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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

Background: Satisfactory management of acute pain ~~still~~ 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 is limited data on its effectiveness and safety in Asian patients and therefore a need to better understand its usage patterns in clinical practice.

Objective: 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: REKOVER is a phase-IV, multi-country, multi-centre, prospective, real-world observational study. A total of 750 post-surgical and non-surgical patients (male and female, aged 18-80 years) will be recruited from 13 tertiary-care hospital 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 six 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. 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.

Conclusion: This study will be the first digitally enabled prospective study to evaluate the safety and effectiveness of TRAM/DKP FDC in the real-world setting in Asia.

Keywords: Dexketoprofen Trometamol, Pain, Real-world, TRAM/DKP FDC, and Tramadol

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).

Strengths and limitations of this study

1. REKOVER is the first digitally enabled, prospective multi-country, multi-centre study to evaluate safety and effectiveness of Tramadol and Dexketoprofen Trometamol fixed-dose combination (TRAM/DKP FDC) in the real-world setting in Asia.
2. Our longitudinal study design (with 5 days of follow-up) will allow us to analyse the change in pain intensity by Numerical Pain Rating Scale over time in the same patient under treatment with TRAM/DKP FDC.
3. The patient reported outcome measures such as patient global evaluation will provide information about the patient's satisfaction with the treatment.
4. 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.
5. The key limitation of this study will be the potential loss to follow-up and missing data points. In this study, participants will be followed up every day for 5 days and data from 70% of inpatient participants will be collected and entered by site staff, minimising the possibility of lost to follow-up and missing data.
6. As this is the first 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. To minimise this, proper training will be provided to all the investigators and site staff before the start of recruitment. Furthermore, a video demonstration for their reference will be shared with them. There will be 24-hour virtual assistance available for the study team.

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 post-operative 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 under-treated pain not only represents the most pervasive health problem in the aging 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, i.e. multimodal analgesia.

In this regard, Dexketoprofen (DKP) is a well known nonsteroidal 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 Dexketoprofen 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 (25mg) and TRAM (75mg) is ~~to be~~ 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 (30), soft tissue surgeries (31), and joint replacement surgeries (32) involving some 1,900 patients, it has been granted the indication for the short-term (i.e. 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 (19, 30–32).

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 (33). 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.

***The primary endpoints of this study are*:**

- 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 post-surgical and non-surgical patients

The secondary endpoints of this study are:

- 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 and discontinuation due to adverse drug reactions during TRAM/DKP FDC treatment

METHODS AND ANALYSIS

Setting

REKOVER is an international prospective study that will be conducted in 13 tertiary-care hospital sites from Singapore, Thailand, the Philippines and Malaysia, involving 15 principal investigators. 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. 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 Orthopedics Institute, Cardinal Santos Medical Center, The Medical City Manila, and Adventist Medical Center Manila.

Study Design

This study is a Phase IV, multi-country, multi-centre, 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% post-surgical 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 (post-surgical 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 (post-surgical 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, 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 (hr), 2hr, 4hr, 6hr, and 8hr post first dose, however for day 2 to day 5, pain scores will be recorded 6hr 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 adverse events (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 past medical history, comorbidities, ongoing medications, previous surgical history, and current surgical and non-surgical indications for TRAM/DKP FDC will be captured via a structured questionnaire.

Numerical Pain Rating Scale (NRS):

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, 34)

Patients should complete the assessments in the ClaimIt app within 10 minutes of the defined interval.

Patient global evaluation (PGE):

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.

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

Statistical analysis plan

Primary objective:

To understand the enrollment and real-world usage of TRAM/DKP FDC in Asia, demographic characteristics (i.e., age, BMI, sex, race, etc.) 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 percent 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 standard deviation (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 1st dose and at 30 minutes, 1, 2, 4, 6, and 8 hours after the 1st dose on Day 1, and daily from Day 2 to Day 5. Descriptive statistics in the form of mean, median, and standard deviation (SD) will be calculated for pain scores collected at six different time points (prior to 1st dose, 8 hours post 1st dose, Day 2, Day 3, Day 4, 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 (ANCOVA) 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 1st 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-hour from baseline on Day 1.

Secondary objectives: Safety Data

The secondary objectives of the study is to evaluate the safety of TRAM/DKP FDC treatment in Asia in the real-world setting; the incidence, frequency, distribution, and severity of adverse drug reactions (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 percent 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 standard deviation (SD) will be calculated as well.

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

ETHICAL CONSIDERATIONS

Participation in the study

Participation in this study is wholly voluntary. Participants can stop participating in this study at any time by informing the principal investigator (PI). Likewise, the PI can also discontinue the participation if the patient is found unsuitable to participate in the study (e.g., 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 (TLS) will be used to secure all data in transit. The database will incorporate the needed programmed edit checks to help ensure quality data.

DISCUSSION

Acute pain, when not managed properly has significant psychosocial consequences. It is therefore important to diagnose and manage pain with effective analgesics to reduce complications and progression to chronic pain (20, 35). Even though there are several treatments available for acute and chronic pain, such as paracetamol, non-steroidal anti-inflammatory drugs, opioids, tricyclic antidepressants and anticonvulsants, there is limited clinical evidence in the real-world setting in Asia (36, 37). Furthermore, the adherence to these treatments and the level of patient satisfaction associated with treatment is poorly understood (38, 39).

Studies have shown that attaining effectual pain relief and patient satisfaction with monotherapy is less effective compared to multimodal analgesia. Thus, combination analgesics with different

mechanism of action is widely used due to their potential synergistic effect on reducing pain, improving tolerability and minimising side effects (20, 33, 40). Expert consensus statements and guidelines have highlighted the importance of multidisciplinary and multimodal approaches in pain management and recommend the use of combination analgesics (41–43).

Among the FDC analgesics, TRAM/DKP has shown significant analgesic effect, faster onset and reduced adverse events in clinical trials on musculoskeletal and visceral pain (9, 17-19, 32). However, these studies were conducted on a limited number of patients and were conducted in the Caucasian population with strict inclusion criteria, limiting the generalisability of these studies to the Asian population. A case study in Asian patients has shown that TRAM/DKP FDC is effective in the short-term management of moderate to severe pain and is well tolerated in post-surgical patients (33).

The REKOVER study will evaluate the usage patterns of TRAM/DKP FDC and pain management practices in Asia. This study is designed to evaluate the effectiveness and tolerability of TRAM/DKP FDC in patients with moderate to severe acute pain. REKOVER study will recruit surgical and non-surgical patients experiencing moderate to severe pain from tertiary-care hospitals in four countries in Asia. Recently, greater emphasis has been given to include patient reported outcomes such as quality of life and patient satisfaction in pain management (44, 45). This study will provide an overall assessment of satisfaction with TRAM/DKP FDC treatment using a 5-point PGE questionnaire.

CONCLUSION

REKOVER is the first digitally enabled real-world prospective multi-country, multi-centre study in Asia to evaluate the effectiveness, tolerability and patient satisfaction of using TRAM/DKP

FDC in short-term treatment of moderate to severe acute pain. It will expand our knowledge on the usage of TRAM/DKP FDC and clinical practices in acute pain management in Asia.

Acknowledgments

Menarini Asia-Pacific Holdings Pte Ltd, Singapore is the sponsor of this study. The project management team from ObvioHealth, USA is managing this study.

Author contributions

The study concept and designed was done by DN. BG drafted the manuscript. All author provided intellectual advice and revised the manuscript.

Competing interests

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

Patient involvement and consent

Only those patients who provided consent for this study will be enrolled in this study. Patient consent is not applicable for this publication.

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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 (e.g., 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

TRAM/DKP FDC= Tramadol and Dexketoprofen Trometamol fixed-dose combination
NSAIDs=Non-steroidal anti-inflammatory drugs
MAO= Monoamine oxidase inhibitors

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)	√					
Co-morbid disorders and ongoing medications	√					
Type of surgery performed	√					
All Intraoperative medications	√					
All Post-operative medications	√	√	√	√	√	√
TRAM/DKP FDC dosing frequency and duration of treatment	√	√	√	√	√	√
Post-Surgical (in hospital) started at which day of surgery						
Pain medications prescribed along with TRAM/DKP FDC to manage post- surgical pain and non-surgical pain	√	√	√	√	√	√
Pain medication after completion of TRAM/DKP FDC treatment	√	√	√	√	√	√
Pain score: Numerical Pain Rating Scale (NRS) baseline**	√†	√‡	√‡	√‡	√‡	√‡
Patient global evaluation (PGE) **	At the end of TRAM/DKP FDC treatment					
Adverse events (AE)	√	√	√	√	√	√

*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, 1hr, 2hr, 4hr, 6hr, 8hr post dose
‡After 6 hr. of 1st dose on that day
BP=Blood pressure
PR=Pulse rate
TRAM/DKP FDC= Tramadol and Dexketoprofen Trometamol fixed-dose combination

STROBE Statement—checklist of items that should be included in reports of observational studies
Manuscript: 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

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9-10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	10 and 25
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*11-14*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	13-15
		(*c*) Explain how missing data were addressed	15
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n.a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6, 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

REKOVER Study Protocol: A Prospective Patient Treatment Registry of Tramadol and Dexketoprofen Trometamol Oral Fixed-dose Combination (SKUDEXA^{TM})in Moderate to Severe Acute Pain in Real-World Setting in Asia

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Keywords:	PAIN MANAGEMENT, Follow-Up Studies, Pain management < ANAESTHETICS

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 is 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, multi-country, multi-centre, prospective, real-world observational study. A total of 750 post-surgical 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 six 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.

Keywords: Dexketoprofen Trometamol, Pain, Real-world, TRAM/DKP FDC, and Tramadol

Strengths and limitations of this study

1. 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 TRAM/DKP FDC.
2. The patient reported outcome measures such as patient global evaluation will provide information about the patient's satisfaction with the treatment.
3. 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.
4. The key limitation of this study will be the potential loss to follow-up and missing data points.
5. 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 post-operative 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 under-treated pain not only represents the most pervasive health problem in the aging 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, i.e. multimodal analgesia.

In this regard, Dexketoprofen (DKP) is a well known nonsteroidal 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 Dexketoprofen 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 (25mg) and TRAM (75mg) 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 (30), soft tissue surgeries (31), and joint replacement surgeries (32) involving some 1,900 patients, it has been granted the indication for the short-term (i.e. 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 (19, 30–32).

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 (33). 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.

***The primary endpoints of this study are*:**

- 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 post-surgical and non-surgical patients

The secondary endpoints of this study are:

- 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 and discontinuation due to adverse drug reactions 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. 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. 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 Orthopedics Institute, Cardinal Santos Medical Center, The Medical City Manila, and Adventist Medical Center Manila.

Study Design

This study is a Phase IV, multi-country, multi-centre, 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% post-surgical 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 (post-surgical 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 (post-surgical 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 (hr), 2hr, 4hr, 6hr, and 8hr post first dose, however for Day 2 to Day 5, pain scores will be recorded 6hr 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 adverse events (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 past medical history, comorbidities, ongoing medications, previous surgical history, and current surgical and non-surgical indications for TRAM/DKP FDC will be captured via a structured questionnaire.

Numerical Pain Rating Scale (NRS):

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, 34)

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

Patient global evaluation (PGE):

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 (34, 35).

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 of post-surgical 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 enrollment and real-world usage of TRAM/DKP FDC in Asia, demographic characteristics (i.e., age, BMI, sex, race, etc.) 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 percent 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 standard deviation (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 1st dose and at 30 minutes, 1, 2, 4, 6, and 8 hours after the 1st dose on Day 1, and daily from Day 2 to Day 5. Descriptive statistics in the form of mean, median, and standard deviation (SD) will be calculated for pain scores collected at six different time points (prior to 1st dose, 8 hours post 1st dose, Day 2, Day 3, Day 4, 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 (ANCOVA) 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 1st 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-hour 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 adverse drug reactions (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 percent 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 standard deviation (SD) will be calculated as well.

A standardisation process to group the patients will be adopted at the end, post-completion 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 statement

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 principal investigator (PI). Likewise, the PI can also discontinue the participation if the patient is found unsuitable to participate in the study (e.g., 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 (TLS) will be used to secure all data in transit. The database will incorporate the needed programmed edit checks to help ensure quality data.

Author contributions

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, MAC, PS, RS, 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 Pte Ltd, Singapore. All other authors report receiving investigator fee for this study from A. Menarini Asia-Pacific Holdings Pte Ltd, Singapore.

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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 (e.g., 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

TRAM/DKP FDC= Tramadol and Dexketoprofen Trometamol fixed-dose combination
NSAIDs=Non-steroidal anti-inflammatory drugs
MAO= Monoamine oxidase inhibitors

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)	√					
Co-morbid disorders and ongoing medications	√					
Type of surgery performed	√					
All Intraoperative medications	√					
All Post-operative medications	√	√	√	√	√	
TRAM/DKP FDC dosing frequency and duration of treatment Post-Surgical (in hospital) started at which day of surgery	√	√	√	√	√	
Pain medications prescribed along with TRAM/DKP FDC to manage post- surgical pain and non-surgical pain	√	√	√	√	√	
Pain medication after completion of TRAM/DKP FDC treatment	√	√	√	√	√	
Pain score: Numerical Pain Rating Scale (NRS) baseline**	√†	√‡	√‡	√‡	√‡	
Patient global evaluation (PGE) **	At the end of TRAM/DKP FDC treatment					
Adverse events (AE)	√	√	√	√	√	√

*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, 1hr, 2hr, 4hr, 6hr, 8hr post dose

‡After 6 hr. of 1st dose on that day

BP=Blood pressure

PR=Pulse rate

TRAM/DKP FDC= Tramadol and Dexketoprofen Trometamol fixed-dose combination

STROBE Statement—checklist of items that should be included in reports of observational studies
Manuscript: 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

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	9-10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	10 and 25
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*11-14*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	13-15
		(*c*) Explain how missing data were addressed	15
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n.a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6, 17-18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.