomitant medications and/or health services, medical devices	742 (74.1%)	766 (74.7%)	737 (75.8%)	635 (70.9%)	991 (86.7%)
	Oral form: daily dose>16 mg per day	50 (5.0%)	33 (3.2%)	48 (4.9%)	32 (3.6%)	90 (7.9%)
	IM form: daily dose>8 mg per day	71 (7.1%)	24 (2.3%)	16 (1.6%)	13 (1.5%)	37 (3.2%)
	Oral form: >7 consecutive days	866 (86.4%)	797 (77.7%)	730 (75.1%)	632 (70.5%)	959 (83.9%)
	IM form: >5 consecutive days	135 (13.5%)	82 (8.0%)	86 (8.8%)	60 (6.7%)	134 (11.7%)
	Long term treatment	529 (52.8%)	475 (46.3%)	426 (43.8%)	320 (35.7%)	678 (59.3%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	921 (91.9%)	950 (92.6%)	909 (93.5%)	805 (89.8%)	1090 (95.4%)
In women of child bearing potential:						
	Pregnancy	83 (8.3%)	68 (6.6%)	51 (5.2%)	75 (8.4%)	154 (13.5%)
	Lactation	5 (0.5%)	2 (0.2%)	1 (0.1%)	2 (0.2%)	5 (0.4%)
	No contraceptive use	1001 (99.9%)	1023 (99.7%)	972 (100.0%)	895 (99.9%)	1141 (99.8%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

Table 15.3-62: Summary of off label use of systemic TCC in TCC prescribers – Rheumatologists France – included patients

		Baseline period[1] (N=75)	Study period year 1[2] (N=81)	Study period year 2[3] (N=80)	Study period year 3[4] (N=72)	Study period years 1, 2 and 3[5] (N=92)
Detail of off label use (at least one off-label use):						
	Age <16 years old	3 (4.0%)	1 (1.2%)	1 (1.3%)	2 (2.8%)	4 (4.3%)
	No concomitant medications/and or health health services, medical devices	55 (73.3%)	65 (80.2%)	56 (70.0%)	49 (68.1%)	82 (89.1%)
	Oral form: daily dose>16 mg per day	-	2 (2.5%)	-	-	2 (2.2%)
	IM form: daily dose>8 mg per day	41 (54.7%)	44 (54.3%)	40 (50.0%)	36 (50.0%)	61 (66.3%)
	Oral form: >7 consecutive days	62 (82.7%)	50 (61.7%)	48 (60.0%)	41 (56.9%)	63 (68.5%)
	IM form: >5 consecutive days	34 (45.3%)	32 (39.5%)	39 (48.8%)	28 (38.9%)	49 (53.3%)
	Long term treatment	27 (36.0%)	20 (24.7%)	14 (17.5%)	17 (23.6%)	31 (33.7%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	66 (88.0%)	69 (85.2%)	68 (85.0%)	57 (79.2%)	83 (90.2%)
In women of child bearing potential:						
	Pregnancy	-	-	-	-	-
	Lactation	-	-	-	-	-
	No contraceptive use	75 (100.0%)	81 (100.0%)	80 (100.0%)	72 (100.0%)	92 (100.0%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-63: Summary of off label use of systemic TCC in TCC prescribers – GPs Italy – included patients

DUS TCC **Page 1 of 1**

		Baseline period[1] (N=593)	Study period year 1[2] (N=588)	Study period year 2[3] (N=592)	Study period year 3[4] (N=585)	Study period years 1, 2 and 3[5] (N=615)
Detail of off label use (at least one off-label use):						
	Age <16 years old	33 (5.6%)	13 (2.2%)	18 (3.0%)	13 (2.2%)	39 (6.3%)
	No concomitant medications/and or health health services, medical devices	504 (85.0%)	472 (80.3%)	465 (78.5%)	434 (74.2%)	567 (92.2%)
	Oral form: daily dose>16 mg per day	13 (2.2%)	6 (1.0%)	6 (1.0%)	5 (0.9%)	13 (2.1%)
	IM form: daily dose>8 mg per day	4 (0.7%)	3 (0.5%)	2 (0.3%)	2 (0.3%)	6 (1.0%)
	Oral form: >7 consecutive days	202 (34.1%)	174 (29.6%)	171 (28.9%)	151 (25.8%)	247 (40.2%)
	IM form: >5 consecutive days	241 (40.6%)	221 (37.6%)	212 (35.8%)	214 (36.6%)	275 (44.7%)
	Long term treatment	100 (16.9%)	72 (12.2%)	63 (10.6%)	62 (10.6%)	124 (20.2%)
	Indication: other than painful muscle contractures associated with acute spinal pathology	534 (90.1%)	518 (88.1%)	520 (87.8%)	493 (84.3%)	587 (95.4%)
In women of child bearing potential:						
	Pregnancy	123 (20.7%)	95 (16.2%)	97 (16.4%)	89 (15.2%)	199 (32.4%)
	Lactation	3 (0.5%)	2 (0.3%)	1 (0.2%)	-	3 (0.5%)
	No contraceptive use	593 (100.0%)	588 (100.0%)	592 (100.0%)	585 (100.0%)	615 (100.0%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period year 3[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[6] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential

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Table 15.3-64: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 1 vs. baseline – GPs France – included patients

		Baseline period[1] (N=34460)	Study period year 1[2] (N=37771)	p-value
Age (years)	N	34442 (99.9)	37766 (100.0)	<0.001 [c]
	Missing (N)	18 (0.1)	5 (0.0)	
	Mean (SD)	45.9 (15.89)	46.8 (15.69)	
	Median (Q1 - Q3)	46.0 (34.0-57.0)	46.0 (35.0-57.0)	
	Range	(2.0,98.0)	(2.0,100.0)	
Age (years) -classes	Missing (N)	18	5	<0.001 [b]
	<16 years	414 (1.2%)	264 (0.7%)	
	[16;30[	5273 (15.3%)	5381 (14.2%)	
	[30;40[	6517 (18.9%)	7006 (18.6%)	
	[40;50[	8321 (24.2%)	8931 (23.6%)	
	[50;60[	7088 (20.6%)	8092 (21.4%)	
	[60;70[	4140 (12.0%)	5006 (13.3%)	
	≥70 years	2689 (7.8%)	3086 (8.2%)	
Gender	Missing (N)	25	-	0.005 [b]
	Male	14907 (43.3%)	16743 (44.3%)	
	Female	19528 (56.7%)	21028 (55.7%)	
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	37771 (100.0)	0.751 [c]
	Mean (SD)	1.0 (0.04)	1.0 (0.04)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes	1	34412 (99.9%)	37715 (99.9%)	0.751 [b]
	2	48 (0.1%)	56 (0.1%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

		Baseline period[1] (N=34460)	Study period year 1[2] (N=37771)	p-value
Off label use[3]	Missing (N)	7106	6954	<0.001 [b]
	Yes	20008 (73.1%)	18920 (61.4%)	
	No	7346 (26.9%)	11897 (38.6%)	
If yes, detail of off label use:				
Age <16 years old	Yes	318 (1.6%)	227 (1.2%)	0.001 [b]
	No	19690 (98.4%)	18693 (98.8%)	
No concomitant medications/ and or health health services, medical devices	Yes	1757 (8.8%)	2163 (11.4%)	<0.001 [b]
	No	18251 (91.2%)	16757 (88.6%)	
Oral form: daily dose>16 mg per day	Yes	87 (0.4%)	61 (0.3%)	0.065 [b]
	No	19474 (99.6%)	18557 (99.7%)	
IM form: daily dose>8 mg per day	Yes	171 (37.8%)	104 (33.1%)	0.180 [b]
	No	281 (62.2%)	210 (66.9%)	
Oral form: >7 consecutive days	Yes	13913 (71.1%)	9912 (53.2%)	<0.001 [b]
	No	5648 (28.9%)	8706 (46.8%)	
IM form: >5 consecutive days	Yes	384 (85.0%)	200 (63.7%)	<0.001 [b]
	No	68 (15.0%)	114 (36.3%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	11625 (58.1%)	12662 (66.9%)	<0.001 [b]
	No	8383 (41.9%)	6258 (33.1%)	
In women of child bearing potential:				
N	Yes	6532 (100.0%)	5813 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	59 (0.9%)	46 (0.8%)	0.498 [b]
	No	6473 (99.1%)	5767 (99.2%)	
Lactation	Yes	3 (0.0%)	3 (0.1%)	0.886 [b]
	No	6529 (100.0%)	5810 (99.9%)	
No contraceptive use	Yes	5644 (86.4%)	5182 (89.1%)	<0.001 [b]
	No	888 (13.6%)	631 (10.9%)	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test
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Table 15.3-65: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 1 vs. baseline – Rheumatologists France – included patients

		Baseline period[1] (N=1383)	Study period year 1[2] (N=1247)	p-value
Age (years)	N	1383 (100.0)	1246 (99.9)	0.002 [c]
	Missing (N)	0	1 (0.1)	
	Mean (SD)	60.3 (14.41)	62.1 (14.30)	
	Median (Q1 - Q3)	61.0 (50.0-72.0)	62.0 (52.0-72.0)	
	Range	(16.0,98.0)	(19.0,94.0)	
Age (years) -classes	Missing (N)	-	1	0.142 [b]
	<16 years	-	-	
	[16;30[	21 (1.5%)	12 (1.0%)	
	[30;40[	82 (5.9%)	69 (5.5%)	
	[40;50[	222 (16.1%)	164 (13.2%)	
	[50;60[	330 (23.9%)	288 (23.1%)	
	[60;70[	333 (24.1%)	330 (26.5%)	
	≥70 years	395 (28.6%)	383 (30.7%)	
Gender	Missing (N)	91	60	0.590 [b]
	Male	396 (30.7%)	352 (29.7%)	
	Female	896 (69.3%)	835 (70.3%)	
Number of systemic TCC prescriptions per patient				0.274 [c]
	N	1383 (100.0)	1247 (100.0)	
	Mean (SD)	1.0 (0.08)	1.0 (0.06)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes				0.268 [b]
	1	1373 (99.3%)	1242 (99.6%)	
	2	10 (0.7%)	5 (0.4%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_11_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:20;

		Baseline period[1] (N=1383)	Study period year 1[2] (N=1247)	p-value
Off label use[3]	Missing (N)	312	234	0.218 [b]
	Yes	784 (73.2%)	717 (70.8%)	
	No	287 (26.8%)	296 (29.2%)	
If yes, detail of off label use:				
Age <16 years old	Yes	-	-	N/A [b]
	No	784 (100.0%)	717 (100.0%)	
No concomitant medications/ and or health health services, medical devices	Yes	137 (17.5%)	146 (20.4%)	0.153 [b]
	No	647 (82.5%)	571 (79.6%)	
Oral form: daily dose>16 mg per day	Yes	-	-	N/A [b]
	No	566 (100.0%)	524 (100.0%)	
IM form: daily dose>8 mg per day	Yes	87 (39.7%)	54 (28.0%)	0.012 [b]
	No	132 (60.3%)	139 (72.0%)	
Oral form: >7 consecutive days	Yes	447 (79.0%)	360 (68.7%)	<0.001 [b]
	No	119 (21.0%)	164 (31.3%)	
IM form: >5 consecutive days	Yes	159 (72.6%)	129 (66.8%)	0.203 [b]
	No	60 (27.4%)	64 (33.2%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	310 (39.5%)	317 (44.2%)	0.067 [b]
	No	474 (60.5%)	400 (55.8%)	
In women of child bearing potential:				
N	Yes	120 (100.0%)	90 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	-	-	N/A [b]
	No	120 (100.0%)	90 (100.0%)	
Lactation	Yes	-	-	N/A [b]
	No	120 (100.0%)	90 (100.0%)	
No contraceptive use	Yes	120 (100.0%)	90 (100.0%)	N/A [b]
	No	-	-	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_11_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:20;

Table 15.3-66: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 1 vs. baseline – GPs Italy – included patients

		Baseline period[1] (N=19877)	Study period year 1[2] (N=16140)	p-value
Age (years)	N	19865 (99.9)	16128 (99.9)	<0.001 [c]
	Missing (N)	12 (0.1)	12 (0.1)	
	Mean (SD)	55.4 (15.93)	56.7 (15.49)	
	Median (Q1 - Q3)	55.0 (44.0-67.0)	56.0 (46.0-68.0)	
	Range	(12.0,101.0)	(11.0,101.0)	
Age (years) -classes	Missing (N)	12	12	<0.001 [b]
	<16 years	34 (0.2%)	9 (0.1%)	
	[16;30[	1002 (5.0%)	683 (4.2%)	
	[30;40[	2263 (11.4%)	1543 (9.6%)	
	[40;50[	4156 (20.9%)	3130 (19.4%)	
	[50;60[	4388 (22.1%)	3811 (23.6%)	
	[60;70[	3752 (18.9%)	3298 (20.4%)	
	≥70 years	4270 (21.5%)	3654 (22.7%)	
Gender	Missing (N)	2894	2297	0.003 [b]
	Male	6081 (35.8%)	5185 (37.5%)	
	Female	10902 (64.2%)	8658 (62.5%)	
Number of systemic TCC prescriptions per patient				<0.001 [c]
	N	19877 (100.0)	16140 (100.0)	
	Mean (SD)	1.0 (0.09)	1.0 (0.07)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes				<0.001 [b]
	1	19699 (99.1%)	16051 (99.4%)	
	2	178 (0.9%)	89 (0.6%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_11_01.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Baseline period[1] (N=19877)	Study period year 1[2] (N=16140)	p-value
Off label use[3]	Missing (N)	15241	12780	<0.001 [b]
	Yes	3885 (83.8%)	2909 (86.6%)	
	No	751 (16.2%)	451 (13.4%)	
If yes, detail of off label use:				
Age <16 years old	Yes	15 (0.4%)	2 (0.1%)	0.005 [b]
	No	3870 (99.6%)	2907 (99.9%)	
No concomitant medications/ and or health health services, medical devices	Yes	629 (16.2%)	408 (14.0%)	0.014 [b]
	No	3256 (83.8%)	2501 (86.0%)	
Oral form: daily dose>16 mg per day	Yes	26 (1.9%)	8 (0.9%)	0.055 [b]
	No	1345 (98.1%)	865 (99.1%)	
IM form: daily dose>8 mg per day	Yes	4 (0.2%)	4 (0.2%)	0.756 [b]
	No	2549 (99.8%)	2046 (99.8%)	
Oral form: >7 consecutive days	Yes	865 (63.1%)	637 (73.0%)	<0.001 [b]
	No	506 (36.9%)	236 (27.0%)	
IM form: >5 consecutive days	Yes	2444 (95.7%)	1968 (96.0%)	0.648 [b]
	No	109 (4.3%)	82 (4.0%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	1217 (31.3%)	793 (27.3%)	<0.001 [b]
	No	2668 (68.7%)	2116 (72.7%)	
In women of child bearing potential:				
N	Yes	881 (100.0%)	560 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	40 (4.5%)	29 (5.2%)	0.582 [b]
	No	841 (95.5%)	531 (94.8%)	
Lactation	Yes	1 (0.1%)	-	0.321 [b]
	No	880 (99.9%)	560 (100.0%)	
No contraceptive use	Yes	820 (93.1%)	525 (93.8%)	0.616 [b]
	No	61 (6.9%)	35 (6.3%)	

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Table 15.3-67: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 2 vs. baseline – GPs France – included patients

		Baseline period[1] (N=34460)	Study period year 2[2] (N=34330)	p-value
Age (years)	N	34442 (99.9)	34317 (100.0)	<0.001 [c]
	Missing (N)	18 (0.1)	13 (0.0)	
	Mean (SD)	45.9 (15.89)	47.1 (15.69)	
	Median (Q1 - Q3)	46.0 (34.0-57.0)	47.0 (36.0-58.0)	
	Range	(2.0,98.0)	(3.0,98.0)	
Age (years) -classes	Missing (N)	18	13	<0.001 [b]
	<16 years	414 (1.2%)	212 (0.6%)	
	[16;30[	5273 (15.3%)	4704 (13.7%)	
	[30;40[	6517 (18.9%)	6378 (18.6%)	
	[40;50[	8321 (24.2%)	8080 (23.5%)	
	[50;60[	7088 (20.6%)	7461 (21.7%)	
	[60;70[	4140 (12.0%)	4592 (13.4%)	
	≥70 years	2689 (7.8%)	2890 (8.4%)	
Gender	Missing (N)	25	-	0.009 [b]
	Male	14907 (43.3%)	15200 (44.3%)	
	Female	19528 (56.7%)	19130 (55.7%)	
Number of systemic TCC prescriptions per patient				0.403 [c]
	N	34460 (100.0)	34330 (100.0)	
	Mean (SD)	1.0 (0.04)	1.0 (0.03)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes				0.403 [b]
	1	34412 (99.9%)	34290 (99.9%)	
	2	48 (0.1%)	40 (0.1%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=34460)	Study period year 2[2] (N=34330)	p-value
Off label use[3]	Missing (N)	7106	6919	<0.001 [b]
	Yes	20008 (73.1%)	16752 (61.1%)	
	No	7346 (26.9%)	10659 (38.9%)	
If yes, detail of off label use:				
Age <16 years old	Yes	318 (1.6%)	174 (1.0%)	<0.001 [b]
	No	19690 (98.4%)	16578 (99.0%)	
No concomitant medications/ and or health health services, medical devices	Yes	1757 (8.8%)	1948 (11.6%)	<0.001 [b]
	No	18251 (91.2%)	14804 (88.4%)	
Oral form: daily dose>16 mg per day	Yes	87 (0.4%)	52 (0.3%)	0.046 [b]
	No	19474 (99.6%)	16464 (99.7%)	
IM form: daily dose>8 mg per day	Yes	171 (37.8%)	63 (26.0%)	0.002 [b]
	No	281 (62.2%)	179 (74.0%)	
Oral form: >7 consecutive days	Yes	13913 (71.1%)	8837 (53.5%)	<0.001 [b]
	No	5648 (28.9%)	7679 (46.5%)	
IM form: >5 consecutive days	Yes	384 (85.0%)	191 (78.9%)	0.047 [b]
	No	68 (15.0%)	51 (21.1%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	11625 (58.1%)	11157 (66.6%)	<0.001 [b]
	No	8383 (41.9%)	5595 (33.4%)	
In women of child bearing potential:				
N	Yes	6532 (100.0%)	5170 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	59 (0.9%)	27 (0.5%)	0.015 [b]
	No	6473 (99.1%)	5143 (99.5%)	
Lactation	Yes	3 (0.0%)	1 (0.0%)	0.426 [b]
	No	6529 (100.0%)	5169 (100.0%)	
No contraceptive use	Yes	5644 (86.4%)	4585 (88.7%)	<0.001 [b]
	No	888 (13.6%)	585 (11.3%)	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test
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Table 15.3-68: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 2 vs. baseline – Rheumatologists France – included patients

		Baseline period[1] (N=1383)	Study period year 2[2] (N=1185)	p-value
Age (years)	N	1383 (100.0)	1184 (99.9)	<0.001 [c]
	Missing (N)	0	1 (0.1)	
	Mean (SD)	60.3 (14.41)	62.8 (14.37)	
	Median (Q1 - Q3)	61.0 (50.0-72.0)	63.0 (53.0-73.5)	
	Range	(16.0,98.0)	(17.0,97.0)	
Age (years) -classes	Missing (N)	-	1	0.005 [b]
	<16 years	-	-	
	[16;30[	21 (1.5%)	13 (1.1%)	
	[30;40[	82 (5.9%)	57 (4.8%)	
	[40;50[	222 (16.1%)	149 (12.6%)	
	[50;60[	330 (23.9%)	270 (22.8%)	
	[60;70[	333 (24.1%)	279 (23.6%)	
	≥70 years	395 (28.6%)	416 (35.1%)	
Gender	Missing (N)	91	56	0.014 [b]
	Male	396 (30.7%)	295 (26.1%)	
	Female	896 (69.3%)	834 (73.9%)	
Number of systemic TCC prescriptions per patient				0.487 [c]
	N	1383 (100.0)	1185 (100.0)	
	Mean (SD)	1.0 (0.08)	1.0 (0.07)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes				0.483 [b]
	1	1373 (99.3%)	1179 (99.5%)	
	2	10 (0.7%)	6 (0.5%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=1383)	Study period year 2[2] (N=1185)	p-value
Off label use[3]	Missing (N)	312	220	0.503 [b]
	Yes	784 (73.2%)	719 (74.5%)	
	No	287 (26.8%)	246 (25.5%)	
If yes, detail of off label use:				
Age <16 years old	Yes	-	-	N/A [b]
	No	784 (100.0%)	719 (100.0%)	
No concomitant medications/ and or health health services, medical devices	Yes	137 (17.5%)	160 (22.3%)	0.020 [b]
	No	647 (82.5%)	559 (77.7%)	
Oral form: daily dose>16 mg per day	Yes	-	-	N/A [b]
	No	566 (100.0%)	492 (100.0%)	
IM form: daily dose>8 mg per day	Yes	87 (39.7%)	69 (30.1%)	0.033 [b]
	No	132 (60.3%)	160 (69.9%)	
Oral form: >7 consecutive days	Yes	447 (79.0%)	370 (75.2%)	0.145 [b]
	No	119 (21.0%)	122 (24.8%)	
IM form: >5 consecutive days	Yes	159 (72.6%)	144 (62.9%)	0.028 [b]
	No	60 (27.4%)	85 (37.1%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	310 (39.5%)	285 (39.6%)	0.969 [b]
	No	474 (60.5%)	434 (60.4%)	
In women of child bearing potential:				
N	Yes	120 (100.0%)	96 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	-	-	N/A [b]
	No	120 (100.0%)	96 (100.0%)	
Lactation	Yes	-	-	N/A [b]
	No	120 (100.0%)	96 (100.0%)	
No contraceptive use	Yes	120 (100.0%)	96 (100.0%)	N/A [b]
	No	-	-	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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Table 15.3-69: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 2 vs. baseline – GPs Italy – included patients

DUS TCC

		Baseline period[1] (N=19877)	Study period year 2[2] (N=16201)	p-value
Age (years)	N	19865 (99.9)	16184 (99.9)	<0.001 [c]
	Missing (N)	12 (0.1)	17 (0.1)	
	Mean (SD)	55.4 (15.93)	56.9 (15.62)	
	Median (Q1 - Q3)	55.0 (44.0-67.0)	57.0 (46.0-69.0)	
	Range	(12.0,101.0)	(12.0,103.0)	
Age (years) -classes	Missing (N)	12	17	<0.001 [b]
	<16 years	34 (0.2%)	13 (0.1%)	
	[16;30[	1002 (5.0%)	729 (4.5%)	
	[30;40[	2263 (11.4%)	1493 (9.2%)	
	[40;50[	4156 (20.9%)	3076 (19.0%)	
	[50;60[	4388 (22.1%)	3734 (23.1%)	
	[60;70[	3752 (18.9%)	3330 (20.6%)	
	≥70 years	4270 (21.5%)	3809 (23.5%)	
Gender	Missing (N)	2894	2360	0.118 [b]
	Male	6081 (35.8%)	5075 (36.7%)	
	Female	10902 (64.2%)	8766 (63.3%)	
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	16201 (100.0)	<0.001 [c]
	Mean (SD)	1.0 (0.09)	1.0 (0.07)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient-classes	1	19699 (99.1%)	16128 (99.5%)	<0.001 [b]
	2	178 (0.9%)	73 (0.5%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_11_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

		Baseline period[1] (N=19877)	Study period year 2[2] (N=16201)	p-value
Off label use[3]	Missing (N)	15241	12870	0.007 [b]
	Yes	3885 (83.8%)	2865 (86.0%)	
	No	751 (16.2%)	466 (14.0%)	
If yes, detail of off label use:				
Age <16 years old	Yes	15 (0.4%)	6 (0.2%)	0.188 [b]
	No	3870 (99.6%)	2859 (99.8%)	
No concomitant medications/ and or health health services, medical devices	Yes	629 (16.2%)	356 (12.4%)	<0.001 [b]
	No	3256 (83.8%)	2509 (87.6%)	
Oral form: daily dose>16 mg per day	Yes	26 (1.9%)	22 (2.7%)	0.209 [b]
	No	1345 (98.1%)	785 (97.3%)	
IM form: daily dose>8 mg per day	Yes	4 (0.2%)	2 (0.1%)	0.569 [b]
	No	2549 (99.8%)	2066 (99.9%)	
Oral form: >7 consecutive days	Yes	865 (63.1%)	588 (72.9%)	<0.001 [b]
	No	506 (36.9%)	219 (27.1%)	
IM form: >5 consecutive days	Yes	2444 (95.7%)	2013 (97.3%)	0.003 [b]
	No	109 (4.3%)	55 (2.7%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	1217 (31.3%)	725 (25.3%)	<0.001 [b]
	No	2668 (68.7%)	2140 (74.7%)	
In women of child bearing potential:				
N	Yes	881 (100.0%)	513 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	40 (4.5%)	24 (4.7%)	0.906 [b]
	No	841 (95.5%)	489 (95.3%)	
Lactation	Yes	1 (0.1%)	-	0.338 [b]
	No	880 (99.9%)	513 (100.0%)	
No contraceptive use	Yes	820 (93.1%)	496 (96.7%)	0.003 [b]
	No	61 (6.9%)	17 (3.3%)	

Baseline period[1]: year 2013
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test
Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_11_02.sas; By: Ncoulombel; Date & time: 04OCT18 12:24;

Table 15.3-70: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 3 vs. baseline – GPs France – included patients

DUS TCC

		Baseline period[1] (N=34460)	Study period year 3[2] (N=23079)	p-value
Age (years)	N	34442 (99.9)	23073 (100.0)	<0.001 [c]
	Missing (N)	18 (0.1)	6 (0.0)	
	Mean (SD)	45.9 (15.89)	48.3 (15.86)	
	Median (Q1 - Q3)	46.0 (34.0-57.0)	48.0 (37.0-59.0)	
	Range	(2.0,98.0)	(2.0,97.0)	
Age (years) - classes	Missing (N)	18	6	<0.001 [b]
	<16 years	414 (1.2%)	106 (0.5%)	
	[16;30[	5273 (15.3%)	2862 (12.4%)	
	[30;40[	6517 (18.9%)	4177 (18.1%)	
	[40;50[	8321 (24.2%)	5230 (22.7%)	
	[50;60[	7088 (20.6%)	5111 (22.2%)	
	[60;70[	4140 (12.0%)	3221 (14.0%)	
	≥70 years	2689 (7.8%)	2366 (10.3%)	
Gender	Missing (N)	25	1	0.024 [b]
	Male	14907 (43.3%)	10211 (44.2%)	
	Female	19528 (56.7%)	12867 (55.8%)	
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	23079 (100.0)	0.467 [c]
	Mean (SD)	1.0 (0.04)	1.0 (0.03)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes				0.465 [b]
	1	34412 (99.9%)	23052 (99.9%)	
	2	48 (0.1%)	27 (0.1%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_11_02.sas; By: Alampure; Date & time: 19AUG19 09:36;

		Baseline period[1] (N=34460)	Study period year 3[2] (N=23079)	p-value
Off label use[3]	Missing (N)	7106	6668	<0.001 [b]
	Yes	20008 (73.1%)	9879 (60.2%)	
	No	7346 (26.9%)	6532 (39.8%)	
If yes, detail of off label use:				
Age <16 years old	Yes	318 (1.6%)	72 (0.7%)	<0.001 [b]
	No	19690 (98.4%)	9807 (99.3%)	
No concomitant medications and/or health services, medical devices	Yes	1757 (8.8%)	1250 (12.7%)	<0.001 [b]
	No	18251 (91.2%)	8629 (87.3%)	
Oral form: daily dose>16 mg per day	Yes	87 (0.4%)	17 (0.2%)	<0.001 [b]
	No	19474 (99.6%)	9689 (99.8%)	
IM form: daily dose>8 mg per day	Yes	171 (37.8%)	25 (14.3%)	<0.001 [b]
	No	281 (62.2%)	150 (85.7%)	
Oral form: >7 consecutive days	Yes	13913 (71.1%)	4705 (48.5%)	<0.001 [b]
	No	5648 (28.9%)	5001 (51.5%)	
IM form: >5 consecutive days	Yes	384 (85.0%)	137 (78.3%)	0.050 [b]
	No	68 (15.0%)	38 (21.7%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	11625 (58.1%)	6848 (69.3%)	<0.001 [b]
	No	8383 (41.9%)	3031 (30.7%)	
In women of child bearing potential[4]:				
N	Yes	6532 (100.0%)	2845 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	59 (0.9%)	34 (1.2%)	0.197 [b]
	No	6473 (99.1%)	2811 (98.8%)	
Lactation	Yes	3 (0.0%)	1 (0.0%)	0.813 [b]
	No	6529 (100.0%)	2844 (100.0%)	
No contraceptive use	Yes	5644 (86.4%)	2599 (91.4%)	<0.001 [b]
	No	888 (13.6%)	246 (8.6%)	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_11_02.sas; By: Alampure; Date & time: 19AUG19 09:36;

Table 15.3-71: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 3 vs. baseline – Rheumatologists France – included patients

DUS TCC

		Baseline period[1] (N=1383)	Study period year 3[2] (N=1063)	p-value
Age (years)	N	1383 (100.0)	1062 (99.9)	<0.001 [c]
	Missing (N)	0	1 (0.1)	
	Mean (SD)	60.3 (14.41)	62.7 (14.54)	
	Median (Q1 - Q3)	61.0 (50.0-72.0)	63.0 (53.0-73.0)	
	Range	(16.0,98.0)	(14.0,98.0)	
Age (years) - classes	Missing (N)	-	1	0.004 [b]
	<16 years	-	1 (0.1%)	
	[16;30[	21 (1.5%)	17 (1.6%)	
	[30;40[	82 (5.9%)	44 (4.1%)	
	[40;50[	222 (16.1%)	133 (12.5%)	
	[50;60[	330 (23.9%)	250 (23.5%)	
	[60;70[	333 (24.1%)	244 (23.0%)	
	≥70 years	395 (28.6%)	373 (35.1%)	
Gender	Missing (N)	91	43	0.074 [b]
	Male	396 (30.7%)	278 (27.3%)	
	Female	896 (69.3%)	742 (72.7%)	
Number of systemic TCC prescriptions per patient				0.554 [c]
	N	1383 (100.0)	1063 (100.0)	
	Mean (SD)	1.0 (0.08)	1.0 (0.10)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes				0.555 [b]
	1	1373 (99.3%)	1053 (99.1%)	
	2	10 (0.7%)	10 (0.9%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=1383)	Study period year 3[2] (N=1063)	p-value
Off label use[3]	Missing (N)	312	207	0.026 [b]
	Yes	784 (73.2%)	587 (68.6%)	
	No	287 (26.8%)	269 (31.4%)	
If yes, detail of off label use:				
Age <16 years old	Yes	-	1 (0.2%)	0.193 [b]
	No	784 (100.0%)	586 (99.8%)	
No concomitant medications and/or health services, medical devices	Yes	137 (17.5%)	110 (18.7%)	0.547 [b]
	No	647 (82.5%)	477 (81.3%)	
Oral form: daily dose>16 mg per day	Yes	-	-	N/A [b]
	No	566 (100.0%)	434 (100.0%)	
IM form: daily dose>8 mg per day	Yes	87 (39.7%)	71 (45.8%)	0.241 [b]
	No	132 (60.3%)	84 (54.2%)	
Oral form: >7 consecutive days	Yes	447 (79.0%)	301 (69.4%)	<0.001 [b]
	No	119 (21.0%)	133 (30.6%)	
IM form: >5 consecutive days	Yes	159 (72.6%)	87 (56.1%)	<0.001 [b]
	No	60 (27.4%)	68 (43.9%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	310 (39.5%)	243 (41.4%)	0.488 [b]
	No	474 (60.5%)	344 (58.6%)	
In women of child bearing potential[4]:				
N	Yes	120 (100.0%)	65 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	-	-	N/A [b]
	No	120 (100.0%)	65 (100.0%)	
Lactation	Yes	-	-	N/A [b]
	No	120 (100.0%)	65 (100.0%)	
No contraceptive use	Yes	120 (100.0%)	65 (100.0%)	N/A [b]
	No	-	-	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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Table 15.3-72: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Study period year 3 vs. baseline – GPs Italy – included patients

DUS TCC

		Baseline period[1] (N=19877)	Study period year 3[2] (N=14957)	p-value
Age (years)	N	19865 (99.9)	14939 (99.9)	<0.001 [c]
	Missing (N)	12 (0.1)	18 (0.1)	
	Mean (SD)	55.4 (15.93)	57.4 (15.57)	
	Median (Q1 - Q3)	55.0 (44.0-67.0)	57.0 (46.0-69.0)	
	Range	(12.0,101.0)	(11.0,103.0)	
Age (years) - classes	Missing (N)	12	18	<0.001 [b]
	<16 years	34 (0.2%)	9 (0.1%)	
	[16;30[	1002 (5.0%)	609 (4.1%)	
	[30;40[	2263 (11.4%)	1355 (9.1%)	
	[40;50[	4156 (20.9%)	2735 (18.3%)	
	[50;60[	4388 (22.1%)	3467 (23.2%)	
	[60;70[	3752 (18.9%)	3105 (20.8%)	
	≥70 years	4270 (21.5%)	3659 (24.5%)	
Gender	Missing (N)	2894	2152	0.067 [b]
	Male	6081 (35.8%)	4717 (36.8%)	
	Female	10902 (64.2%)	8088 (63.2%)	
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	14957 (100.0)	<0.001 [c]
	Mean (SD)	1.0 (0.09)	1.0 (0.06)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes	1	19699 (99.1%)	14896 (99.6%)	<0.001 [b]
	2	178 (0.9%)	61 (0.4%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=19877)	Study period year 3[2] (N=14957)	p-value
Off label use[3]	Missing (N)	15241	12011	0.065 [b]
	Yes	3885 (83.8%)	2515 (85.4%)	
	No	751 (16.2%)	431 (14.6%)	
If yes, detail of off label use:				
Age <16 years old	Yes	15 (0.4%)	5 (0.2%)	0.176 [b]
	No	3870 (99.6%)	2510 (99.8%)	
No concomitant medications and/or health services, medical devices	Yes	629 (16.2%)	303 (12.0%)	<0.001 [b]
	No	3256 (83.8%)	2212 (88.0%)	
Oral form: daily dose>16 mg per day	Yes	26 (1.9%)	20 (2.9%)	0.154 [b]
	No	1345 (98.1%)	670 (97.1%)	
IM form: daily dose>8 mg per day	Yes	4 (0.2%)	2 (0.1%)	0.671 [b]
	No	2549 (99.8%)	1829 (99.9%)	
Oral form: >7 consecutive days	Yes	865 (63.1%)	482 (69.9%)	0.002 [b]
	No	506 (36.9%)	208 (30.1%)	
IM form: >5 consecutive days	Yes	2444 (95.7%)	1785 (97.5%)	0.002 [b]
	No	109 (4.3%)	46 (2.5%)	
Indication: other than painful muscle contractures associated with acute spinal pathology				<0.001 [b]
	Yes	1217 (31.3%)	655 (26.0%)	
	No	2668 (68.7%)	1860 (74.0%)	
In women of child bearing potential[4]:				
N	Yes	881 (100.0%)	424 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	40 (4.5%)	15 (3.5%)	0.392 [b]
	No	841 (95.5%)	409 (96.5%)	
Lactation	Yes	1 (0.1%)	-	0.375 [b]
	No	880 (99.9%)	424 (100.0%)	
No contraceptive use	Yes	820 (93.1%)	408 (96.2%)	0.019 [b]
	No	61 (6.9%)	16 (3.8%)	

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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Table 15.3-73: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Cumulated study period years 1, 2 and 3 vs. baseline – GPs France – included patients

		Baseline period[1] (N=34460)	Study period years 1, 2 and 3[2] (N=81690)	p-value
Age (years)	N	34442 (99.9)	81668 (100.0)	<0.001 [c]
	Missing (N)	18 (0.1)	22 (0.0)	
	Mean (SD)	45.9 (15.89)	46.9 (15.93)	
	Median (Q1 - Q3)	46.0 (34.0-57.0)	47.0 (35.0-58.0)	
	Range	(2.0,98.0)	(2.0,100.0)	
Age (years) - classes	Missing (N)	18	22	<0.001 [b]
	<16 years	414 (1.2%)	570 (0.7%)	
	[16;30[	5273 (15.3%)	11877 (14.5%)	
	[30;40[	6517 (18.9%)	15222 (18.6%)	
	[40;50[	8321 (24.2%)	18913 (23.2%)	
	[50;60[	7088 (20.6%)	17210 (21.1%)	
	[60;70[	4140 (12.0%)	10767 (13.2%)	
	≥70 years	2689 (7.8%)	7109 (8.7%)	
Gender	Missing (N)	25	1	<0.001 [b]
	Male	14907 (43.3%)	36478 (44.7%)	
	Female	19528 (56.7%)	45211 (55.3%)	
Number of systemic TCC prescriptions per patient	N	34460 (100.0)	81690 (100.0)	0.396 [c]
	Mean (SD)	1.0 (0.04)	1.0 (0.03)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes	1	34412 (99.9%)	81592 (99.9%)	0.400 [b]
	2	48 (0.1%)	98 (0.1%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=34460)	Study period years 1, 2 and 3[2] (N=81690)	p-value
Off label use[3]	Missing (N)	7106	17332	<0.001 [b]
	Yes	20008 (73.1%)	38651 (60.1%)	
	No	7346 (26.9%)	25707 (39.9%)	
If yes, detail of off label use:				
Age <16 years old	Yes	318 (1.6%)	463 (1.2%)	<0.001 [b]
	No	19690 (98.4%)	38188 (98.8%)	
No concomitant medications and/or health services, medical devices	Yes	1757 (8.8%)	4719 (12.2%)	<0.001 [b]
	No	18251 (91.2%)	33932 (87.8%)	
Oral form: daily dose>16 mg per day	Yes	87 (0.4%)	120 (0.3%)	0.016 [b]
	No	19474 (99.6%)	37909 (99.7%)	
IM form: daily dose>8 mg per day	Yes	171 (37.8%)	177 (27.7%)	<0.001 [b]
	No	281 (62.2%)	462 (72.3%)	
Oral form: >7 consecutive days	Yes	13913 (71.1%)	19912 (52.4%)	<0.001 [b]
	No	5648 (28.9%)	18117 (47.6%)	
IM form: >5 consecutive days	Yes	384 (85.0%)	449 (70.3%)	<0.001 [b]
	No	68 (15.0%)	190 (29.7%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	11625 (58.1%)	25599 (66.2%)	<0.001 [b]
	No	8383 (41.9%)	13052 (33.8%)	
In women of child bearing potential[4]:				
N	Yes	6532 (100.0%)	11928 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	59 (0.9%)	86 (0.7%)	0.184 [b]
	No	6473 (99.1%)	11842 (99.3%)	
Lactation	Yes	3 (0.0%)	5 (0.0%)	0.901 [b]
	No	6529 (100.0%)	11923 (100.0%)	
No contraceptive use	Yes	5644 (86.4%)	10702 (89.7%)	<0.001 [b]
	No	888 (13.6%)	1226 (10.3%)	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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Table 15.3-74: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Cumulated study period years 1, 2 and 3 vs. baseline – Rheumatologists France – included patients

		Baseline period[1] (N=1383)	Study period years 1, 2 and 3[2] (N=3016)	p-value
Age (years)	N	1383 (100.0)	3014 (99.9)	<0.001 [c]
	Missing (N)	0	2 (0.1)	
	Mean (SD)	60.3 (14.41)	62.3 (14.53)	
	Median (Q1 - Q3)	61.0 (50.0-72.0)	63.0 (53.0-73.0)	
	Range	(16.0,98.0)	(14.0,98.0)	
Age (years) - classes	Missing (N)	-	2	0.025 [b]
	<16 years	-	1 (0.0%)	
	[16;30[	21 (1.5%)	41 (1.4%)	
	[30;40[	82 (5.9%)	154 (5.1%)	
	[40;50[	222 (16.1%)	398 (13.2%)	
	[50;60[	330 (23.9%)	684 (22.7%)	
	[60;70[	333 (24.1%)	737 (24.5%)	
	≥70 years	395 (28.6%)	999 (33.1%)	
Gender	Missing (N)	91	118	0.053 [b]
	Male	396 (30.7%)	803 (27.7%)	
	Female	896 (69.3%)	2095 (72.3%)	
Number of systemic TCC prescriptions per patient	N	1383 (100.0)	3016 (100.0)	0.439 [c]
	Mean (SD)	1.0 (0.08)	1.0 (0.07)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes	1	1373 (99.3%)	3000 (99.5%)	0.447 [b]
	2	10 (0.7%)	16 (0.5%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=1383)	Study period years 1, 2 and 3[2] (N=3016)	p-value
Off label use[3]	Missing (N)	312	547	0.084 [b]
	Yes	784 (73.2%)	1737 (70.4%)	
	No	287 (26.8%)	732 (29.6%)	
If yes, detail of off label use:				
Age <16 years old	Yes	-	1 (0.1%)	0.388 [b]
	No	784 (100.0%)	1736 (99.9%)	
No concomitant medications and/or health services, medical devices	Yes	137 (17.5%)	378 (21.8%)	0.012 [b]
	No	647 (82.5%)	1359 (78.2%)	
Oral form: daily dose>16 mg per day	Yes	-	-	N/A [b]
	No	566 (100.0%)	1207 (100.0%)	
IM form: daily dose>8 mg per day	Yes	87 (39.7%)	176 (33.0%)	0.081 [b]
	No	132 (60.3%)	357 (67.0%)	
Oral form: >7 consecutive days	Yes	447 (79.0%)	822 (68.1%)	<0.001 [b]
	No	119 (21.0%)	385 (31.9%)	
IM form: >5 consecutive days	Yes	159 (72.6%)	334 (62.7%)	0.008 [b]
	No	60 (27.4%)	199 (37.3%)	
Indication: other than painful muscle contractures associated with acute spinal pathology	Yes	310 (39.5%)	754 (43.4%)	0.068 [b]
	No	474 (60.5%)	983 (56.6%)	
In women of child bearing potential[4]:				
N	Yes	120 (100.0%)	225 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	-	-	N/A [b]
	No	120 (100.0%)	225 (100.0%)	
Lactation	Yes	-	-	N/A [b]
	No	120 (100.0%)	225 (100.0%)	
No contraceptive use	Yes	120 (100.0%)	225 (100.0%)	N/A [b]
	No	-	-	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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Table 15.3-75: Comparison of patients' characteristics between pre- and post-implementation of RMMs at index date – Cumulated study period years 1, 2 and 3 vs. baseline – GPs Italy – included patients

		Baseline period[1] (N=19877)	Study period years 1, 2 and 3[2] (N=41061)	p-value
Age (years)	N	19865 (99.9)	41021 (99.9)	<0.001 [c]
	Missing (N)	12 (0.1)	40 (0.1)	
	Mean (SD)	55.4 (15.93)	56.6 (15.73)	
	Median (Q1 - Q3)	55.0 (44.0-67.0)	57.0 (46.0-69.0)	
	Range	(12.0,101.0)	(11.0,103.0)	
Age (years) - classes	Missing (N)	12	40	<0.001 [b]
	<16 years	34 (0.2%)	30 (0.1%)	
	[16;30[	1002 (5.0%)	1912 (4.7%)	
	[30;40[	2263 (11.4%)	3968 (9.7%)	
	[40;50[	4156 (20.9%)	7891 (19.2%)	
	[50;60[	4388 (22.1%)	9393 (22.9%)	
	[60;70[	3752 (18.9%)	8348 (20.4%)	
	≥70 years	4270 (21.5%)	9479 (23.1%)	
Gender	Missing (N)	2894	5863	0.008 [b]
	Male	6081 (35.8%)	13021 (37.0%)	
	Female	10902 (64.2%)	22177 (63.0%)	
Number of systemic TCC prescriptions per patient	N	19877 (100.0)	41061 (100.0)	<0.001 [c]
	Mean (SD)	1.0 (0.09)	1.0 (0.07)	
	Median (Q1 - Q3)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	
	Range	(1.0,2.0)	(1.0,2.0)	
Number of systemic TCC prescriptions per patient - classes	1	19699 (99.1%)	40867 (99.5%)	<0.001 [b]
	2	178 (0.9%)	194 (0.5%)	
	3	-	-	
	>3	-	-	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

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		Baseline period[1] (N=19877)	Study period years 1, 2 and 3[2] (N=41061)	p-value
Off label use[3]	Missing (N)	15241	32664	0.008 [b]
	Yes	3885 (83.8%)	7183 (85.5%)	
	No	751 (16.2%)	1214 (14.5%)	
If yes, detail of off label use:				
Age <16 years old	Yes	15 (0.4%)	12 (0.2%)	0.030 [b]
	No	3870 (99.6%)	7171 (99.8%)	
No concomitant medications and/or health services, medical devices				<0.001 [b]
	Yes	629 (16.2%)	961 (13.4%)	
	No	3256 (83.8%)	6222 (86.6%)	
Oral form: daily dose>16 mg per day	Yes	26 (1.9%)	45 (2.1%)	0.685 [b]
	No	1345 (98.1%)	2105 (97.9%)	
IM form: daily dose>8 mg per day	Yes	4 (0.2%)	7 (0.1%)	0.843 [b]
	No	2549 (99.8%)	5053 (99.9%)	
Oral form: >7 consecutive days	Yes	865 (63.1%)	1528 (71.1%)	<0.001 [b]
	No	506 (36.9%)	622 (28.9%)	
IM form: >5 consecutive days	Yes	2444 (95.7%)	4897 (96.8%)	0.022 [b]
	No	109 (4.3%)	163 (3.2%)	
Indication: other than painful muscle contractures associated with acute spinal pathology				<0.001 [b]
	Yes	1217 (31.3%)	1941 (27.0%)	
	No	2668 (68.7%)	5242 (73.0%)	
In women of child bearing potential[4]:				
N	Yes	881 (100.0%)	1356 (100.0%)	N/A [b]
	No	-	-	
Pregnancy	Yes	40 (4.5%)	64 (4.7%)	0.844 [b]
	No	841 (95.5%)	1292 (95.3%)	
Lactation	Yes	1 (0.1%)	-	0.172 [b]
	No	880 (99.9%)	1356 (100.0%)	
No contraceptive use	Yes	820 (93.1%)	1293 (95.4%)	0.023 [b]
	No	61 (6.9%)	63 (4.6%)	

Baseline period[1]: year 2013
Study period years 1, 2 and 3[2]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Off label use[3] definition based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential
[4]: percentage based on women of child bearing potential
*[-]: [a] Fisher's exact test [b] Chi-square test [c] Student's t-test [d] Wilcoxon signed-rank test

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_11_03.sas; By: Alampure; Date & time: 19AUG19 09:36;

Table 15.3-76: Analysis of pregnancies exposed to TCC – GPs France – included patients

		Women of child bearing potential				
		Baseline period[1] (N=11319)	Study period year 1[2] (N=11779)	Study period year 2[3] (N=10616)	Study period year 3[4] (N=6689)	Study period years 1, 2 and 3[5] (N=25249)
Pregnancy	Yes	73 (0.6%)	57 (0.5%)	35 (0.3%)	53 (0.8%)	146 (0.6%)
	No	11246 (99.4%)	11722 (99.5%)	10581 (99.7%)	6636 (99.2%)	25103 (99.4%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Pregnancies exposed: At least one TCC prescription during pregnancy within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_12.sas;
By: Alampure; Date & time: 29AUG19 09:31;

Table 15.3-77: Analysis of pregnancies exposed to TCC – Rheumatologists France – included patients

		Women of child bearing potential				
		Baseline period[1] (N=202)	Study period year 1[2] (N=159)	Study period year 2[3] (N=149)	Study period year 3[4] (N=136)	Study period years 1, 2 and 3[5] (N=401)
Pregnancy	Yes	-	-	-	-	-
	No	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Pregnancies exposed: At least one TCC prescription during pregnancy within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_12.sas;
By: Alampure; Date & time: 29AUG19 09:31;

Table 15.3-78: Analysis of pregnancies exposed to TCC – GPs Italy – included patients

		Women of child bearing potential				
		Baseline period[1] (N=3782)	Study period year 1[2] (N=2617)	Study period year 2[3] (N=2616)	Study period year 3[4] (N=2275)	Study period years 1, 2 and 3[5] (N=6788)
Pregnancy	Yes	156 (4.1%)	125 (4.8%)	108 (4.1%)	95 (4.2%)	317 (4.7%)
	No	3626 (95.9%)	2492 (95.2%)	2508 (95.9%)	2180 (95.8%)	6471 (95.3%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Pregnancies exposed: At least one TCC prescription during pregnancy within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_12.sas;
By: Alampure; Date & time: 29AUG19 09:31;

Table 15.3-79: Analysis of breastfeeding patients exposed to TCC – GPs France – included patients

		Women of child bearing potential				
		Baseline period[1] (N=11319)	Study period year 1[2] (N=11779)	Study period year 2[3] (N=10616)	Study period year 3[4] (N=6689)	Study period years 1, 2 and 3[5] (N=25249)
Lactation	Yes	6 (0.1%)	3 (0.0%)	1 (0.0%)	1 (0.0%)	5 (0.0%)
	No	11313 (99.9%)	11776 (100.0%)	10615 (100.0%)	6688 (100.0%)	25244 (100.0%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Breastfeeding patients exposed[3] At least one TCC prescription concomitant to a lactation record within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_13.sas; By: Alampure;
Date & time: 29AUG19 09:31;

Table 15.3-80: Analysis of breastfeeding patients exposed to TCC – Rheumatologists France – included patients

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		Women of child bearing potential				
		Baseline period[1] (N=202)	Study period year 1[2] (N=159)	Study period year 2[3] (N=149)	Study period year 3[4] (N=136)	Study period years 1, 2 and 3[5] (N=401)
Lactation	Yes	-	-	-	-	-
	No	202 (100.0%)	159 (100.0%)	149 (100.0%)	136 (100.0%)	401 (100.0%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Breastfeeding patients exposed[3] At least one TCC prescription concomitant to a lactation record within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_13.sas; By: Alampure;
Date & time: 29AUG19 09:31;

Table 15.3-81: Analysis of breastfeeding patients exposed to TCC – GPs Italy – included patients

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		Women of child bearing potential				
		Baseline period[1] (N=3782)	**Study period year 1[2] (N=2617)**	**Study period year 2[3] (N=2616)**	**Study period year 3[4] (N=2275)**	**Study period years 1, 2 and 3[5] (N=6788)**
Lactation	Yes	3 (0.1%)	2 (0.1%)	1 (0.0%)	-	3 (0.0%)
	No	3779 (99.9%)	2615 (99.9%)	2615 (100.0%)	2275 (100.0%)	6785 (100.0%)

Baseline period[1]: year 2013
Study period[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Study period[4]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period[5]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Breastfeeding patients exposed[3] At least one TCC prescription concomitant to a lactation record within the defined study period

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_13.sas; By: Alampure;
Date & time: 29AUG19 09:31;

Table 15.3-82: Analysis of systemic TCC prescriptions – Women of child bearing potential (16-49 years old) – Baseline and study period years 1 and 2 – GPs France – included patients

		Study period year 1[2]		Study period year 2[3]	
	Baseline period[1] (N=44108)	Overall (N=49100)	Incident[3] (N=20356)	Overall (N=44691)	Incident[4] (N=17954)
Number of prescriptions: total	44108 (100.0%)	49100 (100.0%)	20356 (100.0%)	44691 (100.0%)	17954 (100.0%)
Number of prescriptions made to women	25260 (57.3%)	27592 (56.2%)	11102 (54.5%)	25382 (56.8%)	9781 (54.5%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	14269 (56.5%)	14782 (53.6%)	6581 (59.3%)	13491 (53.2%)	5726 (58.6%)
Number of prescription made to women presenting a pregnancy during the period	307 (2.2%)	284 (1.9%)	123 (1.9%)	138 (1.0%)	56 (1.0%)
Number of TCC prescriptions concomitant to pregnancy	77 (25.1%)	70 (24.6%)	22 (17.9%)	48 (34.8%)	15 (26.8%)
Number of prescription made to women presenting a diagnosis of lactation during the period	19 (0.1%)	17 (0.1%)	3 (0.0%)	7 (0.1%)	3 (0.1%)
Number of TCC prescriptions concomitant to lactation	6 (31.6%)	5 (29.4%)	1 (33.3%)	1 (14.3%)	1 (33.3%)
Number of prescription made to women not presenting a contraception prescription during the period	10921 (76.5%)	12086 (81.8%)	5498 (83.5%)	11009 (81.6%)	4770 (83.3%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_16.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

Table 15.3-83: Analysis of systemic TCC prescriptions – Women of child bearing potential (16-49 years old) – Baseline and study period years 1 and 2 – Rheumatologists France – included patients

		Study period year 1[2]		Study period year 2[3]	
	Baseline period[1] (N=1721)	Overall (N=1494)	Incident[3] (N=685)	Overall (N=1409)	Incident[4] (N=660)
Number of prescriptions: total	1721 (100.0%)	1494 (100.0%)	685 (100.0%)	1409 (100.0%)	660 (100.0%)
Number of prescriptions made to women	1099 (68.9%)	998 (70.6%)	467 (70.0%)	987 (73.7%)	479 (75.0%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	262 (23.8%)	186 (18.6%)	86 (18.4%)	174 (17.6%)	87 (18.2%)
Number of prescription made to women presenting a pregnancy during the period	-	-	-	-	-
Number of TCC prescriptions concomitant to pregnancy	-	-	-	-	-
Number of prescription made to women presenting a diagnosis of lactation during the period	-	-	-	-	-
Number of TCC prescriptions concomitant to lactation	-	-	-	-	-
Number of prescription made to women not presenting a contraception prescription during the period	261 (99.6%)	186 (100.0%)	86 (100.0%)	174 (100.0%)	87 (100.0%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017

Table 15.3-84: Analysis of systemic TCC prescriptions – Women of child bearing potential (16-49 years old) – Baseline and study period years 1 and 2 – GPs Italy – included patients

		Study period year 1[2]		Study period year 2[3]	
	Baseline period[1] (N=23527)	Overall (N=18695)	Incident[3] (N=7105)	Overall (N=18833)	Incident[4] (N=7098)
Number of prescriptions: total	23527 (100.0%)	18695 (100.0%)	7105 (100.0%)	18833 (100.0%)	7098 (100.0%)
Number of prescriptions made to women	12884 (64.0%)	9957 (62.1%)	3803 (61.1%)	10110 (63.0%)	3840 (62.2%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	4290 (33.3%)	2900 (29.1%)	1515 (39.8%)	2904 (28.7%)	1513 (39.4%)
Number of prescription made to women presenting a pregnancy during the period	353 (8.2%)	263 (9.1%)	154 (10.2%)	225 (7.7%)	146 (9.6%)
Number of TCC prescriptions concomitant to pregnancy	169 (47.9%)	136 (51.7%)	76 (49.4%)	110 (48.9%)	76 (52.1%)
Number of prescription made to women presenting a diagnosis of lactation during the period	8 (0.2%)	5 (0.2%)	5 (0.3%)	3 (0.1%)	2 (0.1%)
Number of TCC prescriptions concomitant to lactation	4 (50.0%)	2 (40.0%)	2 (40.0%)	1 (33.3%)	1 (50.0%)
Number of prescription made to women not presenting a contraception prescription during the period	3509 (81.8%)	2430 (83.8%)	1275 (84.2%)	2904 (100.0%)	1513 (100.0%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017

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Table 15.3-85: Analysis of systemic TCC prescriptions - Women of child bearing potential (16-49 years old) – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs France - included patients

		Study period year 3[2]		Study period years 1, 2 and 3[3]	
	Baseline period[1] (N=44108)	Overall (N=29631)	Incident[4] (N=12287)	Overall (N=123429)	Incident[4] (N=50597)
Number of prescriptions: total	44108 (100.0%)	29631 (100.0%)	12287 (100.0%)	123429 (100.0%)	50597 (100.0%)
Number of prescriptions made to women	25260 (57.3%)	16712 (56.4%)	6714 (54.6%)	69690 (56.5%)	27597 (54.5%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	14269 (56.5%)	8272 (49.5%)	3645 (54.3%)	36548 (52.5%)	15952 (57.8%)
Number of prescription made to women presenting a pregnancy during the period	307 (2.2%)	193 (2.3%)	89 (2.4%)	615 (1.7%)	268 (1.7%)
Number of TCC prescriptions concomitant to pregnancy	77 (25.1%)	58 (30.1%)	28 (31.5%)	176 (28.6%)	65 (24.3%)
Number of prescription made to women presenting a diagnosis of lactation during the period	19 (0.1%)	3 (0.0%)	3 (0.1%)	27 (0.1%)	9 (0.1%)
Number of TCC prescriptions concomitant to lactation	6 (31.6%)	1 (33.3%)	1 (33.3%)	7 (25.9%)	3 (33.3%)
Number of prescription made to women not presenting a contraception prescription during the period	10921 (76.5%)	7805 (94.4%)	3460 (94.9%)	30903 (84.6%)	13728 (86.1%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Table 15.3-86: Analysis of systemic TCC prescriptions – Women of child bearing potential (16-49 years old) – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

		Study period year 3[2]		Study period years 1, 2 and 3[3]	
	Baseline period[1] (N=1721)	Overall (N=1281)	Incident[4] (N=578)	Overall (N=4184)	Incident[4] (N=1923)
Number of prescriptions: total	1721 (100.0%)	1281 (100.0%)	578 (100.0%)	4184 (100.0%)	1923 (100.0%)
Number of prescriptions made to women	1099 (68.9%)	881 (72.2%)	412 (72.9%)	2866 (72.1%)	1358 (72.6%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	262 (23.8%)	152 (17.3%)	82 (19.9%)	512 (17.9%)	255 (18.8%)
Number of prescription made to women presenting a pregnancy during the period	-	-	-	-	-
Number of TCC prescriptions concomitant to pregnancy	-	-	-	-	-
Number of prescription made to women presenting a diagnosis of lactation during the period	-	-	-	-	-
Number of TCC prescriptions concomitant to lactation	-	-	-	-	-
Number of prescription made to women not presenting a contraception prescription during the period	261 (99.6%)	152 (100.0%)	82 (100.0%)	512 (100.0%)	255 (100.0%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Table 15.3-87: Analysis of systemic TCC prescriptions – Women of child bearing potential (16-49 years old) – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

		Study period year 3[2]		Study period years 1, 2 and 3[3]	
	Baseline period[1] (N=23527)	Overall (N=17364)	Incident[4] (N=6471)	Overall (N=54892)	Incident[4] (N=20674)
Number of prescriptions: total	23527 (100.0%)	17364 (100.0%)	6471 (100.0%)	54892 (100.0%)	20674 (100.0%)
Number of prescriptions made to women	12884 (64.0%)	9316 (62.7%)	3466 (61.2%)	29383 (62.6%)	11109 (61.5%)
Number of prescriptions made to women of child bearing potential (16-49 years old)	4290 (33.3%)	2543 (27.3%)	1312 (37.9%)	8347 (28.4%)	4340 (39.1%)
Number of prescription made to women presenting a pregnancy during the period	353 (8.2%)	219 (8.6%)	131 (10.0%)	707 (8.5%)	431 (9.9%)
Number of TCC prescriptions concomitant to pregnancy	169 (47.9%)	103 (47.0%)	61 (46.6%)	349 (49.4%)	213 (49.4%)
Number of prescription made to women presenting a diagnosis of lactation during the period	8 (0.2%)	1 (0.0%)	-	9 (0.1%)	7 (0.2%)
Number of TCC prescriptions concomitant to lactation	4 (50.0%)	-	-	3 (33.3%)	3 (42.9%)
Number of prescription made to women not presenting a contraception prescription during the period	3509 (81.8%)	2236 (87.9%)	1146 (87.3%)	7570 (90.7%)	3934 (90.6%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Table 15.3-88: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline and study period years 1 and 2 – GPs France – included patients

			Study period year 1[2]		Study period year 2[2]	
		Baseline period[1] (N=44108)	Overall (N=49100)	Incident[4] (N=20356)	Overall (N=44691)	Incident[4] (N=17954)
Total systemic TCC prescriptions	Yes	44108 (100.0%)	49100 (100.0%)	20356 (100.0%)	44691 (100.0%)	17954 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	20	5	3	15	10
	<16 years	452 (1.0%)	306 (0.6%)	239 (1.2%)	238 (0.5%)	195 (1.1%)
	[16;30[	6208 (14.1%)	6269 (12.8%)	3682 (18.1%)	5529 (12.4%)	3208 (17.9%)
	[30;40[	8075 (18.3%)	8786 (17.9%)	3840 (18.9%)	8014 (17.9%)	3440 (19.2%)
	[40;50[	10817 (24.5%)	11599 (23.6%)	4484 (22.0%)	10417 (23.3%)	3816 (21.3%)
	[50;60[	9475 (21.5%)	10961 (22.3%)	3780 (18.6%)	10181 (22.8%)	3452 (19.2%)
	[60;70[	5453 (12.4%)	6872 (14.0%)	2576 (12.7%)	6234 (14.0%)	2253 (12.6%)
	≥70 years	3608 (8.2%)	4302 (8.8%)	1752 (8.6%)	4063 (9.1%)	1580 (8.8%)
In patients with age less 16 years old						
Age at prescription (years)	N	452 (100.0)	306 (100.0)	239 (100.0)	238 (100.0)	195 (100.0)
	Mean (SD)	13.8 (1.94)	13.9 (2.14)	13.9 (2.00)	14.0 (1.81)	14.0 (1.95)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)
	Range	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)	(3.0,15.0)	(3.0,15.0)

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_17.sas;
By: Ncoulombel; Date & time: 04OCT18 12:13;

Table 15.3-89: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline and study period years 1 and 2 – Rheumatologists France – included patients

			Study period year 1[2]		Study period year 2[2]	
		Baseline period[1] (N=1721)	Overall (N=1494)	Incident[4] (N=685)	Overall (N=1409)	Incident[4] (N=660)
Total systemic TCC prescriptions	Yes	1721 (100.0%)	1494 (100.0%)	685 (100.0%)	1409 (100.0%)	660 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	-	1	1	1	1
	<16 years	-	-	-	-	-
	[16;30[	26 (1.5%)	13 (0.9%)	9 (1.3%)	13 (0.9%)	10 (1.5%)
	[30;40[	98 (5.7%)	76 (5.1%)	39 (5.7%)	68 (4.8%)	34 (5.2%)
	[40;50[	288 (16.7%)	202 (13.5%)	76 (11.1%)	187 (13.3%)	82 (12.4%)
	[50;60[	420 (24.4%)	361 (24.2%)	155 (22.7%)	323 (22.9%)	140 (21.2%)
	[60;70[	414 (24.1%)	393 (26.3%)	182 (26.6%)	328 (23.3%)	150 (22.8%)
	≥70 years	475 (27.6%)	448 (30.0%)	223 (32.6%)	489 (34.7%)	243 (36.9%)
In patients with age less 16 years old						
Age at prescription (years)	N					
	Mean (SD)					
	Median (Q1 - Q3)					
	Range					

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_17.sas;
By: Ncoulombel; Date & time: 04OCT18 12:20;

Table 15.3-90: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline and study period years 1 and 2 – Baseline and study period years 1 and 2 – GPs Italy – included patients

			Study period year 1[2]		Study period year 2[2]	
		Baseline period[1] (N=23527)	Overall (N=18695)	Incident[4] (N=7105)	Overall (N=18833)	Incident[4] (N=7098)
Total systemic TCC prescriptions	Yes	23527 (100.0%)	18695 (100.0%)	7105 (100.0%)	18833 (100.0%)	7098 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	14	15	6	21	10
	<16 years	36 (0.2%)	10 (0.1%)	9 (0.1%)	13 (0.1%)	12 (0.2%)
	[16;30[	1083 (4.6%)	729 (3.9%)	531 (7.5%)	777 (4.1%)	589 (8.3%)
	[30;40[	2573 (10.9%)	1708 (9.1%)	898 (12.6%)	1664 (8.8%)	898 (12.7%)
	[40;50[	4851 (20.6%)	3577 (19.1%)	1490 (21.0%)	3517 (18.7%)	1459 (20.6%)
	[50;60[	5180 (22.0%)	4418 (23.7%)	1495 (21.1%)	4335 (23.0%)	1454 (20.5%)
	[60;70[	4496 (19.1%)	3825 (20.5%)	1242 (17.5%)	3904 (20.8%)	1229 (17.3%)
	≥70 years	5294 (22.5%)	4413 (23.6%)	1434 (20.2%)	4602 (24.5%)	1447 (20.4%)
In patients with age less 16 years old						
Age at prescription (years)	N	36 (100.0)	10 (100.0)	9 (100.0)	13 (100.0)	12 (100.0)
	Mean (SD)	14.2 (0.92)	14.1 (1.29)	14.4 (0.73)	13.8 (1.21)	13.8 (1.22)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	14.5 (14.0-15.0)	15.0 (14.0-15.0)	14.0 (13.0-15.0)	14.0 (12.5-15.0)
	Range	(12.0,15.0)	(11.0,15.0)	(13.0,15.0)	(12.0,15.0)	(12.0,15.0)

Baseline period[1]: year 2013
Study period year 1 [2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[2]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_17.sas;
By: Ncoulombel; Date & time: 04OCT18 12:24;

Table 15.3-91: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs France – included patients

			Study period year 3[2]		Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=44108)	Overall (N=29631)	Incident[4] (N=12287)	Overall (N=123429)	Incident[4] (N=50597)
Total systemic TCC prescriptions	Yes	44108 (100.0%)	29631 (100.0%)	12287 (100.0%)	123429 (100.0%)	50597 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	20	7	5	27	18
	<16 years	452 (1.0%)	117 (0.4%)	99 (0.8%)	661 (0.5%)	533 (1.1%)
	[16;30[	6208 (14.1%)	3322 (11.2%)	1943 (15.8%)	15120 (12.3%)	8833 (17.5%)
	[30;40[	8075 (18.3%)	5085 (17.2%)	2258 (18.4%)	21889 (17.7%)	9538 (18.9%)
	[40;50[	10817 (24.5%)	6719 (22.7%)	2591 (21.1%)	28736 (23.3%)	10891 (21.5%)
	[50;60[	9475 (21.5%)	6735 (22.7%)	2421 (19.7%)	27879 (22.6%)	9653 (19.1%)
	[60;70[	5453 (12.4%)	4385 (14.8%)	1633 (13.3%)	17491 (14.2%)	6462 (12.8%)
	≥70 years	3608 (8.2%)	3261 (11.0%)	1337 (10.9%)	11626 (9.4%)	4669 (9.2%)
In patients with age less 16 years old						
Age at prescription (years)	N	452 (100.0)	117 (100.0)	99 (100.0)	661 (100.0)	533 (100.0)
	Mean (SD)	13.8 (1.94)	13.6 (2.57)	13.6 (2.46)	13.9 (2.12)	13.9 (2.07)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	15.0 (13.0-15.0)	15.0 (13.0-15.0)	15.0 (14.0-15.0)	15.0 (14.0-15.0)
	Range	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)	(2.0,15.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_17_02.sas; By: Alampure; Date & time: 20AUG19 09:30;

Table 15.3-92: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

			Study period year 3[2]		Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=1721)	Overall (N=1281)	Incident[4] (N=578)	Overall (N=4184)	Incident[4] (N=1923)
Total systemic TCC prescriptions	Yes	1721 (100.0%)	1281 (100.0%)	578 (100.0%)	4184 (100.0%)	1923 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	-	1	-	3	2
	<16 years	-	1 (0.1%)	1 (0.2%)	1 (0.0%)	1 (0.1%)
	[16;30[	26 (1.5%)	18 (1.4%)	12 (2.1%)	44 (1.1%)	31 (1.6%)
	[30;40[	98 (5.7%)	52 (4.1%)	26 (4.5%)	196 (4.7%)	99 (5.2%)
	[40;50[	288 (16.7%)	153 (12.0%)	74 (12.8%)	542 (13.0%)	232 (12.1%)
	[50;60[	420 (24.4%)	312 (24.4%)	122 (21.1%)	996 (23.8%)	417 (21.7%)
	[60;70[	414 (24.1%)	296 (23.1%)	139 (24.0%)	1017 (24.3%)	471 (24.5%)
	≥70 years	475 (27.6%)	448 (35.0%)	204 (35.3%)	1385 (33.1%)	670 (34.9%)
In patients with age less 16 years old						
Age at prescription (years)	N		1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)
	Mean (SD)		14.0 ()	14.0 ()	14.0 ()	14.0 ()
	Median (Q1 - Q3)		14.0 (14.0-14.0)	14.0 (14.0-14.0)	14.0 (14.0-14.0)	14.0 (14.0-14.0)
	Range		(14.0,14.0)	(14.0,14.0)	(14.0,14.0)	(14.0,14.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Table 15.3-93: Analysis of systemic TCC prescriptions – Less than 16 years old – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

			Study period year 3[2]		Study period years 1, 2 and 3[2]	
		Baseline period[1] (N=23527)	Overall (N=17364)	Incident[4] (N=6471)	Overall (N=54892)	Incident[4] (N=20674)
Total systemic TCC prescriptions	Yes	23527 (100.0%)	17364 (100.0%)	6471 (100.0%)	54892 (100.0%)	20674 (100.0%)
	No	-	-	-	-	-
Age at prescription (years)	Missing (N)	14	18	11	54	27
	<16 years	36 (0.2%)	9 (0.1%)	9 (0.1%)	32 (0.1%)	30 (0.1%)
	[16;30[	1083 (4.6%)	649 (3.7%)	487 (7.5%)	2155 (3.9%)	1607 (7.8%)
	[30;40[	2573 (10.9%)	1539 (8.9%)	821 (12.7%)	4911 (9.0%)	2617 (12.7%)
	[40;50[	4851 (20.6%)	3124 (18.0%)	1329 (20.6%)	10218 (18.6%)	4278 (20.7%)
	[50;60[	5180 (22.0%)	4043 (23.3%)	1306 (20.2%)	12796 (23.3%)	4255 (20.6%)
	[60;70[	4496 (19.1%)	3632 (20.9%)	1192 (18.5%)	11361 (20.7%)	3663 (17.7%)
	≥70 years	5294 (22.5%)	4350 (25.1%)	1316 (20.4%)	13365 (24.4%)	4197 (20.3%)
In patients with age less 16 years old						
Age at prescription (years)	N	36 (100.0)	9 (100.0)	9 (100.0)	32 (100.0)	30 (100.0)
	Mean (SD)	14.2 (0.92)	13.8 (1.39)	13.8 (1.39)	13.9 (1.25)	14.0 (1.16)
	Median (Q1 - Q3)	14.0 (14.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)	14.0 (13.0-15.0)
	Range	(12.0,15.0)	(11.0,15.0)	(11.0,15.0)	(11.0,15.0)	(11.0,15.0)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_17_02.sas; By: Alampure; Date & time: 20AUG19 09:30;

Table 15.3-94: Analysis of systemic TCC prescriptions – Off label indication – Baseline and study period years 1 and 2 – GPs France – included patients

			Study period year 1[2]		Study period year 2[3]	
		Baseline period[1] (N=44108)	Overall (N=49100)	Incident[4] (N=20356)	Overall (N=44691)	Incident[4] (N=17954)
Total systemic TCC prescriptions		44108 (100.0%)	49100 (100.0%)	20356 (100.0%)	44691 (100.0%)	17954 (100.0%)
On label prescriptions	Missing (N)	6494	6140	2568	6760	2567
	Yes	20057 (53.3%)	23257 (54.1%)	10753 (60.5%)	20553 (54.2%)	9401 (61.1%)
	No	17557 (46.7%)	19703 (45.9%)	7035 (39.5%)	17378 (45.8%)	5986 (38.9%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	6140	2568	6760	2567
	Other deforming dorsopathies including - M43	1115 (3.0%)	1229 (2.9%)	747 (4.2%)	1098 (2.9%)	640 (4.2%)
	Dorsalgia - M54	18942 (50.4%)	22028 (51.3%)	10006 (56.3%)	19455 (51.3%)	8761 (56.9%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	19703 (45.9%)	7035 (39.5%)	17378 (45.8%)	5986 (38.9%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	875 (2.0%)	380 (2.1%)	716 (1.9%)	307 (2.0%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	685 (1.6%)	160 (0.9%)	560 (1.5%)	125 (0.8%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	624 (1.5%)	144 (0.8%)	489 (1.3%)	106 (0.7%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	812 (1.9%)	263 (1.5%)	731 (1.9%)	194 (1.3%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	5547 (12.9%)	2403 (13.5%)	4680 (12.3%)	1995 (13.0%)
	Contracture of muscle - M62.4	1129 (3.0%)	1226 (2.9%)	680 (3.8%)	1172 (3.1%)	618 (4.0%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	1380 (3.2%)	555 (3.1%)	1399 (3.7%)	540 (3.5%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	1354 (3.2%)	725 (4.1%)	1111 (2.9%)	574 (3.7%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	7659 (17.8%)	2131 (12.0%)	6827 (18.0%)	1839 (12.0%)
	Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	4882 (11.4%)	1128 (6.3%)	4259 (11.2%)	945 (6.1%)
	Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	1523 (3.5%)	621 (3.5%)	1338 (3.5%)	505 (3.3%)
	Other	1049 (2.8%)	1391 (3.2%)	418 (2.3%)	1354 (3.6%)	412 (2.7%)

	Baseline period[1] (N=44108)	Study period year 1[2] Overall (N=49100)	Study period year 1[2] Incident[4] (N=20356)	Study period year 2[3] Overall (N=44691)	Study period year 2[3] Incident[4] (N=17954)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_19.sas; By: Ncoulombel; Date & time: 04OCT18 12:13;

Table 15.3-95: Analysis of systemic TCC prescriptions – Off label indication – Baseline and study period years 1 and 2 – Rheumatologists France – included patients

			Study period year 1[2]		Study period year 2[3]	
		Baseline period[1] (N=1721)	Overall (N=1494)	Incident[4] (N=685)	Overall (N=1409)	Incident[4] (N=660)
Total systemic TCC prescriptions	Yes	1721 (100.0%)	1494 (100.0%)	685 (100.0%)	1409 (100.0%)	660 (100.0%)
On label prescriptions	Yes	1227 (71.3%)	1051 (70.3%)	440 (64.2%)	994 (70.5%)	429 (65.0%)
	No	494 (28.7%)	443 (29.7%)	245 (35.8%)	415 (29.5%)	231 (35.0%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	18 (1.2%)	11 (1.6%)	24 (1.7%)	15 (2.3%)
	Dorsalgia - M54	1209 (70.2%)	1033 (69.1%)	429 (62.6%)	970 (68.8%)	414 (62.7%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	443 (29.7%)	245 (35.8%)	415 (29.5%)	231 (35.0%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	369 (24.7%)	205 (29.9%)	355 (25.2%)	196 (29.7%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	38 (2.5%)	29 (4.2%)	31 (2.2%)	20 (3.0%)
	Other specified arthrosis - M19.8	-	-	-	6 (0.4%)	4 (0.6%)
	Pain in shoulder - M25.51	21 (1.2%)	21 (1.4%)	12 (1.8%)	25 (1.8%)	12 (1.8%)
	Pain in knee - M25.56	24 (1.4%)	17 (1.1%)	7 (1.0%)	42 (3.0%)	21 (3.2%)
	Other spondylosis - M47.8	-	-	-	37 (2.6%)	16 (2.4%)
	Other shoulder lesions - M75.8	41 (2.4%)	26 (1.7%)	14 (2.0%)	-	-
	Enthesopathy, unspecified - M77.9	18 (1.0%)	12 (0.8%)	7 (1.0%)	3 (0.2%)	1 (0.2%)
	Rheumatism, unspecified - M79.0	16 (0.9%)	18 (1.2%)	6 (0.9%)	-	-
	Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	50 (3.3%)	27 (3.9%)	11 (0.8%)	6 (0.9%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	31 (2.1%)	16 (2.3%)	38 (2.7%)	22 (3.3%)
	Pain, unspecified - R52.9	31 (1.8%)	30 (2.0%)	15 (2.2%)	37 (2.6%)	22 (3.3%)
	Other	25 (1.5%)	43 (2.9%)	24 (3.5%)	22 (1.6%)	13 (2.0%)

		Study period year 1[2]		Study period year 2[3]	
	Baseline period[1] (N=1721)	Overall (N=1494)	Incident[4] (N=685)	Overall (N=1409)	Incident[4] (N=660)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_19.sas; By: Alampure; Date & time: 20AUG19 15:03;

Table 15.3-96: Analysis of systemic TCC prescriptions – Off label indication – Baseline and study period years 1 and 2 – GPs Italy – included patients

			Study period year 1[2]		Study period year 2[3]	
		Baseline period[1] (N=23527)	Overall (N=18695)	Incident[4] (N=7105)	Overall (N=18833)	Incident[4] (N=7098)
Total systemic TCC prescriptions	Yes	23527 (100.0%)	18695 (100.0%)	7105 (100.0%)	18833 (100.0%)	7098 (100.0%)
On label prescriptions	Missing (N)	2063	1549	616	1588	667
	Yes	16228 (75.6%)	13223 (77.1%)	4887 (75.3%)	13361 (77.5%)	4892 (76.1%)
	No	5236 (24.4%)	3923 (22.9%)	1602 (24.7%)	3884 (22.5%)	1539 (23.9%)
Treatment indication for TCC prescription at index date (ICD9)	Missing	2063	1549	616	1588	667
	Other deforming dorsopathies including - M43	1082 (5.0%)	757 (4.4%)	295 (4.5%)	748 (4.3%)	292 (4.5%)
	Dorsalgia - M54	15146 (70.6%)	12466 (72.7%)	4592 (70.8%)	12613 (73.1%)	4600 (71.5%)
	Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	3923 (22.9%)	1602 (24.7%)	3884 (22.5%)	1539 (23.9%)
	Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	2499 (14.6%)	932 (14.4%)	2493 (14.5%)	915 (14.2%)
	Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	475 (2.8%)	133 (2.0%)	436 (2.5%)	140 (2.2%)
	Spasm Of Muscle - 728.85	392 (1.8%)	291 (1.7%)	142 (2.2%)	299 (1.7%)	145 (2.3%)
	Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	233 (1.4%)	80 (1.2%)	224 (1.3%)	94 (1.5%)
	Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	418 (2.4%)	186 (2.9%)	420 (2.4%)	169 (2.6%)
	Injury And Poisoning (800-999)	524 (2.4%)	425 (2.5%)	214 (3.3%)	366 (2.1%)	189 (2.9%)
	Other	743 (3.5%)	581 (3.4%)	270 (4.2%)	605 (3.5%)	266 (4.1%)

Baseline period[1]: year 2013
Study period year 1[2]: France: 26th April 2016 - 25th April 2017 / Italy: 8th October 2015-7th October 2016
Study period year 2[3]: France: 26th April 2017 - 25th April 2018 / Italy: 8th October 2016-7th October 2017
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-2/Statistics/Analysis/program/tables/T_19.sas; By: Ncoulombel; Date & time: 04OCT18 15:46;

Table 15.3-97: Analysis of systemic TCC prescriptions – Off label indication – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs France – included patients

			Study period year 3[2]		Study period years 1, 2 and 3[3]	
		Baseline period[1] (N=44108)	Overall (N=29631)	Incident[4] (N=12287)	Overall (N=123429)	Incident[4] (N=50597)
Total systemic TCC prescriptions		44108 (100.0%)	29631 (100.0%)	12287 (100.0%)	123429 (100.0%)	50597 (100.0%)
On label prescriptions	Missing (N)	6494	5114	2111	18015	7246
	Yes	20057 (53.3%)	13043 (53.2%)	6204 (61.0%)	56854 (53.9%)	26358 (60.8%)
	No	17557 (46.7%)	11474 (46.8%)	3972 (39.0%)	48560 (46.1%)	16993 (39.2%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	6494	5114	2111	18015	7246
	Other deforming dorsopathies including - M43	1115 (3.0%)	700 (2.9%)	410 (4.0%)	3027 (2.9%)	1797 (4.1%)
	Dorsalgia - M54	18942 (50.4%)	12343 (50.3%)	5794 (56.9%)	53827 (51.1%)	24561 (56.7%)
	Other than painful muscle contractures associated with acute spinal pathology	17557 (46.7%)	11474 (46.8%)	3972 (39.0%)	48560 (46.1%)	16993 (39.2%)
	Diseases of the nervous system - (G00-G99)	666 (1.8%)	457 (1.9%)	184 (1.8%)	2048 (1.9%)	871 (2.0%)
	Diseases of the circulatory system - (I00-I99)	356 (0.9%)	427 (1.7%)	83 (0.8%)	1672 (1.6%)	368 (0.8%)
	Essential (primary) hypertension - I10.0	302 (0.8%)	364 (1.5%)	66 (0.6%)	1477 (1.4%)	316 (0.7%)
	Diseases of the respiratory system - (J00-J99)	694 (1.8%)	481 (2.0%)	116 (1.1%)	2024 (1.9%)	573 (1.3%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	4766 (12.7%)	2957 (12.1%)	1305 (12.8%)	13187 (12.5%)	5703 (13.2%)
	Contracture of muscle - M62.4	1129 (3.0%)	760 (3.1%)	441 (4.3%)	3159 (3.0%)	1739 (4.0%)
	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	1255 (3.3%)	866 (3.5%)	348 (3.4%)	3646 (3.5%)	1443 (3.3%)
	Injury, poisoning and certain other consequences of external causes - (S00-T98)	1279 (3.4%)	661 (2.7%)	356 (3.5%)	3126 (3.0%)	1655 (3.8%)
	Factors influencing health status and contact with health services - (Z00-Z99)	7492 (19.9%)	4650 (19.0%)	1296 (12.7%)	19137 (18.2%)	5266 (12.1%)
	Encounter for issue of repeat prescription - Z76.0	4607 (12.2%)	2943 (12.0%)	645 (6.3%)	12084 (11.5%)	2718 (6.3%)
	Persons encountering health services in other specified circumstances - Z76.8	1747 (4.6%)	851 (3.5%)	354 (3.5%)	3713 (3.5%)	1480 (3.4%)
	Other	1049 (2.8%)	975 (4.0%)	284 (2.8%)	3720 (3.5%)	1114 (2.6%)

	Baseline period[1] (N=44108)	Study period year 3[2] Overall (N=29631)	Study period year 3[2] Incident[4] (N=12287)	Study period years 1, 2 and 3[3] Overall (N=123429)	Study period years 1, 2 and 3[3] Incident[4] (N=50597)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_19_02.sas; By: Alampure; Date & time: 20AUG19 15:03;

Table 15.3-98: Analysis of systemic TCC prescriptions – Off label indication – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – Rheumatologists France – included patients

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		Baseline period[1] (N=1721)	Study period year 3[2] Overall (N=1281)	Study period year 3[2] Incident[4] (N=578)	Study period years 1, 2 and 3[3] Overall (N=4184)	Study period years 1, 2 and 3[3] Incident[4] (N=1923)
Total systemic TCC prescriptions	Yes	1721 (100.0%)	1281 (100.0%)	578 (100.0%)	4184 (100.0%)	1923 (100.0%)
On label prescriptions	Yes	1227 (71.3%)	921 (71.9%)	381 (65.9%)	2966 (70.9%)	1250 (65.0%)
	No	494 (28.7%)	360 (28.1%)	197 (34.1%)	1218 (29.1%)	673 (35.0%)
Treatment indication for TCC prescription at index date (ICD10)	Missing	-	-	-	-	-
	Other deforming dorsopathies including - M43	18 (1.0%)	17 (1.3%)	7 (1.2%)	59 (1.4%)	33 (1.7%)
	Dorsalgia - M54	1209 (70.2%)	904 (70.6%)	374 (64.7%)	2907 (69.5%)	1217 (63.3%)
	Other than painful muscle contractures associated with acute spinal pathology	494 (28.7%)	360 (28.1%)	197 (34.1%)	1218 (29.1%)	673 (35.0%)
	Diseases of the musculoskeletal system and connective tissue - (M00-M99)	436 (25.3%)	309 (24.1%)	163 (28.2%)	1033 (24.7%)	564 (29.3%)
	Osteoarthritis of knee, unspecified - M17.9	31 (1.8%)	26 (2.0%)	14 (2.4%)	95 (2.3%)	63 (3.3%)
	Other specified arthrosis - M19.8	29 (1.7%)	7 (0.5%)	3 (0.5%)	18 (0.6%)	10 (0.8%)
	Pain in shoulder - M25.51	21 (1.2%)	32 (2.5%)	15 (2.6%)	78 (1.9%)	39 (2.0%)
	Pain in knee - M25.56	24 (1.4%)	20 (1.6%)	8 (1.4%)	79 (1.9%)	36 (1.9%)
	Other spondylosis - M47.8	44 (2.6%)	40 (3.1%)	20 (3.5%)	78 (1.9%)	38 (2.0%)

	Baseline period[1] (N=1721)	Study period year 3[2] Overall (N=1281)	Study period year 3[2] Incident[4] (N=578)	Study period years 1, 2 and 3[3] Overall (N=4184)	Study period years 1, 2 and 3[3] Incident[4] (N=1923)
Other shoulder lesions - M75.8	41 (2.4%)	2 (0.2%)	2 (0.3%)	28 (0.7%)	16 (0.8%)
Enthesopathy, unspecified - M77.9	18 (1.0%)	3 (0.2%)	2 (0.3%)	18 (0.4%)	10 (0.5%)
Rheumatism, unspecified - M79.0	16 (0.9%)	-	-	18 (0.4%)	6 (0.3%)
Pain in limb, hand, foot, fingers and toes - M79.6	61 (3.5%)	8 (0.6%)	3 (0.5%)	69 (1.6%)	36 (1.9%)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified - (R00-R99)	33 (1.9%)	31 (2.4%)	19 (3.3%)	100 (2.4%)	57 (3.0%)
Pain, unspecified - R52.9	31 (1.8%)	29 (2.3%)	17 (2.9%)	96 (2.3%)	54 (2.8%)
Other	25 (1.5%)	20 (1.6%)	15 (2.6%)	85 (2.0%)	52 (2.7%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_19_02.sas; By: Alampure; Date & time: 20AUG19 15:03;

Table 15.3-99: Analysis of systemic TCC prescriptions – Off label indication – Baseline, study period year 3 and cumulated study period years 1, 2 and 3 – GPs Italy – included patients

		Baseline period[1] (N=23527)	Study period year 3[2] Overall (N=17364)	Study period year 3[2] Incident[4] (N=6471)	Study period years 1, 2 and 3[3] Overall (N=54892)	Study period years 1, 2 and 3[3] Incident[4] (N=20674)
Total systemic TCC prescriptions	Yes	23527 (100.0%)	17364 (100.0%)	6471 (100.0%)	54892 (100.0%)	20674 (100.0%)
On label prescriptions	Missing (N)	2063	1532	601	4669	1884
	Yes	16228 (75.6%)	12392 (78.3%)	4449 (75.8%)	38976 (77.6%)	14228 (75.7%)
	No	5236 (24.4%)	3440 (21.7%)	1421 (24.2%)	11247 (22.4%)	4562 (24.3%)
Treatment indication for TCC prescription at index date (ICD9)	Missing	2063	1532	601	4669	1884

	Baseline period[1] (N=23527)	Study period year 3[2] Overall (N=17364)	Study period year 3[2] Incident[4] (N=6471)	Study period years 1, 2 and 3[3] Overall (N=54892)	Study period years 1, 2 and 3[3] Incident[4] (N=20674)
Other deforming dorsopathies including - M43	1082 (5.0%)	659 (4.2%)	238 (4.1%)	2164 (4.3%)	825 (4.4%)
Dorsalgia - M54	15146 (70.6%)	11733 (74.1%)	4211 (71.7%)	36812 (73.3%)	13403 (71.3%)
Other than painful muscle contractures associated with acute spinal pathology	5236 (24.4%)	3440 (21.7%)	1421 (24.2%)	11247 (22.4%)	4562 (24.3%)
Diseases Of The Musculoskeletal System And Connective Tissue (710-739)	3378 (15.7%)	2144 (13.5%)	788 (13.4%)	7136 (14.2%)	2635 (14.0%)
Osteoarthrosis Unspecified Whether Generalized Or Localized - 715.9	650 (3.0%)	398 (2.5%)	114 (1.9%)	1309 (2.6%)	387 (2.1%)
Spasm Of Muscle - 728.85	392 (1.8%)	224 (1.4%)	107 (1.8%)	814 (1.6%)	394 (2.1%)
Other Affections Of Shoulder Region Not Elsewhere Classified - 726.2	272 (1.3%)	182 (1.1%)	71 (1.2%)	639 (1.3%)	245 (1.3%)
Symptoms, Signs, And Ill-Defined Conditions (780-799)	591 (2.8%)	386 (2.4%)	196 (3.3%)	1224 (2.4%)	551 (2.9%)
Injury And Poisoning (800-999)	524 (2.4%)	335 (2.1%)	159 (2.7%)	1126 (2.2%)	562 (3.0%)
Other	743 (3.5%)	575 (3.6%)	278 (4.7%)	1761 (3.5%)	814 (4.3%)

Baseline period[1]: year 2013
Study period year 3[2]: France: 26th April 2018 - 25th April 2019 / Italy: 8th October 2017 - 7th October 2018
Study period years 1, 2 and 3[3]: France: 26th April 2016 - 25th April 2019 / Italy: 8th October 2015 - 7th October 2018
Incident case[4]: New TCC prescription in all patient history with at least one year of medical history

Program: /data/IMS/equipes/Analytics/Stats/FR-SAV14104MDT-3/Statistics/Analysis/program/tables/T_19_02.sas; By: Alampure; Date & time: 20AUG19 15:03;

Analysis of RMMs impact on off-label rate in included patients

The effect of RMMs on off label incidence for treatment indication was performed. The analysis used a segmented regression analysis [Wagner et al., 2002]. In this analysis, off-label rates (proportion of off-label TCC prescriptions among evaluable TCC prescriptions) were computed by month before (baseline: 2013) and after RMMs implementation (study period) according to each country. The model included an intercept (mean outcome rate at beginning of the study) and main period (before / after RMMs) effect and separate time trends before and after RMMs.

The segmented regression analysis of interrupted time series data was used to estimate the effect of the intervention on the monthly off-label rates, immediately after intervention period and also to identify whether there was a monthly trend in the rate of off-label use in the baseline period and in the post-intervention period (study period).

The rate of off-label use during the intervention period (January 2014 to October 7th, 2015 in Italy, January 2014 to April 25th, 2016 for France) was excluded from analysis.

The following model was used to estimate the level and the trend in off label rate before the intervention period and also the change in level and trend after the intervention period:

Off-label $rate_t = \beta_0+\beta_1*time_t + \beta_2*intervention_t + \beta_3*time\ after\ intervention_t+e_t$
where:

- Off-label $rate_t$ is the proportion of off label TCC prescriptions per month
- β_0 is the baseline off label rate at the beginning of the baseline period
- β_1 estimates the change in the off-label rate before intervention (baseline linear trend of the monthly off-label rate)
- $time_t$ is the time in months from the beginning of the baseline period
- β_2 estimates the level change in the off-label rate immediately after the intervention (study period)
- β_3 estimates the change in the trend of the off-label rate after intervention (study period) compared to the trend of the off-label rate during baseline period
- e_t is the random error

The stationarity (constant mean on period, constant variance on period and autocorrelation) was tested per period by using the Dicker-Fuller unit root test.

There were also some other limitations in this segmented regression analysis:

- The number of observations at each data point for rheumatologists France is around 100 prescriptions per month for analysis of off-label rate. This is the limit of the number of observations required to get an acceptable level of variability of estimate for each data point [Wagner et al., 2002].
- Due to the exclusion of the intervention period, the baseline and study period are not “continuous” i.e. the last month of the baseline period is December (2013) while the first month of the study period is October (2015) for Italy and May (2016) for France. Ideally the first month of the post-intervention period should be January, whatever the year involved. In case of seasonality or autocorrelations, the non-calendar continuity of the period could lead to incorrect inference and interpretations of results.

It was initially planned to analyze a global off-label rate based on the collected variables on relevant characteristics of use including dose, duration, indication, no concomitant medication and pregnancy or lactation for women of childbearing potential. This analysis induced some limitations in interpretation of the results mostly for Italy: the global off-label rate should be calculated on evaluable TCC prescriptions, i.e. prescriptions with information on indication, posology and duration available. The percentage of evaluable TCC prescriptions was 80% in both GPs and rheumatologists France for baseline and study periods. The percentage of evaluable TCC prescriptions in Italy was respectively 24% in baseline period, 21% in study period year 1 and year 2, and 20% in study period year 3. The reason of this percentage of non-evaluable TCC prescriptions in GPs Italy is due to a high level of no recorded posology.

Regarding proportions of off-label pregnancy, lactation and use of contraception, they were calculated in women of childbearing potential (16-49 years), proportions of off-label dosage > 16 mg and duration > 7 days were calculated for prescriptions in oral form, and proportions of off-label dosage > 8 mg and duration > 5 days were calculated for prescriptions in intramuscular form.

Note: due to the number of missing value, the number of observations per months for an analysis of off-label rate of dosage or duration will be insufficient for a segmented regression analysis of these variables. So, when number of prescriptions was lower than 100 prescriptions, models were not run. It was the case of GPs France and Rheumatologists France for IM dosage > 8 mg and IM duration > 5 days, and also for pregnancy, lactation and contraception for Rheumatologists France. In addition, as numbers of prescriptons for age < 16 years old and oral dosage > 16 mg in Rheumatologists France were negligible, the models were also not run.

Figure 24: Evolution of off-label rate – GPs France – included patients

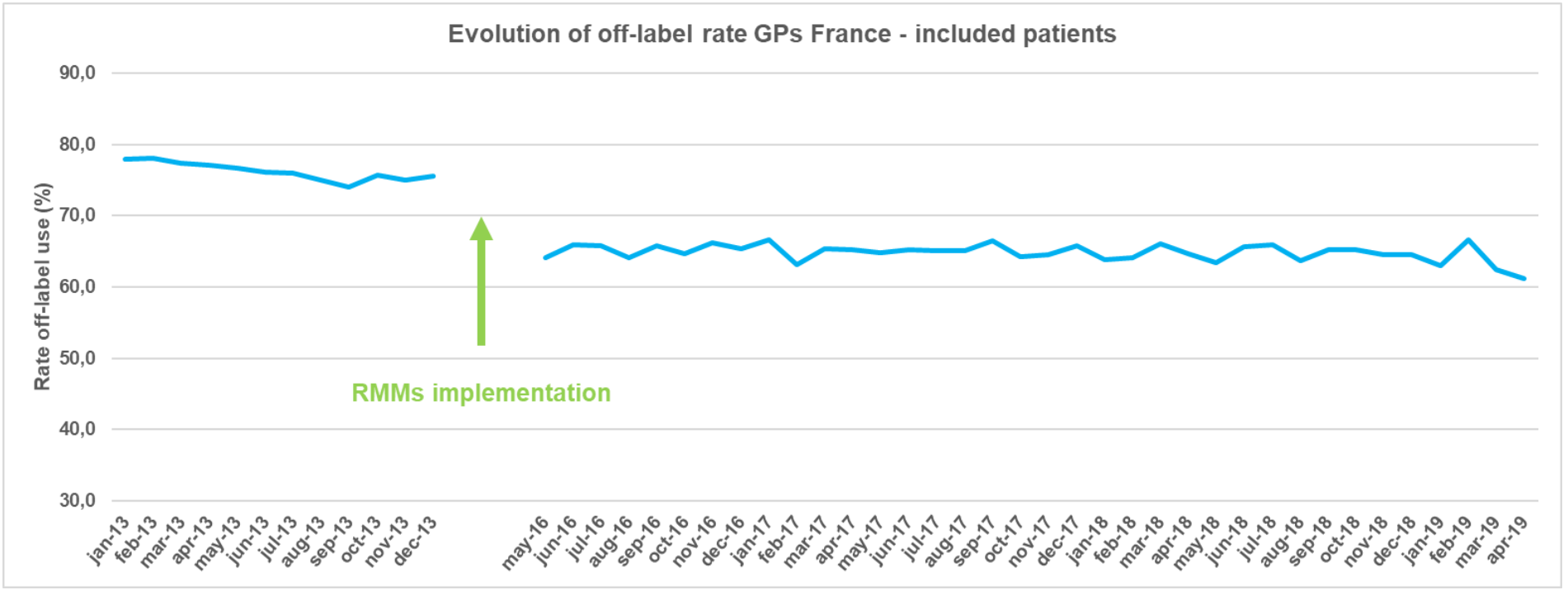

Table 15.3-100: Analysis of the effect of RMMs on off label rate (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	78.2087	0.6512	120.11	<.0001
Time	-0.3021	0.0885	-3.41	0.0014
Intervention	-12.0412	0.8504	-14.16	<.0001
Time after intervention	0.2593	0.0901	2.88	0.0062

This analysis on GPs France shows that the intervention is associated with a statistically significant reduction of off-label rate immediately after intervention and also a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 78.2%.
A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant reduction of 0.3 percentage point with each month (p-value=0.0014).
There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use dropped immediately after the intervention period by -12 percentage points (p-value<0.0001).
The 'time after intervention variable' show a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant increase of 0.26 percentage point with each month in comparison with the previous slop (p-value=0.0062).

Figure 25: Evolution of off-label rate – Rheumatologists France – included patients

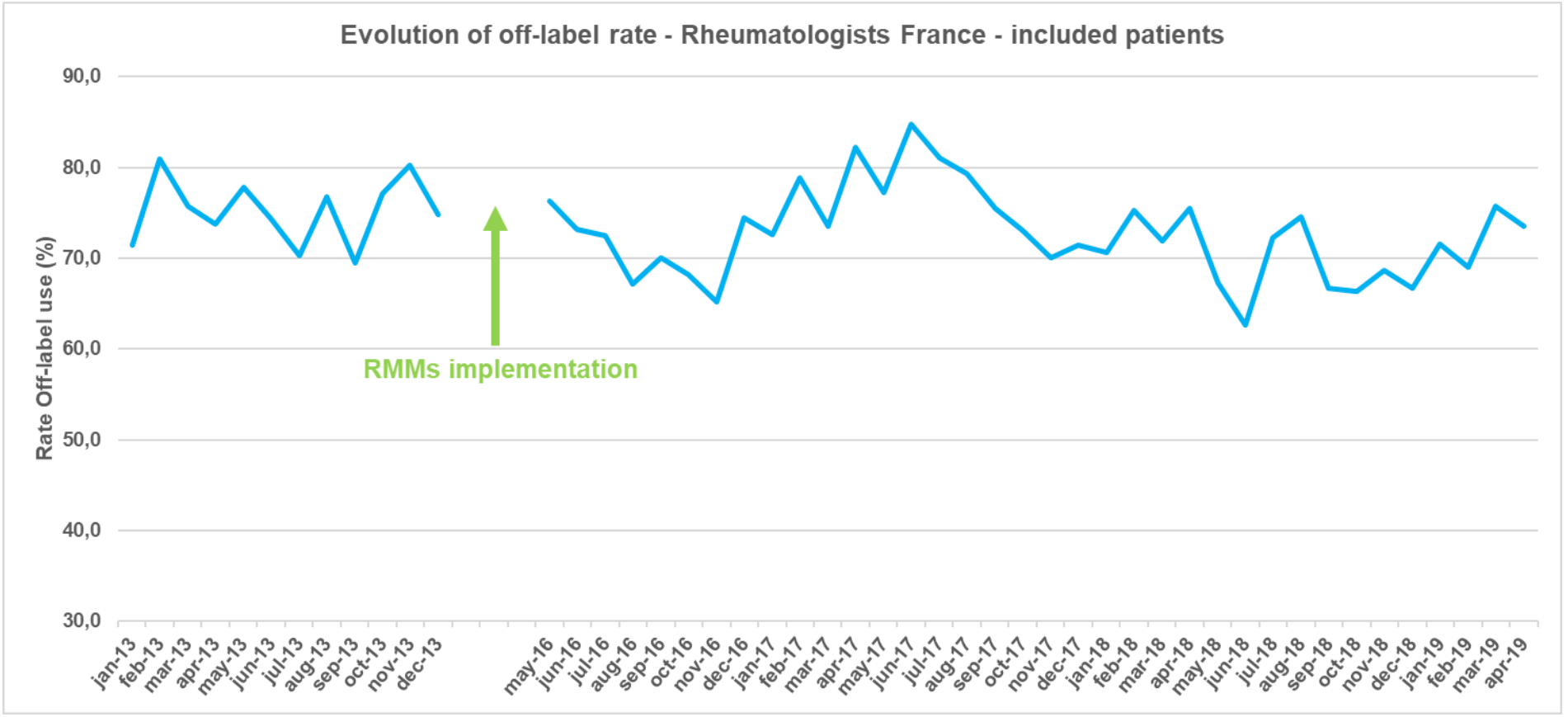

Table 15.3-101: Analysis of the effect of RMMs on off label rate (prescriptions) – Rheumatologists France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	74.9506	2.9065	25.79	<.0001
Time	0.0441	0.3949	0.11	0.9117
Intervention	1.2240	3.7957	0.32	0.7486
Time after intervention	-0.1589	0.4021	-0.40	0.6946

There was no effect of the intervention observed on the monthly off-label rates in Rheumatologists France, immediately after intervention period and also in trend in the rate of off-label in study period. Due the low number of evaluable prescriptions per month, interpretation of the results for rheumatologists France should be interpreted with care.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 75%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.7486).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.6946).

Figure 26: Evolution of off-label rate – GPs Italy – included patients

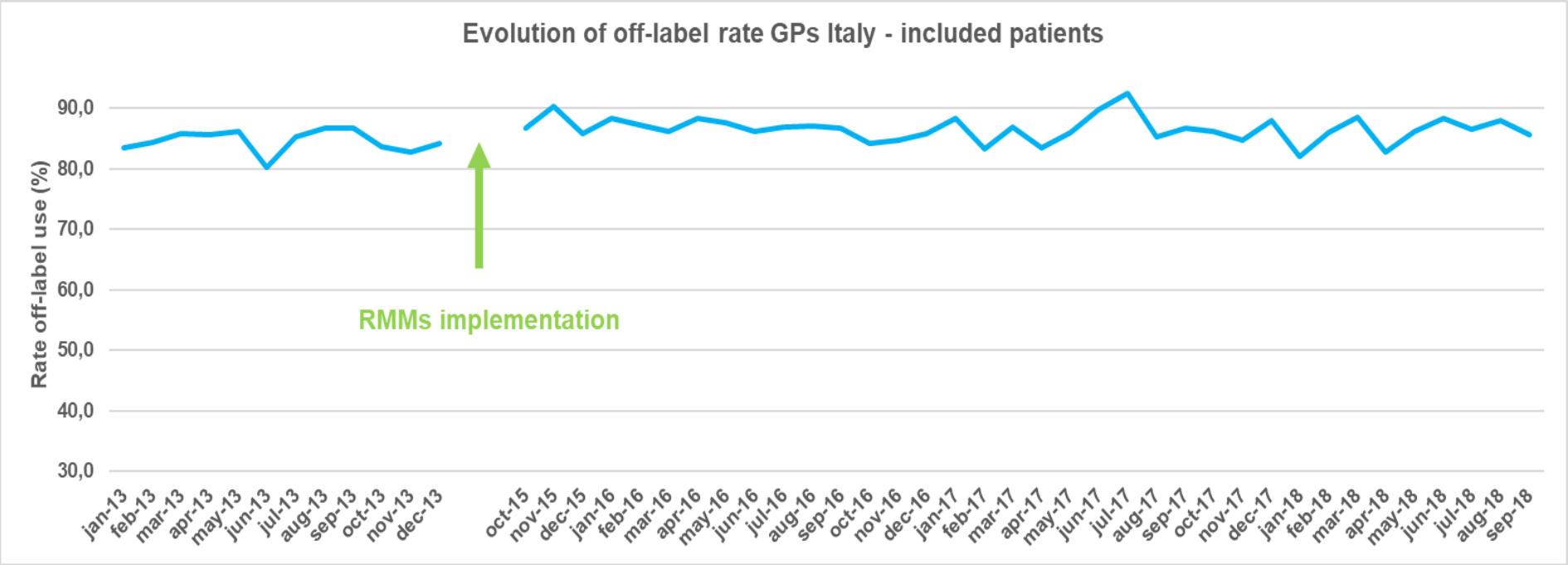

Table 15.3-102: Analysis of the effect of RMMs on off label rate (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	84.7583	1.2795	66.24	<.0001
Time	-0.0359	0.1739	-0.21	0.8375
Intervention	2.7773	1.6710	1.66	0.1036
Time after intervention	0.003853	0.1770	0.02	0.9827

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 84.8%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1036).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.9827).

Figure 27: Evolution of off-label rate (treatment indication) – GPs France – included patients

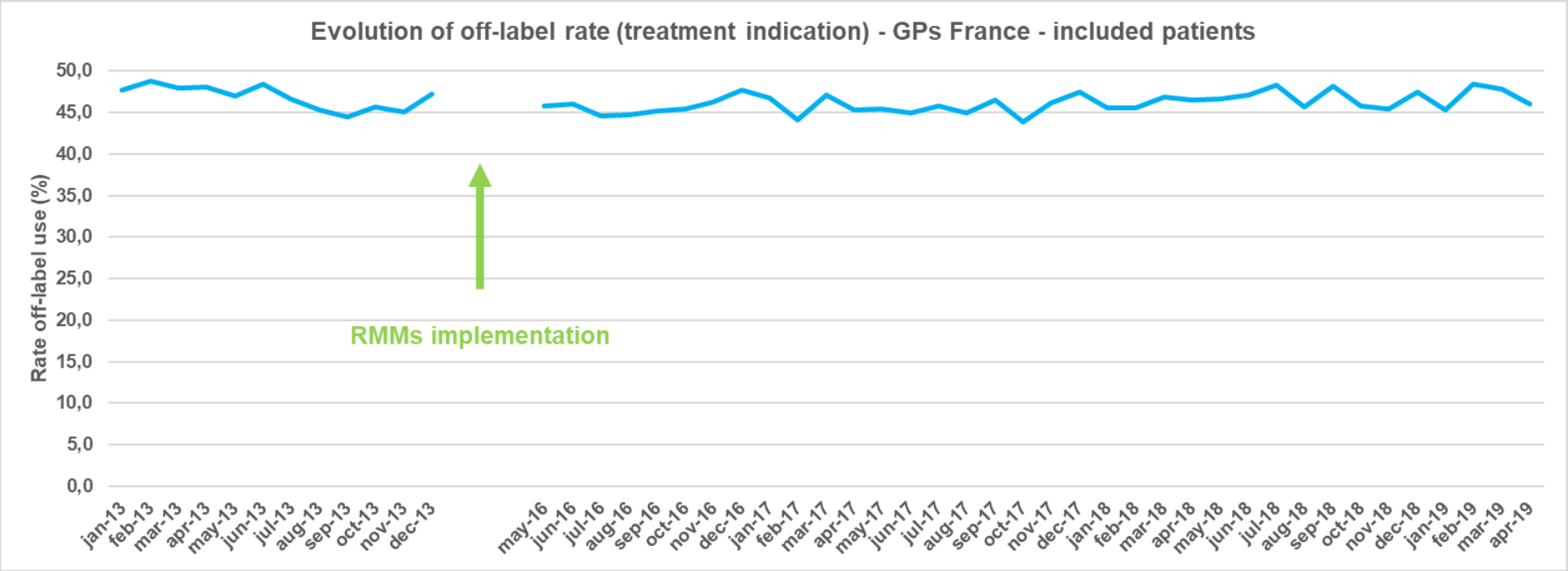

Table 15.3-103: Analysis of the effect of RMMs on off label rate of treatment indication (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	48.6116	0.6579	73.89	<.0001
Time	-0.2734	0.0894	-3.06	0.0038
Intervention	-3.8566	0.8591	-4.49	<.0001
Time after intervention	0.3193	0.0910	3.51	0.0011

This analysis on GPs France shows that the intervention is associated with a statistically significant reduction of off-label rate immediately after intervention and also a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 48.6%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant reduction of 0.27 percentage point with each month (p-value=0.0038).

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use dropped immediately after the intervention period by -3.9 percentage points (p-value<0.0001).

The 'time after intervention variable' shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant increase of 0.32 percentage point with each month in comparison with the previous slop (p-value=0.0011).

Figure 28: Evolution of off-label rate (treatment indication) – Rheumatologists France – included patients

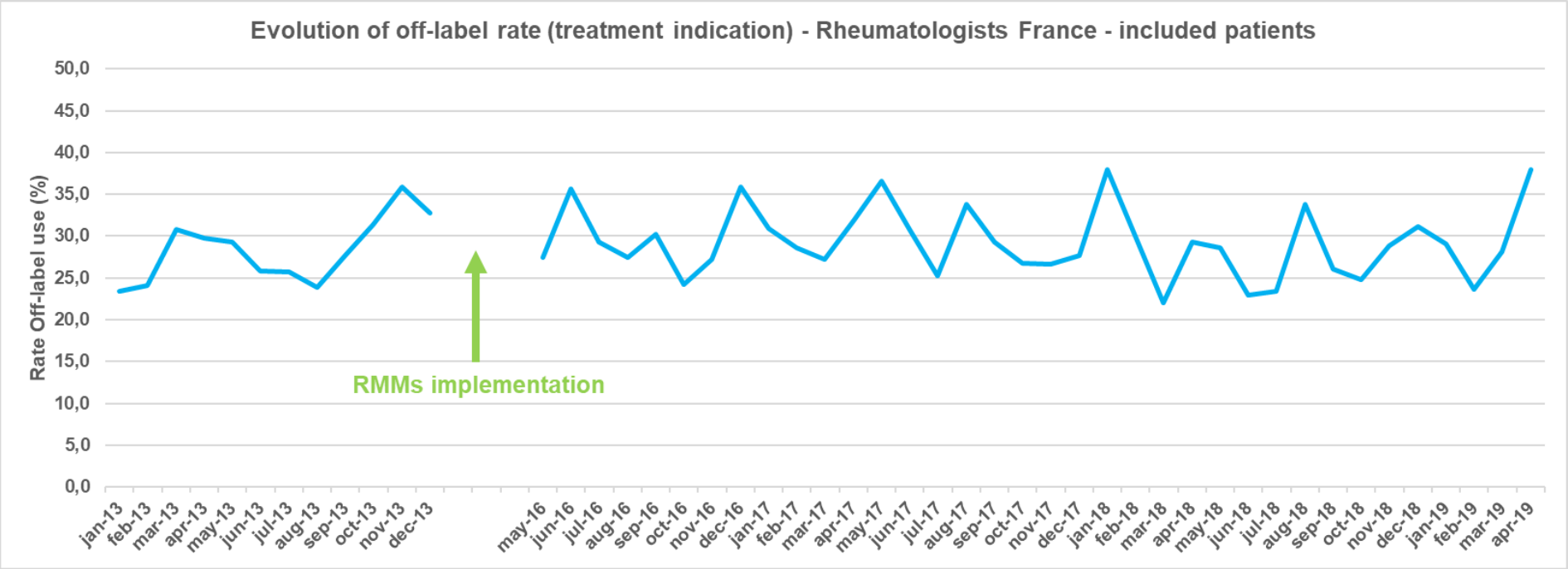

Table 15.3-104: Analysis of the effect of RMMs on off label rate of treatment indication (prescriptions) – Rheumatologists France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	24.3819	2.4068	10.13	<.0001
Time	0.8121	0.3374	2.41	0.0204
Intervention	6.2602	3.1414	1.99	0.0527
Time after intervention	-0.8607	0.3432	-2.51	0.0160
Dummy variable	-5.1300	2.6897	-1.91	0.0632

This analysis on Rheumatologists France shows that the intervention is not associated with a change of off-label rate immediately after intervention but there is a change in the slope after intervention compare to the slope before intervention. Due the low number of evaluable prescriptions per month, interpretation of the results for Rheumatologists France should be interpreted with care.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 24.4%.
A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.8 percentage point with each month (p-value=0.0204).
The ‘time after intervention variable’ shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant decrease of 0.86 percentage point with each month in comparison with the previous slop (p-value=0.0160).
The dummy variable is not interpretable but allows to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 29: Evolution of off-label rate (treatment indication) – GPs Italy – included patients

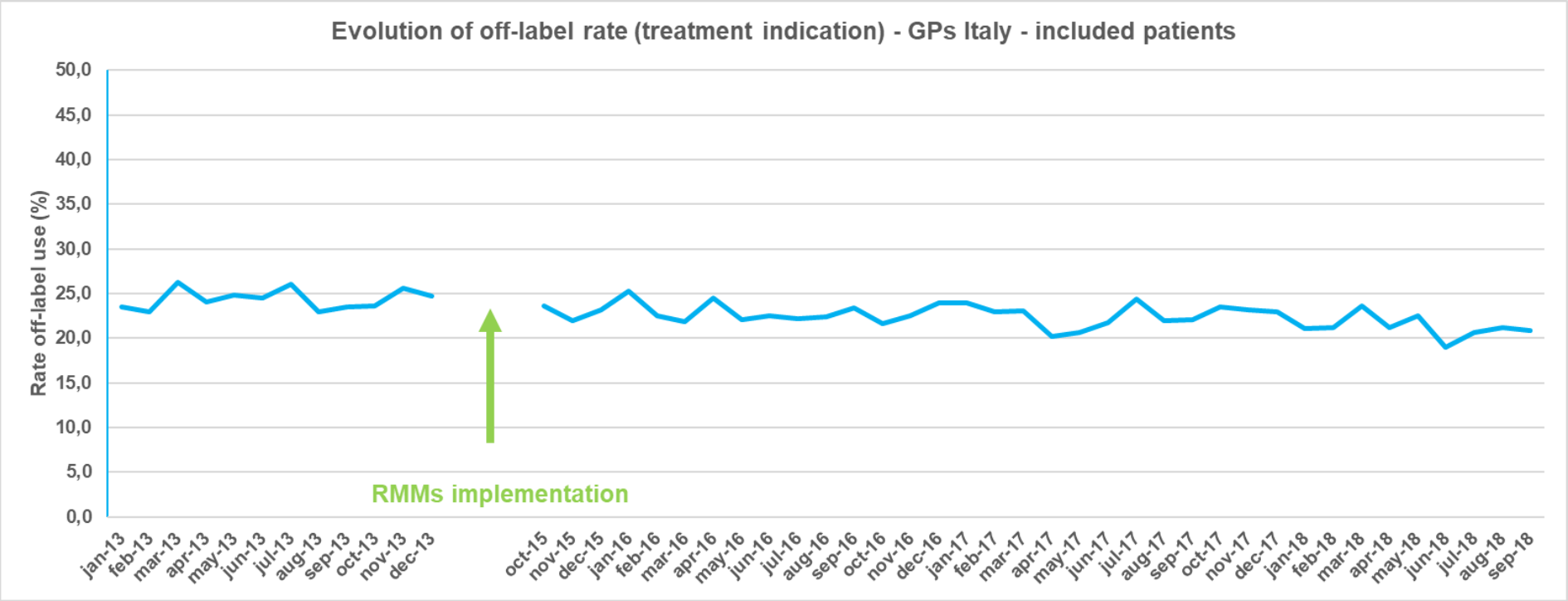

Table 15.3-105: Analysis of the effect of RMMs on off label rate of treatment indication (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	24.1229	0.7384	32.67	<.0001
Time	0.0405	0.1003	0.40	0.6881
Intervention	0.0619	0.9643	0.06	0.9491
Time after intervention	-0.0998	0.1022	-0.98	0.3341

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 24.1%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.9491).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.3341).

Figure 30: Evolution of off-label rate (age<16 years old) – GPs France – included patients

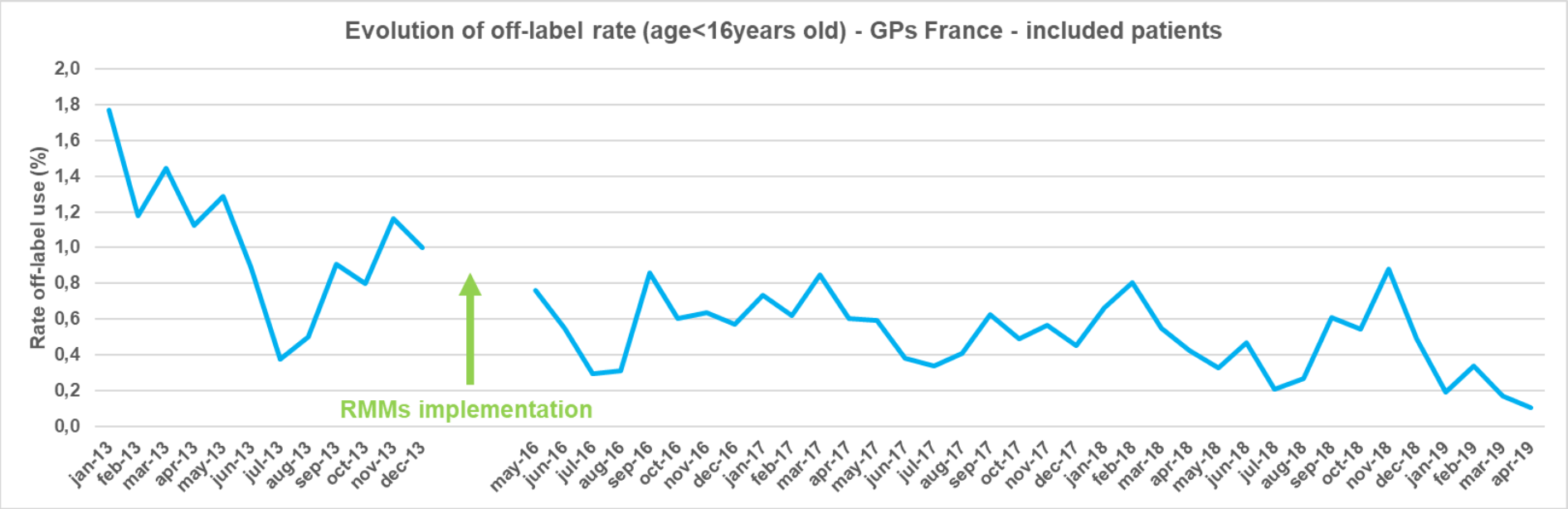

Table 15.3-106: Analysis of the effect of RMMs on off label rate of age < 16 years old (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	1.4246	0.1409	10.11	<.0001
Time	-0.0598	0.0191	-3.13	0.0031
Intervention	-0.6688	0.1840	-3.64	0.0007
Time after intervention	0.0517	0.0195	2.65	0.0111

This analysis on GPs France shows that the intervention is associated with a statistically significant reduction of off-label rate immediately after intervention and also a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 1.4%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant reduction of 0.06 percentage point with each month (p-value=0.0031).

There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use dropped immediately after the intervention period by -0.67 percentage points (p-value=0.0007).

The 'time after intervention variable' shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant increase of 0.05 percentage point with each month in comparison with the previous slop (p-value=0.0111).

Figure 31: Evolution of off-label rate (age<16 years old) – GPs Italy – included patients

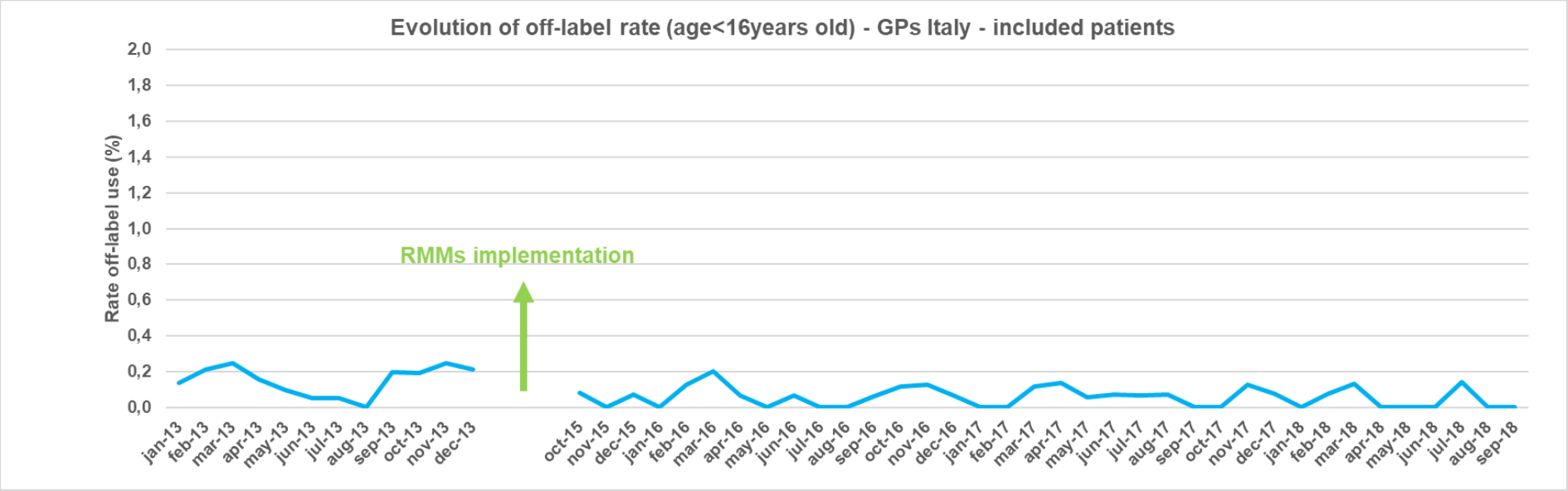

Table 15.3-107: Analysis of the effect of RMMs on off label rate of age < 16 years old (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	0.2061	0.0385	5.36	<.0001
Time	0.0000666	0.004694	0.01	0.9887
Intervention	-0.1260	0.0480	-2.62	0.0120
Time after intervention	-0.000828	0.004778	-0.17	0.8633
Dummy variable	-0.1340	0.0329	-4.08	0.0002

This analysis on GPs Italy shows that the intervention is associated with a significant decrease of off-label rate immediately after intervention but is not associated with a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 0.21%.
There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use dropped immediately after the intervention period by -0.13 percentage points (p-value=0.0120).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.8633).
The dummy variable is not interpretable but allows to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 32: Evolution of off-label rate (no concomitant use) – GPs France – included patients

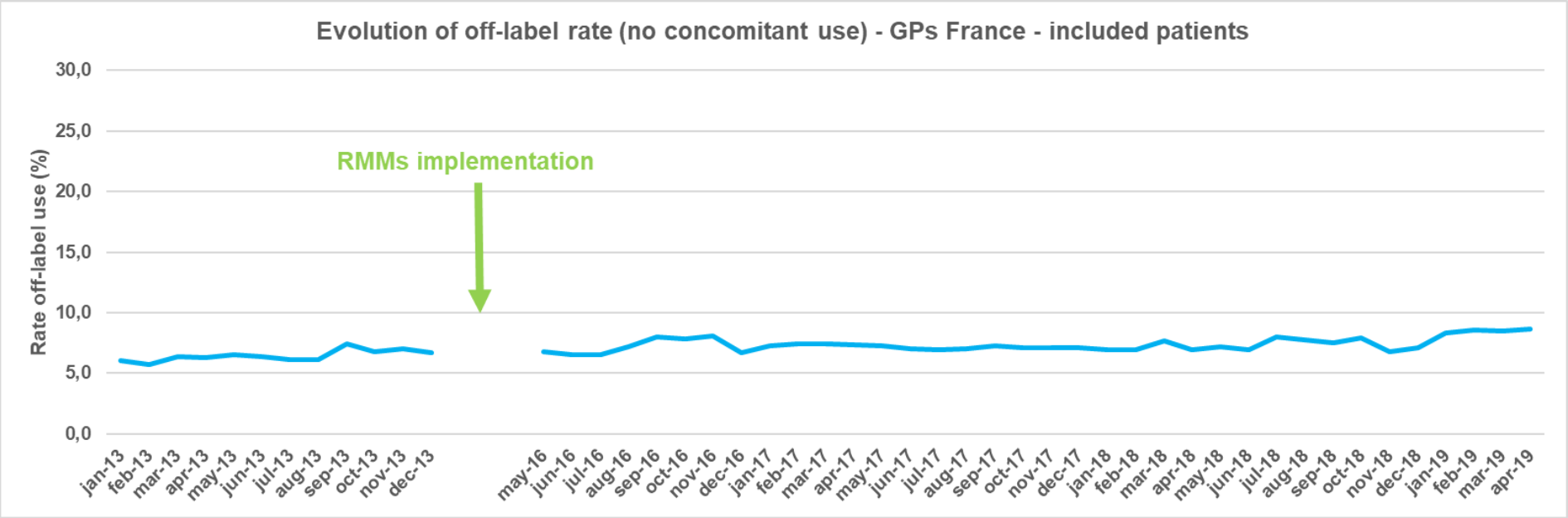

Table 15.3-108: Analysis of the effect of RMMs on off label rate of no concomitant use (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	5.8912	0.2891	20.38	<.0001
Time	0.0884	0.0393	2.25	0.0295
Intervention	0.7260	0.3775	1.92	0.0610
Time after intervention	-0.0632	0.0400	-1.58	0.1213

This analysis on GPs France shows that the intervention is not associated with a change of off-label rate after intervention neither with a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 5.9%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.09 percentage point with each month (p-value=0.0295).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.0610).

There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.1213).

Figure 33: Evolution of off-label rate (no concomitant use) – Rheumatologists France – included patients

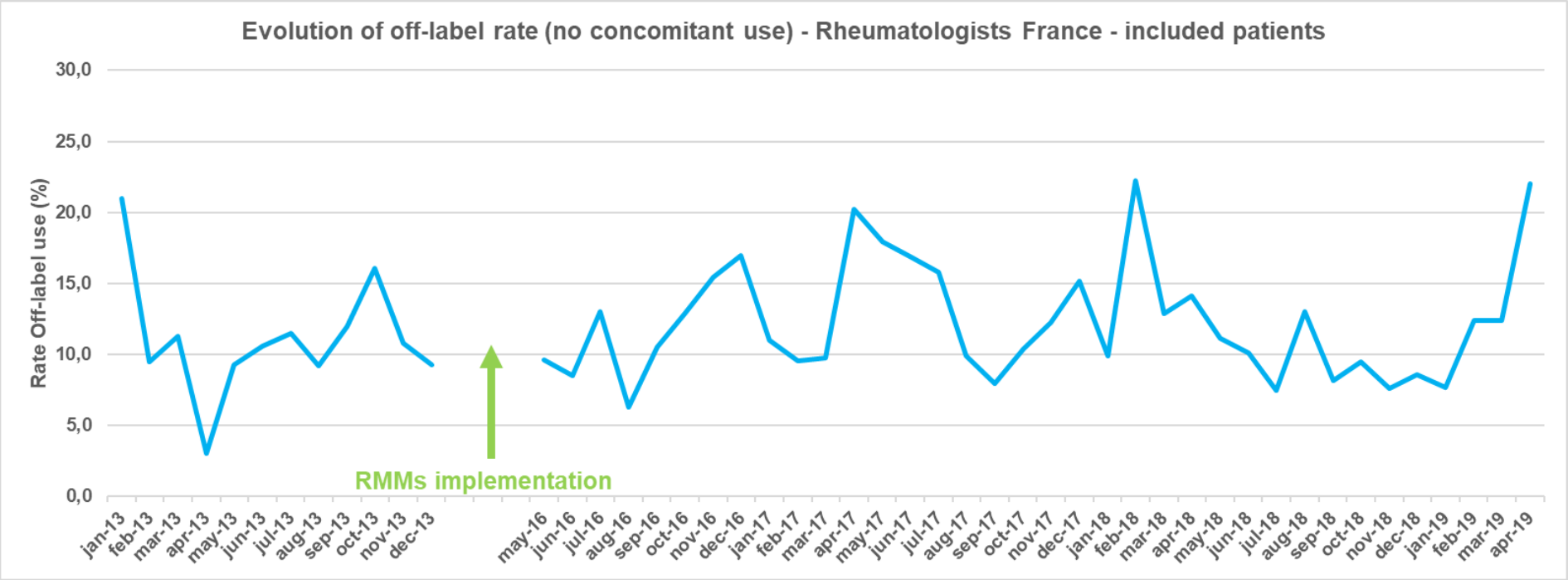

Table 15.3-109: Analysis of the effect of RMMs on off label rate of no concomitant use (prescriptions) – Rheumatologists France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	11.9945	2.6011	4.61	<.0001
Time	-0.1358	0.3534	-0.38	0.7027
Intervention	0.3746	3.3969	0.11	0.9127
Time after intervention	0.1300	0.3599	0.36	0.7197

This analysis on Rheumatologists France shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period. Due the low number of evaluable prescriptions per month, interpretation of the results for Rheumatologists France should be interpreted with care.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 12%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.9127).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.7197).

Figure 34: Evolution of off-label rate (no concomitant use) – GPs Italy – included patients

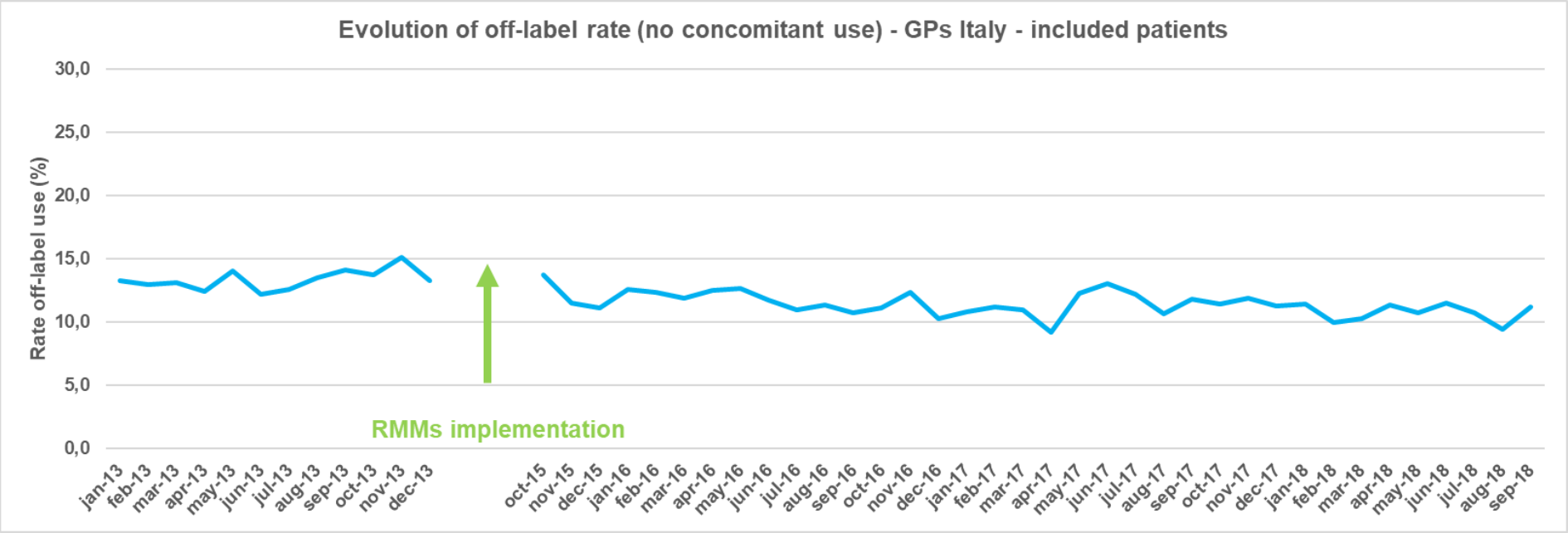

Table 15.3-110: Analysis of the effect of RMMs on off label rate of no concomitant use (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	13.0413	0.5786	22.54	<.0001
Time	0.0872	0.0712	1.23	0.2272
Intervention	-0.3211	0.7212	-0.45	0.6584
Time after intervention	-0.1298	0.0724	-1.79	0.0800
Dummy variable	-0.6975	0.5210	-1.34	0.1877

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 13%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.6584).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.0800).
The dummy variable is not interpretable but allows to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 35: Evolution of off-label rate (IM form dosage>8 mg per day) – GPs Italy – included patients

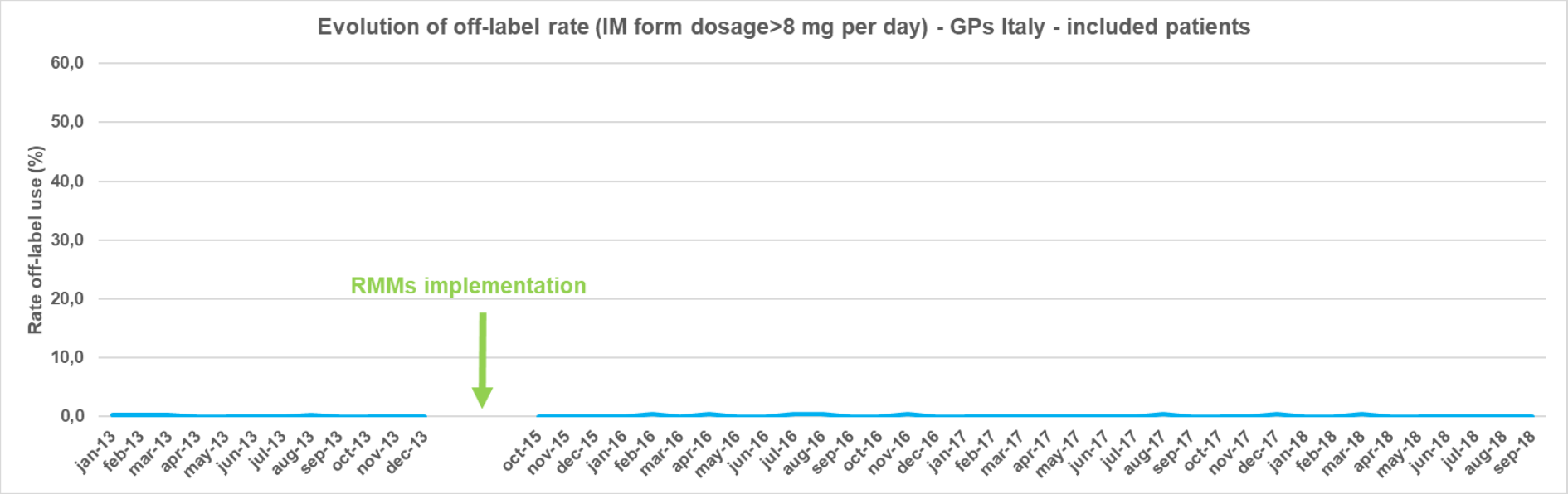

Table 15.3-111: Analysis of the effect of RMMs on off label rate of IM form dosage>8 mg per day (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	0.2274	0.0970	2.34	0.0237
Time	-0.0209	0.0132	-1.59	0.1196
Intervention	-0.0879	0.1267	-0.69	0.4916
Time after intervention	0.0192	0.0134	1.43	0.1596

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 0.23%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.4916).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.1596).

Figure 36: Evolution of off-label rate (oral form dosage>16 mg per day) – GPs France – included patients

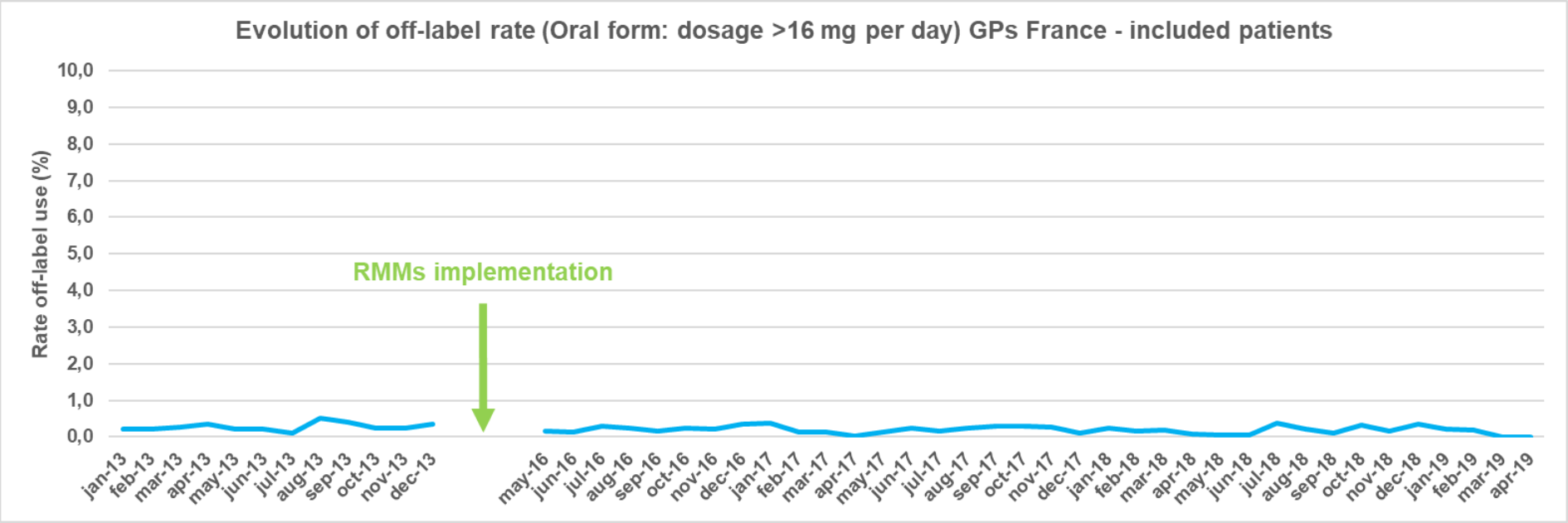

Table 15.3-112: Analysis of the effect of RMMs on off label rate of oral form dosage>16 mg per day (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	0.2149	0.0643	3.34	0.0017
Time	0.009439	0.008738	1.08	0.2859
Intervention	0.0328	0.0840	0.39	0.6976
Time after intervention	-0.0113	0.008897	-1.27	0.2114

This analysis on GPs France shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 0.21%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.6976).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.2114).

Figure 37: Evolution of off-label rate (oral form dosage>16 mg per day) – GPs Italy – included patients

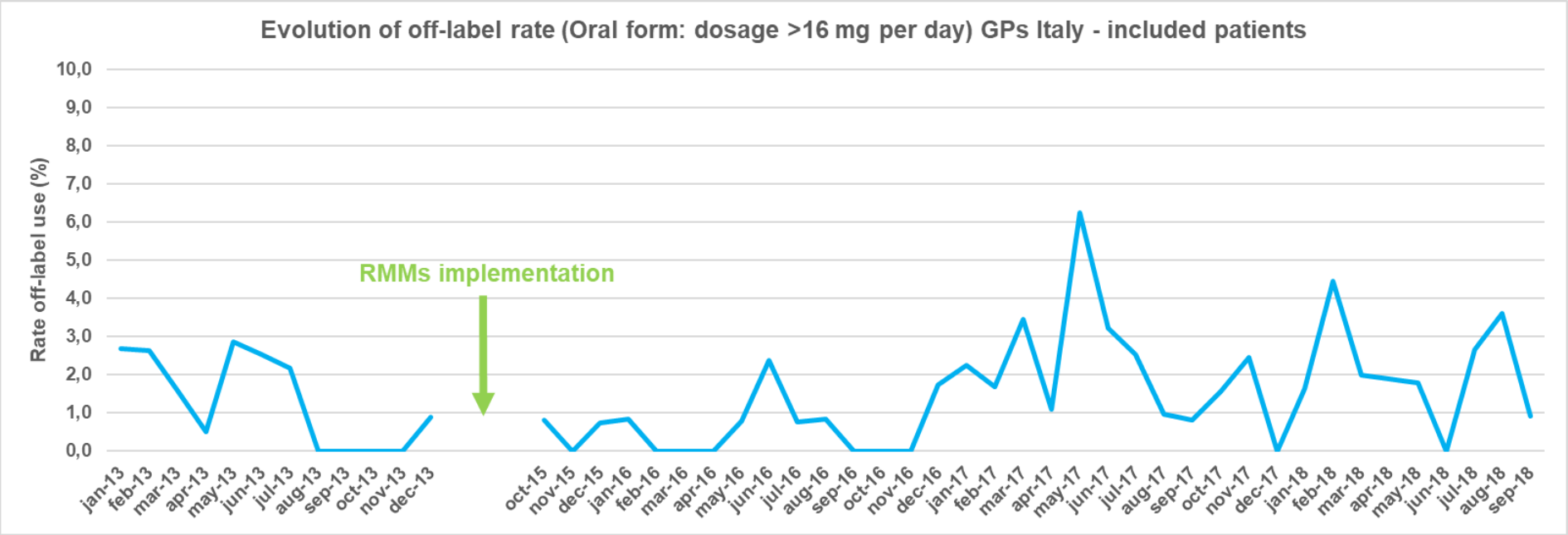

Table 15.3-113: Analysis of the effect of RMMs on off label rate of oral form dosage>16 mg per day (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	2.0033	0.9223	2.17	0.0354
Time	0.0346	0.1992	0.17	0.8629
Intervention	-2.1973	1.1197	-1.96	0.0562
Time after intervention	0.0211	0.2002	0.11	0.9164
Dummy variable	-2.1717	1.3951	-1.56	0.1269

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 2%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.0562).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.9164).
The dummy variable is not interpretable but allows to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.

Figure 38: Evolution of off-label rate (IM form > 5 consecutive days) – GPs Italy – included patients

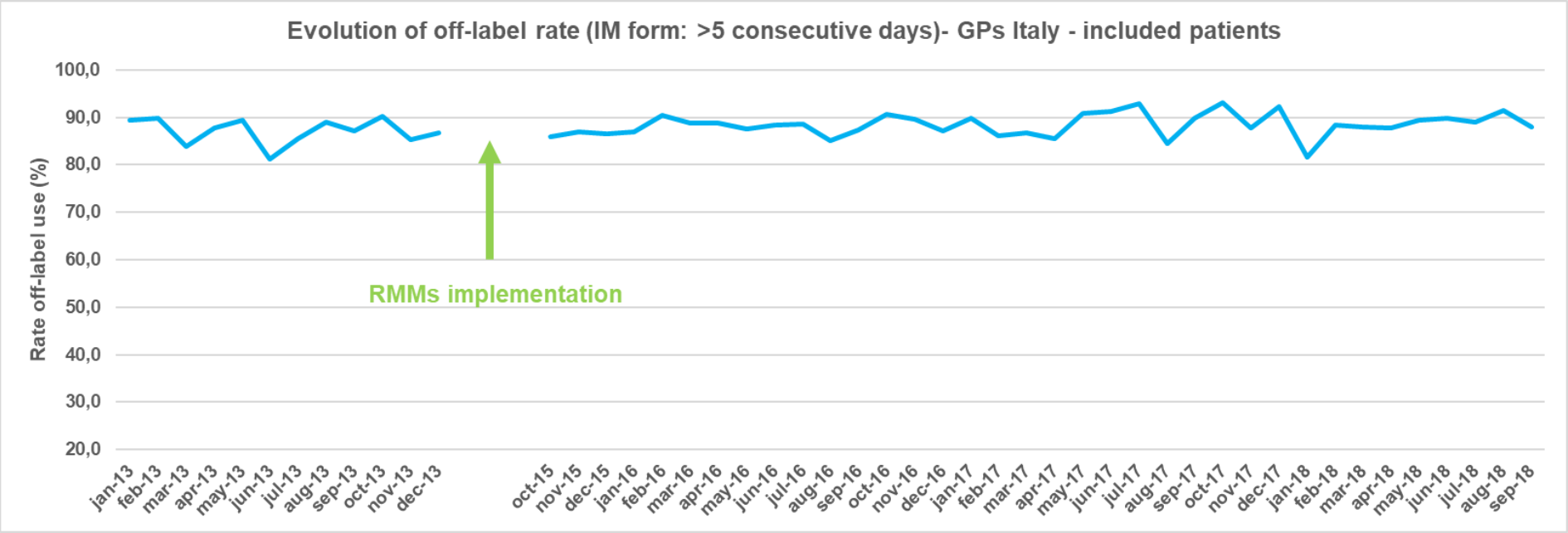

Table 15.3-114: Analysis of the effect of RMMs on off label rate of IM form > 5 consecutive days (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	87.6414	1.5509	56.51	<.0001
Time	-0.0838	0.2107	-0.40	0.6928
Intervention	-0.6855	2.0253	-0.34	0.7366
Time after intervention	0.1321	0.2146	0.62	0.5414

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 87.6%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.7366).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.5414).

Figure 39: Evolution of off-label rate (oral form > 7 consecutive days) – GPs France – included patients

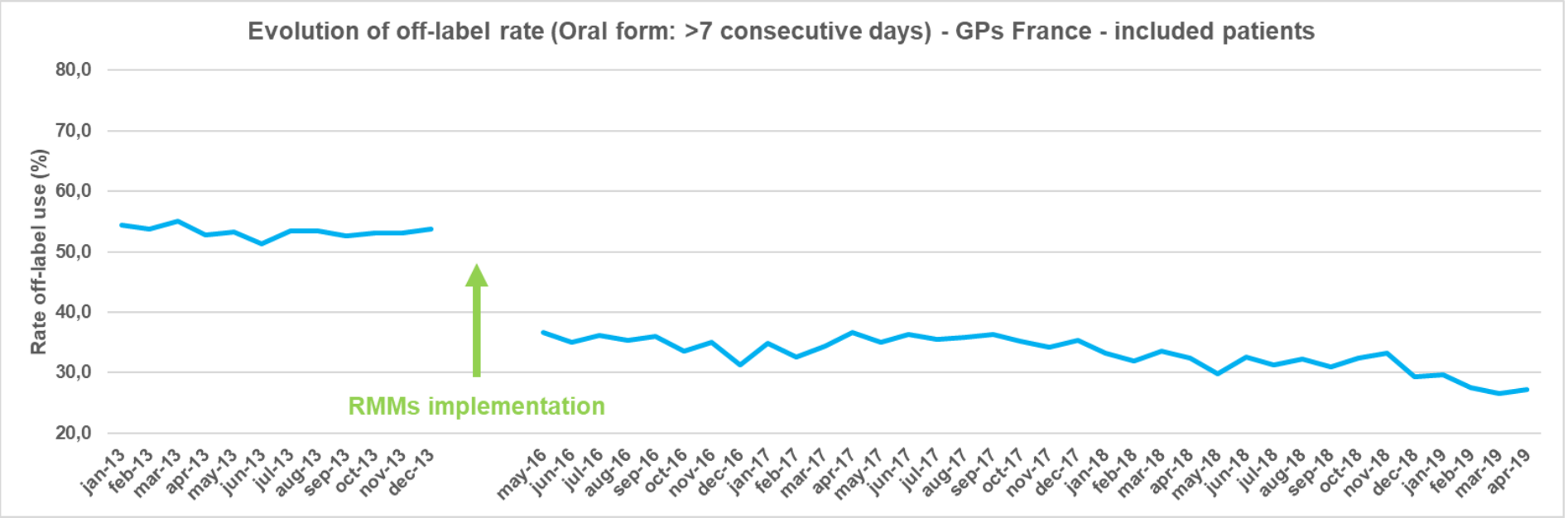

Table 15.3-115: Analysis of the effect of RMMs on off label rate of oral form > 7 consecutive days (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	53.8960	1.0051	53.62	<.0001
Time	-0.0903	0.1366	-0.66	0.5118
Intervention	-14.4824	1.3126	-11.03	<.0001
Time after intervention	-0.1134	0.1391	-0.82	0.4192

This analysis on GPs France shows that the intervention is associated with a significant decrease of off-label rate immediately after intervention but is not associated with a change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 53.9%.
There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use dropped immediately after the intervention period by -14.5 percentage points (p-value<0.0001).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.4192).

Figure 40: Evolution of off-label rate (oral form > 7 consecutive days) – Rheumatologists France – included patients

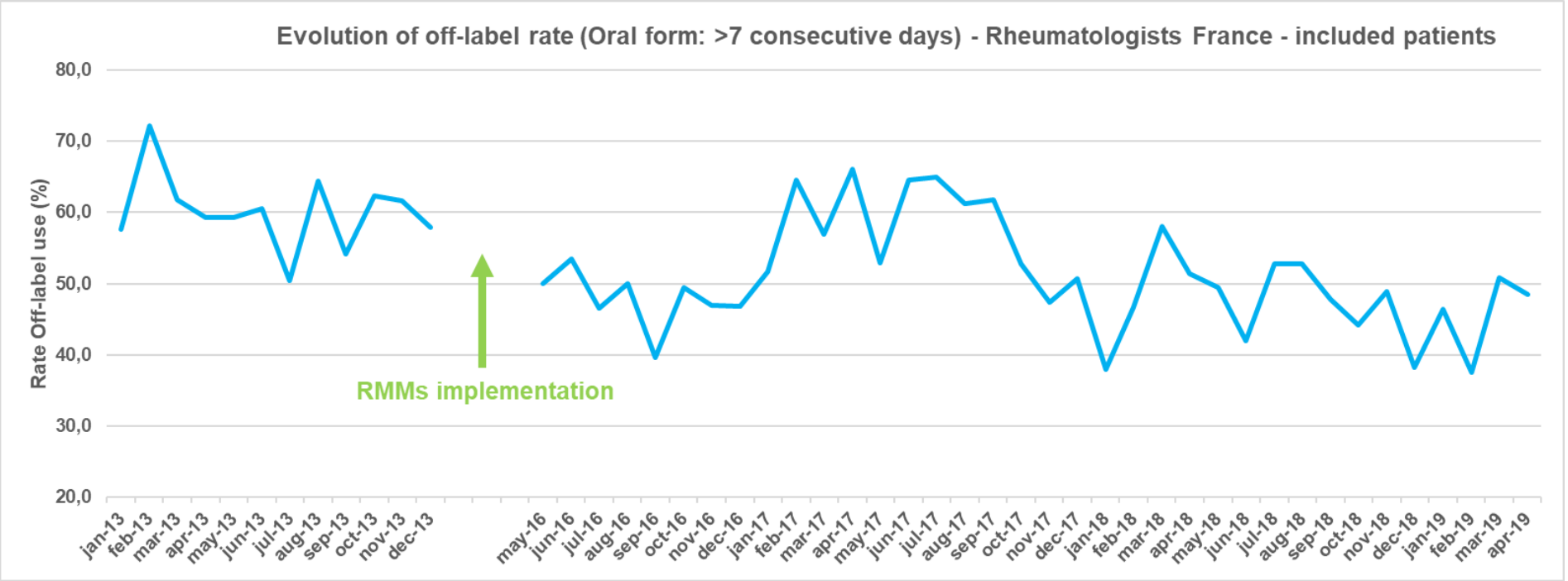

Table 15.3-116: Analysis of the effect of RMMs on off label rate of oral form > 7 consecutive days (prescriptions) – Rheumatologists France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	62.5778	4.3091	14.52	<.0001
Time	-0.3751	0.5855	-0.64	0.5251
Intervention	-5.4423	5.6274	-0.97	0.3388
Time after intervention	0.1698	0.5962	0.28	0.7771

This analysis on Rheumatologists France shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period. Due the low number of evaluable prescriptions per month, interpretation of the results for Rheumatologists France should be interpreted with care.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 62.6%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3388).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.7771).

Figure 41: Evolution of off-label rate (oral form > 7 consecutive days) – GPs Italy – included patients

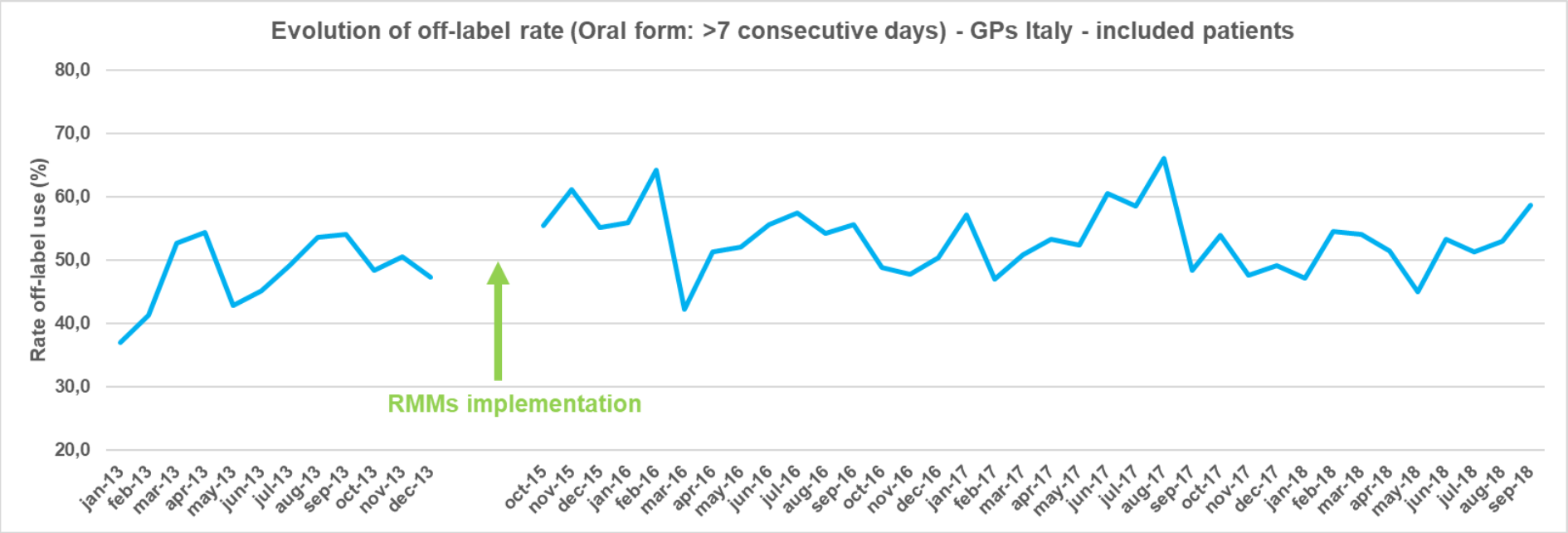

Table 15.3-117: Analysis of the effect of RMMs on off label rate of oral form > 7 consecutive days (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	43.4060	3.1718	13.69	<.0001
Time	0.7118	0.4310	1.65	0.1057
Intervention	12.6268	4.1421	3.05	0.0039
Time after intervention	-0.8002	0.4388	-1.82	0.0750

This analysis on GPs Italy shows that the intervention is associated with a significant decrease of off-label rate immediately after intervention but there is no change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 43.4%.
There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use increased immediately after the intervention period by 12.6 percentage points (p-value=0.0039).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.0750).

Figure 42: Evolution of off-label rate (long-term treatment) – GPs France – included patients

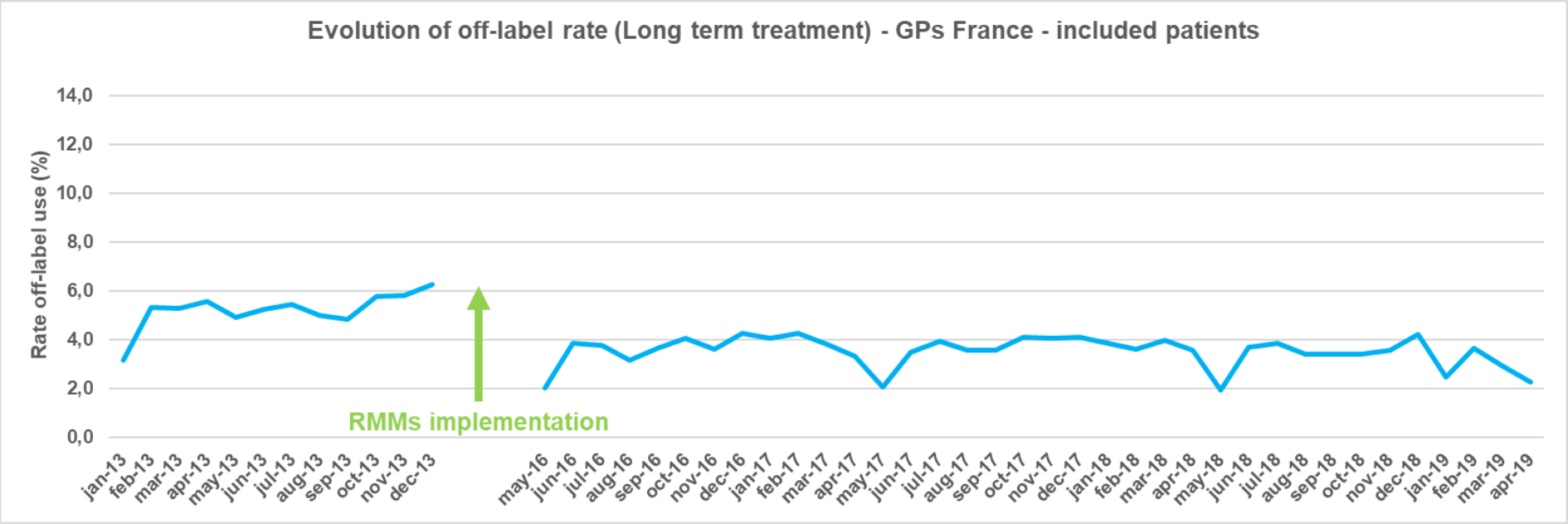

Table 15.3-118: Analysis of the effect of RMMs on off label rate of long-term treatment (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	4.3390	0.3899	11.13	<.0001
Time	0.1367	0.0530	2.58	0.0133
Intervention	-0.4891	0.5092	-0.96	0.3420
Time after intervention	-0.1473	0.0539	-2.73	0.0090

This analysis on GPs France shows that the intervention is not associated with a change of off-label rate after intervention but there is a statistically significant change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 4.3%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.14 percentage point with each month (p-value=0.0133).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3420).

The ‘time after intervention variable’ shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant decrease of 0.15 percentage point with each month in comparison with the previous slop (p-value=0.0090).

Figure 43: Evolution of off-label rate (long-term treatment) – Rheumatologists France – included patients

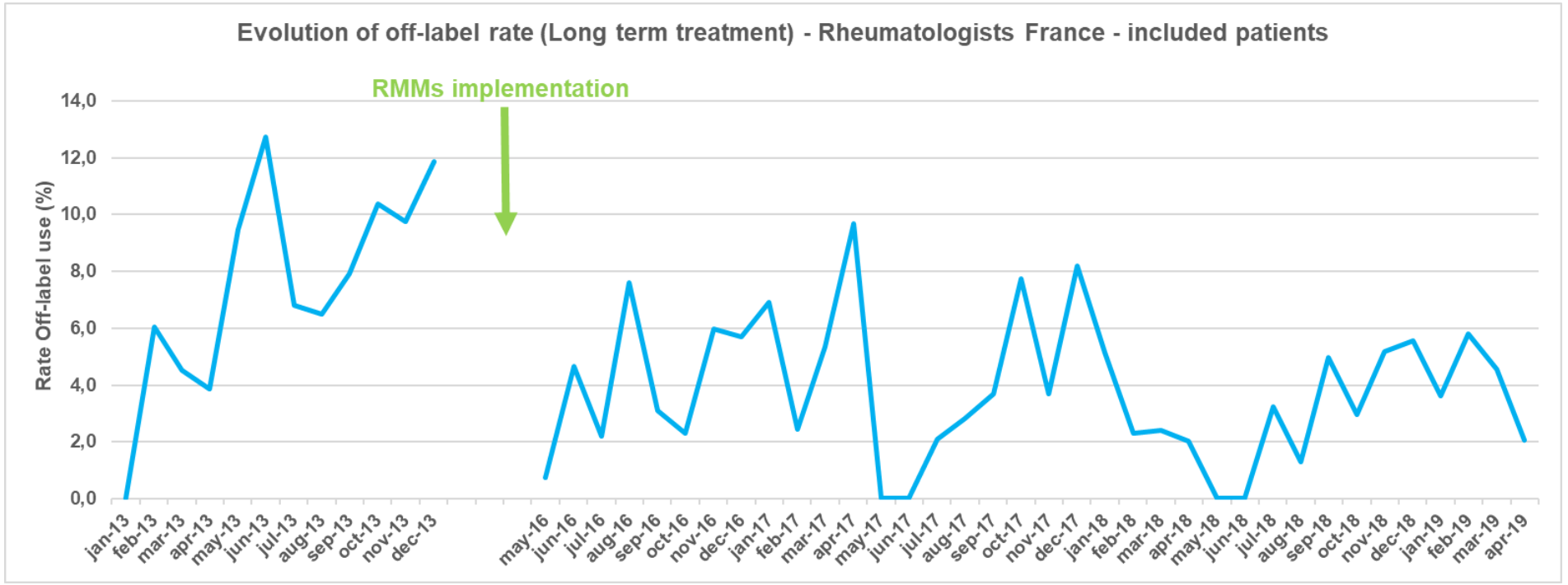

Table 15.3-119: Analysis of the effect of RMMs on off label rate of long-term treatment (prescriptions) – Rheumatologists France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	2.7065	1.5559	1.74	0.0889
Time	0.7359	0.2114	3.48	0.0011
Intervention	1.6231	2.0319	0.80	0.4287
Time after intervention	-0.7540	0.2153	-3.50	0.0011

This analysis on GPs France shows that the intervention is not associated with a change of off-label rate after intervention but there is a statistically significant change in the slope after intervention compare to the slope before intervention. Due the low number of evaluable prescriptions per month, interpretation of the results for Rheumatologists France should be interpreted with care.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 2.7%.

A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.74 percentage point with each month (p-value=0.0011).

There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.4287).

The ‘time after intervention variable’ shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant decrease of 0.75 percentage point with each month in comparison with the previous slop (p-value=0.0011).

Figure 44: Evolution of off-label rate (long-term treatment) – GPs Italy – included patients

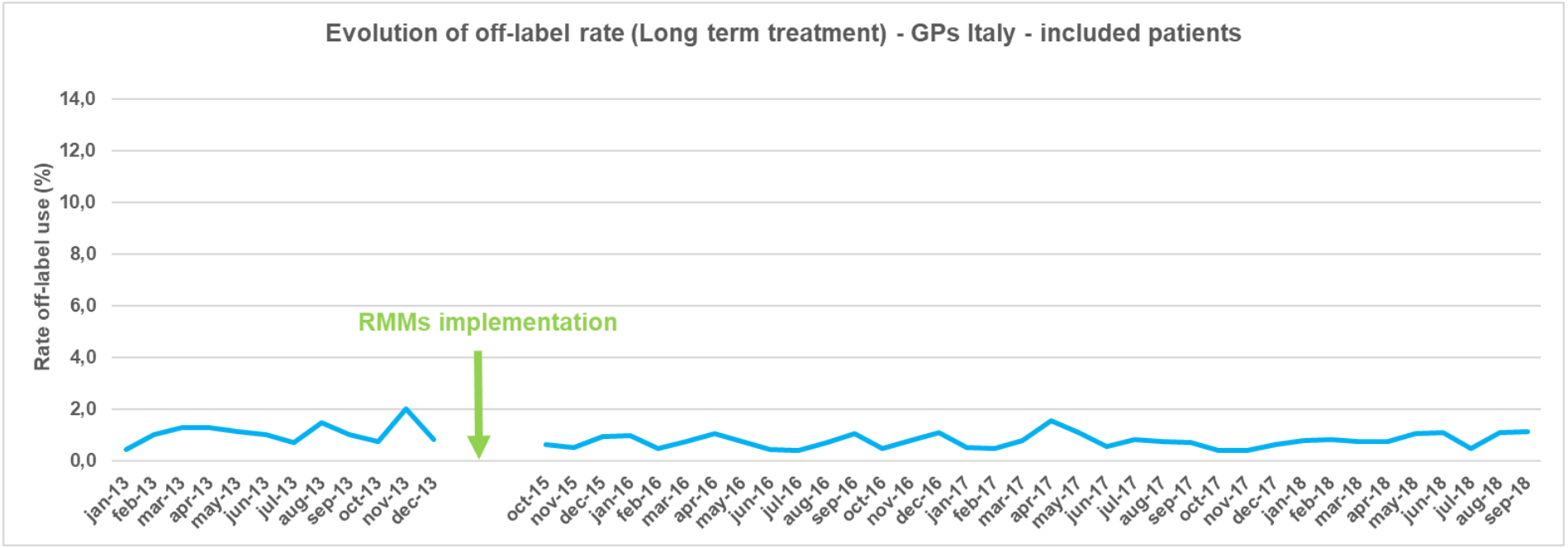

Table 15.3-120: Analysis of the effect of RMMs on off label rate of long-term treatment (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	0.8767	0.1886	4.65	<.0001
Time	0.0314	0.0256	1.22	0.2272
Intervention	-0.2450	0.2462	-1.00	0.3251
Time after intervention	-0.0268	0.0261	-1.03	0.3102

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period and also in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 0.88%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.3251).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.3102).

Figure 45: Evolution of off-label rate (pregnancy) – GPs France – included patients

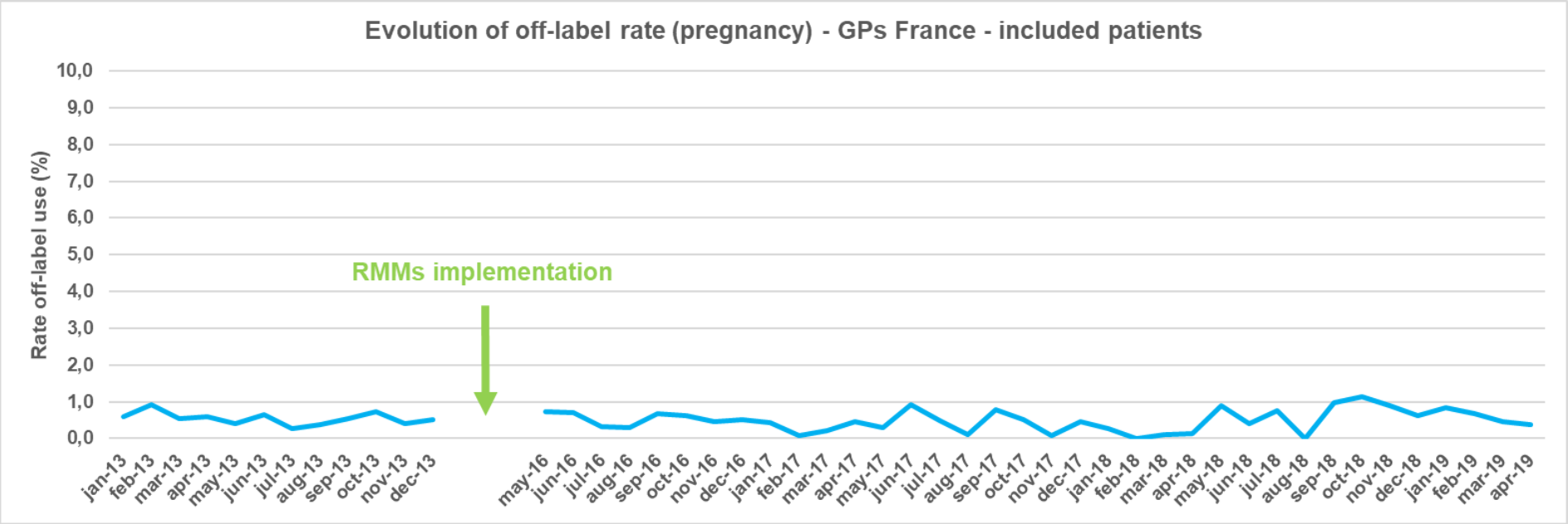

Table 15.3-121: Analysis of the effect of RMMs on off label rate of pregnancy (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	0.6494	0.1708	3.80	0.0004
Time	-0.0166	0.0232	-0.72	0.4783
Intervention	-0.3064	0.2230	-1.37	0.1765
Time after intervention	0.0214	0.0236	0.91	0.3691

This analysis on GPs France shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period, neither in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 0.65%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1765).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.3691).

Figure 46: Evolution of off-label rate (pregnancy) – GPs Italy – included patients

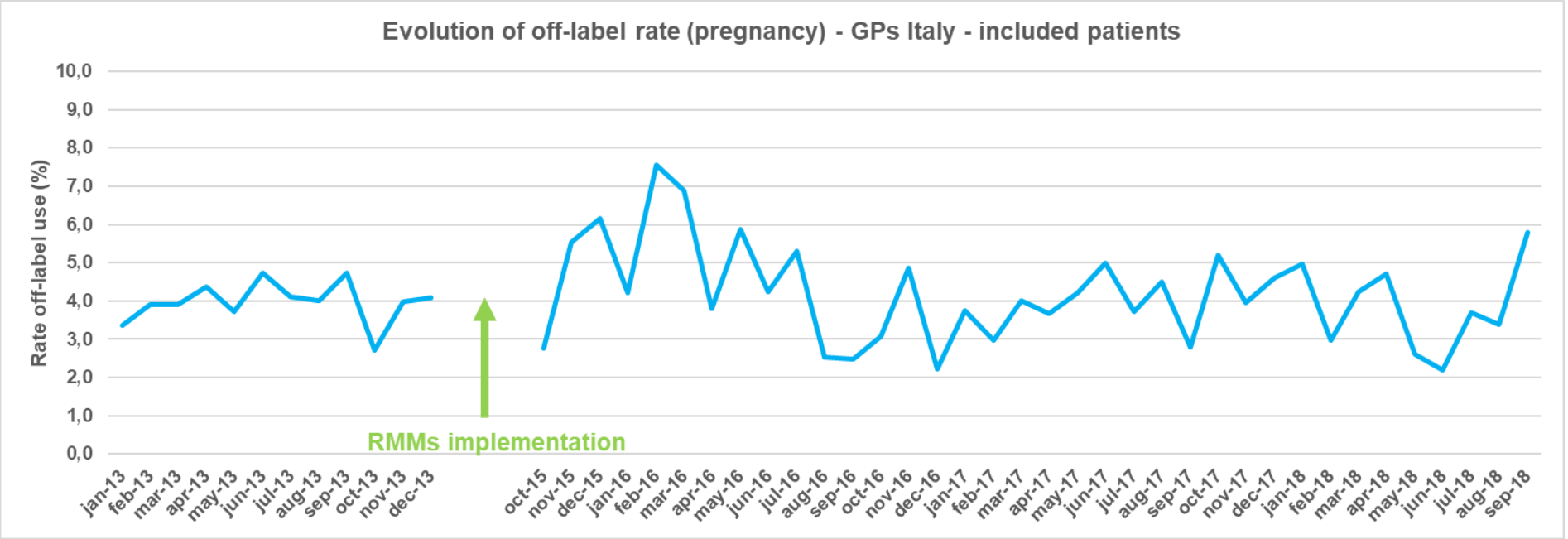

Table 15.3-122: Analysis of the effect of RMMs on off label rate of pregnancy (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	3.9114	0.7105	5.51	<.0001
Time	0.008381	0.0965	0.09	0.9312
Intervention	1.3095	0.9278	1.41	0.1652
Time after intervention	-0.0425	0.0983	-0.43	0.6677

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period, neither in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 3.9%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1652).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.6677).

Figure 47: Evolution of off-label rate (lactation) – GPs France – included patients

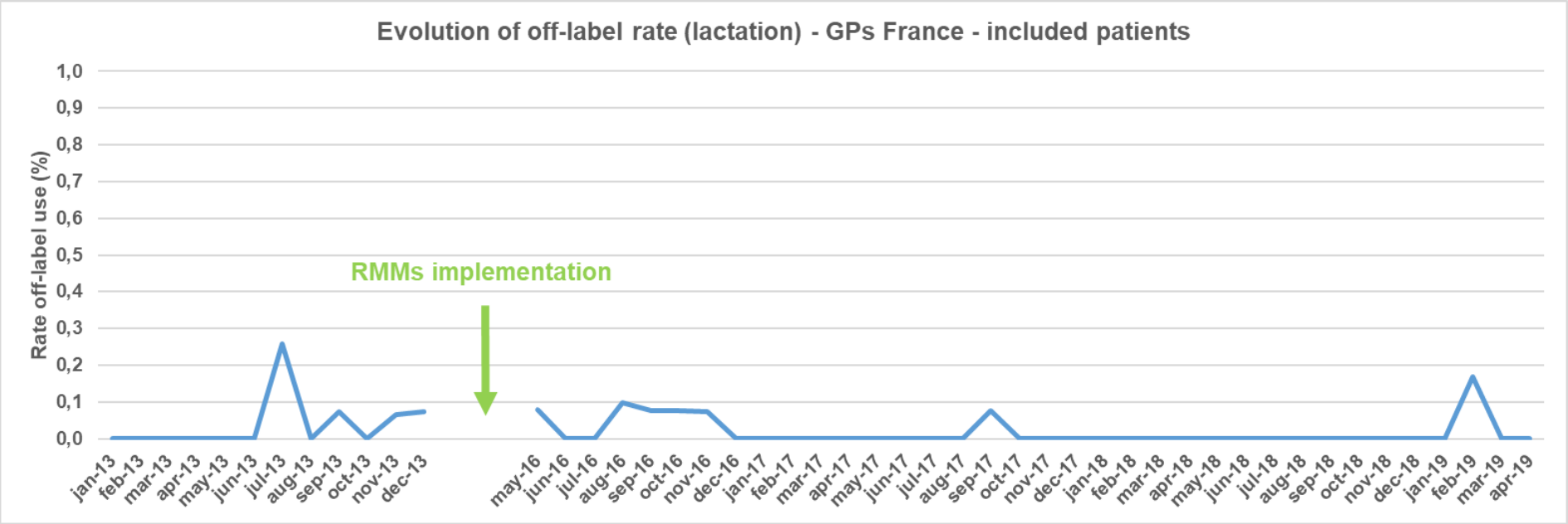

Table 15.3-123: Analysis of the effect of RMMs on off label rate of lactation (prescriptions) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	-0.007146	0.0307	-0.23	0.8172
Time	0.007194	0.004176	1.72	0.0919
Intervention	0.0504	0.0401	1.26	0.2154
Time after intervention	-0.008020	0.004252	-1.89	0.0659

This analysis on GPs France shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period, neither in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was -0.007% (p-value=0.8172).
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.2154).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.0659).

Figure 48: Evolution of off-label rate (lactation) – GPs Italy – included patients

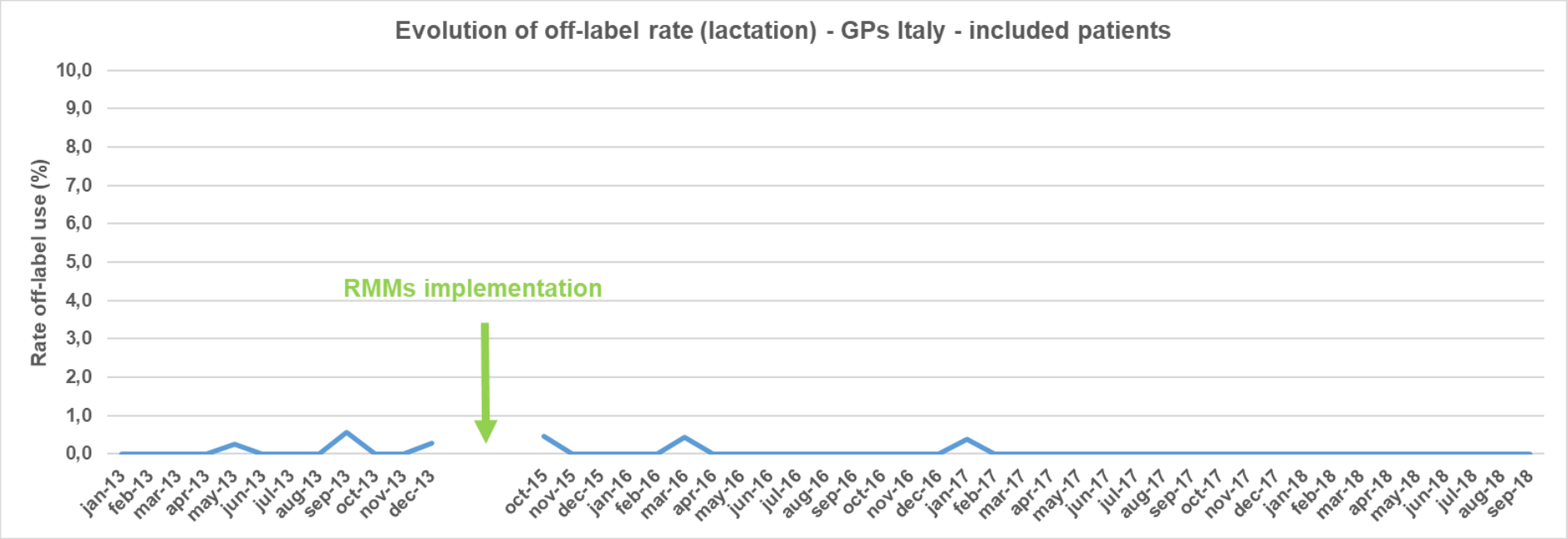

Table 15.3-124: Analysis of the effect of RMMs on off label rate of lactation (prescriptions) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	-0.0218	0.0805	-0.27	0.7874
Time	0.0174	0.0109	1.59	0.1189
Intervention	0.1702	0.1051	1.62	0.1126
Time after intervention	-0.0211	0.0111	-1.89	0.0647

This analysis on GPs Italy shows that there was no effect of the intervention observed on the monthly off-label, immediately after intervention period, neither in trend in the rate of off-label in study period.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was -0.02% (p-value=0.7874).
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1126).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.0647).

Figure 49: Evolution of off-label rate (no contraceptive use) – GPs France – included patients

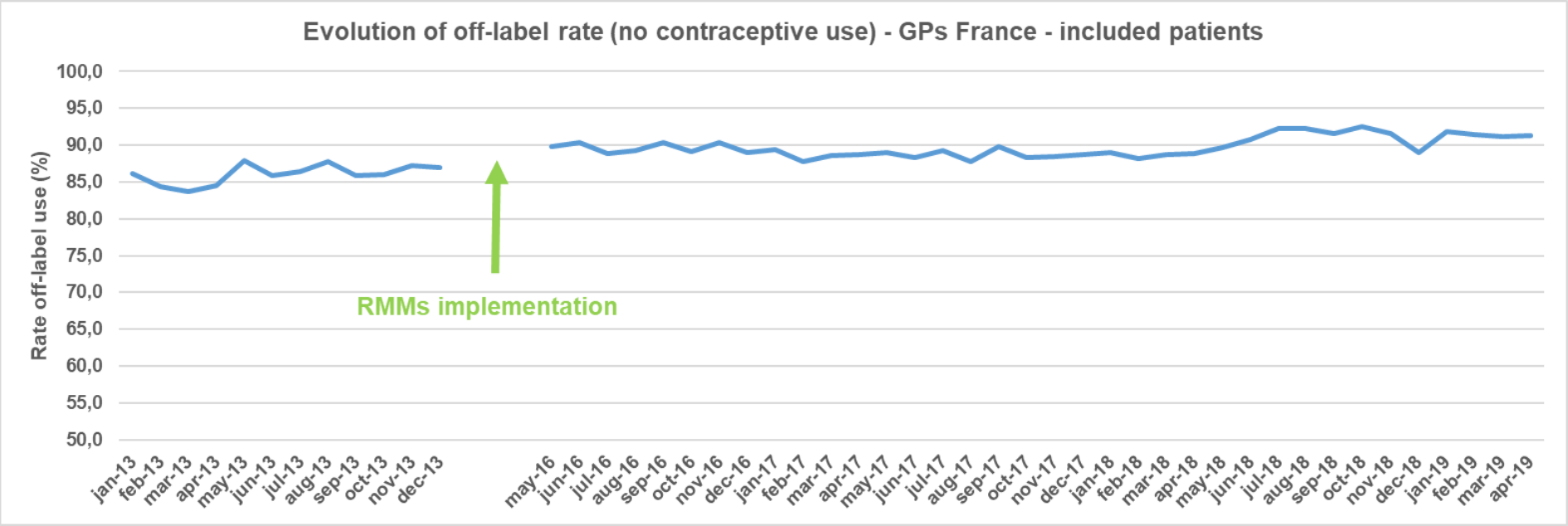

Table 15.3-125: Analysis of the effect of RMMs on off label rate of lactation (no contraceptive use) – GPs France – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	84.7651	0.7222	117.37	<.0001
Time	0.2026	0.0981	2.06	0.0449
Intervention	2.8951	0.9431	3.07	0.0037
Time after intervention	-0.1335	0.0999	-1.34	0.1884

This analysis on GPs France shows that the intervention is associated with a significant increase of off-label rate immediately after intervention but there is no change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 84.8%.
A pre-intervention trend was observed: the variable time shows that before the intervention there was a significant increase of 0.21 percentage point with each month (p-value=0.0449).
There was a significant immediate effect of the intervention on the off-label rate: the 'intervention' variable shows a change on the level of the rate of off-label use that follow the intervention period: the rate of off-label use increased immediately after the intervention period by 2.9 percentage points (p-value=0.0037).
There was no significant change in the trend of the rate of off-label use that follow intervention compared to the baseline period (p-value=0.1884).

Figure 50: Evolution of off-label rate (no contraceptive use) – GPs Italy – included patients

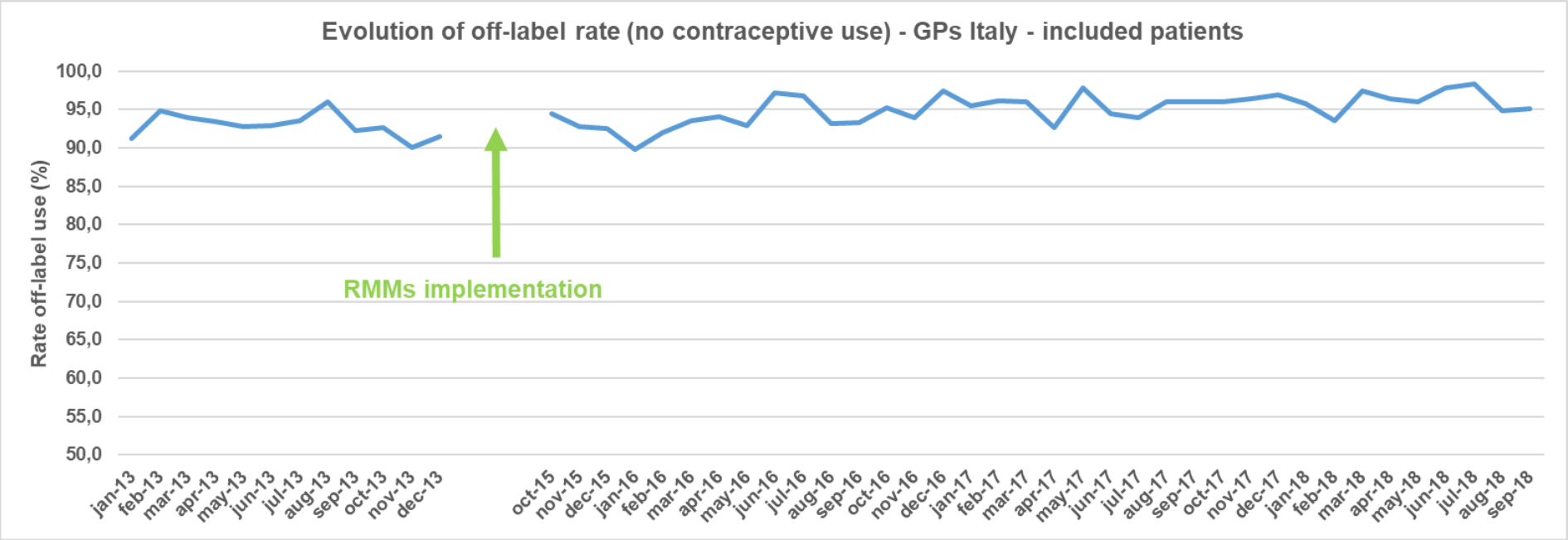

Table 15.3-126: Analysis of the effect of RMMs on off label rate of lactation (no contraceptive use) – GPs Italy – included patients

Variable	Estimate	Standart error	T-statistic	Pvalue
Intercept	93.7950	0.9541	98.30	<.0001
Time	-0.1940	0.1301	-1.49	0.1434
Intervention	-1.9983	1.2437	-1.61	0.1154
Time after intervention	0.3019	0.1325	2.28	0.0277
Dummy variable	2.4341	1.2055	2.02	0.0497

This analysis on GPs Italy shows that the intervention is not associated with a change of off-label rate after intervention but there is a statistically significant change in the slope after intervention compare to the slope before intervention.

The intercept variable shows that the rate of off-label use at the beginning of the baseline period was 93.8%.
There was no significant immediate effect of the intervention on the level of the off-label rate (p-value=0.1154).
The 'time after intervention variable' shows a change in the trend of the rate of off-label use that follow intervention period compared to the baseline period: there is a significant increase of 0.3 percentage point with each month in comparison with the previous slop (p-value=0.0277).
The dummy variable is not interpretable but allows to have stationary data i.e. with a constant mean, variance, and autocorrelation through time.