Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain
Gay-Escoda, Cosme; Hanna, Magdi; Montero, Antonio; Dietrich, Thomas; Milleri, Stefano; Giergiel, Ewa; Bagi Zoltán, Tóth; Varrassi, Giustino

DOI: 10.1136/bmjopen-2018-023715
License: Creative Commons: Attribution-NonCommercial (CC BY-NC)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Gay-Escoda, C, Hanna, M, Montero, A, Dietrich, T, Milleri, S, Giergiel, E, Bagi Zoltán, T & Varrassi, G 2019, 'Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomised, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study)', BMJ, vol. 9, no. 2, e023715. https://doi.org/10.1136/bmjopen-2018-023715

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Gay-Escoda C, Hanna M, Montero A, et al Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomised, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study) BMJ Open 2019;9:bmjopen-2018-023715. doi: 10.1136/bmjopen-2018-023715

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

*Users may freely distribute the URL that is used to identify this publication.
*Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
*User may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
*Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
Tramadol/dexketoprofen (TRAM/DKP) compared with tramadol/paracetamol in moderate to severe acute pain: results of a randomised, double-blind, placebo and active-controlled, parallel group trial in the impacted third molar extraction pain model (DAVID study)

Cosme Gay-Escoda,¹ Magdi Hanna,² Antonio Montero,³ Thomas Dietrich,⁴ Stefano Milleri,⁵,⁶ Ewa Giergiel,⁷ Tóth Bagi Zoltán,⁸ Giustino Varassi⁹

ABSTRACT

Objectives To compare efficacy/safety of oral tramadol 75 mg/dexketoprofen 25 mg (TRAM/DKP) and TRAM 75 mg/paracetamol 650 mg (TRAM/paracetamol) in moderate to severe pain following surgical removal of impacted lower third molar.

Design Multicentre, randomised, double-blind, placebo-controlled, phase IIb study.

Participants Healthy adult patients scheduled for surgical extraction of at least one fully/partially impacted lower third molar requiring bone manipulation. 654 patients were randomised and 653 were eligible for analysis.

Interventions Surgery was performed under local anaesthetic. No sedation was permitted. Patients rated pain intensity (PI) using an 11-Numerical Rating Scale (NRS) (0 = no pain, 10 = worst pain). Participants experiencing moderate/severe pain (>4) within 4 hours of surgery were randomised (2:2:1 ratio) to a single oral dose of TRAM/DKP 75/25 mg, TRAM/paracetamol 75/650 mg or placebo.

Main outcome measures Efficacy was based on patients’ electronic diaries. Analgesia and pain were recorded as follows: pain relief (PAR) on a 5-point Verbal Rating Scale (0 = ‘no relief’, 1 = ‘a little (perceptible) relief’, 2 = ‘some (meaningful) relief’, 3 = ‘lot of relief’, 4 = ‘complete relief’) at the predefined postdose time points 15 min, 30 min, 1 hour, 1.5 hour, 2 hour, 4 hour, 6 hour and 16 hour and PI on the 11-point NRS at 0 and at the same predefined postdose time points. Onset of analgesia documented using double stopwatch method over a 2-hour period. Primary endpoint was total pain relief over 6 hours (TOTPAR6). Rescue medication was available during the treatment period.

Results TRAM/DKP was superior to TRAM/paracetamol and placebo at the primary endpoint TOTPAR6 (p<0.0001). Mean (SD) TOTPAR6 in the TRAM/DKP group was 13 (6.97), while those in the active control and placebo groups were 9.1 (7.65) and 1.9 (3.89), respectively. Superiority of TRAM/DKP over active comparator and placebo was observed at all secondary endpoints. Incidence of adverse events was comparable between active groups.

Conclusions TRAM/DKP (75/25 mg) is effective and superior to TRAM/paracetamol (75/650 mg) 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, together with a favourable safety profile.

Trial registration number EudraCT 2015-004152-22 and NCT02777970.
The majority of patients with moderate to severe acute postoperative pain report inadequate pain relief (PAR). This is in spite of well-known and published negative impact of inadequate PAR on clinical outcomes such as time to functional recovery, postsurgical complications, pain chronification and quality of life. It is consequently associated with increased healthcare costs. Attaining adequate PAR with monotherapy is difficult and multimodal analgesia is now accepted as the cornerstone of effective pain treatment. Combining analgesics with diverse mechanisms of action and potential synergistic effects means that a wider spectrum of pain can be covered, and lower doses of single drug components can be administered, thus enhancing efficacy and minimising adverse events (AEs).

Dexketoprofen (DKP) is a well-known inhibitor of cyclooxygenase (COX-1 and COX-2) with proven analgesic and anti-inflammatory efficacy in a wide spectrum of acute pain syndromes; it appears to be as effective as the double dose of the racemic ketoprofen, but with a faster onset of analgesia. Its fast onset of action and favourable pharmacokinetics profile are enhanced by its formulation as trometamol salt, which has an increased bioavailability compared with the free drug. The rapid dissolution and absorption, \( t_{\text{max}} \) between 0.25 and 0.75 hour, ensure rapid PAR which is crucial for the effective management of acute pain. DKP’s efficacy is complemented by its favourable safety profile with clinical data showing an AE profile similar to that of the new generation NSAIDs.

Tramadol (TRAM), a \( \mu \)-opioid receptor agonist, norepinephrine and serotonin reuptake inhibitor, is a central-acting analgesic and also shows a peripheral and local analgesic effect. Its opioid and non-opioid mechanisms are thought to act synergistically on descending inhibitory pathways in the central nervous system. TRAM’s

**Table 1** Patients by treatment group

| Overall | TRAM/DKP | TRAM/paracetamol | Placebo |
|---------|----------|-----------------|---------|
| Screened patients | 792 | – | – |
| Randomised patients | 654 | 261* | 262 | 131 |
| Intention-to-treat population | 653 | 260 | 262 | 131 |
| Safety population | 653 | 260 | 262 | 131 |
| Per-protocol population | 620 | 246 | 248 | 126 |

*One patient was enrolled and randomised but was excluded from all the analysis populations because younger than 18 years old.

TRAM/DKP, tramadol/dexketoprofen.

**INTRODUCTION**

The majority of patients with moderate to severe acute postoperative pain report inadequate pain relief (PAR). This is in spite of well-known and published negative impact of inadequate PAR on clinical outcomes such as time to functional recovery, postsurgical complications, pain chronification and quality of life. It is consequently associated with increased healthcare costs. Attaining adequate PAR with monotherapy is difficult and multimodal analgesia is now accepted as the cornerstone of effective pain treatment. Combining analgesics with diverse mechanisms of action and potential synergistic effects means that a wider spectrum of pain can be covered, and lower doses of single drug components can be administered, thus enhancing efficacy and minimising adverse events (AEs).

Dexketoprofen (DKP) is a well-known inhibitor of cyclooxygenase (COX-1 and COX-2) with proven analgesic and anti-inflammatory efficacy in a wide spectrum of acute pain syndromes; it appears to be as effective as the double dose of the racemic ketoprofen, but with a faster onset of analgesia. Its fast onset of action and favourable pharmacokinetics profile are enhanced by its formulation as trometamol salt, which has an increased bioavailability compared with the free drug. The rapid dissolution and absorption, \( t_{\text{max}} \) between 0.25 and 0.75 hour, ensure rapid PAR which is crucial for the effective management of acute pain. DKP’s efficacy is complemented by its favourable safety profile with clinical data showing an AE profile similar to that of the new generation NSAIDs.

Tramadol (TRAM), a \( \mu \)-opioid receptor agonist, norepinephrine and serotonin reuptake inhibitor, is a central-acting analgesic and also shows a peripheral and local analgesic effect. Its opioid and non-opioid mechanisms are thought to act synergistically on descending inhibitory pathways in the central nervous system. TRAM’s

**Figure 1** Participant flow chart of study. ITT population consisted of all patients randomised; safety population of all patients who received study drug; PP population of all patients of the ITT who did not experience relevant protocol deviation related to efficacy endpoints of primary interest. *One patient excluded from analysis being aged less than 18 years. ITT, intention to treat; PP, per protocol; TRAM/DKP, tramadol/dexketoprofen.
analgesic efficacy is complemented by a long duration of action (half-life around 6 hours) and by a safety profile that favours TRAM over other opioids.5

The doses of TRAM hydrochloride 75 mg plus DKP 25 mg were selected as the optimal for a combination in a previous dose-finding study11; subsequent multiple-dose clinical trials in well-established models of acute visceral and somatic pain confirmed the combination of TRAM hydrochloride 75 mg with DKP 25 mg (TRAM/DKP) as an effective analgesic for the control of moderate to severe acute pain.13–16 TRAM/DKP offers a number of important advantages including: proven efficacy and tolerability with a 25% overall reduction in the opioid dosage, improved compliance, as well as a convenient mode of administration. TRAM/DKP (75/25 mg) (film-coated tablet) has been registered and released for commercial use in Europe.17

Direct comparisons of newly released drugs with older agents are rarely performed in clinical trials, although this kind of evidence is valuable to improve appropriateness of pharmacotherapy in clinical practice.18 This lack of data can make it difficult for clinicians to determine the optimal therapeutic option.19 To provide a meaningful comparison of the analgesic capabilities of TRAM/DKP fixed combination versus oral TRAM hydrochloride 75 mg/paracetamol 650 mg (TRAM/paracetamol), a head-to-head clinical trial was necessary.

The present phase IIIb trial (Dexketoprofen Analgesic eVolution with tramadol) was designed to compare the analgesic efficacy and safety of a single dose of the fixed oral combination TRAM/DKP (75/25 mg) versus TRAM/paracetamol (75/650 mg) in postoperative moderate to severe pain following extraction of impacted lower third molars. The model has a proven record of assay sensitivity to compare efficacy, including onset of analgesic action, in head-to-head trials.11,20,21

### METHODS

It was performed at 18 centres in five European countries (Hungary, Italy, Poland, Spain and UK) and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The clinical phase of the study started in April 2016 and was concluded in February 2017.

#### Patients

Healthy adult patients (>18 years of age) scheduled to undergo surgical extraction of at least one fully or partially impacted lower third molar requiring bone manipulation were included in the trial. Criteria for randomisation included postoperative pain of moderate to severe intensity (Numerical Rating Scale, NRS ≥4) within a 4-hour time lapse after the completion of the surgery. Pregnant or breastfeeding women or women of childbearing potential not using adequate contraception were excluded from the study. The following conditions did not permit participation in the study: known allergy or hypersensitivity to study treatments, rescue medication (RM) or any other NSAIDs except those permitted in the study protocol, opioids and acetyl salicylic acid; history/presence of any illness or condition that, in the opinion of the Investigator, might pose a risk to the patient or confound the efficacy and safety results of the study. Patients who had received any investigational drug or participated in any other clinical trials (within the previous 4 weeks) were also excluded. Patients who had taken, sedatives, hypnotic agents or analgesics within the previous 4 hours postdose (or five half-lives, which is the longer presurgery), drugs posing a risk to the patient and for 24 hours postdose, were also not enrolled.

### Table 2: Patient demographic and baseline characteristics by treatment group (ITT population)

| Demographic and baseline characteristics | TRAM/DKP, n=260 | TRAM/paracetamol, n=262 | Placebo, n=131 |
|------------------------------------------|----------------|----------------|---------------|
| Race (n, %)                              |                |                |               |
| Asian                                    | 14 (5.4)       | 21 (8.0)       | 6 (4.6)       |
| Black or African American                | 7 (2.7)        | 3 (1.1)        | 6 (4.6)       |
| White                                    | 235 (90.4)     | 233 (88.9)     | 118 (90.1)    |
| Other                                    | 4 (1.5)        | 5 (1.9)        | 1 (0.8)       |
| Gender (n, %)                            |                |                |               |
| Female                                   | 152 (58.5)     | 158 (60.3)     | 78 (59.5)     |
| Male                                     | 108 (41.5)     | 104 (39.7)     | 53 (40.5)     |
| Age (years)                              |                |                |               |
| Mean (SD)                                | 26.8 (7.48)    | 27.1 (8.13)    | 26.5 (7.67)   |
| Range                                    | 18–52          | 18–63          | 18–59         |
| Body mass index                          |                |                |               |
| Mean (SD)                                | 23.5 (4.48)    | 23.4 (4.36)    | 23.7 (4.21)   |
| Range                                    | 16–44          | 15–44          | 16–40         |
| Pain intensity (NRS-PI)                  |                |                |               |
| Mean (SD)                                | 5.7 (1.4)      | 5.5 (1.3)      | 5.6 (1.3)     |
| 4≤ NRS-PI ≤6 (n, %)                      | 508 (77.8)     | 196 (75.4)     | 210 (80.2)    |
| NRS-PI >6 (n, %)                         | 144 (22.1)     | 63 (24.2)      | 52 (19.8)     |

| 4≤ NRS-PI ≤6 corresponding to moderate pain intensity; NRS-PI >6 corresponding to severe pain intensity. ITT, intention to treat; NRS, Numerical Rating Scale; TRAM/DKP, tramadol/dexketoprofen. |
Lastly, patients were excluded if any surgical complication occurred that, in the opinion of the investigator, would interfere with the study procedures or assessments.

**Study design**
This was a multicentre, randomised, double-blind, double-dummy, parallel-group, placebo and active-controlled, single-dose, phase IIIb study including three treatment arms. Participation in the study lasted for approximately 3 weeks for each patient and was made up of: a screening period, (within 2 weeks before randomisation), including the presurgery procedures to be completed at least 1 day prior to surgery and ending within the 4 hours qualification postsurgery; randomisation and treatment administration (day 1, t0) followed by an 8-hour assessment period during which patients recorded efficacy data using an electronic diary (eDiary) both at site (up to t2 hour) and out of site (up to t8 hour); followed by an end of study visit (6±1 days after randomisation).

Surgery was performed under local anaesthetic using 2% lidocaine (with 1:80,000 epinephrine) up to a total volume of 5.4 mL per molar. No sedation was permitted. After surgery, patients rated pain intensity (PI) using an 11-NRS ranging from 0 (no pain) to 10 (worst pain). Participants experiencing moderate to severe pain (≥4) within 4 hours after surgery were randomised with a 2:2:1 ratio to a single oral dose of TRAM/DKP 75/25 mg, TRAM/paracetamol 75/650 mg or placebo. The inclusion of a placebo group was deemed acceptable considering the self-limiting nature of postoperative dental pain, the short duration of the study, and the fact that an effective RM was provided to participants requesting additional PAR; this is in line with

**Table 3** Summary of descriptive statistics TOTPAR, % max TOTPAR SPID and % max SPID over 2, 4, 6 and 8 hours

| Parameter | Time points | TRAM/DKP n=260 | TRAM/paracetamol n=262 | Placebo n=131 | Statistical test TRAM/DKP versus TRAM/paracetamol |
|-----------|-------------|----------------|------------------------|--------------|-------------------------------------------------|
| TOTPAR    | 2 hours     | 4.6 (1.99)     | 3.3 (2.19)             | 0.8 (1.22)   | <0.0001                                         |
|           | 4 hours     | 9.5 (4.47)     | 3.3 (2.19)             | 0.8 (1.22)   | <0.0001                                         |
|           | 6 hours (primary endpoint) | 13.0 (6.97) | 6.5 (4.95)             | 1.5 (2.71)   | <0.0001                                         |
|           | 8 hours     | 15.3 (9.22)    | 9.2 (7.65)             | 1.9 (3.89)   | <0.0001                                         |
| % max     |             |                |                        |              |                                                 |
| TOTPAR    | 2 hours     | 51.5 (22.08)   | 36.7 (24.29)           | 9.1 (13.56)  | <0.0001                                         |
|           | 4 hours     | 56.1 (26.32)   | 38.1 (29.11)           | 8.8 (15.95)  | <0.0001                                         |
|           | 6 hours     | 51.9 (27.87)   | 36.6 (30.62)           | 7.7 (15.57)  | <0.0001                                         |
|           | 8 hours     | 46.5 (27.95)   | 34.2 (30.76)           | 7.1 (15.86)  | <0.0001                                         |
| SPID      | 2 hours     | 6.4 (3.57)     | 4.1 (3.57)             | 0.3 (2.38)   | <0.0001                                         |
|           | 4 hours     | 13.6 (7.49)    | 8.2 (7.63)             | 1.1 (4.57)   | <0.0001                                         |
|           | 6 hours     | 18.4 (11.09)   | 11.7 (11.58)           | 1.6 (6.72)   | <0.0001                                         |
|           | 8 hours     | 21.5 (14.27)   | 14.4 (15.21)           | 2.2 (8.98)   | <0.0001                                         |
| % max     |             |                |                        |              |                                                 |
| SPID      | 2 hours     | 56.1 (27.31)   | 38.1 (32.05)           | 2.4 (23.06)  | <0.0001                                         |
|           | 4 hours     | 59.4 (29.03)   | 38.7 (34.87)           | 4.7 (21.93)  | <0.0001                                         |
|           | 6 hours     | 53.6 (30.14)   | 36.8 (35.27)           | 4.9 (21.58)  | <0.0001                                         |
|           | 8 hours     | 47.2 (29.62)   | 34.1 (34.89)           | 5.2 (21.48)  | <0.0001                                         |

Statistical test performed to compare active treatments only (ITT population).

ITT, intention to treat; SPID, sum of pain intensity difference; TOTPAR, total pain relief over 6 hours; TRAM/DKP, tramadol/dexketoprofen.

Figure 2 Mean TOTP AR at 6 hours (primary endpoint) and at 2, 4 and 8 hours for TRAM/DKP, TRAM/paracetamol and placebo with PAR was measured on a 5-point Verbal Rating Scale (0='no relief' to 4='complete relief'). *Statistically significant comparison of TRAM/DKP versus TRAM/paracetamol (p<0.0001). PAR, pain relief; TRAM/DKP, tramadol/dexketoprofen; TOTPAR6, total pain relief.

Gay-Escoda C, et al. BMJ Open 2019;9:e023715. doi:10.1136/bmjopen-2018-023715
recent academic recommendations.24 RM consisted of oral ibuprofen (400mg) and was permitted during the 8-hour postdose assessment period up to a maximum of two tablets at a minimum interval of 4 hours.

Randomisation and masking
Randomisation was performed through Interactive Voice/Web Response System according to a computer-generated randomisation 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. Double-blind conditions were ensured by the application of double dummy technique.

Table 4  Percentage of responders to treatment over 2, 4, 6 and 8 hours (ITT population)

| Time points | Responder | TRAM/DKP n=260, (%) | TRAM/paracetamol n=262, (%) | Placebo n=131, (%) | Statistical test TRAM/DKP versus TRAM/paracetamol (p value) |
|-------------|-----------|---------------------|-----------------------------|-------------------|----------------------------------------------------------|
| max TOTPAR ≥50% | | | | | |
| 2 hours | Yes | 185 (71.2) | 116 (44.3) | 6 (4.6) | <0.0001 |
| | No | 75 (28.8) | 146 (55.7) | 125 (95.4) | |
| 4 hours | Yes | 185 (71.2) | 113 (43.1) | 8 (6.1) | <0.0001 |
| | No | 75 (28.8) | 149 (56.9) | 123 (93.9) | |
| 6 hours | Yes | 157 (60.4) | 101 (38.5) | 5 (3.8) | <0.0001 |
| | No | 103 (39.6) | 161 (61.5) | 126 (96.2) | |
| 8 hours | Yes | 124 (47.7) | 93 (35.5) | 7 (5.3) | 0.0047 |
| | No | 136 (52.3) | 169 (64.5) | 124 (94.7) | |
| PI reduction >30% | | | | | |
| 2 hours | Yes | 231 (88.8) | 166 (63.4) | 21 (16.0) | <0.0001 |
| | No | 29 (11.2) | 96 (36.6) | 110 (84.0) | |
| 4 hours | Yes | 203 (78.1) | 141 (53.8) | 16 (12.2) | <0.0001 |
| | No | 57 (21.9) | 121 (46.2) | 115 (87.8) | |
| 6 hours | Yes | 146 (56.2) | 115 (43.9) | 11 (8.4) | 0.0066 |
| | No | 114 (43.8) | 147 (56.1) | 120 (91.6) | |
| 8 hours | Yes | 104 (40.0) | 93 (35.5) | 13 (9.9) | 0.2885 |
| | No | 156 (60.0) | 169 (64.5) | 118 (90.1) | |

ITT, intention to treat; PI, pain intensity; TOTPAR, total pain relief over 6 hours; TRAM/DKP, tramadol/dexketoprofen.
Sample size calculation
A sample size of 230 patients per active arm was considered adequate to demonstrate the non-inferiority of TRAM/DKP compared with TRAM/paracetamol assuming a non-inferiority margin of 20%, a power of 80% and an overall significance level of 2.5% (one sided). The mean total pain relief over 6 hours (TOTPAR6) for TRAM/paracetamol is assumed equal to 7.4 (SD 6.30) based on a previously published trial.\textsuperscript{25} One hundred and fifteen patients in the placebo arm were considered sufficient to demonstrate the superiority of both TRAM/paracetamol and TRAM/DKP versus placebo for model sensitivity. Assuming about 10% of major protocol violators and 20% of screening failure rate a total of 640 patients needed to be randomised and 800 patients were expected to be screened.

Efficacy evaluation
Evaluation of efficacy was based on data entered by patients in eDiary. Analgesia and pain were recorded by using the following measures: PAR 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')\textsuperscript{26 27} 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) and PI on the 11-point NRS\textsuperscript{23 24 28} at t0 and at the same predefined postdose time points.

The onset of analgesia was documented using the double stopwatch method over a 2-hour period postdose. Following treatment, two stopwatches were automatically activated in the eDiary. Subjects were instructed to stop the first stopwatch when they felt ‘first perceptible’ PAR (FPPAR, ie, at the moment they first felt any PAR whatsoever) and the second when they experienced a ‘meaningful’ PAR (MPAR, ie, when the relief from pain became meaningful to them). The FPPAR and MPAR could be alternatively defined by using the time point when PAR is assessed as 1 and 2, respectively, in case the stopwatch was not used or used after the recording of the PAR equal to 1 or 2. Furthermore, 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.\textsuperscript{22} The time between treatment administration and first intake of RM, and percentage of patients requiring RM were also evaluated. After first intake of RM, patients were no longer required to use the eDiary, including the stopwatch functionality.
Primary and secondary endpoints

The primary efficacy endpoint was TOTPAR, calculated as the weighted sum of the PAR scores measured according to a 5-point VRS, over 6 hours postdose (TOTPAR6). Secondary efficacy endpoints included the time course of mean PAR and PI scores over 8 hours; TOTPAR over 2, 4 and 8 hours postdose and the percentage of maximum calculated TOTPAR (% max TOTPAR) over 2, 4, 6 and 8 hours; sum of pain intensity difference (SPID) and the percentage of maximum calculated SPID (% max SPID) over 2, 4, 6 and 8 hours; percentage of responders in terms of PAR or PI reduction, namely subjects who achieved at least 50% of max TOTPAR or at least 30% of PI reduction versus baseline at prespecified time points over the 8 hours, respectively; time to FPPAR; time to confirmed FPPAR; time to MPAR; percentage of patients who achieved FPPAR, confirmed FPPAR and MPAR within 30 min, 1 hour and 2 hours; PGE at 8 hours or whenever the patient used RM; time of first intake of RM since study drug intake; percentage of patients using RM at 2, 4, 6 or 8 hours.

Safety

Safety evaluation was based on the incidence, seriousness, intensity and causal relationship of treatment-emergent adverse events (TEAEs). AEs were assessed throughout the study. Safety was evaluated by the assessment of clinically significant changes postdose versus the baseline in the physical examination, vital signs (VS; blood pressure and heart rate) and laboratory safety tests (haematology, biochemistry and urinalysis). Any patient who prematurely withdrew after having received study medication was encouraged to undergo the end of study visit.

Statistical analysis

The primary efficacy variable was analysed on the per-protocol (PP) and intention-to-treat (ITT) populations to assess the non-inferiority hypothesis using analysis of covariance (ANCOVA) with one-sided significance level of 2.5% for testing the differences in treatment efficacy, as quantified by TOTPAR6, between TRAM/DKP and TRAM/paracetamol. The ANCOVA model included terms of treatment and the baseline PI (NRS) as covariates. In case of non-inferiority being confirmed, the superiority of TRAM/DKP versus TRAM/paracetamol was tested on the ITT population. Superiority of TRAM/DKP and TRAM/paracetamol versus placebo was evaluated in order to confirm the model sensitivity on the ITT population. Non-inferiority hypothesis was satisfied if the lower limit of the CI for the estimated difference between TRAM/DKP and TRAM/paracetamol was greater than a non-inferiority margin of 20% of the estimated mean of TRAM/paracetamol.

Secondary efficacy analysis SPID6 was analysed for non-inferiority with the possibility to switch for superiority analogously to the primary efficacy variable. All the other secondary efficacy variables were descriptively analysed and tested for the superiority of TRAM/DKP, when applicable, through ad hoc inferential analyses, as follows: NRS-PI, SPID (excluded SPID6), %max SPID, TOTPAR (excluded TOTPAR6), %max TOTPAR (continuous variables) were analysed by ANCOVA model as for the primary efficacy variable or a repeated measure model if more than one value per patient; VRS-PAR and PGE (categorical variables) were analysed by Wilcoxon rank-sum test; percentage of patients who required RM, and percentage of patients achieving at least 50% max TOTPAR or 30% of PI reduction, with confirmed FPPAR or MPAR were tested using a $\chi^2$ test. Time to use RM, time to FPPAR, confirmed FPPAR and MPAR were assessed using a log-rank test. All analyses were performed in SAS V.9.3 (SAS).

Imputation

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, respectively, before and after the missing one.
This procedure was applied to all efficacy outcomes. If PI was missed at t0, the value recorded during qualification procedure was used as a baseline. After RM intake, PI returned to its baseline (t0) level and PAR to zero (‘no relief’) for all subsequent time points (ie, baseline observation carried forward).
Safety analysis

AEs were coded using the MedDRA dictionary. The incidence of each TEAE was summarised by system organ class, preferred term and treatment. Clinically significant abnormal findings in VS and physical examination were listed by treatment. Safety variables were analysed by descriptive statistics and were run on the safety population.

Definition of analysis population

The ITT population consisted of all patients randomised; safety population of all patients who received study drug; PP population of all patients of the ITT who did not experience relevant protocol deviation related to efficacy endpoints of primary interest.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Role of the funding source

The study sponsor (Menarini Group) contributed to the study design, data analysis and manuscript preparation. MH confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Table 6

| Value          | TRAM/DKP (n=260) | TRAM/paracetamol (n=262) | Placebo (n=131) |
|----------------|------------------|--------------------------|-----------------|
| Score (n, %)   |                  |                          |                 |
| Poor           | 17 (6.5)         | 61 (23.3)                | 91 (69.5)       |
| Fair           | 26 (10.0)        | 40 (15.3)                | 18 (13.7)       |
| Good           | 54 (20.8)        | 55 (21)                  | 14 (10.7)       |
| Very good      | 100 (38.5)       | 62 (23.7)                | 4 (3.1)         |
| Excellent      | 56 (21.5)        | 31 (11.8)                | 2 (1.5)         |
| Not assessed   | 7 (2.7)          | 13 (5.0)                 | 2 (1.5)         |
| Mean score (SD)* | 3.6 (1.14)      | 2.8 (1.37)               | 1.5 (0.92)      |

*Statistical test TRAM/paracetamol versus TRAM/DKP (p<0.0001).

ITT, intention to treat; TRAM/DKP, tramadol/dexketoprofen; VRS, Verbal Rating Scale.

RESULTS

Of the 792 patients screened, 654 were randomised and received study treatment, one patient was excluded from any analysis being <18 years old (figure 1, table 1).

Figure 8

Kaplan-Meier estimation of time to patient report of confirmed first perceptible pain relief (FPPAR) represents the cumulative percentage of patients reporting confirmed FPPAR over the time (in minutes) in the TRAM/DKP arm and TRAM/paracetamol arm. TRAM/DKP, tramadol/dexketoprofen.
The safety population comprised 653 patients as did the ITT group. Patients were enrolled at hospital clinics and dental surgeries across five European countries (66 patients in Hungary, 180 in Italy, 127 in Poland, 141 in Spain and 139 in the UK).

Efficacy analyses for non-inferiority were performed on the PP population, including a total of 620 randomised patients as 33 participants were excluded due to major protocol deviations related to efficacy endpoints of primary interest. Patients’ assignment to the different analysis populations occurred before the study blind was broken. One patient in the TRAM/paracetamol arm was lost at follow-up and did not

**Figure 9** Kaplan-Meier estimation of time to patient report of meaningful pain relief (MPAR) represents the cumulative percentage of patients reporting MPAR over the time (in minutes) in the TRAM/DKP arm and TRAM/paracetamol arm. TRAM/DKP, tramadol/dexketoprofen.

**Figure 10** Mean scores of patients’ global evaluation by treatment arm assessed on 5-point Verbal Rating Scale (1=poor to 5=excellent). ‘Statistically significant TRAM/DKP versus TRAM/paracetamol (p<0.0001). TRAM/DKP, tramadol/dexketoprofen.

**Figure 11** Percentage of subjects who rated the treatment as poor, fair, good, very good or excellent on patients’ global evaluation by treatment arm. TRAM/DKP, tramadol/dexketoprofen.
attending end of study visit (figure 1). Demography and baseline characteristics of different treatment groups were comparable (table 2).

The mean (SD) age was 26.8 (7.48) years (range 18–52) in TRAM/DKP, 27.1 (8.13) years (range 18–63) in TRAM/Paracetamol; 26.5 (7.67) years (18–59) in placebo arm. Percentages of women were 58.5% in TRAM/DKP, 60.3% in TRAM/Paracetamol and 59.5% in placebo arm (table 2). Patients reported mean (SD) PI values at baseline of 5.7 (1.36); 5.5 (1.34) and 5.6 (1.30) in the TRAM/DKP, TRAM/paracetamol and placebo arm, respectively (table 2).

Figure 12  Percentage of patient taking first rescue medication within 2, 4, 6 and 8 hours after drug intake. * Statistically significant TRAM/DKP versus TRAM/paracetamol (p<0.01). TRAM/DKP, tramadol/dexketoprofen.

Figure 13 Kaplan-Meier estimation of time to RM intake represents the cumulative percentage of patients using RM over the time (in minutes) in the TRAM/DKP arm and TRAM/paracetamol arm. RM, rescue medication; TRAM/DKP, tramadol/dexketoprofen.
Efficacy results

Primary endpoint

Overall, the combination TRAM/DKP showed the greatest sustained analgesia during the 6-hour postdose period as demonstrated by the TOTPAR6 primary endpoint, compared with the TRAM/paracetamol and placebo groups. Since non-inferiority was confirmed, the ITT population was used to perform superiority analyses on the primary endpoint, as prespecified. The mean (SD) TOTPAR6 reported by patients in the TRAM/DKP group was 13 (7.0), while those in TRAM/paracetamol and placebo groups were 9.2 (7.7) and 1.9 (3.9), respectively, demonstrating that the combination TRAM/DKP was statistically superior (p<0.0001) to TRAM/paracetamol (table 3 and figure 2). The results of the analysis conducted on ITT population were consistent with those conducted on the PP, therefore, the model sensitivity was confirmed.

Secondary endpoints

The time course of the mean PAR and PI scores showed that TRAM/DKP provided a more rapid onset of action compared with TRAM/paracetamol as differences were statistically significant already 30 min postdose. Furthermore, patients in the TRAM/DKP arm constantly had greater analgesia and lower PI, in a statistically and clinically significant fashion, at each prespecified time points until 6 hours after drug intake, in comparison to those in the comparator arm (figures 3 and 4). In addition, the PI analysis with repeated measures indicated superiority of the combination TRAM/DKP in comparison to TRAM/paracetamol during the overall 8-hour period of assessment (p=0.0009). The superiority of TRAM/DKP was also confirmed by mean values of the main secondary efficacy variable SPI6 (table 3). Analysis of summary efficacy measures including TOTPAR2, 4 and 8; SPI2, 4 and 8; % max TOTPAR over 2, 4, 6 and 8 hours; % max SPI over 2, 4, 6 and 8 hours provided further confirmation of the superiority of TRAM/DKP versus TRAM/paracetamol (p<0.0001) (table 3, figures 2 and 5). Regarding percentage of responders (patients achieving at least 50% of maxTOTPAR), the best results were detected in patients treated with TRAM/DKP, who were considered responders: 71.2%, 2 hours and at 4 hours, 60.4% at 6 hours and 47.7% at 8 hours. While responders in the TRAM/paracetamol group were 44.3%, 43.1%, 38.5% and 35.5% at 2, 4, 6 and 8 hours, respectively (p<0.01 for each time point) (table 4). In addition, when responders were defined as subjects who achieved at least 30% of PI reduction versus baseline, the best results were observed with TRAM/DKP versus TRAM/paracetamol at 2, 4 and 6 hours (p<0.01) (table 4, figure 6).

The onset of analgesia, evaluated with the double stop-watch method, was significantly faster in the TRAM/DKP group in comparison to TRAM/paracetamol group considering all the relevant secondary endpoints (FPPAR, confirmed FPPAR and MPAR) measured within different time periods (30 min, 1 hour and 2 hours postdose). Significantly more patients in the TRAM/DKP group reported a confirmed FPPAR compared with patients in the TRAM/paracetamol group: 76.9% vs 60.3% at 30 min, 90.0% vs 72.5% at 1 hour, and 90.4% vs 72.9% at 2 hours (p<0.0001) (table 5, figure 7).

The median (95% CI) times to confirmed FPPAR and MPAR after single dose of TRAM/DKP were 22 (18 to 24) and 42 (33 to 45) min, respectively; while the ones in the TRAM/paracetamol group were 27 (23 to 27) and 57 (49 to 57) min, respectively. Log-rank test between TRAM/DKP and active comparator showed a statistically significant difference (p<0.0001) (figures 8 and 9). PGE data also showed a better performance of the combination containing DKP and TRAM over the comparator. Significantly more patients in TRAM/DKP arm (80.8%) rated the study medication as ‘good’, ‘very good’ or ‘excellent’, than that in the TRAM/paracetamol (56.6%) and placebo (15.3%) groups (table 6, figures 10 and 11).

RM was required by significantly fewer patients in the TRAM/DKP group (7.7% within 2 hours; 14.6% within 4 hours; 33.8% within 6 hours) than in the TRAM/paracetamol group (20.6% within 2 hours; 36.3% within 4 hours; 45.8% within 6 hours) (p<0.01). The majority of patients randomised to placebo took RM (73.3% within 2 hours; 82.4% within 4 hours; 87.8% within 6 hours). Patients in TRAM/paracetamol group used RM more quickly than patients in TRAM/DKP group (p=0.0373) (figures 12 and 13).

Safety

Overall, 53 patients (8.1%) experienced one or more adverse drug reactions (97 ADRs in total) but none of the ADRs were considered to be serious (table 7).

No clinically relevant differences were identified in ADRs incidences between treatment groups. Overall, the most common ADRs were: vomiting (3.8%), nausea (3.4%), dizziness (2.9%) and somnolence (2.1%) (table 8). No deaths or other significant ADRs occurred. There were no clinically relevant changes in the VSs or physical examination versus baseline. Overall, TRAM/
DKP was safe and well tolerated, presenting a safety and tolerability profile fully in line with that observed in previous clinical experience.

**Table 8** Overview of adverse drug reactions by MedDRA system organ class (SOC) and preferred term (PT)

| SOC/PT                                | TRAM/DKP n=260, (%) | TRAM/paracetamol n=262, (%) | Placebo n=131, (%) | Overall n=653, (%) |
|---------------------------------------|---------------------|------------------------------|--------------------|-------------------|
| Overall                               | 43/22 (8.5)         | 52/29 (11.1)                 | 2/2 (1.5)          | 97/53 (8.1)       |
| Cardiac disorders                     |                     |                              |                    |                   |
| Overall                               | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Palpitations                          | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Gastrointestinal disorders            |                     |                              |                    |                   |
| Overall                               | 22/16 (6.2)         | 27/21 (8.0)                  | 0/0 (0.0)          | 49/37 (5.7)       |
| Abdominal discomfort                  | 1/1 (0.4)           | 0/0 (0.0)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Diarrhoea                             | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Nausea                                | 10/10 (3.9)         | 12/12 (4.6)                  | 0/0 (0.0)          | 22/22 (3.4)       |
| Vomiting                              | 11/11 (4.2)         | 14/14 (5.3)                  | 0/0 (0.0)          | 25/25 (3.8)       |
| General disorders and administration site conditions |         |                              |                    |                   |
| Overall                               | 4/3 (1.2)           | 2/2 (0.8)                    | 0/0 (0.0)          | 6/5 (0.8)         |
| Asthenia                              | 1/1 (0.4)           | 1/1 (0.4)                    | 0/0 (0.0)          | 2/2 (0.3)         |
| Fatigue                               | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Malaise                               | 3/3 (1.2)           | 0/0 (0.0)                    | 0/0 (0.0)          | 3/3 (0.5)         |
| Nervous system disorders              |                     |                              |                    |                   |
| Overall                               | 17/14 (5.4)         | 21/17 (6.5)                  | 2/2 (1.5)          | 40/33 (5.1)       |
| Amnesia                               | 1/1 (0.4)           | 0/0 (0.0)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Dizziness                             | 6/6 (2.3)           | 13/13 (5.0)                  | 0/0 (0.0)          | 19/19 (2.9)       |
| Headache                              | 2/2 (0.8)           | 1/1 (0.4)                    | 1/1 (0.8)          | 4/4 (0.6)         |
| Presyncope                            | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Somnolence                            | 8/8 (3.1)           | 5/5 (1.9)                    | 1/1 (0.8)          | 14/14 (2.1)       |
| Tremor                                | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Vascular disorders                    |                     |                              |                    |                   |
| Overall                               | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |
| Hypotension                           | 0/0 (0.0)           | 1/1 (0.4)                    | 0/0 (0.0)          | 1/1 (0.2)         |

TRAM/DKP, tramadol/dexketoprofen. Results are expressed as number of events/number of patients (%) (safety population).

**DISCUSSION**

This study shows that TRAM/DKP provides an effective analgesia for the control of moderate to severe pain following removal of impacted lower third molar and is superior to TRAM/paracetamol in terms of rapidity of onset and intensity of analgesia. Statistically and clinically significant superiority of TRAM/DKP over TRAM/paracetamol was demonstrated with an overall consistency not only at the primary endpoint (ie, TOTP6), but also at all different outcome measures adopted in the study. Study participants receiving TRAM/DKP combination reported lower pain scores already at the 30 min time point after drug administration.

**Limitations**

The main limitation is that this was a single-dose study and as such assessed only the short-term analgesic efficacy of TRAM/DKP in comparison with TRAM/paracetamol. In addition, although it has been proposed that systematic differences in the estimate of analgesic efficacy between dental and postsurgical pain models are unlikely, and efficacy in the dental model is highly predictive of efficacy in later stage models in drug development, further studies with similar design applied in other acute pain conditions are warranted.

**Generalisability**

The results of this head-to-head trial can guide physicians in choosing the adequate analgesic medication to optimise clinical outcomes in the treatment of a wide range of acute pain. This is particularly true in a moment in which there is a clear tendency to abandon the early treatment...
with strong opioids, in patients suffering from acute moderate to severe pain. Results of the present trial reinforce the clinical benefit of TRAM/DKP that emerged in the whole developmental clinical programme of this fixed combination that involved some 1900 patients with moderate to severe acute pain assessed using well-established human models of acute visceral and somatic moderate to severe pain.11–16

Interpretation
Fast action is an important feature for an analgesic intended to be used in the treatment of acute pain.20 The earlier onset of analgesic efficacy with TRAM/DKP compared with TRAM/paracetamol may be attributable to the rapid and high bioavailability of DKP,29,30 that favours the rapid onset of action of the combination. Better analgesic efficacy was maintained consistently over the entire observation period, confirming the sustained analgesic action observed in previous clinical trials assessing efficacy following third molar extraction, abdominal hysterectomy and total hip arthroplasty.11,13,14 The greater analgesic efficacy of TRAM/DKP results from the balanced and synergistic combination of peripheral and central analgesia, complemented with an anti-inflammatory action.13 The combination TRAM/paracetamol is substantially lacking in anti-inflammatory activity, as paracetamol only inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation, but unlike NSAIDs, it is not a peripheral COX inhibitor.31,32 It can be hypothesised that this difference could have contributed to the observed reduced analgesic efficacy.

The two combinations showed clinically comparable safety profiles. Gastrointestinal disorders including abdominal discomfort, diarrhoea, nausea and vomiting were reported with similar frequencies between the two groups of patients who received active intervention. Adverse reactions regarding the nervous system disorders were also observed in a similar proportion in both arms, although a trend towards improved tolerability could be detected in patients receiving TRAM/DKP, as compared with patients treated with TRAM/paracetamol.

CONCLUSION
This study has confirmed that TRAM hydrochloride/DKP trometamol 75/25mg oral fixed combination is effective and superior over TRAM hydrochloride/paracetamol 75/650mg in relieving moderate to severe acute pain following removal of impacted lower third molar. TRAM hydrochloride/DKP trometamol 75/25mg oral fixed combination shows faster onset of effect, greater and durable analgesia, together with a favourable safety profile. The rapid onset of analgesic effect of DKP, with its anti-inflammatory activity, associated to the sustained action of TRAM, makes this combination a valuable tool to achieve multimodal analgesia.

REFERENCES
1. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American pain society, the American society of regional anesthesia and pain medicine, and the American Society of Anesthesiologists’ Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016;17:131–57.
2. Joshi GP, Ogunniake BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North America 2005;23:21–36.
3. Langley P, Muller-Schwefe G, Nicolaou A, et al. The societal impact of pain in the European Union: health-related quality of life and healthcare resource utilization. J Med Econ 2010;13:571–81.
4. Pasero C. Persistent postsurgical and posttrauma pain. Journal of PeriAnesthesia Nursing 2011;26:38–42.
5. White PF. Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Investig Drugs 2008;9:76–82.
6. McGurk M, Robinson P, Rajayogeswaran V, et al. Clinical comparison of dexketoprofen trometamol, ketoprofen, and placebo in postoperative dental pain. J Clin Pharmacol 1998;38:465–54.
7. Barden J, Derry S, McQuay HJ, et al. Single dose oral ketoprofen and dexketoprofen for acute post-operative pain in adults. Cochrane Database Syst Rev 2009;7:CD007355.
8. Varrassi G, Hanna M, Macheras G, et al. Multimodal analgesia in moderate-to-severe pain: a role for a new fixed combination of dexketoprofen and tramadol. Curr Med Res Opin 2017;33:1165–73.
9. Lehmann KA, Tramadol for the management of acute pain. Drugs 1994;47 Suppl 1:19–32.
10. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004;43:879–923.

11. Moore RA, Gay-Escoda C, Figueiredo R, et al. Dexketoprofen/tramadol: randomised double-blind trial and confirmation of empirical theory of combination analgesics in acute pain. J Headache Pain 2015;16:541.

12. Singla NK, Desjardins PJ, Chang PD. A comparison of the clinical and experimental characteristics of four acute surgical pain models: dental extraction, buccinectomy, joint replacement, and soft tissue surgery. Pain 2014;155:441–56.

13. Moore RA, McQuay HJ, Tomaszewski J, et al. Dexketoprofen/tramadol 25 mg/75 mg: randomised double-blind trial in moderate-to-severe acute pain after abdominal hysterectomy. BMC Anesthesiol 2016;16:9.

14. McQuay HJ, Moore RA, Berta A, et al. Randomized clinical trial of dexketoprofen/tramadol 25 mg/75 mg in moderate-to-severe pain after total hip arthroplasty. Br J Anaesth 2016;116:269–76.

15. Derry S, Cooper TE, Phillips T. Single fixed-dose oral dexketoprofen plus tramadol for acute postoperative pain in adults. Cochrane Database Syst Rev 2016;9:CD012232.

16. Montero Matamala A, Bertolotti M, Contini MP, et al. Tramadol hydrochloride 75 mg/dexketoprofen 25 mg oral fixed-dose combination in moderate-to-severe acute pain: sustained analgesic effect over a 56-h period in the postoperative setting. Drugs Today 2017;53:339–47.

17. Skudexa SmPC. http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1489125195346.pdf (Accessed May 2017).

18. R F, R L, J S S. Review of head-to-head study designs in rheumatoid arthritis. Semin Arthritis Rheum 2016;46:279–85.

19. Ioannidis JP. Indirect comparisons: the mesh and mess of clinical trials. Lancet 2006;368:1470e2–.

20. Desjardins P, Black P, Papageorge M, et al. Ibuprofen arginate provides effective relief from postoperative dental pain with a more rapid onset of action than ibuprofen. Eur J Clin Pharmacol 2002;58:387–94.

21. Daniels SE, Desjardins PJ, Talwalker S, et al. The analgesic efficacy of valdecoxib vs. oxycodone/acetaminophen after oral surgery. J Am Dent Assoc 2002;133:611–21.

22. Breivik H, Borghgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth 2008;101:17–24.

23. Akural EI, Järvinäi V, Länsineva A, et al. Effects of combination treatment with ketoprofen 100 mg + acetaminophen 1000 mg on postoperative dental pain: a single-dose, 10-hour, randomized, double-blind, active- and placebo-controlled clinical trial. Clin Ther 2009;31:560–8.

24. Cooper SA, Desjardins PJ, Turk DC, et al. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. Pain 2016;157:288–301.

25. Fricke JR, Hewitt DJ, Jordan DM, et al. A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. Pain 2004;109:250–7.

26. Barden J, Edwards JE, McQuay HJ, et al. Pain and analgesic response after third molar extraction and other postsurgical pain. Pain 2004;107:86–90.

27. Yue Y, Collaku A, Brown J, et al. Efficacy and speed of onset of pain relief of fast-dissolving paracetamol on postsurgical dental pain: two randomized, single-dose, double-blind, placebo-controlled clinical studies. Clin Ther 2013;35:1306–20.

28. Cooper SA, Voelker M. Evaluation of onset of pain relief from micronized aspirin in a dental pain model. Inflammopharmacology 2012;20:233–42.

29. Rodríguez MJ, Arbós RM, Amaro SR. Dexketoprofen trometamol: clinical evidence supporting its role as a painkiller. Expert Rev Neurother 2008;8:1625–40.

30. Mazzei P, Milleri S, Paredes Lario I, et al. Pharmacokinetics of Dexketoprofen and tramadol given in combination: an open-label, randomized, single-dose, double-blind, placebo-controlled clinical trial. Clin Ther 2015;37:e124.

31. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 syntheses. Clin Pharmacol Ther 2006;79:9–19.

32. Graham GG, Scott KF. Mechanism of action of paracetamol. Am J Ther 2005;12:46–55.