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STUDY PROTOCOL

DANTE Study: The First Randomized, Double-Blind, Placebo and Active-Controlled, Parallel Arm Group Study Evaluating the Analgesic Efficacy and Safety of Dexketoprofen TrometAmol aNd Tramadol Hydrochloride Oral FixEd Dose Combination on Moderate to Severe Acute Pain in Patients with Acute Low Back Pain—Rationale and Design

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ABSTRACT

Introduction: Despite a wide range of treatment approaches and the availability of treatment recommendations or guidelines, no consensus on the most effective pharmacological therapy of low back pain (LBP) has been reached yet. Therefore, additional clinical evidence, particularly if built upon a rigorous clinical trial design, an evidence-based medication choice, and broader inclusion criteria better acknowledging the heterogeneity and intrinsic variability of LBP is needed. The DANTE study has been designed to comprehensively assess the analgesic efficacy and tolerability of dexketoprofen/tramadol (DKP/TRAM) 75/25 mg in a large cohort of patients with moderate to severe acute LBP.

Methods: The DANTE study is a phase IV, multicenter, randomized, double-blind, double-dummy parallel group, placebo, and active controlled study. The DANTE study encompasses a single-dose phase (day 1, t0–t8h) and a multiple-dose phase (from t8h to 8 h after intake of last dose at day 5). The DANTE study population includes patients naïve to LBP or patients with previous history of LBP experiencing a new episode of moderate to severe intensity with or without radiculopathy. The clinical phase of the DANTE study started in September 2020 and the anticipated completion date is April 2022.

Planned Outcomes: The primary endpoint is the time to first achieve a numeric rating scale-pain intensity (NRS-PI) score of < 4 or a pain intensity reduction $\geq 30\%$ from drug intake up to 8 h after the first dose (t8h). Secondary objectives aim are: (1) to evaluate the analgesic efficacy of TRAM/DKP 75/25 mg versus TRAM 100 mg after the first dose; (2) to evaluate the analgesic efficacy of TRAM/DKP 75/25 mg versus TRAM 100 mg after the multiple doses (from

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t8h until day 5, multiple dose); and (3) to assess the safety and tolerability of the TRAM/DKP 75/25 mg fixed combination after single and multiple doses.
DANTE Study Registration: EudraCT number: 2019-003656-37.

Keywords: Low back pain; Dexketoprofen; Tramadol; Acute pain; Radiculopathy

Key Summary Points

Why carry out this study?

Despite a wide range of treatment approaches and the availability of treatment recommendations or guidelines, no consensus on the most effective pharmacological therapy of low back pain (LBP) has been reached yet.

Additional clinical evidence, particularly if built upon a rigorous clinical trial design, an evidence-based medication choice, and broader inclusion criteria better acknowledging the heterogeneity and intrinsic variability of LBP is needed.

The DANTE study has been designed to comprehensively assess the analgesic efficacy and tolerability of dexketoprofen/tramadol (DKP/TRAM) 75/25 mg in a large cohort of patients with moderate to severe acute LBP.

What will be learned from the study?

The DANTE study will better elucidate the clinical benefits of TRAM/DKP 75/25 mg in the treatment of acute moderate to severe LBP in both naïve, recurrent, and exacerbating chronic LBP patients versus existing standard of care options.

The DANTE study will provide the first evidence of the effect of TRAM/DKP on the functional disability of patients with LBP through the Roland-Morris Disability Questionnaire, measured both at baseline and at the end of the study treatment period

The DANTE study will explore, for the first time, satisfaction of patients affected by LBP and treated with TRAM/DKP 75/25 mg using both the Treatment Satisfaction Questionnaire for Medication and patient global evaluation at the end of treatment period even in comparison to the active comparator.

Overall, the DANTE study will expand current knowledge and clinical evidence supporting the use of TRAM/DKP 75/25 mg in LBP management.

INTRODUCTION

Low back pain (LBP), the most prevalent musculoskeletal condition, stands as a global health concern characterized by an estimated lifetime prevalence of 50–80% [1]. Although LBP incidence is estimated to be between 13 and 31%, that of radicular symptoms in LBP patients ranges from 12% to 40% [2]. Over the last decades, a significant rise in disability has been documented worldwide in patients with LBP, with a peak at 45–49 years of age and a higher burden among women compared to men [3]. Hence, LBP is a leading cause of activity limitation and work absenteeism resulting in a relevant social and economic burden [4, 5].

According to current international guidelines, a diagnostic triage classification into one of the following categories is generally recommended: non-specific LBP, specific LBP, or radiculopathy/sciatica. Radiculopathy/sciatica is a term used to describe a pain syndrome caused by compression or irritation of nerve roots in the lower back [2, 6]. Symptoms may also be accompanied by numbness, weakness and loss of reflexes [2] and can be characterized by greater pain intensity, disability and, consequentially health care expenses [7–9]. Indeed, non-specific LBP is defined as low back pain not attributable to a specific cause and represents 90–95% of the cases. These data may highlight the lack of specificity of the commonly

employed diagnostic and clinical tests as well as imaging techniques when considered in isolation [10], and the need for greater advances in pathoanatomical understanding of pain symptoms to address the causes of non-specific LBP [11].

Thus, the diagnostic evaluation of patients with LBP can be challenging and requires complex clinical decision-making. Nevertheless, the identification of the source of the pain is essential to determine the therapeutic approach [12].

Along with appropriate and effective pain relief, LBP treatment goals should also include the prevention of recurrent acute pain episodes because at least one third of patients experience a recurrence within 1 year of recovering from a previous episode, thus becoming prone to develop chronicity [13, 14]. Hence, given the strong tendency of LBP to become chronic, early intervention is important in patients with acute LBP to prevent progression to chronic pain whose management is particularly challenging and for which the most effective pharmacological therapy is still controversial [15, 16].

Several treatment options are available for the management of acute LBP although most of them lack a high level of evidence [6, 17, 18]. Furthermore, adherence to such treatments is largely variable [19–21] and associated with modest patient treatment satisfaction [22]. Studies suggest that more than one quarter of LBP care is inappropriate [23] and that care appears to be insufficient in patients with comorbidities [24]. Thus, there is a need to provide high-quality care in the pharmacological treatment of LBP and improve its appropriateness by implementing and expanding current clinical evidence of available medications.

Pharmacological treatments for the management of patients with LBP generally encompass paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) as first-line treatment options, along with other pain medications, such as opioids, tricyclic antidepressants (TCAs), and anticonvulsants [25, 26], when the LBP becomes chronic, and whose use depends on the type of LBP and patient history [24, 27]. However, evidence regarding the efficacy of paracetamol [28, 29] is insufficient for drawing firm conclusions as it has not shown to be effective in reducing acute LBP [30], nor able to affect the time of recovery compared to placebo at a regular or as-needed dosing regimen [28]. In addition, a systematic review suggested that for acute LBP, there is high-quality evidence for no difference between paracetamol and placebo in primary outcomes (e.g., pain and disability) at 1 week (immediate term) and at 2, 4 and 12 weeks (short term), and on the quality of life, function, global impression of recovery, and sleep quality [31]. Finally, results are conflicting on the efficacy of several NSAIDs, such as naproxen, piroxicam, and diclofenac, in the treatment of LBP [32–34]. Accomplishing an adequate pain control with monotherapy is difficult, thus combining drugs with non-redundant mechanisms of action to provide adequate pain relief and reduce the side effects from higher doses of individual drugs is paramount. In this regard, combining an oral opioid (such as tramadol) and a non-opioid (such as paracetamol or NSAIDs) offers a plausible option.

In this regard, multimodal analgesia is regarded as the cornerstone of effective pain treatment [35, 36], and all currently available guidelines emphasize the importance of a multimodal and multidisciplinary approach to develop a strategy able to solve the problem and not simply to relieve pain [12].

Combining medicines may provide greater pain relief and/or improved tolerability [37]. In this regard, cyclo-oxygenase (COX) inhibitor/opioid receptor agonist combinations hold great potential as effective pillars in the multimodal pain management by providing adequate analgesia with fewer safety risks due to COX inhibitors' opioid-sparing effect [38]. Combination drug therapy, such as an opioid analgesic combined with acetaminophen or an NSAID or a muscle relaxant, is frequently used in clinical practice to manage back pain [37]. In line with this, in a recent Delphi survey, most respondents agreed with the use of a combination opioid and NSAID/paracetamol in moderate to severe–acute refractory LBP [24]. However, the lack of studies and the overall low quality of

current evidence limit the recommendation of a combination drug therapy for the management of LBP [37].

Among the clinically available fixed-dose combinations of COX inhibitor and opioid receptor agonist, the combination tramadol/dexketoprofen 75/25 mg (TRAM/DKP) holds great promise as a multimodal analgesic option due to its analgesic efficacy, fast onset of action, and sustained duration, as documented in surgical models of both somatic and visceral pain [39–43].

Recent evidence of the potential effectiveness of TRAM/DKP in LBP has been reported in observational studies. These studies showed that the oral fixed-dose combination can be a valuable and effective option in patients with acute LBP associated to lumbar disc herniation [44] and in patients with non-specific LBP [45].However, such studies were single-center retrospective clinical trials with relatively small sample sizes (< 100 patients each) and excluded patients with history of chronic LBP [45].

Therefore, to further define the value of TRAM/DKP, we have designed a large multicenter, randomized, double-blind, double-dummy, parallel group trial, the DANTE study, to prospectively assess the efficacy of TRAM/DKP and ultimately provide high-quality evidence in moderate to severe acute LBP with or without radiculopathy (EudraCT Number: 2019-003656-37). The aim of this publication is to describe the rationale and design of the DANTE study.

METHODS

Study Design

The DANTE study is a phase IV, multicenter, randomized, double-blind, double-dummy parallel group, placebo, and active controlled study. The DANTE study encompasses two phases: a single-dose phase (day 1, t0–t8h), and a multiple-dose phase starting immediately after the single-dose phase (from t8h to 8 h after intake of the last dose at day 5). The individual study participation will last up to 8 days, including: (1) visit 1 (day 1), which is the screening phase, randomization, and first administration of study treatment; (2) complete treatment and assessment period, from day 1 to day 5; after the last dose intake on day 5, the "follow-up period" will last until visit 2 (day 6 ± 2 days); and (3) visit 2 (day 6 with an allowed time-window of +2 days), which is the end of the study and last study visit. Figure 1 shows the DANTE study scheme. A follow-up phone call after each of visit 1 and visit 2 will be placed within 24 h of receiving the laboratory tests performed either at screening (visit 1) or at the end of study (visit 2) only in case of any abnormality and clinically relevant results, and in accordance with investigator judgement. Patients will be randomized at a 4:4:1:1 ratio to one of three treatment groups: TRAM/DKP 75/25 mg, administered orally as a single film-coated tablet every 8 h, tramadol 100 mg, or placebo. The double-dummy technique will be applied to ensure double-blind condition of TRAM/DKP 75/25 mg versus TRAM 100 mg versus placebo administration. To date, TRAM/DKP 75/25 mg as well as the placebo tablets will be provided as film-coated tablets with matching appearance and weight. The active comparator, TRAM 100 mg, will be provided as two capsules of a marketed drug, tramadol 50 mg, and, for blinding, two capsules of placebo will be provided with matching appearance and weight. Paracetamol 500 mg for a maximum of 2 g per day is the recommended rescue medication (RM).

The study will be conducted in the primary care and hospital setting in six European countries (Croatia, Estonia, Hungary, Latvia, Poland, and Spain), involving approximately 50 participating centers (Electronic Supplementary Material). The study aims to recruit approximately 510 evaluable patients with moderate to severe acute LBP. The clinical phase started in September 2020 and is planned to be completed by the end of April 2022. The study is being conducted in accordance with the International Conference on Harmonization/Good Clinical Practice guidelines and the Declaration of Helsinki of 1964 and later amendments. The protocol was approved by the local ethics committees. All patients will have provided a

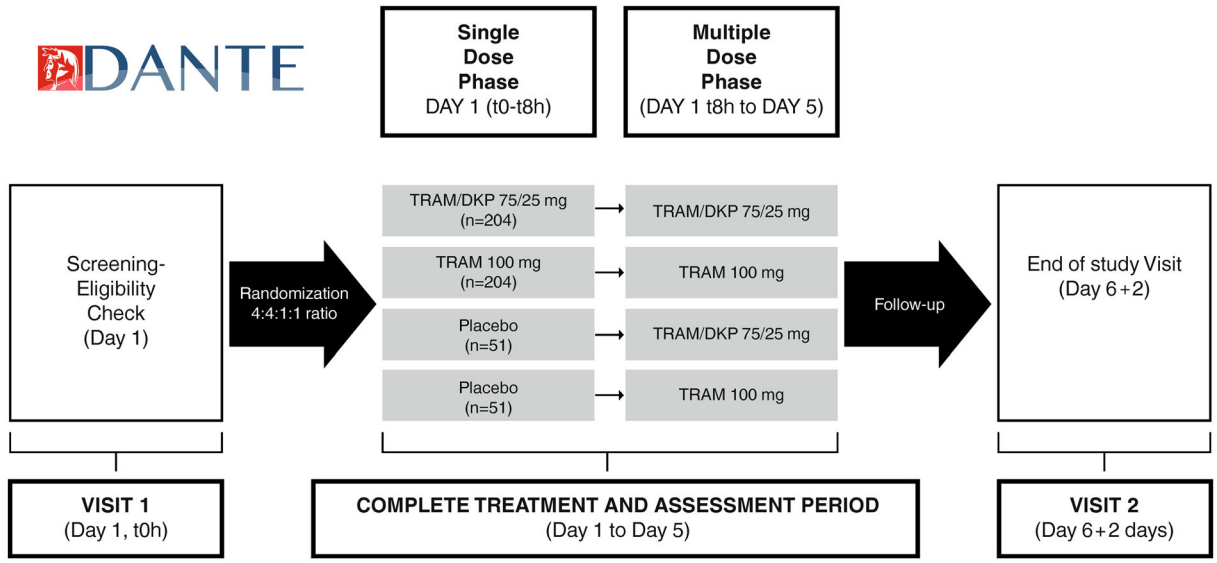

Fig. 1 DANTE study design. Participants experiencing moderate to severe acute low-back pain (*LBP*) will be randomized at a 4:4:1:1 ratio to one of three treatment groups: tramadol/dexketoprofen (*TRAM/DKP*) 75/25 mg administered orally as a single film-coated tablet every 8 h; TRAM 100 mg administered as two capsules each containing TRAM 50 mg every 8 h; or placebo. TRAM/DKP 75/25 mg as well as the placebo tablets will be provided as film-coated tablets with matching appearance and weight. The active comparator, TRAM 100 mg, will be provided as two capsules of a marketed drug tramadol 50 mg and, for blinding, two capsules of placebo will be provided with matching appearance and weight. In the multiple-dose phase, patients who received placebo will switch to TRAM/DKP 75/25 mg or TRAM 100 mg according to the randomization scheme

written informed consent before participating in any study procedures.

Patient Selection

The DANTE study will enroll naïve patients to LBP or patients with a previous history of LBP in which new episodes of moderate to severe intensity were experienced [numerical rating scale (NRS) score ≥ 5], with or without radiculopathy. Full inclusion criteria are listed in Table 1. Exclusion criteria include: acute LBP and radiation to limb with presence of neurologic signs (focal weakness, asymmetry of reflexes, sensory loss in a dermatome, or loss of bowel, bladder, or sexual function) according to the Quebec Task Force Classification [46]; spinal surgery within the preceding 6 months; known or suspected serious spinal pathology (e.g., metastatic, inflammatory or infective diseases of the spine, cauda equine syndrome, trauma, spinal fracture); treatment with topical preparations/medications within 4 h prior to screening, anesthetics and muscle relaxants within 8 h prior to screening, short-acting analgesics (e.g., paracetamol) within 4 h prior to screening, other analgesics within 5 half-lives prior to screening, or use of an opioid within the 14 days preceding screening; treatment with high doses of salicylates (≥ 3 g/day), anticoagulants, thrombolytic and antiplatelet agents, heparins, corticosteroids (except inhalers and topical agents), lithium, methotrexate, used at high doses of ≥ 15 mg/week, hydantoins (including phenytoin) and sulphonamides, antiepileptics, antipsychotics, serotonin reuptake inhibitors [selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)], and TCAs, and analgesics within 48 h or 5 half-lives (whichever is the longer) prior to screening; treatment with sedatives (e.g., benzodiazepines) and hypnotic agents within 8 h before screening; any chronic or acute painful condition

Table 1 DANTE study inclusion criteria

DANTE study inclusion criteria
Male or female patients aged 18–65 years with acute LBP of moderate to severe intensity (NRS score ≥ 5 to ≥ 7 for moderate pain and NRS > 7 for severe pain), whose onset of the current acute LBP episode is within 48 h prior to screening
Patients with or without radiculopathy, excluding those with neurologic signs, according to the Quebec Task Force classification [46]
Naïve patients to any LBP or patients with previous history of LBP experiencing a new episode, preceded by a period of at least 2 months without any LBP prior to screening
Patients should be free from analgesic due to previously administered pain killer (immediate or slow-release formulations)

LBP Lower back pain, *NRS* numerical rating scale

other than the study indication that may interfere with the assessment of the efficacy of the study treatment and any non-pharmacological interventional therapy for LBP (physical therapy, acupuncture, massage, etc.) 1 month before screening. Pregnant and breastfeeding women and patients presenting any of the contraindications reported for TRAM/DKP, TRAM or RM (according to the summary of product characteristics) will be not enrolled.

Procedures and Study Visits

The activities, procedures, and tests to be performed at each study visit are shown in Table 2. During the screening, the patients will be asked to rate their pain intensity (PI) to assess their eligibility for randomization. The randomized patient will receive an e-diary and related instructions about its usage; a box with investigation medicinal products (IMP); and RM and instructions on its usage; the patients will also be given instructions on how to record the NRS-PI and Verbal Rating Scale-Pain Relief (VRS-PAR) scores to the e-diary before RM intake and how to complete the patient's pain and analgesia assessments. The treatment and assessment period will consist of a single-dose phase (t0 to t8h, day 1) and a multiple-dose phase (t8h to day 5). Prior to the administration of the study treatment, a baseline PI (t0h, visit 1) will be recorded based on the NRS-PI, and the Roland Morris Disability Questionnaire (RMQ) will be administered to patients. The RMQ is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale. Each question is worth 1 point, so scores can range from 0 (no disability) to 24 (severe disability) [47, 48].

Single-Dose Phase (t0-t8h, Day 1)

The single-dose phase corresponds to the first 8 h after the first study treatment administration (TRAM/DKP 75/25 mg or TRAM 100 mg or placebo) that will take place on day 1. NRS-PI and VRS-PAR will be recorded by the patients on the e-diary at predefined timeframes (from 15 min up to 8 h after the study drug intake and immediately before the RM intake, if any). At the end of the single-dose phase (t8h), subjects will be asked to answer the question: "How would you rate the medication received for your pain?" using a 5-point VRS, where: 1 = 'poor,, 2 = 'fair,' 3 = 'good,' 4 = 'very good,' and 5 = 'excellent' [patient global evaluation (PGE)]. First intake of RM, if any, as well as the occurrence of any adverse event (AE) as spontaneous reporting and changes in concomitant medications (CMs), if any, will be collected by study staff while the patients are at the site.

Multiple-Dose Phase (t8h Day 1-Day 5)

The multiple-dose phase will begin 8 h after the first dose has been administered. Patients receiving TRAM/DKP 75/25 mg or TRAM 100 mg during the first 8 h will continue with

Table 2 DANTE study visits and procedures

Procedure	VISIT 1: Eligibility check[a] Screening (day 1)	Complete treatment and assessment period					VISIT 2: end of study[c]
		Single-dose phase: day 1			Multiple-dose phase: days 1 to 5[b]		
		t0	t15m, t30m, t1h, t1.5 h, t2h, t4h, t6h	t8h	From 2nd dose to last dose on day 5	8 h after last study dose	Day 6 + 2 days (allowed window)
Informed consent	X						
Demographics	X						
Inclusion/exclusion criteria	X						
Medical history	X						
Physical examination	X						X
Height and weight	X						
Vital signs (HR, BP)	X						X
Safety laboratory tests	X						X
Pregnancy test	X						X
e-Diary instructions, dispensing and training	X						
Return of e-diary, IMP, RM, and empty blister							X
IMP and RM dispensation	X						
Randomization to treatment	X						
NRS-PI	X	X	X	X	X (every day BEFORE and 2 h AFTER each dose intake)	X	
PAR-VRS			X	X	X (every day BEFORE and 2 h AFTER each dose intake)	X	
PGE				X		X	
RMQ		X				X	
TSQM						X	

Table 2 continued

Procedure	VISIT 1: Eligibility check[a] Screening (day 1)	Complete treatment and assessment period			VISIT 2: end of study[c]
		Single-dose phase: day 1	Multiple-dose phase: days 1 to 5[b]		
		t0 t15m, t30m, t1h, t1.5 h, t2h, t4h, t6h t8h	From 2nd dose to last dose on day 5	8 h after last study dose	Day 6 + 2 days (allowed window)
IMP and RM return and accountability					X
Concomitant/ prohibited medication	Throughout the study period				
Adverse events	Throughout the study period				
Treatment compliance[d]	Throughout the study period				

BP Blood pressure, *HR* heart rate, *IMP* investigational medicinal product, *NRS-PI* pain intensity as assessed by Numerical Rating Scale (NRS), *PAR-VRS* pain relief as assessed by Verbal Rating Scale (VRS), *PGE* patient global evaluation, RM rescue medication, *RMQ* Roland Morris Disability Questionnaire, *TSQM* Treatment Satisfaction Questionnaire for Medication

[a]A follow-up phone call after visit 1 will be made within 24 h of receiving the laboratory test results ONLY when there are abnormal and clinically relevant laboratory test results according to the investigator judgement

[b]After the last dose intake on day 5, the "follow-up period" will last until visit 2

[c]A follow-up phone call after visit 2 will be made within 24 h of receiving the results ONLY when there are abnormal and clinically relevant laboratory test results according to investigator judgement

[d]Treatment compliance will be monitored from visit 1 to end of study treatment

the same treatment while patients who receive placebo will switch to TRAM/DKP 75/25 mg or TRAM 100 mg according to the randomization scheme specified above. In detail, patients will be randomized in a 4:4:1:1 ratio to one of the four possible treatment arms (204 patients for TRAM/DKP 75/25 mg arm; 204 patients for TRAM 100 mg arm; 102 for placebo arm, with 51 switching to TRAM/DKP 75/25 mg and 51 switching to TRAM 100 mg in the multiple-dose phase). During the multiple-dose phase, 12 doses of study treatment will be administered, with the last study drug intake administered within day 5 and a dosing frequency of 8 h.

During the multiple-dose phase, the patients will continue recording NRS-PI and VRS-PA scores on their e-diaries; RMQ, PGE, and Treatment Satisfaction Questionnaire for Medication (TSQM) scores will also be recorded as assessments performed on day 5, 8 h after the last dose or whenever patients discontinue treatment. The TSQM comprises 14 questions that provide scores on four scales: effectiveness (3 items), side effects (5 items), convenience (3 items), and global satisfaction (3 items) [49]. Of note, during the multiple-dose phase, the study team will record AEs on spontaneous reporting. After the last dose intake on day 5, the "follow-up period" will last until visit 2 (day 6 + 2 days). A patient will be considered lost to follow-up if he or she fails to return for the scheduled visits and is unable to be contacted by the study site staff.

Study Endpoints

The DANTE study evaluates the analgesic efficacy of TRAM/DKP fixed combination versus placebo in patients with moderate to severe acute LBP after the first dose [first 8 h (t8h), primary objective]. The primary endpoint is the time to first achieve a NRS-PI score of < 4 or a pain intensity reduction $\geq 30\%$ from drug intake up to 8 h after the first dose (t8h). Secondary objectives aim at: (1) to evaluate the analgesic efficacy of TRAM/DKP 75/25 mg versus tramadol (TRAM) 100 mg after the first dose; (2) to evaluate the analgesic efficacy of TRAM/DKP 75/25 mg versus tramadol (TRAM) 100 mg after the multiple doses (from t8h until day 5, multiple dose); (3) to assess the safety and tolerability of TRAM/DKP 75/25 mg fixed combination after single and multiple doses. Several secondary endpoints will also be analyzed, related to the single and multiple study phases as well as to the complete treatment and assessment period; the complete list of secondary endpoints is provided in Table 3. Safety endpoints include incidence, intensity (severity), seriousness, and treatment causality of treatment-emergent AEs (TEAEs, reported starting from the study medication intake) as well as the frequency of clinically significant changes in clinical laboratory evaluations, physical examination, and vital signs post-dose versus baseline.

Sample Size

A sample size of 510 patients is required to detect the difference between TRAM/DKP 75/25 mg and placebo and to demonstrate the non-inferiority of TRAM/DKP 75/25 mg versus TRAM 100 mg for the time to first achieve an NRS-PI score < 4 or a pain intensity reduction of $\geq 30\%$ from drug intake up to 8 h after the first dose. A sample size of 204 patients (102 for each treatment arm) was considered appropriate for detecting the superiority of TRAM/DKP 75/25 mg versus placebo, assuming a power of 80%, alpha of 0.05, and a hazard ratio of 1.5 with a relative Wald confidence interval of 1.17–1.97 and the probability of event of 0.961 and 0.835 in the treatment and placebo groups, respectively, based on previous studies. Additionally, a total of 408 randomized patients (204 for each treatment arm) is also sufficient assessing the non-inferiority of TRAM/DKP 75/25 mg versus TRAM 100 mg, assuming a hazard ratio of 1.06, a non-inferiority margin of 0.8, a power of 80%, alpha of 0.025, and proportions of events of 96.1% and 94.7%, respectively (based on previous studies). The 510 patients will be randomized in a 4:4:1:1 ratio (204 for TRAM/DKP 75/25 mg; 204 for TRAM 100 mg; and 102 for placebo, with 51 switching to TRAM/DKP 75/25 mg and 51 switching to TRAM 100 mg in the multiple-dose phase). Assuming an approximately 20% screen failure rate, 612 patients are expected to be screened.

Statistical Analysis

The efficacy analysis will be run on the intention-to-treat (ITT) population, that is, all of the randomized patients. The primary efficacy variable, time to first achieve an NRS-PI score < 4 or a pain intensity reduction $\geq 30\%$ from drug intake up to 8 h after the first dose, will be analyzed for the superiority of TRAM/DKP 75/25 mg versus placebo on the ITT population using a Cox proportional hazard (CPH) model with treatment, baseline PI categories, and baseline radiculopathy categories as covariates. A two-sided significance level of 5% will be used. Non-inferiority of TRAM/DKP 75/25 mg versus TRAM 100 mg will be tested with a one-sided significance level of 2.5%. Non-inferiority will be satisfied if the lower limit of the confidence interval is greater than a non- inferiority margin: 0.80 (based on hazard ratio) for time to "event" variables, 20% (based on least significant means) for continuous variables, and 0.80 (based on the odds ratio) for binary variables. Non-inferiority will be tested on the PP population. Secondary efficacy variables will be analyzed by an analysis of covariance (ANCOVA) with treatment and the baseline value as covariates.

Table 3 Secondary endpoints

Single-dose phase (day 1: t0-t8h)
PAR-VRS scores at each prespecified time point (t15m, t30m, t1h, t1.5 h, t2h, t4h, t6h, t8h) over the 8 h after the first dose
TOTPAR at 4, 6, and 8 h (TOTPAR4, TOTPAR6, TOTPAR8) after the first dose
Percentage of maximum TOTPAR (% max TOTPAR) at 4, 6 and 8 h after the first dose
Percentage of patients achieving at least 50% of maximum TOTPAR at 4, 6, and 8 h after the first dose
Mean PI-VAS scores at each prespecified time points (t15m, t30m, t1h, t1.5 h, t2h, t4h, t6h, t8h) over the 8 h after the first dose
SPID at 4, 6, and 8 h (SPID4, SPID6, SPID8) after the first dose
Percentage of maximum SPID (% max SPID) at 4,6, and 8 h after the first dose
Percentage of patients achieving at least 30% of pain intensity reduction versus baseline at 4, 6, and 8 h after the first dose
PGE of the study medication at 8 h after the first dose
Time to RM: time elapsed between treatment administration and the first dose of RM from baseline till 8 h after the first dose
Percentage of patients who required RM within the first 4, 6, or 8 h after the first dose
Multiple-dose phase: (from t8h to 8h after the last dose intake at day 5)
PAR-VRS scores at each prespecified time point over the multiple-dose phase
TOTPAR at 24, 48, 72, and 96 h (TOTPAR24, TOTPAR48, TOTPAR72, TOTPAR96) of the multiple-dose phase
Percentage of maximum TOTPAR (% max TOTPAR) at 24, 48, 72, and 96 h of the multiple-dose phase
Percentage of patients achieving at least 50% of maximum TOTPAR at 24, 48, 72, and 96 h of the multiple-dose phase
PI-VAS scores at each prespecified time point over the multiple-dose phase
SPID at 24, 48, 72, and 96 h (SPID24, SPID48, SPID72, SPID96) of the multiple-dose phase
Percentage of maximum SPID (% max SPID) at 24, 48, 72, and 96 h of the multiple-dose phase
Percentage of patients achieving at least 30% of PI reduction versus baseline at 24, 48, 72, and 96 h of the multiple-dose phase
PGE at 96 h of the multiple-dose phase
Percentage of patients who required RM within 24, 48, 72, and 96 h of the multiple-dose phase
RMQ score at 96 h of the multiple-dose phase
TSQM at 96 h of the multiple-dose phase

Table 3 continued

Complete treatment and assessment period: from t0 on day 1 to 8 h after last dose intake on day 5
Time to first achieve an NRS score < 4 or a pain intensity reduction of $\geq$ 30% from the first drug intake till 5 days after the first dose, excluding patients assigned to the placebo treatment arms during the single-dose phase
TOTPAR at 104 h from the first drug intake up to 5 days after the first dose (TOTPAR104), excluding patients assigned to the placebo treatment arms during the single-dose phase
SPID at 104 h from the first drug intake up to 5 days after the first dose (SPID104), excluding patients assigned to the placebo treatment arms during the single-dose phase
Time to RM: Time elapsed between the first drug intake till 5 days after the first dose, excluding patients assigned to the placebo treatment arms during the single-dose phase
Exploratory endpoint:
Time to first achieve an NRS-PI score < 4 AND a pain intensity reduction of $\geq$ 30% from drug intake up to 8 h after the first dose

PAR-VRS Pain Relief–verbal rating scale; *PGE* patient global evaluation; *PI-VAS*, mean pain intensity-visual analogue scale, *RMQ* Roland Morris Disability Questionnaire, *SPID* summed pain intensity difference, *TOTPAR* total pain relief, *TSQM* Treatment Satisfaction Questionnaire for Medication

DISCUSSION

Despite a wide range of pharmacological and non-pharmacological treatment approaches and the availability of treatment recommendations or guidelines [6, 17, 18], no consensus on the most effective pharmacological therapy for LBP has been reached yet because of the lack of high level of evidence [6]. Of note, LBP treatment is often inappropriate in patients presenting comorbidities [23, 24]. In addition, the variable adherence of clinicians to current recommendations [19–21] may likely stem from the limited treatment guidance they retrieve for everyday clinical practice, with a concerning number of patients remaining at a higher risk of recurrence and chronicity. Overall, current LBP management may benefit from additional clinical evidence, particularly if built upon a rigorous clinical trial design, an evidence-based medication choice, and broader inclusion criteria that may better acknowledge the high degree of heterogeneity and intrinsic variability of LBP [50]. In addition, the use of a non-surgical clinical pain model and a comprehensive assessment of both patients' recovery from functional disability and their satisfaction with the prescribed pain medication is also of clinical interest to fully investigate TRAM/DKP efficacy in LBP setting.

The DANTE study has been designed to comprehensively assess the analgesic efficacy and tolerability of DKP/TRAM 75/25 mg in a large cohort of patients with moderate to severe acute LBP. The DANTE study population resembles the heterogeneity observed in LBP clinical practice by including patients with or without radiculopathy, naïve patients, and those experiencing an acute exacerbation of chronic LBP.

A placebo-controlled design has been selected for the single-dose phase (the first 8 h after randomization), in agreement with both the Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain (CPMP/EWP/612/00) [51] and Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain (CPMP/EWP/252/03) [52]. To date, it has been well documented that in LBP trials placebo responses can be clinically significant and may disclose the psychosocial effects of the therapeutic encounter [53]. The use of placebo is limited to the first dose intake and to less than one fifth of

the study population. Moreover, paracetamol is allowed as RM for the entire study treatment period [54]. Tramadol is considered the standard of care for severe acute pain, and it is indicated as an effective option for acute LBP by international guidelines either as first- [17] or second-line [18] treatment, and it has been selected as active comparator. Several analgesic efficacy assessments (pain intensity, pain relief, time to analgesic effect) have been included to provide an accurate evaluation of the onset and duration of action of TRAM/DKP.

Mounting evidence suggests placing greater emphasis on disability outcomes and functional status to fully explore the multifaced dimensions of pain experience as observed in patients with LBP [55, 56]. The DANTE study will provide first evidence for TRAM/DKP effect on LBP patients' functional disability through the RMQ, measured both at baseline and at the end of the study treatment period [57]. The RMQ has been chosen as it is a simple and easily understandable questionnaire, with a high sensitivity to changes in patients with mild-to-moderate disability. It is also well suitable to follow the progress of individual patients in clinical settings [58, 59].

Previous studies highlighted that patient treatment satisfaction appeared to be very modest in the LBP setting [22]. So far, few data on LBP patients' satisfaction with analgesic treatments are available. Accordingly, the DANTE study explores, for the first time, LBP patients' satisfaction with TRAM/DKP 75/25 mg using both TSQM and PGE at the end of treatment period even in comparison to the active comparator. TSQM has proved to be a valid measure for the main dimensions of patients' satisfaction to medications effectively predicting patients' adherence across different patient populations [49]. These outcomes will provide a measure of the perceived analgesic benefit and potentially the patients' willingness to receive TRAM/DKP 75/25 mg in case of future acute exacerbation of LPB.

Earlier evidence suggests that owing to its mechanisms of action (central analgesic effect, peripheral analgesic action, and anti-inflammatory activity) [34, 60], TRAM/DKP 75/25 mg may contribute to pain relief in acute exacerbations of LBP since mono-components have been proven to be effective when nociceptive and neuropathic mechanisms are involved at both local and central levels [60]. To date, the effectiveness of TRAM/DKP 75/25 mg in terms of intensity, rapidity of onset, and duration of analgesia in patients with either moderate or severe acute PI at baseline [36] may confer an additional benefit, thus ensuring a fast recovery of functional status and return to work and social activity.

The main strengths of the DANTE study are the large sample size (larger than previous COX inhibitors and COX inhibitor/opioid combination study cohorts enrolling LBP patients) [33, 34, 44, 45, 50], the heterogeneity of the study population, resembling real-life conditions, the use of multiple analgesic and function assessments, and the comprehensive evaluation of patients' perspective, often neglected in previous clinical trials [28, 33, 34, 50]. One limitation of the study is the lack of a treatment arm receiving a COX inhibitor/opioid combination; nevertheless, in a previous acute moderate-to-severe pain model, TRAM/DKP 75/25 mg demonstrated to be more effective than paracetamol/TRAM in the largest study so far performed in acute patients undergoing impacted third molar extraction [42].

Overall, the DANTE study will better elucidate the clinical benefits of TRAM/DKP 75/25 mg in the treatment of acute moderate-to-severe LBP in both naïve patients and patients with recurrent and exacerbating chronic LBP versus existing standard of care options. Finally, the DANTE study will expand current knowledge and clinical evidence [44, 45] supporting the use of TRAM/DKP 75/25 mg in LBP management.

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Compliance with Ethics Guidelines. The study is being conducted in accordance with the International Conference on Harmonization/Good Clinical Practice guidelines and the Declaration of Helsinki of 1964 and later ammendments. The protocol was approved by the local ethics committees (see ESM files). All patients will have provided a written informed consent before participating in any study procedures.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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