DKP-TRAM

Title	**Drug Utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen (DKP-TRAM)**
Protocol version identifier	v03
Date of last version of protocol	v02 26th September 2018
EU PAS register number	EUPAS24858
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 the pattern of prescriptions of DKP-TRAM. To assess the risk of adverse events (nausea, vomiting, diarrhoea, vertigo, constipation) in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations. To evaluate the effect modification exerted by age (75 or older vs. 74 or younger) on the risk of adverse events in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations users. To evaluate the effect modification exerted by frailty (mild, moderate or severe) on the risk of adverse events in DKP-TRAM versus tramadol monotherapy and tramadol-paracetamol combinations users aged 65 years or older.
Country(-ies) of study	Italy and Spain
Author	Francesco Lapi, PharmD, PhD, Research Director 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

Name of the main author of the Final Study Report: Francesco Lapi

Date: January 14, 2022

Signature: 

1. TABLE OF CONTENTS

1. Table of contents 3

2. List of abbreviations 5

3. Responsible parties 6

4. Abstract 7

5. Amendments and updates 12

6. Milestones 15

7. Rationale and background 15

8. Research question and objectives 17

9. Research methods 18

9.1. Study design 18

9.2. Setting 19

9.2.1 Study population 19

9.2.2 Study period 19

9.2.3 In- and exclusion criteria 19

9.2.4 Follow-up 19

9.3. Variables 20

9.3.1 Primary objective 20

9.3.2 Secondary objectives 23

9.4. Data sources 25

9.5. Study size 27

9.6. Data management 27

9.6.1 Definition of data extraction algorithm 28

9.7. Data analysis 28

9.7.1 Primary objectives 28

9.7.2 Secondary objectives 28

9.7.3 Secondary analyses 30

9.8. Quality control 30

9.9. Limitations of the research methods 30

10. Results 31

10.1. PRIMARY OBJECTIVES 31

10.1.1 Incidence rate of DKP-TRAM use 31

10.1.2 Indications for which DKP-TRAM 38

10.1.3 Dosage and Duration of treatments with DKP-TRAM 39
11. Discussion 43
11.1 Key results 43
11.2 Limitations 43
11.3 Interpretation 44
12. Conclusion 45
13. Protection of human subjects 45
14. Management and reporting of adverse events/adverse reactions 46
15. Plans for disseminating and communicating study results 46
16. References 47
Annex 1. List of stand-alone documents 51
Annex 2. ENCePP checklist for study protocols 52
Annex 3. Additional information 61
Annex 4. Results tables and figures 68

2. LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
COX	Cyclooxygenase
CUI	Concept Unique Identifier
DDD	Defined Daily Doses
DKP-TRAM	Dexketoprofen trometamol - tramadol hydrochloride
DUS	Drug Utilization Study
eFI	electronic Frailty Index
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
OR	Odds Ratio
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
SmPC	Summary of Product Characteristics
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 Research Director 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 President 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: Talita Duarte Salles, PhD Senior Clinical Research Fellow IDIAP Jordi Gol Scientific Coordinator SIDIAP Database (www.sidiap.org) e-mail: tduarte@idiapjgol.org
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. There is still limited evidence in the real-life use of the product in the primary care settings, particularly in elderly and/or frail patients where the use of the 75 mg dose (with no possibility of dose titration) of tramadol 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 through a real-world study involving an Italian and a Spanish database. Furthermore, we will test the potential effect modification exerted by age (75 years or older vs. younger patients) or frailty (mild, moderate, severe) among elderly patients (aged 65 or older) on the risk of adverse events (AEs) likely due to DKP-TRAM.
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 (nausea, vomiting, diarrhoea, vertigo, hallucinations, somnolence, and constipation) in incident users of DKP-TRAM vs. incident users of tramadol as monotherapy and fixed combination tramadol-paracetamol. ● To evaluate the effect modification exerted by age (75 or older vs. 74 or younger) on the risk of adverse events in DKP-TRAM vs. tramadol monotherapy and tramadol-paracetamol combinations users.

	● To evaluate the effect modification exerted by frailty (mild, moderate or severe) on the risk of adverse events in DKP-TRAM vs. tramadol monotherapy and tramadol-paracetamol combinations users aged 65 years or older.
Study design	A bi-national database cohort study will be conducted. data will be derived from two electronic health care databases from two European countries: 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 or tramadol-paracetamol combinations from January 1, 2017 and with at least 1-year of database history will be included in the study. To evaluate the effect modification due to frailty, all patients, aged 65 years or older, prescribed for the first time with DKP-TRAM and/or tramadol monotherapy or tramadol-paracetamol combinations from January 1, 2017 and with at least 1-year of database history will be included in the study.
Variables	Indication, duration and dosage of medications used, demographic factors, life style factors, comorbidities, co-medications and prescriber type (GP or specialist). Adverse Events: nausea, vomiting, diarrhoea, vertigo, hallucinations, somnolence, and constipation.
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	2,763 and 7,945 patients have been prescribed with this medication in 2017 in HSD and SIDIAP, respectively. Thus, assuming an estimated yearly incidence rate of medication use of almost 0.2 and 1% in HSD and SIDIAP, respectively, these numbers of users would be large enough to assume a 0.01 precision with 95% Confidence Intervals (CI). Given that HSD currently includes almost 1 million patients and SIDIAP almost 7,6 million, these numbers should ensure stable estimates. 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 a Hazard Ratio (HR)=1.2 with 80% power and 5% type I error when comparing DKP-TRAM vs. tramadol (including tramadol-paracetamol). The number of DKP-TRAM users aged 75 years or older resulted in 705 and 949 for HSD and SIDIAP, respectively. Indeed,

	still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal to 1.2 with 80% power and 5% type I error when comparing DKP-TRAM vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category 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. Duration of DKP-TRAM use will be evaluated by means of Kaplan-Meier method as well, by following DKP-TRAM users up to the fifth day of follow-up, namely the maximum length of use be allowed by the SmPC. **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 and as tramadol-paracetamol combination by estimating HR with related 95% CI trough Cox regression model. Tramadol monotherapy or tramadol/paracetamol combination users will be the reference category. The risk of AEs in users of different dosages and durations of DKP-TRAM will be compared with the risk of AEs in users of tramadol or tramadol-paracetamol combination different dosages and durations by estimating Odds Ratio (OR) with related 95% CI, according to a nested case-control analysis, trough conditional logistic regression model. Such a model will be adopted to evaluate the presence of effect modifications due to age or frailty on the risk of AEs.
Results	In Italy, the IR of DKP-TRAM use in the general population was 2.81‰ and 3.44‰ in 2017 and 2018, respectively. Females and elderly patients were associated with higher IRs. Similar results were found calculating the IR of DKP-TRAM use with person-times as denominator. Regarding comorbidities, obese patients (7.54‰), alcohol abusers (4.66‰), patients with mild hepatic impairment (5.33‰) and mild kidney failure (6.14‰) showed the highest IRs of DKP-TRAM use during the study period. Among prior or concurrent pharmacotherapies, the highest IRs of DKP-TRAM use were found in patients prescribed with tramadol (21.72%), other opioids (15.95%) and erythromycin (10.74%).

	In HSD, we were unable to assess the prescriber type, namely GP or specialist. Evaluating the indication for DKP-TRAM prescriptions across the two years under study, low back pain (32.5%), osteoarticular pain (17.8%), and osteoarthritis (8.9%) resulted the most frequent indications for DKP-TRAM prescriptions. In accordance to SmPC, around 97% of patients treated with DKP-TRAM (9705 prescriptions; only tablet-based formulation are reported) did not exceed three tablets per day corresponding to 225 mg of tramadol and 75 mg of dexketoprofen based on PDD. Most patients prescribed with DKP-TRAM were associated with a total cumulative duration of treatment equal to 10 days varying from 72.1% at 3 months to 68.8% at 12 months with a number of "5-day" courses less than 4 at 12 months. A Kaplan-Meier curve was adopted in order to estimate the burden of DKP-TRAM discontinuation because of potential medication-related AEs. As a whole, 182 (2.9%) patients treated with DKP-TRAM discontinued during the first month of follow-up. The probability of surviving (i.e., no-discontinuation) occurred soon after (first day: 32 cases) starting DKP-TRAM treatment and steadily decreased over time. Finally, among users of DKP-TRAM, tramadol or tramadol-paracetamol combination, there was an overall IR of AEs equal to 3.73 per 10,000 person-days. They were mainly due to nausea, vomiting, vertigo and constipation, and most of them (48.2%) were directly reported in the section of GP's electronic charts recording events of drug intolerance. DPK-TRAM use reported the highest incidence rate of AEs (5.03 per 10,000 person-days). In Spain the DKP-TRAM use in the general population was 2.41‰ in 2017 and 1.80‰ in 2018 (as a whole, . 26322 prescriptions of DKP-TRAM were registered) Most of the patients receiving a new prescription of DKP-TRAM were middle aged women with a past history of smoking and frequently diagnosed with obesity. Those with an incident prescription of DKP-TRAM also were likely to have depression (8.22‰), dyspepsia (7.41 ‰) and mental disorders (6.81‰). Among those who had a hepatic or renal impairment, the highest IR of DKP-TRAM prescription was seen for those with chronic hepatic impairment (6.6 ‰) and severe kidney impairment (5.89‰), however only 3 patients were included in this category. Prior and or concurrent medications included tramadol (IR of 13.72‰ followed by other opioids (12.44‰) and carbamazepine (12.44‰). Most of the prescriptions

	of DKP-TRAM were initiated for musculoskeletal disorders (56.33%). In SIDIAP, GPs (40% or higher) were the main prescribers of DKP-TRAM. With regards of the dosage, the majority used a dose lower than 225/75mg per day (65% and 99% using the PPD and DDD approach respectively). The median duration of the DKP-TRAM prescription in SIDIAP was 11 days, with nearly half of the patients reporting shorter durations and nearly a third longer durations of treatment. For all durations of follow-up, there was almost 8% of DKP-TRAM users with less than 5 days of therapy duration. With respect to the 5-day courses of treatment, approximately 69% of the new users of DKP-TRAM had less than 4 courses. Overall, 226 patients discontinued their treatment at the end of the 30 days. Most of the adverse events were reported in the first 10 days (138 events) and more precisely during the first day (58 events). According to the Kaplan-Meier curves, the highest discontinuation was seen at the first day of treatment and this likelihood of discontinuation continued until the 15th day when it seemed to stabilize. The overall IR of adverse events in the DKP-TRAM, tramadol or tramadol-paracetamol exposure cohorts was 1.98 cases per 10,000 persons-day. These were mostly due to vertigo (63.26%), constipation (27.44%) and diarrhoea (7.57%), an already well - known pattern of AEs for products like DKP-TRAM. When analysing per exposure category, the IR of AEs of DKP/TRAM was similar to that of tramadol-paracetamol (2.06 vs. 2.04, respectively). For HSD, when the risk of AEs for DKP-TRAM use were compared with tramadol or tramadol-paracetamol use, a statistically significantly increase of 66% was estimated by the multivariate Cox model. The relative risk was 2.3-fold higher in the direct comparison between DKP-TRAM vs. tramadol-paracetamol. These estimates were not modified among patients aged 75 or older (p value for interaction 0.18). Indeed, similar point estimates were obtained when the analysis was stratified by age >=75 years or younger individuals. Consistent results were obtained with the nested case-control analysis, where current users (within 1 month preceding the date of AE, inclusive) of DKP-TRAM reported an increased rate of AEs than tramadol or tramadol-paracetamol combination. The nested case-control analysis also indicated that there was a dosage (>=150 mg/daily) and duration-response (<10 days) relationship

	between use of DKP-TRAM and occurrence of AEs. When the effect modification due to frailty was evaluated, the interaction term (i.e. exposure categories for medications (5)*frail categories (3)) showed statistically significant effect modification for DKP-TRAM users within the highest tertile of HS-FI (p value equal to 0.01). Specifically, the risk of AEs among current users DKP-TRAM was 3.24-fold higher among highly frail patients. To be noted that the risk of AEs is not linearly related to the level of frailty; specifically, it was 3.1 higher for low frail patients and 2.52-fold higher for moderate frail patients. For SIDIAP, adjusted models showed that patients who were prescribed with DKP-TRAM had a 30% increased risk of reporting an AE compared to those exposed to tramadol or tramadol-paracetamol. This increased risk was more pronounced compared with tramadol, with 48% higher risk of AEs with DKP-TRAM. When the effect modification due to age >= or < 75 years was tested, the p value for interaction was not significant (p= 0.06); an increased risk for AEs for DKP-TRAM vs. tramadol/tramadol paracetamol use was seen in patients aged 74 years or younger, while no association was found among older patients. The results were consistent with those described above, when the exposure was categorized into recent or current use for the nested case-control analysis. A higher risk of adverse events was seen in patients who had a current exposure to DKP-TRAM compared to those with current use of tramadol or tramadol-paracetamol. In addition, the nested case-control analysis confirmed that there was a dosage (>=150 mg/daily) and duration-response (<10 days) relationship between use of DKP-TRAM and occurrence of AEs. No effect modification due to frailty was revealed. For both databases, the sensitivity analyses provided results which were consistent with those obtained for the primary analyses.

Discussion	This final report describes the pattern of drug use and investigates the safety profile of DKP-TRAM vs. tramadol or tramadol-paracetamol combinations in primary care in Italy and Spain. The IR of DKP-TRAM use was higher in female and elderly patients. This finding reflected the indication of DKP-TRAM prescriptions being quantified in the study. Indeed, low back pain, osteoarticular pain and osteoarthritis are common diseases in female and older patients. Overall, we found that this treatment was scarcely used in patients affected by clinical conditions which could lead to poor tolerance of DKP-TRAM because of occurrence of AEs. This finding likely reflects the high appropriate prescribing pattern among GPs. For instance, patients affected by mild hepatic impairment showed the highest IR of DKP-TRAM use compared to the other patients with moderate to severe hepatic conditions. Similar results were found for patients with kidney disease. High IRs of DKP-TRAM use was found in patients prescribed with tramadol, other opioids and erythromycin. DKP-TRAM was recently launched on the market. As such, patients were likely treated with tramadol or other opioids before the entry date, so already titrated to verify drug effectiveness and tolerability before increasing the tramadol dosage up to 75 mg. In accordance to SmPC, around 97% of patients treated with DKP-TRAM did not exceed three tablets per day corresponding to 225 mg of tramadol and 75 mg of dexketoprofen based on PDD. Most patients prescribed with DKP-TRAM were associated with a total duration of treatment equal to 10 days, with a number of "5-day" courses less than 4 at 12 months. This result may suggest that patients exposed with DKP-TRAM resolved their painful conditions during the first 3 months. Indeed, negligible variations in the distributions of therapy courses was found from 3 to 12 months. The Kaplan-Meier curve showed the discontinuation likely due to AEs appeared common during the first 5 days of therapy. The initial exposure to 75 mg of tramadol could be a cause of AEs leading to drug discontinuation, especially for incident users, while these AEs were sensibly reduced during follow-up. This evidence also supports the fact that most of the patients did not extend DKP-TRAM use over the 5-day duration as recommended by the SmPC. These results were confirmed by comparative safety study which showed a greater risk for DKP-TRAM vs. tramadol or tramadol/paracetamol. These findings

	were further demonstrated by the nested case-control analysis, with which we found an acute occurrence of AEs, given the significant association between a short-term use (less than 10 days) of DKP-TRAM and the occurrence of AEs. Furthermore, the higher dosage (>=150 mg) initially prescribed for DKP-TRAM resulted associated with greater risk of AEs vs. recent (prevalent) users. Consistently, a prior (prevalent) use of opioids might have mitigated the risk of AEs among current users of DKP-TRAM. The IR of DKP-TRAM use during the study period decreased in Spain from 2017 to 2018. Incident users of DKP-TRAM in Spain were similar to the one found in Italy, namely middle-aged females with a prescription of DKP-TRAM indicated for musculoskeletal disorders which is in accordance with previous evidence, given that musculoskeletal disorders are a leading cause of pain and disability in industrialized countries. Moreover, the indications for which the DKP-TRAM were prescribed mostly reflects the indication in SmPC; over 34% of the indications were for musculoskeletal disorders. A higher proportion of inappropriate prescriptions was detected in Spain, namely higher IR of DKP-TRAM prescription among patients with chronic liver disease or severe renal function, which could be due to the higher proportion of induced prescriptions from the private health sector. Regarding the prior or concurrent medications, we found similar findings as those reflected in Italy with high IR in patients with previous or concurrent prescription of tramadol or other opioids. As in Italy, and according to the SmPC, in Spain between 65% and 99% (using the PDD and DDD respectively) took less than 225/75mg per day. The median cumulative duration, evaluated for the first prescription, of the DKP-TRAM prescription in SIDIAP was of 11 days, with almost half of the patients reporting shorter durations, and with 69% of the new users having less than 4 “5-day” courses of treatment. This treatment discontinuation could be due either to a decrease in pain, a lack of effect and switching to another type of painkiller or an AE. In this line, the estimated burden of DKP-TRAM discontinuation due to AEs in this study showed an increasing trend of discontinuation which was more pronounced in the first 15 days, after which it was attenuated. Approximately 39% of the incident DKP-TRAM users in Spain had cumulative treatment durations longer than 11 days and 20% had >6 courses of “5-day” treatment during the 3, 6 and 13 months of follow-up. The overall IR (per 10,000 persons-day) of AEs in the

	DKP-TRAM , tramadol or tramadol-paracetamol exposure cohorts in SIDIAP was lower than that found in Italy (5.03 vs. 2.06 for DKP-TRAM, 3.76 vs. 1.69 for tramadol and 2.44 vs. 1.94 for tramadol-paracetamol, respectively). Differences in the IR of AEs with Italy are likely due to the voluntary notification of the AEs reporting in Spain (conversely to Italy where there is a specific section for drug intolerance in the GPs' software); the AE reporting is not routinely collected and therefore our results likely underestimate the real rates of AEs in this population. A residual confounding factor related to the difference between treatments linked to the time they have been on the market at the time of analysis (many years for tramadol or tramadol-paracetamol, months to 2 years for DKP-TRAM) cannot be ruled out in creating this higher IR of AEs for DKP-TRAM. When comparing the AEs per exposure categories, a 30% higher risk of AEs was seen among those exposed to DKP-TRAM compared to tramadol or tramadol-paracetamol combination. When analysing the exposure by recent and current use, an increased risk of AEs was seen with the current use of DKP-TRAM (adjusted OR equal to 1.31) compared to the current use of tramadol-paracetamol. However, this increased risk was of borderline significance. This increased risk was more pronounced when comparing the current use of DKP-TRAM to the current use of tramadol (adjusted OR equal to 1.53). Propensity score matching and the multiple imputation for BMI and smoking further confirmed this increased risk of current use of DKP-TRAM compared to current tramadol/tramadol-paracetamol users. This increased rate among DKP-TRAM current users could be due to the higher tramadol starting dosage in this medication compared to a lower starting dose of tramadol and tramadol-paracetamol. The AEs more frequently reported in SIDIAP were, vertigo, constipation and diarrhoea which were also the most frequently reported AEs in Italy.. The current dosage (of at least 2 pills/day, equivalent to 150 mg of tramadol) of DKP-TRAM and the current shorter duration of treatment (<11 days) were also associated with an increased OR of AEs compared with the recent user. This higher risk found with shorter duration of tramadol could respond to the tolerance effect that occurs to longer exposure of opioids and that could translate into lower rates of AEs. For what concerns the effect modification likely due to age, no association was found in HSD for patients aged >=75 vs 74 and younger. Also for

	SIDIAP, no association was detected for patients >=75 years while patients aged 74 years or less showed an increased risk of AEs if exposed to DKP-TRAM vs. tramadol/tramadol-paracetamol. When considering the relation to frail patients, in HSD it has been found a positive correlation between the increase of AEs IR and the level of frailty in current vs. recent DKP/TRAM users while no association was observed for SIDIAP.
Milestones	Start of data collection, 1st January 2017 Registration in the EU PAS register, May 2021 End of data collection, 31st December 2018 Study progress report, 28th February 2020 Interim report, 31st January 2021 Final report of study results, 7th January 2022

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	March 11, 2019	7. Rationale and background	In the Italian market there are other products containing ("high" dose)) 75 mg of tramadol (i.e. tramadol-paracetamol combinations. In particular, tramadol-paracetamol combinations is featured by a place in therapy similar to DKP-TRAM, with the same suggested dosage for tramadol (i.e. 75 mg) according to SmPC. Nevertheless, given that tramadol-paracetamol formulation contains tablets of 37,5 mg of tramadol, clinicians are able to titrate the dosage on the bases of patient's response.	Further information on the reason why the PASS has been requested.
2	March 11, 2019	7. Rationale and background	Certain sales have been reached also in France. the available French claims database (SNIIRAM and EGB) is able to track reimbursed medications only. Nevertheless, the DKP-TRAM has been approved for reimbursement by the French national HTA authority (HAS) in March 2018, but it has not appeared yet in the reimbursement database, as of August, 2018. The inclusion of this data source, with information until December 2018 should	Information on the potential inclusion of French database has been requested.

			be therefore underpowered.	
3	March 11, 2019	9.3.1 Primary objective Duration of treatment	In HSD, the duration of treatment with DKP-TRAM will be evaluated, for the first prescription, as longer or shorter than 5 days, namely the maximum durations allowed by the SmPC [1], along with describing the different treatment courses (i.e., number of courses, related durations and 5-day courses) being identified and cumulated during follow-up. The length of follow-up will be set on three, six or twelve months. Thus, we will compare durations (and related number of 5-day courses) of DKP-TRAM being calculated using PDD or dosage reported in the SmPC for different period of follow-up. With this approach, given that PDD is the actual dosage indicated by GPs, we will identify potential inconsistencies in using the SmPC dosage. Furthermore, duration of prescriptions with DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM or switch to another therapy. Stopping will	The Kaplan-Meier analysis on treatment duration with DKP-TRAM was revised.

			be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.	
4	March 11, 2019	9.3.2 Secondary objectives Outcomes	Constipation was added to the potential AEs under study (see Table 3).	We extended the event definition to other types of AEs.
5	March 11, 2019	9.5 Study size	Still from preliminary evaluation, the number of DKP-TRAM users aged 75 years or older resulted 705 and 949 for HSD and SIDIAP, respectively. These numbers would ensure stable estimates to test the presence of effect modifications due to age on the risk of AEs. Indeed, still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal 1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category as well.	We reported the evaluation on the study size for what concerns the DKP-TRAM users aged 75 years or older.
6	March 11, 2019	9.7 Data analysis	The duration of prescriptions of DKP-TRAM will be	Data analysis using Kaplan-Meier method

			investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM and/or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.	needed to be revised given the use absence of actual daily dose in Spain data.
7	March 19th 2021	9.3 Variables	SIDIAP will use prescriptions for the drug exposure	Drug dispensations in SIDIAP lack an accurate start date given that pharmacy invoices have a delay of 15-30 days. Given that the AEs are likely to happen in the first days, prescription instead of dispensation, needs to be used to have the exact date when the drug was prescribed.

8	April 15th 2021	9.3.2 Secondary objective Frailty index	Health Search Frailty Index (HS-FI); SIDIAP will adapt the Frailty index	Health Search developed its own Frailty Index (HS-FI) according to a different methodology, so adopting an iterative algorithm instead of Clegg's approach. The Frailty index used in HSD will need to be adapted for SIDIAP given that we will not be able to account for the deficit "Partial or total economic support to medical expenses" and will have only limited hospital admissions information for the deficit "Any hospital overnight staying in the last 6 months".

9	April 15th 2021	9.3.1 Primary objective Duration of treatment	SIDIAP will adapt the calculation of duration of treatment	In SIDIAP we have used prescriptions and the number of prescriptions is not available. Therefore, the definition of duration had to be adapted. We have considered all prescriptions (pills and days) in each period (3,6 and 12 months). The duration of treatment has been calculated by adding the quantities (pills)/days.
10	April 15th 2021	9.3.1 Primary objective: Comorbidities	The hepatic impairment could not be classified through the Child Pugh classification	In SIDIAP we use ICD-10 CM codes and the Child Pugh classification is not included as routinely collected information. Therefore, we have classified the hepatic impairment in: Hepatic impairment (overall), Chronic hepatic impairment and Cirrhosis. The ICD-10CM Codes for each classification have been added to the Annex 3.

11	April 15th 2021	9.1 Study design	Nested case-control matching	Information on GPs is not available in SIDIAP, so cases and controls will not be able to be matched by this. Furthermore, there was a new health policy at the end of 2017 limiting the use of DKP-TRAM so patients receiving this drug in 2017 could differ from the ones receiving it in 2018 therefore we decided to match per month and year too.

12	April 16th 2021	9.7.3 Secondary analysis	Analysis on prevalent users	The nested case-control analysis allowed us to compare current vs. recent users. The recent users can be considered as prevalent users and adopted as reference category.
13	April 16th 2021	Sensitivity analysis	Changing the time window to define the current users	The AEs were mainly coded in the first 30 days of DKP-TRAM use as demonstrated by the duration-response relationship as well. Thus, this sensitivity analysis does not add any informative result.
14 (Protocol v04)	December 29th 2021	Variables Prescriber type	Further explanation on the analyses concerning the prescriber type	There is no variable assessing the prescribed type in HSD.

14 (Protocol v04)	December 29th 2021	Discussion	Further explanation on the results concerning the prescriber type	There is no variable assessing the prescriber type in HSD. In SIDIAP, in which is possible to identify the prescriber type, most of the patients were prescribed with DK-TRAM by GPs.
15 (Protocol v04)	December 29th 2021	Duration of treatments with DKP-TRAM	Additional information on users of DKP-TRAM for 4 days or lower were provided.	This information should be featured by reduced sensitivity given that the use of PDDs and total strengths (in mgs) of DKP-TRAM did not reflect the actual duration of use as indicated by physicians.
16 (Protocol v04)	December 29th 2021	Discussion	Additional information on users of DKP-TRAM for 4 days or lower.	To evaluate the consistency of the maximum duration of use, as indicated by the SmPC. Nevertheless, with the dosage instruction being available in the data sources, this information was poorly sensible.

17 (Protocol v04)	December 29th 2021	10.2.1 Incidence rate of AEs	Further details on AEs were provided: their relative proportions were reported by age (>=75 year) and exposure category.	To provide a description of AEs according to individual molecules.
18 (Protocol v04)	January, 7th 2022	10.2.2 Risk of AEs in DKP-TRAM users vs. Tramadol or Tramadol-Paracetamol users Cohort analysis	P values describing the characteristics among exposure categories were provided in the related Tables.	
19 (Protocol v04)	January, 7th 2022	Cohort analysis	A specific Table (for HSD and SIDIAP) presenting the results on effect modification due to age was provided.	To provide further details on effect modification due to age.
20 (Protocol v04)	January, 7th 2022	Nested case-control analysis	Specific Tables (for HSD and SIDIAP) presenting the results on effect modification due to frailty (among patients aged 65 years or older) was provided.	To provide further details on effect modification due to frailty.

6. MILESTONES

Milestone Planned date	
Start of data collection	1st January 2017
End of data collection	31st December 2018
Study progress report	28th February 2020
Interim report	31st January 2021
Registration in the EU PAS register	May 2021
Final report of study results	7th January 2022

7. RATIONALE AND BACKGROUND

This study was imposed as a condition of the marketing authorisation during the procedure ES/H/0317-0318/001/DC to address concerns regarding the safety and tolerability of this high fixed tramadol and dexketoprofen dose in the general population *DKP-TRAM/vo3*

including frail-elderly and very elderly patients in the approved indication. This PASS is part of the currently approved Risk Management Plan (RMP) v.3.2 (dated 01 February 2021) with the following title:

- **Category 1** (imposed): TBD Drug utilization Study (DUS) and Post Authorization Safety Study (PASS) on the fixed combination tramadol-dexketoprofen. Cohort, population-based, study.

Acute and chronic pain represent one of the most relevant public health concerns, with socioeconomic impact in both Europe [2] and USA [3]. Furthermore, a poor pain control may result in reduced patients' quality of life, increasing risk of developing chronic pain and other medical complications [4].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 been adequately controlled. This scale includes nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol 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 [5].
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) [6]. 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.
From when the product was launched on the market (i.e. from December 31, 2016 to March 31, 2017) to June 2018, Italy and Spain are the European countries with the highest sales, reporting 746,553 and 1,271,703 dispensed packs (internal sales data), respectively, along with Poland, France, and Portugal with 1,039,551, 214,083, and 267,546 dispensed packs (internal sales data), respectively. Spain is the only European country in which DKP-TRAM is partially reimbursed (almost 40%) by the public health system.
Tramadol is a weak opioid with central analgesic activity and long-lasting effect [9]. It has a double mechanism of action: activation of the μ-opioids receptors and inhibition of the reuptake of serotonine and noradrenaline [9,10]. Dexketoprofen trometamol is a NSAID, in particular is the S(+)-enantiomer of ketoprofen, with a quick onset of action and demonstrated effectiveness on acute pain relief [12], [13]. The pharmacological properties of dexketoprofen consists of strong inhibition of COX-1 along with moderate inhibition of COX-2, allowing the drug to have anti-inflammatory effects in both the peripheral tissue and in the spinal cord.

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%) [14].
Given the dose-related risk of AE due to tramadol, which lead to drug discontinuation in 20% of users [14], the choice of initial dosage is usually the lowest one (50 mg) with a subsequent increase according to the patient's response in terms of drug efficacy and tolerability. This concern is of particular relevance in special populations, such as in older patients, who are the most frequent users of this therapy and are more prone to AEs because of age-related factors including the growing frailty.
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 in which it could be prescribed for several and frequent pain conditions such as low back pain and other musculoskeletal disorders. Indeed, the initial exposure to 75 mg of tramadol, with no possibility of titration could be a cause of AEs leading to drug discontinuation, especially for incident users (i.e.: those previously unexposed to other tramadol-containing formulations). Furthermore, this is particularly relevant among elderly and frail patients who, as mentioned above, may be at greater risk of AEs than younger patients.
Currently, there are other 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. In particular, tramadol-paracetamol combinations is featured by a place in therapy similar to DKP-TRAM, with the same suggested dosage for tramadol (i.e. 75 mg) according to SmPC even if tramadol-paracetamol formulation contains tablets of 37,5 mg of tramadol.
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 populations, such as older (75+ years of age) and/or frail patients, who may be more prone to AEs or drug discontinuation because of gastrointestinal and central AEs when compared with younger patients [19]. To answer these research questions, we will conduct an observational study in Italy and Spain given the fact that, within the territories where the product has been launched, only these two countries have a relevant consumption of DKT-TRAM along with two research databases fully validated and already used for several observational, population-based, multi-country investigations [20]–[22]. Indeed, certain sales have been reached also in France. The available French claims database (SNIIRAM and EGB) is able to track reimbursed medications only [23]. Nevertheless, the DKP-TRAM has been approved for reimbursement by the French national HTA authority (HAS) in March 2018, but it has not appeared yet in the

reimbursement database, as of August, 2018. The inclusion of this data source, with information until December 2018 should be therefore underpowered.
High sales have been revealed in Portugal and Poland as well, but these countries don't have a reliable database (so far) to provide adequate information, as per study requirement.

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 (or tramadol-paracetamol combination), 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 in 2017 and 2018.

Specific aims:

- To estimate the population-based yearly incidence rate (IR) of DKP-TRAM use in patients aged 18 years or older.
- To describe the demographic, clinical characteristics, and prescriber type (GP-General Practitioners or specialist) for 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 (and fixed combinations tramadol-paracetamol), and to evaluate the presence of effect modification exerted by age (75 or older) or frailty (mild, moderate, severe) on the risk of AEs in 2017 and 2018.

Specific aims:

- To calculate the IR of AEs occurring during the first 3 months of follow-up among patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To estimate the hazard ratios (HR) of AEs in patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To evaluate the presence of effect modification exerted by age (75 years or older vs. 74 or younger) on the risk of AEs in patients aged 18 years or older and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations tramadol-paracetamol).
- To evaluate the presence of effect modification exerted by frailty (mild, moderate, severe) on the risk of AEs in patients aged 65 years or older

and prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy (and fixed combinations 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 patients' features, prescriber type (i.e. GP or specialist), indication of use, dosages, and duration of treatment.
Furthermore, this study will assess the safety profile of DKP-TRAM compared to monotherapy with tramadol (and tramadol-paracetamol combinations) 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) and gender. In SIDIAP the data on GP is not available and therefore we will stratify by primary health care centre. The date of cases will be the index date and assigned to the respective controls. This same nested case-control dataset will be adopted to investigate the presence of effect modification due to age on the risk of AEs, and it will be limited to patients aged 65 years or older when frailty will be evaluated as effect modification on the risk of AEs.

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 (March 2017) and Spain (January 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 least 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 entire period (up to 1998 and 2010 for HSD and SIDIAP, respectively) 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 (including tramadol-paracetamol), the expected short-time of onset for these AEs as well as the GP's delay for AEs registration.

9.3. VARIABLES

9.3.1 PRIMARY OBJECTIVE
Exposure
The drug of interest can be prescribed by GP and specialist physicians. Both HSD and SIDIAP contain information on primary care prescriptions. Only in SIDIAP has the opportunity to distinguish between prescriptions stemming from GPs or specialists.

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 [1].
All diagnoses associated to prescriptions of DKP-TRAM will be identified and classified according to ICD9CM (International Classification of Diseases, 9th rev., Clinical Modification) and ICD-10 International Classification of Diseases, 10th rev., Clinical Modification). 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 both HSD and SIDIAP to minimize the burden of miscoding.

Dosage
The distribution of the PDD will be described for all users of DKP-TRAM. 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. We will evaluate the PDD related to the initial prescriptions and those registered during follow-up. For this analysis, the length of follow-up will be set on three, six or twelve months.

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

- Total units*Strength/PDD value (in HSD).
- Total number of daily doses being prescribed/dispensed, calculated as total Units*Strength/ daily dose as indicated in the Summary of Product Characteristics, which will be considered the standard DDD (SmPC; in HSD and SIDIAP).

In SIDIAP the PPD was calculated taking into consideration all the prescriptions (pills/days) in each period (3, 6 and 12 months) and calculating the duration dividing the quantity of pills /days in each period.

In HSD and SIDIAP, the duration of treatment with DKP-TRAM will be evaluated, for the first prescription, as longer or shorter than 5 days, namely the maximum durations allowed by the SmPC [1], along with describing the different treatment courses (i.e., number of courses, related durations and 5-day courses) being identified and accumulated during follow-up. The length of follow-up will be set on three, six or twelve months. Thus, we will compare durations (and related number of 5-day courses) of DKP-TRAM being calculated using PDD or dosage reported in the SmPC for different periods of follow-up. With this approach, given that PDD is the actual dosage indicated by GPs, we will identify potential inconsistencies in using the SmPC dosage.

Furthermore, duration of prescriptions with DKP-TRAM will be investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, the fifth day of follow-up, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.

Demographics and life style factors
Information on patients' age and sex will be retrieved on the index date. Furthermore, lifestyle 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, Annex 1 and Annex 3).

After defining ICD9CM codes, ICD10CM will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [24].

Previous and subsequent use of tramadol (or tramadol-paracetamol) will be investigated in terms of dosage according to the criteria indicated below.

Prescriber type

Patterns of DKP-TRAM use (i.e. prevalence and IR of use, dosage and duration) will be evaluated according to the prescriber type. Namely, prescriptions of DKP-TRAM will be differentiated whether they will be made by GPs or specialists. This distinction will be directly obtained in SIDIAP in which the prescriber type is codified.

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

Cerebro/cardiovascular disease	410*-414*, 428*, 402.91, 404.91, 402.01, 402.11, 404.01, 430-2*, 433.01, 433.11, 434.01, 434.11, 436*, 438*, V45.81
Gastrointestinal haemorrhages	531.00, 531.10, 532.00, 533.00, 535.01, 535.41, 535.51, 535.61, 578.0, 578.1, 578.9

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

Co-medications	Anatomical Therapeutic Chemical (ATC)
Tramadol	N02AX02
NSAIDs (nonsteroidal anti-inflammatory drugs)	M01A*
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

Adverse Events, during drug exposure, have been identified to define patients being intolerant to tramadol. We will capture all events which have been previously considered as the leading cause of drug discontinuation [13].

Each event will be therefore identified in HSD and SIDIAP via ICD9CM and ICD-10CM coding system, respectively (Table 3 and Annex 1). After defining ICD9CM codes, ICD-10CM will be identified using the CodeMapper system and then harmonized with the related ICD9CM codes through manual revision [24].

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
Constipation	564.0
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 (and as tramadol-paracetamol combinations (ATC: N02AJ13)). We chose this comparator because it includes the most used tramadol formulations whose dose can be escalated. Furthermore, tramadol-paracetamol combinations will be helpful as comparator because the initial dosage (as indicated by SmPC) is equivalent to 75 mg of tramadol (i.e. two tablets of 37,5 mg tramadol). Both HSD and SIDIAP contain information on primary care prescriptions.

Dosage

The PDD of DKP-TRAM and tramadol monotherapy will be evaluated in the period preceding and/or on the date of AEs registration. To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or the compared medications, in the month preceding or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. Operationally, we will therefore identify the cumulated dosage of tramadol (i.e., it is expected a multiple of 75 mgs for DKP-TRAM and more heterogeneous doses for the other formulations containing tramadol) being registered by the current users.

Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the dosage (in mg) in tertiles (or other categories according to the observed results) as it will be registered in the controls as reference for the general population. This approach will allow us to compare the individual dosage categories being prescribed for DKP-TRAM users versus those being prescribed for tramadol (or tramadol-paracetamol combination) users.

Duration of treatment

The duration of treatment with DKP-TRAM and with tramadol as monotherapy (and as tramadol-paracetamol combinations) in HSD will be calculated using:

- Total units*Strength/PDD value (in HSD).
- Total number of daily doses being prescribed/dispensed, calculated as total Units*Strength/ daily dose as indicated in the Summary of Product Characteristics, which will be considered the standard DDD (SmPC; in HSD and SIDIAP)

In SIDIAP the PPD was calculated taking into consideration all the prescriptions (pills/days) in each period (3, 6 and 12 months) and calculating the duration dividing the quantity of pills /days in each period.

Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the duration (in days) in tertiles as it will be registered in the controls as reference of general population. To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or the compared medications, in the month preceding and/or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. Operationally, we will therefore identify the cumulated duration of tramadol (in days) being registered by the current users. Given that this exposure will be modelled according to a nested case-control analysis, we will categorise the durations in terciles (or other categories according to the observed results) as it will be registered in the controls as reference of general population. Furthermore, we will check the presence of 5-day courses and related multipliers (e.g. 1=one course, 2=two courses etc…) of therapy among current users. This approach will allow us to compare the cumulative duration categories among DKP-TRAM versus tramadol (or tramadol-paracetamol combination) users. In addition, the reference category will be split into tramadol and tramadol-paracetamol.

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)).

Frailty

For the purposes of our study, we developed and validated the Health Search Fraily Index (HS-FI) using a cohort of 308,280 individuals older than 60, with at least 5 years of HSD follow up (median follow up time: 6.9 years) within a timeframe from the 1st of January 2013 and the 31st of December 2019. Data were randomly split in a train dataset (N=184,968 - 60.0%), employed for the HS-FI construction, and a test dataset (N=123,312

- 40.0%), used for its internal validation. To externally validate the HS-FI, we used data from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), an ongoing population-based study started in 2001. Persons living in a central area of Stockholm (Sweden) and older than 60 years old were asked to participate the study. In total, 3363 persons (73.3% response rate) underwent a comprehensive assessment using standard questionnaire administered by trained nurses, medical examinations, instrumental and blood tests to retrieve information about demographic, clinical and functional status. Data from National Registries were also linked to the study participants' records. An in-depth description of data collection protocols is available elsewhere. Physical frailty was evaluated according to the frailty phenotype proposed by Fried L. *et al.*, using a cut-off of at least 3 out of 5 frailty criteria (details on the construction of the frailty phenotype criteria in SNAC-K are available elsewhere). Grip strength was dichotomized using sex-adjusted cut-offs suggested by the EWGSOP2 guidelines on sarcopenia. Dementia diagnosis was based on DSM-IV criteria and details about the dementia diagnosis procedure employed in SNAC-K are available elsewhere. An informed consent was obtained from each participant, or from a proxy in case of cognitive impairment. The study was approved by the Regional Ethical Review Board in Stockholm. To select the deficits to be included in the HS-FI, we employed a *genetic algorithm (Zucchelli et al*. under peer-review). A *genetic algorithm* is an optimization algorithm employed to find near-optimal solutions in problems where is not computationally feasible to evaluate all possible combinations of elements (e.g. the deficits to include in a frailty index). An in-depth explanation of this methodology applied to frailty indices is available elsewhere. Shortly, the *genetic algorithm* starts by randomly creating a group of frailty indices and testing their ability to predict mortality in the train dataset. The frailty indices exhibiting a higher accuracy in mortality prediction are randomly combined and the newly generated frailty indices replace those with lower predictive power. A random deficit can be randomly included or removed ("mutation", in *genetic algorithm* methodology). All frailty indices are again tested for their predictive ability and, again, those with higher fitness are combined. Iteration by iteration, the predictive ability of the frailty indices created by combination increases. The algorithm stops when a certain number of iterations is run or when it fails to find a better frailty index (i.e. "termination criteria").
In this study, the number of frailty indices evaluated in each iteration was 1500. The ability in the prediction of mortality was calculated as the average c-statistic obtained in Cox regression models for mortality in the whole sample and in sex- (male and female), age- (younger and older than 71 – the median age), and geographic area (Northern, Central, and Southern Italy) subsamples. In every iteration, the 98% of previously created frailty indices was replaced by the ones obtained by combination. The probability of mutation in each iteration was 0.75% and the algorithm stopped when either 120 iterations were run, or it failed to find a better frailty index for four continuative iterations. To decrease the probability of overfitting, we slightly modified our previously published protocol. The *genetic algorithm* was run, from the random creation of frailty indices till one termination criterion was met, 50 times: each time, the train sample was based on different group of 10,000 randomly chosen participants among those included in the train dataset. To explore the "relative importance" of each deficit, we counted the number of times each deficit was included in the frailty index that exhibited the highest average c-

statistic in its iteration. We then built 100 frailty indices, sequentially adding deficits according to their relative importance: we started including only the two most selected deficits and we ended by including all 101 deficits. The frailty index exhibiting the highest average c-statistic for mortality prediction in the whole train dataset was chosen as the HS-FI. This latter was based on 26 final deficits. An individual score was therefore obtained by dividing the number of registered deficits by 26. These proportions were therefore categorized in tertiles, whose cut-offs were <4, 4-12, >12%.
Given the external validity obtained for HS-FI, the same cut-offs were adopted for SIDIAP.

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 [27], [28] 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	5.8
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)	Twice a year (January/July)
Outpatient Rx	Yes (largely incomplete for specialists)	Yes
Coding of drugs	ATC	ATC
Dosing regimen	Yes	Yes (incomplete)
Hospitalisations	Yes (incomplete)	Yes
Outpatient diagnoses	Yes	Yes
Coding of disease	ICD9CM	ICD-10CM

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

HSD –Longitudinal Patient Database, Italy

DKP-TRAM/vo3

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 [29]. The database contains clinical (diagnoses, patient referrals, hospital admissions, clinical investigations' results and date of death), life style records (BMI, smoking and alcohol use) along with 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 [30].
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 [31].
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. Representativeness of HSD has been previously demonstrated by compared distributions of patients' categories in age and sex with the National Institute of Statistics (https://www.healthsearch.it/). For these reasons, HSD has been used as data source in many studies and publications [32]–[36].
Approval for use of data was obtained from the Italian College of General Practitioners and Primary Care for the current study.

SIDIAP Database, Spain

General Practitioners 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 SIDIAP has been shown to be highly representative of the regional population, both in terms of socio-demographics as well as in terms of burden of long-term disease [37]. 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-10CM 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 [37].

Approval for the current study was obtained from both the SIDIAP Scientific and the IDIAPJGol (Institut d'Investigació en Atenció Primària Jordi Gol i Gurina) primary care research Ethics Committee.
A direct measure of frailty is not available in HSD and SIDIAP. Therefore, we have adopted the HS-FI which have been recently developed and validate using HSD. Although this is not yet published, the HS-FI has been externally validated (see above the paragraph on "Frailty") and was therefore applied to SIDIAP as well.
Italy and Spain are at this time the only 2 countries included in this study since they have a reliable database for clinical research able to track information about reimbursed and non-reimbursed medications. [38].

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, 2,763 and 7,945 patients have been prescribed with this medication in 2017 in HSD and SIDIAP, respectively. Thus, assuming an estimated yearly incidence rate of medication use of almost 0.2 and 1% in HSD and SIDIAP, respectively, these numbers of users would be large enough to assume a 0.01 precision with 95% Confidence Intervals (CI). Given that HSD currently includes almost 1 million patients and SIDIAP almost 7,6 million, 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, which is the proportion of users incurring in opioids discontinuation [14]. Such a prevalence would allow to estimate of HR=1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol). Still from preliminary evaluation, the number of DKP-TRAM users aged 75 years or older resulted in 705 and 949 for HSD and SIDIAP, respectively. These numbers would ensure stable estimates to test the presence of effect modifications due to age on the risk of AEs. Indeed, still assuming an occurrence of opioid-related AEs greater than 20% (likely higher among patients aged 75 or older), a minimum OR equal 1.2 with 80% power and 5% type I error when comparing DKT-TMD vs. tramadol (or tramadol-paracetamol) is estimable among this patients' category as well.

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. ICD9CM and ICD10CM) and their content comes from different data sources (e.g., general practitioners' records, and hospital discharge diagnoses).
To reunite differences across coding systems, all variables will be defined according to a multi-step and iterative process for the harmonization of event data.

9.6.1 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 and 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 January 1st, 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 direct 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 [39], [40].

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 investigated according to Kaplan-Meier methods (using both SIDIAP and HSD databases) in an attempt to clarify the burden of drug discontinuation, namely those DKP-TRAM users who will stop DKP-TRAM and/or switch to another therapy. Stopping will be defined as the occurrence of any AEs (see 9.3.2 SECONDARY OBJECTIVES: Outcome), end of registration of patient' data, death, whichever will come first. In the light of the GP's delay for AEs registration, the longest durations of follow-up (i.e. censoring criteria) will be varied from the 5th to the 15th, or the 30th day of follow-up.

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 (and as tramadol-paracetamol combinations). 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.

Risk of AEs

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 (or as tramadol-paracetamol combinations), 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 (including tramadol-paracetamol as well). To control for potential confounding, the following covariates (all measured prior or at the index date) will be included in the final model (see Table 1-2) considering both clinical and statistical associations with the exposure and the outcome as well as they will be considered risk factor for the outcome occurrence:

- Age
- Gender
- Comorbidity
- Concomitant drug use

We will estimate conditional logistic regression in case of nested case-control analysis, which will provide Odds Ratio (OR) and related 95% CI. 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.

To account for the presence of different treatment courses during follow-up, we will categorise the exposure into two mutually exclusive subgroups according to the recency of use. Namely, patients exposed to DKP-TRAM, or to the compared medications, in the month preceding and/or on the index date will be the current users. Those being excluded from this category will be the recent users. By doing so, the exposure categories will be modelled according to a time-dependent fashion. In addition, we will identify “new” current users (i.e. those who will not exposed to treatment in the recent time-window but in the current time-window only) and “old” current users (i.e. those who will be exposed to treatment in the current and recent time-window).

Operationally, we will therefore identify the cumulated dosages or duration of tramadol (in days) being registered by the current users. We will categorise the durations in terciles as it will be registered in the controls as the reference of general population. This

approach will allow us to compare the cumulative dosage and duration categories among DKP-TRAM users versus those cumulated by tramadol (or tramadol-paracetamol combination) users.

9.7.3 SECONDARY ANALYSES

The prescription of DKP-TRAM is likely influenced by previous prescription of tramadol (or tramadol-paracetamol combination), especially in terms of AEs already experienced by patients. Indeed, we will exclude previous use of tramadol preceding the first prescription date in the study period to minimize the selection bias. However, the knowledge of how GPs select patients to use DKP-TRAM and how this behaviour acts on the risk of AEs might be informative. The nested case-control analysis will provide this information by comparing current users of DKP-TRAM, tramadol or tramadol-paracetamol vs. recent users (i.e. those exposed to one of the medications excluding the current time-window). In addition, given that older patients are more prone to incur in such AEs [1], 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 re-run the primary model by limiting AEs to those specifically recorded by GPs in section of drug intolerance (only for HSD). Then, we will re-run the primary model by imputing missing data for smoking and BMI according to multiple imputation methods [41]. 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 [42]. Finally, the primary model will be rerun by recoding the exposure into three categories: DKP-TRAM, tramadol and tramadol-paracetamol combination.

9.8. QUALITY CONTROL

The study will be conducted according to the guidelines for Good Pharmaco-epidemiology Practice (GPP) [43].

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, 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. Finally, we included only two European data sources and the results may suffer from limitations that they will not be fully representative.

10. RESULTS

This is the final study report concerning the results on DKP-TRAM utilization and the comparative safety study using HSD and SIDIAP.

10.1. PRIMARY OBJECTIVES

10.1.1 INCIDENCE RATE OF DKP-TRAM USE

Crude population-based IRs of DKP-TRAM use in HSD, in 2017 and 2018 are reported in **Table 5.1** and **Table 5.2**, respectively.
Of 1,047,701 patients (mean age (years): 52.60, SD: 19; 52.10% females) being registered in HSD in 2017, 2,941 were newly prescribed with DKP-TRAM, with an IR equal to 2.81‰ (95% CI: 2.71 – 2.91). The standardized IR (by age and sex) was equal to 2.73‰. Overall, the crude IR of DKP-TRAM use increased with age, and IR peaked (5.46‰ (95% CI: 5.03 – 5.92)) for patients aged 75-84 years. The crude IR was higher in females than males with estimates of 3.49‰ (95 CI: (3.34 - 3.65) vs. 2.06‰ (95% CI: 1.93 – 2.19). Such a difference decreases for age-standardized estimates (females: 3.42‰ vs. males: 2.00‰).
Of 1,011,537 patients (mean age (years): 52.80, SD: 19; 52.80% females) being registered in HSD in 2018, 3,485 were newly prescribed with DKP-TRAM, with an IR equal to 3.44‰ (95% CI: 3.33 - 3.56). The standardized IR (by age and sex) was equal to 3.36‰. Overall, the crude IR of DKP-TRAM increased with age, and IR peaked (IR 5.76‰ (95% CI 5.30 – 6.24)) for patients aged 75-84 years. The crude IR was higher in females than males with estimates of 4.11‰ (95% CI: 3.93 – 4.28) and 2.73‰ (95% CI: 2.59 – 2.88). As in 2017, such a difference further decreases for age-standardized estimates (females: 4.03‰ vs. males: 2.66‰).
The results on IR (with 95% CIs) of DKP-TRAM use calculated using person-years over the two years under study are shown in **Table 6a.** Among 1,984,297.8 person-years being accumulated during follow-up, the IR of DKP-TRAM use was 2.89/1,000 person-years in 2017. Females showed higher IR (3.61/1,000 person-years) than males (2.11/1,000 person-years). IR of DKP-TRAM use increased with age, with the highest value (IR 5.70/1,000 person-years) for those aged from 75 to 84 years.

In 2018, the overall IR of DKP-TRAM use increased, and it was 3.54/1,000 person-years. As in 2018, female patients reported higher IR of DKP-TRAM when compared with males (females: 4.21/1,000 person-years vs. males: 2.81/1,000 person-years). Still, the IR of DKP-TRAM use increased with age, with the highest IR for those aged 75-84 years (IR 5.86/1,000 person-years).

Crude population-based IRs of DKP-TRAM prescription in SIDIAP in 2017 and 2018 are reported in **Table 5.3** and **Table 5.4**, respectively.
A total of 4,731,692 patients were registered in the SIDIAP database in 2017. Of these, 11,390 received a new prescription of DKP-TRAM (mean age (years): 53.6, SD:16; 59.7% female). The overall IR of the new prescriptions of DKP-TRAM in this year was 2.41‰ (95%CI: 2.36-2.45). This IR increased with age, reaching a maximum of 3.39‰ (95%CI: 3.23-3.55) for those patients aged 65 to 74 years old. The analysis of the IR per sex showed several differences; first, females had an overall higher IR of DKP-TRAM prescription compared to males (1.98‰ vs 2.81‰ in males and females, respectively). This difference in the IR between males and females was more pronounced at the age of 65 to 74 years old, where the IR in women nearly doubled the one found in men (IR of 4.34‰ vs. 2.29‰ in women and men, respectively). Second, the highest IR in males and females peaked at different age bands, 65-74 for females and 55-64 for males.
A total of 4,720,302 patients were registered in the SIDIAP database in 2018. Of these, 8,522 received a new prescription of DKP-TRAM (mean age (years): 51.3, SD:15; 56.8% females). The overall IR of the new prescriptions of DKP-TRAM was 1.80‰ (95% CI: 1.76-1.84). This IR increased with age, reaching a maximum of 2.36‰ (95% CI: 2.26-2.46) between the ages of 45 to 54 years old. When analysing the IR per sex, females had an overall higher IR of newly prescribed DKP-TRAM compared to male (2.01‰ vs. 1.59‰). The analysis per age revealed that the IR of DKP-TRAM peaked at a lower age band in females than in males (2.75‰ between the age of 45- and 54-years old vs. 2.06‰ between the age of 55 and 64 years old, respectively).
The two-year IR (per 1,000 persons-year) of newly prescribed DKP-TRAM are reported in **Table 6b**. An overall of 9,115,214 person-years were accumulated during follow-up. The IR (95%CI) of new prescriptions of DKP-TRAM was higher in 2017 compared to the 2018 (2.45‰ (2.40-2.49) vs. 1.91‰ (1.87-1.95)). Regarding the IR per sex, in both years females reported higher IR of DKP-TRAM prescription compared to males (2.86‰ vs. 2.02‰ in 2017 and 2.12 vs. 1.69 in 2018). When analysing the IR per age bands, there is a trend towards prescribing DKP-TRAM at younger ages in 2018 compared to 2017 (highest IR in 2017 was for patients aged 65 to 74 years old whereas the highest IR in 2018 was for patients aged 45 to 54 years old).

Crude Incidence Rate of DKP-TRAM use and related patients' features

The crude IR of DKP-TRAM (with 95% CIs) use during study period (2017-2018) according to demographics and baseline life style factors, comorbidities and prior and/or concurrent medications in HSD are presented in **Table 7a**.

Females showed higher IR of DKP-TRAM use (3.93‰ (95% CI: 3.81 - 4.05) than males (2.47‰ (95% CI: 2.37 - 2.57)). Considering age categories, IR increased with age, and the highest rate was found for those aged from 75 to 84 years (5.94‰ (95% CI: 5.61 - 6.29)). Past smokers showed the highest IR of DKP-TRAM use (4.49‰ (95% CI: 4.22 - 4.78)), followed by non-smokers (3.96‰ (95% CI: 3.81 - 4.11)) and current smokers (3.67‰ (95% CI: 3.45 – 3.89)). The IR of DKP-TRAM use was 7.54‰ (95% CI: 6.98 – 8.15) and 4.66‰ (95% CI: 4.13 – 5.27), among obese patients and alcohol abusers, respectively. For what concerns comorbidities, IRs of DKP-TRAM use in patients affected by hepatic impairment was 4.05‰ (95% CI: 3.83 - 4.29). In specific, among those with mild to moderate or severe hepatic dysfunction (Child-Pugh classification), IR was 5.33‰ (95% CI: 4.55 - 6.25) and 4.56‰ (95% CI: 2.84 – 7.34), respectively. No incident user of DKP-TRAM with severe hepatic impairment was found in the database. The IR of DKP-TRAM use in patients with kidney disease was 5.07‰ (95% CI: 4.77 - 5.38). For what concerns the renal function, IR of DKP-TRAM use was 6.14‰ (95% CI: 5.52 – 6.83), 4.93‰ (95% CI: 4.57 - 5.31), 3.64‰ (95% CI: 2.63 – 5.05) and 2.81‰ (95% CI: 1.80 - 4.41) in patients with mild, moderate, severe and kidney failure, respectively. Regarding the other comorbidities, the highest IRs of DKP-TRAM use were found in patients being diagnosed with dyspepsia (5.14‰ (95% CI: 4.82 - 5.48)), dementia (4.93‰ (95% CI: 4.46 – 5.46)) and mental disorders (4.86‰ (95% CI: 4.65 - 5.08)). For the other conditions, the IRs was still higher than 2.5‰.
For what concerns the prior and/or concurrent medications being registered at baseline, the highest IRs of DKP-TRAM use were found in patients prescribed with tramadol (21.72‰ (95% CI: 19.71 - 23.94)), followed by other opioids (15.95‰ (95% CI: 15.20 - 16.73)), erythromycin (10.74‰ (95% CI: 3.46 - 33.31)) and NSAIDs (9.42‰ (95% CI: 9.12 – 9.72)). For the other prior and/or concurrent medications, the IRs of DKP-TRAM use resulted around or higher than 4.8‰, except for cimetidine, ondansetron and ketoconazole for which there was no prescription.

The crude IR of DKP-TRAM (with 95% CIs) prescription during study period (2017-2018) according to demographics and baseline life style factors, comorbidities and prior and/or concurrent medications in SIDIAP are presented in **Table 7b.**
During the study period a total of 19,912 subjects received a new prescription of DKP-tramadol. A decrease in the IR of DKP-TRAM is seen from 2017 to 2018 (IR of 2.41‰ vs. 1.81‰, respectively). When analysing by sex, females had higher incidence rates of DKP-TRAM prescription than males (4.81‰, 95%CI (4.73-4.90) vs. 3.57‰ (95% CI (3.50-3.65), respectively). The IR of DKP-TRAM prescription increased with age and reached its maximum in subjects aged between 55-64 years old (5.65‰, 95% CI (5.47-5.83)). The characterization of the patient initiating DKP-TRAM showed that they were frequently diagnosed with obesity (7.03‰, 95%CI: 6.85-7.22) and had a history of tobacco use (5.16‰, 95%CI: f 4.99-5.33). Other frequent comorbidities included a depression diagnosis (8.22‰, 95%CI: 7.95-8.5) followed by those with dyspepsia (7.41‰, 95%CI: 7.08-7.75), mental disorders (6.81‰, 95%CI: 6.64-6.68) and asthma/COPD (6.07‰, 95%CI: 5.87-6.27). The IR of the rest of comorbidities ranged from 3.09‰ (95% CI: 2.78-3.42) for dementia to 4.92 ‰ (95% CI: 4.3-5.6) for epilepsy. Regarding the patients with hepatic or a kidney impairment, the IR of DKP-TRAM prescription was highest among

those with a chronic hepatic impairment (6.67‰, 95% CI: 4.75-9.12) and among those with a severe renal function (5.89‰, 95% CI: 1.22-17.22, respectively), however, the latter only included 3 patients in this category.
For what concerns prior and or concurrent medications registered at baseline, most of the patients with a new prescription f DKP-TRAM were also prescribed tramadol (IR of 13.72‰ (95%CI: 12.71-14-78), followed by other opioids (12.44‰ (95%CI: 7.89-18.66)) and carbamazepine (12.44‰ (95%CI: 7.89-18.66). No prescription of ketoconazole nor MAO-inhibitors were found in this database. The IR of the other medications ranged from 3.23‰ (95%CI: 2.95-3.54) for NSAIDs to 7.50‰ (95%CI: 6.89-8.16) for antidepressants and antipsychotics.

Table 5.1. Incidence Rate of DKP-TRAM use in HSD broken down by gender and age (2017).

2017	Male			Female			Total		
	N	IR (‰)	95% CI	N	IR (‰)	95% CI	N	IR (‰)	95% CI
Age									
18-24	17	0.43	(0.25 - 0.69)	18	0.49	(0.29 - 0.78)	35	0.46	(0.32 - 0.64)
25-34	47	0.69	(0.51 - 0.91)	60	0.89	(0.68 - 1.14)	107	0.79	(0.64 - 0.95)
35-44	117	1.42	(1.18 - 1.70)	156	1.84	(1.57 - 2.16)	273	1.64	(1.49 – 1.84)
45-54	189	1.95	(1.68 - 2.25)	325	3.19	(2.85 - 3.56)	514	2.58	(2.37 - 2.82)
55-64	203	2.45	(2.12 - 2.81)	386	4.42	(3.99 - 4.89)	589	3.46	(3.19 - 3.75)
65-74	229	3.36	(2.94 - 3.83)	432	5.86	(5.33 - 6.44)	661	4.66	(4.32 - 5.03)
75-84	187	4.07	(3.51 - 4.70)	391	6.53	(5.90 – 7.20)	578	5.46	(5.03 - 5.92)
≥85	43	2.47	(1.78. - 3.32)	141	4.02	(3.39 - 4.74)	184	3.51	(3.02 - 4.05)
Total	***1,032***	***2.06***	***(1.93 - 2.19)***	***1,909***	***3.49***	***(3.34 - 3.65)***	***2,941***	***2.81***	***(2.71 - 2.91)***
STD		***2.00§***			***3.42§***			***2.73****	

§ standardized (direct method) by age; *standardized (direct method) by age and sex

Table 5.2. Incidence Rate of DKP-TRAM use in HSD broken down by gender and age (2018).

2018	Male			Female			Total		
	N	IR (‰)	95% CI	N	IR (‰)	95% CI	N	IR (‰)	95% CI
Age									
18-24	21	0.56	(0.35 - 0.86)	16	0.47	(0.27 - 0.77)	37	0.52	(0.37 - 0.72)
25-34	58	0.87	(0.66 - 1.13)	75	1.16	(0.91 - 1.45)	133	1.01	(0.85 - 1.20)
35-44	160	2.06	(1.76 - 2.41)	180	2.27	(1.95 - 2.63)	340	2.17	(1.94 - 2.41)
45-54	280	2.98	(2.64 - 3.35)	410	4.18	(3.79 - 4.61)	690	3.60	(3.33 - 3.87)
55-64	266	3.21	(2.84 - 3.62)	440	5.09	(4.63 - 5.59)	706	4.17	(3.87 - 4.49)
65-74	274	4.07	(3.60- 4.58)	510	7.14	(6.53 - 7.78)	784	5.65	(5.26 - 6.06)
75-84	202	4.52	(3.92 - 5.19)	385	6.72	(6.07 - 7.42)	587	5.76	(5.30 - 6.24)
≥85	70	4.11	(3.21 - 5.19)	138	4.09	(3.43 - 4.83)	208	4.09	(3.56 - 4.69)
Total	***1,331***	***2.73***	***(2.59 - 2.88)***	***2,154***	***4.11***	***(3.93 - 4.28)***	***3,485***	***3.44***	***(3.33 – 3.56)***

STD	***2.66§***	***4.03§***	***3.36****

§ standardized (direct method) by age; *standardized (direct method) by age and sex

Table 5.3. Incidence Rate of DKP-TRAM use in SIDIAP broken down by gender and age (2017).

2017	**Male**			**Female**			**Total**		
	N	**IR (‰)**	**95% CI**	**N**	**IR (‰)**	**95% CI**	**N**	**IR (‰)**	**95% CI**
Age									
18-24	124	0.63	(0.52 - 0.75)	179	0.95	(0.82 - 1.10)	303	0.79	(0.70 - 0.88)
25-34	485	1.38	(1.26 - 1.51)	521	1.48	(1.35 - 1.61)	1,006	1.43	(1.34 - 1.52)
35-44	1,064	2.02	(1.90 - 2.15)	1,153	2.36	(2.22 - 2.50)	2,217	2.18	(2.09 - 2.28)
45-54	1,083	2.41	(2.27 - 2.56)	1,506	3.51	(3.34 - 3.69)	2,589	2.95	(2.84 - 3.06)
55-64	891	2.70	(2.52 - 2.88)	1,354	3.89	(3.68 - 4.10)	2,245	3.31	(3.17 - 3.45)
65-74	570	2.29	(2.11 - 2.49)	1,239	4.34	(4.10 - 4.59)	1,,809	3.39	(3.23 - 3.55)
75-84	306	2.20	(1.80 - 2.26)	692	3.35	(3.11 - 3.61)	998	2.79	(2.62 - 2.97)
≥85	63	1.07	(0.82 - 1.37)	160	1.32	(1.12 - 1.54)	223	1.24	(1.08 - 1.41)
Total	***4,586***	***1.98***	***(1.93 - 2.04)***	***6,804***	***2.81***	***(2.74 - 2.88)***	***11,390***	***2.41***	***(2.36 - 2.45)***
STD		***1.99§***			***2.84§***			***2.43****	

§ standardized (direct method) by age; *standardized (direct method) by age and sex

Table 5.4. Incidence Rate of DKP-TRAM use in SIDIAP broken down by gender and age (2018).

2018	Male			Female			Total		
	N	IR (‰)	95% CI	N	IR (‰)	95% CI	N	IR (‰)	95% CI
Age									
18-24	136	0.69	(0.58 - 0.82)	164	0.87	(0.75 - 1.02)	300	0.78	(0.69 - 0.87)
25-34	427	1.22	(1.11 - 1.34)	469	1.33	(1.21 - 1.46)	896	1.28	(1.19 - 1.36)
35-44	881	1.68	(1.57 - 1.79)	945	1.94	(1.82 - 2.06)	1,826	1.80	(1.72 - 1.89)
45-54	891	1.99	(1.86 - 2.12)	1,176	2.75	(2.60 - 2.91)	2,067	2.36	(2.26 - 2.46)
55-64	679	2.06	(1.91 - 2.22)	907	2.61	(2.45 - 2.79)	1,586	2.35	(2.23 - 2.46)
65-74	451	1.82	(1.65 - 1.99)	753	2.65	(2.47 - 2.85)	1,204	2.26	(2.14 - 2.39)
75-84	188	1.25	(1.07 - 1.44)	356	1.73	(1.56 - 1.92)	544	1.53	(1.40 - 1.66)
≥85	24	0.41	(0.26 - 0.61)	75	0.62	(0.49 - 0.77)	99	0.55	(0.45 - 0.67)
Total	***3,677***	***1.59***	***(1.54 - 1.65)***	***4,845***	***2.01***	***(1.95 - 2.06)***	***8,522***	***1.80***	***(1.76 - 1.84)***
STD		***1.60§***			***2.03§***			***1.82****	

§ standardized (direct method) by age; *standardized (direct method) by age and sex

Table 6a. Incidence Rate (person-years) of DKP-TRAM use in HSD broken down by age and gender over the two years under study.

	2017			2018		
	N	**IR***	**95% CI**	**N**	**IR***	**95% CI**
Age						
18-24	35	0.47	(0.33 - 0.65)	37	0.53	(0.38 - 0.73)
25-34	107	0.81	(0.67 - 0.97)	133	1.04	(0.88 - 1.23)
35-44	273	1.68	(1.50 - 1.90)	340	2.24	(2.01 - 2.49)
45-54	514	2.65	(2.431 - 2.89)	690	3.70	(3.44 - 3.99)
55-64	589	3.54	(3.27 - 3.84)	706	4.29	(3.99 - 4.62)
65-74	661	4.79	(4.44 - 5.17)	784	5.76	(5.37 - 6.18)
75-84	578	5.70	(5.25 - 6.19)	587	5.86	(5.40 - 6.35)
≥85	184	3.86	(3.34 - 4.47)	208	4.28	(3.74 - 4.90)
Gender						
Male	1,032	2.11	(1.99 - 2.25)	1,331	2.81	(2.66 - 2.96)
Female	1,909	3.61	(3.45 - 3.77)	2,154	4.21	(4.04 – 4.39)
Total	***2,941***	***2.89***	***(2.79 - 3.00)***	***3,485***	***3.54***	***(3.42 - 3.65)***

* 1000 person-years

Table 6b. Incidence Rate (person-years) of DKP-TRAM use in SIDIAP broken down by age and gender over the two years under study.

	2017			2018		
	N	**IR***	**95% CI**	**N**	**IR***	**95% CI**
Age						
18-24	303	0.80	(0.71 - 0.89)	300	0.81	(0.72 - 0.91)
25-34	1,006	1.45	(1.36 - 1.54)	896	1.35	(1.26 - 1.44)
35-44	2,217	2.21	(2.12 - 2.31)	1,826	1.89	(1.80 - 1.97)
45-54	2,589	2.98	(2.87 - 3.10)	2,067	2.44	(2.34 - 2.55)
55-64	2,245	3.35	(3.21 - 3.49)	1,586	2.43	(2.31 - 2.55)
65-74	1,809	3.44	(3.28 - 3.60)	1,204	2.37	(2.23 - 2.50)
75-84	998	2.87	(2.70 - 3.06)	544	1.69	(1.55 - 1.84)
≥85	223	1.35	(1.18 - 1.54)	99	0.78	(0.63 - 0.95)
Gender						
Female	6,804	2.86	(2.79 - 2.93)	4,845	2.12	(2.06 - 2.18)
Male	4,586	2.02	(1.96 - 2.08)	3,677	1.69	(1.64 - 1.75)
Total	***11,390***	***2.45***	***(2.40 - 2.49)***	***8,522***	***1.91***	***(1.87 - 1.95)***

* 1000 person-years

Table 7a. Incidence Rate of DKP-TRAM use in HSD broken down by demographics, life-style factors, comorbidities and prior and/or concurrent medications in the overall study period.

	N	IR (‰)	95% CI
Total (2017-2018)	6403	3.23	(3.15 - 3.31)
Year			
2017	2941	1.48	(1.43 - 1.54)
2018	3462	1.74	(1.69 - 1.80)
Gender			
Male	2349	2.47	(2.37 - 2.57)
Female	4054	3.93	(3.81 - 4.05)
Age			
18-24	80	0.54	(0.43 - 0.67)
25-34	249	0.96	(0.85 - 1.08)
35-44	639	2.02	(1.87 - 2.19)
45-54	1216	3.21	(3.03 - 3.39)
55-64	1285	3.95	(3.74 - 4.17)
65-74	1425	5.28	(5.01 - 5.56)
75-84	1169	5.94	(5.61 - 6.29)
>=85	340	3.82	(3.44 - 4.25)
Smoking status			
Current smokers	1068	3.67	(3.45 - 3.89)
Non-smokers	2,710	3.96	(3.81 - 4.11)
Past smokers	987	4.49	(4.22 - 4.78)
Missing	*1638*	*2.08*	*(1.98 - 2.18)*
Obesity	643	7.54	(6.98 - 8.15)
Alcohol abuse	257	4.66	(4.13 - 5.27)
Drug abuse	17	2.64	(1.64 - 4.25)
Comorbidities			
Hepatic impairment	1165	4.05	(3.83 - 4.29)
Hepatic impairment (codified with Child-Pugh classification)			
Mild	153	5.33	(4.55 - 6.25)
Moderate	17	4.56	(2.84 - 7.34)
Severe	0	0	-
Missing	*995*	*3.90*	*(3.67 - 4.15)*
Kidney disease	1091	5.07	(4.77 - 5.38)
Renal function (GFR (ml/min/1.73 m^2))*			
Mild	335	6.14	(5.52 - 6.83)
Moderate	679	4.93	(4.57 - 5.31)
Severe	36	3.64	(2.63 - 5.05)
Kidney failure	19	2.81	(1.80 - 4.41)
Missing	*22*	*3.47*	*(2.28 - 5.27)*
Depression	624	4.99	(4.61 - 5.40)
COPD/asthma	1811	4.35	(4.16 - 4.56)
Epilepsy	49	2.51	(1.89 - 3.32)

Dyspepsia	928	5.14	(4.82 - 5.48)
Mental disorders	1937	4.86	(4.65 - 5.08)
Hallucinations	6	4.27	(1.92 - 9.50)
Dementia	378	4.93	(4.46 - 5.46)
Cognitive impairment after trauma	0	0	-
Cerebro-cardiovascular disease	552	4.22	(3.88 - 4.58)
Gastrointestinal haemorrhages	237	4.24	(3.73 - 4.81)
Prior and/or concurrent medications			
Tramadol	407	21.72	(19.71 - 23.94)
Other opioids	1677	15.95	(15.20 - 16.73)
NSAIDs	3762	9.42	(9.12 - 9.72)
Anticoagulants or anti-platelet, anti-aggregation drugs	1839	5.76	(5.50 - 6.03)
Carbamazepine	44	7.29	(5.42 - 9.79)
Cimetidine	0	0	-
Antidepressants	1047	6.78	(6.38 - 7.20)
MAO-Inhibitors	19	4.77	(3.04 - 7.48)
Antipsychotics	346	5.57	(5.01 - 6.19)
Anxiolytics	918	7.61	(7.13 - 8.12)
Ondansetron	0	0	-
Ketoconazole	0	0	-
Erythromycin	3	10.74	(3.46 - 33.31)

*among patients with kidney impairments

Table 7b. Incidence Rate of DKP-TRAM use in SIDIAP broken down by demographics, life-style factors, comorbidities and prior and/or concurrent medications in the overall study period.

	N	IR (‰)	95% CI
Total (2017-2018)	19,912	4.21	(4.15 - 4.27)
Year			
2017	11,390	2.41	(2.36 - 2.45)
2018	8,522	1.81	(1.77 - 1.84)
Gender			
Female	11,649	4.81	(4.73 - 4.90)
Male	8,263	3.57	(3.50 - 3.65)
Age			
18-24	603	1.57	(1.44 - 1.70)
25-34	1,902	2.70	(2.58 - 2.83)
35-44	4,043	3.98	(3.86 - 4.11)
45-54	4,656	5.30	(5.15 - 5.46)
55-64	3,831	5.65	(5.47 - 5.83)
65-74	3,013	5.64	(5.44 - 5.84)
75-84	1,542	4.31	(4.10 - 4.53)
>=85	322	1.79	(1.60 - 1.99)

Smoking status			
Current smokers	3,403	5.09	(4.92 - 5.26)
Non-smokers	7,316	4.23	(4.13 - 4.32)
Past smokers	3,582	5.16	(4.99 - 5.33)
Missing	5,611	3.43	(3.34 - 3.52)
Obesity			
Obese	5,658	7.03	(6.85 - 7.22)
Non obese	10,852	4.31	(4.23 - 4.39)
Missing	3,402	2.41	(2.33 - 2.49)
Alcohol abuse	783	5.88	(5.47 - 6.3)
Drug abuse	399	6.55	(5.92 - 7.23)
Comorbidities			
Hepatic impairment Classification			
Hepatic impairment (overall)	122	4.88	(4.05 - 5.82)
Chronic	39	6.67	(4.75 - 9.12)
Cirrhosis	51	4.78	(3.56 - 6.28)
Kidney disease	1,194	4.35	(4.11 - 4.61)
Renal function (GFR (ml/min/1.73 m^2)*			
Mild	321	4.31	(3.85 - 4.8)
Moderate	38	4.05	(2.86 - 5.56)
Severe	3	5.89	(1.22 - 17.22)
Kidney failure	0	0.00	-
Missing	832	4.38	(4.09 - 4.69)
Depression	3,408	8.22	(7.95 - 8.50)
COPD/asthma	3,608	6.07	(5.87 - 6.27)
Epilepsy	228	4.92	(4.30 - 5.60)
Dyspepsia	1,877	7.41	(7.08 - 7.75)
Mental disorders	6,178	6.81	(6.64 - 6.98)
Hallucinations	10	3.63	(1.74 - 6.67)
Dementia	361	3.09	(2.78 - 3.42)
Cognitive impairment after trauma	0	0	-
Cerebral-cardiovascular disease	744	3.64	(3.38 - 3.91)
Gastrointestinal haemorrhages	219	5.69	(4.96 - 6.49)
Prior and/or concurrent medications			
Tramadol	699	13.72	(12.72 - 14.78)
Other opioids	23	12.44	(7.89 - 18.66)
NSAIDs	473	3.23	(2.95 - 3.54)
Anticoagulants or anti-platelet, anti-aggregation drugs	632	6.72	(6.20 - 7.26)
Carbamazepine	23	12.44	(7.89 - 18.66)
Cimetidine	0	0	-
Antidepressants	547	7.50	(6.89 - 8.16)
MAO-Inhibitors	0	0	-
Antipsychotics	547	7.50	(6.89 - 8.16)
Anxiolytics	873	6.53	(6.11 - 6.98)
Ondansetron	19	4.08	(2.46 - 6.37)
Ketoconazole	0	0	-
Erythromycin	24	5.32	(3.41 - 7.91)

*among patients with kidney impairments

The prevalence rate of the first prescription of DKP-TRAM per prescriber type was assessed in SIDIAP only, and reported in **Table 7c**. Out of the information available, we found that most of the prescriptions were issued by the GP and by the dentist. However, information regarding the prescriber was missing in over 54% of the prescription.

Table 7c. Prevalence of the first prescription of DKP-TRAM according to prescriber type.

Prescriber type	N	%
GP	8,082	40.59
Dentistry	867	4.35
Paediatrics	22	0.11
Gynaecology	1	0.01
Missing	10,940	54.94

10.1.2 INDICATIONS FOR PRESCRIPTIONS OF DKP-TRAM

The indications of DKP-TRAM being prescribed during the overall study period in the HSD database (2017-2018) are shown in **Table 8a.** The most common indication for DKP-TRAM use was low back pain counting for 32.6% among the overall prescriptions. It was followed by osteoarticular pain (17.8%), osteoarthritis (8.9%), peripheral enthesopathies (8.0%), post traumatic pain (7.1%) and neck pain (6.4%). The proportions of the remaining indications were lower than 6%.

Table 8a. Distribution of Indications for which DKP-TRAM is prescribed in HSD in the overall study period (2017-2018).

Classification	N	%
Low back pain	2,035	32.59
Osteoarticular pain	1,113	17.82
Osteoarthritis	555	8.89
Peripheral enthesopathies	498	7.98
Post traumatic pain	442	7.08
Neck pain	399	6.39
Other	370	5.93
Visceral pain	166	2.66
Headache	144	2.31
Cancer	110	1.76
Peripheral neuropathy	98	1.57
Diseases of oral cavity, salivary glands and jaws	60	0.96
Postherpetic neuralgia	59	0.94
Fibromyalgia	49	0.78
Diseases of the circulatory system	38	0.61
Rheumatoid arthritis	33	0.53

Diseases of the skin and subcutaneous tissue	27	0.43
Acute Respiratory Infection	24	0.38
Trigeminal neuralgia	17	0.27
Connective tissue disease	7	0.11

The indications of DKT-TRAM during the whole study period in SIDIAP are shown in **Table 8b**. All the indications identified within 7 days of the DKP-TRAM prescription were grouped in the 23 categories shown in the table. Overall, the most frequent indication of DKP-TRAM was for musculoskeletal disorders (56.33%), namely low back pain (22.6%), peripheral enthesopathies (15.50%) and osteoarticular pain (11.62%). Other diagnoses involving urologic or dental problems were also frequent indications linked to the prescription of DKP-TRAM (7.09% and 4.65% respectively). The proportion of the rest of the indications was lower than 4%.

Table 8b. Distribution of Indications for which DKP-TRAM is prescribed in SIDIAP in the overall study period (2017-2018).

Classification	N	%
Low back pain	1,789	22.60
Peripheral enthesopathies	1,227	15.50
Osteoarticular pain	920	11.62
Post traumatic pain	703	8.88
Other-urologic problem	561	7.09
Other	514	6.49
Other-dental problem	368	4.65
Neck pain	354	4.47
Visceral pain	265	3.35
Diseases of the skin and subcutaneous tissue	223	2.82
Acute respiratory infection	192	2.43
Osteoarthritis	169	2.14
Headache	145	1.83
Diseases of oral cavity, salivary glands and jaws	111	1.40
Postherpetic neuralgia	99	1.25
Diseases of the circulatory system	91	1.15
Cancer	52	0.66
Connective tissue disease	48	0.61
Peripheral neuropathy	32	0.40
Fibromyalgia	21	0.27
Trigeminal neuralgia	20	0.25
Postherpetic pain	7	0.09
Rheumatoid arthritis	4	0.05

10.1.3 DOSAGE AND DURATION OF TREATMENT WITH DKP-TRAM

Dosage of DKP-TRAM

The daily dosages in HSD, reported as PDDs and DDDs (being calculated as the average dosage among those indicated by the SmPC: 2 pills daily) of DKP-TRAM being prescribed overall study period are shown in **Table 8.1** and **Table 8.2.** Almost every patient was treated with PDD lower than the maximum daily dose (225 mg (tramadol)/75 mg (dexketoprofen)) being indicated for adults in the SmPC. The results were consistent at 3, 6 and 12 months of follow-up. Around 2,6% of patients reported a dosage of DKP-TRAM equal to 225 mg/75 mg for each time-point of follow-up. Only one patient was associated with a PDD higher than 225 mg/75 mg of DKP-TRAM (0.02%). When the standard DDDs was used, all patients prescribed with DKP-TRAM reported a dosage lower than 225 mg/75 mg.
The results of the PDD and DDD in SIDIAP are reported in **Table 8.3** and **Table 8.4**. Most of the patients were prescribed DKP-TRAM at a dose lower than 225/75mg of DKP-TRAM during the whole follow up (64.2, 64.7 and 65.0% at 3, 6 and 12 months respectively) while approximately one third of the patients had a daily dose prescription of 225/75mg of DKP-TRAM with similar results during the whole follow-up.
When the standard DDD was used (namely, the dose reported in the SmPC) almost all of the patients (99.1% at 3 and 6 months and 99.0% at 12 months) were prescribed a dose lower than 225/75 mg of DKP-TRAM

Duration of treatments with DKP-TRAM

The duration of treatments of DKP-TRAM in both HSD and SIDIAP during the study period was based on both PDD and DDD (see previous paragraph for the calculation). The results are reported in **Table 9.1** and **Table 9.2** for HSD and in **Table 9.3** and **Table 9.4** for SIDIAP.
In HSD, according to PDD, around 2% of DKP-TRAM users during the study period reported a total duration of treatments lower than 10 days at 3, 6 or 12 months of follow-up. Such a proportion went down from 2.3% to 2.1% at 12 months. Most of the patients reported a total duration of DKP-TRAM treatment equal to 10 days. Namely, 72.1% at 3 months, followed by 70.1% and 68.8% at 6 and 12 months, respectively. Finally, 25.7% of patients reported a total duration of treatment of DKP-TRAM higher than 10 days at 3 months. The proportion of these patients increased during follow-up, ranging from 27.7% at 6 months to 29.1% at 12 months.
According to DDD, there was no patients with duration of DKP-TRAM treatment lower than 10 days. More than 80% of patients reported a cumulative duration of treatment of DKP-TRAM equal to 10 days, decreasing from 84.7% at 3 months to 80.6% at 12 months. Considering the proportion of patients with cumulative duration of DKP-TRAM treatment higher than 10 days, 15.3% of patients reported a cumulative duration of treatment higher than 10 days up to 3 months. Furthermore, these proportions increased during follow-up, ranging from 17.7% at 6 months to 19.4% at 12 months.

Using HSD, we were unable to identify patients with duration of DKP-TRAM use lower than 5 days.

In SIDIAP, the median cumulative duration with DKP-TRAM was 11 days. According to the PDD, almost half of the patients (49.9%, 49.7% and 49.5% at 3,6 and 12 months) had a cumulative treatment duration with DKP-TRAM of less than 11 days and 35.6%, 36.0% and 36.2% at 3, 6 and 12 months had a prescription that lasted more than 11 days. Approximately 14% of the patients reported an exact cumulative duration of 11 days in the whole follow-up. Around 8% of patients resulted exposed to DKP-TRAM for less than 5 days during 3, 6 and 12 months of follow-up.
According to DDD, the proportion of patients with a cumulative treatment duration under 11 days increased (50.6%, 50.4 % and 50.2% at 3, 6 and 12 months) as well as those with a cumulative treatment durations over 11 days (38.6%, 38.9% and 39.1% at 3, 6 and 12 months).

The distribution of DKP-TRAM users according to the number of 5-day courses of DKP-TRAM treatment (calculated through the PDD) during the overall study period are presented in **Table 10a** for HSD and in **Table 10b** for SIDIAP.
In HSD, namely, more than 71% of patients reported less than 4 courses of DKP-TRAM treatments up to 1 year: 75.0%, 73.0% and 71.7% at 3, 6 and 12 months, respectively. 18.7% of patients prescribed with DKP-TRAM reported 4-5 course treatment at 3 months, while 19.5% and 19.8% were treated with 4-5 courses of DKP-TRAM at 6 and 12 months, respectively. Finally, 6.4%, 7.5% and 8.5% of patients were treated with more than 5-day courses of DKP-TRAM at 3, 6 and 12 months of follow-up.
In SIDIAP, most of the patients reported less than 4 "5 day" courses of DKP-TRAM during the whole follow-up (69.6%, 68.9% and 68.2% at 3, 6 and 12 months) and over one fifth of the patients reported over 6 "5-day" at the end of the 12 months of follow-up (20.5%, 21.2% and 21.9% at 3, 6 and 12 months).

The Kaplan-Meier curves for DKP-TRAM discontinuation because of potential AEs in HSD are reported in **Table 11a.** At the 5th, 15th and 30th day of follow-up and are presented in **Annex 4 (Figure 1.1 – Figure 1.3)**. Overall, 182 (2.9%) patients treated with DKP-TRAM discontinued the treatment in the first month of follow-up. Most of the AEs were recorded in the 1st day of DKP-TRAM treatment, namely 32 (17,2% of the 182) patients interrupted the treatment. The probability of surviving (no discontinuation) at 5th day was 0.9876 (95% CI: 0.9846- 0.9901), while it was (0.9784 (95% CI: 0.9745 - 0.9817) and 0.9714 (95% CI: 0.967 - 0.9752) at 15th and 30th day, respectively. The probability of surviving (no discontinuation) showed a greatest reduction at the 1st day of treatment 0.995 (95% CI: 0.9929 - 0.9965), and also ranging from the 1st to the 5th day (0.9876 (95% CI: 0.9846 - 0.9901)). A lower reduction for likelihood of DKP-TRAM discontinuation was found at the 15th and 30th day of follow-up.
The Kaplan-Meier curves for DKP-TRAM discontinuation due to potential AEs in SIDIAP are reported in **Table 11b.** At the 5th, 15th and 30th day of follow-up and are presented in **Annex 4 (Figure 1.4 - Figure 1.6)**. During the first months of follow-up, a total of 101 (0.5%), 159 (0.8%) and 226 patients (1.14%) that received a prescription with DKP-TRAM

discontinued the treatment due to adverse events at 5, 15 and 30 days respectively. Overall, there was a higher number of adverse events during the first 10 days (a total of 138 AE reported). During this initial period, the higher number of adverse events were reported during the first day of treatment with DKP-TRAM (n=58) and during the first 3 days after the DKP-TRAM initiation. After that it peaked at the end of the first week and on the 10th day. The likelihood of discontinuation during the follow-up is reflected in the Kaplan-Meier curves; patients were more likely to interrupt the DKP-TRAM treatment the first day of treatment and this likelihood to discontinuation continued to increase and was more pronounced up to the 15th day where it was attenuated.

Table 8.1. Categories of PDDs of DKP-TRAM being prescribed in HSD at 3, 6 and 12 months of follow-up.

Dosage (mg)	3 months		6 months		12 months	
	N	%	N	%	N	%
<225/75	6,234	97.36	6,234	97.36	6,235	97.38
=225/75	168	2.62	168	2.62	167	2.61
>225/75	1	0.02	1	0.02	1	0.02

Table 8.2 Categories of DDDs of DKP-TRAM being prescribed in HSD at 3, 6 and 12 months of follow-up.

Dosage (mg)	3 months		6 months		12 months	
	N	%	N	%	N	%
<225/75	6403	100	6403	100	6403	100
=225/75	0	0	0	0	0	0
>225/75	0	0	0	0	0	0

Table 8.3 Categories of PDDs of DKP-TRAM being prescribed in SIDIAP at 3, 6 and 12 months of follow-up.

Dosage (mg)	3 months	6 months	12 months
	N (%)	N (%)	N (%)
<225/75	12,781 (64.2)	12,879 (64.7)	12,936 (65.0)
=225/75	6,933 (34.8)	6,821 (34.3)	6,745 (33.9)
>225/75	44 (0.2)	46 (0.2)	49 (0.2)
Missing	154 (0.8)	166 (0.8)	182 (0.9)

Table 8.4 Categories of DDDs of DKP-TRAM being prescribed in SIDIAP at 3, 6 and 12 months of follow-up.

Dosage (mg)	3 months	6 months	12 months
	N (%)	N (%)	N (%)
<225/75	19,734 (99.1)	19,722 (99.0)	19,705 (99.0)
=225/75	1 (0.0)	1 (0.0)	1 (0.0)
>225/75	23 (0.1)	23 (0.1)	24 (0.1)
Missing	154 (0.8)	166 (0.8)	182 (0.9)

Table 9.1 Duration (days) of DKP-TRAM treatment in HSD at 3, 6 and 12 months of follow-up using PDDs.

Duration	3 months		6 months		12 months	
	N	%	N	%	N	%
<10 days	144	2.25	139	2.17	134	2.09
=10 days	4,615	72.08	4,491	70.14	4,406	68.81
>10 days	1,644	25.67	1,773	27.69	1,863	29.10

Table 9.2 Duration (days) of DKP-TRAM treatment in HSD at 3, 6 and 12 months of follow-up using DDDs.

Duration	3 months		6 months		12 months	
	N	%	N	%	N	%
<10 days	0	0	0	0	0	0
=10 days	5,421	84.66	5,269	82.29	5,161	80.60
>10 days	982	15.34	1134	17.71	1242	19.40

Table 9.3 Duration (days) of DKP-TRAM treatment in SIDIAP at 3, 6 and 12 months of follow-up using PDDs.

Duration	3 months	6 months	12 months
	N (%)	N (%)	N (%)
<5 days	1611 (8.1)	1610 (8.1)	1601 (8.0)
<11 days	9,931 (49.9)	9,890 (49.7)	9,864 (49.5)
=11 days	2,896 (14.5)	2,860 (14.4)	2,832 (14.2)
>11 days	7,085 (35.6)	7,162 (36.0)	7,216 (36.2)

Table 9.4 Duration (days) of DKP-TRAM treatment in SIDIAP at 3, 6 and 12 months of follow-up using DDDs.

Duration	3 months	6 months	12 months
	N (%)	N (%)	N (%)
<11 days	10,081 (50.6)	10,035 (50.4)	9,998 (50.2)
=11 days	1,993 (10.0)	1,971 (9.9)	1,947 (9.8)
>11 days	7,684 (38.6)	7,740 (38.9)	7,785 (39.1)
Missing	154 (0.8)	166 (0.8)	182 (0.9)

Table 10a. Number of "5-day" courses of DKP-TRAM treatment in HSD at 3, 6 and 12 months of follow-up.

Number of "5-day courses"	3 months		6 months		12 months	
	N	%	N	%	N	%
<4	4,802	75.00	4,676	73.03	4,590	71.68
4-6	1,194	18.65	1,246	19.46	1,269	19.82
>6	407	6.36	481	7.51	544	8.50

Table 10b. Number of "5-day" courses of DKP-TRAM treatment at 3, 6 and 12 months of follow-up in SIDIAP.

Number of "5-day courses"	3 months	6 months	12 months
	N (%)	N (%)	N (%)
<4	13,856 (69.6)	13,711 (68.9)	13,588 (68.2)
4-6	1,977 (9.9)	1,973 (9.9)	1,973 (9.9)
>6	4,079 (20.5)	4,228 (21.2)	4,351 (21.9)

Table 11a. Kaplan-Meier estimates of DKP-TRAM discontinuation in HSD because of potential adverse events during the first 5, 15 or 30 days of follow-up.

Time (days)	Patients at risk	AEs	Censored	Survivor Function	95% CI (Lower - Upper)	
1	6,403	32	8	0.995	0.9929	0.9965
2	6,363	15	1	0.9927	0.9902	0.9945
3	6,347	12	6	0.9908	0.9881	0.9928
4	6,329	8	3	0.9895	0.9867	0.9917
5	***6,318***	***12***	0	***0.9876***	***0.9846***	***0.9901***
6	6,306	11	0	0.9859	0.9827	0.9885
7	6,295	10	3	0.9844	0.981	0.9871
8	6,282	5	0	0.9836	0.9801	0.9864
9	6,277	6	2	0.9826	0.9791	0.9856
10	6,269	5	14	0.9819	0.9783	0.9848
11	6,250	5	4	0.9811	0.9774	0.9841
12	6,241	3	13	0.9806	0.9769	0.9837
13	6,225	1	6	0.9804	0.9767	0.9836
14	6,218	9	13	0.979	0.9752	0.9823
15	***6,196***	***4***	0	***0.9784***	***0.9745***	***0.9817***
16	6,192	3	1	0.9779	0.974	0.9812
17	6,188	3	16	0.9774	0.9735	0.9808
18	6,169	6	9	0.9765	0.9725	0.9799

19	6,154	3	9	0.976	0.972	0.9795
20	6,142	3	9	0.9755	0.9714	0.9791
21	6,130	3	8	0.9751	0.9709	0.9786
22	6,119	1	1	0.9749	0.9708	0.9785
23	6,117	2	1	0.9746	0.9704	0.9782
24	6,114	1	10	0.9744	0.9702	0.978
25	6,103	1	14	0.9743	0.9701	0.9779
26	6,088	4	14	0.9736	0.9694	0.9773
27	6,070	4	15	0.973	0.9687	0.9767
28	6,051	5	8	0.9722	0.9678	0.9759
29	6,038	4	1	0.9715	0.9671	0.9753
30	***6,033***	***1***		***0.9714***	***0.967***	***0.9752***

Table 11b. Kaplan-Meier estimates of DKP-TRAM discontinuation in SIDIAP due to potential adverse events during the first 5, 15 or 30 days of follow-up.

Time (days)	Patients at risk	AEs	Censored	Survivor Function	95% CI (Lower - Upper)	
1	19,912	58	43	0.9971	0.9978	0.9963
2	19,811	10	8	0.9966	0.9974	0.9958
3	19,793	12	21	0.9960	0.9969	0.9951
4	19,760	8	23	0.9956	0.9965	0.9947
5	***19,729***	***13***	***14***	***0.9949***	***0.9959***	***0.9939***
6	19,702	10	14	0.9944	0.9955	0.9934
7	19,678	7	20	0.9941	0.9951	0.9930
8	19,651	7	16	0.9937	0.9948	0.9926
9	19,628	3	12	0.9936	0.9947	0.9924
10	19,613	10	36	0.9930	0.9942	0.9919
11	19,567	2	32	0.9929	0.9941	0.9918
12	19,533	3	25	0.9928	0.9940	0.9916
13	19,505	4	25	0.9926	0.9938	0.9914
14	19,476	5	30	0.9923	0.9936	0.9911
15	**19,441**	**7**	**4**	**0.9920**	**0.9932**	**0.9907**
16	19,430	8	6	0.9916	0.9928	0.9903
17	19,416	3	26	0.9914	0.9927	0.9901
18	19,387	3	29	0.9913	0.9926	0.9900
19	19,355	6	26	0.9910	0.9923	0.9896
20	19,323	4	18	0.9908	0.9921	0.9894
21	19,301	5	22	0.9905	0.9918	0.9891
22	19,274	3	7	0.9903	0.9917	0.9890
23	19,264	5	7	0.9901	0.9915	0.9887

24	19,252	3	18	0.9899	0.9913	0.9885
25	19,231	4	5	0.9897	0.9911	0.9883
26	19,222	4	20	0.9895	0.9909	0.9881
27	19,198	6	36	0.9892	0.9907	0.9878
28	19,156	9	27	0.9887	0.9902	0.9873
29	19,120	1	16	0.9887	0.9902	0.9872
30	**19,103**	**2**	**10**	**0.9886**	**0.9901**	**0.9871**

10.2. SECONDARY OBJECTIVES

10.2.1 INCIDENCE RATE OF AES

Crude population-based IRs of AEs occurring among users of DKP-TRAM, tramadol or tramadol-paracetamol (fixed) combinations, are reported in **Table 12a** for HSD and in **Table 12b** for SIDIAP **.**

In HSD, of 19722 patients (mean age (years): 63.5, SD: 16; 60.63% females; cumulating 1,615,749 person-days of follow-up) being considered eligible for the inclusion criteria, 4968 (25.3%), 9501 (48.2%) and 5204 (26.4%) were prescribed with DKP-TRAM, tramadol or tramadol-paracetamol users on the index date, respectively. On the same (index) date, 14, 10 and 7 patients (0.15%, taken as a whole) were prescribed with tramadol plus tramadol-paracetamol combination, tramadol plus DKP-TRAM, and tramadol-paracetamol combination plus DKP-TRAM on the same (index) date, respectively. Overall, 602 patients incurred in AEs, with an IR equal to 3.73 per 10000 person-days. Females showed IR of AEs higher than males (4.44 vs. 2.63 per 10000 person-days); the IRs of AEs generally increased with age with some discontinuation (ranging 1.62-5.13 per 10000 person-days). In specific, those aged 75 years or older reported a higher IR vs. those aged 74 or younger (4.92 vs. 3.3 per 10000 person-days). For what concerns the individual therapies, DKP-TRAM users reported an IR of AEs equal to 5.03 per 10000 person-days, while an IR equal to 3.8 and 2.44 per 10000 person-days were obtained for those exposed to tramadol or tramadol-paracetamol, respectively. Among those being prescribed with two exposure categories on the same (index) date, only 1 AE was captured (i.e.: for tramadol plus DKP-TRAM users). Given that less than 5 events were coded for these mixed users, they were not shown in the related Tables or Figures.

In SIDIAP a total of 152,819 were eligible and were prescribed DKP-TRAM, tramadol or tramadol-paracetamol, of which, 54.6% were female with a mean (SD) age of 54.8 years old, with an accumulated total follow-up of 12,799,865 persons-year.

Most of the subjects, 143,832 (93.7%), were prescribed tramadol and/or tramadol-paracetamol, 8,987 (5.9%) subjects were prescribed DKP-TRAM and 119 patients (0.17%) had combined prescriptions of DKP-TRAM with tramadol and/or tramadol-paracetamol. During follow-up, 2,482 patients had an adverse event (accumulated follow-up of 12,820,534 persons-day) which corresponds to an IR of 1.94 per 10,000 person-days. The highest IR of adverse events was seen for those exposed to DKP-TRAM (2.06 per 10,000 persons-day) followed by those exposed to tramadol-paracetamol (2.04 per 10,000 persons-day) According to the stratification by sex and age, males showed higher IR of adverse events compared to females (2.23 vs. 1.58 per 10,000 persons-day respectively). The incidence of adverse events increased with age and peaked in those aged at least 85 years old (4.01 per 10,000 persons-day).

Table 12a. Incidence rate of AEs in HSD according to sex, age, and exposure category.

	N	person-days	Incidence rate (*10000)	95% CI
Sex				
M	168	638122	2.63	(2.26 - 3.06)
F	434	977627	4.44	(4.04 - 4.88)
Age class				
18-24	6	18094	3.32	(1.49 - 7.38)
25-34	9	55589	1.62	(0.84 - 3.11)
35-44	42	137975	3.04	(2.25 - 4.12)
45-54	88	280347	3.14	(2.55 - 3.87)
55-64	95	312726	3.04	(2.48 - 3.71)
65-74	141	361841	3.9	(3.3 - 4.6)
75-84	163	318002	5.13	(4.4 - 5.98)
>=85	58	131175	4.42	(3.42 - 5.72)
Exposure category				
DKP-TRAM	204	405833	5.03	(4.38 - 5.77)
Tramadol	291	773610	3.76	(3.35 - 4.22)
Tramadol-paracetamol combination	106	434030	2.44	(2.02 - 2.95)
Total	**602**	**1615749**	**3.73**	**(3.44 - 4.04)**

Table 12b. Incidence rate of AEs in SIDIAP according to sex, age, and exposure category.

	N	person-days	Incidence rate (*10000)	95% CI
Sex				
M	1,564	7,004,621	2.23	(2.12 - 2.35)
F	918	5,815,913	1.58	(1.48 - 1.68)
Age class				
18-24	68	463,017	1.47	(1.14 - 1.86)
25-34	190	1,243,143	1.53	(1.32 - 1.76)
35-44	305	2,273,578	1.34	(1.20 - 1.50)
45-54	346	2,540,634	1.36	(1.22 - 1.51)
55-64	403	2,337,466	1.72	(1.56 - 1.90)
65-74	457	2,082,862	2.19	(2.00 - 2.40)
75-84	511	1,376,409	3.71	(3.40 - 4.05)
>=85	202	503,425	4.01	(3.48 - 4.61)

Exposure category				
DKP-TRAM	160	775,512	2.06	(1.76 - 2.41)
Tramadol	620	3,665,004	1.69	(1.56 - 1.83)
Tramadol-paracetamol combination	1,698	8,338,680	2.04	(1.94 - 2.14)
Total	2,482	12,820,534	1.94	(1.86 - 2.01)

For what concerns the type of AEs in HSD, most of them (43.4%) were those coded in the electronic chart directly reporting the drug-related intolerance. The other AEs included constipation (43.4%) followed by vertigo (14.6%), diarrhoea (10.8) and nausea (10.5). Somnolence and hallucinations showed prevalence values lower than 1%. Patients aged 75 years or older manly reported AEs listed in specific section of drug-related intolerance (34.8%), followed by constipation (29.4%) and vertigo (16.3%), while the other AEs showed proportions lower than 10%.
Furthermore, among DKT-TRAM users, most of the AEs were reported in the specific section (60.8%) followed by constipation (13.2%). Among tramadol users, most of them reported AEs in the specific section (36.4%), followed by constipation (22.3%), vertigo (16.2%) and diarrhoea (11%). A similar pattern of AEs was observed among users of tramadol-paracetamol (**Table 13a**). Of 261 AEs being listed in the specific section of the electronic chart identifying the drug-related intolerance, 96% consistently included nausea, vomiting and vertigo.
The type of AE in SIDIAP is reported in **Table 13b.** All AEs in SIDIAP were gathered through ICD-10-CM codes from the routinely collected medical records. The most frequent AE reported was vertigo (63.26%) and constipation (27.44%), followed by diarrhoea (7.57%). The rest of AE were 1% or under. Patients aged 75 years or older mainly reported vertigo (51.2%) and constipation (39.4%), while the other AEs showed proportions lower than 5%. Furthermore, most of the AEs of vertigo were registered among DKT-TRAM users (65.8%), who then reported constipation (23.6%) as the second most frequent event; the rest of AEs were reported in less than 10% of patients. Among tramadol users, most of them reported AEs still due to vertigo (59.2%) and constipation (31.8%). Users of tramadol-paracetamol showed a pattern of AEs which was very similar to that observed for DKP-TRAM users.

Table 13a. Type of incident AEs being identified during follow-up in HSD.

Events	**N**	**%**	**Age >=75**	**DKP-TRAM**	**Tramadol**	**Tramadol-paracetamol**
listed in drug intolerance section*	261	43.36	77 (34.84)	124 (60.78)	106 (36.43)	31 (29.25)
constipation	120	19.93	65 (29.41)	27 (13.24)	66 (22.68)	27 (25.47)
vertigo	88	14.62	36 (16.29)	19 (9.31)	47 (16.15)	22 (20.75)

diarrhoea	65	10.80	18 (8.14)	19 (9.31)	32 (11)	14 (13.21)
nausea	63	10.47	22 (9.95)	14 (6.86)	38 (13.06)	10 (9.43)
somnolence	3	0.50	1 (0.45)	1 (0.49)	1 (0.34)	1 (0.94)
hallucinations	2	0.33	2 (0.9)	0 (0)	1 (0.34)	1 (0.94)
Total	**602***	**100**	**221 (100)**	**204 (100)**	**291 (100)**	**106 (100)**

*1 cases exposed to tramadol and DKP-TRAM on the entry date

*reported by general practitioner in a specific software section

Table 13b. Type of incident AEs being identified during follow-up in SIDIAP.

Events	**N**	**%**	**Age >=75**	**DKP-TRAM**	**Tramadol**	**Tramadol-paracetamol**
vertigo	1,570	63.26	370 (51.89)	106 (65.84)	368 (59.16)	1096 (64.51)
constipation	681	27.44	281 (39.41)	38 (23.60)	198 (31.83)	445 (26.19)
diarrhoea	188	7.57	35 (4.91)	15 (9.32)	43 (6.91)	130 (7.65)
somnolence	25	1.01	12 (1.68)	2 (1.24)	6 (0.96)	17 (1)
hallucinations	17	0.68	15 (2.10)	0	6 (0.96)	11 (0.65)
nausea	1	0.04	0	0	0	0
Total	**2,482***	**100.00**	**713**	**161**	**622**	**1699**

*some cases reported combination of the exposure categories (SIDIAP is not authorized to provide details of cases with a less than 5 counts)

10.2.2 RISK OF AES IN DKP-TRAM USERS VS. TRAMADOL OR TRAMADOL-PARACETAMOL USERS

COHORT ANALYSIS

For HSD, baseline demographics and clinical characteristics of patients being prescribed with DKP-TRAM, tramadol or tramadol-paracetamol combinations are shown in **Table 14a.**

Females were disproportionally greater than males across the three exposure categories (DKP-TRAM: 60.43%; tramadol: 59.52%; tramadol-paracetamol: 62.9%; p=0.002). Considering age categories, while tramadol and tramadol-paracetamol users were characterised by very similar distributions for age strata, DKP-TRAM users were generally younger, having 14.04 and 4.5% individuals aged 75-84 or >=85, respectively. In contrast, 21.21 and 23.52, 9.57 and 9.87% were the proportions for the same age class in tramadol and tramadol-paracetamol combinations users, respectively.

In terms of lifestyles variables, current smokers showed slightly lower prevalence for those exposed to tramadol-paracetamol combination (14.97%) when compared with tramadol (16.27%) and DKP-TRAM users (16.67%). Obesity and alcohol abuse showed similar proportions (3.87-3.93%) across the three exposure categories, while prior drug or other substance abuse were a little higher in tramadol users (0.38%) than other exposure categories (0.21 and 0.28%).

For what concerns comorbidities, DKP-TRAM users showed a slightly lower prevalence for hepatic impairment, especially for those with mild dysfunctions (7.64 vs. 8.51 and 10.31% for tramadol and tramadol-paracetamol users, respectively). The presence of kidney disease was sensibly lower among DKP-TRAM users (14.04) when compared with tramadol (20.1) or tramadol-paracetamol users (20.5%), which was due to patients with moderate or severe kidney impairment. Along this line, the prevalence of depression in DKP-TRAM users showed lower values (7.8 vs. 10.1 and 9%) compared with the other exposure categories, as well as COPD and asthma (24.72 vs. 28.6 and 26.4%), epilepsy (0.6 vs. 1.13 and 0.8%), mental disorders (26.6. vs. 27.1 and 28%), dementia (7.8 vs. 10.1 and 9%), cerebral/cardiovascular disease (7.3 vs. 12.7 and 12.3%) and gastrointestinal haemorrhages (2.9 vs. 4.21 and 3.4%). The other comorbidities were not disproportionally different among the exposure categories.

For what concerns the prior and/or concurrent medications being registered at baseline, the results were consistent with those reported for the concurrent diseases. Namely, prescriptions

of anticoagulants or anti-platelet, anti-aggregation drugs were proportionally lower among DKP-TRAM (25.2%) than tramadol (37.8%) or tramadol-paracetamol (35.6%) users as well as antidepressants (13.1 vs. 17.6 and 16.5%), MAO-inhibitors (0.2 vs. 0.6 and 0.4%), antipsychotics (4.6 vs. 6.1 and 5%) and anxiolytics (0.2 vs. 0.6 and 0.4%). The other concurrent medications were featured by few prescriptions or did not show substantial difference across the exposure categories.

For SIDIAP, baseline demographics and clinical characteristics of patients prescribed with DKP-TRAM, tramadol or tramadol-paracetamol combination are reported in **Table 14b.**

The proportion of males and females with an incident DKP-TRAM prescription was similar (49.9% vs. 50.1%). In females the most frequently prescribed drug was tramadol-paracetamol (57.2%) and in males tramadol (50.2%). The analysis per age categories also varied with different exposures; DKP-TRAM was more frequently prescribed to younger patients (35-44 years old) compared to those receiving either a tramadol or tramadol-paracetamol prescription (45-54 years old). Regarding the life-style habits and comorbidities, patients who were current smokers were more likely to receive a DKP-TRAM prescription (18.9%) and patients with a diagnosis of depression, COPD, asthma, epilepsy and cerebrovascular disease were more likely to receive a prescription of tramadol or tramadol-paracetamol.

Compared to subjects who were prescribed with tramadol or tramadol-paracetamol, those who received DKP-TRAM had frequently a history of drug abuse (2.3% vs. 1.9% and 1.4% for tramadol and tramadol-paracetamol, respectively) or mental disorders (28.2% vs. 25.5% and 26.3% for tramadol and tramadol-paracetamol, respectively).

For what concerns the prior and/or concurrent medications being registered at baseline, patients with a DKP-TRAM prescription were less frequently prescribed with most of the medications analysed with the exception of anxiolytics (9.3% vs. 7.2% and 7.8% in the tramadol and tramadol-paracetamol exposures groups, respectively).

The Hazard Ratios (HRs) of AEs in patients prescribed with DKP-TRAM vs. those prescribed with tramadol as monotherapy or fixed combinations tramadol-paracetamol in HSD and in SIDIAP are reported in **Table 15a**. In HSD, DKP-TRAM users showed a significantly greater risk of incurring in AEs when compared with those exposed to tramadol or tramadol-paracetamol combination (adjusted HR=1.66; 95% CI: 1.40-1.98). When the exposure was stratified by individual medications using tramadol as reference category, DKP-TRAM users consistently showed a greater risk of incurring in AEs (adjusted HR=1.44; 95% CI: 1.2-1.73). When the category of tramadol-paracetamol use was the reference category, the risk of AEs among those exposed to DKP-TRAM was even higher (adjusted HR=2.3; 95% CI: 1.81 – 2.92). For each model, the multivariate analysis did not substantially change the point estimate being obtained for the univariate analyses.

In SIDIAP, after adjusting for potential confounders, DKP-TRAM users showed a statistically significant greater risk of experiencing an AE compared to those who were prescribed with tramadol, tramadol-paracetamol or tramadol-paracetamol combinations (HR of 1.30, 95%CI (1.11-1.53)). When analysing and comparing the risk per exposure, the greater risk difference was found compared to subjects who were prescribed with tramadol (HR of 1.48, 95%CI: 1.09-1.76), followed by those who were prescribed with tramadol-paracetamol combinations (HR=1.24, 95%CI: 1.05-1.46).

For both SIDIAP and HSD, when the multivariate model tested the interaction between age (>=75 or 74 years) and exposure categories DKP-TRAM or tramadol/tramadol-paracetamol, no statistically significant association was observed for HSD (p value equal to 0.18), while a borderline non-significance estimate (p value equal to 0.06) was obtained for SIDIAP. The stratum-specific sizes and estimates are reported in Table 15b. As expected, for HSD, the point estimates revealed in the two subgroups were consistent with those observed for the primary model. In SIDIAP, a statistically significant increased risk was observed for those aged 75 or lower (HR=1.40, 95% CI: 1.20-1.4), while no association was found for older patients (HR=0.74, 95% CI: 0.40-1.34).

Table 14a. Demographic and clinical patients' features in HSD among the exposure categories.

	DKP-TRAM N (%)	**Tramadol N (%)**	**Tramadol-paracetamol combination N (%)**	**p value**
Total	**4986**	**9501**	5204	
Sex				0.002
Male	1,973 (39.57)	3844 (40.46)	1932(37.13)	
Female	3013 (60.43)	5657 (59.54)	3272 (62.87)	
Age				< 0.001
15-24	75 (1.5)	103 (1.08)	41 (0.79)	
25-34	234 (4.69)	288 (3.03)	137 (2.63)	
35-44	573 (11.49)	729 (7.67)	376 (7.23)	
45-54	1048 (21.02)	1523 (16.03)	771 (14.82)	
55-64	1074 (21.54)	1810 (19.05)	929 (17.85)	
65-74	1058 (21.22)	2123 (22.35)	1213 (23.31)	
75-84	700 (14.04)	2014 (21.2)	1222 (23.48)	
>=85	224 (4.49)	911 (9.59)	515 (9.9)	
Smoke				< 0.001
Current smokers	831 (16.67)	1546 (16.27)	779 (14.97)	
Non-smokers	1927 (38.65)	3495 (36.79)	2179 (41.87)	
Past smokers	697 (13.98)	1458 (15.35)	809 (15.55)	
Missing	*1531 (30.71)*	*3002 (31.6)*	*1437 (27.61)*	
Obesity	481 (9.65)	911 (9.59)	495 (9.51)	0.949
Alcohol	195 (3.91)	372 (3.92)	200 (3.84)	0.934
Comorbidities				
Hepatic impairment	854 (17.13)	1663 (17.5)	947 (18.2)	0.272
Hepatic impairment (Child-Pugh classification)				< 0.001
Mild	379 (7.6)	977 (10.28)	444 (8.53)	
Moderate	44 (0.88)	98 (1.03)	37 (0.71)	
Severe	0 (0)	0 (0)	0 (0)	
Missing	*4563 (91.52)*	*8426 (88.69)*	*4723 (90.76)*	
Kidney disease	700 (14.04)	1947 (20.49)	1046 (20.1)	< 0.001
Renal function (GFR (ml/min/1.73 m^2))*				< 0.001
Mild	3557 (71.34)	6240 (65.68)	3524 (67.72)	
Moderate	442 (8.86)	1227 (12.91)	677 (13.01)	
Severe	15 (0.3)	144 (1.52)	48 (0.92)	
Kidney failure	10 (0.2)	68 (0.72)	20 (0.38)	
Missing	*962 (19.29)*	*1822 (19.18)*	*935 (17.97)*	
Depression	387 (7.76)	959 (10.09)	465 (8.94)	< 0.001
COPD-Asthma	1231 (24.69)	2722 (28.65)	1372 (26.36)	< 0.001

DKP-TRAM/vo3

Epilepsy	28 (0.56)	108 (1.14)	41 (0.79)	0.020
Dyspepsia	600 (12.03)	1070 (11.26)	621 (11.93)	0.380
Drug abuse	14 (0.28)	36 (0.38)	11 (0.21)	0.648
Mental disorders	1321 (26.49)	2569 (27.04)	1456 (27.98)	0.149
Hallucinations	2 (0.04)	10 (0.11)	1 (0.02)	0,483
Dementia	219 (4.39)	602 (6.34)	323 (6.21)	< 0.001
Cognitive impairment after trauma	0 (0)	0 (0)	1 (0.02)	0.732
Cerebro-cardiovascular disease	362 (7.26)	1210 (12.74)	637 (12.24)	< 0.001
Gastrointestinal haemorrhages	144 (2.89)	401 (4.22)	176 (3.38)	0.001
Prior and/or concurrent medications				
NSAIDs	2716 (54.47)	5333 (56.13)	2700 (51.88)	< 0.001
Anticoagulants	1253 (25.13)	3594 (37.83)	1849 (35.53)	< 0.001
Carbamazepine	27 (0.54)	67 (0.71)	21 (0.4)	0.340
Cimetidine	0 (0)	0 (0)	0 (0)	-
Other opioids	936 (18.77)	2307 (24.28)	1554 (29.86)	< 0.001
Antidepressants	647 (12.98)	1663 (17.5)	860 (16.53)	< 0.001
MAO-Inhibitors	10 (0.2)	54 (0.57)	18 (0.35)	0.040
Antipsychotics	227 (4.55)	579 (6.09)	260 (5)	0.002
Anxiolytics	590 (11.83)	1306 (13.75)	833 (16.01)	< 0.001
Ondansetron	0 (0)	0 (0)	2 (0.04)	0.349
Ketoconazole	1 (0.02)	0 (0)	0 (0)	0.707
Erythromycin	3 (0.06)	1 (0.01)	1 (0.02)	0.655

*among patients with kidney impairments

Table 14b. Demographic and clinical patients' features in SIDIAP in each exposure category.

	DKP-TRAM N (%)	Tramadol N (%)	Tramadol-paracetamol combination N (%)	p value
Total	8,987	44,073	99,618	
Sex				<0.001
Male	4,488 (49.9)	22,122 (50.2)	42,617 (42.8)	
Female	4,499 (50.1)	21,951 (49.8)	57,001 (57.2)	
Age				<0.001
15-24	515 (5.7)	1,862 (4.2)	3,047 (3.1)	
25-34	1,339 (14.9)	4,696 (10.7)	8,623 (8.7)	
35-44	2,241 (24.9)	7,598 (17.2)	16,967 (17.0)	
45-54	2,112 (23.5)	8,127 (18.4)	19,795 (19.9)	
55-64	1,418 (15.8)	7,547 (17.1)	18,819 (18.9)	
65-74	912 (10.1)	7,134 (16.2)	16,878 (16.9)	
75-84	372 (4.1)	4,822 (10.9)	11,533 (11.6)	
>=85	78 (0.9)	2,287 (5.2)	3,956 (4.0)	
Smoke				<0.001
Current smokers	1,699 (18.9)	7,194 (16.3)	15,269 (15.3)	
Non-smokers	3,250 (36.2)	15,541 (35.3)	38,785 (38.9)	
Past smokers	1,548 (17.2)	8,889 (20.2)	19,597 (19.7)	
Missing	2,490 (27.7)	12,449 (28.2)	25,967 (26.1)	
Obesity				<0.001
Non obese	4,945 (55.0)	24,992 (56.7)	57,154 (57.4)	
Obese	1,946 (21.7)	10,006 (22.7)	25,903 (26.0)	
Missing	2,096 (23.3)	9,075 (20.6)	16,561 (16.6)	
Alcohol	330 (3.7)	2,003 (4.5)	3,742 (3.8)	<0.001
Comorbidities				
Hepatic impairment classification				
Hepatic impairment overall	45 (0.5)	490 (1.1)	815 (0.8)	<0.001
Chronic	15 (0.2)	81 (0.2)	198 (0.2)	0.946
Cirrosis	18 (0.2)	261 (0.6)	350 (0.4)	<0.001
Kidney disease	361 (4.0)	4,592 (10.4)	9,724 (9.8)	<0.001
Renal function (GFR (ml/min/1.73 m2))*				<0.001
Mild	106 (1.2)	1,233 (2.8)	2,768 (2.8)	
Moderate	0 (0.0)	1 (0.0)	2 (0.0)	
Severe	11 (0.1)	155 (0.4)	324 (0.3)	

DKP-TRAM/vo3

Kidney failure	1 (0.0)	10 (0.0)	28 (0.0)	
Missing	8,869 (98.7)	42,674 (96.8)	96,496 (96.9)	
Depression	1,061 (11.8)	5,510 (12.5)	12,610 (12.7)	0.073
COPD-Asthma	1,371 (15.3)	8,222 (18.7)	18,248 (18.3)	<0.001
Epilepsy	95 (1.1)	580 (1.3)	1045 (1.0)	0.001
Dyspepsia	668 (7.4)	3,338 (7.6)	8,530 (8.6)	<0.001
Drug abuse	210 (2.3)	818 (1.9)	1,389 (1.4)	<0.001
Mental disorders	2,535 (28.2)	11,258 (25.5)	26,213 (26.3)	<0.001
Hallucinations	1 (0.0)	38 (0.1)	61 (0.1)	0.192
Dementia	106 (1.2)	1,748 (4.0)	2,734 (2.7)	<0.001
Cognitive impairment after trauma	0 (0)	0 (0)	1 (0.02)	-
Cerebral-cardiovascular disease	219 (2.4)	3,388 (7.7)	6,830 (6.9)	<0.001
Gastrointestinal haemorrhages	78 (0.9)	655 (1.5)	1,220 (1.2)	<0.001
Prior and/or concurrent medications				
NSAIDs	511 (5.7)	3,984 (9.0)	6,459 (6.5)	<0.001
Anticoagulants	440 (4.9)	5,873 (13.3)	4,338 (4.4)	<0.001
Carbamazepine	14 (0.2)	86 (0.2)	100 (0.1)	0.001
Cimetidine	0 (0)	0 (0)	0 (0)	-
Other opioids	14 (0.2)	86 (0.2)	100 (0.1)	0.001
Antidepressants	262 (2.9)	1,371 (3.1)	2,834 (2.8)	0.002
MAO-Inhibitors	0 (0.0)	1 (0.0)	3 (0.0)	0.997
Antipsychotics	262 (2.9)	1,371 (3.1)	2,834 (2.8)	0.002
Anxiolytics	834 (9.3)	3,182 (7.2)	7,769 (7.8)	<0.001
Ondansetron	18 (0.2)	306 (0.7)	206 (0.2)	<0.001
Ketoconazole	0 (0.0)	0 (0)	0 (0)	-
Erythromycin	10 (0.1)	49 (0.1)	117 (0.1)	0.995

*among patients with kidney impairments

Table 15aa. Hazard Ratio of AEs for DKP-TRAM vs. tramadol or tramadol-paracetamol users in HSD and in SIDIAP

DKP-TRAM/vo3

	Crude HR (95% CI)	Adjusted* HR (95% CI)
HSD		
Tramadol or Tramadol-paracetamol combination	Ref.	Ref.
DKP-TRAM	1.52 (1.29 - 1.8)	1.66 (1.40 - 1.98)
SIDIAP		
Tramadol or Tramadol-paracetamol combination	Ref.	Ref.
DKP-TRAM	1.08 (0.92 - 1.27)	1.30 (1.11 - 1.53)

*for all the covariates reported in Table 14a and Table 14b

Table 15b. Effect modification between age and exposure categories DKP-TRAM or tramadol/tramadol-paracetamol.

	person-days	Adjusted HR* (95% CI)*
HSD		
Age >=75		
Tramadol or Tramadol-paracetamol combination	380475	Ref.
DKP-TRAM	74818	1.7 (1.25 - 2.31)
Age < 75		
Tramadol or Tramadol-paracetamol combination	841425	Ref.
DKP-TRAM	336026	1.6 (1.3 - 1.97)
SIDIAP		
Age >=75		
Tramadol or Tramadol-paracetamol combination	11218252	Ref
DKP-TRAM	234224	0.74 (0.40 – 1.34)
Age < 75		

Tramadol or Tramadol-paracetamol combination	61481243	Ref.
DKP-TRAM	4464446	1.39 (1.17 – 1.64)

*for all the covariates reported in Table 14a and Table 14b

NESTED CASE-CONTROL ANALYSES

For HSD, the results concerning the nested case-control analyses are reported across **Table 16 - 23 (see also Annex 4: Table 1** and **Table 2).**

For what concerns the comparative safety study, the Odds Ratio (OR) of AEs in patients exposed to any kind of opioids (i.e. DKP-TRAM, tramadol or tramadol-paracetamol) in the prior 30 days was significantly 3-fold higher vs. those prescribed with DKP-TRAM in the period >=31st day preceding the index date in (OR=3.0; 95% CI: 2.1-4.3; **Table 16).** The current use of tramadol was also associated with a higher risk of AEs vs. recent users (OR=1.8; 95% CI: 1.3-2.5). When we changed the reference category in the same multivariate model, similar point estimate was found, among current users DKP-TRAM, when current use tramadol-paracetamol was the reference category (OR=3.0; 95% CI: 2.2-4.2). Although with lower point estimate, a statistically significant increased risk of AEs was found among current DKP-TRAM vs. tramadol users (OR=1.67; 95% CI: 1.29-2.16).

When the exposure was stratified according to current "new" (i.e. no prior use of DKP-TRAM) and "old" (i.e. current and prior use DKP-TRAM) use of DKP-TRAM, the point estimate for AEs occurrence among new users was even higher than that obtained for the primary model (OR=3.3; 95% CI: 2.2-4.8; **Table 17**). No significant association with the outcome was found among the "old" DKP-TRAM users.

We found similar effect size when the current exposure to DKP-TRAM was stratified by medium daily dosage (>= or < 150 mg in the controls as reference for general population). Those patients being prescribed with >=150 mg/daily of tramadol showed a 3.4 increased risk of AEs (OR=3.4; 95% CI: 1.9-6.2). However, a statistically significantly association was revealed for those using < 150 mg (OR=3.0; 95% CI: 2.0-4.3) as well (**Table 18**). When the current use of DKP-TRAM was categorized according to duration of use (>= or < 10 days, medium value in the controls as reference for general population), those patients being exposed for <10 days showed the highest effect size vs. recent use of any opioids (OR= 13.56; 95% CI: 4.83-38.07). Significant association with occurrence of AEs was found for those currently exposed to DKP-TRAM for 10 days or longer (OR=2.85; 95% CI: 4.83-38.07) vs. recent users as well (**Table 19**).

Table 16 Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in HSD.

	Cases (N=602)	**Controls (N=4892)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	197 (32.72)	2198 (44.93)	*Ref.*	*Ref.*
Current use**				

DKP-TRAM	142 (23.59)	615 (12.57)	2.95 (2.06 - 4.23)	3.01 (2.09 - 4.33)
Tramadol	194 (32.23)	1296 (26.49)	1.82 (1.31 - 2.54)	1.81 (1.29 - 2.52)
Tramadol-paracetamol	65 (10.8)	756 (15.45)	1.02 (0.69 - 1.51)	1.00 (0.67 - 1.48)
Mixed	4 (0.66)	27 (0.55)	2.06 (0.7 - 6.1)	2.27 (0.76 - 6.75)

*for all the covariates reported in Table 1 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 17. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in HSD: current use of DKP-TRAM is further categorized into "new" and "old" use.

	Cases (N=602)	**Controls (N=4892)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	197 (32.72)	2198 (44.93)	*Ref.*	*Ref.*
Current use**				
"new" DKP-TRAM use	138 (22.92)	586 (11.98)	3.21 (2.19 - 4.7)	3.29 (2.24 - 4.84)
"old" DKP-TRAM use	4 (0.66)	29 (0.59)	1.58 (0.54 - 4.6)	1.56 (0.53 - 4.6)
Tramadol	194 (32.23)	1296 (26.49)	1.92 (1.37 - 2.69)	1.91 (1.35 - 2.68)
Tramadol-paracetamol	65 (10.8)	756 (15.45)	1.08 (0.72 - 1.6)	1.05 (0.7 - 1.57)
Mixed	4 (0.66)	27 (0.55)	2.16 (0.73 - 6.39)	2.38 (0.8 - 7.08)

*for all the covariates reported in Table 1 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 18. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in HSD: dosage-response relationship is tested.

	Cases (N=602)	**Controls (N=4892)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	197 (32.72)	2198 (44.93)	*Ref.*	*Ref.*
Current use**				
DKP-TRAM use >= 150 mg	19 (3.16)	78 (1.59)	3.39 (1.88 - 6.14)	3.38 (1.85 - 6.17)
DKP-TRAM use < 150 mg	123 (20.43)	537 (10.98)	2.89 (2 - 4.17)	2.95 (2.03 - 4.29)
Tramadol	194 (32.23)	1296 (26.49)	1.82 (1.31 - 2.54)	1.81 (1.29 - 2.52)
Tramadol-paracetamol	65 (10.8)	756 (15.45)	1.02 (0.69 - 1.51)	0.99 (0.67 - 1.48)
Mixed	4 (0.66)	27 (0.55)	2.07 (0.7 - 6.13)	2.28 (0.77 - 6.76)

*for all the covariates reported in Table 1 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 19. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in HSD: duration-response relationship is tested.

	Cases (N=602)	**Controls (N=4892)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	197 (32.72)	2198 (44.93)	*Rif.*	*Rif.*

Current use**				
DKP-TRAM use < 10 days	9 (1.5)	8 (0.16)	15 (5.39 - 41.7)	13.56 (4.83 - 38.07)
DKP-TRAM use >= 10 days	133 (22.09)	607 (12.41)	2.8 (1.95 - 4.02)	2.85 (1.98 - 4.12)
Tramadol	194 (32.23)	1296 (26.49)	1.83 (1.31 - 2.55)	1.81 (1.3 - 2.53)
Tramadol-paracetamol	65 (10.8)	756 (15.45)	1.03 (0.7 - 1.52)	1 (0.67 - 1.48)
Mixed	4 (0.66)	27 (0.55)	2.09 (0.71 - 6.18)	2.31 (0.78 - 6.88)

*for all the covariates reported in Table 1 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

For SIDIAP, **Table 20** reports the ORs of AEs with the current use of DKP-TRAM, tramadol and tramadol-paracetamol compared to recent users. A total of 2,467 patients with a prescription of DKP-TRAM, tramadol or tramadol-paracetamol who had an AE were identified as cases and were matched to 16,929 controls. The proportion of patients in each exposure category in cases and controls was similar, although a slightly higher use of DKP-TRAM and tramadol-paracetamol was found among the cases. No statistically significant difference was found between the current and recent use of DKP-TRAM, tramadol or tramadol-paracetamol with respect to the AEs in both the crude and adjusted models. An analysis was carried out changing the reference category to current users of tramadol-paracetamol. After adjusting for potential confounders and compared to current users of tramadol-paracetamol, there was only an increased risk of AEs in patients who had a current use of DKP-TRAM (OR of 1.31, 95%CI: 1.04-1.65), the rest of comparisons remained without statistical significance; when current use of tramadol was the reference category, an increased risk of AEs of borderline significance was seen in current user of tramadol-paracetamol (OR=1.17, 95% CI of 1.03-1.32), in all recent users (OR=1.23, 95% CI: 1.04-1.45) and a higher risk was found among current users of DKP-TRAM (OR=1.53, 95% CI: 1.20-1.96).

Table 21 reports the risk of AEs when classifying current users in "new" or "old" current users of DKP-TRAM in SIDIAP. Compared with recent use of DKP-TRAM, tramadol or tramadol paracetamol, neither new nor old current use of DKP-TRAM was associated with an increased risk in AEs.

Table 22 reports the risk of AEs according to the dosage of tramadol, namely current use of <150 or >=150 mg (medium values among the controls as the reference for general population) and over per day and compared to recent use in SIDIAP. Compared to recent use, the current prescription of at least 150 mg of tramadol or more per day in the conferred an increased risk of AEs in both the crude and adjusted models (OR=1.37; 95% CI: 1.04-1.81; OR=1.35; 95% CI: 1.02-1.78). No differences were found regarding the current use of <150 mg/daily.

Table 23 reports the risk of AEs according to the median duration of the prescription in SIDIAP <11 days or 11 days or more (medium values among the controls as the reference for general population) and compared to recent use. Compared to recent use, the current use of DKP-TRAM for a period of time <11 days was associated with an increased risk of adverse events in both the crude and adjusted models (crude ORs=1.68, 95% CI: 1.22-2.32 and adjusted ORs=1.66, 95% CI: 1.20-2.30). No significant association was found for current longer treatment durations.

Table 20. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in SIDIAP.

DKP-TRAM/vo3

	Cases (N=2467)	Controls (N=16929)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	690 (27.97)	5,142 (30.37)	Ref.	Ref.
Current use**				
DKP-TRAM	108 (4.38)	534 (3.15)	1.24 (0.96-1.61)	1.25 (0.96-1.62)
Tramadol	440 (17.84)	3,232 (19.09)	0.82 (0.70-0.97)	0.81 (0.69-0.96)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	0.95 (0.82-1.09)	0.95 (0.83-1.10)
Mixed	3 (0.12)	16 (0.09)	1.05 (0.30-3.74)	0.98 (0.28-3.50)

*for all the covariates reported in Table 2 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 21. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in SIDIAP: current use of DKP-TRAM is further categorized into "new" and "old" use.

	Cases (N=2467)	Controls (N=16929)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	690 (27.97)	5,142 (30.37)	Ref.	Ref.
Current use**				
"New" DKP-TRAM use	101 (4.09)	500 (2.95)	1.24 (0.95-1.61)	1.23 (0.95-1.61)
"Old" DKP-TRAM use	7 (0.28)	34 (0.2)	1.39 (0.59-3.23)	1.52 (0.65-3.55)
Tramadol	440 (17.84)	3,232 (19.09)	0.82 (0.7-0.97)	0.81 (0.69-0.96)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	0.95 (0.82-1.09)	0.95 (0.82-1.1)
Mixed	3 (0.12)	16 (0.09)	1.06 (0.3-3.75)	0.98 (0.28-3.5)

for all the covariates reported in Table 2 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 22. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in SIDIAP: dosage-response relationship is tested.

	Cases (N=2467)	Controls (N=16926)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	690 (27.97)	5,142 (30.37)	Ref.	Ref.
Current use**				
DKP-TRAM (< 150 mg)	16 (0.65)	123 (0.73)	0.86 (0.50-1.49)	0.93 (0.54-1.62)
DKP-TRAM (>= 150 mg)	92 (3.73)	408 (2.41)	1.37 (1.04-1.81)	1.35 (1.02-1.78)
Tramadol	440 (17.84)	3,232 (19.09)	0.82 (0.70-0.97)	0.81 (0.69-0.96)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	0.95 (0.82-1.09)	0.95 (0.83-1.10)
Mixed	3 (0.12)	16 (0.09)	1.06 (0.30-3.75)	0.99 (0.28-3.50)

for all the covariates reported in Table 2 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 23. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis in SIDIAP: duration-response relationship is tested.

	Cases (N=2467)	Controls (N=16929)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	690 (27.97)	5,142 (30.37)	*Ref.*	*Ref.*
Current use**				
DKP-TRAM (< 11 days use)	68 (2.76)	244 (1.44)	1.68 (1.22-2.32)	1.66 (1.20-2.30)
DKP-TRAM (>= 11 days use)	40 (1.62)	290 (1.71)	0.89 (0.62-1.28)	0.91 (0.64-1.32)
Tramadol	440 (17.84)	3,232 (19.09)	0.83 (0.70-0.97)	0.82 (0.69-0.97)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	0.95 (0.83-1.10)	0.96 (0.83-1.10)
Mixed	3 (0.12)	16 (0.09)	1.06 (0.30-3.78)	0.99 (0.28-3.53)

for all the covariates reported in Table 2 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Testing on effect modification due to frailty

To test the presence of effect modification likely exerted by frailty on DKP-TRAM-related AEs, we used the frailty categories, as calculated by the HS-FI, for both Italian and Spanish patients aged 65 or older. These three categories were operationally defined as the tertiles of individual FI being calculated by dividing the number of deficits coded in the database out of the potential 26 deficits forming the HS-FI. In HSD and SIDIAP (in which an FI was adapted: see Appendix 3), among the controls (as the reference for the general population), we identified no or mild, moderate, and high- frail patients, as definedin the overall period preceding the index date according to the FI tertiles,). The related stratum-specific sizes and estimates are reported in Table 24.

In HSD, the multivariate model including the interaction term (i.e. exposure categories for medications (5)*frail categories (3)) showed statistically significant effect modification for DKP-TRAM users within the highest tertile of HS-FI (p value equal to 0.01). Namely, the risk of AEs among current users DKP-TRAM was 3.24-fold higher among highly frail patients (OR=3.24; 95% CI: 1.70-6.38), while it was 3.1 and 2.52-fold higher for low and moderate frail patients (OR=3.1; 95% CI: 1.50-6.38; OR=2.52; 95% CI: 1.40-4.61), respectively. . Also for SIDIAP, the interaction with frailty was assessed to determine whether the different stages of frailty were associated with the risk of AEs in the different exposure categories. When the multivariate model tested the interaction between frailty (i.e. no/mild, moderate, severe) and exposure categories DKP-TRAM or tramadol/tramadol-paracetamol in the subgroup of those aged 65 or older, no statistically significant value was revealed (p value > 0.05). As expected, the stratum-specific estimates did not show any significant difference across the exposure categories.

Table 24. Effect modification between level of frailty and recency of use for DKP-TRAM, tramadol or tramadol-paracetamol.

	Cases N (%)	Controls N (%)	Adjusted* OR (95% CI)
HSD			
Mild frail			
Recent use**	27 (39.71)	331 (45.22)	Ref.
Current use**			
DKP-TRAM	22 (32.35)	93 (12.7)	3.09 (1.5 - 6.37)
Tramadol	9 (13.24)	175 (23.91)	0.73 (0.31 - 1.68)
Tramadol-paracetamol	9 (13.24)	130 (17.76)	0.94 (0.4 - 2.22)
Mixed	1 (1.47)	3 (0.41)	6.82 (0.66 - 70.15)
Moderate frail			
Recent use	51 (75)	568 (77.6)	Ref.
Current use			
DKP-TRAM	27 (39.71)	136 (18.58)	2.52 (1.38 - 4.61)
Tramadol	44 (64.71)	398 (54.37)	1.29 (0.76 - 2.2)
Tramadol-paracetamol	21 (30.88)	216 (29.51)	1.1 (0.59 - 2.06)
Mixed	0 (0)	9 (1.23)	0 (0 - 0)
High frail			
Recent use	41 (60.29)	425 (58.06)	Ref.
Current use			
DKP-TRAM	23 (33.82)	87 (11.89)	3.24 (1.65 - 6.37)
Tramadol	66 (97.06)	307 (41.94)	2.41 (1.41 - 4.11)
Tramadol-paracetamol	18 (26.47)	151 (20.63)	1.08 (0.54 - 2.17)
Mixed	3 (4.41)	5 (0.68)	8.16 (1.76 - 37.86)
SIDIAP			
Mild frail	212	1513	

Recent use**	49 (23.11)	358 (23.66)	Ref.
Current use**			
DKP-TRAM	5 (2.36)	111 (7.34)	0.54 (0.12-2.44)
Tramadol	45 (21.23)	279 (18.44)	1.13 (0.55-2.33)
Tramadol-paracetamol	113 (53.3)	761 (50.3)	1.12 (0.59-2.14)
Mixed	0 (0)	4 (0.26)	0 (0)
Moderate frail	280	1460	
Recent use	76 (27.14)	401 (27.47)	Ref.
Current use			
DKP-TRAM	6 (2.14)	53 (3.63)	0.7 (0.19-2.57)
Tramadol	54 (19.29)	301 (20.62)	0.59 (0.32-1.11)
Tramadol-paracetamol	144 (51.43)	705 (48.29)	0.64 (0.38-1.09)
Mixed	0	0	0
High frail	241	981	
Recent use	75 (31.12)	272 (27.73)	Ref.
Current use			
DKP-TRAM	1 (0.41)	15 (1.53)	0.09 (0-1.63)
Tramadol	61 (25.31)	234 (23.85)	0.5 (0.22-1.17)
Tramadol-paracetamol	104 (43.15)	458 (46.69)	0.63 (0.29-1.4)
Mixed	0 (0)	2 (0.2)	0 (0)

*for all the covariates reported in Table 2 (see Appendix 4); **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Sensitivity analyses

When we limited the AEs to those registered in the section of electronic clinical charts for drug intolerance (i.e. those AEs which were assessed by GPs as directly related to medication use), the results were consistent with those obtained for the primary analysis. Namely, DPK-TRAM users

were featured by a greater risk of AEs when compared with tramadol/tramadol-paracetamol (adjusted HR=2.71; 95% CI: 2.12-3.50; Table 25). When the nested case-controls analysis was conducted by matching cases with controls according to age, sex, calendar period (month, year of cohort entry), duration of follow-up and PS (i.e. the same quartiles) the results were consistent with those obtained for the primary analyses. Along this line, when BMI and smoking variables were imputed according to MI methods (up to 5 iterations), the point estimates fully adjusted with these two imputed variables were still consistent with those revealed by the primary analyses (**Annex 4. Table 3 – Table 14**).

Table 25. Hazard Ratio of AEs for DKP-TRAM vs. tramadol or tramadol-paracetamol users in HSD : AEs are those reported in the specific section on drugs intolerance.

	person-days	Crude HR (95% CI)	Adjusted* HR (95% CI)
HSD			
Tramadol or Tramadol-paracetamol combination	1221900	Ref.	Ref.
DKP-TRAM	410844	2.69 (2.11 - 3.43)	2.71 (2.12 - 3.48)

*for all the covariates presented in Table 14a

11. DISCUSSION

11.1 KEY RESULTS

IN HSD:

During the study period, the IR of DKP-TRAM use was 2.81‰ and 3.44‰ in 2017 and 2018, respectively. Females and elderly patients were associated with higher IRs. Similar results were found calculating the IR of DKP-TRAM use with person-times as denominators (2.89/1,000 person-years in 2017 and 3.54/1,000 person-years in 2018).
Females, older patients, and past smokers were associated with higher IR of DKP-TRAM use (4.49‰) compared to the other categories. Regarding comorbidities, IRs of DKP-TRAM use ranged from 7.5‰ to 0‰. In particular, obese patients, as well as patients with mild kidney failure and mild hepatic impairment showed the highest IRs of DKP-TRAM use during the study period. For what concern prior and/or concurrent medications, the highest IRs of DKP-TRAM use were found in patients prescribed with tramadol, other opioids and erythromycin.
In HSD there was no information with which to assess the prescriber type, nominally GPs or specialist physicians.

Describing the indication for DKP-TRAM prescriptions across the two years of study, low back pain, osteoarticular pain, and osteoarthritis resulted the most frequent indication for DKP-TRAM prescriptions by GPs.
In terms of DKP-TRAM dosages, around 97% of incident users was prescribed with dosages lower than 225 mg (tramadol)/75 mg (dexketoprofen). Instead, when the analysis adopted the DDDs, all patients were prescribed with DKP-TRAM dosage lower than 225 mg/75 mg.
Evaluating the duration (days) of DKP-TRAM treatments being estimated using the PDD, most patients reported cumulative durations of treatment equal to 10 days, varying from 72.1% at 3 months to 68.8% at 12 months. Similar results were found for DKP-TRAM users with cumulative durations lower than 10 days. At the same time, the proportion of patients with a DKP-TRAM treatment higher than 10 days increased from 3 months (25.7%) to 12 months (29.1%). Similar results were obtained calculating the duration of DKP-TRAM treatment based on DDD.
Considering the number of 5-days courses of DKP-TRAM treatment, most patients reported less than 4 "5-day" courses at 3, 6 and 12 months. However, the proportion of patients treated with 4-5 and more than 6 "5-days" courses of DKP-TRAM use increased during the year.
Furthermore, a Kaplan-Meier method was adopted in order to estimate the burden of DKP-TRAM discontinuation because of potential AEs. As a whole, 182 out of 6403 patients (2.9%) treated with DKP-TRAM discontinued during the first month of follow-up. As shown by Kaplan-Meier curves, the highest reduction for the probability of surviving (i.e., no-discontinuation) occurred early after the start (first 5 days) of DKP-TRAM treatment and stably diminished over time.
Finally, the cohort of DKP-TRAM, tramadol or tramadol-paracetamol users reported an overall IR of AEs equal to 3.73 cases per 10000 person-days. Most of them were due to nausea, vomiting, vertigo, diarrhoea and constipation. DKP-TRAM use was associated with a higher IR of AEs (5.03 per 10000 person-days) than tramadol (3.8) or tramadol-paracetamol (2.44) use. Along this line, the adjusted models estimated an HR of AEs for DKP-TRAM use which was 66% statistically significantly higher than tramadol/tramadol-paracetamol use. When tramadol use was the reference category, the HR was 44% significantly higher for DKP-TRAM use, and was 2.3-fold greater vs. tramadol-paracetamol use. When the nested case-control analysis was conducted, the adjusted model confirmed that the risk of AEs, among users of DKP-TRAM, was 3-fold higher versus tramadol-paracetamol and 67% higher vs. tramadol. This analysis allowed us to compare the exposure categories in the month preceding the date of AEs, inclusive. By doing so, we confirmed the very acute occurrence of these AEs after being prescribed with DKP-TRAM. Consistently, new current users of DKP-TRAM, namely those prescribed with this medication for the first time in the month preceding the AEs, confirmed the effect size (3.29-fold higher) of the association being estimated with the primary model. Unsurprisingly, a current exposure to >=150 mg and a duration of use <10 days of DKP-TRAM further confirmed the acute occurrence of AEs by reporting even higher ORs (3.38 and 13.56, respectively).

When considering effect of age among DKP-TRAM users aged 75 years no association with an increased rate of AEs was observed when compared with younger individuals. An effect modification due to frailty was observed only in highly frail patients who resulted more prone to incur in AEs when compared with those featured by moderate or mild frailty (OR=3.24 vs. 2.52

and 2.84, respectively). The sensitivity analysis reported results which were consistent with those obtained for the primary analysis.

In SIDIAP:

We report findings for the incidence rate (IR per 1,000 persons) and AEs among users of DKP-TRAM during the years 2017 and 2018.
During this two-year period, there was a decreasing trend of new prescriptions of DKP-TRAM in Spain, with an overall incidence rate of 2.41 ‰ in 2017 and of 1.80 ‰ in 2018.
The IR of new prescriptions of DKP-TRAM increased with age in both years, however, the highest IR was found at younger ages in 2018 (2.36‰ for those aged 45 to 54 years old) compared to 2017 (3.39‰ between the ages of 65 to 74 years old).
The profile of those receiving a new prescription of DKP-TRAM was that of a middle age woman (mean age of 53.6 and 51.3 years old in 2017 and 2018 respectively) with a history of past smoking (5.16‰), and diagnosed of obesity (7.03‰). Regarding the comorbid conditions, DKP-TRAM were mostly prescribed to patients with a diagnosis of depression (8.22‰), dyspepsia (7.41‰) and mental disorder (6.81‰,). Among those with hepatic and renal impairment, higher IR of DKP-TRAM was reported for those with a chronic hepatic impairment (6.67‰) and those with a severe renal function (5.89‰), however, only 3 patients were included in the latter category. Prior and concurrent medications show that incident users of DKP-TRAM were also frequently prescribed with tramadol (13.72‰) as well as with other opioids (12.44‰) and carbamazepine (12.44‰).
We found that most of the prescriptions were issued by the GP (40.6%) and by the dentist. Nevertheless, information regarding the prescriber was missing in over 54% of the prescriptions.The analysis of the disorders for which DKP-TRAM was prescribed reveals that in most cases musculoskeletal disorders, namely low back pain (22.6%), peripheral enthesopathies (15.50%) and osteoarticular pain (11.62%) were the main indications.

In terms of the dosage, the analysis using the prescribed daily dose or the defined daily dose showed similar results; in both approaches, approximately 65% of the patients and 99% respectively, took less than 225/75mg per day.
The median cumulative duration of the DKP-TRAM prescription in SIDIAP was 11 days, with nearly half of the patients reporting shorter durations and nearly a third longer durations of treatment. With respects to the 5-day courses of treatment, approximately 69% of the new users of DKP-TRAM had less than 4 courses and approximately 20% more than 6 courses during the whole follow-up, the latter increased during the follow up ranging from 20.5% at 3 months to 21.9% at 12 months. Kaplan Meier curves to estimate the burden of DKP-TRAM discontinuation likely due to AEs, showed an increasing trend of discontinuation of DKP-TRAM at 5 (0.5%), 15 (0.8%) and 30 days (1.14%). Overall, 226 patients discontinued their treatment at the end of the 30 days. Most of the AEs were reported in the first 10 days (138 events) and more precisely during the first day (58 events). The likelihood of discontinuation during the follow-up show that patients were more likely to interrupt the DKP-TRAM treatment the first day of treatment and this continued to increase up to the 15th day, after which it was attenuated. The overall IR of AEs in the DKP-TRAM, tramadol or tramadol-paracetamol exposure cohorts was 1.94 cases per 10,000 persons-day. These were mostly due to vertigo (63.26%), constipation (27.44%) and

diarrhoea (7.57%). When analysing per exposure category, the highest IR of AEs was seen for those exposed to DKP TRAM followed by those exposed to tramadol-paracetamol.

In SIDIAP, after adjusting for potential confounders, patients who were prescribed DKP-TRAM showed a 30% increased risk of reporting an AE compared to those who were prescribed any of the other study drugs used as reference (tramadol or tramadol-paracetamol). This increased risk was more pronounced compared with tramadol, with 48% higher risk of AEs with DKP-TRAM compared to those who were prescribed tramadol.
When analysing the exposure by recent and current use, an increased risk of adverse events was seen with the current use of DKP-TRAM (adjusted OR equal to 1.31) compared to the current use of tramadol-paracetamol. This increased risk was more pronounced when comparing the current use of DKP-TRAM to the current use of tramadol (adjusted OR of 1.53).

When considering the effect modification likely due to of age, among those aged 75 years or younger there was an increased rate of AEs for the DKP-TRAM vs. tramadolo/tramadol paracetamol exposure. Instead, no association was found among older individuals. No interaction with frailty was detected.

The sensitivity analysis reported results which were consistent with those obtained for the primary analysis.

11.2 LIMITATIONS

These findings are featured by limitations which need to be discussed.
First, as a retrospective study, prescriptions of DKP-TRAM might be underreported because DKP-TRAM is not reimbursed by the Italian public health system. As such, the IRs of medication use might be underestimated. Nevertheless, as stated in the background, Italy is one of the countries with the highest sales for DKP-TRAM after it was launched, and the absolute numbers are solid to provide estimates with acceptable accuracy. As such, the results obtained from our analyses (i.e. indication of use and prescribed dosage and durations) might be inferred to the general populations suffering from the same clinical conditions (e.g. low back pain). Second, as we demonstrated, some differences could be found using PDD instead of DDD. For these reasons Kaplan-Meier analysis gave us further insight on the duration of DKP-TRAM use and it will be useful to compare Italian vs. Spanish data (the latter have no PDDs available). Third, the dosage instructions being available in HSD did not allow an accurate calculation of patients exposed to DKP-TRAM for less than 5 days, which was the maximum duration according to the SmPC. However, we complemented the results on median duration of use with the number of 5-day cycles, which was consistent with the fact that almost every patient was exposed to this therapy in keeping with SmPC.
Fourth, HSD has information on prescriptions not on actual drug intake. However, the risk of misclassification of exposure is likely lower because it is known that adherence to drugs is higher at initiation of therapy. Fifth, the identification of AEs related to DKP-TRAM is based on GPs registration. Given that, patients might have discontinued DKP-TRAM treatment due to AEs, without reporting it to their GPs. Nevertheless, we found most of the AEs occurred soon after the start of DKP-TRAM therapy, which is consistent with the risk profile of tramadol and other opioids [44]–[47]. Not surprisingly, many DKP-TRAM users were previously exposed to opioids,

indicating the potential presence of drug titration to assess a patient's responsiveness and tolerability to this pharmacotherapy. In this respect, we conducted several sensitivity analyses to verify the robustness of the results after completion of comparative safety study. Sixth, none of the databases gathered information or excluded patients with cancer or those who had suffered a traffic accident. These patients would have likely been prescribed opioids to control pain such as DKP-TRAM, tramadol or tramadol paracetamol and would have an increased risk of suffering the adverse events analysed, therefore confounding remains at these respects and limits the interpretation of our results.
Finally, the results stemming from the comparative safety study might be biased by the underestimation of patients exposed to DKP-TRAM because this is not reimbursed by the Italian public health system, while its comparators are reimbursed medications. Thus, there would be some uncertainty about the risk of AEs for the unmeasured use of DKP-TRAM. Nevertheless, the type of indications (i.e. low back pain) being reported for DKP-TRAM, the higher point estimates gathered with the sensitivity analyses, as well as the precision estimates being obtained for the IRs and HRs, the outcome misclassification is likely negligible. Reassuringly, the results obtained in HSD were consistent with those gathered by SIDIAP, in which DKP-TRAM is partly reimbursed. Furthermore, the significant association revealed by the observed dose and duration-response relationship with occurrence of AEs were reassuring as well. There are some limitations inherent to the SIDIAP database. First, it is possible that patients who are visited by private GPs or specialists are prescribed any of the study drugs analysed in this report. The prescriptions would not be reflected in the SIDIAP database and could underestimate the IR, however given that all these medications are reimbursed by the government it is likely that patients attend afterwards to the public GP to get their reimbursement for the prescription issued in the private sector, minimizing the effect of the underestimation. In SIDIAP we were unable to account for the prescriptions issued by the hospital specialist or at the emergency room, however, these are usually unique prescriptions and for longer treatments patients are always referred to the GP. Regarding the frailty index, in Spain we have adopted the frailty index from HSD, which is not validated in our country, and there were some deficits which were not available and could not be assessed.

11.3 INTERPRETATION

This final report concerns the pattern of drug use of DKP-TRAM as well as the safety profile of DKP-TRAM compared with tramadol or tramadol-paracetamol in primary care in Italy and Spain.
For what concerns the Italian data, the IR of DKP-TRAM use was higher in female patients and elderly patients. This finding reflected the indication of DKP-TRAM prescription as quantified in the study. Indeed, low back pain, osteoarticular pain and osteoarthritis are common disease in older patients. Furthermore, these clinical conditions are frequently associated with female gender [48]–[50].
The IRs of DKP-TRAM use did not exceed the 10‰. This finding likely reflects the appropriate prescription of DKP-TRAM by GPs and the awareness regarding risk profile of this treatment. For instance, patients affected by mild hepatic impairment showed the highest IR of DKP-TRAM use compared to the other patients with worse hepatic impairment. Indeed, DKP-TRAM should

not be used in patients with severe hepatic dysfunction, and patients with mild to moderate hepatic dysfunction should be closely monitored during the treatment. Similar results were found for patients with kidney disease.
High IRs of DKP-TRAM use was found in patients prescribed with tramadol, opioids and erythromycin. DKP-TRAM is recently launched on the market. As such, patients were likely treated with tramadol or other opioids before the entry date, so already titrated to verify drug effectiveness and tolerability before increasing the tramadol dosage up to 75 mg or more.
Although we were unable to assess the prescriber type for HSD, GPs were the main prescribers for SIDIAP. Given the most frequent type of aforementioned indications (i.e. low back pain, osteoarticular pain and osteoarthritis) of use for DKP-TRAM seen in both data sources, it is expected that the majority of drug treatments are directly filled by GPs for HSD as well.
The distribution of the PDD and DDD was described for all users of DKP-TRAM. In accordance to SmPC, around 97% and 100% of patients treated with DKP-TRAM did not exceed three tablets per day corresponding to 225 mg of tramadol and 75 mg of dexketoprofen based on PDD and DDD, respectively.
The duration of treatment with DKP-TRAM was evaluated, for the first prescription, as longer or shorter than 10 days based on both PDD and DDD, along with describing the distribution of patients based on the number of 5-day courses. Most patients prescribed with DKP-TRAM were associated with a cumulative duration of treatment equal to 10 days and with a number of "5-day" courses less than <4 at 12 months. It is worth mentioning that this duration was calculated on the bases of GPs' prescription, given that there is no data on the duration of therapy as indicated by GP. Thus, these days are likely not consecutive and we were unable to capture those durations of DKP-TRAM use < 5 days (i.e. maximum duration as indicated in the SmPC) . For this reason, this analysis was complemented with the count of 5-day courses as per SmPC. This result may therefore suggest that patients exposed with DKP-TRAM resolved their painful conditions during the first 3 months. Indeed, negligible variations in the distributions of therapy courses was found from 3 to 12 months.
Finally, the Kaplan-Meier methods showed a discontinuation due to AEs only at the beginning of therapy. The initial exposure to 75 mg of tramadol, could be a cause of AEs leading to drug discontinuation, especially for incident users.
In specific, the higher effect size (HR=2.3) revealed by the comparison with tramadol-paracetamol could be due to the difference between the dosage (37.5 vs. 75 mg) that could have been initially taken. Consistently, both dosage and duration-response relationship with the occurrence of AEs was found for current DKP-TRAM users (OR equal to 3.38 and 13.56 vs. recent users, respectively) and the effect size was reduced for less than 150 mg/day and 10 days of use (OR equal to 2.85 and 2.95 vs. recent users, respectively). Indeed, the fact that the nested case-control analysis investigated the current new or old (i.e. prevalent use) of DKP-TRAM, allowed us to raise that the tolerability of DKP-TRAM was related to be a new user even though with the same well known spectrum of AEs. However, it should also be mentioned that a residual confounding factor related to the difference between treatments could be linked to the time they have been on the market at the time of the present analysis (many years for tramadol or tramadol-paracetamol, months to 2 years for DKP-TRAM) cannot be ruled out in creating this higher IR AEs for DEX-TRAM.

These estimates do not seem to be modified by age of 75 or older. Indeed, while these patients reported higher IRs of AEs (4.44 vs. 2.63 per 10,000 person-days), the DKP-TRAM users were a slightly younger with a reduced prevalence of some comorbidities (i.e. hepatic impairment, kidney failure, dementia, cerebro/cardiovascular diseases) generally predisposing to AEs. However, a high level of frailty was an effect modified for AEs occurrence among DKP-TRAM users, so suggesting the presence of age-independent predisposing factors.

For what concerns the Spanish data, patterns of use and AEs for patients with a DKP-TRAM prescription in 2017-2018 compared to other similar painkillers such as tramadol in monotherapy or tramadol-paracetamol in combination. The IR of DKP-TRAM during the study period decreased from 2.41‰ in 2017 to 1.80‰ in 2018. This decrease could be explained by changes in the policies of the local health authority in Catalonia, the *CatSalut* [55]. In August 2017, the *CatSalut* concluded that there was no indication for a first line use of DKP-TRAM given the actual evidence and classified this medication as "medication with no added value" compared to other painkillers.
The characterization of incident users of DKP-TRAM in Spain is similar to the one found in Italy, namely middle-aged females with a prescription of DKP-TRAM indicated for musculoskeletal disorders. Musculoskeletal disorders are a leading cause of pain and disability in industrialized countries [56] and are frequently diagnosed in females [48]-[50]. Furthermore, we found higher rates of DKP-TRAM among patients with a diagnosis of obesity which is closely related to osteoarthritis [57], one of the main musculoskeletal disorders for which patients take pain killers. Our analysis of the indications for which the DKP-TRAM was prescribed goes in the same line; over 34% of the indications in our population was for low-back pain or osteoarticular pain, both very much interlinked with osteoarthritis.
Patients in SIDIAP receiving a prescription of DKP-TRAM were also more likely to be diagnosed with depression and mental disorders. There is evidence of a direct association between pain and depression; in fact, reports from 2014 in Spain, already showed that the prevalence of depression and chronic pain was high in primary care and specialised settings (up to 69%) [58] and a possible bidirectional association between depression and pain has been described recently [59].
Both, the SmPC and the specification sheet of the DKP/TRAM issued by the Spanish Agency of Medicines (AEMPS) [60] warns against the prescription of DKP/TRAM in patients with renal or liver impairment. Nonetheless, in our data we found high IR of new prescriptions in patients with these disorders and those with higher IRs were the ones with chronic hepatic impairment (6.67‰) and severe renal function (5.89‰). However, these findings contrast with previous reports from the European observatory on health systems and policies where it reflects that the pharmaceutical sector in Spain is highly regulated by the Government and focused on evidence-based prescriptions to avoid inappropriate prescribing [61].
Regarding the prior or concurrent medications, we found similar findings as those reflected in Italy with high IR in patients with previous or concurrent prescription of tramadol or other opioids. Given that DKP/TRAM initiates with 75mg of tramadol, patients would have probably already taken previous lower doses of tramadol to control pain.
According to SmPC, in Spain around between 65% and 99% (using the PDD and DDD respectively), took less than 225/75mg per day. A possible explanation for these discrepancies,

between the recommended dose and the actually prescribed dose results, could be due to the restrictions imposed by the health care authorities to the DKP-TRAM prescription [55], which could have led patients to seek this medication at the private health insurance companies and afterwards go to the Public GP to get the medication reimbursed. In this case, the GP would have not participated in the clinical assessment and therefore non-appropriate prescriptions could have been overlooked.

The cumulative median duration, evaluated for the first prescription, of the DKP-TRAM prescription in SIDIAP was of 11 days, with almost half of the patients reporting shorter durations, and with 69% of the new users having less than 4 "5-day" courses of treatment. Small variations were seen during the follow-up. Although the operational definition on duration is not enough sensible to reflect the actual duration as prescribed by GPs, in Spain it was possible to capture the exposure to DKP/TRAM for < 5 days which results in 8%. This was possible because, differently to Italy in which only tablet-based prescriptions were available, different formulations, such as tablets (i.e. 20 pills) and granulates (up to 10 sachets) are largely available in Spain.

Reasons for treatment cessation during the first 3 months cannot be fully assessed with this data but could encompass a range of possibilities starting from decrease of the pain to the lack of effectiveness of the medication prescribed. Another possibility is the occurrence of an AE and regarding this, the estimated burden of DKP-TRAM discontinuation due to AEs in this study showed an increasing trend of discontinuation up to the end of the first month (1.14%) which was more pronounced in the first 15 days. This could partly explain the aforementioned results on the dosage and duration. Approximately 39% of the incident DKP-TRAM users in Spain had cumulative treatment durations longer than 11 days and 20% had >6 courses of "5-day" treatment during the 3, 6 and 13 months of follow-up.

The overall IR (per 10,000 persons-day) of AEs in the DKP-TRAM, tramadol or tramadol-paracetamol exposure cohorts in SIDIAP was lower than the one found in Italy (5.03 vs. 2.06 for DKP-TRAM, 3.76 vs. 1.69 for tramadol and 2.44 vs. 1.94 for tramadol-paracetamol respectively). First the higher IR of AE in DKP-TRAM compared to the other tramadol formulations is likely explained by the lower starting dose of tramadol used with the other treatments. Second, differences in the IR of AE with Italy are probably due to the voluntary notification of the adverse event reporting in Spain (conversely to Italy where this is mandatory) [62].

The analysis per exposure category showed a higher IR of AEs for patients exposed to DKP TRAM compared to tramadol or tramadol/paracetamol. This was confirmed by the adjusted HRs where a 30% increased risk of AEs was seen among incident users of DKP-TRAM compared to tramadol or tramadol-paracetamol users. When analysing the exposure by recent and current use, an increased risk of adverse events was seen with the current use of DKP-TRAM (adjusted OR of 1.31) compared to the current use of tramadol-paracetamol. However, this increased risk was of borderline significance. This increased risk was more pronounced when comparing the current use of DKP-TRAM to the current use of tramadol (adjusted OR equal to 1.53). The fact that we found an effect modification due to age in patient younger than 75 years and no effect modification due to frailty might be still explained by changes in the policies of the local health authority in Catalonia, the *CatSalut* [55], which led physicians to be more careful with elderly and more frail subjects.

DKP-TRAM/vo3

Propensity score matching and the multiple imputation for BMI and smoking further confirmed this increased risk of current use of DKP-TRAM compared to current tramadol and current tramadol-paracetamol users. A large randomized controlled trial [63] (the DAVID study) carried out in 5 European countries (including Spain) aiming to assess the analgesic efficacy and safety of DKP-TRAM compared to tramadol paracetamol was published in 2018. The safety assessment found a higher proportion of AEs in patients allocated to the tramadol-paracetamol group compared to those in the DKP-TRAM group. Differences with our results could be due to differences in the population and the starting dosage of TRAM-paracetamol which in the DAVID study was taken as recommended by SmPC. Randomized controlled trials have stringent selection criteria, in contrast with our population which is based on real-world data and routinely collected medical information.
The AEs more frequently reported in SIDIAP were, vertigo, constipation and diarrhoea which were also the most frequently reported AEs in Italy and represent well-known AEs for this products.
Conversely, the current dosage (>=2 pills (150 mg)/day) of DKP-TRAM and the current shorter duration of treatment (<11 days) were also associated with an increased OR of AEs compared with the recent user. This higher risk found with shorter exposure could respond to the tolerance effect that occurs to longer exposure of opioids and that could translate into lower AEs.

12. CONCLUSION

In this retrospective study, the population-based IR of DKP-TRAM use in HSD increased, ranging from 2.81‰ (n= 2,941) to 3.44‰ (n= 3,485) in 2017 and 2018, respectively while in SIDIAP it decreased from 2.41 ‰(n=11,390) to 1.80‰ (n=8,522). In both countries, females and older patients showed higher IRs of DKP-TRAM use. In both countries, the prescription of DKP-TRAM in most of the patients was lower than the maximum daily dose. The evaluation of cumulative treatment duration and the number of 5-day courses suggested that patients were exposed to more than one course and they usually resolved pain conditions during the first 3 months. Analysing the burden of discontinuation, the highest rate of discontinuation likely due to AEs was found in the first days of treatment with DKP-TRAM. The risk of early AEs resulted higher in DKP-TRAM users than those treated with tramadol or tramadol-paracetamol combination. Furthermore, a dose and duration-response relationship were found. Namely, the higher risk for those exposed to DKP-TRAM for less than 10 or 11 days, confirmed the acuteness of the AEs. In contrast, those with prior use of opioids (i.e. prevalent users likely undergone to tramadol titration), showed a reduced risk of AEs. These associations were not modified by aged 75 years or older, but some effected modification due to the highest level of frailty has to be considered.

13. 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 [43], the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [53], 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' [54].

14. 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.

15. 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.

16. REFERENCES

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

[2] 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.

[3] 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.

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

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

[6] 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.

[7] 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.

[8] 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.

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

[10] 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.

[11] 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.

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

[13] 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.

[14] 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.

[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] E. M. Heintjes *et al.*, "Factors Associated with Type 2 Diabetes Mellitus Treatment Choice Across Four European Countries," *Clin. Ther.*, vol. 39, no. 11, pp. 2296-2310 e14, 2017.

[21] J. A. Overbeek *et al.*, "Type 2 Diabetes Mellitus Treatment Patterns Across Europe: A Population-based Multi-database Study," *Clin. Ther.*, vol. 39, no. 4, pp. 759–770, 2017.

[22] V. E. Valkhoff *et al.*, "Validation study in four health-care databases: Upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk," *J. Clin. Epidemiol.*, 2014.

[23] J. Bezin *et al.*, "The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology," *Pharmacoepidemiol. Drug Saf.*, vol. 26, no. 8, pp. 954–962, Aug. 2017.

[24] 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.

[25] A. Clegg, J. Young, S. Iliffe, M. O. Rikkert, and K. Rockwood, "Frailty in elderly people," *Lancet*, vol. 381, no. 9868, pp. 752–762, Mar. 2013.

[26] A. Clegg *et al.*, "Development and validation of an electronic frailty index using routine primary care electronic health record data," *Age Ageing*, vol. 45, no. 3, pp. 353–360, May 2016.

[27] 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.

[28] 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.

[29] A. Filippi, D. Vanuzzo, A. A. Bignamini, G. Mazzaglia, C. Cricelli, and A. L. Catapano, "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, 2005.

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

[31] 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.

[32] V. Guglielmi *et al.*, "Drug interactions in users of tablet vs. oral liquid levothyroxine formulations: a real-world evidence study in primary care," *Endocrine*, vol. 59, no. 3, pp. 585–592, 2018.

[33] P. M. Coloma *et al.*, "Drug-induced acute myocardial infarction: identifying 'prime suspects' from electronic healthcare records-based surveillance system," *PLoS One*, vol. 8, no. 8, p. e72148, 2013.

[34] F. Lapi *et al.*, "Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care," *Bone*, vol. 50, no. 1, pp. 85–90, 2012.

[35] C. Sterrantino *et al.*, "Burden of community-acquired pneumonia in Italian general practice," *European Respiratory Journal*, vol. 42, no. 6. pp. 1739–1742, 2013.

[36] A. Filippi, D. Vanuzzo, A. A. Bignamini, E. Sessa, O. Brignoli, and G. Mazzaglia, "Computerized general practice databases provide quick and cost-effective information on the prevalence of angina pectoris.," *Ital. Heart J.*, vol. 6, no. 1, pp. 49–51, 2005.

[37] 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.

[38] A. Pacurariu *et al.*, "Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation.," *BMJ Open*, vol. 8, no. 9, p. e023090, Sep. 2018.

[39] 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.

[40] 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.

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

[42] 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.

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

[44] M. L. G. Pascual, R. R. B. Fleming, T. J. Gana, and G. J. Vorsanger, "Open-label study of the safety and effectiveness of long-term therapy with extended-release tramadol in the management of chronic nonmalignant pain.," *Curr. Med. Res. Opin.*, vol. 23, no. 10, pp. 2531–42, Oct. 2007.

[45] G. Mongin *et al.*, "Efficacy and Safety Assessment of a Novel Once-Daily Tablet

Formulation of Tramadol : A Randomised, Controlled Study versus Twice-Daily Tramadol in Patients with Osteoarthritis of the Knee.," *Clin. Drug Investig.*, vol. 24, no. 9, pp. 545–58, 2004.

[46] H. Malonne *et al.*, "Long-term tolerability of tramadol LP, a new once-daily formulation, in patients with osteoarthritis or low back pain.," *J. Clin. Pharm. Ther.*, vol. 30, no. 2, pp. 113–20, Apr. 2005.

[47] 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," *Current Medical Research and Opinion*, vol. 26, no. 1. pp. 239–251, Jan-2010.

[48] J. I. Park and H. H. Jung, "Estimation of years lived with disability due to noncommunicable diseases and injuries using a population-representative survey.," *PLoS One*, vol. 12, no. 2, p. e0172001, Feb. 2017.

[49] Y. X. J. Wáng, J.-Q. Wáng, and Z. Káplár, "Increased low back pain prevalence in females than in males after menopause age: evidences based on synthetic literature review.," *Quant. Imaging Med. Surg.*, vol. 6, no. 2, pp. 199–206, Apr. 2016.

[50] A. Bailey, "Risk factors for low back pain in women: still more questions to be answered.," *Menopause*, vol. 16, no. 1, pp. 3–4, Jan. 2009.

[51] M. Marcucci *et al.*, "Interventions to prevent, delay or reverse frailty in older people: A journey towards clinical guidelines," *BMC Med.*, vol. 17, no. 1, p. 193, Oct. 2019.

[52] C. J. Huang *et al.*, "Effect Modification by Age on the Benefit or Harm of Antihypertensive Treatment for Elderly Hypertensives: A Systematic Review and Meta-analysis," *Am. J. Hypertens.*, vol. 32, no. 2, pp. 163–174, Jan. 2019.

[53] 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.

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

[55] Programa d'Harmonització Farmacoterapèutica. Tramadol/dexketoprofèn per al tractament del dolor agut de moderat a intens. Barcelona: Servei Català de la Salut; 2019. http://hdl.handle.net/11351/3405.2

[56] Malik KM, Beckerly R, Imani F. Musculoskeletal Disorders a Universal Source of Pain and Disability Misunderstood and Mismanaged: A Critical Analysis Based on the U.S. Model of Care. Anesth Pain Med. 2018 Dec 15;8(6):e85532. doi: 10.5812/aapm.85532. PMID: 30775292; PMCID: PMC6348332.

[57] Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population-Based Cohort Study. Arthritis Rheumatol. 2016 Aug;68(8):1869-75. doi: 10.1002/art.39707.

[58] Giner J, Saiz Ruiz J, Bobes J, Zamorano E, López F, Hernando T, Rico-Villademoros F, Álamo C, Cervilla JA, Ibáñez Cuadrado Á, Ibáñez Guerra E, López S, Morán P, Palao DJ, Romacho

M; Development Group Recommendations on Physical Health in Patients with Depression. Spanish consensus on the physical health of patients with depressive disorders. Rev Psiquiatr Salud Ment. 2014 Oct-Dec;7(4):195-207. English, Spanish. doi: 10.1016/j.rpsm.2014.05.003. Epub 2014 Jul 30. PMID: 25087131.

[59] Bondesson E, Larrosa Pardo F, Stigmar K, Ringqvist Å, Petersson IF, Jöud A, Schelin MEC. Comorbidity between pain and mental illness - Evidence of a bidirectional relationship. Eur J Pain. 2018 Aug;22(7):1304-1311. doi: 10.1002/ejp.1218. Epub 2018 Apr 16. PMID: 29577509.

[60] https://cima.aemps.es/cima/dochtml/p/84869/P_84869.html

[61] Bernal-Delgado E, García-Armesto S, Oliva J, Sánchez Martínez FI, Repullo JR, Peña-Longobardo LM, Ridao-López M, Hernández-Quevedo C. Spain: Health system review. Health Systems in Transition, 2018;20(2):1–179.

[62] https://sinasp.es/

[63] Gay-Escoda C, Hanna M, Montero A, Dietrich T, Milleri S, Giergiel E, Zoltán TB, Varrassi G. Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomised, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study). BMJ Open. 2019 Feb 19;9(2):e023715. doi: 10.1136/bmjopen-2018-023715. Erratum in: BMJ Open. 2019 Jun 14;9(6):e023715corr1. PMID: 30782886; PMCID: PMC6377526.

ANNEX 1. CODES FOR VARIABLES

1- List of ICD9CM/ICD-10 codes defining comorbidities.

Comorbidities	ICD9CM	ICD-10CM
Hepatic impairment	570*, 573.3*, 794.8*, 572.2*	K72.00, K72.01, K72.0, K71*, K72.91, K75.9, R94.5, K73*, K74*
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	E10.21, E10.22,E10.29, E11.21, E11.22, E11.29, I12, I12.0, I12.9, I13, I13.0, I13.10, I13.11, I13.2, I70.1, I72.2, I82.3, M10.30, N00, N00.3, N00.8, N00.9, N01.3, N02.2, N03, N03.2, N03.3, N03.5, N03.8, N03.9, N04, N04.0, N04.3, N04.4, N04.8, N04.9, N05, N05.2, N05.5, N05.8, N05.9, N08, N13.4, N13.5, N13.7, N13.70, N13.721, N13.722, N13.729, N13.8, N17, N17.0, N17.1, N17.2, N17.8, N17.9, N18, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N19, N25, N25.0, N25.1, N25.8, N25.81, N25.89, N25.9, N26.9, N27, N27.0, N27.1, N27.9, N28, N28.0, N28.1, N28.81, N28.83, N28.89, N28.9, Q60.2, Q63.8, R80.2, R80.9, S37.0, S37.009A, S37.019A, S37.029A, S37.039A, S37.069A
Depression	296.2, 296.3, 311*,	F32, F32.0-5, F32.89, F32.9, F33*
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*)	J40, J41*, J42, J43*, J44*, J45.2, J45.20, J45.21, J45.22,J45.30, J45.31, J45.32, J45.40, J45.41, J45.42, J45.50, J45.51, J45.52, J45.9, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998, J45.902, J45.909, J47.0, J47.1, J47.9, J67, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9
Epilepsy	345*	G40.001, G40.009, G40.101, G40.109, G40.201, G40.209, G40.211, G40.301, G40.309, G40.319, G40.401, G40.409, G40.509, G40.801, G40.802, G40.811, G40.812, G40.822, G40.89, G40.9, G40.901, G40.909, G40.911, G40.919, G40.A01, G40.A09, G40.A19, G40.B09, G40.B11, G40.B19
Chronic dyspepsia	536.8	K30, K31.89, K31.83, K31.2

Alcohol abuse and/or alcohol-related diseases	303*, 305.0, 357.5, 425.5, 535.3, 571.0-3, 790.3, V11.3,	F10.1, F10.10, F10.11, F10.120, F10.121, F10.129, F10.14, F10.180, F10.181, F10.188, F10.19, F10.2, F10.20, F10.21, F10.229, F10.230, F10.231, F10.232, F10.239, F10.24, F10.250, F10.251, F10.259, F10.280, F10.282, F10.288, F10.29, G62.1, I42.6, K29.20, K29.21, K70.0, K70.10, K70.11, K70.2, K70.30, K70.31, K70.40, K70.9, R78.0,Y90.9, Z87.898
Drug abuse or dependence	304* 305.2- 305.9.	F11.10, F11.121, F11.129, F11.19, F11.20, F11.21, F11.23, F11.282, F11.29, F11.90, F11.959, F11.988, F11.99, F12, F12.1, F12.10, F12.120, F12.129, F12.150, F12.159, F12.180, F12.188, F12.19, F12.20, F12.21, F12.220, F12.222, F12.229, F12.23, F12.250, F12.259, F12.280, F12.288, F12.29, F12.90, F12.922, F12.929, F12.93, F12.951, F12.959, F12.980, F12.988, F12.99, F13.10, F13.120, F13.129, F13.180, F13.181, F13.188, F13.19, F13.2, F13.20, F13.229, F13.230, F13.231, F13.239, F13.24, F13.280, F13.282, F13.29, F13.90, F13.920, F13.929, F13.930, F13.939, F13.959, F13.96, F13.988, F13.99, F14.10, F14.120, F14.122, F14.129, F14.14, F14.180, F14.188, F14.19, F14.20, F14.21, F14.229, F14.23, F14.24, F14.250, F14.280, F14.29, F14.90, F14.920, F14.929, F14.94, F14.959, F14.980, F14.988, F14.99, F15.10, F15.11, F15.122, F15.129, F15.150, F15.180, F15.19, F15.20, F15.21, F15.221, F15.222, F15.23, F15.288, F15.29, F15.90, F15.920, F15.922, F15.929, F15.93, F15.94, F15.950, F15.980, F15.988, F15.99, F16.159, F16.20, F16.288, F16.29, F16.929, F16.950, F16.959, F16.988, F18.10, F18.188, F18.19, F18.20, F18.921, F18.988, F18.99, F19.10, F19.120, F19.121, F19.122, F19.129, F19.180, F19.20, F19.231, F19.239, F19.24, F19.251, F19.280, F19.29, F19.90, F19.920, F19.929, F19.959, F19.96, F19.98, F19.980, F19.988, F19.99

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	F05, F06, F06.0, F06.1, F06.2, F06.30, F06.4, F06.8, F20, F20.0, F20.1, F20.2, F20.5, F20.81, F20.89, F20.9, F21, F22, F23, F24, F25.9, F28, F29, F30, F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F31, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.9,, F40, F40.01, F40.02, F40.10, F40.241, F40.9, F41, F41.0, F41.1, F41.8, F41.9, F42, F44.0, F44.1, F44.81, F44.89, F44.9, F45, F45.0, F45.1, F45.21, F45.8, F48, F48.1, F48.8, F48.9, F60, F60.0, F60.1, F60.2, F60.3, F60.4, F60.5, F60.6, F60.7, F60.81, F60.89, F60.9, F68, F68.11, F68.12, F68.8, F84, F84.0, F84.3, F84.8, F84.9, Z86.59
Hallucinations	368.16; 780.1	H53.16,R44.0, R44.1, R44.2, R44.3, R44.8, R44.9
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	A81.0, F01, F01.5, F01.50, F01.51, F02, F02.80, F02.81, F03, F03.90, F03.91, F04, F05, F07.0, F10.27, F19.96, F19.97, G20, G30, G30.0, G30.1, G30.8, G30.9, G31.01, G31.09, G31.1, G31.2, G31.83, G31.84, G31.85, G31.89, G31.9, G94,
Cognitive Impairment after trauma	907.0	S06.9X9S

Cerebro/cardiovascular disease	410*-414*, 428*, 402.91, 404.91, 402.01, 402.11, 404.01, 430-2*, 433.01, 433.11, 434.01, 434.11, 436*, 438*, V45.81	I11.0, I13.0, I20, I20.0, I20.1, I20.8, I20.9, I21, I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.0, I24.1, I24.8, I24.9, I25, I25.1, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.3, I25.41, I25.42, I25.5, I25.6, I25.718, I25.760, I25.761, I25.811, I25.82, I25.83, I25.84, I25.89, I25.9, I50, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.812, I50.813, I50.814, I50.82, I50.84, I50.9, I60.9, I61.9, I62, I62.00, I62.1, I62.9, I63.22, I63.239, I63.30, I63.40, I67.89, I69.9, I69.90, I69.91, I69.920, I69.921, I69.922, I69.923, I69.928, I69.939, I69.949, I69.959, I69.965, I69.969, I69.990, I69.991, I69.992, I69.993, I69.998, Z95.1
Gastrointestinal haemorrhages	531.00, 531.10, 532.00, 533.00, 535.01, 535.41, 535.51, 535.61, 578.0, 578.1, 578.9	K25.0, K25.1,K25.2, K26.0, K26.1, K26.2, K27.0, K27.1, K27.2, K29.01, K29.61, K29.71, K29.81, K29.91, K92.0, K92.1, K92.2

2. List of ATC codes defining co-medications.

Co-medications	Anatomical Therapeutic Chemical (ATC)
Tramadol	N02AX02
NSAIDs (nonsteroidal anti-inflammatory drugs)	M01A*
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

3. List of ICD9CM/ ICD10CM coding adverse events.

Terms	ICD9CM	ICD-10CM
Nausea, vomiting	563.2 ; 787.0*	R11, R11.0, R11.10*, R11.11, R.11.12, R.11.13, R11.14, R11.2
Diarrhoea	787.91	R19.7, K52.29, K52.89
Constipation	564.0	K59.0, K59.00, K59.01, K59.02, K59.03, K59.04, K59.09
Hallucinations	368.16; 780.1/00	H53.16 ,R44.0, R44.1, R44.2, R44.3, R44.8, R44.9, R48.3x, R48.1x
Vertigo	780.4	R42, R26.81, R26.89

Somnolence	780.09	R40.0, R40.0XX0, R40.0XX1, R40.0XX2, R40.0XX3, R40.0XX4, x, R40.1, R40.1XX0, R40.1XX1, R40.1XX2, R40.1XX3, R40.1XX4x y R40.4, R40.4XX0, R40.4XX1, R40.4XX2, R40.4XX3, R40.4XX4x

4-Frailty deficit index adaptation for SIDIAP

Deficit Name	ATC codes used	Exemption codes used	ICD-9 HSD	HSD coding for procedures	ICD-10CM SIDIAP
Cognitive decline or dementia	N06DA, N06DX01	M011, M029, M049, C02	780.83, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 294.1, 294.11, 294.20, 294.21, 331.11, 331.19, 331.2, 331.0, 331.6, 331.7, 331.81, 331.82, 331.83, 331.89, 331.9, 330.0, 330.1, 330.2, 330.3, 330.8, 330.9, 797		E7502, E7523, F0150, F0151, F02 F0280, F0281, F03, F0390, F0391, F05, G30, G300, G301, G308, G309, G31, G310, G3101, G3109, G311, G312, G318, G3181, G3182, G3183, G3184, G3185, G3189, G319, G937, G9389, G939, G94, R4181
High level of disability		CO2, A08			Z933, Z7401, Z7408, Z7409, Z749
Cerebrovascular diseases			443.21, 430, 431, 432.0, 432.1, 432.9, 433.00, 433.01, 433.10, 433.11, 433.20, 433.21, 433.30, 433.31, 433.8, 433.81, 433.9, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436., 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438, 438.10, 438.11, 438.12, 438.13, 438.14, 438.19, 438.20, 438.21, 438.22, 438.30, 438.31, 438.32, 438.4, 438.41, 438.42, 438.5, 438.51, 438.52, 438.53, 438.6, 438.7, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9		G450, G451, G452, I639, I630, I6300, I6301, I63011, I63012, I63013, I63019, I6302, I6303, I63031, I63032, I63033, I63039, I631, I6310, I6311, I6311, I63112, I63113, I63119, I6312, I6313, I63131, I63132, I63133, I63139, I6319, I632, I6320, I6321, I63211, I63212, I63213, I63219, I633, I630, I6331, I63311, I63312, I63313, I63319, I6332, I63321, I63322, I63323, I63329, I634, I6340, I6341, I63411, I63412, I63413, I63419, I6342, I63421, I63422, I63423, I63429, I6343, I63431, I63432, I63433, I63439, I6344, I63441, I63442, I63443, I63449, I635, I6350, I6351, I63511, I63512, I63513, I63519, I6352, I63521, I63522, I63523, I63529, I6353, I63531, I63532, I63533, I63539, I6354, I63541, I63542, I63543, I63549, I6359, I636, I638, I6381, I6389, I639, G454, G458, G459, I60, I600, I6000, I6001, I6002, I601, I6010, I6011, I6012, I602, I603, I6030, I6031, I6032, I604, I605, I6050, I6051, I6052, I606, I607, I608, I609, I61, I610, I611, I612, I613, I614, I615,

					I616, I618, I619, I620, I6200, I6201, I6202, I6203, I621, I629, I65, I650, I6501, I6502, I6503, I6509, I651, I652, I6521, I6522, I6523, I6529, I658, I659, I66, I660, I6601, I6602, I6603, I6609, I661, I6611, I6612, I6613, I6619, I662, I6621, I6622, I6623, I6629, I663, I668, I669, I671, I672, I674, I675, I676, I677, I678, I6781, I6782, I6789, I679, I690,, I6900, I69010, I69011, I69012, I69013, I69014, I69015, I69018, I69019, I6902, I69020, I69021, I69022, I69023, I69028, I6903, I69031, I69032, I69033, I69034, I69039, I6904, I69041, I69042, I69043, I69044, I69049, I6905, I69051, I69052, I69053, I69054, I69059, I6906, I69061, I69062, I69063, I69064, I69065, I69069, I6909, I69090, I69091, I69092, I69093, I69098, I691, I6910, I6911, I69110, I69111, I69112, I69113, I69114, I69115, I69119, I6912, I69120, I69121, I69122, I69123, I69128, 16913, 169131, 169132, 169133, 169139, 169134, I6914, I69141, I69142, I69143, I69144, I69149, I6915, I69151, I69152, I69153, I69154, I69159, I6916, I69161, I69162, I69163, I69164, I69165, I69169, I6919, I69190, I69191, I69192, I69193, I69198, I692, I6920, I6921, I69210, I69211, I69212, I69213, I69214, I69215, I69218, I69219, I6922, I69220, I69221, I69222, I69223, I69228, I6923, I69231, I69232, I69233, I69234, I69239, I6924, I69241, I69242, I69243, I69244, I69249, I6925, I69251, I69252, I69253, I69254, I69259, I6926, I69261, I69262, I69263, I69265, I69269, I6929, I69290, I69291, I69292, I69293, I69298, I693, I6930, I6931, I69310, I69311, I69312, I69313, I69315, I69319, I6932, I69320, I69321, I69322, I69323, I69328, I6933, I69331, I69332, I69333, I69334, I69339, I6934, I69341, I69342, I69343, I69344, I69349, I6935, I69351, I69352, I69353, I69354, I69359, I6936, I69361, I69362, I69363, I69364, I69365, I69369, I6939, I69390, I69391, I69392, I69393, I69398, I698, I6980, I6981, I69810, I69811, I69812, I69813, I69818, I69819, I69814, I69815, I6982, I69820, I69821, I69822, I69823, I69828, I6983, I69831, I69832, I69833, I69834, I69839, I6984, I69841, I69842, I69843, I69844, I69849, I6985,I69851, I69852, I69853, I69854, I69859, I6986, I69861, I69862, I69863, I69864, I69865, I69869, I6989, I69890, I69891, I69892, I69893, I69898, I699, I6990, I6991, I69910, I69911, I69912, I69913, I69914, I69915, I69919, I6986, I69861, I69862, I69863, I69864, I69865, I69869, I6980, I69801, I69802, I69803, I69808, I6991, I69910, I69911, I69912,

					I69913, I69914, I69915, I69918, I69919, I6992, I69920, I69921, I69922, I69923, I69928, I6993, I69930, I69931, I69932, I69933, I69934, I69939, I6994, I69941,I69942, I69943, I69944, I69949, I6995, I69951, I69952, I69953, I69954, I69959, I6996, I69961, I69962, I69963, I69964, I69965, I69969, I6999, I69990, I69991, I69992, I69993, I69999, I7771
Solid neoplasms		M048	140.0, 140.1, 140.3, 140.4, 140.5, 140.6, 140.8, 140.9, 141.0, 141.1, 141.2, 141.3, 141.4, 141.5, 141.6, 141.8, 141.9, 142.0, 142.1, 142.2, 142.8, 142.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0, 145.1, 145.2, 145.3, 145.4, 145.5, 145.6, 145.8, 145.9, 146, 146.1, 146.2, 146.3, 146.4, 146.5, 146.6, 146.7, 146.8, 146.9, 147.0, 147.1, 147.2, 147.3, 147.8, 147.9, 148, 148.1, 148.2, 148.3, 148.8, 148.9, 149, 149.1, 149.8, 149.9, 150, 150.1, 150.2, 150.3, 150.4, 150.5, 150.8, 150.9, 151, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9, 152, 152.1, 152.2, 152.3, 152.8, 152.9, 153, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154, 154.1, 154.2, 154.3, 154.8, 155, 155.1, 155.2, 156, 156.1, 156.2, 156.8, 156.9, 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9, 158, 158.8, 158.9, 159, 159.1, 159.8, 159.9, 160, 160.1, 160.2, 160.3, 160.4, 160.5, 160.8, 160.9, 161, 161.1, 161.2, 161.3, 161.8, 161.9, 162, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 163, 163.1, 163.8, 163.9, 164, 164.1, 164.2, 164.3, 164.8, 164.9, 165, 165.8, 165.9, 170, 170.1, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 170.8, 170.9, 171.0, 171.2, 171.3, 171.4, 171.5, 171.6, 171.7, 171.8, 171.9, 172, 172.1, 172.2, 172.3, 172.4, 172.5, 172.6, 172.7, 172.8, 172.9, 173, 173.01, 173.02, 173.09, 173.1, 173.11, 173.12,	1783, 1883, 1930, 1986, 5245, 5246, MW00_1783, MW00_1883, MW00_1930, MW00_1986, 6428, 5152, 5153, LA92.24.4_2, CM11790, CM30620, CM30881, CM30882, CM30883, CM30884, CM30885, CM30940, CM31000, CM31010, CP38.99.1, CP38.99.2, CP92.31.1, CP92.40.2, CP92.24.4, CP92.24.A, CP92.24.B, CP92.31.4, CP92.40.1, CT1981, CT1982, CT1983, CT1984, CT2176, CT2358, CT2360, CT2361, IU49451, IU41349, IU41350, IU49440, IU49457, CV92.24.7_2, CV92.29.L_0, CV92.29.K_0, CV92.24.8_0, LS707038992, LS70019229M, LS707092247, LS707092248, LS70709229H, LS70709229J, PU39121, PU39141, PU54431, VD92.24.4_1, VD38.99.1_1, VD38.99.2_1, VD89.04_1, VD92.24.B_1, VD92.31.1_1, VD92.31.4_1, VD92.40.2_1, NB1001456, NB1000168, NB1000169, ILC01724600,	C00, C000, C001, C002, C003, C004, C005, C006, C008, C009, C01, C02, C020, C021, C022, C023, C024, C028, C029, C03, C030, C031, C039, C04, C040, C041, C048, C049, C05, C050, C051, C052, C058,C059, C06, C060, C061, C062, C068, C0680, C0689, C069, C07, C08, C080, C081, C089, C09, C090, C091,C098, C099, C10, C100, C101, C102, C103, C108,, C109, C11, C110, C111, C112, C113, C118, C119, C12, C13, C130, C131, C132, C138, C139, C14,C140, C142, C148, C15, C153, C154, C155, C158, C159, C16, C160, C161, C162, C163, C164, C165, C166, C168, C169, C17, C170, C171, C172, C173, C178, C179, C18, C180, C181, C182, C183,C184, C185, C186, C187, C188, C189, C19, C20, C21, C210, C211, C212, C218, C23, C24, C240, C241, C248, C249, C25, C250, C251, C252, C253, C254, C258, C259, C26, C260, C261, C269, C300, C301, C310, C311, C312, C313, C318, C319, C320, C321, C322, C323, C328, C329, C33, C34, C3400, C3401, C3402, C3410, C3411, C3412, C342, C3430, C3431, C3432, C3480, C3481, C349, C3490, C3491, C3492, C37, C380, C381, C382, C383, C384, C388, C390, C399, C4000, C4010, C4012, C4020, C4021, C4030, C4032, C4080, C4090, C4092, C410, C411, C412, C413, C414, C419, C43, C430, C4310, C4320, C4330, C4339, C434, C4359, C4360, C4370, C4372, C438, C439, C44, C4400, C4401, C4402, C4409, C44101, C441022, C44111, C44119, C441192, C44122, C44129, C441291, C44131, C441321, C44191, C44192, C441992, C44201, C44202, C44209, C44211, C44212, C44219, C44221, C44229, C44292, C44300, C44301, C44309, C44310, C44311, C44319, C44320, C44321, C44329, C44390, C44391, C44399, C4440, C4441, C4442, C4449, C44501, C44509, C44510, C44511, C44519, C44520, C44521, C44529, C44599, C44601, C44602, C44609, C44611, C44612, C44619, C44621, C44622, C44629, C44691, C44701, C44709, C44711, C44712, C44719, C44721, C44722, C44729, C44791, C44792, C44799, C4480, C4481, C4482, C4489, C449, C4490, C4491, C4492, C4499, C450, C451, C452, C457, C459, C460, C461, C462, C463, C4652, C467, C469, C470, C4710, C4720, C473, C474,

			173.19, 173.20, 173.21, 173.22, 173.29, 173.30, 173.31, 173.32, 173.39, 173.40, 173.41, 173.42, 173.49, 173.50, 173.51, 173.52, 173.59, 173.60, 173.61, 173.62, 173.69, 173.70, 173.71, 173.72, 173.79, 173.80, 173.81, 173.82, 173.89, 173.9, 173.91, 173.92, 173.99, 174, 174.1, 174.2, 174.3, 174.4, 174.5, 174.6, 174.8, 174.9, 175, 175.9, 176, 176.1, 176.2, 176.3, 176.4, 176.5, 176.8, 176.9, 179, 180, 180.1, 180.8, 180.9, 181., 182.0, 182.1, 182.8, 183, 183.2, 183.3, 183.4, 183.5, 183.8, 183.9, 184, 184.1, 184.2, 184.3, 184.4, 184.8, 184.9, 185, 186, 186.9, 187.1, 187.2, 187.3, 187.4, 187.5, 187.6, 187.7, 187.8, 187.9, 188, 188.1, 188.2, 188.3, 188.4, 188.5, 188.6, 188.7, 188.8, 188.9, 189, 189.1, 189.2, 189.3, 189.4, 189.8, 189.9, 190, 190.1, 190.2, 190.3, 190.4, 190.5, 190.6, 190.7, 190.8, 190.9, 191, 191.1, 191.2, 191.3, 191.4, 191.5, 191.6, 191.7, 191.8, 191.9, 192.0, 192.1, 192.2, 192.3, 192.8, 192.9, 193, 194,	ILC01614300, NS92244, NS38991, NS92401, NS92402, NSPACC409, FV562, FV567, FV729, FV730, FV731, FV732, FV800, IA0001119, IA0001120, IA0001627	C475, C478, C479, C48, C480, C481, C482, C488, C49, C490, C4910, C4911, C4912, C4920, C4921, C4922, C493, C494, C495, C496, C498, C499, C49A0, C49A1, C49A2, C49A3, C49A4, C49A5, C49A9, C4A39, C4A4, C4A52, C4A59, C4A62, C4A71, C4A9, C50, C50011, C50012, C50019, C50111, C50112, C50119, C50121, C50211, C50212, C50219, C50311, C50312, C50319, C50321, C50411, C50412, C50419, C50511, C50512, C50519, C50522, C50611, C50612, C50619, C50811, C50812, C50819, C509, C50911, C50912, C50919, C50921, C50922, C50929, C510, C511, C512, C518, C519, C52, C53, C530, C531, C538, C539, C540, C541, C542, C543, C548, C549, C55, C56, C561, C562, C569, C5700, C5701, C574, C577, C578, C579, C58, C600, C601, C602, C608, C609, C61, C6200, C6201, C6202, C6210, C6211, C6212, C629, C6290, C6291, C6292, C6300, C6302, C6310, C6311, C632, C637, C638, C639, C64, C641, C642, C649, C651, C652, C659, C66, C661, C662, C669, C67, C670, C671, C672, C673, C674, C675, C676, C677, C678, C679, C680, C681, C688, C689, C6900, C6910, C6920, C6921, C6922, C6930, C6931, C6950, C6951, C6960, C6980, C6981, C6990, C6991, C6992, C700, C701, C709, C71, C710, C711, C712, C713, C714, C715, C716, C717, C718, C719, C720, C721, C7221, C7230, C7240, C7241, C7250, C729, C73, C7400, C7401, C7402, C7410, C7412, C7490, C7492, C750, C751, C752, C753, C754, C755, C758, C759, C760, C761, C762, C763, C7640, C7650, C7652, C768, C770, C771, C772, C773, C774, C775, C778, C779, C7800, C7801, C7802, C781, C782, C7830, C784, C785, C786, C787, C7880, C7889, C79, C7900, C7901, C7902, C7910, C7911, C792, C793, C7931, C7932, C7940, C7949, C7951, C7952, C7960, C7970, C7971, C7972, C798, C7981, C7982, C7989, C799, C80, C800, C801, C8100, C8102, C8105, C8110, C8111, C8112, C8113, C8114, C8116, C8118, C8119, C8120, C8121, C8122, C8124, C8128, C8129, C8130, C8131, C8132, C8133, C8135, C8138, C8141, C8142, C8170, C8171, C8172, C8174, C8178, C8179, C819, C8190, C8191, C8192, C8193, C8195, C8197, C8198, C8199, C8200, C8201, C8202, C8203, C8204, C8208, C8209, C8210, C8213, C8215, C8216, C8218, C8220, C8223, C8224, C8227, C8230, C8233, C8234, C8235, C8237, C8239, C8240, C8250, C8251, C8253, C8256, C8257, C8260, C8261, C8265, C8266, C8267, C8269, C8280, C8281, C8285, C8288, C8290, C8291, C8292, C8293, C8295, C8296, C8297, C8298, C8299, C83, C8300, C8302, C8304, C8305, C8308, C8309, C8310, C8311, C8313, C8315, C8317, C8318, C8319, C8330, C8331, C8332, C8333, C8334, C8335, C8336, C8337, C8338, C8339, C8350,

					C8353, C8358, C8370, C8371, C8372, C8373, C8380, C8381, C8385, C8386, C8388, C8389, C839, C8390, C8391, C8392, C8393, C8396, C8398, C8399, C840, C8400, C8401, C8404, C8405, C8408, C8409, C8410, C8440, C8441, C8443, C8446, C8447, C8448, C8449, C8460, C8461, C8462, C8463, C8466, C8468, C8469, C8470, C8471, C8473, C8474, C8475, C8478, C8490, C8491, C8499, C84A0, C84A1, C84A2, C84A3, C84A4, C84A5, C84A7, C84A8, C84Z0, C84Z7, C85, C8510, C8511, C8512, C8513, C8515, C8517, C8518, C8519, C8520, C8521, C8525, C858, C8580, C8581, C8582, C8583, C8584, C8585, C8586, C8587, C8588, C8589, C859, C8590, C8591, C8593, C8594, C8595, C8596, C8597, C8598, C8599, C862, C863, C864, C866, C88, C880, C882, C883, C884, C888, C889

			194.1, 194.3, 194.4, 194.5, 194.6, 194.8, 194.9, 195, 195.1, 195.2, 195.3, 195.4, 195.5, 195.8, 196, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197, 197.1, 197.2, 197.3, 197.4, 197.5, 197.6, 197.7, 197.8, 198, 198.1, 198.2, 198.3, 198.4, 198.5, 198.6, 198.7, 198.81, 198.82, 198.89, 199, 199.1, 199.2		
COPD, emphysema and chronic bronchitis	R03BB	M057, M024	491.0, 491.1, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494.0, 494.1, 496		J41, J410, J411, J418, J42, J43, J430, J431, J432, J438, J439,J44, J440, J441, J449, J47, J470, J471, J479
Ischemic heart disease	C01DA, C01EB18		V45.81, V45.82, 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.3, 410.31, 410.32, 410.4, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411, 411.1, 411.81, 411.89, 412, 413, 413.1, 413.9, 414, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9		I20, I200, I201, I208, I209, I21, I2101, I2102, I2109, I2111, I2119, I2121, I2129, I213, I214, I219, I21A, I21A1, I21A9, I24, I240, I241, I248, I249, I25, I2510, I2511, I25110, I25111, I25118, I25119, I252, I253, I254, I2541, I2542, I255, I256, I257, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25/18, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25739, I2575, I25750, I25751, I25758, I25759, I2576, I25760, I25761, I25768, I25769, I2579, I25790,

					I25791, I25798, I25799, I258, I2581, I25810, I25811, I25812, I2582, I2583, I2584, I2589, I259
Heart failure		M021	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 429.5, 429.6, 429.71, V42.1, V53.32, 428.21, 428.23, 428.31, 428.33, 428.41, 428.43, 416.2, 416.9, 425.11, 425.18, 425.5, 425.7, 425.8, 425.9, 428, 428.1, 428.20, 428.22, 428.3, 428.32, 428.4, 428.42, 428.9	3551, 3552, 3761, 4020, 4244, 4251, MW00_3551, MW00_4020, MW00_4244, 4476	I110, I130, I132, I2781, I2782, I421, I422, I426, I427, I43, I43,I50, I501, I502, I5020, I5021, I5022, I5023, I503, I5030, I5031, I5032, I5033, I504, I5040, I5041, I5042, I5043, I508, I5081, I50810, I50811, I50812, I50813, I50814, I5082, I5083, I5084, I5089, I509, I510, I511, I512, Z4502, Z941
Chronic kidney disease		M023, M061, M062	403.91, 404.92, 404.93, 753.0, V45.73, V42.0, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 587., 588.0, 588.1, 588.81, 588.89, 588.9, 589.0, 589.1, 589.9, 753.10, 753.11, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19	1401, 1402, 1403, 1404, 1405, 1410, 1413, 1414, 3733, MW00_1402, MW00_1403, MW00_1404, MW00_1405, MW00_1410, MW00_3733, 1412, LA39.95.3_3, LA39.95.1_2, LA39.95.1_3, LA39.95.2_2, LA39.95.2_3, LA39.95.4_2, LA39.95.4_3, LA39.95.9_2, LA39.95.9_3, LA54.98.1_2, LA54.98.1_3, LA54.98.2_2, LA54.98.2_3, LA89.03_2, LA90.30.4_5, LA90.30.4_6, LA97.29.1_2, LA97.29.1_3, LAGSX5[, LAGSX5{, CM17071, CM500575, CM500590, CM500825, CM500996, CM501195, CM501300, CM501410, CM501445, CM503730, MW00_1401, CLJ8901*G, CP3995A.0, CP54.98.3, CP54.98.4, CP8903.07, CP8907.4, CP93.01.C, CP93.01.D, 6388, 6389, 6395, MW00_6388, MW00_6389, CT1626, CT1709, CT1494, CT1495, CT2175,	I120, I129, I130, I131, I1310, I1311, I132, N030, N031, N032, N033, N034, N035, N036, N037, N038, N039, N08, N18, N181, N182, N183, N184, N185, N186, N189, N25, N250, N251, N258, N2581, N2589, N259, N261,N269, N270, N271, N279, Q600, Q601, Q602, Q6101, Q6119, Q612, Q613, Q614, Q615, Q618, Q619, Z905, Z940

				CV39.95.3_0, CV39.95.1_0, CV39.95.2_0, CV39.95.4_0, CV39.95.9_0, CV54.98.1_0, CV54.98.2_0, CV90.30.4_5, CV90.30.4_6, CV97.29.1_2, CV97.29.1_3, CV54.93_0, MW00_5788, MW00_5789, 5970, 5789, 5788, MW00_5970, LS292989031, PU39226, PU39341, 1416, PU49012, PU42102, PU55351, PU55361, 6114, VD54.98.1_1, VD54.98.2_1, VD29050, VD38.95_1, VD39.95.3_1, VD39.95.4_1, VD39.95.9_1, VD54.98.1_2, VD88.49.1_1, VD89.03_29, NB1000166, NB1000235, NB1000236, NB1000173, NB1000174, NB1000179, NB1001838, NB1002192, NB1002721, NB1003745, ILC00497400,	

				ILC00497500, ILC00496800, ILC00496900, ILC00496700, ILC00988600, ILC00994700, ILC00996600, ILC00996700, NS3895, NS54981, NS54982, NS39953, NS39959, NS39954, NS39955, FV1871, FV1879, FV26067, FV26068, FV26069, FV26070, FV26071, FV26072, FV26074, FV26138,	

				FV26139, FV26143, FV26145, FV26146, FV26147, FV26148, FV26149, FV26150, FV26151, FV26156, FV26157, FV26158, FV339, FV353, FV467, FV468, FV5030, FV8416, , IA2004273, IA2004275, IA0001797, IA0001117, IA2004274, IA0001124, IA0001129, IA0001130, IA0001131, IA0001184, IA0001186, IA0001187, IA2004272, IA2004279	
Atrial fibrillation			427.31, 427.32		I480, I481, I482, I4891, I4892
Parkinson and parkinsonism	N04BA, N04BC, N04BX	M038	332.0, 332.1, 333.0, 333.1		G20, G211, G2111, G2119, G238, G239, G252
Previous hip fracture			820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19, 820.20, 820.21, 820.22, 820.30, 820.31, 820.32, 820.8, 820.9, E820.00, E820.01, E820.02, E820.03, E820.04, E820.05, E820.06, E820.07, E820.08, E820.09, 821, 821.01, 821.10, 821.11, 821.2, 821.21, 821.22, 821.23, 821.29, 821.3, 821.31, 821.32, 821.33, 821.39, E821.10, E821.11, E821.12, E821.13, E821.14, E821.15, E821.16, E821.17, E821.18, E821.19		S720, S7200, S72001, S72001A, S72001B, S72001C, S72001D, S72001E, S72001F, S72001G, S72001H, S72001J, S72001K, S72001M, S72001N, S72001P, S72001Q, S72001R, S72001S, S72002, S72002A, S72002B, S72002C, S72002D, S72002E, S72002F, S72002G, S72002H, S72002J, S72002K, S72002M, S72002N, S72002P, S72002Q, S72002R, S72002S, S72009, S72009A, S72009B, S72009C, S72009D, S72009E, S72009F, S72009G, S72009H, S72009J, S72009K, S72009M, S72009N, S72009P, S72009Q, S72009R, S72009S, S7201, S72011, S72011A, S72011B, S72011C, S72011D, S72011E, S72011F, S72011G, S72011H, S72011J, S72011K, S72011M, S72011N, S72011P, S72011Q, S72011R, S72011S, S72012, S72012A, S72012B, S72012C, S72012D, S72012E, S72012F, S72012G, S72012H, S72012J, S72012K, S72012M, S72012N, S72012P, S72012Q, S72012R, S72012S, S72019, S72019A, S72019B, S72019C, S72019D, S72019E, S72019F, S72019G, S72019H, S72019I, S72019J, S72019K, S72019M,

					S72019N, S72019P, S72019Q, S72019R, S72019S, S7202, S72021, S72021A, S72021B, S72021C, S72021D, S72021E, S72021F, S72021G, S72021H, S72021J, S72021K, S72021M, S72021N, S72021P, S72021Q, S72021R, S72021S, S72022, S72022A, S72022B, S72022C, S72022D, S72022E, S72022F, S72022G, S72022H, S72022J, S72022K, S72022M, S72022N, S72022P, S72022Q, S72022R, S72022S, S72023, S72023A, S72023B, S72023C, S72023F, S72023G, S72023H, S72023J, S72023K, S72023M, S72023N, S72023P, S72023Q, S72023R, S72023S, S72024, S72024A, S72024B, S72024C, S72024D, S72024E, S72024F, S72024G, S72024H, S72024J, S72024K, S72024M, S72024N, S72024P, S72024Q, S72024R, S72024S, S72025, S72025A, S72025B, S72025C, S72025D, S72025E, S72025F, S72025G, S72025H, S72025J, S72025K, S72025M, S72025N, S72025P, S72025Q, S72025R, S72025S, S72026, S72026A, S72026B, S72026C, S72026D, S72026E, S72026F, S72026G, S72026H, S72026J, S72026K, S72026M, S72026N, S72026P, S72026Q, S72026R, S72026S, S7203, S7203, S72031, S72031A, S72031B, S72031C, S72031D, S72031E, S72031F, S72031G, S72031H, S72031J, S72031K, S72031M, S72031N, S72031P, S72031Q, S72031R, S72031S, S72032, S72032A, S72032B, S72032C, S72032D, S72032E, S72032F, S72032G, S72032H, S72032J, S72032K, S72032M, S72032N, S72032P, S72032Q, S72032R, S72032S, S72033, S72033A, S72033B, S72033C, S72033D, S72033E, S72033F, S72033G, S72033H, S72033J, S72033K, S72033M, S72033N, S72033P, S72033Q, S72033R, S72033S, S72034, S72034A, S72034B, S72034C, S72034D, S72034E, S72034F, S72034G, S72034H, S72034J, S72034K, S72034M, S72034N, S72034P, S72034Q, S72034R, S72034S, S72035, S72035A, S72035B, S72035C, S72035D, S72035E, S72035F, S72035G, S72035J, S72035K, S72035H, S72035M, S72035N, S72035P, S72035Q, S72035R, S72035S, S72036, S72036A, S72036B, S72036C, S72036D, S72036E, S72036F, S72036G, S72036H, S72036J, S72036K, S72036M, S72036N, S72036P, S72036Q, S72036R, S72036S, S7204, S72041, S72041A, S72041B, S72041C, S72041D, S72041E, S72041F, S72041G, S72041H, S72041J, S72041K, S72041M, S72041N, S72041P, S72041Q, S72041R, S72042, S72042A, S72042B, S72042C, S72042D, S72042E, S72042F, S72042G, S72042H, S72042J, S72042K,

					S72042M, S72042N, S72042P, S72042Q, S72042R, S72042S, S72043, S72043A, S72043B, S72043C, S72043D, S72043E, S72043F, S72043G, S72043H, S72043J, S72043K, S72043M, S72043N, S72043P, S72043Q, S72043R, S72043S, S72044, S72044A, S72044B, S72044C, S72044D, S72044E, S72044F, S72044G, S72044H, S72044J, S72044K, S72044M, S72044N, S72044P, S72044Q, S72044R, S72044S, S72045, S72045A, S72045B, S72045C, S72045D, S72045E, S72045F, S72045G, S72045H, S72045J, S72045K, S72045M, S72045N, S72045P, S72045Q, S72045R, S72045S, S72046, S72046A, S72046B, S72046C, S72046D, S72046E, S72046F, S72046G, S72046H, S72046J, S72046K, S72046M, S72046N, S72046P, S72046Q, S72046R, S72046S, S7205, S72051, S72051A, S72051B, S72051C, S72051D, S72051E, S72051F, S72051G, S72051H, S72051J, S72051K, S72051M, S72051N, S72051P, S72051Q, S72051R, S72051S, S72052, S72052A, S72052B, S72052C, S72052D, S72052E, S72052F, S72052G, S72052H, S72052J, S72052K, S72052M, S72052N, S72052P, S72052Q, S72052R, S72052S, S72059, S72059A, S72059B, S72059C, S72059D, S72059E, S72059F, S72059G, S72059H, S72059J, S72059K, S72059M, S72059N, S72059P, S72059Q, S72059R, S72059S, S7206, S72061, S72061A, S72061B, S72061C, S72061D, S72061E, S72061F, S72061G, S72061H, S72061J, S72061K, S72061M, S72061N, S72061P, S72061Q, S72061R, S72061S, S72062, S72062A, S72062B, S72062C, S72062D, S72062E, S72062F, S72062G, S72062H, S72062J, S72062K, S72062M, S72062N, S72062P, S72062Q, S72062R, S72062S, S72063, S72063A, S72063B, S72063C, S72063D, S72063E, S72063F, S72063G, S72063H, S72063J, S72063K, S72063M, S72063N, S72063P, S72063Q, S72063R, S72063S, S72064, S72064A, S72064B, S72064C, S72064D, S72064E, S72064F, S72064G, S72064H, S72064J, S72064K, S72064M, S72064N, S72064P, S72064Q, S72064R, S72064S, S72065, S72065A, S72065B, S72065C, S72065D, S72065E, S72065F, S72065G, S72065H, S72065J, S72065K, S72065M, S72065N, S72065P, S72065Q, S72065R, S72065S, S72066, S72066A, S72066B, S72066C, S72066D, S72066E, S72066F, S72066G, S72066H, S72066J, S72066K, S72066M, S72066N, S72066P, S72066Q, S72066R, S72066S, S7209, S72091, S72091A, S72091B, S72091C, S72091D, S72091E, S72091F, S72091G, S72091H, S72091J,

					S72091K, S72091M, S72091N, S72091P, S72091Q, S72091R, S72091S, S72092, S72092A, S72092B, S72092C, S72092D, S72092E, S72092F, S72092G, S72092H, S72092J, S72092K, S72092M, S72092N, S72092P, S72092Q, S72092R, S72092S, S72099, S72099A, S72099B, S72099C, S72099D, S72099E, S72099F, S72099G, S72099H, S72099J, S72099K, S72099M, S72099N, S72099P, S72099Q, S72099R, S72099S, S721, S72101, S72101A, S72101B, S72101C, S72101D, S72101E, S72101F, S72101G, S72101H, S72101J, S72101K, S72101M, S72101N, S72101P, S72101Q, S72101R, S72101S, S72102, S72102A, S72102B, S72102C, S72102D, S72102E, S72102F, S72102G, S72102H, S72102J, S72102K, S72102M, S72102N, S72102P, S72102Q, S72102R, S72102S, S72109, S72109A, S72109B, S72109C, S72109D, S72109E, S72109F, S72109G, S72109H, S72109J, S72109K, S72109M, S72109N, S72109P, S72109Q, S72109R, S72109S, S7214, S72141, S72141A, S72141B, S72141C, S72141D, S72141E, S72141F, S72141G, S72141H, S72141J, S72141K, S72141M, S72141N, S72141P, S72141Q, S72141R, S72141S, S72142, S72142A, S72142B, S72142C, S72142D, S72142E, S72142F, S72142G, S72142H, S72142J, S72142K, S72142M, S72142N, S72142P, S72142Q, S72142R, S72142S, S72143, S72143A, S72143B, S72143C, S72143D, S72143E, S72143F, S72143G, S72143H, S72143J, S72143K, S72143M, S72143N, S72143P, S72143Q, S72143R, S72143S, S72144, S72144A, S72144B, S72144C, S72144D, S72144E, S72144F, S72144G, S72144H, S72144J, S72144K, S72144M, S72144N, S72144P, S72144Q, S72144R, S72144S, S72145, S72145A, S72145B, S72145C, S72145D, S72145E, S72145F, S72145G, S72145H, S72145J, S72145K, S72145M, S72145N, S72145P, S72145Q, S72145R, S72145S, S72146, S72146A, S72146B, S72146C, S72146D, S72146E, S72146F, S72146G, S72146H, S72146J, S72146K, S72146M, S72146N, S72146P, S72146Q, S72146R, S72146S, S722, S7221, S7221A, S7221B, S7221C, S7221D, S7221E, S7221F, S7221G, S7221H, S7221J, S7221K, S7221M, S7221N, S7221P, S7221Q, S7221R, S7221S, S7222, S7222A, S7222B, S7222C, S7222D, S7222E, S7222F, S7222G, S7222H, S7222J, S7222K, S7222M, S7222N, S7222P, S7222Q, S7222R, S7222S, S7223, S7223A, S7223B, S7223C, S7223D, S7223E, S7223F, S7223G, S7223H, S7223J, S7223K, S7223M,

					S7223N, S7223P, S7223Q, S7223R, S7223S, S7224, S7224A, S7224B, S7224C, S7224D, S7224E, S7224F, S7224G, S7224H, S7224J, S7224K, S7224M, S7224N, S7224P, S7224Q, S7224R, S7224S, S7225, S7225A, S7225B, S7225C, S7225D, S7225E, S7225F, S7225G, S7225H, S7225J, S7225K, S7225M, S7225N, S7225P, S7225Q, S7225R, S7225S, S7226, S7226A, S7226B, S7226C, S7226D, S7226E, S7226F, S7226G, S7226H, S7226J, S7226K, S7226M, S7226N, S7226P, S7226Q, S7226R, S7226S, S7290XB
Anaemia	B03A, B03XA	M003	284.01, 284.09, 284.81, 284.89, 280.0, 280.1, 280.8, 280.9, 281.0, 281.1, 281.2, 281.3, 281.4, 281.8, 281.9, 282, 282.1, 282.2, 282.3, 282.40, 282.41, 282.42, 282.43, 282.44, 282.45, 282.46, 282.47, 282.49, 282.5, 282.60, 282.61, 282.62, 282.63, 282.64, 282.68, 282.69, 282.7, 282.8, 282.9, 283, 283.1, 283.11, 283.19, 283.2, 283.9, 285.0, 285.1, 285.21, 285.22, 285.29, 285.3, 285.8, 285.9		D500, D501, D508, D509, D510, D513, D520, D521, D528, D529, D530, D531, D532, D538, D539, D551, D558, D559, D560, D561, D562, D563, D565, D568, D569, D570, D5700, D5701, D5702,D571, D5720, D5721, D57211, D57212, D57219, D573, D574, D5740, D5741, D57411, D57412, D57419, D578, D5780, D5781, D57811, D57812, D57819, D58, D580, D581, D582, D589, D588, D59, D590, D591, D592, D593, D594, D596, D599, D60, D600, D601, D609, D608, D610, D6101, D6109, D6189, D62, D630, D631, D638, D640, D641, D642, D643, D644, D6481, D6489, D649
Partial or total economic support to medical expenses		RE01, RE02, RE03, RE04, RE1, RE2, RE3, RE4, RE14, RE35, RED, REI			no code for SIDIAP
Oxygen prescription in the last 6 months	V03AN01				Z9981 (last 6 months)

Any hospital overnig ht staying in the last 6 months				5631, 4295, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052,	no code for SIDIAP

				2053, 3331, CV99.99.46_0, CV57830_0, CV99.99.53_0, CV99.99.44_0, CV99.99.43_0, CV99.99.50_0, CV99.99.52_0, CV99.99.45_0, CV99.99.51_0, LS29293995A, LS9901MAC09, PU54356, NSPACC317, 1511	
Chronic ulcers of the skin			454.0, 454.2, 707.00, 707.01, 707.02, 707.03, 707.04, 707.05, 707.06, 707.07, 707.09, 707.1, 707.11, 707.12, 707.13, 707.14, 707.15, 707.19, 707.20, 707.21, 707.22, 707.23, 707.24, 707.25, 707.8, 707.9		I830, I8300, I83001, I83002, I83003, I83004, I83005, I83008, I83009, I8301, I83011, I83012, I83013, I83014, I83015, I83018, , I83019, I8302, I83021, I83022, I83023, I83024, I83025, I83028, I83029, I832, I8320, I83201, I83202, I83203, I83204, I83205, I83208, I83209, I8321, I83211, I83212, I83213, I83214, I83215, I83218, I83219, I8322, I83221, I83222, I83223, I83224, I83225, I83228, I83229, L89, L890, L8900, L89000, L890001, L890002, L890003, L890004, L890009, L891, L8910, L89100, L89101, L89102, L89103, L89104, L89105, L89106, L89107, L89108, L89109, L8911, L89110, L89111, L89112, L89113, L89114, L89115, L89116, L89117, L89118, L89119, L8912, L89120, L89121,L89122, L89123,L89124, L89125, L89126, L89127, L89128, L89129, L8913, L89130, L89131, L89132, L89133, L89134, L89135, L89136, L89137, L89138, L89139, L8914, L89140, L89141, L89142,L89143, L89144,L89145, L89146, L89147, L89148, L89149, L8915, L89150,L89151, L89152, L89153, L89154, L89155, L89156,

					L89157, L89158, L89159, L892, L8920, L89200, L89201, L89202, L89203, L89204, L89205, L89206, L89207, L89208, L89209, L8921, L89210, L89211, L89212, L89213, L89214, L89215, L89216, L89217, L89218, L89219, L8922, L89220, L89221, L89222, L89223,L89224, L89225, L89226, L89227, L89228, L89229, L893, L8930, L89300,L89301, L89302, L89303, L89304, L89305,L89306, L89307, L89308, L89309, L8931, L89310,L89311, L89312, L89313, L89314, L89315, L89316, L89317, L89318, L89319, L8932, L89320,L89321, L89322,L89323, L89324,L89325, L89326, L89327, L89328, L89329, L894, L8940, L8941, L8942, L8943, L8944, L8945, L895, L8950, L89500, L89501, L89502, L89503, L89504, L89505, L89506, L89507, L89508, L89509, L89510, L89511, L89512, L89513, L89514, L89515,L89516, L89517, L89518, L89519, L89520, L89521, L89522,L89523, L89524,L89525, L89526, L89527, L89528, L89529, L89600, L89601, L89602, L89603,L89604, L89605,L89606, L89607, L89608, L89609, L89610, L89611, L89612, L89613, L89614, L89615, L89616, L89617, L89618, L89619, L89620, L89621, L89622, L89623, L89624, L89625, L89626, L89627, L89628, L89629, L898, L8981, L89810, L89811, L89812, L89813, L89814, L89815, L89816, L89817, L89818, L89819, L8989, L89890,L89891, L89892, L89893, L89894, L89895, L89896,L89897,L89898, L89899, L899, L8990, L8991, L8992, L8993, L8994, L8995 L97, L971, L9710, L97101, L97101, L97102, L97103, L97104, L97105, L97106, L97107, L97108, L97109, L9711, L97111, L97112, L97113, L97114, L97115, L97116, L97117, L97118, L97119, L9712, L97121, L97122, L97123, L97124, L97125, L97126, L97127, L97128, L97129, L972, L9720, L97201, L97202, L97203, L97204, L97205, L97206, L97207, L97208, L97209, L9721, L97211, L97212, L97213, L97214, L97215, L97216, L97217, L97218, L97219, L9722, L97221, L97222, L97223, L97224, L97225, L97226, L97227, L97228, L97229, L973, L9730, L97301, L97301, L97302, L97303, L97304, L97305, L97306, L97307, L97308, L97309, L9731, L97311, L97312, L97313, L97314, L97315, L97316, L97317, L97318, L97319, L9732, L97321, L97322, L97323, L97324, L97325, L97326,

					L97327, L97328, L97329, L974, L9740, L97401, L97402, L97403, L97404, L97405, L97406, L97407, L97408, L97409, L9741, L97411, L97412, L97413, L97414, L97415, L97416, L97417, L97418, L97419, L9742, L97421, L97422, L97423, L97424, L97425, L97426, L97427, L97428, L97429, L975, L9750, L97501, L97502, L97503, L97504, L97505, L97506, L97507, L97508, L97509, L9751, L97511, L97512, L97513, L97514, L97515, L97516, L97517, L97518, L97519, L9752, L97521, L97522, L97523, L97524, L97525, L97526, L97527, L97528, L97529, L978, L9780, L97801, L97802, L97803, L97804, L97805, L97806, L97807, L97808, L97809, L97811, L97812, L97813, L97814, L97815, L97816, L97817, L97818, L97819, L9782, L97821, L97822, L97823, L97824, L97825, L97826, L97827, L97828, L97829, L979, L9790, L97901, L97902, L97903, L97904, L97905, L97906, L97907, L97908, L97909, L9791, L97911, L97912, L97913, L97914, L97915, L97916, L97917, L97918, L97919, L9792, L97921, L97922, L97923, L97924, L97925, L97926, L97927, L97928, L97929, L984, L9841, L98411, L98412, L98413, L98414, L98415, L98416, L98417, L98418, L98419, L9842, L98421, L98422, L98423, L98424, L98425, L98426, L98427, L98428, L98429, L9849, L98491, L98492, L98493, L98494, L98495, L98496, L98497, L98498, L98499
Bradycardias and rhythm conduction disorders			427.81, V45.01, 746.86, 426.0, 426.10, 426.11, 426.12, 426.13, 426.2, 426.3, 426.4, 426.5, 426.51, 426.52, 426.53, 426.54, 426.6, 426.7, 426.81, 426.82, 426.89, 426.9	38, 3111, MW00_38, LA89.48.1_2, CT1509, CT1511, CV89.50.2_0, NB1000632, ILC00481700, NS89481, NSPACC117, NSPACC118, NSPACC551, NSPACC552, FV26124, FV26125, FV26126, FV4620, , IA0002364	I44, I440, I441, I442, I443, I4430, I4439, I444, I445, I446, I4460,I4469, I447, I45, I450, I451, I4510, I4519, I452, I453, I454, I455, I456, I458, I4581, I4589, I459, I495, Q246, Z950

Other neurological diseases		M017	333.89, 333.90, 333.94, 137.1, 238.1, 344.1, 326., 333.4, 334.0, 334.1, 334.2, 334.3, 334.4, 334.8, 334.9, 335, 335.1, 335.11, 335.19, 335.20, 335.21, 335.22, 335.23, 335.24, 335.29, 335.8, 335.9, 333.71, 333.72, 333.79, 333.6, 352.0, 352.1, 352.2, 352.3, 352.4, 352.5, 352.6, 352.9, 358, 358.01, 358.1, 358.2, 358.30, 358.31, 358.39, 358.8, 358.9, 359.0, 359.1, 359.21, 359.22, 359.23, 359.24, 359.29, 359.3, 359.4, 359.5, 359.6, 359.71, 359.79, 359.81, 359.89, 359.9, 331.4, 331.5, 331.3, 348.81, 348.82, 348.89, 336.9, 349, 349.1, 349.2, 349.31, 349.39, 349.81, 349.82, 349.89, 349.9, 740, 740.1, 740.2, 742.1, 742.3, 742.4, 741, 741.01, 741.02, 741.03, 741.9, 741.91, 741.92, 741.93, 742.51, 742.53, 742.59, 742.8, 781.2, 781.3		B900, D481, G09, G10, G110, G111, G112, G113, G114, G118, G119, G12, G120, G121, G122,G1220, G1221, G1222, G1223,G1224, G1225, G1229, G128, G129, G240, G2401, G2402, G2409, G241, G248, G249, G2581, G259, G328, G3281, G3289,G520, G521, G522, G523, G527, G528, G529, G70, G700, G7000, G7001, G701,G702, G708, G7080, G7081, G7089, G709, G710, G7100, G7101, G7102, G7109, G711, G7111, G7112, G7113, G7114, G7119, G712, G720, G721, G722, G723, G724, G7241, G7249, G728, G7281, G7289, G729, G731, G733, G737, G803, G822, G8221, G8222,G8220, G910, G911, G912, G92, G9381, G9382, G9389, G959, G96, G960, G9611, G9619, G968, G969, G9741, G9782, Q00, Q001, Q002, Q02, Q038, Q048, Q05, Q05, Q050, Q051, Q052, Q055, Q056, Q057, Q062, Q064, Q068, Q078, R2689, R279
Constipation	A06A		564.00, 564.01, 564.02, 564.09, 564.1, 564.2, 564.3, 564.4, 564.5, 564.6, 564.7, 564.81, 564.89, 564.9		K589, K5900, K5901, K5902, K5909, K591, K592, K593, K594, K598, K599, K910, K911, K9189
Prescription of low molecular weight heparin in the last 6 months	B01AB				drug_exposure, drug_source_value LIKE 'B01AB%' AND drug_exposure_start_date <= index.date AND drug_exposure_start_date >= index.date - index.months6
Peripheral vascular diseases	B01AC23	M036	440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.30, 440.31, 440.32, 440.4, 443.21, 443.22, 443.23, 443.24, 443.29, 443.9		I7020, I70201-9, I7022, I70221-9, I7023, I70231-9, I7024, I70241-9, I7025, I7026, I70261-9, I7029, I70291-9, I7039, I70391-9, I7049, I70491-9, I7059, I70591-9,I7092, I739, I7771, I7772, I7773, I7774, I7779
Nutritional problems			783.0, 783.3, 783.7, 783.9, 787.20, 787.21, 787.22, 787.23, 787.24, 787.29, 262., 263, 263.1, 263.2, 263.8, 263.9, 783.21, 783.22	CT2448, IU49721, 5986, 5949, VD97.01.1_1, VD97.01.1_2, NB1003142, NB1003144, NB1003145, FV2891	E43, E441, E45, E46, E46, E46, R1310, R1311, R1312, R1313, R1314, R1319, R627, R630, R633, R634, R636, R638
Diabetes	A10	M013	251.3, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62,		E10, E1010, E1011, E1021, E1022, E1029, E10311, E10319, E103292, E103293, E103392, E103393, E103399, E103493, E103513, E103533, E103553, E103559, E10359, E103593, E1036, E1037X9, E1039, E1040, E1042, E1049, E105,

			250.63, 250.70, 250.71, 250.72, 250.73, 250.8, 250.81		E1051, E1052, E1059, E10610, E10618, E10621, E10622, E10628, E10641, E10649, E1065, E1069, E108, E109, E11, E1100, E1101, E1110, E1111, E112, E1121, E1122, E1129, E113, E11311, E11319, E11329, E113292, E113293, E113312, E113393, E113513, E113519, E113553, E1136, E1139, E1140, E1141, E1142, E1143, E1144, E1149, E115, E1151, E1152, E1159, E11610, E11618, E11620, E11621, E11622, E11628, E11630, E11638, E11641, E11649, E1165, E1169, E118, E119, E1300, E1310, E1311, E1321, E1329, E13311, E13319, E133311, E133411, E133551, E133553, E1339, E1340, E1341, E1342, E1349, E1351, E1352, E1359, E13610, E13618, E13621, E13641, E1365, E1369, E138, E139, E891
Schizophrenia and other delusional diseases		M044	295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.6, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85,		F20, F200, F201, F202, F203, F205, F208, F2081, F2089, F209, F22, F24, F25, F250, F251, F259, F258, F29

			295.9, 295.91, 295.92, 295.93, 295.94, 295.95, 297, 297.1, 297.2, 297.3, 298.9		
Oedema			782.3		R60, R600, R601, R609

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	Comorbidity definition
Annex 4	v03	12 February 2020	Results tables and figures

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:

EUPAS24858

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? (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:				

	12.1.1 Selection bias? 12.1.2 Information bias? 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 9.7.3, 9.9 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:

ANNEX 3. ADDITIONAL INFORMATION

Annex 3.1 Co-morbidity definition

Hepatic impairment

In HSD the hepatic impairment will be assessed through the child pugh classification. All codes (ICD9CM) 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, 7-9c)
- **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*

In SIDIAP the hepatic impairment will be assessed through ICD-10C-M codes solely following this classification

Terms	ICD10CM
Hepatic impairment overall	K71.0, K71.10, K71.2, K71.3, K71.50, K71.51, K71.6, K71.7, K71.8, K71.9, K72.00, K72.01, K72.0, K72.91, K75.9, R94.5, K73.0, K73.1, K73.2, K73.8, K73.9, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69, K71.4
Chronic hepatic impariment	K71.3,K71.4, K71.50, K71.51, K73.0, K73.1, K73.2, K73.8, K73.9
Cirrhosis	K71.7, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69

Kidney disease

All codes (ICD9CM or ICD10CM) 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

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

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

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

ANNEX 4 - RESULTS TABLES AND FIGURES

Figure 1.1 Kaplan-Maier curve – Adverse Events (AEs) at 5th day in HSD

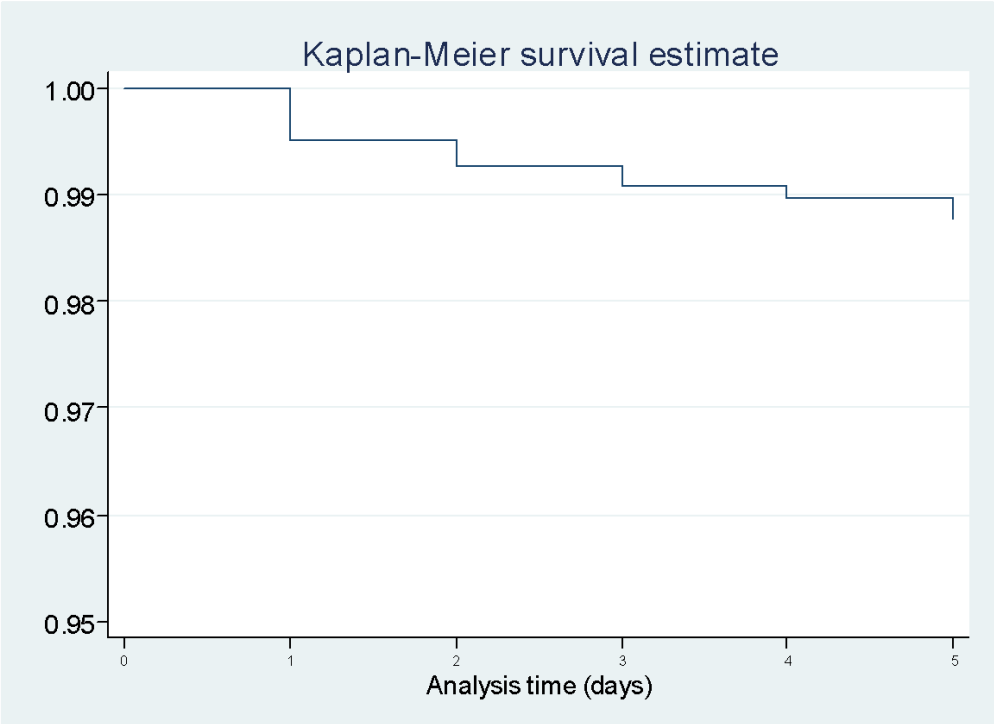


Figure 1.2 Kaplan-Maier curve – Adverse Events (AEs) at 15th day in HSD

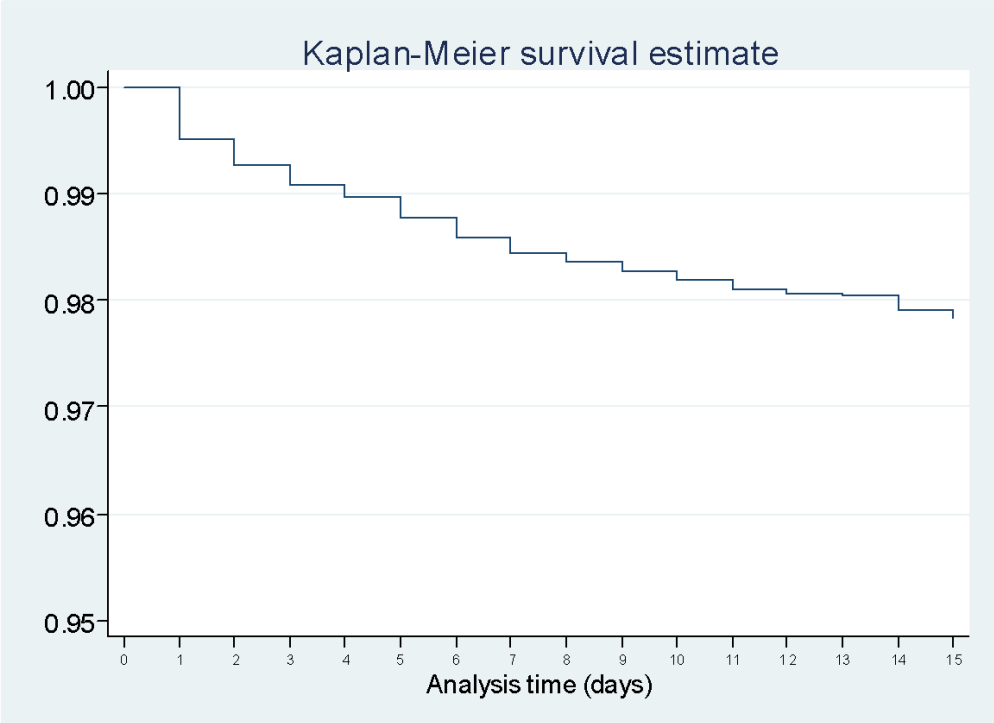


Figure 1.3 Kaplan-Maier curve – Adverse Events (AEs) at 30th day

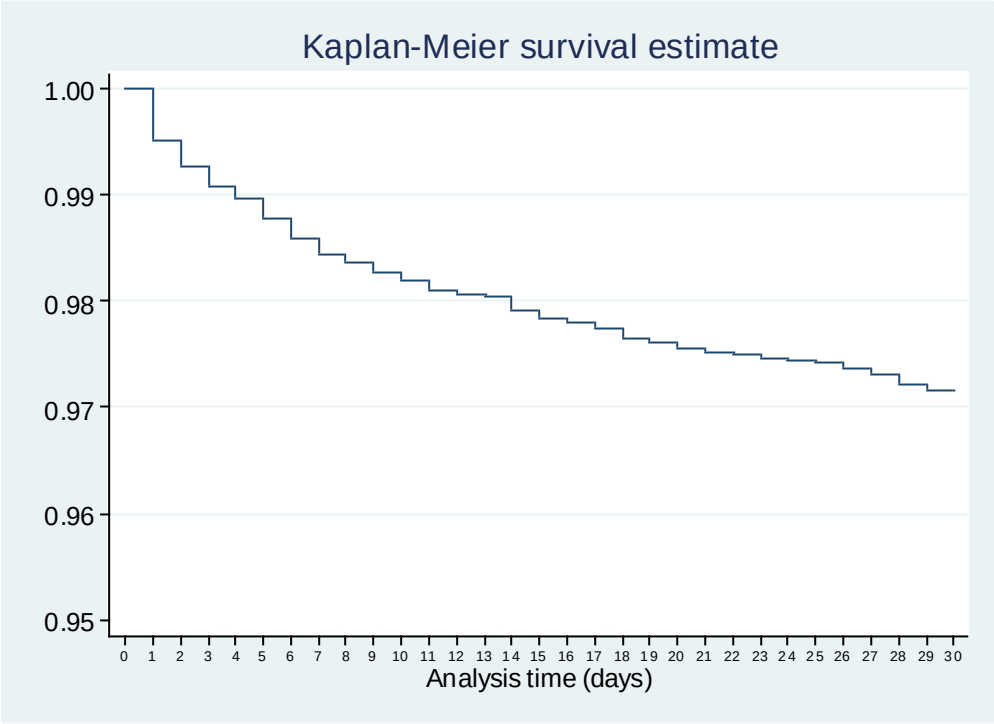


Figure 1.4 Kaplan-Maier curve – Adverse Events (AEs) at 5th day in SIDIAP

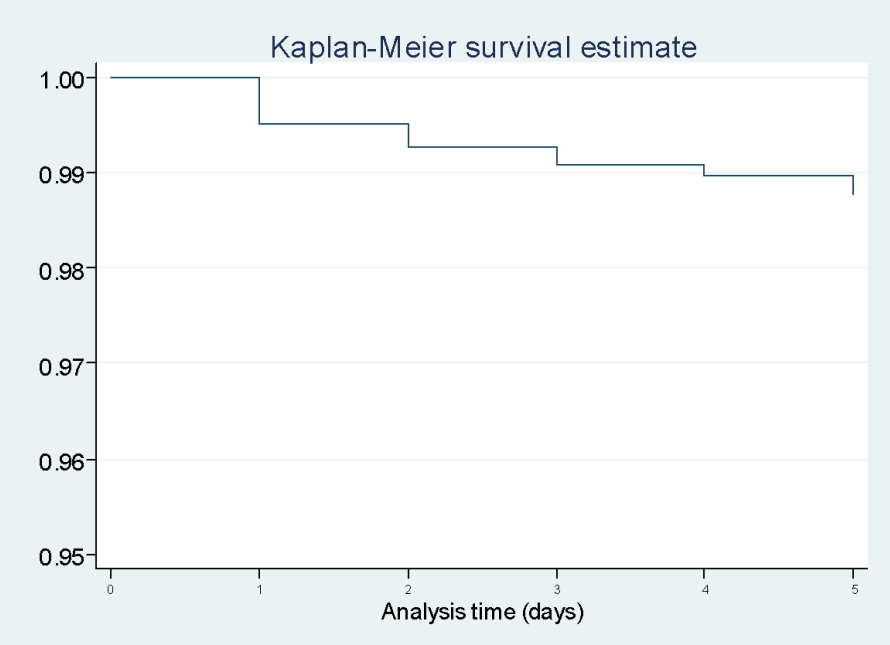


Figure 1.5 Kaplan-Maier curve – Adverse Events (AEs) at 15th day in SIDIAP

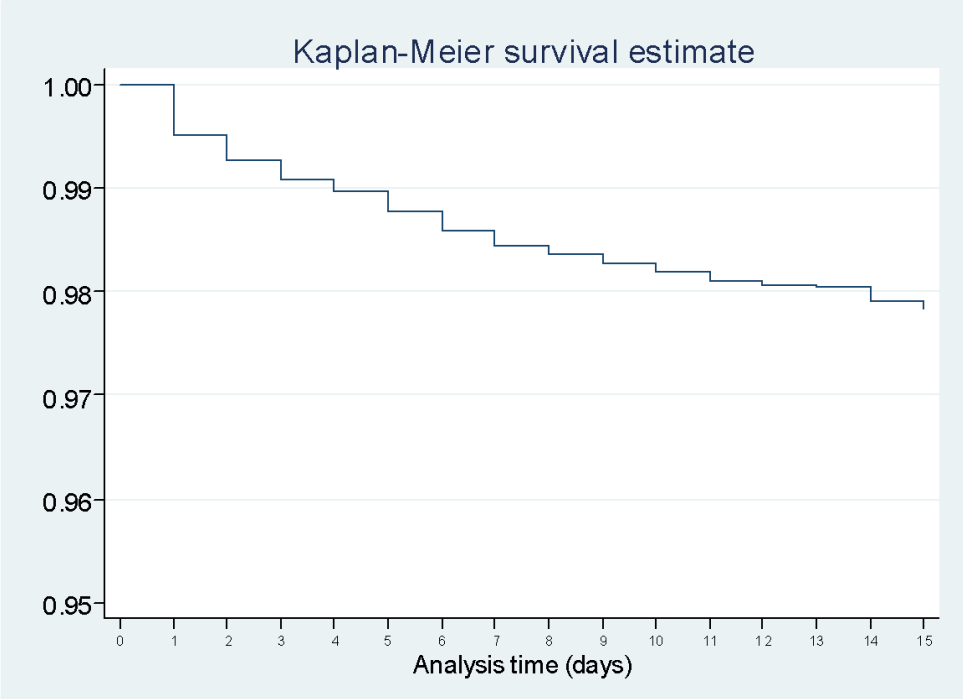
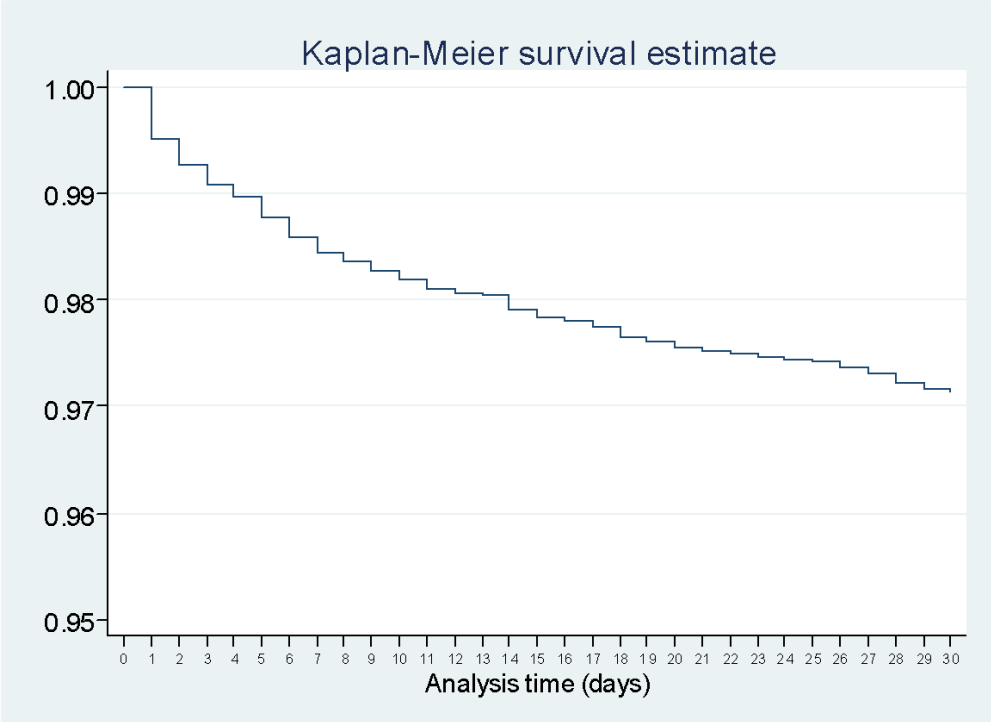


Figure 1.6 Kaplan-Maier curve – Adverse Events (AEs) at 30th day in SIDIAP



Case-controls characteristics.

Table 1. Characteristics of cases or adverse events and matched controls.

	Cases (N=602)	**Controls (N=4892)**
Total		
Gender		
Male	168 (38.71)	1353 (38.23)
Female	434 (61.29)	3539 (61.77)
Age		
15-24	6 (1.38)	18 (0.51)
25-34	9 (2.07)	76 (2.15)
35-44	42 (9.68)	342 (9.66)
45-54	88 (20.28)	720 (20.34)
55-64	95 (21.89)	702 (19.84)
65-74	141 (32.49)	1226 (34.64)
75-84	163 (37.56)	1339 (37.84)
>=85	58 (13.36)	469 (13.25)
Smoke		
Current smokers	82 (18.89)	675 (19.07)
Non-smokers	291 (67.05)	2074 (58.6)
Past smokers	95 (21.89)	697 (19.69)
Missing	*134 (30.88)*	*1446 (40.86)*
Obesity	85 (19.59)	524 (14.81)
Alcohol	23 (5.3)	197 (5.57)
Comorbidities		
Hepatic impairment	110 (25.35)	807 (22.8)
Hepatic impairment (codified with Child-Pugh classification)		
Mild	71 (16.36)	472 (13.34)
Moderate	5 (1.15)	44 (1.24)
Severe	0	0
Missing	*526 (82.49)*	*4376 (85.42)*
Kidney disease	154 (35.48)	1068 (30.18)
Renal function (GFR (ml/min/1.73 m^2))*		
Mild	430 (99.08)	3300 (93.25)
Moderate	94 (21.66)	693 (19.58)
Severe	9 (2.07)	64 (1.81)
Kidney failure	3 (0.69)	24 (0.68)
Missing	*66 (15.21)*	*811 (22.92)*
Depression	67 (15.44)	462 (13.05)
COPD-Asthma	201 (46.31)	1407 (39.76)

Epilepsy	5 (1.15)	46 (1.3)
Dyspepsia	82 (18.89)	577 (16.3)
Drug abuse	1 (0.23)	13 (0.37)
Mental disorders	213 (49.08)	1408 (39.79)
Hallucinations	1 (0.23)	3 (0.08)
Dementia	46 (10.6)	336 (9.49)
Cognitive impairment after trauma	0 (0)	0 (0)
Cerebro-cardiovascular disease	74 (17.05)	611 (17.26)
Gastrointestinal haemorrhages	25 (5.76)	167 (4.72)
Prior and/or concurrent medications		
NSAIDs	354 (81.57)	2652 (74.94)
Anticoagulants	225 (51.84)	1856 (52.44)
Carbamazepine	1 (0.23)	31 (0.88)
Cimetidine	0 (0)	0 (0)
Other opioids	173 (39.86)	1296 (36.62)
Antidepressants	113 (26.04)	782 (22.1)
MAO-Inhibitors	1 (0.23)	29 (0.82)
Antipsychotics	55 (12.67)	289 (8.17)
Anxiolytics	106 (24.42)	758 (21.42)
Ondansetron	0 (0)	1 (0.03)
Ketoconazole	0 (0)	1 (0.03)
Erythromycin	0 (0)	0 (0)

*among patients with kidney impairments

Table 2. Characteristics of cases or adverse events and matched controls in SIDIAP.

	Cases (N=2467)	**Controls (N=16929)**
Gender		
Female	1555 (63.0)	10936 (64.6)
Male	912 (37.0)	5993 (35.4)
Age		
18-24	61 (2.5)	199 (1.2)
25-34	192 (7.8)	1157 (6.8)
35-44	305 (12.4)	2401 (14.2)
45-54	347 (14.1)	2730 (16.1)
55-64	409 (16.6)	3201 (18.9)
65-74	459 (18.6)	3501 (20.7)
75-84	508 (20.6)	3131 (18.5)
>=85	186 (7.5)	609 (3.6)
Smoke		
Current smokers	328 (13.3)	2207 (13.0)

Non-smokers	968 (39.2)	6936 (41.0)
Past smokers	515 (20.9)	3372 (19.9)
Missing	656 (26.6)	4414 (26.1)
Obesity		
Obese	700 (28.4)	4563 (27.0)
Non obese	1466 (59.4)	10062 (59.4)
Missing	301 (12.2)	2304 (13.6)
Alcohol	91 (3.7)	570 (3.4)
Comorbidities		
Hepatic impairment Classification		
Hepatic impairment (overall)	23 (0.9)	173 (1.0)
Chronic	3 (0.1)	42 (0.2)
Cirrosis	12 (0.5)	78 (0.5)
Kidney disease	373 (15.1)	1934 (11.4)
Renal function (GFR (ml/min/1.73 m^2))*		
Mild	91 (3.7)	518 (3.1)
Moderate	13 (0.5)	73 (0.4)
Severe	0 (0.0)	4 (0.0)
Kidney failure	0 (0.0)	0 (0.0)
Missing	2363 (95.8)	16334 (96.5)
Depression	411 (16.7)	2338 (13.8)
COPD-Asthma	544 (22.1)	3399 (20.1)
Epilepsy	42 (1.7)	176 (1.0)
Dyspepsia	297 (12.0)	1508 (8.9)
Drug abuse	34 (1.4)	180 (1.1)
Mental disorders	774 (31.4)	4345 (25.7)
Hallucinations	3 (0.1)	13 (0.1)
Dementia	123 (5.0)	668 (3.9)
Cognitive impairment after trauma	0 (0)	0 (0)
Cerebro-cardiovascular disease	266 (10.8)	1372 (8.1)
Gastrointestinal haemorrhages	44 (1.8)	240 (1.4)
Prior and/or concurrent medications		
NSAIDs	117 (4.7)	1049 (6.2)
Anticoagulants	172 (7.0)	1148 (6.8)
Carbamazepine	6 (0.2)	20 (0.1)
Cimetidine	0 (0)	0 (0)
Other opioids	6 (0.2)	20 (0.1)
Antidepressants	92 (3.7)	475 (2.8)
MAO-Inhibitors	0 (0)	0 (0)

Antipsychotics	92 (3.7)	475 (2.8)
Anxiolytics	178 (7.2)	1176 (6.9)
Ondansetron	9 (0.4)	53 (0.3)
Ketoconazole	0 (0)	0 (0)
Erythromycin	2 (0.1)	17 (0.1)

*among patients with kidney impairments

Sensitivity analyses

Propensity Score analysis

Table 3. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching in HSD.

	Cases (N=601)	**Controls (N=5666)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use*	197 (32.78)	2917 (51.48)	*Ref.*	*Ref.*
Current use**				
DKP-TRAM	142 (23.63)	601 (10.61)	7.21 (5.35 - 9.72)	7.55 (5.57 - 10.23)
Tramadol	194 (32.28)	1357 (23.95)	4 (3.07 - 5.21)	4.08 (3.12 - 5.33)
Tramadol-paracetamol	64 (10.65)	772 (13.63)	2.25 (1.61 - 3.15)	2.35 (1.67 - 3.28)
Mixed	4 (0.67)	19 (0.34)	5.5 (1.78 - 17)	5.89 (1.85 - 18.75)

*for smoke, obesity, kidney disease, COPD-asthma, mental disorders, antipsychotic use; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 4. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching: the current use of tramadol-paracetamol is the reference category in HSD.

	Cases (N=601)	**Controls (N=5666)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	197 (32.78)	2917 (51.48)	0.44 (0.32 - 0.62)	0.43 (0.3 - 0.6)
Current use**				
Tramadol-paracetamol	64 (10.65)	772 (13.63)	*Ref.*	*Ref.*
DKP-TRAM	142 (23.63)	601 (10.61)	3.2 (2.3 - 4.45)	3.22 (2.31 - 4.49)
Tramadol	194 (32.28)	1357 (23.95)	1.77 (1.31 - 2.4)	1.74 (1.28 - 2.36)
Mixed	4 (0.67)	19 (0.34)	2.44 (0.78 - 7.66)	2.51 (0.78 - 8.11)

*for smoke, obesity, kidney disease, COPD-asthma, mental disorders, antipsychotic use; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 5. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching: the current use of tramadol is the reference category.

	Cases (N=601)	Controls (N=5666)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	197 (32.78)	2917 (51.48)	0.25 (0.19 - 0.33)	0.25 (0.19 - 0.32)
Current use**				
Tramadol	194 (32.28)	1357 (23.95)	*Ref.*	*Ref.*
DKP-TRAM	142 (23.63)	601 (10.61)	1.8 (1.4 - 2.33)	1.85 (1.43 - 2.4)
Tramadol-paracetamol	64 (10.65)	772 (13.63)	0.56 (0.42 - 0.76)	0.58 (0.42 - 0.78)
Mixed	4 (0.67)	19 (0.34)	1.38 (0.45 - 4.24)	1.45 (0.46 - 4.59)

*for smoke, obesity, kidney disease, COPD-asthma, mental disorders, antipsychotic use; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 6. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching in SIDIAP.

	Cases (N=2221)	Controls (N=6577)	OR (95% CI)
Recent use**	626 (28.19)	2,049 (31.15)	*Ref.*
Current use**			
DKP-TRAM	100 (4.5)	192 (2.92)	1.3 (0.95-1.78)
Tramadol	392 (17.65)	1,237 (18.81)	0.85 (0.70-1.03)
Tramadol-paracetamol	1,101 (49.57)	3,088 (46.95)	0.97 (0.82-1.15)
Mixed	2 (0.09)	11 (0.17)	0.23 (0.03-1.94)

**recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 7. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching: the current use of tramadol-paracetamol is the reference category in SIDIAP.

	Cases (N=2221)	Controls (N=6577)	OR (95% CI)
Recent use**	626 (28.19)	2,049 (31.15)	1.03 (0.87-1.22)
Current use**			
Tramadol-paracetamol	1,101 (49.57)	3,088 (46.95)	*Ref.*
DKP-TRAM	100 (4.5)	192 (2.92)	1.34 (1.00-1.77)
Tramadol	392 (17.65)	1,237 (18.81)	0.87 (0.75-1.01)
Mixed	2 (0.09)	11 (0.17)	0.24 (0.03-2.00)

**recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 8. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adopting propensity score matching: the current use of tramadol is the reference category in SIDIAP.

	Cases (N=2221)	Controls (N=6577)	OR (95% CI)
Recent use**	626 (28.19)	2,049 (31.15)	1.18 (0.97-1.43)
Current use**			
DKP-TRAM	100 (4.5)	192 (2.92)	1.53 (1.13-2.07)
Tramadol-paracetamol	1,101 (49.57)	3,088 (46.95)	1.15 (0.99-1.33)
Tramadol	392 (17.65)	1,237 (18.81)	*Ref.*
Mixed	2 (0.09)	11 (0.17)	0.28 (0.03-2.30)

**recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Adjusted analyses after multiple imputation for BMI and smoking

Table 9. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation.

	Cases (N=602)	Controls (N=4911)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	197 (32.72)	2199 (44.78)	*Ref.*	*Ref.*
Current use**				
DKP-TRAM	142 (23.59)	631 (12.85)	2.83 (1.99 - 4.04)	2.89 (2.03 - 4.14)
Tramadol	194 (32.23)	1320 (26.88)	1.75 (1.27 - 2.42)	1.79 (1.29 - 2.49)
Tramadol-paracetamol	65 (10.8)	740 (15.07)	1.04 (0.71 - 1.53)	1.03 (0.7 - 1.52)
Mixed	4 (0.66)	21 (0.43)	2.68 (0.89 - 8.01)	2.55 (0.84 - 7.74)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 10. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation: current use of tramadol-paracetamol is the reference category.

	Cases (N=602)	Controls (N=4911)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	197 (32.72)	2199 (44.78)	0.96 (0.65 - 1.4)	0.97 (0.66 - 1.43)
Current use**				
Tramadol-paracetamol	65 (10.8)	740 (15.07)	*Ref.*	*Ref.*
DKP-TRAM	142 (23.59)	631 (12.85)	2.71 (1.95 - 3.77)	2.81 (2.01 - 3.92)
Tramadol	194 (32.23)	1320 (26.88)	1.68 (1.24 - 2.27)	1.74 (1.28 - 2.36)
Mixed	4 (0.66)	21 (0.43)	2.56 (0.85 - 7.7)	2.47 (0.81 - 7.54)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 11. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation: current use of tramadol is the reference category.

	Cases (N=602)	Controls (N=4911)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	197 (32.72)	2199 (44.78)	0.57 (0.41 - 0.79)	0.56 (0.4 - 0.78)
Current use**				
Tramadol	194 (32.23)	1320 (26.88)	*Ref.*	*Ref.*
DKP-TRAM	142 (23.59)	631 (12.85)	1.62 (1.26 - 2.09)	1.62 (1.25 - 2.09)
Tramadol-paracetamol	65 (10.8)	740 (15.07)	0.6 (0.44 - 0.81)	0.58 (0.42 - 0.78)
Mixed	4 (0.66)	21 (0.43)	1.53 (0.52 - 4.52)	1.42 (0.47 - 4.28)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 12. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation in SIDIAP.

	Cases (N=2467)	Controls (N=16929)	OR (95% CI) Crude	OR (95% CI) Adjusted*
Recent use**	690 (27.97)	5,142 (30.37)	*Ref.*	*Ref.*
Current use**				
Tramadol	440 (17.84)	3,232 (19.09)	0.82 (0.70-0.97)	0.81 (0.69-0.96)
DKP-TRAM	108 (4.38)	534 (3.15)	1.24 (0.96-1.61)	1.25 (0.96-1.62)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	0.95 (0.82-1.09)	0.95 (0.82-1.10)

DKP-TRAM/vo3

Mixed	3 (0.12)	16 (0.09)	1.05 (0.30-3.74)	0.98 (0.28-3.49)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 13. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation: current use of tramadol-paracetamol is the reference category in SIDIAP.

	Cases (N=2467)	**Controls (N=16929)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	690 (27.97)	5,142 (30.37)	1.06 (0.92-1.22)	1.05 (0.91-1.21)
Current use**				
Tramadol	440 (17.84)	3,232 (19.09)	0.87 (0.77-0.98)	0.86 (0.76-0.97)
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	*Ref.*	*Ref.*
DKP-TRAM	108 (4.38)	534 (3.15)	1.31 (1.05-1.65)	1.31 (1.04-1.65)
Mixed	3 (0.12)	16 (0.09)	1.11 (0.32-3.94)	1.04 (0.29-3.66)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Table 14. Recency of use of DKP-TRAM, tramadol and tramadol-paracetamol combinations and related adverse events according to the nested case-control analysis adjusted by BMI and smoking after multiple imputation: current use of tramadol is the reference category in SIDIAP.

	Cases (N=2467)	**Controls (N=16929)**	**OR (95% CI) Crude**	**OR (95% CI) Adjusted***
Recent use**	690 (27.97)	5,142 (30.37)	1.22 (1.03-1.44)	1.23 (1.04-1.45)
Current use**				
Tramadol-paracetamol	1,226 (49.7)	8,005 (47.29)	1.15 (1.02-1.30)	1.17 (1.03-1.32)
DKP-TRAM	108 (4.38)	534 (3.15)	1.52 (1.19-1.93)	1.53 (1.20-1.96)
Tramadol	440 (17.84)	3,232 (19.09)	*Ref.*	*Ref.*
Mixed	3 (0.12)	16 (0.09)	1.28 (0.36-4.55)	1.21 (0.34-4.29)

*for all the covariates reported in Table 16; **recent: within 31 days or before the index date; current: within 30 days preceding or on the index date

Name of the main author of the Final Study Report: Francesco Lapi

Date: January 14, 2022

Signature: 