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ORIGINAL RESEARCH

Co-crystal of Tramadol-Celecoxib Versus Tramadol or Placebo for Acute Moderate-to-Severe Pain After Oral Surgery: Randomized, Double-Blind, Phase 3 Trial (STARDOM1)

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ABSTRACT

Introduction: Co-crystal of tramadol-celecoxib (CTC) is the first analgesic co-crystal for acute pain. This completed phase 3 multicenter, double-blind trial assessed the efficacy and safety/tolerability of CTC in comparison with that of tramadol in the setting of moderate-to-severe pain up to 72 h after elective third molar extraction requiring bone removal.

Methods: Adults ($n = 726$) were assigned randomly to five groups (2:2:2:2:1): orally administered twice-daily CTC 100 mg (44 mg *rac*-tramadol hydrochloride/56 mg celecoxib; $n = 164$), 150 mg (66/84 mg; $n = 160$) or 200 mg (88/112 mg; $n = 160$); tramadol 100 mg four times daily ($n = 159$); or placebo four times daily ($n = 83$). Participants in CTC groups also received twice-daily placebo. The full analysis set included all participants who underwent randomization. The primary endpoint was the sum of pain intensity differences over 0 to 4 h ($SPID_{0–4}$; visual analog scale). Key secondary endpoints included 4-h 50% responder and rescue medication use rates. Safety endpoints included adverse events (AEs), laboratory measures, and Opioid-Related Symptom Distress Scale (OR-SDS) score.

Results: All CTC doses were superior to placebo ($P < 0.001$) for primary and key secondary endpoints. All were superior to tramadol for $SPID_{0–4}$ (analysis of covariance least squares mean differences [95% confidence interval]: − 37.1 [− 56.5, − 17.6], − 40.2 [− 59.7, − 20.6], and − 41.7 [− 61.2, − 22.2] for 100, 150, and 200 mg CTC, respectively; $P < 0.001$) and 4-h 50% responder rate. Four-hour 50% responder rates were 32.9% (CTC 100 mg), 33.8% (CTC 150 mg), 40.6% (CTC 200 mg), 20.1% (tramadol), and 7.2%

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(placebo). Rescue medication use was lower in the 100-mg (P = 0.013) and 200-mg (P = 0.003) CTC groups versus tramadol group. AE incidence and OR-SDS scores were highest for tramadol alone.
Conclusions: CTC demonstrated superior pain relief compared with tramadol or placebo, as well as an improved benefit/risk profile versus tramadol.
Trial registration: ClinicalTrials.gov identifier, NCT02982161; EudraCT number, 2016-000592-24.

Keywords: Acute pain; Celecoxib; Co-crystal; CTC; Efficacy; $SPID_{0–4}$; Tramadol

Key Summary Points

Why carry out this study?

We evaluated the efficacy and safety/tolerability of the novel, multimodal co-crystal of tramadol-celecoxib (CTC) versus tramadol in the setting of moderate-to-severe pain up to 72 h after elective third molar extraction requiring bone removal.

Although guidelines recommend multimodal analgesia, outpatient postoperative pain management is often inadequate, partly because of non-adherence. Novel, multimodal, opioid-sparing analgesia, incorporating an anti-inflammatory, is needed.

What was learned from the study?

CTC provides better pain relief than tramadol alone over the 72-h treatment period with a total cumulative tramadol dose of 528 mg from CTC 200 mg compared with 1200 mg from tramadol alone.

Compared with tramadol alone, CTC had an improved benefit/risk profile, being associated with fewer side effects and facilitating lower opioid dosing overall.

INTRODUCTION

Acute pain resulting from trauma, illness, or surgery affects millions of people annually [1, 2] across multiple settings [3, 4]. Many report pain of moderate or greater intensity [2, 3, 5, 6], and management is often inadequate [2, 3, 7–9], with negative consequences for patients, healthcare systems, and society [2, 9]. Effective management can enhance recovery, improve rehabilitation, shorten hospital stays, and decrease costs [9, 10]. Inadequate management occurs for several reasons [10], including lack of adherence [11, 12] due to side effects or 'pill burden' [13]. Adherence is a particular issue after ambulatory surgery [13].

Postoperative pain guidelines recommend multimodal analgesia [8, 14]. There is a need for novel, multimodal, opioid-sparing analgesia—incorporating an anti-inflammatory—for the management of ambulatory postoperative pain [4, 8, 9, 13, 15].

Co-crystal of tramadol-celecoxib (CTC; previously E-58425/MR308) is the first analgesic co-crystal that incorporates racemic tramadol hydrochloride and celecoxib (1:1) in a supramolecular crystal network [16, 17]. Tramadol is a racemic compound with two enantiomers: the (+)-enantiomer has higher affinity for μ-opioid receptors and is a more potent inhibitor of serotonin reuptake, whereas the (−)-enantiomer is a more potent inhibitor of noradrenaline reuptake. Additionally, the *O*-desmethyl metabolite of tramadol, which has a higher affinity for the μ-opioid receptors than the parent compound, also contributes to its analgesic effects [18, 19]. Treatment with tramadol (an opioid analgesic) and celecoxib (an effective, potent, nonopioid analgesic with improved gastrointestinal and cardiovascular safety versus other nonsteroidal anti-inflammatory drugs [NSAIDs]) [20–22] may achieve effective analgesia while reducing side effects and opioid consumption.

In CTC, a μ-opioid agonist and norepinephrine and serotonin reuptake inhibitor (tramadol) and a selective cyclooxygenase-2 inhibitor (celecoxib) target four central and peripheral analgesic mechanisms [23]. The

crystalline structure of the 'co-crystal' formulation modifies the physicochemical characteristics as well as the pharmacokinetics of the active molecules—decreasing the maximum concentration of tramadol in plasma while prolonging the time to achieve this and shortening the time to reach the maximum concentration of celecoxib in plasma [24]—in a manner that is not attainable via coadministration or conventional fixed-dose combination. This may underlie clinical trial findings [25, 26]. CTC demonstrated a benefit/risk profile that was significantly improved versus that of tramadol and placebo in a phase 2 trial on postoperative management of oral pain [27]. In a phase 3 trial of pain following bunionectomy with osteotomy, CTC was associated with greater pain relief than similar daily doses of tramadol or celecoxib, with comparable tolerability as tramadol [28]. CTC 200 mg was also found to be noninferior and to have an improved benefit/risk profile compared with tramadol in a phase 3 trial of pain following abdominal hysterectomy [29]. CTC was approved by the US Food and Drug Administration in 2021 [30], and received its first European regulatory approval (in Spain) in September 2023 [31].

The present phase 3 trial, STARDOM1, addresses the need for a phase 3 study assessing the efficacy and safety of repeated doses of CTC compared with that of placebo and full daily doses of tramadol in an established model of acute moderate-to-severe postoperative oral surgery pain. STARDOM1 aimed to test the null hypothesis that there was no difference in analgesic efficacy among CTC, tramadol, and placebo in this patient population.

METHODS

Study Design and Oversight

STARDOM1 (NCT02982161; EudraCT number: 2016-000592-24) was a double-blind, randomized controlled (placebo and active comparator) trial conducted from December 2016 to January 2018 at 31 sites in Canada, Germany, Hungary, Italy, Poland, and Spain. Data from one site were excluded from all analyses, before hard data lock and while the study was blinded, because of non-compliance with Good Clinical Practice. The study protocol was approved by the local ethics committee for each country and/or study site (listed in Methods S1 in the electronic supplementary material). The principal investigator was from Spain, and the Spanish ethics committee was the Comité Ético de Investigación Clínica con Medicamentos del Hospital Universitario de la Princesa (Madrid), resolution no. 20/17 of 10 November 2016. All patients provided written informed consent during the screening period of the study (i.e. before surgery). The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

The complete eligibility criteria are described in the electronic supplementary material, Methods S2. Briefly, eligible patients comprised healthy males and females aged ≥ 18 years. Patients had undergone an elective dental surgical procedure (extraction of ≥ 2 impacted third molars, including ≥ 1 mandibular molar) that required bone removal within 28 days of the screening visit; extractions were completed without immediate complication. Patients were eligible if they had experienced acute pain of moderate-to-severe intensity (defined as a rating of ≥ 45 mm on a 100-mm pain intensity–visual analog scale [PI-VAS]) as a result of the surgery, measured within 6 h of the procedure. Patients were excluded from the study if they had any contraindications to tramadol, celecoxib, acetaminophen (paracetamol), NSAIDs, sulfonamides, opioids, cyclooxygenase-2 inhibitors, or other related compounds or had previously experienced inadequate pain relief from tramadol, celecoxib, or acetaminophen. Patients receiving regular opioid analgesia or NSAIDs within 30 days before screening, a long- acting NSAID within 3 days before surgery, or any analgesic (other than short-acting pre- or intraoperative local anesthetics) within 12 h before surgery, or perioperatively until randomization, were also ineligible.

Randomization and Masking

Patients were screened up to 28 days before surgery (Fig. S1). Randomization of eligible patients occurred after a 6-h postoperative assessment period. The treatment period lasted 72 h, with a 7-day follow-up. Patients could leave the study center 4 h after first study treatment intake (after the time point for the primary efficacy endpoint) until the beginning of the follow-up period.

Patients who reached a qualifying PI-VAS after molar extraction were assigned randomly to one of five groups (2:2:2:2:1) to receive orally administered CTC 100 mg (*rac*-tramadol hydrochloride 44 mg/celecoxib 56 mg) given twice daily (BID), CTC 150 mg (tramadol hydrochloride 66 mg/celecoxib 84 mg) BID, CTC 200 mg (tramadol hydrochloride 88 mg/celecoxib 112 mg) BID; tramadol 100 mg four times daily (QID); or placebo QID. (To maintain blinding, participants receiving CTC BID also received placebo BID to match the intake of tramadol capsules [two capsules, four times daily].) Patients began PI-VAS self-assessment $\sim$ 30 min after extraction and continued to self-assess every 30 min for up to 6 h after surgery, or until the qualifying pain score for randomization was reached. Randomization was performed using interactive response technology and stratified by qualifying pain intensity (QPI): moderate, PI-VAS $\geq$ 45 and $<$ 70 mm; severe, PI-VAS $\geq$ 70 mm. Patients and all personnel were blinded to treatment.

Interventions

Topical and subcutaneous short-acting local anesthetics, including lidocaine, articaine, and mepivacaine, with/without adrenaline, were allowed during the third molar extraction. Bupivacaine was not permitted.

For the purposes of blinding, CTC and tramadol capsules were over-encapsulated, and patients were given additional placebo capsules BID to match the posology of tramadol (Methods S3).

Oral acetaminophen, taken as required up to QID for a maximum daily dose of 4000 mg, was permitted as rescue medication during the double-blind period. The following concomitant medications were prohibited: serotonergic drugs (including selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors), tricyclic antidepressants, monoamine oxidase inhibitors, antipsychotics, anticonvulsants (and other products that lower the seizure threshold), opioids, NSAIDs (including acetaminophen), and acetylsalicylic acid (aspirin; although low doses were permitted for anti-thrombosis/cardiac prophylaxis).

Assessments and Endpoints

The primary efficacy endpoint was the sum of pain intensity differences over 0–4 h ($SPID_{0–4}$). SPID was defined as the weighted difference (baseline [predose] pain minus current pain), measured using the PI-VAS at different time points. Time between two consecutive measurements was used for weighting, with larger values indicating greater pain relief. Pain intensity assessments (PI-VAS) were recorded in an e-Diary by the patient at 0 min (predose), at 15-min intervals after the first treatment dose up to 4 h, at 6 and 8 h after the first treatment dose, and then at 6-h intervals from 12 to 72 h.

Key secondary endpoints included 50% responder rate at 4 h (patients with a $\geq$ 50% reduction in PI-VAS score from 0–4 h) and rate of rescue medication use (use of $\geq$ 1 dose of rescue medication during the first 4 h). Other secondary endpoints included SPID and total pain relief (TOTPAR) scores over 0–12, 0–24, 0–48, and 0–72 h; 30% responder rate at 4 h (patients with a $\geq$ 30% reduction in PI-VAS score from 0–4 h); time to 30% and 50% responses; time to perceptible and meaningful pain relief (as recorded in e-Diaries); time to first receipt of rescue medication; and average dose of rescue medication per 24 h. To determine TOTPAR, patients were asked to record their assessment of pain relief on a 5-point categorical pain relief rating scale (0 = no relief; 4 = complete relief) every 15 min after the first treatment dose up to 4 h post dose, and subsequently at 6 and 8 h after the first dose, as well as at each visit during the treatment period.

TOTPAR was defined as the sum of respective pain relief values, weighted by the time between consecutive measurements. Health-related quality of life was assessed using the EQ-5D-5L at 4, 24, 48, and 72 h after the first treatment dose. The EQ-5D-5L assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression at five levels (no problems, or 'any problems,' including slight, moderate, severe, or extreme). Results were converted to index scores (0 = worst imaginable, 1 = best imaginable) for each time point and for an average score. Additionally, patients reported EQ-VAS health scores (100-mm scale; 0 = worst imaginable, 100 = best imaginable). Permission was obtained to use EQ-5D-5L in this study.

Safety was assessed by evaluation of adverse events (AEs; coded using the Medical Dictionary for Regulatory Activities, v19.0) and laboratory safety results, as well as by physical examination, vital signs, and electrocardiograms. Opioid-related symptoms were assessed on the Opioid-Related Symptom Distress Scale (OR-SDS), a 4-point scale evaluating the three dimensions of frequency, severity, and bothersomeness for 10 symptoms (fatigue, drowsiness, inability to concentrate, confusion, nausea, dizziness, constipation, itching, difficulty with urination, retching/vomiting). OR-SDS assessments were completed electronically by patients at 4, 24, 48, and 72 h. Permission was obtained to use OR-SDS in this study.

Sparse blood sampling (2, 24, 59, and 72 h after first dose), analyzed with a high-performance liquid chromatography–tandem mass spectrometer (Agilent 1200 series pump and API4000 mass spectrometer detector; Sciex, Framingham, MA), was employed in exploratory pharmacokinetic analyses of tramadol, the tramadol metabolite *O*-desmethyltramadol, and celecoxib.

Statistical Analyses

Sample size and power calculations were performed using nQuery software (Statsols, Boston, MA) for a two-sample *t*-test at the initial significance level of 0.83%. The primary goal for sample size calculations was to detect clinically relevant superior treatment effects of CTC compared with tramadol, also considering the need to demonstrate CTC's superiority over placebo and its noninferiority to tramadol. To show noninferiority of CTC versus tramadol (assuming a noninferiority margin of 40 mm·h), a sample of 170 patients in each active treatment arm ensured sufficient marginal powers of > 90%, for treatment differences of 20 mm·h and assuming 10–20% of patients would not be included in the per-protocol analysis set (PPAS). For the assessment of superiority of CTC doses versus placebo, a sample of 170 patients in each CTC arm and 85 in the placebo arm provided ≥ 95% marginal power for all three comparisons, assuming treatment differences of 75, 85, and 90 mm·h versus placebo for the CTC 100-, 150-, and 200-mg doses, respectively. Assumptions for treatment effect size were based on the results from the previous phase 2 study [27]. Therefore, a sample of 170 patients in each active treatment arm and 85 in the placebo arm was determined to provide sufficient power to demonstrate efficacy of the CTC doses—a total of 765 randomized patients.

The primary objective of the study was to establish the efficacy of CTC doses based on $SPID_{0–4}$, by first demonstrating superiority compared with placebo and noninferiority in relation to tramadol, followed by superiority versus tramadol. The secondary efficacy objective involved comparison of the efficacy of CTC doses with that of tramadol and placebo by demonstrating superiority in the two main secondary endpoints of 50% responder rate at 4 h and use of rescue medication during the first 4 h. The formal evaluation of the primary efficacy endpoint used a parallel gatekeeping method [32] to adjust for multiplicity. This analysis was combined with the formal evaluation of the two key secondary endpoints using the same approach (see Methods S4). Through this gatekeeping procedure, adjusted *P*-values (for multiplicity) and adjusted confidence intervals (CI; based on the alpha levels assigned to each hypothesis) were derived for each comparison.

The primary efficacy endpoint ($SPID_{0–4}$) was evaluated using an analysis of covariance

(ANCOVA) model, with treatment and QPI as fixed effects, study center as a random effect, and predose (0 h) PI-VAS as a covariate. The last observation carried forward (LOCF) method was used to account for missing PI-VAS values. For patients who took rescue medication, the last available PI-VAS value before the first intake of rescue medication was carried forward for all consecutive time points.

The key secondary efficacy endpoints were each analyzed using respective logistic regression models, with treatment and QPI group as fixed effects, study center as a random effect, and predose PI-VAS as a covariate. Exploratory statistical analyses were conducted for additional secondary endpoints. A similar LOCF approach was used for the secondary endpoints as for the primary analysis.

The full analysis set (FAS) included all participants who had undergone randomization and formed the main analysis set for superiority comparisons of the primary and key secondary endpoints. The PPAS—patients in the FAS who had no major deviation from study protocol—was the main analysis set for noninferiority hypotheses. The role of both analysis sets was interchanged for supportive superiority and noninferiority analyses. The safety analysis set (SAS) comprised all participants who had undergone randomization and had received ≥ 1 dose of study drug; of these, participants with ≥ 1 pharmacokinetic measurement were included in the pharmacokinetics analysis set.

Post-hoc subgroup QPI analyses were also conducted for key efficacy endpoints, with PI-VAS categories of ≥ 45 to ≤ 60 mm for moderate pain and > 60 mm for severe pain (in line with the threshold used to define severe pain in other studies in this model, including for CTC [27]).

For all statistical analyses, results were considered significant if $P < 0.05$. Statistical analyses were performed using SAS, v9.4 or higher (SAS Institute, Cary, NC).

RESULTS

Patients

Of the 887 patients screened, 726 were randomized and included in the FAS and SAS; 573 were included in the PPAS and 136 in the pharmacokinetics analysis set (Fig. 1). Overall, 685 patients (94.4%) completed the study across countries and study centers (Table S1). The highest completion rate was among patients from the CTC 100-mg group (98.2%); the lowest was reported in patients from the tramadol group (86.8%). Forty-one patients discontinued the study: 21 (2.9%) withdrew consent, 19 (2.6%) discontinued because of AEs, and 1 (0.1%) was lost to follow-up.

Demographic characteristics and QPI scores were well balanced across treatment groups, with no clinically relevant differences observed (Table 1). Overall, the mean (standard deviation [SD]) age was 25.8 (6.25) years, 61.7% were female, and 97.2% were White. The median qualifying PI-VAS score was 53.0 mm. Most patients (91.5%) had a qualifying PI-VAS score categorized as moderate (≥ 45 to < 70 mm). When post hoc categories were applied, 76.4% of randomized patients were classed as having moderate pain (≥ 45 to ≤ 60 mm) and 23.6% as having severe pain (> 60 mm).

Primary Endpoint

Mean (SD) $SPID_{0–4}$ was higher in all three CTC groups (200 mg, 66.17 [99.57] mm·h; 150 mg, 64.15 [94.87] mm·h; 100 mg, 60.61 [98.18] mm·h) than in the tramadol (23.45 [81.73] mm·h) or placebo (− 9.12 [69.39] mm·h) groups. For the FAS, ANCOVA confirmed that all three CTC doses demonstrated superiority over both placebo and tramadol ($P < 0.001$ all comparisons; Fig. 2) in a dose-dependent manner. The parallel gatekeeping procedure confirmed the superiority of all CTC doses over placebo and

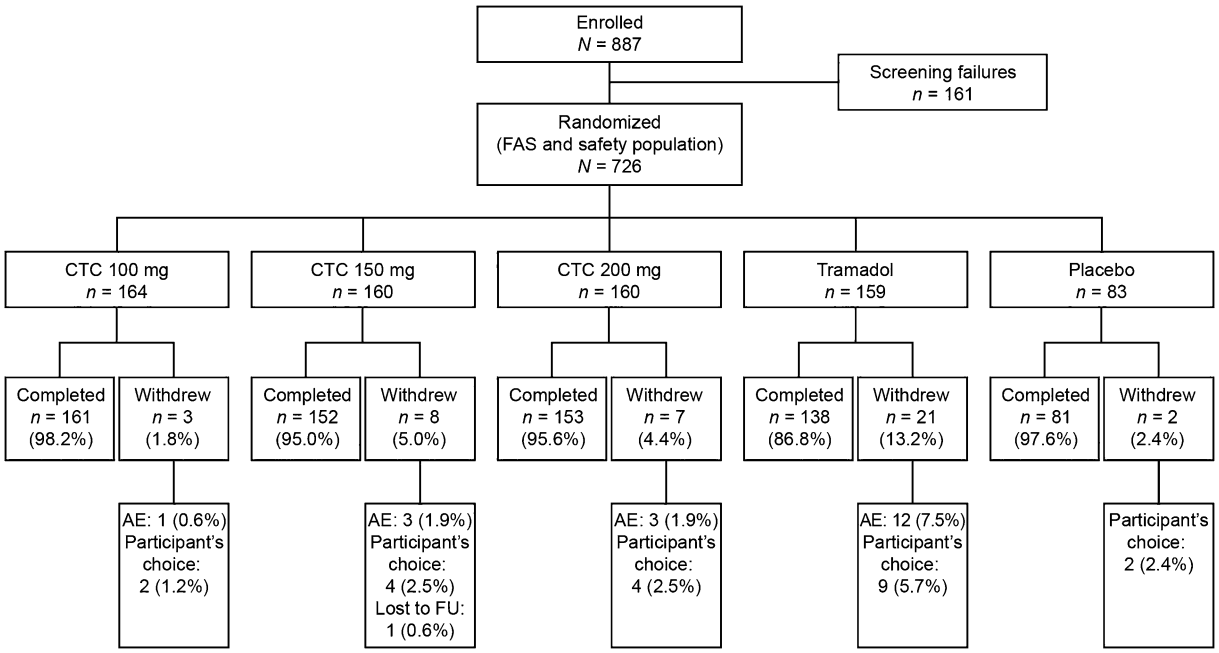


Fig. 1 Patient disposition. *AE* adverse event, *CTC* co-crystal of tramadol-celecoxib, *FAS* full analysis set; FU, follow-up

tramadol (Table S2). Results were similar in the PPAS (Table S3).

A post hoc subgroup analysis of mean $SPID_{0–4}$ by patients with moderate QPI at baseline (PI-VAS $\geq$ 45 to $\leq$ 60 mm) and severe QPI at baseline (PI-VAS > 60 mm) was consistent with the overall analysis (Table S4). Subgroup analyses for mean $SPID_{0–4}$ by sex and country, and various sensitivity analyses, were also consistent with the overall analysis.

In patients receiving active treatment, small pain intensity differences (PID) were observed after 30 min (Fig. 3). The greatest mean (SD) PID was observed in the CTC 100-mg group (4.5 [16.31] mm) and the smallest in the tramadol group (0.6 [12.63] mm). All CTC doses were associated with a rapid decrease in pain intensity, with maximal effect occurring after ~ 2 h. Mean (SD) PID at 2 h was 18.2 (29.32), 20.2 (27.48), and 20.4 (29.85) mm in the CTC 100-, 150-, and 200-mg groups, respectively (FAS). PID remained relatively stable after this time point in CTC groups. In the tramadol group, mean pain intensity decreased more gradually and to a lesser extent than with CTC during the first 4 h post dose: mean (SD) PID was 7.2 (24.88) mm after 2 h, increasing to 8.1 (28.11) mm after 4 h. Placebo treatment resulted in a mean (SD) PID of − 5.5 (23.03) mm after 4 h.

Key Secondary Endpoints

The highest proportion of 50% responders at 4 h was found in the CTC 200-mg group, with 40.6% of patients achieving $\geq$ 50% reduction in pain intensity (FAS; Fig. 4a). All three CTC doses demonstrated superiority versus placebo ($P < 0.001$) and versus tramadol ($P \leq 0.014$) at 4 h. This was confirmed by the parallel gatekeeping procedure (Table S2). A similar pattern was also observed in logistic regression data up to 72 h post dose, with the CTC 200-mg group showing significant benefits over tramadol at 24 and 72 h post dose (Table S5). Proportions of responders were higher for CTC dose groups compared with tramadol or placebo, regardless of QPI (Fig. S2).

Rescue medications were used during the first 4 h in 39.4% of patients in the CTC 200-mg group compared with 79.5% receiving placebo and 55.7% receiving tramadol (FAS; Fig. 4b). All three CTC doses demonstrated superiority versus placebo ($P < 0.001$ for all comparisons).

Table 1 Demographics and baseline characteristics of participants (full analysis set)

Characteristic	CTC			Tramadol 100 mg (*n* = 159)	Placebo (*n* = 83)	Total (*N* = 726)
	100 mg (*n* = 164)	150 mg (*n* = 160)	200 mg (*n* = 160)			
Age, years						
n	164	160	160	159	83	726
Mean (SD)	26.0 (7.12)	25.6 (5.75)	25.6 (5.95)	25.8 (6.11)	25.8 (6.33)	25.8 (6.25)
Median	24.0	24.0	24.0	25.0	26.0	24.0
Min, max	18, 69	18, 52	18, 47	18, 48	18, 44	18, 69
Categorized age, *n* (%)						
18–64 y	163 (99.4)	160 (100.0)	160 (100.0)	159 (100.0)	83 (100.0)	725 (99.9)
65–84 y	1 (0.6)	–	–	–	–	1 (0.1)
≥ 85 years	–	–	–	–	–	–
Sex, *n* (%)						
Male	68 (41.5)	66 (41.3)	53 (33.1)	63 (39.6)	28 (33.7)	278 (38.3)
Female	96 (58.5)	94 (58.8)	107 (66.9)	96 (60.4)	55 (66.3)	448 (61.7)
Race, *n* (%)						
American Indian or Alaska Native	–	–	–	–	–	–
Asian	2 (1.2)	–	–	1 (0.6)	1 (1.2)	4 (0.6)
Black or African American	2 (1.2)	–	–	1 (0.6)	–	3 (0.4)
Native Hawaiian or other Pacific Islander	–	–	–	–	–	–
White	158 (96.3)	157 (98.1)	156 (97.5)	155 (97.5)	80 (96.4)	706 (97.2)
Other	2 (1.2)	3 (1.9)	4 (2.5)	2 (1.3)	2 (2.4)	13 (1.8)

Table 1 continued

Characteristic	CTC			Tramadol 100 mg (*n* = 159)	Placebo (*n* = 83)	Total (*N* = 726)
	100 mg (*n* = 164)	150 mg (*n* = 160)	200 mg (*n* = 160)			
Weight, kg						
n	164	160	159	159	83	725
Mean (SD)	70.68 (15.75)	71.02 (16.54)	69.85 (15.12)	69.46 (14.11)	68.82 (14.20)	70.09 (15.25)
Median	68.75	67.05	67.00	66.00	65.00	67.00
Min, max	40.0, 117.9	43.3, 125.0	44.6, 129.9	44.7, 124.0	48.8, 112.0	40.0, 129.9
Height, cm						
n	164	160	159	159	83	725
Mean (SD)	171.2 (9.20)	171.5 (8.82)	171.0 (9.43)	170.4 (9.54)	169.7 (8.68)	170.9 (9.18)
Median	170.0	170.0	170.0	169.0	167.0	170.0
Min, max	154, 202	155, 194	153, 196	148, 197	154, 193	148, 202
BMI, kg/m^2						
n	164	160	159	159	83	725
Mean (SD)	23.94 (4.21)	23.98 (4.42)	23.83 (4.44)	23.88 (4.08)	23.76 (4.03)	23.89 (4.25)
Median	23.40	23.20	22.80	23.10	22.60	23.10
Min, max	16.2, 39.8	15.9, 40.8	17.0, 39.4	17.3, 38.1	18.4, 40.2	15.9, 40.8
Categorized BMI, *n* (%)						
Underweight	11 (6.7)	10 (6.3)	8 (5.0)	7 (4.4)	1 (1.2)	37 (5.1)
Normal weight	90 (54.9)	98 (61.3)	101 (63.5)	98 (61.6)	56 (67.5)	443 (61.1)
Overweight	47 (28.7)	39 (24.4)	36 (22.6)	40 (25.2)	20 (24.1)	182 (25.1)
Obese	16 (9.8)	13 (8.1)	14 (8.8)	14 (8.8)	6 (7.2)	63 (8.7)
Missing	–	–	1	–	–	1
Duration of surgery, min						
n	164	160	160	159	83	726
Mean (SD)	34.1 (15.7)	35.6 (17.0)	35.3 (15.6)	33.9 (18.2)	34.2 (18.7)	34.6 (16.9)

Table 1 continued

Characteristic	CTC			Tramadol 100 mg (*n* = 159)	Placebo (*n* = 83)	Total (*N* = 726)
	100 mg (*n* = 164)	150 mg (*n* = 160)	200 mg (*n* = 160)			
Qualifying PI-VAS score						
n	164	160	160	159	83	726
Mean (SD)	55.6 (8.38)	56.2 (10.45)	56.5 (9.43)	56.1 (8.58)	55.0 (8.53)	56.0 (9.15)
Median	53.0	53.0	54.0	54.0	52.0	53.0
Min, max	45, 87	40, 100	45, 100	45, 88	45, 78	40, 100
Categorized qualifying PI-VAS score, *n* (%)						
Moderate (≥ 45 and < 70 mm)	153 (93.3)	143 (89.4)	145 (90.6)	147 (92.5)	76 (91.6)	664 (91.5)
Severe (≥ 70 mm)	11 (6.7)	17 (10.6)	15 (9.4)	12 (7.5)	7 (8.4)	62 (8.5)
Predose (0 h) PI-VAS score[a]						
n	163	160	160	158	83	724
Mean (SD)	60.8 (11.35)	60.8 (15.68)	61.8 (11.77)	61.1 (12.35)	59.0 (10.60)	60.9 (12.64)
Median	57.0	60.0	60.0	58.0	57.0	58.0
Min, max	23, 89	2, 100	25, 99	27, 91	37, 84	2, 100
	CTC			**Tramadol 100 mg (*n* = 158)**	**Placebo (*n* = 83)**	**Total (*N* = 724)**
	100 mg (*n* = 163)	**150 mg (*n* = 160)**	**200 mg (*n* = 160)**			
Post-hoc analysis						
Categorized predose (0 h) PI-VAS score, *n* (%)[a]						
Moderate (≥ 45 and ≤ 60 mm)	125 (76.7)	121 (75.6)	119 (74.4)	122 (77.2)	66 (79.5)	553 (76.4)
Severe (> 60 mm)	38 (23.3)	39 (24.4)	41 (25.6)	36 (22.8)	17 (20.5)	171 (23.6)

Percentages are based on the number of patients with data present

BMI body mass index, *CTC* co-crystal of tramadol-celecoxib, *PI-VAS* pain intensity–visual analog scale, *SD* standard deviation

[a]Two subjects did not perform the predose assessment

CTC 100 mg ($P = 0.013$) and CTC 200 mg ($P = 0.003$) demonstrated superiority versus tramadol, while the difference between CTC 150 mg and tramadol narrowly failed to reach significance ($P = 0.059$). Findings were confirmed by the parallel gatekeeping approach (Table S2). Results were similar regardless of QPI (Fig. S3).

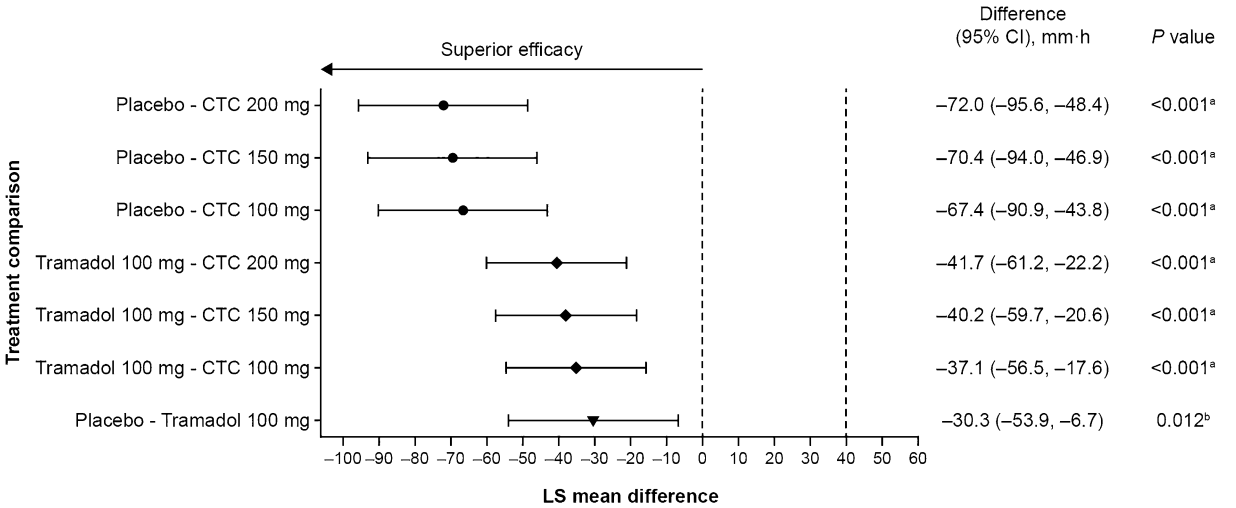


Fig. 2 Sum of pain intensity differences over 0–4 h (full analysis set, last observation carried forward). Data were analyzed by analysis of covariance, with treatment and qualifying pain intensity at randomization (moderate, severe) as fixed effects, pooled center as a random effect, and predose (0 h) pain intensity as a covariate. [a]*P* value from one-sided test of superiority for testing the null hypothesis that the difference of means is ≥ 0 mm·h. [b]*P* value from two-sided test of no difference for testing the null hypothesis that the difference of means is zero. *CI* confidence interval, *CTC* co-crystal of tramadol-celecoxib, *LS* least squares

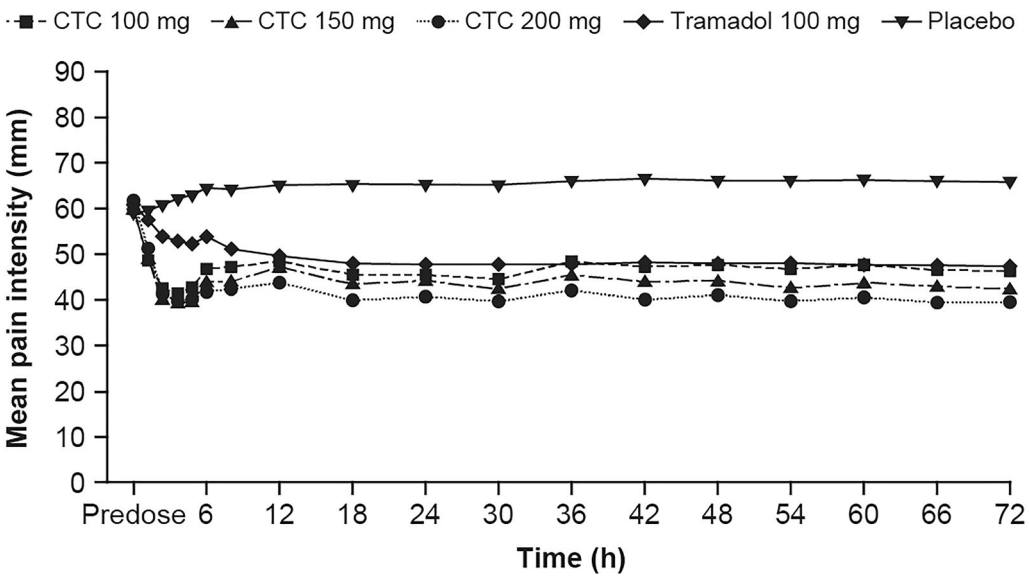
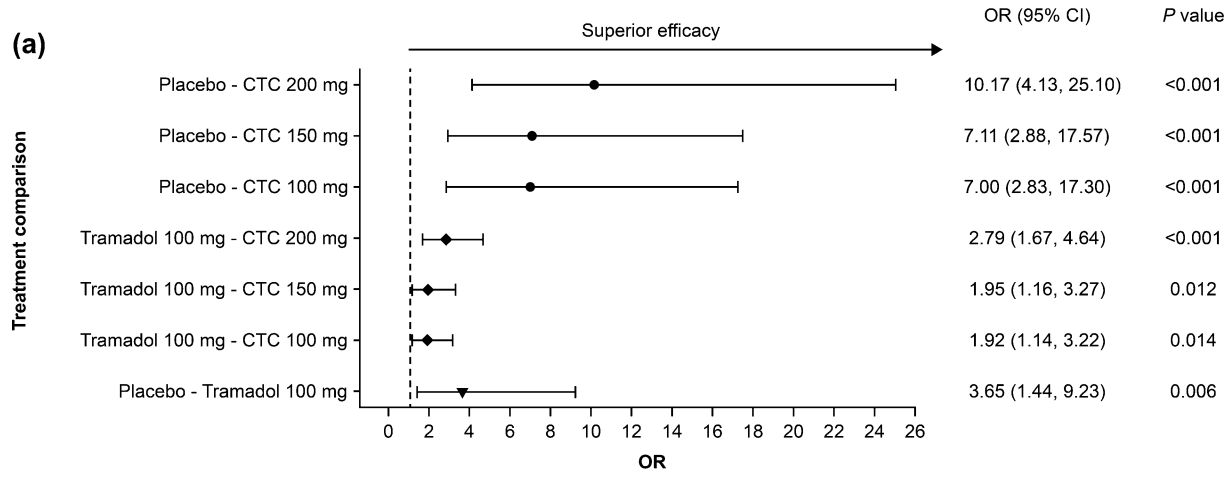
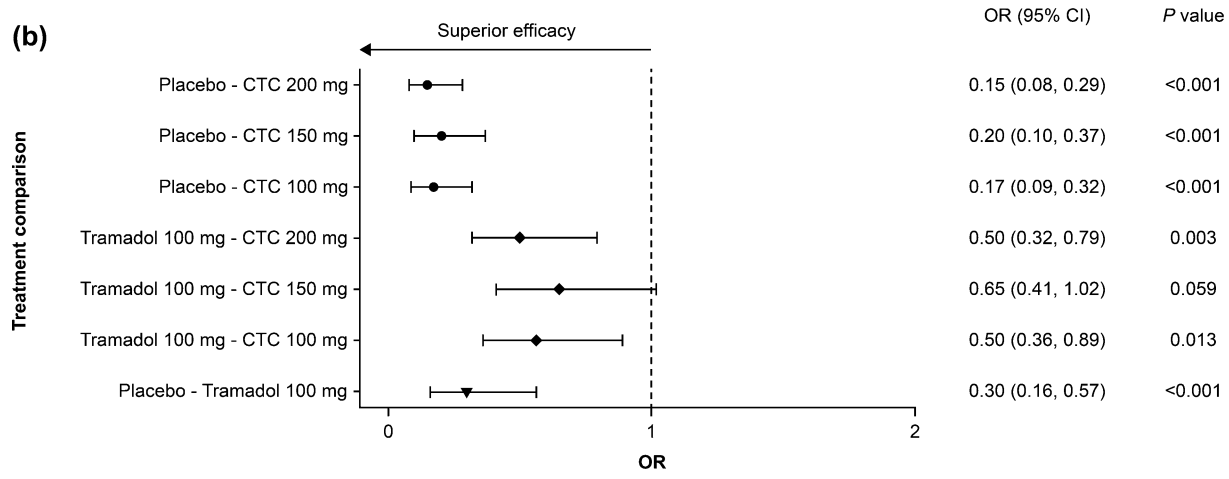


Fig. 3 Mean pain intensity–visual analog scale values over time (full analysis set—last observation carried forward). *CTC* co-crystal of tramadol-celecoxib



	CTC 100 mg	CTC 150 mg	CTC 200 mg	Tramadol 100 mg	Placebo
50% responders, *n* (%)	54 (32.9)	54 (33.8)	65 (40.6)	32 (20.1)	6 (7.2)



	CTC 100 mg	CTC 150 mg	CTC 200 mg	Tramadol 100 mg	Placebo
Rescue medication use in 4 h, *n* (%)	67 (40.9)	71 (44.4)	63 (39.4)	89 (56.0)	66 (79.5)

Fig. 4 Summary of key secondary efficacy endpoints (full analysis set): **a** 50% responder rate at 4 h and **b** use of rescue medication during the first 4 h. Data were analyzed using a logistic regression model with treatment and qualifying pain intensity at randomization (moderate, severe) as fixed effects, pooled center as a random effect, and predose pain intensity as a covariate. 50% responder defined as: 50% reduction from baseline in pain intensity–visual analog scale. *P*-values obtained from two-sided test of no difference for testing the null hypothesis that the OR = 1. For each treatment comparison, OR is calculated as '2nd term: 1st term,' as indicated. *CI* confidence interval, *CTC* co-crystal of tramadol-celecoxib, *OR* odds ratio

Table 2 Summary of TEAEs and most frequently occurring treatment-related TEAEs (safety analysis set)

	CTC			Tramadol 100 mg (n = 160)	Placebo (n = 83)
	100 mg (n = 164)	150 mg (n = 159)	200 mg (n = 160)		
TEAEs	120 (73.2)	119 (74.8)	132 (82.5)	137 (85.6)	49 (59.0)
Treatment-related AEs	98 (59.8)	106 (66.7)	120 (74.4)	132 (82.5)	30 (36.1)
Severe TEAEs	19 (11.6)	16 (10.1)	28 (17.5)	57 (35.6)	9 (10.8)
TEAEs leading to discontinuation	1 (0.6)	1 (0.6)	1 (0.6)	12 (7.5)	0
Serious TEAEs	0	0	0	1 (0.6)	0
Deaths	0	0	0	0	0
Most frequent treatment-related TEAEs (≥ 2% of patients in any group)					
Somnolence	62 (37.8)	73 (45.9)	96 (60.0)	98 (61.3)	23 (27.7)
Dizziness	41 (25.0)	47 (29.6)	59 (36.9)	89 (55.6)	11 (13.3)
Fatigue	44 (26.8)	46 (28.9)	59 (36.9)	69 (43.1)	21 (25.3)
Nausea	41 (25.0)	44 (27.7)	46 (28.8)	87 (54.4)	12 (14.5)
Vomiting	39 (23.8)	29 (18.2)	35 (21.9)	84 (52.5)	6 (7.2)
Disturbance in attention	24 (14.6)	23 (14.5)	33 (20.6)	50 (31.3)	14 (16.9)
Pruritus	4 (2.4)	18 (11.3)	25 (15.6)	44 (27.5)	3 (3.6)
Confusional state	11 (6.7)	9 (5.7)	16 (10.0)	29 (18.1)	8 (9.6)
Constipation	11 (6.7)	12 (7.5)	16 (10.0)	28 (17.5)	4 (4.8)
Dysuria	1 (0.6)	4 (2.5)	13 (8.1)	33 (20.6)	2 (2.4)
Retching	2 (1.2)	4 (2.5)	4 (2.5)	13 (8.1)	2 (2.4)
Headache	4 (2.4)	2 (1.3)	1 (0.6)	5 (3.1)	1 (1.2)
Pruritus, generalized	0	2 (1.3)	3 (1.9)	7 (4.4)	0
Hyperhidrosis	3 (1.8)	1 (0.6)	1 (0.6)	4 (2.5)	0
Asthenia	0	2 (1.3)	1 (0.6)	4 (2.5)	1 (1.2)
Malaise	0	0	5 (3.1)	2 (1.3)	0
TEAEs of further interest					
Gastrointestinal signs and symptoms	58 (35.4)	51 (32.1)	56 (35.0)	108 (67.5)	15 (18.1)
Nausea	48 (29.3)	47 (29.6)	50 (31.3)	90 (56.3)	15 (18.1)
Vomiting	40 (24.4)	32 (20.1)	36 (22.5)	88 (55.0)	9 (10.8)
Neurologic disorders	89 (54.3)	93 (58.5)	112 (70.0)	114 (71.3)	33 (39.8)
Dizziness	46 (28.0)	48 (30.2)	61 (38.1)	90 (56.3)	12 (14.5)
Somnolence	75 (45.7)	83 (52.2)	105 (65.6)	101 (63.1)	31 (37.3)

Data are n (%) of patients. A patient may have had > 1 AE in any category. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) v19.0

AE adverse event, *CTC* co-crystal of tramadol-celecoxib, *TEAE* treatment-emergent adverse event

Additional Secondary Endpoints

All doses of CTC were superior to placebo regarding SPID over 0–12, 0–24, 0–48, and 0–72 h, and CTC 200 mg was superior to tramadol in each case (Table S6 and Fig. S4). CTC 150 mg was superior to tramadol at 0–12 h. All doses of CTC were superior to placebo and tramadol in terms of TOTPAR over 0–12, 0–24, 0–48, and 0–72 h, with the difference in mean TOTPAR between tramadol/placebo and CTC groups increasing over time (Table S6).

The 30% responder rate at 4 h was significantly higher in all CTC groups compared with tramadol and placebo (Table S7). Time to 30% response was significantly shorter for all CTC groups compared with placebo, as well as for CTC 150 and 200 mg versus tramadol by log-rank or Cox proportional-hazards tests (Table S8 and Fig. S5). For CTC 200 mg versus tramadol, the hazard ratio (95% CI) was 1.44 (1.07–1.93; $P = 0.016$). Findings were similar for time to 50% response: significant differences versus tramadol were observed for CTC 200 mg (hazard ratio 1.38, 95% CI 1.01–1.90; $P = 0.045$) (Table S8 and Fig. S6). Time to first perceptible pain relief and time to first meaningful pain relief were not significantly different from tramadol for any CTC dose (Table S8).

Time to first intake of rescue medication was significantly longer in the CTC groups compared with placebo, while the difference versus tramadol was significantly longer for CTC 200 mg. Median (95% CI) time to first rescue medication was 14.6 (5.93–not available), 2.32 (1.67–5.00), and 1.47 (0.98–2.12) h for CTC 200 mg, tramadol, and placebo, respectively (Table S8 and Fig. S7). In all CTC groups, the percentage of patients taking rescue medication was lower than placebo across the assessment period. The maximum proportion of patients needing rescue medication was reached during the first 4-h interval for all treatment groups: ~ 40% for all doses of CTC, 55% for tramadol, and 80% for placebo (Fig. S8). The mean (SD) daily dose of rescue medication was 567.1 (948.49) mg of acetaminophen in the CTC 200-mg group versus 743.7 (1077.51) mg and 1331.3 (1153.11) mg in the tramadol and placebo groups, respectively. Differences versus placebo were significant for all CTC doses; differences between CTC and tramadol were not statistically significant (Table S9).

For each EQ-5D-5L dimension except pain/discomfort, the percentage of patients in the FAS with 'any problems' was higher for tramadol than for other groups at each post-baseline time point, whereas CTC was generally similar to placebo (Table S10). Logistic regression showed significant differences ($P < 0.05$) in odds ratios between CTC groups and tramadol for most dimensions and time points (other than pain/discomfort, 4-h self-care [in the case of CTC 150 and 200 mg] and anxiety/depression [in the case of CTC 200 mg]) (Table S11). Mean index scores were significantly different at all time points for CTC versus tramadol, and the average score for CTC 200 mg was significantly different from placebo. EQ-VAS scores for CTC 150 and 200 mg differed significantly from tramadol at each time point. CTC 150 mg was significantly different to placebo regarding the average score and at 4, 48, and 72 h. CTC 200 mg was significantly different from placebo with respect to the average and at 4 and 24 h.

Safety, Tolerability, and Pharmacokinetics

Altogether, 2599 treatment-emergent AEs (TEAEs) were reported in 557 (76.7%) patients. The rate of TEAEs was highest (85.6%) in the tramadol group, while in the CTC groups, TEAE rate increased with increasing dose. A total of 394 TEAEs were classified as severe, occurring in 129 (17.8%) patients. Severe TEAEs were seen in the highest proportion of patients (35.6%) in the tramadol group. In total, 2277 TEAEs in 485 (66.8%) patients were considered treatment related. The rate of treatment-related TEAEs was highest in the tramadol group (82.5%). Consistent with data for all TEAEs, the rates of treatment-related TEAEs increased with increasing dose in the CTC groups, up to 74.4% in the 200-mg group. The only serious TEAE in the study was a patient in the tramadol group who experienced treatment-related vomiting (Table 2), leading to discontinuation from the study and hospitalization for intravenous treatment. The most frequently occurring

treatment-related TEAEs are shown in Table 2 and Fig. S9. For all TEAEs except malaise, the greatest proportion of patients experiencing each treatment-related TEAE occurred in the tramadol group. In CTC groups, a dose-dependent pattern was observed for most treatment-related TEAEs. Regarding TEAEs of further interest, 288 (39.7%) patients experienced nausea and/or vomiting and 441 (60.7%) experienced TEAEs indicative of central nervous system depression (dizziness, somnolence). Rates were highest in the tramadol group (67.5% for nausea/vomiting, 71.3% for central nervous system depression symptoms versus 35.0% and 70.0%, respectively, for CTC 200 mg). Fifteen patients (2.1%) discontinued the trial because of TEAEs: 12 (7.5%) in the tramadol group and 1 (0.6%) in each of the CTC treatment groups. There were no clinically significant changes in laboratory parameters or vital signs, and no deaths were reported during the trial.

Patient-reported mean OR-SDS scores were highest in the tramadol group for all ten symptoms. Mean OR-SDS scores were generally higher in the CTC groups than placebo, and increased with increasing CTC dose, but were notably lower than in the tramadol group.

Results of sparse pharmacokinetic sampling (Fig. S10) showed that drug levels aligned with expectations, based on phase 1 findings [26, 33].

DISCUSSION

This phase 3 trial (STARDOM1) involving patients with acute moderate-to-severe pain following oral surgery met its primary efficacy endpoint of $SPID_{0–4}$: all CTC doses were found to be superior to tramadol or placebo. All doses were also superior to tramadol and placebo for the key secondary efficacy endpoint of 50% responder rate at 4 h. The lower rate of rescue medication use in the first 4 h for all CTC doses proved to be superior to placebo, and CTC 100 and 200 mg demonstrated superiority over tramadol. Various additional secondary efficacy endpoints were evaluated for which CTC 200 mg, the recommended clinical dose, showed the most encouraging results versus tramadol. Regarding non-pain EQ-5D-5L measures, CTC was similar to placebo and was not associated with the quality-of-life impairments observed for tramadol. The occurrence of TEAEs, severe TEAEs, and TEAEs leading to discontinuation were lower in CTC groups than in the tramadol group. TEAEs related to study drug were 74.4% for CTC 200 mg versus 82.5% for tramadol. Patients in CTC groups reported fewer opioid-related symptoms than in the tramadol group. Overall, the efficacy and safety of CTC were dose dependent.

CTC exhibited an opioid-sparing effect compared with tramadol. At the recommended clinical dosing regimen of CTC 200 mg (containing 88 mg tramadol), superior pain relief in the first 4 h ($SPID_{0–4}$) was seen compared with tramadol (100 mg). Superiority was sustained over 24 h (cumulative daily tramadol dose of 176 mg from CTC 200 mg) and to study completion at 72 h (total cumulative tramadol dose of 528 mg from CTC 200 mg). By contrast, the tramadol group received a higher daily dose of tramadol (cumulative daily dose of 400 mg, the maximum licensed European dose) than patients in CTC groups, resulting in a cumulative opioid dose of 1200 mg over the 72-h treatment period. The importance of considering cumulative opioid dose may also be relevant when looking at rescue medication use. Between 4 and 8 h, the proportion of patients in the CTC group receiving rescue medication decreased. Further decreases were seen in the tramadol group between 8 and 12 h, although this might be explained by the 6-h tramadol dose received by patients in this group (44–88 mg in the CTC groups versus 200 mg in the tramadol group). For subsequent dosing periods, including in the second half of each period, use of rescue medication decreased in the CTC and tramadol groups. Use in the placebo group also decreased but remained higher than in other groups. These observations further support an improved benefit/risk profile for CTC over tramadol.

The results of this trial are consistent with findings of a dose-finding phase 2 study [27] and a phase 3 trial involving patients who had undergone bunionectomy together with osteotomy [28]. They are also consistent with

previously reported preclinical and phase 1 data showing that CTC has modified physiochemical properties and pharmacokinetics compared with tramadol and celecoxib, whether used alone or in free combination [23–26]. In a recently reported phase 1 study [24], celecoxib from CTC resulted in a lower C_{max}, reduced area under the drug concentration-time curve (AUC), and faster T_{max}. Tramadol (and its active metabolite *O*-desmethyltramadol) from CTC was associated with lower C_{max}, lower AUC, and longer T_{max}. These modified pharmacokinetic properties likely underlie the improved efficacy and safety/tolerability profiles seen in the present trial versus tramadol alone.

The favorable benefit/risk profile of CTC has important clinical implications. Gold standard for management of acute pain following oral surgery is use of an agent that is anti-inflammatory with analgesic properties. Nevertheless, even strong opioids have been commonly prescribed following dental surgical procedures, although there are geographical variations in such prescribing [9, 34–37]. The extent of the opioid crisis in the US and beyond is driving strategies to reduce the use of opioids [38]. The results of this study should be considered in the context of an alternative for acute pain of considerable intensity, as combining analgesics with different mechanisms of action means that a wider spectrum of pain (beyond that modeled by third molar extraction) can be covered. CTC provides anti-inflammatory and analgesic components and exhibits improvements over tramadol alone, enabling the reduced tramadol daily dose in CTC. There are important implications in the context of ambulatory surgery. A recent study to develop consensus on core outcome domains for use in the management of perioperative pain highlighted the importance of treatment being not only effective at managing pain intensity but also in minimizing AEs and optimizing patient self-management [39]. In this context, it is notable to consider the high rate of treatment discontinuation in the group that received tramadol in this study, which was motivated by the appearance of adverse effects: 12 (7.5%) patients experienced a total of 26 AEs leading to discontinuation. The most frequently occurring AEs leading to discontinuation were nausea, vomiting, and dizziness (each occurring in 6 patients), of which one case of vomiting was serious. No patients in any group discontinued due to lack of efficacy. This is particularly relevant to ambulatory surgery, as patients manage breakthrough pain and AEs at home; so the lower rate of AEs reported here for CTC versus tramadol, combined with consistent efficacy over time, might improve patient adherence and therefore outcomes. To our knowledge, ours is the first report of the addition of celecoxib to tramadol analgesia resulting in both decreased tramadol consumption (versus tramadol monotherapy) and reduced AEs. CTC is likely to have utility in patients requiring multimodal analgesia, whose pain is not sufficiently managed by treatment with an NSAID or acetaminophen alone, per Step 2 of the World Health Organization's analgesic ladder [40].

Our results align with earlier data showing that oral tramadol is efficacious postoperatively, including after oral surgery [40–43], and with reports of improved efficacy when tramadol is combined with acetaminophen [44]. Our findings, including response rates, are also comparable with controlled trials of dexketoprofen/tramadol fixed-dose combination (versus tramadol or NSAIDs alone) [45, 46].

This was a large, multicenter, randomized, double-blind, placebo-controlled, multidose (72-h treatment) phase 3 trial. Further strengths of the study include that the third molar extraction model is predictable, shows high sensitivity, and is predictive of efficacy in other somatic acute pain scenarios [47, 48]. The third molar extraction model has been well characterized, the anesthetic protocol is straightforward, and the surgical procedure is widely standardized. In this study, the anesthetic regimens and the duration of the procedure were well balanced between all treatment groups, and all patients (100% in each group) had bone removed during surgery. NSAIDs and opioids have demonstrable utility in this model [41, 49, 50]. Additionally, as oral surgery is ambulatory, results are expected to be generalizable to other ambulatory procedures causing acute pain of moderate-to-severe intensity. A further strength of STARDOM1 is that study

sensitivity was confirmed by superiority of tramadol over placebo. CTC was shown to have analgesic efficacy in the study, with lower cumulative daily opioid doses than in the tramadol group.

Although tramadol can cause serotonin syndrome in some patients, rates of side effects such as respiratory depression are lower compared with potent opioids [51]. While the frequency of serotonin syndrome has not been fully established [52], it can be associated with supratherapeutic doses of tramadol [51], meaning that the lower cumulative opioid exposure seen with CTC, compared with tramadol alone, may confer a lower risk of this syndrome. It is possible that fewer NSAID-related AEs may occur with CTC compared with celecoxib alone because of the lower dose of celecoxib in CTC (celecoxib 112 mg in CTC 200 mg; cumulative celecoxib daily dose of 224 mg) versus the required dose if using celecoxib alone (maximum maintenance daily dose of 400 mg [53]).

A limitation of the current study is the absence of a celecoxib monotherapy arm. Although celecoxib monotherapy is not approved for use in acute pain in Europe, it is approved for this indication in other geographic regions. A recent phase 3 trial—of postoperative pain following abdominal hysterectomy—included both tramadol and celecoxib comparator arms and found CTC 200 mg to be noninferior, but not superior, to tramadol [29]. Another recent phase 3 trial of CTC 200 mg after bunionectomy with osteotomy [28] included a celecoxib comparator arm (100 mg BID) and demonstrated that CTC significantly improved efficacy over celecoxib, as well as over tramadol. Other potential limitations are the relatively young age of participants (overall mean [SD] 25.8 [6.25] years), (although this is characteristic for third molar extraction surgeries), and that most participants were White; thus, the study population may not be reflective of the wider post-surgical patient populations. In the present study, the proportion of patients with severe baseline pain was lower than expected, probably because of the relatively high definition used (70 mm) compared with other studies conducted in this model [27, 54]. When a 60-mm threshold was applied post hoc, as in other studies, the proportion was better aligned with literature reports [27, 47, 54].

CONCLUSIONS

Following oral surgery in this phase 3 trial, CTC provided superior pain relief versus placebo or full daily doses of tramadol and improved safety and tolerability, therefore showing an improved benefit/risk profile compared with tramadol alone. Pharmacokinetic results confirmed that the co-crystal formulation confers profiles not achievable by coadministration or standard combination formulation. As cumulative daily tramadol doses were lower for CTC than for tramadol alone, CTC could be tramadol-sparing for patients who might otherwise require maximum daily tramadol dosing for acute moderate-to-severe somatic pain, thus enabling improved tolerability and compliance, particularly for pain management after ambulatory surgery. CTC's multimodal and pharmacokinetic features, together with lower exposure to tramadol, may be postulated to account for the above profile.

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Langford, Esther M. Pogatzki-Zahn, Adelaida Morte, Mariano Sust, Jesús Cebrecos, Anna Vaqué, Esther Ortiz, James Fettiplace, Shola Adeyemi, Neus Gascón, and Carlos Plata-Salamán contributed to data analysis or interpretation. All authors discussed the results and commented on the manuscript, reviewed and critically revised the manuscript, approved the final draft, and agree to be accountable for the accuracy and integrity of the work.

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Data Availability. ESTEVE Pharmaceuticals S.A. will consider requests for de-identified patient-level data and supporting study documents from qualified external researchers. Approval of requests will be at the discretion of ESTEVE Pharmaceuticals S.A. and will depend on the scientific merit of the proposed research and intended use of the data. If approval is granted, a data sharing agreement must be signed, and access to data will be provided only if ESTEVE Pharmaceuticals S.A. has legal authority to provide the data and there are no contradictory requirements relating to regulatory filings or reviews. Proposals should be sent to esteve@esteve.com.

Declarations

Conflict of interest. Richard Langford has received fees from Pfizer, Eli Lilly, Compass, GSK, Avenue Therapeutics, MedinCell, Heron, Camurus, BioQ Pharma, Mundipharma, Grünenthal GmbH, Grünenthal Ltd and Syntetica for consultancy and speaker activities, and travel support from ESTEVE. Esther M. Pogatzki-Zahn received financial support for research activities, advisory board activities and lecture fees from Grünenthal, Medtronic, Mundipharma, and Novartis; she also receives scientific support from the German Research Foundation (DFG), the Federal Ministry of Education and Research (BMBF), the Federal Joint Committee (G-BA) and the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 777500. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation program and the European Federation of Pharmaceutical Industries and Associations. All money went to the institutions (WWU/UHM) where Esther M. Pogatzki-Zahn is employed. Adelaida Morte, Mariano Sust, Jesús Cebrecos, Anna Vaqué, Esther Ortiz, and Neus Gascón are employees of ESTEVE Pharmaceuticals. Socorro Bescós's institution was paid commercial fees from Mundipharma Research GmbH & Co. KG for work on the study. Carlos Plata-Salamán was an employee of ESTEVE Pharmaceuticals and has pending or issued patents relevant to CTC. James Fettiplace and Shola Adeyemi were employees of Mundipharma Research Limited at the time of study. José Luis López-Cedrún has nothing to disclose.

Ethical Approval. The study protocol was approved by the local ethics committee for each country and/or study site; the ethics committees included in this study are listed in the Supplementary Methods S1. The principal investigator was from Spain, and the Spanish ethics committee was the Comité Ético de Investigación Clínica con Medicamentos del Hospital Universitario de la Princesa (Madrid), resolution No. 20/17 of 10 November 2016. All patients provided written informed consent during the screening period of the study (i.e. before surgery). The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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