PASS information

DKP-TRAM

Title	**Drug Utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)**
Protocol version identifier	v01
Date of last version of protocol	v01 26th March 2018
EU PAS register number	Study not registered
Active substance	Dexketoprofen and tramadol hydrochloride (DKP-TRAM) (ATC: N02AJ14)
Medicinal product	Dextradol®, Lenizak® for Italy Enanplus®, Takudex® for Spain
Product reference	DKP-TRAM
Marketing authorisation holder(s)	Menarini International Operations Luxembourg SA (MIOL) - Laboratorios Menarini S.A. - Guidotti Farma S.L.U
Joint PASS	No
Research question and objectives	To evaluate pattern of prescriptions of DKP-TRAM and assess the risk of adverse events (e.g. nausea, vomiting, diarrhoea, vertigo) in DKP-TRAM vs. tramadol monotherapy (including tramadol-paracetamol combinations) users, with a special focus on patients 75 years old and over.
Country(-ies) of study	Italy and Spain
Author	Health Search, Italian College of General Practitioners and Primary Care Via Del Sansovino 179, 50141, Florence (Italy)

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Menarini International Operations Luxembourg SA (MIOL) - Laboratorios Menarini S.A. - Guidotti Farma S.L.U.
MAH contact person	Dr. Alessandro Zappalorto, MSc Corporate Pharmacovigilance Risk Evaluation Coordinator A. Menarini Industrie Farmaceutiche Riunite Srl, Via Sette Santi 3, 50131, Florence, Italy E-mail: riskevaluationunit@menarini.it

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CI	Confidence Interval
COX	Cyclooxygenase
CUI	Concept Unique Identifier
DDD	Defined Daily Doses
DUS	Drug Utilization Study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practice
HR	Hazard Ratio
HSD	Health Search Database
ICD-10-CM	International Classification of Diseases, 10th rev., Clinical Modification
ICD-9-CM	International Classification of Diseases, 9th rev., Clinical Modification
IR	Incidence rate
NHS	National Health System
NSAIDs	Nonsteroidal anti-inflammatory drugs
PASS	Post Authorization Safety Study
PDD	Prescribed daily doses
RCT	Randomized clinical trial
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCA	Tricyclic antidepressant
USA	United States of America
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Role	Person
Coordinating center	Health Search, Italian College of General Practitioners and Primary Care
Project leaders and principal investigators (PI)	Francesco Lapi, PharmD, PhD Health Search, Italian College of General Practitioners and Primary Care Via del Sansovino 179 50141, Florence Italy Tel: +39-055-7399199 e-mail: lapi.francesco@simg .it Claudio Cricelli, MD Italian College of General Practitioners and Primary Care Via del Sansovino 179 50141, Florence Italy Tel: +39-055-7399199 e-mail: cricelli@gmail.com
Sub-investigator	Spain: Daniel Prieto-Alhambra, MD PhD Senior Clinical Research Fellow IDIAP Jordi Gol & NDORMS Department (University of Oxford) Scientific Coordinator SIDIAP Database (www.sidiap.org) e-mail: dprieto@idiapjgol.info
MAH contact person	Dr. Fabrizzi Paolo, Medical Scientific Management A. Menarini Industrie Farmaceutiche Riunite Srl, Via Sette Santi 1, 50131, Florence, Italy E-mail: pfabrizzi@menarini.it
Scientific advisory committee	Not applicable

4. ABSTRACT

Title	Drug Utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)
Rationale and background	DKP-TRAM is a pharmacological fixed association with analgesic activity, which has been registered for treatment of acute pain in 2017 in several European Countries. In Spain and Italy the product has been launched in January 2017 and March 2017, respectively. The safety and efficacy of DKP-TRAM (25 mg – 75 mg) combination has been extensively demonstrated in the clinical development program in more than 1800 patients, especially from randomized clinical trials (RCTs) in post-operative pain. However, there is limited evidence in the real-life use of the product in the primary care settings particularly in elderly patients where the use of the 75 mg dose of tramadol contained in the combination could be a source of safety concerns for the prescribers. In the light of this background, the evaluation of the patterns of use and the safety profile of DKP-TRAM combination will be investigated in a real-world setting with particular relevance in special population, such as older patients (with a special focus on patients 75 years old and over), who may be more prone to adverse events (AEs) or drug discontinuation because of gastrointestinal and central AEs.
Research question and objectives	**Primary objectives:** To evaluate pattern of drug use (i.e. indication, dosage, and duration) of DKP-TRAM. **Secondary objectives:** To assess the risk of AEs (e.g. nausea, vomiting, diarrhoea, vertigo, hallucinations and somnolence) in incident users of DKP-TRAM vs. incident users of tramadol as monotherapy (including fixed combination tramadol-paracetamol), with a special focus on patients 75 years old and over.
Study design	A bi-national database cohort study will be conducted. These data will be derived from two electronic health care databases from two European countries (i.e. Italy and Spain).
Population	**Primary objective (drug utilisation):** All patients, aged 18 years or older, prescribed with DKP-TRAM from January 1, 2017 up to December 31, 2018, will be included in the study. **Secondary objective (comparative safety):** All patients, aged 18 years or older, prescribed for the first time with DKP-TRAM and/or tramadol monotherapy from January 1, 2017 and with at least 1-year of database history will be included in the study.
Variables	AEs: e.g..: nausea, vomiting, diarrhoea, vertigo, hallucinations, and somnolence. Demographic factors, life style factors, indication, duration and dosage of medications use, comorbidities and co-medications.
Data sources	The Health Search Database (HSD) from Italy, and the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain.
Study size	Assuming an estimated yearly incidence rate of almost 8% for DKP-TRAM use in HSD, a population of 2828 patients would be large enough to assume a 0.01 precision with 95% confidence levels. Given that HSD currently includes almost 1,5 million patients, these numbers should ensure the study power.

	For what concerns the safety study, occurrence of opioid-related AEs is observed in greater than 20% of users (almost 15,000 DKP-TRAM users in HSD), these numbers allow to estimate a Hazard Ratio (HR) equal to 1.2 of incurring in AEs in DKP-TRAM users vs. tramadol monotherapy (including tramadol-paracetamol) users, assuming 5% type I error and 80% power. Given that SIDIAP contains a larger population, the study power should be ensured for the Spanish database as well.
Data analysis	**Primary objectives:** Crude, age- and sex-standardised incidence rate (IR) of DKP-TRAM use will be computed, along with descriptive analysis concerning indication, duration and dosage. Continuous variables will be described as means with standard deviations or median with interquartile range. Categorical variables will be described as N and percentages. **Secondary objectives:** The risk of AEs in users of DKP-TRAM will be compared with the risk of AEs in users of tramadol as monotherapy by estimating HR with related 95% confidence intervals (CI) trough Cox regression model. Tramadol monotherapy users will be the reference category. All these analyses will be updated with information on data entering the databases in 2018.
Milestones	Start of data collection, 1st January 2017 End of data collection, 31st December 2018 Study progress report, 28th February 2019 Interim report, 31st January 2020 Registration in the EU PAS register, TBD Final report of study results, 29th February 2020

5. AMENDMENTS AND UPDATES

NA

Number	Date	Section of study protocol	Amendment or update	Reason
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

6. MILESTONES

Milestone Planned date	
Start of data collection	1st January 2017
End of data collection	31st December 2018
Study progress report	28th February 2019
Interim report	31st January 2020
Registration in the EU PAS register	TBD
Final report of study results	29th February 2020

7. RATIONALE AND BACKGROUND

Acute and chronic pain represent one of the most relevant public health concerns, with socioeconomic impact in both Europe [1] and USA [2]. Furthermore, a poor pain control may result in reduced patients' quality of life, increasing risk of developing chronic pain and other medical complications [3].

In 1986 the World Health Organization (WHO) has proposed an analgesic ladder to treat patients with pain. This scale suggests a first treatment with a non-opioid analgesic drug and an eventual add-on therapy with and/or switch to opioids if pain has not adequately controlled. Namely, this scale includes nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants at the first step; weak opioids for mild-moderate pain +/- non opioids +/- adjuvants at the second step; therapy with strong opioids for moderate-severe pain +/- non opioids +/-adjuvants at the last step [4].

In patients with moderate and severe acute pain, it is difficult to obtain a pain relief with a single drug therapy and, at the same time, the increase of dosage needs to be accurately evaluated because of the risk of adverse events (AEs) [5]. Therefore, the optimal strategy is combining different analgesic drugs with results in potential benefits such as wider spectrum of action, better compliance and greater efficacy and safety [6,7].

Dexketoprofen trometamol plus tramadol hydrochloride (25 mg – 75 mg) (DKP-TRAM) is a new pharmacological fixed-dose combination with analgesic activity and is indicated in the symptomatic short-term treatment of moderate to severe acute pain in adult patients. DKP-TRAM has been registered in 2017 in 31 European countries, including Italy and Spain.

Tramadol is a weak opioid with central analgesic activity and long-lasting effect [8]. It is featured by a double mechanism of action including partial agonism on the μ-opioid receptor and inhibition of serotonin and noradrenaline reuptake [9,10]. Tramadol is generally considered safer than other opioids. Namely, the most important tramadol-related AEs include nausea (ranging 11.3-53,7%), dizziness (5.3-36.7%), vomiting (4.3-19%), headache (2.1-22%), constipation (3.4-45%) and somnolence (6.7-37.2%) [11, 12].

Dexketoprofen trometamol is a non-steroidal anti-inflammatory drug (NSAID), in particular is the S(+)-enantiomer of ketoprofen, with a quick onset of action [13] and demonstrated effectiveness on acute pain relief [14]. The pharmacological properties of dexketoprofen consists of strong inhibition of COX-1 along with moderate inhibition of COX-2, so allowing the drug to have anti-inflammatory effects in both the peripheral tissue and in spinal cord.

Currently, there are pharmacological fixed combinations to treat pain including weak (e.g., codeine, tramadol) or strong (e.g., oxycodone) opioids combined with paracetamol, a medication with negligible peripheral anti-inflammatory activity. DKP-TRAM represents one of the first combinations of a new pharmacological class, in which the opioid centrally-acting analgesic has been combined with a drug with peripheral and central (spinal) anti-inflammatory activity [15]. Such a combination allows a rapid onset, long duration of action and a reduction in tramadol dosage, potentially minimizing the risk of AEs [16].

Indeed, the safety and efficacy of DKP-TRAM (25 mg – 75 mg) combination has been extensively demonstrated in the clinical development program in more than 1800 patients, especially from randomized clinical trials (RCTs) in post-operative pain [17], [18]. However, there is limited evidence in the real-life use of the product in the primary

care settings particularly in elderly patients where the use of the 75 mg of tramadol contained in the combination could be a source of safety concerns for the prescribers. In the light of this background, the evaluation of the patterns of use and safety profile of DKP-TRAM combination will be investigated in a real-world setting with particular relevance in special population, such as older patients (with a special focus on patients 75 years old and over), who may be more prone to AEs or drug discontinuation because of gastrointestinal and central AEs [19].

8. RESEARCH QUESTION AND OBJECTIVES

The aim of the present project is to evaluate the pattern/s of drug use of DKP-TRAM, and to assess the risk of AEs among users of DKP-TRAM vs. those using tramadol as monotherapy, in real-world primary care data from Italy and Spain.

Primary Objectives: To describe the pattern of drug use of DKP-TRAM in primary care in Italy and Spain.

Specific aims:

- To estimate the population-based incidence rate (IR) of DKP-TRAM use in patients aged 18 years or older.
- To describe the demographic and clinical characteristics of patients aged 18 years or older and prescribed with DKP-TRAM.
- To describe the indications for which DKP-TRAM is prescribed.
- To describe the prescribed daily doses (PDD) and durations of treatment with DKP-TRAM.

Secondary Objectives: To assess the risk of AEs in patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (including fixed combination tramadol-paracetamol), with a special focus on patients 75 years old and over.

In specific:

- To calculate the IR of AEs occurring during the first 3 months of follow-up, and those captured in the entire available follow-up, among patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (including fixed combination tramadol-paracetamol).
- To estimate the hazard ratios (HR) of AEs in patient aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (including fixed combination tramadol-paracetamol).

9. RESEARCH METHODS

9.1. STUDY DESIGN

This is a post-authorization, bi-national, multi-database, non-interventional, retrospective, population-based cohort study.
A retrospective cohort study was deemed the best design to characterize the use of DKP-TRAM in terms of indication, dosages, duration of treatment, and patients' features. Furthermore, this study will assess the safety profile of DKP-TRAM compared to monotherapy with tramadol for what concerns the risk of AEs.
When the dosage and duration of use will be modelled as exposure variable, a nested case-control analysis will be adopted. Each case will be matched up to ten controls (i.e. person-times) according to age (+/- 5 years), gender and General Practitioner (GP). The date of cases will be the index date and assigned to the respective controls.

9.2. SETTING

9.2.1 STUDY POPULATION

This study will be conducted on data collected in 2 European electronic health care databases, namely the Health Search Database (HSD) for Italy, and the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), for Spain.
All patients aged 18 years or older being registered in the databases between January 1, 2017 and December 31, 2018.

9.2.2 STUDY PERIOD

This study will contain patients' data from the first launch of DKP-TRAM in Italy (January 2017) and Spain (March 2017). The end of the study will be December 31, 2018.

9.2.3 IN- AND EXCLUSION CRITERIA

Inclusion criteria

Primary objectives (drug utilisation): all patients aged 18 years or older with at 1-year medical history in the database and prescribed with DKP-TRAM coded via the Anatomical Therapeutic Chemical (ATC) classification system (ATC: N02AJ14) will be identified. For each patient, the date of the first prescription of DKP-TRAM being registered in the study period will be the index date.

Secondary objectives (comparative safety): all patients aged 18 years or older and newly prescribed with DKP-TRAM (ATC: N02AJ14) or tramadol (ATC: N02AX02) or tramadol-paracetamol (ATC: N02AJ13) will be identified. For each patient, the date of the first DKP-TRAM or tramadol (including tramadol-paracetamol) prescription in the study period will be the index date.

Exclusion criteria

Primary objectives (drug utilisation): Patients 1) with missing data on age or gender, 2) with less than 1-year medical history in the database, 3) aged 17 years or younger.

Secondary objectives (comparative safety): Patients 1) with missing data on age or gender, 2) with less than 1-year medical history in the database, 3) aged 17 years or younger, 4) being prescribed with tramadol (or tramadol-paracetamol) in the period preceding the index date.

9.2.4 FOLLOW-UP

Primary objectives (drug utilisation): Eligible patients will be followed up from the index date until the occurrence of these events whichever will come first: i) patient's exit from the database, ii) patient's death, iii) end of data availability (December 31st, 2018).

Secondary objectives (comparative safety): Eligible patients will be followed up from the index date until the occurrence of these events whichever will come first: i) occurrence of one of the AEs under study (event date), ii) third month of follow-up), iii) patient's exit from the database, iv) patient's death, v) end of data availability (December 31st, 2018). We will end the follow-up at the 3rd month of observation in an attempt to consider titration for tramadol (or tramadol-paracetamol) as well as the expected short-time of onset for these AEs.

9.3. VARIABLES

9.3.1 PRIMARY OBJECTIVE

Exposure

The drug of interest is DKP-TRAM (ATC: N02AJ14). HSD contains information on primary care prescriptions, while SIDIAP contains information on drug dispensing.

Indication

DKP-TRAM is indicated in symptomatic short-term treatment of moderate-severe acute pain in adult patients whose symptomatology is considered to require a combination therapy [20].

All diagnoses associated to prescriptions of DKP-TRAM will be identified and classified according to ICD9CM and ICD-10. While HSD is able to identify the actual indication of use (i.e. every prescription has to be coupled with diagnosis by GP), in SIDIAP all diagnoses registered in 1 week before or after the index date will be captured. The selected indications will be manually reviewed in HSD to minimize the burden of miscoding.

Dosage

The distribution of the PDD will be described for all users of DKP-TRAM. The PDD and dosing instructions are recorded in HSD only, so this analysis will be limited to Italian data.

Considering that daily dose should not exceed three tablets per day (corresponding to 225 mg of tramadol and 75 mg of dexketoprofen), we will evaluate cases with a PDD higher vs. lower than 225 mg of tramadol and 75 mg of dexketoprofen.

Duration of treatment

The duration of treatment with DKP-TRAM will be calculated using:

- Total units*Strength/PDD value (in HSD).
- Total number of defined daily doses (DDDs) prescribed/dispensed, calculated as total Units*Strength/DDD value (in HSD and SIDIAP).

In HSD, the duration of treatment with DKP-TRAM will be evaluated as longer or shorter than 5 days [20]. Given that in SIDIAP the individual dosing instructions will not be

available, duration of prescriptions with DKP-TRAM will be investigated according to Kaplan- Meier methods.

Demographics and life style factors

Information on patients' age and sex will be retrieved on the index date.
Furthermore, life style information will be captured on:

- Smoking status (if available); patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date.
- Obesity, also defined as body mass index (BMI) higher than 30 kg/m^2, considering the last BMI measurement before the index date.
- Alcohol abuse and/or alcohol-related disorders, considering the last assessment before the index date.

Comorbidities and co-medications

Comorbidities and co-medications will be assessed through codes registered in the databases. Operationally, diagnoses and medications will be defined in the overall period and 1 year preceding and/or on the index date, respectively (see Table 1-2 and Annex 3). After defining ICD9CM codes, ICD10 will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [21].
Previous and subsequent use of tramadol (or tramadol-paracetamol) will be investigated in terms of dosage according to the criteria indicated below.

Table 1. List of ICD9CM codes defining comorbidities.

Comorbidities	ICD9CM
Hepatic impairment	570*, 573.3*, 794.8*, 572.2*
Kidney disease	580*-589*, 250.4*, 403.0*, 403.1*, 403.9*, 404*, 274.10, 440.1, 442.1, 453.3, 593*, 753.0, 753.3, 866*, 585, 250.4, 581.1, 581.8, 791.0 V45.1, V56.0, V56.8 V42.0, 996.81
Depression	296.2, 296.3, 311*,
Chronic obstructive pulmonary disease and allied conditions and Asthma	493, 493.90, 493.1, 493.0, 493.02, 493.12, 493.91, 493.01, 493.10, 493.11, 493.2, 493.8 490-496.99 (excluding 493*)
Epilepsy	345*
Chronic dyspepsia	536.8
Alcohol abuse and/or alcohol-related diseases	303*, 305.0, 357.5, 425.5, 535.3, 571.0-3, 790.3, V11.3,
Drug abuse or dependence	304* 305.2- 305.9.
Mental health diagnoses and personal history of mental disorder	293.0-301.9 (excluding 294.0, 296.2, 296.3) V11.0, V11.1, V11.2, V11.8, V11.9

Hallucinations	368.16; 780.1
Dementia and memory deficit	294.0, 310.1, 331.0, 290.0, 290.1, 290.2, 290.3, 290.4, 046.1, 046.3, 291.2, 292.82, 331.1, 331.2, 331.7, 331.8, 331.9, 332.0, 292.83, 780.9
Cognitive Impairment after trauma	907.0

Table 2. List of ATC codes defining co-medications.

Co-medications	Anatomical Therapeutic Chemical (ATC)
Tramadol	N02AX02
Anticoagulants or anti-platelet, anti-aggregation drugs	B01*
Carbamazepine	N03AF01
Cimetidine	A02BA01
Opioid drugs (excluding tramadol)	N02A*
Antidepressants (Selective serotonin reuptake inhibitors (SSRIs), Serotonin-norepinephrine reuptake inhibitors (SNRIs), Tricyclic antidepressants (TCA); Other seizure threshold-lowering medicinal product	N06A* (excluded N06AF*, N06AG, N04BD02, N04BD01, N04BD03, J01XX08)
Patients currently receiving (or received within the last 14 days) MAO inhibitors	N06AF, N06AG, N04BD02, N04BD01, N04BD03, J01XX08
Antipsychotics	N05A
Anxiolytics	N05B
Ondansetron	A04AA01
Ketoconazole	J02AB02
Erythromycin	D10AF02

9.3.2 SECONDARY OBJECTIVES

Outcomes

AEs will be identified in an attempt to define patients being intolerant to tramadol. These codes (see example in Table 3) will be therefore identified in HSD and SIDIAP via ICD9CM and ICD-10, respectively. After defining ICD9CM codes, ICD-10 will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [21].

In HSD these events will be also identified through a specific electronic file coding medications intolerance. Eligible patients might experience two or more AEs at the same time.

Table 3. List of ICD9CM coding adverse events.

Terms	ICD9CM
Nausea, vomiting	563.2; 787.0*
Diarrhoea	787.91
Hallucinations	368.16; 780.1/00
Vertigo	780.4
Somnolence	780.09

Exposure
The drugs of interest will be DKP-TRAM (ATC: N02AJ14) and tramadol (ATC: N02AX02) as monotherapy (including tramadol-paracetamol (ATC: N02AJ13)). HSD contains information on primary care prescriptions, while SIDIAP contains information on drug dispensing.

Dosage
The PDD of DKP-TRAM and tramadol monotherapy will be evaluated in the period preceding and/or on the date of AEs registration. The PDD and dosing instructions are recorded in HSD only, so this analysis will be limited to Italian data. Operationally, we will identify the highest dosage being registered in the month preceding or on the event date. Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the dosage (in mg) in terciles as it will be registered in the controls as reference of general population.

Duration of treatment
The duration of treatment with DKP-TRAM and with tramadol monotherapy will be calculated using:

- Total units*Strength/PDD value (in HSD).
- Total number of defined daily doses (DDDs) prescribed/dispensed, calculated as total Units*Strength/DDD value (in HSD and SIDIAP).

Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the duration (in days) in terciles as it will be registered in the controls as reference of general population.

Demographics
Information on patients' age and sex will be retrieved on the index date.
Furthermore, life style information will be captured on:

- Smoking status (if available); patients will be classified as "current smoker", "past smoker", "non-smoker" or "smoking status unknown" at the time of the index date.
- Obesity, also defined as BMI higher than 30 kg/m2, considering the last BMI measurement before the index date.
- Alcohol abuse and/or alcohol-related disorders, considering the last assessment before the index date.

Comorbidities and co-medications (potential confounders)
Comorbidities and co-medications will be assessed through codes registered in the databases. Operationally, diagnoses and medications will be defined in the overall period and 1 year preceding and/or on the index date, respectively (see Table 1-2 (excluding previous use of tramadol)).

9.4. DATA SOURCES
The database included in this study will be HSD (Italy) and SIDIAP (Spain). These two databases comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological research [22, 23]

and they are listed under the ENCePP resources database: (www.encepp.eu/encepp/resourcesDatabase.jsp).

Table 4. Overview of databases

	Italy	Spain
Name of the database	HSD	SIDIAP
Type of database	MR	MR
Number of patients, *millions*	1.5	5.1
Date in	Yes	Yes
Date out	Yes	Yes
Date of death	Yes	Yes
Cause of death	No	No
Updates	Twice a year: (30/06 and 31/12)	Yearly (April/May)
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)
Coding of drugs	ATC	ATC
Dosing regimen	Yes	Yes (incomplete)
Hospitalisations	Yes (incomplete)	Yes
Outpatient diagnoses	Yes	Yes
Coding of disease	ICD-9 CM	ICD-10

ATC = Anatomical Therapeutic Chemical; ICD = International classification of disease, MR = Medical Records

HSD –Longitudinal Patient Database, Italy

The HSD is a general practice research database and it covers data from computer-based patient records covering a total of 1.5 million patients. HSD was established in 1998 by the Italian College of General Practitioners and Primary Care [24]. The database contains clinical records (diagnoses, patient referrals, hospital admissions, clinical investigations' results and date of death) and prescription data (drug name, prescription date, number of days' supply) for the drugs which are reimbursed by the National Health System (NHS). All prescription data were coded with ATC classification system while the ICD-9-CM for all medical records [25].
The GPs included in the study had to meet 'up-to-standard' quality criteria for epidemiological studies, in particular: levels of coding, prevalence of well-known diseases, and mortality rates. Furthermore, only GPs who provided data at least one year were included in the analysis [26].
HSD is a valid data source for scientific research and it is aligned to the European Union guidelines on the use of medical data for research. For these reasons, HSD has been used as data source in many studies and publications [27].
Approval for use of data was obtained from the Italian College of General Practitioners and Primary Care for the current study.

SIDIAP Database, Spain

GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.9 million patients (about 80% of the total of 7.5 million population of Catalonia) from 279 primary care practices with 3,414 participating GPs. The size of the SIDIAP base population has increased in the current compared to the previous year's (First Interim Report) extraction by more than 800,000 patients both retrospective and prospectively. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, reimbursed prescription/s and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.
Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, BMI, tobacco and alcohol use, blood pressure measurements, blood, and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP. Recent reports have shown the SIDIAP data to be useful for epidemiological research [28].
Approval for the current study was obtained from both the SIDIAP Scientific and the IDIAP (Institut d'Investigació en Atenció Primària) Jordi Gol primary care research Ethics Committee.

9.5. STUDY SIZE

DKP-TRAM -containing medications have been launched in Italy and Spain in January 2017 and March 2017, respectively. From preliminary counts conducted in HSD, 1165 patients have been prescribed with this medication in the first trimester 2017. Thus, assuming an estimated yearly prevalence of almost 8% in HSD, a population of 2828 patient would be large enough to assume a 0.01 precision with 95% Confidence Intervals (CI). Given that HSD currently includes almost 1.2 million patients these numbers should ensure the study power.

For what concerns the safety study, the occurrence of opioid-related AEs is observed in greater than 20% of users. Such a prevalence would allow to estimate of HR=1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramandol (or tramadol-paracetamol).

There are not yet preliminary estimates for SIDIAP given that 2017 database is not yet available. However, we can expect similar or greater cohort size than HSD, given that the dimension of population registered in SIDIAP is larger than that registered in HSD (Table 4).

9.6. DATA MANAGEMENT

Data from the two different databases will be pooled after local extraction, validation and data-cleaning, and not with single data extraction algorithm for all the databases. The reason for this is that these databases use different coding schemes (e.g. ICD9-CM and ICD-10) and their content comes from different data sources (e.g., general practitioners' records, and hospital discharge diagnoses).

To reunite differences across coding system, all variables will be defined according to a multi-step and iterative process for the harmonization of event data.

9.6.2 DEFINITION OF DATA EXTRACTION ALGORITHM

Based on the relevant diagnostic codes and key words (for free-text search), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented in HSD and SIDIAP. Every extraction will be validated by data providers according to pre-specified criteria. Expected frequency of diagnoses and medications use. Correctness of variables categorization (e.g. smoking categories) will be checked including the burden of missing data.

9.7. DATA ANALYSIS

9.7.1 PRIMARY OBJECTIVES

Incidence rate of DKP-TRAM use

The crude IR of use of DKP-TRAM will be calculated considering patients prescribed with DKP-TRAM during the year (numerator) on the total number of patients being active (alive and currently registered with their GPs) in the database on December 31, 2017. This calculation will be repeated for 2018 by excluding patients prescribed with DKP-TRAM in the year prior. The crude IR will be calculated considering patient's person-times as denominator as well. Age and sex-standardized IR will be calculated according to indirect method.

Concerning the other events under study, continuous variables will be described as absolute numbers (considering both valid and missing cases), means with standard deviations and/or median values with interquartile range, according to the shape of data distribution.
Categorical variables will be described as percentages. Missing data will be quantified and used as specific categories in the analysis [29, 30].
To characterize patterns of use for DKP-TRAM, we will calculate the crude IR using the total number of patients exposed to DKP-TRAM (numerator), and the total number of person-years cumulated during follow-up by the whole source population (denominator) stratified by age, gender, study period, country/database, comorbidities and co-medications. The 95% CI will be derived for IR using Poisson distribution.
The duration of prescriptions of DKP-TRAM will be also investigated according to Kaplan-Meier method considering drug discontinuation as response variable.

9.7.2 SECONDARY OBJECTIVES

For this objective, both descriptive and inferential analysis will be performed.
Continuous variables will be described as absolute numbers, and as means with standard deviations or median values with interquartile range, according to the shape of data distribution. Mean or median values will be performed using the t-Student or Mann-Whitney test, respectively. Categorical variables will be described as percentages, and they will be compared among different categories of covariates, using Chi-square test. Missing data will be described and included in the analyses using a specific category. Patients exposed to DKP-TRAM will be compared to those exposed to tramadol (or tramadol-paracetamol). When the nested case-control analysis will be adopted, the same analyses will be conducted to compare cases and respective controls.

Incidence rates of acute AEs

We will calculate the IR for each AEs using the total number of patients incurred in an AE (numerator), and the total person-years cumulated during follow-up by the exposed population (denominator) stratified by new users of DKP-TRAM and new users of tramadol as monotherapy. The person-times of exposure will be split according to a time-dependent approach. The 95% CI will be derived for IR using Poisson distribution. IR will only be estimated in case of at least 5 events per exposure category.
We will estimate the HR, and related 95% CI, for AEs occurred in new users of DKP-TRAM vs. new users of tramadol as monotherapy, using Cox regression time-dependent models. HRs will only be estimated in case of at least 5 events per exposure category. The reference category will be the use of tramadol as monotherapy (always including tramadol-paracetamol as well). To control for potential confounding, the following covariates (all measured at the index date) will be included in the final model (see Table 1-2):

- Age
- Gender
- Comorbidity
- Concomitant drug use

We will estimate conditional logistic regression in case of nested case-control analysis. The exposure will be categorized according to dose and duration of use in DKP-TRAM users, defining mixed users of tramadol and DKP-TRAM as a separated category.

9.7.3 Secondary analyses

The prescription of DKP-TRAM is likely influenced by previous prescription of tramadol (or tramadol-paracetamol), especially in terms of AEs already experienced by patients. Indeed, we will exclude previous use of tramadol preceding the index date to minimize selection bias. However, the knowledge of how GPs select patients to use DKP-TRAM and the how this behaviour acts on the risk of AEs might be informative. The Cox regression model comparing the risk of AEs among DKP-TRAM users vs. tramadol users, will be therefore re-run including in the cohort previous users of tramadol as well. In addition, given that older patients are more prone to incur in such AEs [20], the analyses concerning the risk of AEs among DKP-TRAM users will be re-run limiting the cohort to patients aged 75 years or older.

Sensitivity analyses

In the sensitivity analysis we will change the follow-up for the evaluation of acute AEs. We will therefore change the duration of follow-up from 90 to 30, 60, 120 days, and the entire available follow-up. Then, we will re-run the primary model by imputing missing data for smoking and BMI according to multiple imputation methods [31]. Finally, given the potential difference in terms of indication and severity of pain among DKP-TRAM users vs. tramadol users, we will re-run the primary model by adjusting the analysis for propensity score. The covariates reported in Table 1-2 (except for previous use of tramadol) will be used in a logistic regression model to estimate the propensity score to be prescribed with DKP-TRAM instead or tramadol as monotherapy [32].

9.8. Quality control

The study will be conducted according to the guidelines for Good Pharmaco-epidemiology Practice (GPP) [33].

The two databases have experience in conducting pharmaco-epidemiological research and research is done by researchers trained in pharmaco-epidemiology. In addition; the databases are representative of the respective countries and database specific disease prevalence rates are in line with what has been published before.

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) will be used for statistical analyses.

9.9. Limitations of the research methods

The limitations of this study will be related to the availability and level of detail of data. In fact, not all potential confounders (e.g. life style factors such as smoking, BMI, race) are contained in databases and not all variables contain the information in desired detail. Both databases have information on prescriptions or on dispensing and not on actual drug intake. However, the risk of misclassification of exposure is lower in a new-user design study, because it is known that adherence to drugs is higher at initiation of therapy.

Misclassification of endpoints as well as confounders is possible, especially because the information on underlying diseases is based on disease codes. For this reason, validation of endpoints will be conducted and comparison of IRs of endpoints between databases will allow checking for internal and external validity. Furthermore, the primary objective of data collection of these databases is the management of patients and not medical research. For this reason, only relevant events related to the patient's care are collected in the databases.

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are currently already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

The protocols will be reviewed by the Institutional Review Boards of the respective databases. As this is a non-interventional observational study, there is no need for ethical approval in Italy.

For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology [33], the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [34], and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' [35].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for reporting of adverse drug reactions from secondary use of data (such as electronic health care databases). Reports of adverse events/reactions will not be provided on an individual case level; only aggregated safety results, i.e. the overall association between an exposure and an outcome will be reported in the final study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As the study progresses, Menarini will submit the progress/interim reports and final study report to EMA. The study progress and interim results will be reported in yearly intervals following first launch of DKP-TRAM in Europe.

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.). In order to allow EMA to review in advance the results and interpretations to be published, Menarini will communicate to the EMA the final manuscript of an article within two weeks after first acceptance for publication.

13. REFERENCES

[1] H. Breivik, E. Eisenberg, and T. O'Brien, "The individual and societal burden of chronic pain in Europe: The case for strategic prioritisation and action to improve knowledge and availability of appropriate care," *BMC Public Health*, vol. 13, no. 1, 2013.

[2] D. J. Gaskin and P. Richard, "The economic costs of pain in the United States," *J. Pain*, vol. 13, no. 8, pp. 715–724, 2012.

[3] R. Sinatra, "Multimodal management of acute pain: the role of IV NSAIDs," *New York,NY Mac Mahon Pub*, pp. 571–581, 2011.

[4] W. H. Organization, "Cancer pain relief," *Cancer Pain Reli. Geneva, Switzerland, World Heal. Organ.*, 1986.

[5] S. A. Schug, W. Robert Garrett, and G. Gillespie, "Opioid and non-opioid analgesics," *Best Practice and Research: Clinical Anaesthesiology*, vol. 17, no. 1. pp. 91–110, 2003.

[6] R. B. Raffa, J. V. Pergolizzi, and R. J. Tallarida, "The determination and application of fixed-dose analgesic combinations for treating multimodal pain," *Journal of Pain*, vol. 11, no. 8. pp. 701–9, 2010.

[7] R. A. Moore, C. J. Derry, S. Derry, S. Straube, and H. J. McQuay, "A conservative method of testing whether combination analgesics produce additive or synergistic effects using evidence from acute pain and migraine," *European Journal of Pain*, pp. 585–91, 2012.

[8] S. Grond and A. Sablotzki, "Clinical pharmacology of tramadol," *Clinical Pharmacokinetics*, vol. 43, no. 13. pp. 879–923, 2004.

[9] B. D. Beakley, A. M. Kaye, and A. D. Kaye, "Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review," *Pain Physician*, vol. 18, no. 4, pp. 395–400, 2015.

[10] K. Minami, J. Ogata, and Y. Uezono, "What is the main mechanism of tramadol?," *Naunyn. Schmiedebergs. Arch. Pharmacol.*, vol. 388, no. 10, pp. 999–1007, 2015.

[11] P. C. Langley, A. D. Patkar, K. a Boswell, C. J. Benson, and J. R. Schein, "Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain.," *Curr. Med. Res. Opin.*, vol. 26, no. 1, pp. 239–51, 2010.

[12] C. Angeletti *et al.*, "Tramadol Extended-Release for the Management of Pain due to

Osteoarthritis," *ISRN Pain*, vol. 2013, pp. 1–16, 2013.

[13] M. McGurk *et al.*, "Clinical comparison of dexketoprofen trometamol, ketoprofen, and placebo in postoperative dental pain," *J. Clin. Pharmacol.*, vol. 38, no. 12 Suppl, p. 46S–54S, 1998.

[14] J. Barden, S. Derry, H. J. McQuay, and R. A. Moore, "Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults.," *Cochrane Database Syst Rev*, no. 4, p. CD007355, 2009.

[15] G. Varrassi *et al.*, "Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol," *Current Medical Research and Opinion*, vol. 33, no. 6. pp. 1165–1173, 2017.

[16] H. J. McQuay *et al.*, "Randomized clinical trial of dexketoprofen/tramadol 25 mg/75 mg in moderate-to-severe pain after total hip arthroplasty," *Br. J. Anaesth.*, vol. 116, no. 2, pp. 269–276, 2016.

[17] R. A. Moore *et al.*, "Dexketoprofen/tramadol: randomised double-blind trial and confirmation of empirical theory of combination analgesics in acute pain," *J. Headache Pain*, vol. 16, no. 1, 2015.

[18] R. A. Moore *et al.*, "Dexketoprofen/tramadol 25mg/75mg: randomised double-blind trial in moderate-to-sever acute pain after abdominal hysterectomy," *BMC Anesthesiol.*, no. 16, p. 9, 2016.

[19] E. Marrett, W. J. Kwong, F. Frech, and C. Qian, "Health Care Utilization and Costs Associated with Nausea and Vomiting in Patients Receiving Oral Immediate-Release Opioids for Outpatient Acute Pain Management," *Pain Ther.*, vol. 5, no. 2, pp. 215–226, 2016.

[20] "farmaci.agenziafarmaco.gov.it/aifa/servlet/RCP.pdf." .

[21] B. F. H. Becker *et al.*, "CodeMapper: semiautomatic coding of case definitions. A contribution from the ADVANCE project," *Pharmacoepidemiol. Drug Saf.*, vol. 26, no. 8, pp. 998–1005, 2017.

[22] M. Cazzola *et al.*, "The prevalence of asthma and COPD in Italy: A practice-based study," *Respir. Med.*, vol. 105, no. 3, pp. 386–391, 2011.

[23] a E. Vlug *et al.*, "Postmarketing surveillance based on electronic patient records: the IPCI project.," *Methods Inf. Med.*, vol. 38, no. 4–5, pp. 339–44, 1999.

[24] C. AL Filippi A, Vanuzzo D, Bignamini AA, Mazzaglia G, Cricelli C, "The database of Italian general practitioners allows a reliable determination of the prevalence of myocardial infarction," *Ital Hear. J*, vol. 6, no. 4, pp. 311–4.

[25] "The selection and use of essential medicines," *World Heal. Organ. - Tech. Rep. Ser.*, no. 950, p. backcover, vii-174., 2008.

[26] C. Cricelli *et al.*, "Prevalence estimates for chronic diseases in Italy: Exploring the differences between self-report and primary care databases," *J. Public Health Med.*, vol. 25, no. 3, pp. 254–257, 2003.

[27] V. Guglielmi *et al.*, "Drug interactions in users of tablet vs. oral liquid levothyroxine formulations: a real-world evidence study in primary care," *Endocrine*, pp. 1–8, 2017.

[28] M. D. M. García-Gil *et al.*, "Construction and validation of a scoring system for selection of high quality data in a Spanish population primary care database (SIDIAP)," *Inf. Prim Care*, vol. 19, no. 3, pp. 135–45, 2011.

[29] J. A. Delaney, S. S. Daskalopoulou, J. M. Brophy, R. J. Steele, L. Opatrny, and S. Suissa, "Lifestyle variables and the risk of myocardial infarction in the general practice research database," *BMC Cardiovasc Disord*, vol. 7, p. 38, 2007.

[30] J. A. C. Delaney, E. E. M. Moodie, and S. Suissa, "Validating the effects of drug treatment on blood pressure in the General Practice Research Database," *Pharmacoepidemiol. Drug Saf.*, vol. 17, no. 6, pp. 535–45, 2008.

[31] A. B. Pedersen *et al.*, "Missing data and multiple imputation in clinical epidemiological research," *Clin. Epidemiol.*, vol. 9, pp. 157–166, 2017.

[32] S. Schneeweiss, "Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics," *Pharmacoepidemiol. Drug Saf.*, vol. 15, no. 5, pp. 291–303, 2006.

[33] M. Epstein, "Guidelines for good pharmacoepidemiology practices (GPP)," *Pharmacoepidemiology and Drug Safety*, vol. 17, no. 2. pp. 200–208, 2008.

[34] E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche, and J. P. Vandenbroucke, "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies," *J. Clin. Epidemiol.*, vol. 61, no. 4, pp. 344–9, 2008.

[35] "The ENCePP Code of Conduct." .

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
Annex 2	v01	26 March 2018	ENCePP checklist for study protocols
Annex 3	v01	26 March 2018	Additional information
Annex 3.1	v01	26 March 2018	Co-morbidity definition

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 (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)

Study reference number:

Study not registered

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☒	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[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.

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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3, 9.7
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)	☒	☐	☐	9.7
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)	☐	☒	☐	

Comments:

This is the case of primary data collection. Thus, adverse Events will not be collected.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.2
4.2.2 Age and sex?	☒	☐	☐	9.2.3
4.2.3 Country of origin?	☒	☐	☐	9.4
4.2.4 Disease/indication?	☒	☐	☐	9.3
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

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)	☒	☐	☐	9.3.1, 9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1, 9.3.2
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.4

Comments:

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?	☒	☐	☐	9.3.1, 9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1, 9.3.2
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)	☒	☐	☐	9.7
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment?				

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
(e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Several sensitivity analyses will be conducted to verify the robustness of the results.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.1, 9.3.2, 9.7
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.3
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.7.3, 9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.7.3, 9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7.3

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 analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

The analysis will be re-run among patients aged 75 or older given their higher risk of incurring in the events under study.

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, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.3
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

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)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	9.7.3, 9.9
12.1.2 Information bias?	☒	☐	☐	9.7.3, 9.9
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)	☒	☐	☐	9.7.3, 9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

Comments:

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Francesco Lapi

Date: 26/03/2018

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1 Co-morbidity definition

Hepatic impairment

All codes (ICD9CM and ICD10) reported in databases ever before the period preceding or on the index date and the **ALT>40 UI/l; AST >35 UI/l; AP>140 UI/l; 7**

Furthermore, mild to moderate hepatic dysfunction or severe hepatic dysfunction were codified with Child-Pugh classification.

- **Mild to moderate hepatic dysfunction** (Score 5-6, 7-9)
- **Severe hepatic dysfunction** (score 10-15)

The Child-Pugh classification

Assessment	Degree of abnormality	Score
Encephalopathy	None Moderate Severe	1 2 3
Ascites	Absent Slight Moderate	1 2 3
Bilirubin (mg/dL)	<2 2.1-3 >3	1 2 3
Albumin (g/dL)	>3.5 2.8-3.5 <2.8	1 2 3
Prothrombin Time (seconds > control)	0-3.9 4-6 >6	1 2 3

Total Score	Group	Severity
5-6	A	Mild
7-9	B	Moderate
10-15	C	Severe

Terms	ICD9CM
Acute and subacute necrosis of liver, acute and subacute yellow atrophy of the liver, parenchymatous degeneration of liver, Acute or subacute non-viral hepatitis, acute liver failure	570*
Hepatitis	573.3*
Abnormal results of liver function studies	794.8*
Hepatic coma	572.2*

Kidney disease

All codes (ICD9CM or ICD10) or free text "dialysis" or "renal transplant" (including the presence in a waiting list for renal transplantation), ever before the period preceding or on the entry date.

Patients renal function was codified as:

- **Mild** (glomerular filtration rate ≥60 ml/min/1.73 m2),
- **Moderate** (glomerular filtration rate of 30 to 59 mL/min/1.73 m2),
- **Severe** (glomerular filtration rate 15 to 29 mL/min/1.73 m2),
- **Kidney failure** (glomerular filtration rate less than 15 mL/min/1.73 m2)

Terms	ICD9CM
Acute glomerulonephritis (included acute nephritis)	580*
Small kidney of unknown cause	589*
Diabetes with renal manifestations	250.4*
Malignant Hypertensive nephropathy	403.0*
Benign hypertensive nephropathy	403.1*
hypertensive Nephropathy (non-specific)	403.9*
Hypertensive heart and renal disease	404*
Gouty Nephropathy	274.10
Stenosis of renal artery	440.1
Renal artery aneurysm	442.1
Renal vein thrombosis and embolism	453.3
Other disorders of kidney and ureter	593*
Renal agenesis and dysgenesis	753.0
Other specified anomalies of kidney	753.3
Injury of kidney	866*
Chronic kidney disease	585
Diabetes with renal manifestations	250.4
Nephrotic syndrome with lesion of membranous glomerulonephritis	581.1
Nephrotic syndrome with other specified pathological lesion in kidney	581.8
Proteinuria	791.0
Postsurgical renal dialysis status	V45.1
Encounter for extracorporeal dialysis	V56.0

Encounter for other dialysis	V56.8
Kidney replaced by transplant	V42.0
Complications of transplanted kidney	996.81

Depression

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Major depressive disorder single episode	296.2
Major depressive disorder recurrent episode	296.3
Depressive disorder, not elsewhere classified	311*

Chronic obstructive pulmonary disease and allied conditions and Asthma

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Asthma	493
Asthma, unspecified	493.90
Nonallergic asthma Intrinsic asthma	493.1
Mixed asthma	
Atopic asthma	
extrinsic allergic asthma	493.0
Predominantly allergic asthma	
Extrinsic asthma with asthma attack	493.02
Intrinsic asthma + attack	493.12
Status asthmaticus	493.91
Extrinsic asthma with status asthmaticus	493.01
Intrinsic asthma NOS	493.10
Intrinsic asthma with status asthmaticus	493.11
chronic obstructive asthma	493.2
Other forms of asthma	493.8
Bronchitis, not specified as acute or chronic	490
Chronic bronchitis	491
Emphysema	493
Bronchiectasis	494
Extrinsic allergic alveolitis	495
Chronic airway obstruction, not elsewhere classified	496

Epilepsy

Code (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Epilepsy	345*

Chronic dyspepsia

Code (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Chronic dyspepsia	536.8

Alcohol abuse and/or alcohol-related diseases

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Alcohol dependence syndrome	303*
Alcohol abuse	305.0
Alcoholic polyneuropathy	357.5
Alcoholic cardiomyopathy	425.5
Alcoholic gastritis	535.3
Alcoholic fatty liver	571.0
Acute alcoholic hepatitis	571.1
Alcoholic cirrhosis of liver	571.2
Alcoholic liver damage, unspecified	571.3
Excessive blood level of alcohol	790.3
Personal history of alcoholism	V11.3

Drug abuse or dependence

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Drug dependence	304*
Nondependent cannabis abuse	305.2
Nondependent hallucinogen abuse	305.3
Nondependent sedative, hypnotic or anxiolytic abuse	305.4
Nondependent opioid abuse	305.5
Nondependent cocaine abuse	305.6
Nondependent amphetamine or related acting sympathomimetic abuse	305.7
Nondependent antidepressant type abuse	305.8
Nondependent other mixed or unspecified drug abuse	305.9

Mental health diagnoses and personal history of mental disorder

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Transient mental disorders	293*
Persistent mental disorders	294* (excluding 294.0, 294.1)
Schizophrenic disorders	295*
Episodic mood disorders	296* (excluding 296.2, 296.3)
Delusional disorders	297*
Other nonorganic psychoses	298*
Pervasive developmental disorders	299*
Anxiety, dissociative and somatoform disorders	300*
Personality disorders	301*
Personal history of schizophrenia	V11.0
Personal history of affective disorders	V11.1
Personal history of neurosis	V11.2
Personal history of other mental disorders	V11.8
Personal history of unspecified mental disorder	V11.9

Hallucinations

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Psychophysical visual disturbances	368.16
Hallucinations	780.1

Dementia and memory deficit

All codes (ICD9CM) ever before the period preceding or on the index date.

Terms	ICD9CM
Amnestic disorder	294.0
Personality change due to conditions classified elsewhere	310.1
Alzheimer's disease	331.0
Senile dementia, uncomplicated	290.0
Presenile dementia	290.1
Senile dementia with delusional features	290.2
Senile dementia with delirium	290.3
Vascular dementia	290.4
Jakob-Creutzfeldt disease	046.1
Progressive multifocal leukoencephalopathy	046.3
Other alcoholic dementia	291.2
Drug-induced dementia	292.82
Pick's disease	331.1
Senile degeneration of brain	331.2
Cerebral degeneration in diseases classified elsewhere	331.7
Other cerebral degeneration	331.8
Cerebral degeneration, unspecified	331.9
Parkinson's disease	332.0
Drug-induced persistent amnestic disorder	292.83
Amnesia (retrograde)	780.9

Cognitive Impairment after trauma

Codes (ICD9CM) ever before the period preceding or on the index date

Terms	ICD9CM
Late effect of intracranial injury without mention of skull fracture	907.0