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ORIGINAL RESEARCH

Tramadol/Dexketoprofen Analgesic Efficacy Compared with Tramadol/Paracetamol in Moderate to Severe Postoperative Acute Pain: Subgroup Analysis of a Randomised, Double-Blind, Parallel Group Trial - DAVID Study

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ABSTRACT

Introduction: recently the DAVID study demonstrated the better analgesic efficacy of tramadol hydrochloride/dexketoprofen 75/25mg (TRAM/DKP) over tramadol hydrochloride/paracetamol 75/650mg (TRAM/paracetamol) in a model of moderate to severe acute pain following surgical removal of impacted 3d molar. The aim of this subpopulation analysis was to drill deeper in understanding the relationship between baseline pain intensity (PI) level and the effectiveness in pain control of the TRAM/DKP combination in comparison with the TRAM/paracetamol combination. This will further improve and facilitate the accurate design of future acute pain studies for the use of the TRAM/DKP combination.

Methods: patients experiencing at least moderate pain, defined as a PI score ≥4 in an 11-point Numerical Rating Scale (NRS) were stratified according to NRS-PI at baseline (NRS ≥4, 5, 6,7 or 8) or aggregated in two groups: i) moderate: NRS-PI ≥4 to ≤6; ii) severe: NRS-PI >6. Analgesic efficacy was assessed at pre-specified time points by using pain relief (PAR) on a 5-point verbal rating scale (VRS) and PI on an 11-point NRS. The primary endpoint was total PAR over 6 hours post-dose (TOTPAR6); secondary endpoints included, among others, the time course of mean PAR and PI scores over 8 hours, TOTPAR over 2, 4 and 8 hours post-dose, and the sum of PI difference (SPID) over 2, 4, 6 and 8 hours. Safety evaluation was based on the incidence, seriousness, intensity and causal relationship of treatment-emergent adverse events (TEAEs).

Results: the analgesic efficacy evaluated by TOTPAR6 (primary endpoint) remained steady across increasing baseline PI-NRS cut-off groups with of TRAM/DKP, but not with TRAM/paracetamol. The study also demonstrated the superiority of TRAM/DKP combination over TRAM/paracetamol in terms of TOTPAR over 2, 4 and 8 hours post-dose and SPID at 2, 4, 6 and 8 hours post-dose in both baseline PI groups (moderate or severe); similarly, the time course of PAR and PI indicated

better efficacy with TRAM/DKP as soon as 30 min and up to 4-6 hours. The incidence of adverse drug reactions was not increased in the severe baseline PI group.

Conclusion: overall, the results of this subgroup analysis of the DAVID study confirmed the superiority of the analgesic efficacy of TRAM/DKP vs TRAM/paracetamol, irrespective of the baseline PI.

Keywords: Analgesia; Dexketoprofen; Impacted lower third molar; Paracetamol; Pain intensity

PLAIN LANGUAGE SUMMARY

The combination tramadol/dexketoprofen (TRAM/DPK) was recently shown to exert a better analgesic effect than the combination tramadol/paracetamol (TRAM/paracetamol) after surgical removal of impacted lower third molar in a clinical trial enrolling >600 patients. A subanalysis of the results of this study was performed to assess if the severity of pain intensity (PI) at baseline might modify the analgesic effect and its duration. The results of the subanalysis showed that the analgesic efficacy of TRAM/DKP was independent of baseline PI and persistent up to 6 hours, whereas the effect of TRAM/paracetamol progressively decreased with increasing baseline PI and persisted for a shorter period. The incidence of adverse drug reactions was not increased in patients with severe baseline PI. These results confirmed the better analgesic efficacy of TRAM/DKP vs TRAM/paracetamol, irrespective of the baseline PI.

Key Summary Points

Why carry out this study?

- The DAVID study demonstrated the better analgesic efficacy of tramadol hydrochloride/dexketoprofen 75/25mg (TRAM/DKP) over tramadol hydrochloride/paracetamol 75/650mg (TRAM/paracetamol) in a model of moderate to severe acute pain following surgical removal of impacted 3d molar.
- The aim of this subpopulation analysis was to drill deeper in understanding the relationship between baseline pain intensity level and the effectiveness in pain control of the TRAM/DKP combination in comparison with the TRAM/paracetamol combination.

What was learned from the study?

- The analgesic efficacy evaluated by TOTPAR6 (primary endpoint) remained steady across increasing baseline PI-NRS cut-off groups with of TRAM/DKP, but not with TRAM/paracetamol.
- The incidence of adverse drug reactions was not increased in the severe baseline PI group.
- Overall, the results of this subgroup analysis of the DAVID study confirmed the superiority of the analgesic efficacy of TRAM/DKP vs TRAM/paracetamol, irrespective of the baseline PI.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13311959.

INTRODUCTION

Acute pain has substantial physiological and psychological consequences and becomes more difficult to manage as severity increases. Even brief intervals of painful stimulation can induce suffering, neuronal remodeling, and chronic pain [1]. Therefore, early intervention with an effective, fast-acting analgesic is key to manage acute pain to reduce complications, including progression to chronic pain states [2].

Attaining adequate pain relief (PAR) with monotherapy is difficult and multimodal analgesia is now accepted as the cornerstone of effective pain treatment [3]. Combining analgesics with diverse mechanisms of action and potential synergistic effects yields good pain relief and minimizes side effects. Compared with monotherapy, multimodal analgesia offers several benefits, including a broader spectrum of action, greater efficacy, better compliance and a better efficacy/safety ratio. As a result, analgesic combinations are recommended by the World Health organization (WHO), American Pain Society (APS) American College of Rheumatology (ACR) and European Pain Federation (EFIC) and are commonly used in clinical practice [4].

Dexketoprofen (DKP) is an anti-inflammatory and analgesic drug inhibiting COX-1 and COX-2, with proven high analgesic potency in a wide spectrum of acute pain syndromes [5,6]. It was shown to be as effective as the double dose of the racemic ketoprofen, but with a faster onset of analgesia. The rapid dissolution and absorption (t_{max} between 15 and 45 minutes) ensure rapid PAR, which is crucial for the effective management of acute pain [7]. DKP efficacy and rapid onset of analgesic activity is complemented by a safety profile that favors DKP over many other nonsteroidal anti-inflammatory drugs [8-10].

Tramadol (TRAM) has a dual analgesic mechanism: through its action as a μ-opioid receptor agonist, and as a norepinephrine and serotonin reuptake inhibitor, it is a central acting analgesic with peripheral and local analgesic effects. Its opioid and non-opioid mechanisms are thought to

act synergistically on descending inhibitory pathways in the central nervous system [11]. TRAM's analgesic efficacy is complemented by a long duration of action (half-life ~6 hours) and by a safety profile that favors TRAM over other opioids [12].

A fixed dose combination (FDC) of the fast acting nonsteroidal anti-inflammatory drug (NSAID), DKP trometamol, and the long lasting opioid, TRAM hydrochloride, has been recently developed to generate multimodal analgesia at lower and better tolerated doses than those of the single agents used alone [13-15]. TRAM/DKP FDC offers several important advantages including proven efficacy and tolerability with a 25% overall reduction in the opioid dosage, improved compliance and a convenient mode of administration [3].

The DAVID study compared the combination of TRAM 75mg and DKP 25mg (TRAM/DKP) with TRAM 75mg and paracetamol 650mg (TRAM/paracetamol) in moderate to severe pain [16]. Results showed that TRAM/DKP is effective and superior to TRAM/paracetamol in relieving moderate to severe acute pain following surgical removal of impacted lower third molar, with a faster onset of action, greater and durable analgesia and a favorable safety profile [16].

To further explore if the severity of pain intensity (PI) at baseline impacted on the analgesic efficacy and on the maintenance of analgesic response of the two fixed-dose combinations (TRAM/DKP vs TRAM/paracetamol), the results of the DAVID study were analyzed stratifying patients by baseline PI.

METHODS

Trial Design

The DAVID study was a multicenter, randomized, double-blind, double-dummy, parallel-group, placebo and active-controlled, single-dose, Phase IIIb trial conducted in 18 centers in 5 countries

(Hungary, Italy, Poland, Spain and UK) [16]. The participation of each patient in the study lasted for approximately 3 weeks, encompassing: i) a screening period (within 2 weeks before randomization), including the outpatient surgical extraction of at least one impacted lower third molar and a 4-hour post-surgery qualification period; ii) randomization and treatment administration (Day 1, t0), followed by an 8-hour efficacy assessment period; iii) end of study visit (6 [±1] days after randomization) [16].

During the qualification period, patients rated their post-surgical PI on an electronic diary using an 11-point Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain). Patients experiencing moderate to severe pain (defined as NRS-PI ≥4) were randomized with a 2:2:1 ratio to a single oral dose of three possible treatment arms: TRAM/DKP 75mg/25mg, TRAM/paracetamol 75mg/650mg or placebo. The DAVID study was designed in line with the current academic [17] and regulatory [18] recommendations for acute pain trials. Dose selection of TRAM/DKP and TRAM/paracetamol was based on the posology recommended in the current summary of product characteristics (European package insert) of each drug for the initial treatment of moderate to severe acute pain [19,20].

Ibuprofen 400mg was available as a rescue medication (RM) during the 8-hour post-dose assessment period, up to a maximum of 2 tablets at a minimum interval of 4 hours [16].

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was approved by all the concerned Competent Authorities and Ethics Committees. Patients provided their written consent to participate to the study.

Blinding

Randomization was performed through Interactive Voice/Web Response System according to a computer-generated randomization sequence. Participants, healthcare providers, medical

monitors, other personnel involved in the conduction of the trial, data collectors and biometricians were unaware of the treatment that participants were receiving. Moreover, double-blind conditions were secured by using a double dummy technique; the study dose consisted of one tablet (containing TRAM/DKP 75 mg/25 mg or placebo) plus two tablets (containing TRAM/paracetamol 37.5 mg/325 mg or placebo).

Patients

Healthy adult patients (>18 years of age) scheduled to undergo outpatient surgical extraction of at least one fully or partially impacted lower third molar requiring bone manipulation were included in the trial. Criteria for randomization included postoperative pain of moderate to severe intensity (NRS ≥4) within the 4 hours qualification post-surgery period. Inclusion and exclusion criteria and other study restrictions were based on the reference safety information of both drug combinations [19,20] and were described in detail in a previous publication [16].

For the purpose of the present subgroup analysis, enrolled patients were stratified according to baseline NRS-PI score ≥4, 5, 6, 7, 8, and aggregated in 2 groups, according to the presence of moderate (NRS-PI ≥4 to ≤6) or severe (NRS-PI >6) baseline PI.

Efficacy Evaluation

Evaluation of efficacy was based on data entered by patients in electronic diaries (eDiary). The following measures of analgesia were performed: i) pain relief (PAR) measured on a 5-point Verbal Rating Scale (VRS) (0='no relief', 1='a little (perceptible) relief', 2='some (meaningful) relief', 3='lot of relief', 4='complete relief') at the predefined post-dose time points (t15 min, t30 min, t1 hour, t1.5 hour, t2 hour, t4 hour, t6 hour and t8 hour); ii) PI measured on a 11-point NRS at baseline and at the same predefined post-dose time points. The onset of analgesia was documented using

the double stopwatch method over a 2-hour period post-dose: following treatment, 2 stopwatches were automatically activated in the eDiary. Patients were instructed to stop the first stopwatch when they felt 'first perceptible' PAR (FPPAR, i.e., at the moment they first felt any PAR) and the second when they experienced a 'meaningful' PAR (MPAR, i.e., when the relief from pain became meaningful to them). An overall assessment of the study medication was reported through patient global evaluation (PGE) on a 5-point VRS (1=poor, 2=fair, 3=good, 4=very good, 5=excellent) at the end of the 8-hour assessment period or immediately before the RM intake. The number of patients using RM and the time to first intake RM was also evaluated [16].

The primary efficacy endpoint was total PAR over six hours (TOTPAR6) calculated as the weighted sum of the PAR scores. TOTPAR6 was analyzed in patients stratified according to the baseline PI-NRS score, or aggregated into the moderate or severe baseline PI groups.

Secondary efficacy endpoints included the time course of mean PAR and PI scores over 8 hours; TOTPAR over 2, 4 and 8 hours post-dose; sum of pain intensity difference (SPID) over 2, 4 and 8 hours; percentage of responders in terms of PAR or PI reduction, namely patients who achieved at least 50% of max TOTPAR or at least 30% of PI reduction versus baseline at pre-specified time points over 8 hours; time to confirmed FPPAR (i.e., time to FPPAR if confirmed by experiencing MPAR); time to MPAR; PGE at eight hours or whenever the patient used RM; time of first intake of RM since study drug intake; and percentage of patients using RM at 2, 4 and 8 hours [16].

All secondary endpoints were assessed in the present analysis in patients aggregated into the moderate or severe baseline PI groups.

Safety evaluation was based on the incidence, seriousness, intensity and causal relationship of treatment-emergent adverse events (TEAEs). The occurrence of clinically significant changes post-dose versus the baseline in the physical examination, vital signs (VS; blood pressure and heart rate), and laboratory safety tests (hematology, biochemistry and urinalysis) were also assessed

[16]. In the present analysis, safety evaluations were performed in patients aggregated into the moderate or severe baseline PI groups.

In addition, the number needed to treat (NNT) for at least 50% pain relief over 6- and 8-hours vs placebo was calculated for the moderate or severe baseline PI groups.

Statistical Methods

The sample size was calculated for the original overall non-inferiority analysis between the active treatment groups and the superiority of active groups over placebo for sensitivity purposes [16]. No formal sample size calculation was performed for the analysis of the baseline PI groups. All efficacy variables were descriptively analyzed and tested as follows: NRS-PI, SPID, and TOTPAR (continuous variables) were analyzed by ANCOVA model including terms of treatment and the baseline PI as covariates; PAR and PGE (categorical variables) were analyzed by Wilcoxon rank-sum test; percentage of responders and percentage of patients who required RM were tested using a Chi-squared (χ^2) test. Time to first use of RM and time to confirmed FPPAR and MPAR were assessed using a log-rank test. All analyses were performed in SAS V.9.3 (SAS) software [16].

The method of "last observation carried forward" was applied among patients who missed more than one consecutive data input; otherwise, the missing value was replaced by the mean of the two non-missing data collected before and after the missing one. This procedure was applied to all efficacy outcomes. After RM intake, PI returned to its baseline level and PAR to zero ('no relief') for all subsequent time points (i.e., baseline observation carried forward) [16].

Adverse drug reactions (ADRs) were coded using the MedDRA dictionary. The incidence of each ADR was summarized by system organ class (SOC), preferred term (PT), treatment and baseline PI group. Safety variables were analyzed by descriptive statistics [16].

The subgroup analysis was performed on randomized patients stratified according to their baseline PI.

RESULTS

Study Population

Of a total of 792 patients that were screened, 654 were randomized and received study treatment. One patient was excluded from any analysis for being <18 years old. Another patient qualified for the study initially (NRS >4) but reported a lower value at baseline (NRS-PI=3) and was therefore not included in this analysis (**Figure 1**). The moderate and severe baseline PI groups contained 508 (77.8%) and 144 (22.1%) patients, respectively (**Table 1**).

Demography and baseline characteristics are summarized in **Table 1**. Overall, the different treatment groups were comparable: gender distribution by treatment was homogeneous in the moderate baseline PI group (females around 60% across groups) but showed high variability in the severe baseline PI group (percentage of females ranging from 50.8% to 72.4%). Mean (standard deviation; SD) age was similar in both the moderate and severe baseline PI groups (26.8 [7.93] and 27.2 [7.22], respectively). Most patients in all groups were of Caucasian ethnicity (around 90%). The mean (SD) baseline PI was 5.0 (0.74) in the moderate group and 7.7 (0.82) in the severe group.

Efficacy Results

Primary Endpoint

The mean (SD) TOTPAR6 (primary endpoint) reported by patients in the overall TRAM/DKP group (13 [7.0]) was significantly superior ($p<0.0001$) compared to the TRAM/paracetamol and placebo groups (9.2 [7.7] and 1.9 [3.9], respectively) (**Table 2**), as previously reported [16].

The analgesic efficacy of TRAM/DKP evaluated by TOTPAR6 remained steady across all baseline PI-NRS cut-off groups. In contrast, TRAM/paracetamol analgesic efficacy showed a marked and progressive decrease as baseline PI-NRS cut-offs increased (**Figure 2**).

Considering the baseline PI groups, patients treated with TRAM/DKP reported significantly ($p<0.0001$) higher TOTPAR6 values in both the moderate (12.9 [7.12]) and severe (13.4 [6.37]) baseline PI groups compared with patients in the TRAM/paracetamol (9.7 [7.67] and 7.0 [7.27)], respectively) and placebo groups (2.1 [4.10)] and 1.5 [3.08], respectively) (**Table 2**).

Secondary Endpoints

The superiority of TRAM/DKP was achieved in both baseline PI groups in terms of PAR summary measures (TOTPAR 2, 4, 6- and 8-hours post-dose). The mean values obtained with TRAM/DKP were significantly higher than those obtained with TRAM/paracetamol at all evaluated time points in either moderate or severe baseline PI groups ($p \leq 0.0003$; Supplementary **Table 1 and Figure 3**).

The time course of the mean PAR (**Figure 4**) and PI (**Figure 5**) showed that TRAM/DKP provided a more rapid onset of action compared with TRAM/paracetamol, with statistically significant differences observed after 30 minutes post-dose in both baseline PI groups. In the moderate baseline PI group, the statistically significant difference between TRAM/DKP and TRAM/paracetamol treated patients was maintained for up to 4 hours in terms of PAR (**Figure 4a**) and 6 hours in terms of PI (**Figure 5a**). Among patients with severe baseline PI, the statistically

significant difference was observed up to 6 hours for PAR (**Figure 4b**) and up to 4 hours for PI (**Figure 5b**).

Accordingly, SPID 2, 4, 6, and 8 hours post-dose of TRAM/DKP were significantly higher than those obtained in the TRAM/paracetamol group at all evaluated time points in either moderate or severe baseline PI groups ($p \leq 0.0006$; **Table 3 and Supplementary Figure 1**).

Regarding the percentage of responders in terms of PAR (patients achieving at least 50% of the theoretical maximum TOTPAR), the best results were detected in patients treated with TRAM/DKP, in both the moderate (68.4% were responders at 2 hours, 69.4% at 4 hours, 59.2% at 6 hours and 49.5% at 8 hours) and severe baseline PI groups (81.0% were responders at 2 hours, 77.8% at 4 hours, 65.1% at 6 hours and 42.9% at 8 hours). Conversely, in TRAM/paracetamol treated patients, the percentages of responders were always lower, in both the moderate (45.7% were responders at 2 hours, 45.2% at 4 hours, 40.5% at 6 hours and 36.7% at 8 hours) and the severe baseline PI groups (38.5% were responders at 2 hours, 34.6% at 4 hours and 30.8% at 6 and 8 hours). All differences between treatment groups were statistically significant (except for severe baseline PI group at 8 hours; **Supplementary Table 2** and **Figure 6**).

Similarly, considering the percentage of responders in terms of PI reduction (patients achieving at least 30% of PI reduction vs baseline), the best results were detected in patients treated with TRAM/DKP, with a statistically significant difference in the moderate baseline PI group up to 6 hours and in the severe baseline PI group up to 4 hours (**Table 4** and **Supplementary Figure 2**).

In terms of PGE, a higher percentage of patients rating the study drug as 'good', 'very good' or 'excellent' was observed in the TRAM/DKP in both moderate (80.1%) and severe (84.1%) baseline PI groups, with a statistically significant difference compared with patients treated with TRAM/paracetamol (59.5% and 44.2% in the moderate and severe baseline PI groups,

respectively; **Supplementary Table 3** and **Figure 7**). The distribution of PGE categories by baseline PI group and treatment is shown in **Figure 8**.

When the onset of analgesia was evaluated with the double stopwatch method, it was significantly faster in the TRAM/DKP group than in the TRAM/paracetamol group in both baseline PI groups. In the moderate baseline PI group, the median (95% confidence interval [CI]) times to confirmed FPPAR and MPAR after single dose of TRAM/DKP were 22 (18, 25) and 43 (35, 49) minutes, respectively, compared to the TRAM/paracetamol group with 27 (23, 27) and 52 (47, 57) minutes, respectively. Log-rank test showed a statistically significant difference (p=0.0034 and p=0.0018, respectively). In the severe baseline PI group, the median (95% CI) times to confirmed FPPAR and MPAR after a single dose of TRAM/DKP were 18 (13, 25) and 33 (28, 44) minutes, respectively, compared with 27 (15, 49) and 57 (49, 87) minutes, respectively, in the TRAM/paracetamol group. Log-rank test showed a statistically significant difference (p=0.0010 and p<0.0001, respectively) (**Supplementary Table 4**).

Fewer patients treated with TRAM/DKP vs TRAM/paracetamol used RM in both the moderate (6.6 vs 17.1% within 2 hours, 13.8 vs 32.4% within 4 hours, 30.6 vs 42.4% within 6 hours and 48.0 vs 52.4% within 8 hours) and severe baseline PI groups (7.9 vs 34.6% within 2 hours, 14.3 vs 51.9% within 4 hours, 41.3 vs 59.6% within 6 hours and 58.7 vs 65.4% within 8 hours). The differences were statistically significant up to 6 hours in the moderate baseline PI group and up to 4 hours in severe baseline PI group (**Table 5**).

The median (95% CI) time to first use of RM in the severe baseline PI group was 417 (328, NA) minutes with TRAM/DKP and 233 (124, 414) minutes with TRAM/paracetamol; in the moderate baseline PI group the median time was not achieved with TRAM/DKP and it was 459 (369, NA) with TRAM/paracetamol. Log-rank tests were not statistically significant (Supplementary **Table 5**).

Finally, the NNT (95% CI) for at least 50% max TOTPAR at 6 hours in the overall study population was 1.8 (1.6, 2.0) for TRAM/DKP and 2.9 (2.4, 3.5) for TRAM/paracetamol. The NNT (95% CI) at 8 hours were 2.4 (2.0, 2.8) for TRAM/DKP and 3.3 (2.7, 4.3) for TRAM/paracetamol. In the moderate baseline PI group, the NNT at 6 hours was 1.8 (1.6, 2.2) for TRAM/DKP and 2.8 (2.3, 3.6) for TRAM/paracetamol. The NNT at 8 hours were 2.3 (1.9 ,2.8) for TRAM/DKP and 3.3 (2.6, 4.3) for TRAM/paracetamol. In addition, in the severe baseline PI group, the NNT at 6 hours was 1.5 (1.3, 1.9) for TRAM/DKP and 3.3 (2.3, 5.4) for TRAM/paracetamol. The NNT at 8 hours were 2.5 (1.9, 3.8) for TRAM/DKP and 3.7 (2.4, 7.8) for TRAM/paracetamol (**Supplementary Figure 3**).

Safety Results

Overall, 46 (9.1%) patients in the moderate baseline PI group experienced one or more adverse drug reactions (ADRs; 79 in total). In the severe baseline PI group, 7 (4.9%) patients experienced a total of 18 ADR. No serious ADR was recorded.

The most common ADRs in the moderate baseline PI active treatment groups (TRAM/DKP and TRAM/paracetamol) were: vomiting (5.1% and 5.2%, respectively), nausea (4.6% and 3.8%, respectively), dizziness (3.1% and 3.8%, respectively) and somnolence (3.6% and 1.9%, respectively; **Table 6**). The most common ADRs in the severe baseline PI active treatment groups (TRAM/DKP and TRAM/paracetamol) were nausea (1.6% and 7.7%, respectively), vomiting (1.6% and 5.8%, respectively), somnolence (1.6% and 1.9%, respectively) and dizziness (0% and 9.6%, respectively). The incidence of ADRs was not increased in the severe baseline PI group (**Table 7**).

No clinically relevant change vs baseline was observed in the treatment groups in terms of VS or physical examination. No deaths occurred during the study.

DISCUSSION

The results of the present subgroup analysis confirmed the superiority of TRAM/DKP combination over TRAM/paracetamol in terms of TOTPAR6 (primary endpoint) in patients with moderate and severe PI at baseline. TRAM/DKP (75/25mg) proved to be equally effective in relieving pain in patients with moderate or severe pain, while TRAM/paracetamol analgesia decreased in patients with severe pain at baseline. The superiority of TRAM/DKP combination over TRAM/paracetamol was also confirmed in terms of all secondary endpoints evaluated in either patients with moderate or severe PI at baseline. In particular, the time course of PAR and PI indicated better efficacy with TRAM/DKP in terms of rapidity of onset and duration of the analgesic action. The percentage of responders, defined as at least 50% max TOTPAR at 2, 4, 6 and 8 hours, was also significantly higher in the TRAM/DKP vs TRAM/paracetamol in both moderate and severe PI groups at baseline (with the only exception of the baseline severe PI group at 8 hours). Similarly, the percentage of responders defined as at least 30% PI reduction, was significantly higher with TRAM/DKP at 2, 4 and 6 hours in the moderate baseline PI group and at 2 and 4 hours in the severe baseline PI. Accordingly, the overall PGE was higher in both baseline PI groups with TRAM/DKP vs TRAM/paracetamol. Time to confirmed FPPAR and MPAR was significantly shorter with TRAM/DKP in both baseline PI groups. The percentage of patients using RM was significantly lower with TRAM/DKP in the moderate baseline PI group within 2, 4 and 6 hours and in the severe baseline PI group within 2 and 4 hours. A very low clinical response for patients receiving placebo was identified in terms of TOTPAR (Figure 3) and PI reduction (Supplementary Figure 2), for both moderate and severe baseline PI subgroups. Accordingly, the overall PGE showed that most patients treated with placebo rated the study drug received as poor (Figure 7) in both baseline PI subgroups. These results confirmed the superiority of TRAM/DKP combination over

TRAM/paracetamol in terms of intensity, rapidity of onset and duration of analgesia in patients with either moderate or severe PI at baseline.

A decrease in NRS-PI around 1 point (1.3 mm in a visual analog scale) has been usually considered the minimum clinically relevant in acute moderate to severe pain trials [21,22]. However, according to Cepeda et al. (2003) [23], when baseline pain intensity is severe, larger changes in the NRS appear necessary to obtain a similar degree of pain relief. In their study, different thresholds for 'minimal improvement', 'much improvement' and 'very much improvement' according to moderate or severe baseline PI were identified [23].

The threshold for 'minimal improvement' was a 1.3 points decrease in PI for patients with moderate baseline PI [23]. The mean PI differences in our study were ≥1.3 points with TRAM/DKP from 30 min time point up to 8 hours, while with TRAM/paracetamol it was from 1 to 8 hours.

The threshold for 'minimal improvement' was a 1.8 points decrease in PI for patients with severe baseline PI [23]. The mean PI differences in our study were ≥1.8 points with TRAM/DKP from 30 min time point up to 8 hours, with TRAM/paracetamol it was from 1 to 6 hours.

In moderate baseline PI patients, a difference of 2.4 points corresponded to 'much improvement' [23]: in our study, the mean PI differences were ≥2.4 points with TRAM/DKP from 1 to 4 hours; and with TRAM/paracetamol from 1.5 to 2 hours. A difference of 3.5 points corresponded to 'very much improvement' [23]: in our study, the mean PI differences were ≥3.5 points with TRAM/DKP from 1.5 to 2 hours; and with TRAM/paracetamol this PI difference value was not reached at any time point.

In severe baseline PI, a difference of 4.0 points corresponded to 'much improvement' [23]: in our study, the mean PI differences were ≥4.0 points with TRAM/DKP from 1 to 4 hours; and with TRAM/paracetamol this PI difference value was not reached at any time point. A difference of 5.2

points corresponded to 'very much improvement' [23]: in our study, the mean PI differences were ≥5.2 points with TRAM/DKP from 1.5 to 2 hours (**Supplementary Table 6**).

Accordingly, the percentage of patients using RM was significantly lower with TRAM/DKP than with TRAM/paracetamol. Although the difference between treatment groups were not statistically significant in terms of time to RM, it is noteworthy that in patients with moderate PI at baseline treated with TRAM/DKP the median time to RM was not achieved (vs about 7 hours with TRAM/paracetamol) and was about 7 hours (vs four hours with TRAM/paracetamol) in patients with severe PI at baseline.

The NNT for at least 50% max TOTPAR over placebo at 6 and 8 hours were consistently lower with TRAM/DKP than with TRAM/paracetamol and all differences were ≥1 point (except in the severe baseline PI group at 8 hours=0.9). Despite the limited number of patients, the NNTs presented remarkably narrow 95% CIs (**Figure 11**). Moreover, the NNTs in the overall group for TRAM/paracetamol were similar to those previously reported by Edwards et al., (2002) [24]. The lower NNT (and much narrow 95% CI) of TRAM/DKP vs TRAM/paracetamol makes it a superior oral treatment that is able to achieve optimal and consistent analgesia in moderate to severe acute pain.

In terms of safety, both treatments were well tolerated, and their safety profiles were fully in line with the previously reported studies. No increase in the incidence of ADRs was observed in the severe baseline PI group in comparison with the moderate baseline PI group.

Limitations

As the subgroup analysis was not originally included in the study protocol, no formal sample size estimation was performed, and no measures were implemented to guarantee a minimum

percentage of patients with baseline severe PI. The overall severe baseline PI group encompassed 144 (22.1%) patients vs 508 (77.8%) patients in the moderate baseline PI group.

A recent clinical trial in dental impaction pain model performed similar subpopulation analyses with a severe baseline PI group of 102 patients [25]. In this study sample size was determined according to clinical, not statistical, criteria.

Acute pain trials in severe PI are rare and are usually performed at emergency departments. For example, one study examining the analgesic efficacy of four oral analgesic combinations in severe acute extremity pain included about 100 patients per group [26]. Another study in acute severe pain that examined the analgesic efficacy of an add-on single dose of intranasal sufentanil to the usual intravenous multimodal analgesia included 72 patients per group [27].

Moreover, safety data collected in a single-dose study are not sufficient to adequately characterize the safety profile of the study drugs.

Generalization

The dental impaction pain model is one of several recognized acute pain models and, as such, does not reflect the full scale of all acute pain models. Furthermore, the medications used are not the standard of care for treating acute dental pain in clinical practice. Nevertheless, due to its sensitivity and reproducibility, dental impaction pain is the most studied and the reference model for assessing analgesia in proof-of-concept, dose-ranging and relative efficacy studies [28]. Efficacy in the dental model is highly predictive of efficacy in later stage models. The efficacy and the tolerability profile of the drugs used in this study was previously demonstrated in other models of pain using both the active comparator (TRAM/paracetamol) [29] and study drug (TRAM/DKP) [13,14,30].

CONCLUSION

The results of this subgroup analyses consistently confirmed the superior analgesic efficacy of TRAM/DKP over TRAM/paracetamol, in both primary and all secondary endpoints, irrespective of the baseline PI. Moreover, it showed that TRAM/DKP effective analgesia, unlike that of TRAM/paracetamol, was not decreased in patients with severe baseline PI. Analgesia with TRAM/DKP was faster and durable with a good safety profile.

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Compliance with Ethics Guidelines: The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was approved by all the

concerned Competent Authorities and Ethics Committees. Patients provided their written consent to participate to the study.

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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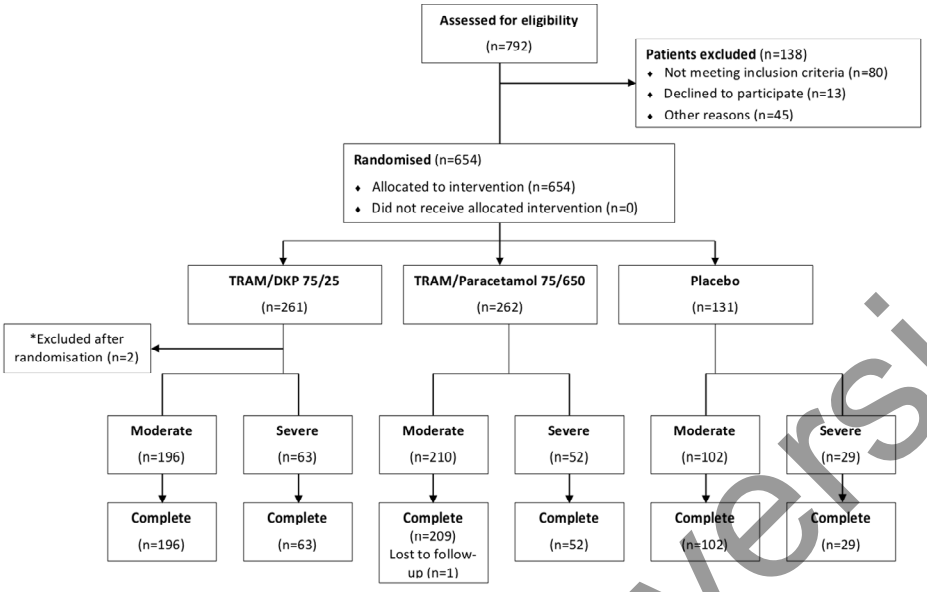


Figure 1. Flow diagram

Participant flow chart of study analysis of baseline pain intensity groups. *One patient was excluded from all analyses being aged less than 18 years, another patient was excluded from the analysis of baseline pain intensity groups having reported a baseline (t0) PI-NRS<4. TRAM/DKP: tramadol/dexketoprofen

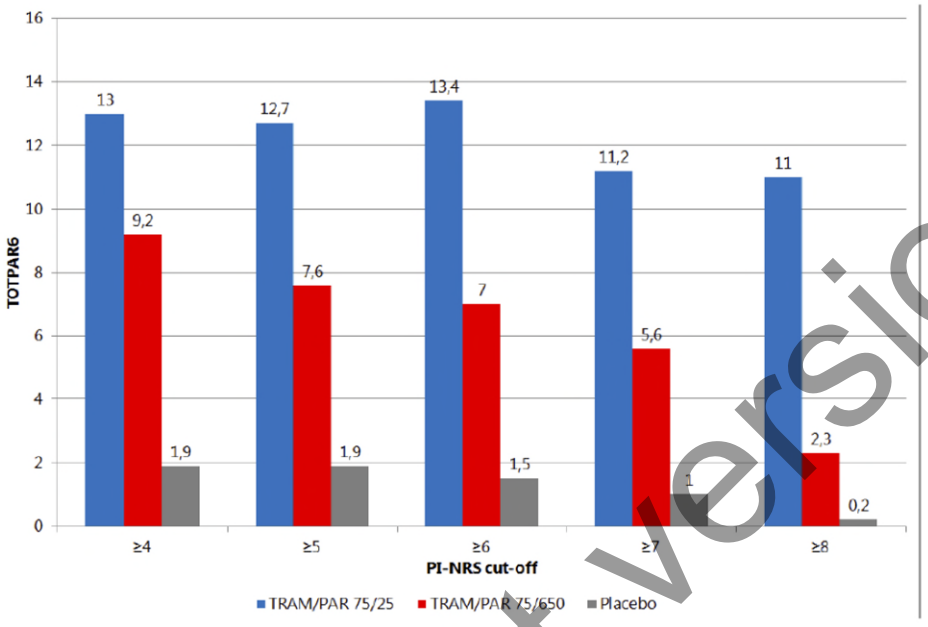


Figure 2. TOTPAR6 by Treatment with Increasing Baseline Pain Intensity (PI) Cut-offs

Total pain Relief (TOTPAR) over 6 hours evaluated across increasing baseline PI-NRS cut-off groups in tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo treatment arms. TOTPAR6 was the primary endpoint of the study.

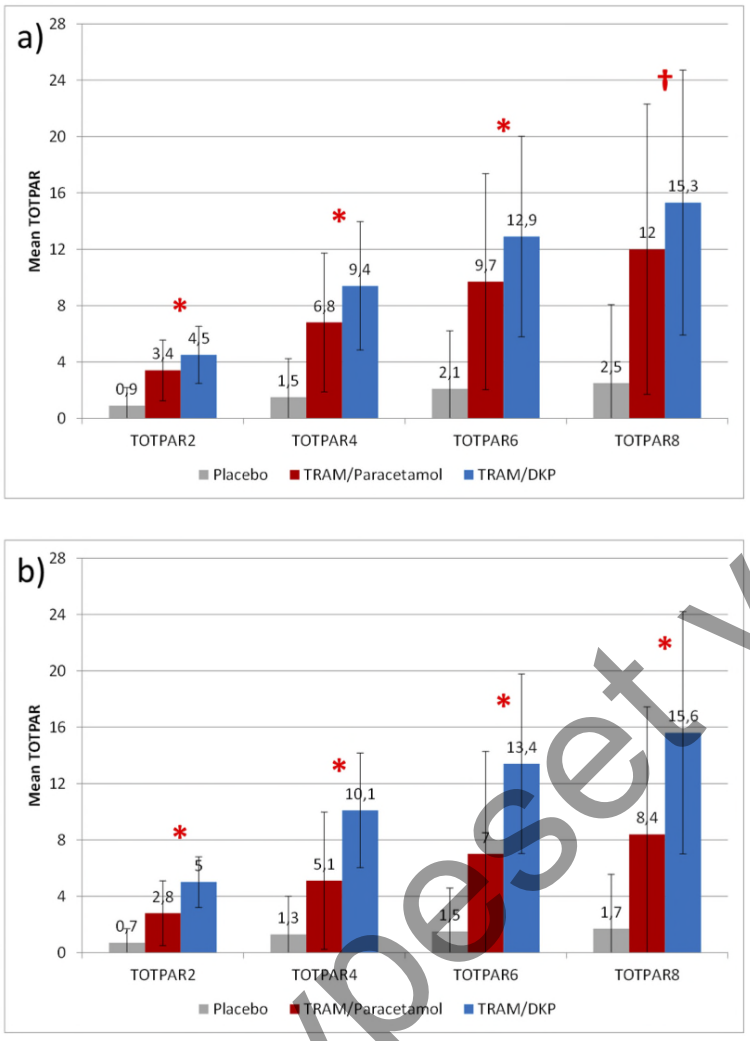


Figure 3. Total pain Relief (TOTPAR) over 2, 4, 6 and 8 hours post-dose in baseline PI moderate group (a) and in baseline PI severe group (b)

Mean (SD) of Total pain Relief (TOTPAR) over 2, 4, 6 and 8 hours post-dose for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo in baseline PI moderate group (a) and in baseline PI severe group (b) *Statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.0001$). †Statistically significant ($p=0.0003$). TOTPAR6 was the primary endpoint of the study.

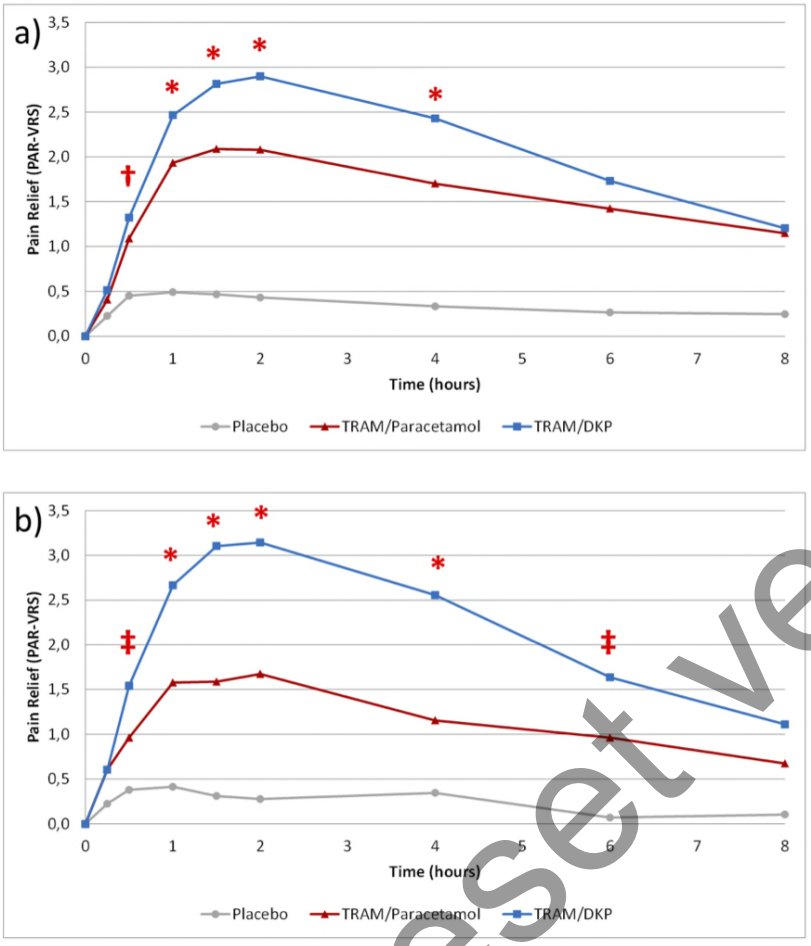
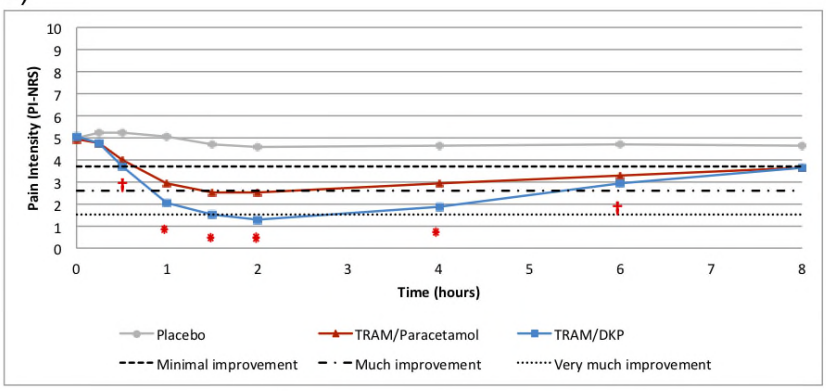


Figure 4. Time course of pain relief (PAR) in baseline PI moderate group (a) and in baseline PI severe group (b)

Time course of mean pain relief (PAR) over 8 hours for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo with PAR measured on a 5-point Verbal Rating Scale (PAR-VRS, ranging from 0='no relief' to 4='complete relief') in baseline PI moderate group (a) and in baseline PI severe group (b). The area under the curve for pain relief at a given time point corresponds to TOTPAR at the same time point. *Statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.0001$); †statistically significant TRAM/DKP versus TRAM/paracetamol ($p=0.0205$); ‡statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.05$).

a)



b)

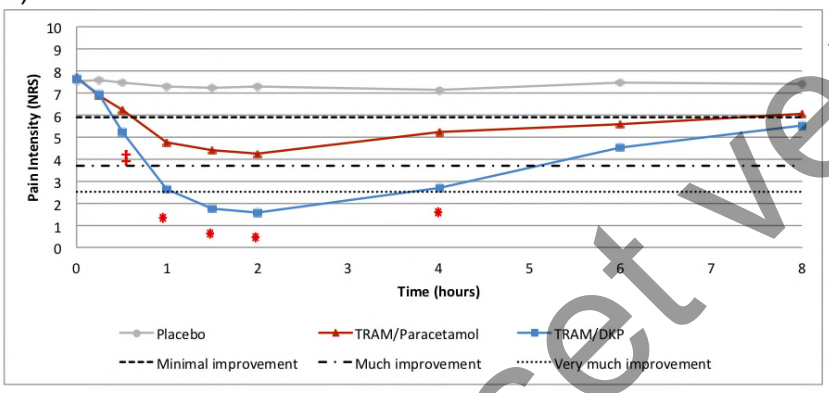


Figure 5. Time course of mean pain intensity (PI) in baseline PI moderate group (a) and in baseline PI severe group (b)

Time course of mean pain intensity (PI) over 8 hours for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo with PI measured on 11-point Numerical Rating Scale (PI-NRS) ranging from 0 (no pain) to 10 (worst pain) in baseline PI moderate group (a) and in baseline PI severe group (b). *Statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.0001$); †statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.05$); ‡statistically significant TRAM/DKP versus TRAM/paracetamol ($p=0.0147$). Dashed lines representing the threshold for 'minimal pain relief', 'much improvement' and 'very much improvement', calculated according to Cepeda et al. (2003), have been included as a reference.

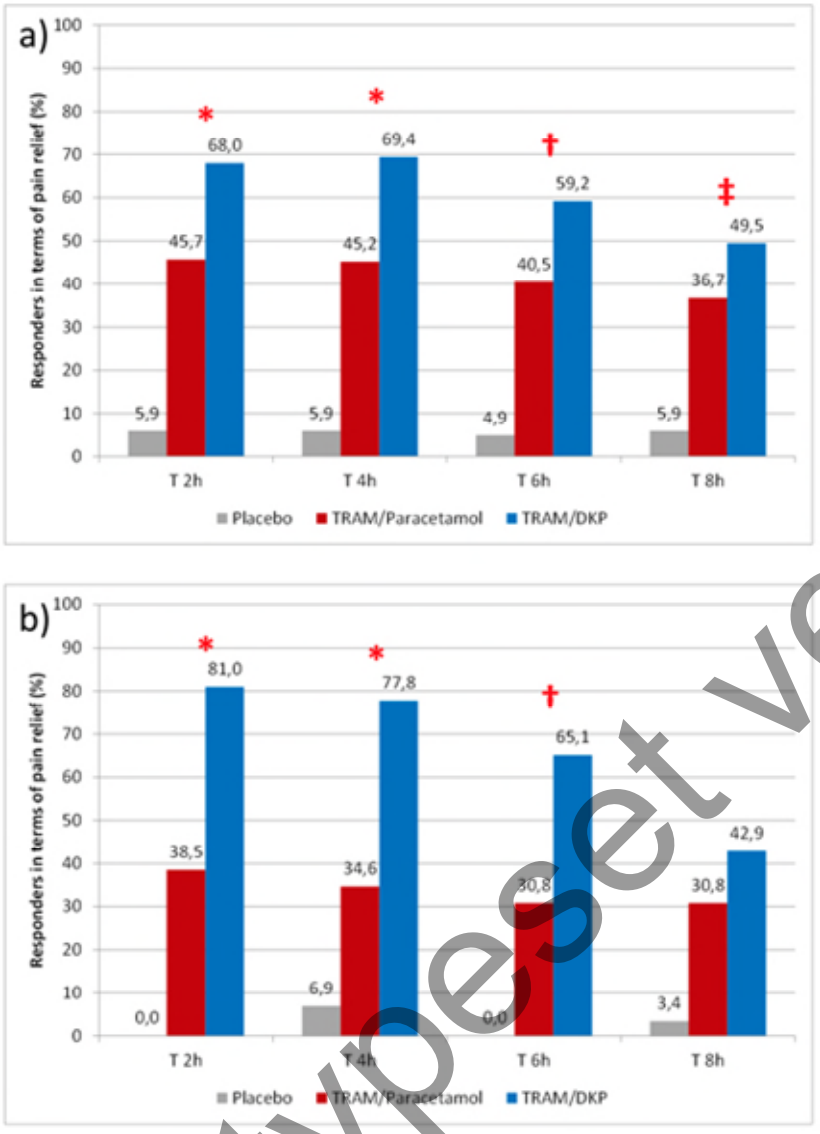


Figure 6. Percentage of responders in terms of pain relief over 2, 4, 6 and 8 hours in baseline PI moderate group (a) and in baseline PI severe group (b)

Percentage of responders in terms of pain relief (patients who achieved at least 50% of theoretical maximum total pain relief [TOTPAR]) over 2, 4, 6 and 8 hours post-dose for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo in baseline PI moderate group (a) and in baseline PI severe group (b). *Statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.0001$). †Statistically significant ($p=0.0002$); ‡statistically significant ($p=0.0091$).

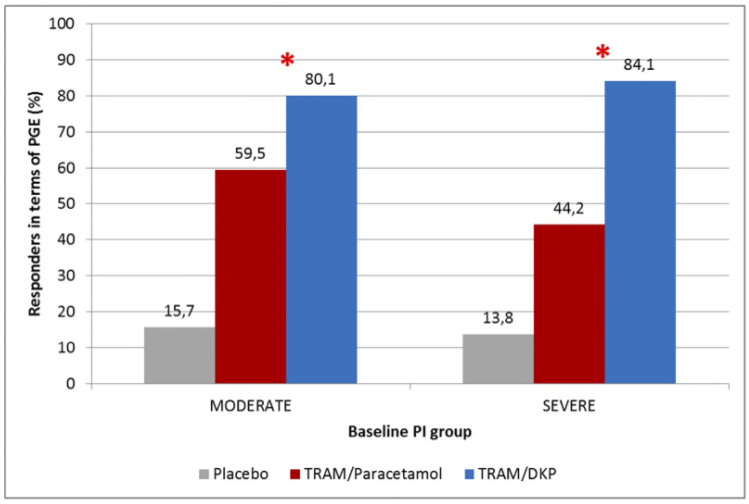


Figure 7. Patient global evaluation (patients who rated the study drug as 'good', 'very good', or 'excellent') by baseline PI group

Percentage of responders in terms of patient global evaluation (PGE, patients who rated the study drug as 'good', 'very good', or 'excellent' at the end of the assessment period or whenever the patient used rescue medication) for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo by baseline PI group *Statistically significant TRAM/DKP versus TRAM/paracetamol ($p<0.0001$).

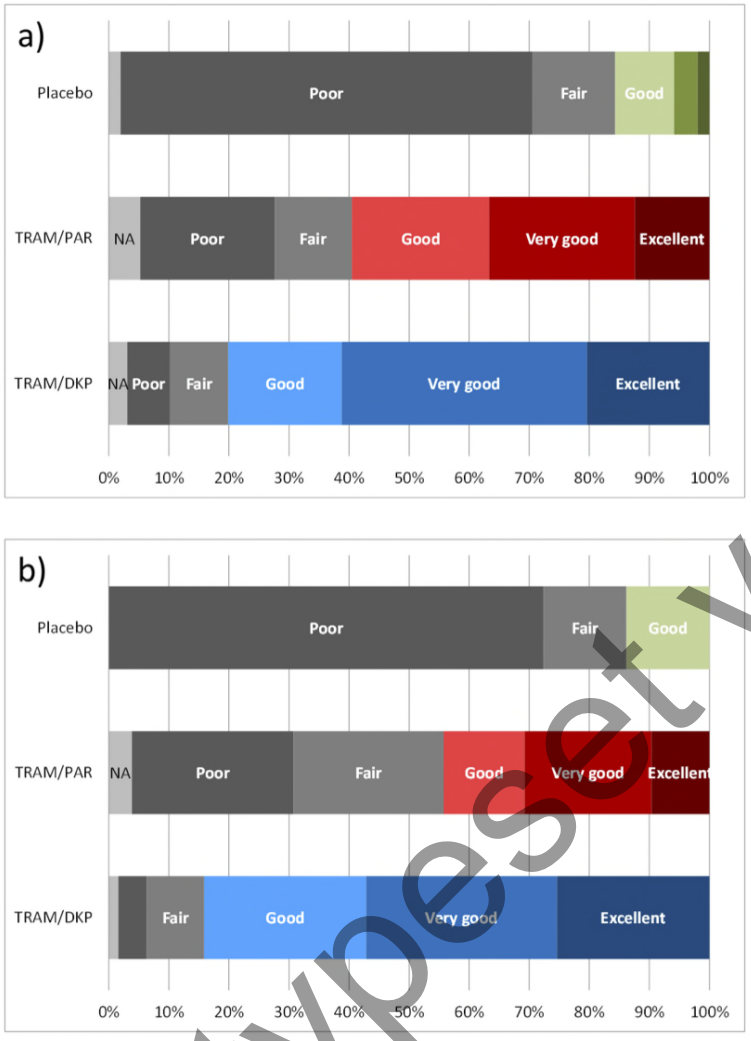


Figure 8. Distribution of responses to patient global evaluation (PGE) by treatment in baseline PI moderate group (a) and in baseline PI severe group (b)

Percentage of patients who rated the treatment as 'poor', 'fair', 'good', 'very good', or 'excellent' on patients' global evaluation (PGE) at the end of the assessment period or whenever they used rescue medication for tramadol/dexketoprofen (TRAM/DKP), tramadol/paracetamol (TRAM/paracetamol) and placebo in baseline PI moderate group (a) and in baseline PI severe group (b).

Table 1. Demographic and Baseline Characteristics by Treatment and by Baseline Pain Intensity Group

		TRAM/DKP	TRAM/PAR	Placebo	Overall
		260 (100%)*	**262 (100%)**	**131 (100%)**	**653 (100%)**
Moderate baseline PI group					
N (%)		196 (75.4%)	210 (80.2%)	102 (77.9%)	508 (77.8%)
Sex n (%)	**Female,**	119 (60.7%)	125 (59.5%)	57 (55.9%)	301 (59.3%)
	Male	77 (39.3%)	85 (40.5%)	45 (44.1%)	207 (40.7%)
Age, mean (SD)		26.7 (7.71)	27.2 (8.45)	26.1 (7.25)	26.8 (7.93)
Race n (%)	**Asian**	11 (5.6%)	19 (9.0%)	5 (4.9%)	35 (6.9%)
	Black or African American	6 (3.1%)	2 (1.0%)	4 (3.9%)	12 (2.4%)
	Other	2 (1.0%)	3 (1.4%)	1 (1.0%)	6 (1.2%)
	White	177 (90.3%)	186 (88.6%)	92 (90.2%)	455 (89.6%)
Baseline PI, mean (SD)		5.1 (0.73)	4.9 (0.74)	5.0 (0.77)	5.0 (0.74)
Severe baseline PI group					
N (%)		63 (24.2%)	52 (19.8%)	29 (22.1%)	144 (22.1%)
Sex n (%)	**Female**	32 (50.8%)	33 (63.5%)	21 (72.4%)	86 (59.7%)
	Male	31 (49.2%)	19 (36.5%)	8 (27.6%)	58 (40.3%)
Age, mean (SD)		27.4 (6.77)	26.6 (6.72)	27.7 (9.03)	27.2 (7.22)

Race n (%)	**Asian**	3 (4.8%)	2 (3.8%)	1 (3.4%)	6 (4.2%)
	Black or African American	1 (1.6%)	1 (1.9%)	2 (6.9%)	4 (2.8%)
	Other	2 (3.2%)	2 (3.8%)	0 (0%)	4 (2.8%)
	White	57 (90.5%)	47 (90.4%)	26 (89.7%)	130 (90.3%)
Baseline PI, mean (SD)		7.7 (0.84)	7.7 (0.87)	7.6 (0.69)	7.7 (0.82)

*One patient was excluded from the analysis of baseline pain intensity groups having reported a baseline (t0) PI-NRS<4. PI: Pain Intensity; SD: Standard Deviation; TRAM/DKP: tramadol/dexketoprofen; TRAM/PAR: tramadol/paracetamol

Table 2. Descriptive Statistics for Primary Endpoint TOTPAR6 by Treatment and by Baseline Pain Intensity Group and Overall

baseline PI group		TRAM/DKP	TRAM/PAR	Placebo	Overall
Moderate	**n**	196	210	102	508
	mean (SD)	12.9 (7.12)*	9.7 (7.67)	2.1 (4.10)	9.4 (7.92)
Severe	**n**	63	52	29	144
	mean (SD)	13.4 (6.37)*	7.0 (7.27)	1.5 (3.08)	8.7 (7.71)
OVERALL	**n**	260	262	131	653
	mean (SD)	13.0 (6.97)*	9.2 (7.65)	1.9 (3.89)	9.2 (7.88)

PI: Pain Intensity; SD: Standard Deviation; TRAM/DKP: tramadol/dexketoprofen; TRAM/PAR: tramadol/paracetamol

*P<0.0001 vs TRAM/PAR and vs placebo

Table 3. Sum of Pain Intensity Differences (SPID) over 2, 4, 6 and 8 hours post-dose by Treatment and by Baseline Pain Intensity Group

baseline PI group	time point	TRAM/DKP	TRAM/PAR	Placebo	TRAM/DKP vs TRAM/PAR
		mean (SD)	mean (SD)	mean (SD)	p-value
Moderate	2 hours	5.6 (2.92)	3.7 (3.27)	0.2 (2.59)	<0.0001
	4 hours	11.9 (6.23)	7.6 (7.01)	1.0 (4.90)	<0.0001
	6 hours	16.2 (9.63)	10.9 (10.58)	1.6 (7.38)	<0.0001
	8 hours	19.0 (12.46)	13.5 (13.99)	2.4 (9.88)	<0.0001
Severe	2 hours	9.3 (3.89)	5.4 (4.35)	0.5 (1.50)	<0.0001
	4 hours	19.2 (8.25)	10.4 (9.52)	1.3 (3.18)	<0.0001
	6 hours	25.5 (12.24)	14.7 (14.68)	1.5 (3.70)	<0.0001
	8 hours	29.8 (16.27)	18.0 (19.11)	1.8 (4.73)	0.0006

*Statistical test (analysis of covariance) performed to compare active treatments only. PI: Pain Intensity; SD: Standard Deviation; TRAM/DKP: tramadol/dexketoprofen; TRAM/PAR: tramadol/paracetamol

Table 4. Percentage of Responders in terms of Pain Intensity (PI) Reduction over 2, 4, 6 and 8 hours by Treatment and by Baseline Pain Intensity Group

baseline PI group	time point	Respon.	TRAM/DKP	TRAM/PAR	Placebo	TRAM/DKP vs TRAM/PAR*
			n (%)	n (%)	n (%)	p-value
Moderate	**2 hours**	**Yes**	174 (88.8%)	134 (63.8%)	21 (20.6%)	<0.0001
		No	22 (11.2%)	76 (36.2%)	81 (79.4%)	
	4 hours	**Yes**	153 (78.1%)	117 (55.7%)	13 (12.7%)	<0.0001
		No	43 (21.9%)	93 (44.3%)	89 (87.3%)	
	6 hours	**Yes**	112 (57.1%)	96 (45.7%)	10 (9.8%)	0.0213
		No	84 (42.9%)	114 (54.3%)	92 (90.2%)	
	8 hours	**Yes**	81 (41.3%)	77 (36.7%)	12 (11.8%)	0.3359
		No	115 (58.7%)	133 (63.3%)	90 (88.2%)	
Severe	**2 hours**	**Yes**	57 (90.5%)	32 (61.5%)	0 (0.0%)	0.0002
		No	6 (9.5%)	20 (38.5%)	29 (100.0%)	
	4 hours	**Yes**	50 (79.4%)	24 (46.2%)	3 (10.3%)	0.0002
		No	13 (20.6%)	28 (53.8%)	26 (89.7%)	
	6 hours	**Yes**	34 (54.0%)	19 (36.5%)	1 (3.4%)	0.0620
		No	29 (46.0%)	33 (63.5%)	28 (96.6%)	
	8 hours	**Yes**	23 (36.5%)	16 (30.8%)	1 (3.4%)	0.5176
		No	40 (63.5%)	36 (69.2%)	28 (96.6%)	

*Statistical test (Chi-Square) performed to compare active treatments only. Patients who achieved at least 30% of PI reduction versus baseline were considered responders. PI: Pain

Intensity; Respon: Responder; TRAM/DKP: tramadol/dexketoprofen; TRAM/PAR: tramadol/paracetamol

Table 5. Percentage of Use of Rescue Medication (RM) over 2, 4, 6 and 8 hours by Active Treatment and Baseline PI Group

baseline PI group	time point	Use of RM	TRAM/DKP	TRAM/PAR	TRAM/DKP vs TRAM/PAR*
			n (%)	n (%)	p-value
Moderate	**2 hours**	**Yes**	13 (6.6%)	36 (17.1%)	0.0012
		No	183 (93.4%)	174 (82.9%)	
	4 hours	**Yes**	27 (13.8%)	68 (32.4%)	<0.0001
		No	169 (86.2%)	142 (67.6%)	
	6 hours	**Yes**	60 (30.6%)	89 (42.4%)	0.0140
		No	136 (69.4%)	121 (57.6%)	
	8 hours	**Yes**	94 (48.0%)	110 (52.4%)	0.3732
		No	102 (52.0%)	100 (47.6%)	
Severe	**2 hours**	**Yes**	5 (7.9%)	18 (34.6%)	0.0004
		No	58 (92.1%)	34 (65.4%)	
	4 hours	**Yes**	9 (14.3%)	27 (51.9%)	<0.0001
		No	54 (85.7%)	25 (48.1%)	
	6 hours	**Yes**	26 (41.3%)	31 (59.6%)	0.0502
		No	37 (58.7%)	21 (40.4%)	
	8 hours	**Yes**	37 (58.7%)	34 (65.4%)	0.4649
		No	26 (41.3%)	18 (34.6%)	

*Statistical test (Chi-Square) performed to compare active treatments only. PI: Pain Intensity; Respon: Responder; TRAM/DKP: tramadol/dexketoprofen; TRAM/PAR: tramadol/paracetamol.

Table 6. Overview of Adverse Drug Reaactions by MedDRA System Organ Class (SOC) and Preferred Term (PT) in Moderate Baseline Pain Intensity Group (Expressed as number of events | number of patients affected (%))

SOC Preferred Term	**TRAM/DKP N=196**	**TRAM/Par N=210**	**Placebo N=102**	**Overall N=508**
Cardiac disorders	**0 | 0 (0.0%)**	**1 | 1 (0.5%)**	**0 | 0 (0.0%)**	**1 | 1 (0.2%)**
Palpitations	0 | 0 (0.0%)	1 | 1 (0.5%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Gastrointestinal disorders	**20 | 15 (7.7%)**	**20 | 17 (8.1%)**	**0 | 0 (0.0%)**	**40 | 32 (6.3%)**
Abdominal discomfort	1 | 1 (0.5%)	0 | 0 (0.0%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Diarrhoea	0 | 0 (0.0%)	1 | 1 (0.5%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Nausea	9 | 9 (4.6%)	8 | 8 (3.8%)	0 | 0 (0.0%)	17 | 17 (3.4%)
Vomiting	10 | 10 (5.1%)	11 | 11 (5.2%)	0 | 0 (0.0%)	21 | 21 (4.1%)
General disorders and administration site conditions	**4 | 3 (1.5%)**	**2 | 2 (1.0%)**	**0 | 0 (0.0%)**	**6 | 5 (1.0%)**
Asthenia	1 | 1 (0.5%)	1 | 1 (0.5%)	0 | 0 (0.0%)	2 | 2 (0.4%)
Fatigue	0 | 0 (0.0%)	1 | 1 (0.5%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Malaise	3 | 3 (1.5%)	0 | 0 (0.0%)	0 | 0 (0.0%)	3 | 3 (0.6%)
Nervous system disorders	**16 | 13 (6.6%)**	**14 | 12 (5.7%)**	**2 | 2 (2.0%)**	**32 | 27 (5.3%)**
Amnesia	1 | 1 (0.5%)	0 | 0 (0.0%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Dizziness	6 | 6 (3.1%)	8 | 8 (3.8%)	0 | 0 (0.0%)	14 | 14 (2.8%)
Headache	2 | 2 (1.0%)	1 | 1 (0.5%)	1 | 1 (1.0%)	4 | 4 (0.8%)
Presyncope	0 | 0 (0.0%)	1 | 1 (0.5%)	0 | 0 (0.0%)	1 | 1 (0.2%)
Somnolence	7 | 7 (3.6%)	4 | 4 (1.9%)	1 | 1 (1.0%)	12 | 12 (2.4%)
Overall	**40 | 20 (10.2%)**	**37 | 24 (11.4%)**	**2 | 2 (2.0%)**	**79 | 46 (9.1%)**

Table 7. Overview of Adverse Drug Reactions by MedDRA System Organ Class (SOC) and Preferred Term (PT) in Severe Baseline Pain Intensity Group (Expressed as number of events | number of patients affected (%))

SOC Preferred Term	**TRAM/DKP N=63**	**TRAM/Par N=52**	**Placebo N=29**	**Overall N=144**
Gastrointestinal disorders	**2 | 1 (1.6%)**	**7 | 4 (7.7%)**	**0 | 0 (0.0%)**	**9 | 5 (3.5%)**
Nausea	1 | 1 (1.6%)	4 | 4 (7.7%)	0 | 0 (0.0%)	5 | 5 (3.5%)
Vomiting	1 | 1 (1.6%)	3 | 3 (5.8%)	0 | 0 (0.0%)	4 | 4 (2. 8%)
Nervous system disorders	**1 | 1 (1.6%)**	**7 | 5 (9.6%)**	**0 | 0 (0.0%)**	**8 | 6 (4.2%)**
Dizziness	0 | 0 (0.0%)	5 | 5 (9.6%)	0 | 0 (0.0%)	5 | 5 (3.5%)
Somnolence	1 | 1 (1.6%)	1 | 1 (1.9%)	0 | 0 (0.0%)	2 | 2 (1.4%)
Tremor	0 | 0 (0.0%)	1 | 1 (1.9%)	0 | 0 (0.0%)	1 | 1 (0.7%)
Vascular disorders	**0 | 0 (0.0%)**	**1 | 1 (1.9%)**	**0 | 0 (0.0%)**	**1 | 1 (0.7%)**
Hypotension	0 | 0 (0.0%)	1 | 1 (1.9%)	0 | 0 (0.0%)	1 | 1 (0.7%)
Overall	**3 | 2 (3.2%)**	**15 | 5 (9.6%)**	**0 | 0 (0.0%)**	**18 | 7 (4.9%)**