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REKOVER study protocol: a pRospective patient treatment rEgistry of tramadol and dexKetoprofen trometamol oral fixed-dose combination (SKUDEXA) in mOderate to seVere acutE pain in Real-world setting in Asia

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ABSTRACT

Introduction Satisfactory management of acute pain remains a major medical challenge despite the availability of multiple therapeutic options including the fixed-dose combination (FDC) drugs. Tramadol and dexketoprofen trometamol (TRAM/DKP) 75/25 mg FDC was launched in 2018 in Asia and is widely used in the management of moderate to severe acute pain. There are limited data on its effectiveness and safety in Asian patients, and therefore, a need to better understand its usage patterns in clinical practice. We aim to understand the usage pattern of TRAM/DKP FDC, its effectiveness and tolerability in patients with moderate to severe acute pain in Asia.

Methods and analysis REKOVER is a phase-IV, multicountry, multicentre, prospective, real-world observational study. A total of 750 postsurgical and non-surgical patients (male and female, aged 18–80 years) will be recruited from 13 tertiary-care hospitals (15 sites) in Singapore, Thailand, the Philippines and Malaysia. All patients prescribed with TRAM/DKP FDC and willing to participate in the study will be enrolled. The recruitment duration for each site will be 6 months. The severity of pain will be collected using Numeric Pain Rating Scale through the treatment period from day 1 to day 5, while satisfaction with the treatment will be evaluated using Patient Global Evaluation Scale at the end of treatment. Any adverse event reported during the study duration will be recorded for safety analysis (up to day 6). The study data will be entered into the ClaimIt portal and mobile application (app) (ObvioHealth, USA). All the inpatient data will be entered into the portal by the study site and for outpatient it will be done by patients through an app.

Ethics and dissemination The study has been approved by the local ethics committee from each study sites in Singapore, Thailand, the Philippines and Malaysia. Findings will be disseminated through local and global conference presentations, publications in peer-reviewed scientific journals and continuing medical education.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Longitudinal study design (follow-up to day 6) will allow us to analyse the change in pain intensity by Numerical Pain Rating Scale over time in the same patient under treatment with tramadol/dexketoprofen fixed-dose combination.
⇒ The patient-reported outcome measures such as patient global evaluation will provide information about the patient's satisfaction with the treatment.
⇒ Analysing commonalities and differences in prescription patterns, usage and pain management practices in four different countries will increase understanding in identifying groups of patients who may need a more individualised pain management plan.
⇒ The key limitation of this study will be the potential loss to follow-up and missing data points.
⇒ As this is a digitally enabled study, the patients, doctors and study teams may not be familiar with the data entry portal/app and hence, may result in wrong entry and untimely entry of data.

INTRODUCTION

Pain is one of the most common reasons for physician consultation and hospital admission.[1] Unrelieved/poorly controlled pain is associated with poor quality of life, psychological distress, increased risk of developing chronic pain and other medical complications.[2–4] Several studies have shown that

postoperative pain, when not adequately managed, can result in chronic pain[5–10] with a reported incidence of up to 50% depending on the type of surgery performed.[11] Similarly, non-surgical pain, such as musculoskeletal pain, and visceral pain are highly prevalent in the general population,[12] with low back pain alone having an estimated lifetime prevalence of 50%–58%.[13] Asian populations also exhibit a similar prevalence of such pain ranging from 26% to 63%.[14 15]

Likewise, the majority of patients with moderate to severe pain reported inadequate pain relief.[16] Untreated and undertreated pain not only represents the most pervasive health problem in the ageing population but is also associated with increased healthcare costs.[17–19] Despite advances in pain medicine, the management of acute pain appears not to be a priority and is still poorly addressed.[20] Multiple options are currently available for pain management, most of which have predominantly unimodal mechanism of analgesic action[21] and cannot be prescribed for a longer duration due to the ceiling effect and/or safety concerns.[22] Indeed, attaining optimal pain care with monotherapy is difficult.[23] Hence, a comprehensive and integrated approach to research, diagnosis and treatment of pain is a present day necessity.[24] It has been recommended that the optimal strategy for adequate pain management is the use of a combination of drugs that acts through multiple modes and sites of action to the therapeutic end-point, that is, multimodal analgesia.

In this regard, dexketoprofen (DKP) is a well-known non-steroidal anti-inflammatory drug commonly used in a wide spectrum of acute pain syndromes.[25] When combined with tromethamine salt, it has a faster onset of action, greater bioavailability, rapid dissolution and absorption. Studies showed that DKP trometamol has a favourable safety profile, making it suitable for effective pain management.[23 26] On the other hand, tramadol (TRAM) is an opioid receptor agonist with central, peripheral and local analgesic effects.[27] The opioid and non-opioid mechanisms act together on descending pain pathways in the central nervous system. The longer duration of action and favourable safety profile makes TRAM a suitable compound for treating different types of moderate to severe pain.[23] Previous studies have shown that a fixed-dose combination (FDC) of DKP (25 mg) and TRAM (75 mg) is the optimal dose for adequate pain relief in different patterns of pain trajectories (continuous pain along with acute flares).[27–29] Hence, FDC compounds with different mechanisms and sites of action would yield better pain relief, prolong the analgesic effect and with fewer side effects.[21]

TRAM/DKP FDC was approved in Europe in 2016. Based on the results of clinical studies in mandibular molar tooth extraction,[28] soft tissue surgeries[30] and joint replacement surgeries[31] involving some 1900 patients, it has been granted the indication for the short-term (ie, up to 5 days) symptomatic treatment of moderate to severe acute pain. Similarly, a previous study using TRAM/DKP FDC in Caucasian patients in dental surgery showed a significant therapeutic effect in relieving moderate to severe acute pain, with a faster onset, prolonged analgesia and favourable safety profile.[19] These studies showed that the clinical benefits of this combination were not only limited to greater efficacy but also better tolerability as shown by reduced severity of pain and lower number and/or severity of adverse events (AEs).[19 28 30 31]

Skudexa (TRAM/DKP FDC) was launched in Asia in 2018, is currently available in five countries and may soon be launched in more countries. There is a limited understanding of the characteristics of patients in which TRAM/DKP FDC can be used in clinical practice in Asia. A recent case series in Asian patients including 13 patients across orthopaedic, soft tissue and laparoscopic surgery showed that TRAM/DKP FDC is well tolerated for postoperative pain management with good pain relief.[32] As there is a lack of real-world data on the tolerability and effectiveness of TRAM/DKP FDC in the larger Asian population, our study aims to explore the use of TRAM/DKP FDC in the management of short-term moderate to severe acute pain in Asia.

Study aims and endpoints

The main aim of this prospective study is to understand the usage pattern of TRAM/DKP FDC in patients with moderate to severe acute pain. The secondary aim is to evaluate the effectiveness and tolerability of TRAM/DKP FDC in patients with moderate to severe acute pain.

Primary endpoints

- The proportion of enrolled patients with different surgical treatments.
- The proportion of enrolled patients with different non-surgical treatments.
- Average dosing frequency and duration of TRAM/DKP FDC treatment in postsurgical and non-surgical patients.

Secondary endpoints

- Percentage of patients achieving ≥30% pain reduction at 8 hours post first dose of TRAM/DKP FDC.
- Satisfaction level at the end of treatment based on Patient Global Evaluation (PGE).
- Incidence, frequency, severity, causal relationship of reported adverse drug reactions (ADRs) and discontinuation due to ADRs during TRAM/DKP FDC treatment.

METHODS AND ANALYSIS

Setting

REKOVER is an international prospective study that will be conducted in 13 tertiary-care hospitals (15 sites) from Singapore, Thailand, the Philippines and Malaysia, involving 15 principal investigators (PIs). In Singapore, this study will be conducted at Mount Alvernia Hospital, BIJOS Hospital and National University Hospital. In Thailand, this study will be conducted at Maharaj Nakorn Chiang Mai Hospital, Ananda Mahidol Hospital, King Chulalongkorn Memorial Hospital and Siriraj Hospital.

Table 1 Study criteria

Inclusion and exclusion criteria	
Inclusion criteria	► Male and female adult patients, ages 18–80 years, prescribed TRAM/DKP FDC for moderate to severe acute pain. ► Patients willing to give consent for the study.
Exclusion criteria	► Hypersensitivity to dexketoprofen, to any other NSAID, or to any of the excipients. ► Patients in whom substances with a similar action (eg, acetylsalicylic acid or other NSAIDs) precipitate attacks of asthma, bronchospasm, acute rhinitis or cause nasal polyps, urticaria or angioneurotic oedema. ► Known photo allergic or phototoxic reactions during treatment with ketoprofen or fibrates. ► Patients with active peptic ulcer/gastrointestinal haemorrhage or any history of gastrointestinal bleeding ulceration or perforation. ► Patients with history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. ► Patients with chronic dyspepsia. ► Patients who have other active bleeding or bleeding disorders. ► Patients with Crohn's disease or ulcerative colitis. ► Patients with a history of bronchial asthma (even if not drug induced). ► Patients with severe heart failure. ► Patients with moderate to severe renal dysfunction (creatinine clearance <59 mL/min). ► Patients with severely impaired hepatic function (Child-Pugh C). ► Patients with haemorrhagic diathesis and other coagulation disorders. ► Patients with severe dehydration (caused by vomiting, diarrhoea or insufficient fluid intake). ► Hypersensitivity to tramadol or to any of the excipients. ► Acute intoxication with alcohol, hypnotics, analgesics, opioids or psychotropic medicinal products. ► Patients receiving MAO inhibitors or who have taken them within the last 14 days. ► Patients with epilepsy not adequately controlled by treatment. ► Severe respiratory depression. ► Pregnancy and lactation.

FDC, fixed-dose combination; MAO, monoamine oxidase inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; TRAM/DKP, tramadol and dexketoprofen trometamol.

In Malaysia, it will be conducted in one site at Pantai Hospital Kuala Lumpur, whereas in the Philippines this study will be conducted at Manila Doctors Hospital, Philippine Orthopedic Institute, Cardinal Santos Medical Center, The Medical City Manila and Adventist Medical Center Manila.

Study design

This study is a phase IV, multicountry, multicentre, prospective, observational, longitudinal, real-world study. The total duration of participation in this study is 6 days. Each investigator can recruit up to 50 patients within 6 months of the study duration. The total patient distribution of the sample size is estimated to be 70% postsurgical and 30% non-surgical patients.

Patient recruitment

Approximately 750 male and female patients, ages 18–80 years, who have been prescribed TRAM/DKP FDC for moderate to severe acute pain (postsurgical or non-surgical) and are willing to give consent for the study will be screened and enrolled if they meet the study criteria (table 1).

Study visits and procedures

The study data listed in table 2 will be collected in the ClaimIt platform after the patient is enrolled in the study. ClaimIt platform is an electronic data capture system developed by Obvio Health, USA. It is available in both web portal and mobile application (app) formats. For the inpatient (postsurgical patients), the study data will be captured by the investigator/site staff in the ClaimIt portal. For the outpatient (non-surgical patients), baseline data will be completed by the investigator/site staff in the ClaimIt portal and subsequent data will be entered by the patient in the ClaimIt app. The investigator/site staff will have read and review access to all study data in the ClaimIt platform but will not be able to make any changes to the data entered by the patient.

Screening visit

At the screening visit, the research team will conduct both screening and informed consent sessions, during which screening checklist questionnaires will be conducted, and anthropometric data, resting blood pressure, and medical history of the potential participant will be recorded. During the screening visit, the Numerical Pain Rating Scale (NRS) will be recorded. Eligible patients will be enrolled after they have consented to participate in the study and met the inclusion criteria.

Study procedures

On day 1, the pain score will be recorded prior to taking Skudexa (baseline) and then 30 min, 1 hour, 2 hours, 4 hours, 6 hours and 8 hours post first dose, however, for

Table 2 Study visits and assessments

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Sign informed consent	√					
Medical Interview	√					
Physical exam, demographics and vitals* Sex, age, vital signs: (BP, PR), weight, height	√					
Diagnosis/indication (TRAM/DKP FDC use)	√					
Comorbid disorders and ongoing medications	√					
Type of surgery performed	√					
All Intraoperative medications	√					
All post-operative medications	√	√	√	√	√	
TRAM/DKP FDC dosing frequency and duration of treatment postsurgical (in hospital) started at which day of surgery	√	√	√	√	√	
Pain medications prescribed along with TRAM/DKP FDC to manage postsurgical pain and non-surgical pain	√	√	√	√	√	
Pain medication after completion of TRAM/DKP FDC treatment	√	√	√	√	√	
Pain score: Numerical Pain Rating Scale baseline†	√‡	√§	√§	√§	√§	
Patient global evaluation†	At the end of TRAM/DKP FDC treatment					
Adverse events	√	√	√	√	√	√

*Based on data available from patient medical records.
†For non-surgical patient types: after baseline data is entered by the investigator then the patient will enter the required data in the ClaimIt App as explained in the study details.
‡30 min, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours postdose.
§After 6 hours of first dose on that day.
BP, blood pressure; FDC, fixed-dose combination; PR, pulse rate; TRAM/DKP, tramadol and dexketoprofen trometamol.

days 2–5, pain scores will be recorded 6 hours after the first dose on that day. Patient satisfaction with the treatment will be recorded after the end of the treatment. The information on any AEs and any discontinuation/withdrawal due to AE will be recorded. Participants will be followed up for another 1 day to record any AE after the end of treatment.

Demographic data

Age and sex will be collected at the screening visit on day 1 after the patient signs the consent form.

Anthropometry

1. Height: measured to the nearest 0.1 cm.
2. Weight: measured to the nearest 0.1 kg.
3. Body mass index (BMI): calculated as (weight) (kg)/(height^2) (m).

Vital signs

Blood pressure and pulse rate will be captured from hospital records.

Medical interview and questionnaire

Information on medical history, comorbidities, ongoing medications, surgical history, and current surgical and non-surgical indications for TRAM/DKP FDC will be captured via a structured questionnaire.

Numerical Pain Rating Scale

The patient is asked to rate self-perceived pain corresponding to current, best and worst pain experienced on a scale from 0 (no pain) to 10 (worst pain imaginable). Pain severity on the NRS scale will be categorised as 0=no pain, 1–3=mild pain, 4–6=moderate pain and 7–10=severe pain.[19 33]

Non-surgical patients should complete the assessments in the ClaimIt app within 10 min of the defined interval.

Patient Global Evaluation

To evaluate patient satisfaction with the treatment, a 5-point PGE Numeric Rating Score will be used to collect patients' self-reported outcomes at the end of the treatment. PGE will be based on a grading scale of 1=poor, 2=fair, 3=good, 4=very good and 5=excellent.[33 34]

Safety monitoring and assessments

AEs will be collected in the study registry from the time of enrolment to day 6. The information to be collected for each event will include the incidence, severity, causality, outcome and any other information requested for the occurred event, according to the ClaimIt portal—AE recording pages. Participants will also be asked if TRAM/DKP FDC treatment was discontinued due to an AE.

Inpatients will report all AEs to the investigator/site staff who will enter the patient's AE data into the ClaimIt portal. Outpatients will enter their AE data using a task

on the ClaimIt app dashboard from the time they are enrolled in the study until day 6.

Sample size

This is a time-bound study and the sample size is based on our assumption that each site over a period of 6 months can approximately recruit 50 eligible patients comprising postsurgical and non-surgical patients. This will give us a sample size of 750 patients (from 15 sites) which will be enough to observe the trends and patterns of our primary endpoints.

Statistical analysis plan

Primary objective

To understand the enrolment and real-world usage of TRAM/DKP FDC in Asia, demographic characteristics (ie, age, BMI, sex, race) of enrolled patients will be descriptively summarised. The demographic characteristics of participants will also be cross-tabulated by surgical status (surgical, non-surgical), and by different surgical and non-surgical types.

To understand the prescription of TRAM/DKP FDC in Asia in the real-world setting, the frequency and per cent distribution will be summarised based on participants' average dosing frequency and the treatment duration for the overall population, and by participants' surgical status (surgical, non-surgical). Descriptive statistics in the form of mean, median and SD will be calculated as well. To further explore the prescription scenario (dosing frequency change during the drug use period) in the real-world setting, the mean and SD of dosing frequency will be calculated for different drug use periods (1 day, 2 days, 3 days, 4 days and 5 days) for the overall population and the subgroups (surgical and non-surgical).

Secondary objectives: efficacy data

To evaluate the efficacy of TRAM/DKP FDC treatment in Asia in the real-world setting, participants' pain intensity based on NRS will be collected prior to the first dose and at 30 min, 1, 2, 4, 6 and 8 hours after the first dose on day 1, and daily from day 2 to day 5. Descriptive statistics in the form of mean, median and SD will be calculated for pain scores collected at six different time points (prior to first dose, 8 hours post first dose, day 2, day 3, day 4 and day 5).

The pain intensity reduction from drug intake to 8 hours after the first dose is of main interest in the efficacy evaluation. The analysis of covariance may be conducted to compare the pain intensity reduction between the surgical and non-surgical groups while controlling covariates of baseline pain score (prior to first dose), site of pain, age, gender and BMI.

Different approaches will be adopted for the last observation carry forward (LOCF), worst observation carry forward (WOCF) and imputation for analysis of the missing data at 8 hours from baseline on day 1.

Secondary objectives: safety data

The secondary objectives of the study are to evaluate the safety of TRAM/DKP FDC treatment in Asia in the real-world setting; the incidence, frequency, distribution and severity of ADRs and the percentage of patients who discontinue TRAM/DKP FDC due to ADRs will be monitored and reported for the overall population and the subgroups (surgical and non-surgical). The number of ADRs along with the number of patients reporting ADR will be reported and the respective percentage based on the safety population. ADRs/AEs will be collected for this study from the time of participant enrolment to day 6. A listing of all ADRs will be created showing the incidence, severity, causality and outcome.

To further explore the impact of prescription scenario (dosing frequency, drug use period) on ADRs leading to TRAM/DKP FDC discontinuation, the mean and SD of dosing frequency will be calculated for different drug use periods (1 day, 2 days, 3 days, 4 days and 5 days) till the ADR occurrence for participants who discontinue treatment due to ADRs, and by patient groups (surgical and non-surgical).

Secondary objective: patient satisfaction data

The frequency and per cent distribution of each response in PGE will be tabulated for the overall population and the subgroups (surgical and non-surgical). Descriptive statistics in the form of mean, median and SD will be calculated as well.

A standardisation process to group the patients will be adopted at the end, postcompletion of data collection to produce proportion and avoid any dispersion in terms of results that summarise the use of TRAM/DKP FDC.

Ethical considerations

Ethics and dissemination

This study has received the following approvals:

Parkway Independent Ethics Committee (PIEC/2022/012) (Mount Alvernia Medical Centre, Singapore and BJIOS Orthopaedics, Singapore); National Healthcare Group Domain Specific Review Board (NHG DSRB Ref: 2022/00386) (National University Hospital, Singapore); Pantai Hospital Kuala Lumpur Research Ethics Committee (PHKL-EC-2022-0008) (Pantai Hospital Kuala Lumpur, Kuala Lumpur); Central Research Ethics Committee Thailand (CREC# CREC092/64BP-BIO15, COA No. COA-CREC062/2022) (Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Ananda Mahidol Hospital, Bangkok, King Chulalongkorn Memorial Hospital, Bangkok, Siriraj Hospital, Bangkok); Manila Doctors Hospital Ethics Committee (MDH IRB 2022-063_CT) (Manila Doctors Hospital, Manila); Cardinal Santos Medical Center Research Ethics and Review Committee (2022/004, 2022/054, 2022/055) (Cardinal Santos Medical Center, San Juan City, Philippine Orthopedic Institute, Quezon City, Adventist Medical Center Manila, Manila), The Medical City Ethics Committee (The Medical City, Pasig City).

Findings of this study will be disseminated through local and global conference presentations, publications in peer-reviewed scientific journals and continuing medical education.

Patient and public involvement

Patients were not involved in the development and design of the study protocol. Only those patients who provided consent for this study will be enrolled in this study. Patient consent is not required for this publication and study results will not be disseminated to participants specifically. The public was not involved in this study.

Participation in the study

Participation in this study is wholly voluntary. Participants can stop participating in this study at any time by informing the PI. Likewise, the PI can also discontinue the participation if the patient is found unsuitable to participate in the study (eg, due to non-compliance with the study protocol or discontinuation due to AE). Once a patient is withdrawn or discontinued from the study, no attempt will be made to further evaluate the patient or to collect additional data.

Informed consent

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and applicable regulatory requirements. Written informed consent will be obtained from each participant before study-related procedures are performed on him or her. Potential participants will be approached individually at an appropriate time when they are not under duress. They will be taken to a quiet and conducive environment to ensure privacy. There, the PI will introduce to him or her the research study and explain the responsibilities, risks and benefits of participating in the study. Each potential participant will be given a copy of the participant's information sheet in English language or the local language (if preferred by the patient).

Data management, oversight and storage

Data collection will be conducted as per the standards and requirements of observational studies ICH/GCP guidelines. It will be initiated after obtaining written approval from respective Institutional Review Boards/Ethics Committees (IRB/EC) for each site and the informed consent signed.

Data collection will involve the use of the ClaimIt Electronic Data Capture system, to which only authorised personnel will have access. The portal/app is designed and developed as per protocol requirements, with internal and sponsor User Acceptance Testing (UAT) being completed prior to go-live. Prior to roll-out, instructions will be prepared and adequate training will be provided on the use of the ClaimIt app and portal.

All data will be hosted on a Microsoft Azure service. All ObvioHealth employees and their affiliates are bound by strict confidentiality agreements. Transport Layer Security will be used to secure all data in transit. The database will incorporate the needed programmed edit checks to help ensure quality data.

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Contributors The study concept and design were done by DN. BG drafted and revised the manuscript and coordinated with investigators. KYH provided intellectual advice, read and approved the final manuscript. CD, EB EME, GR, KWC, KW, LO, MALC, PS, RCS, SAR, ST, VW, ZHO and AG read, and approved the final manuscript.

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Competing interests BG, AG and DN are employees of A. Menarini Asia-Pacific Holdings, Singapore. All other authors report receiving investigator fee for this study from A. Menarini Asia-Pacific Holdings, Singapore.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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