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BRIEF REPORT

Adverse Reactions Following First-Dose Administration of Co-Crystal of Tramadol-Celecoxib Versus Tramadol Alone for Moderate-To-Severe Acute Pain

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ABSTRACT

Introduction: Phase 3 clinical trials in moderate-to-severe acute pain have shown that co-crystal of tramadol-celecoxib (CTC) has improved efficacy and comparable tolerability versus immediate-release tramadol 50 mg alone, with a similar tramadol daily dose, over a 48-h treatment period. However, it is not known how first-dose tolerability compares, given that the administered dose of tramadol is higher in CTC 200 mg (88 mg) versus immediate-release tramadol 50 mg. This was explored in a post hoc analysis of a pivotal phase 3 trial.

Methods: A randomized, double-blind, factorial, active- and placebo-controlled phase 3 trial was conducted in patients with moderate-to-severe acute postoperative pain (NCT03108482) and has been previously reported. This post hoc analysis evaluated the prevalence of the four most common study drug-related, opioid-associated, treatment-emergent adverse reactions reported in phase 3 CTC clinical trials: somnolence, nausea, dizziness, and vomiting. Prevalence was evaluated in 2-h intervals, up to 6 h post first dose (just before second-dose administration) of CTC 200 mg or immediate-release tramadol 50 mg p.o. Descriptive analysis was performed.

Results: Each group comprised 183 participants for analysis. The proportions of patients reporting drug-related, treatment-emergent adverse reactions of somnolence, nausea, dizziness, and vomiting were similar between treatment groups at 2, 4, and 6 h following the first dose.

Conclusions: This post hoc analysis indicates that the higher dose of tramadol (88 mg) given in CTC 200 mg did not result in an increase in drug-related adverse reactions after first-dose administration, and had a similar tolerability profile, compared with immediate-release tramadol 50 mg alone (the lowest dose recommended for the management of moderate-to-severe acute pain). This is in line with earlier findings for the 48-h treatment period of this phase 3 trial and may be explained by CTC's differentiated physiochemical properties related to its co-crystal structure. These findings may have utility for practicing clinicians.

Trial Registration: ClinicalTrials.gov identifier, NCT03108482.

Keywords: Acute pain; Analgesics; Celecoxib; Safety; Tramadol

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Key Summary Points

Why carry out this study?

Co-crystal of tramadol-celecoxib (CTC) is an analgesic co-crystal containing tramadol and celecoxib, with differentiated pharmacological characteristics compared with its constituent drugs.

As the tramadol dosage in CTC 200 mg (the clinically approved dose) is higher than the lowest available oral tramadol dose (88 vs. 50 mg, respectively), doubts may arise over the tolerability of the tramadol content in CTC.

What was learned from the study?

Data from this post hoc analysis of phase 3 safety data for the 6-h period following first-dose administration indicate that 88 mg of tramadol given in 200 mg of CTC has a similar tolerability profile to 50 mg of immediate-release tramadol alone, in patients with moderate-to-severe acute pain.

This finding should help to address any tolerability concerns practitioners may have over the initial dosing of CTC in relation to opioid-associated adverse reactions.

INTRODUCTION

Acute pain, i.e., pain that has a sudden onset, limited duration, and is caused by injury, illness, or disease, is a highly prevalent condition affecting millions of people annually [1–5]. Patients often report acute pain of moderate-to-severe intensity, defined as a score of 4–10 on a standard 0–10 numerical rating scale (NRS; where 0 = no pain, 10 = worst possible pain) [1], following surgery, trauma, musculoskeletal injury, or illness [3, 6–9]. Patients with chronic pain can also report acute pain due to flare-ups; these are referred to as temporary, intense episodes of pain that are more severe than a patient's usual chronic pain [10]. These flare-ups are of limited duration and can be spontaneous, due to stress or caused by activity [10]. Unfortunately, management of acute pain has been reported to be inadequate across healthcare services, such as in emergency departments [1, 6, 11–15], prehospital [1, 16], and in post-surgical settings, including after discharge [17, 18].

Poor management of acute pain can greatly impact patients' quality of life and functioning [17–21]. Conversely, effective management is associated with enhanced recovery, improved rehabilitation, shortened hospital stays, and decreased costs [22]. A wide range of systemic analgesic agents are available to treat moderate-to-severe acute pain, including paracetamol, non-steroidal anti-inflammatory drugs (non-selective agents and cyclo-oxygenase [COX]-2 inhibitors), and opioids [1, 7, 23]. However, the use of many of these medications is limited by toxicities, ceiling effects, administration challenges, and the potential for misuse [7]. Among the most commonly used medications, opioid analgesics are efficacious in the treatment of acute pain of moderate-to-severe intensity [1, 23]. However, bothersome opioid-associated adverse effects such as nausea, vomiting, constipation, and somnolence are commonly reported [24–28] and can lead to treatment discontinuation [24, 27]. These tolerability issues, coupled with the potential for misuse and dependence, may lead to undertreatment or treatment hesitancy [1, 21, 23, 26, 29]. Consequently, there is a need for new pain therapies with improved efficacy and tolerability compared with current options. These new treatments must overcome the dose-limiting side effects and subsequent limited therapeutic window that are often seen with the use of single-agent analgesics [7, 30].

Co-crystal of tramadol-celecoxib (CTC) is the first analgesic co-crystal that contains two active pharmaceutical ingredients (APIs), racemic tramadol hydrochloride (a weak opioid analgesic) and celecoxib (a COX-2 inhibitor), in a supramolecular crystal network at a 1:1 molecular ratio [31, 32]. It is formulated as an orally administered, 100-mg immediate-release tablet (44 mg of tramadol/56 mg of celecoxib). CTC 200 mg (2 × CTC 100 mg; 88 mg of tramadol/112 mg of celecoxib) taken orally twice daily (BID) was first approved in the USA in 2021 [33] and subsequently received European regulatory approval in Spain in September 2023 for

the management of acute moderate-to-severe somatic pain in adults [34].

CTC's multi-modal action targets multiple pain pathways (μ-opioid agonism, norepinephrine and serotonin reuptake inhibition, and COX-2 inhibition), facilitating analgesic efficacy with lower daily doses of tramadol compared with tramadol alone, potentially with an improved side-effect profile [7, 35]. Non-clinical and clinical data suggest that the co-crystallization of tramadol and celecoxib in CTC alters the physicochemical properties and dissolution profiles of both tramadol and celecoxib [31, 32, 36–38]. The data also show that co-crystallization alters the pharmacokinetic properties of tramadol and celecoxib when compared with either agent alone or in concomitant administration (also known as 'free combination'). In phase 1 clinical trials, tramadol from CTC exhibited a lower maximum plasma concentration, at a later timepoint post dose, compared with when immediate-release tramadol was administered alone or in free combination with celecoxib [36–38]. This effect was coupled with a shorter time to reach the maximum plasma concentration of celecoxib following CTC administration compared with the free combination or celecoxib alone.

As co-crystallization of tramadol and celecoxib in CTC modifies their physicochemical properties and bioavailability [31, 32, 36–38], it is important to understand how the efficacy and safety profiles of CTC may differ from those of its individual components. In phase 3 trials in patients with moderate-to-severe acute pain, CTC 200 mg BID (88 mg of tramadol/112 mg of celecoxib) demonstrated greater and more rapid analgesic efficacy than 50 mg of oral immediate-release tramadol taken four times a day (QID) [35, 39]. It also showed greater efficacy than 100 mg of oral immediate-release tramadol QID [35, 39, 40, 41]. Additionally, CTC 200 mg BID reduced rescue medication use, thus permitting lower exposure to opioid-containing medications [35, 39, 40, 41].

Although reported to be common in acute pain, side effects of opioids vary by agent [1, 42, 43] and are dose dependent [28, 42, 44]. Common side effects reported with tramadol include nausea, vomiting, and dizziness [1]. In acute pain, immediate-release tramadol is typically initiated at 100 mg, followed by 50 mg to 100 mg every 4 to 6 h as needed, with a maximum daily dose of 400 mg [1, 45]. As the dosage of tramadol with CTC 200 mg is somewhat higher than the lowest available oral tramadol dose (88 vs. 50 mg, respectively [34, 45]), it is reasonable that doubts may arise regarding the tolerability of the tramadol content in CTC.

Phase 3 clinical data in patients with moderate-to-severe acute pain have shown that CTC 200 mg BID given over a 48-h treatment period is better tolerated than immediate-release tramadol 100 mg QID (with a lower prevalence of opioid-related adverse reactions) and has similar tolerability to immediate-release tramadol 50 mg QID [46]. However, it is not known how the tolerability of CTC compares to tramadol following first-dose administration, when adverse reactions and treatment discontinuations may first occur. With this in mind, we have performed a post hoc analysis of common opioid-related adverse reactions occurring following first-dose administration of CTC 200 mg (containing 88 mg of tramadol) or immediate-release tramadol 50 mg using safety data from one of the pivotal phase 3 clinical trials of CTC in patients with moderate-to-severe acute postoperative pain [39].

METHODS

Briefly, this was a randomized, double-blind, factorial, active- and placebo-controlled phase 3 trial of 637 adults with moderate-to-severe acute pain (pain intensity rating score of 5–9 on the 0–10 NRS) following primary unilateral, first metatarsal osteotomy performed at six US clinical pain research centers (ClinicalTrials.gov identifier, NCT03108482) [39]. In this study, patients were randomized 2:2:2:1 to receive treatment over 48 h with CTC 200 mg BID (total daily dose, 176 mg of tramadol and 224 mg of celecoxib), tramadol 50 mg QID (total daily dose, 200 mg), celecoxib 100 mg BID (total daily dose, 200 mg), or placebo QID [39]. Randomization was stratified by study site and baseline pain score (moderate [NRS, 5–6] vs. severe [NRS, 7–9]). While

assessment of analgesic efficacy was the primary objective, safety/tolerability was a secondary endpoint. Treatment-emergent adverse reactions were defined as those with an onset at the time of or following the start of study treatment, or starting beforehand but increasing in severity at the time of or following the start of study treatment, occurring up to 7 days after the final dose of study medication [39].

The additional post hoc analysis reported here compared safety data in the CTC 200-mg BID and tramadol 50-mg QID arms after first-dose administration, at 2-h intervals up to 6 h post dose, just prior to administration of a second dose of study drug. Specifically, we compared the prevalence of the four most common study drug-related, opioid-associated treatment-emergent adverse reactions reported in phase 3 CTC clinical trials: somnolence, nausea, dizziness, and vomiting [34, 46]. The relationship of treatment-emergent adverse reactions to study medication was determined by investigators who were blinded to treatment assignment. All patients who received a first dose of CTC 200 mg or tramadol 50 mg were included in this safety analysis. As this was a post hoc, hypothesis-driven analysis, no formal inferential testing was performed.

Ethical Approval

This article is based on a previously conducted study (ClinicalTrials.gov identifier, NCT03108482) and does not contain any new studies with human participants or animals performed by any of the authors. The protocol for the study on which this analysis was based was approved by an institutional review board (Atlanta, GA; IRB ID: 5724), and the study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

RESULTS

The findings of this descriptive analysis are summarized in Fig. 1, which shows the percentage of patients reporting the study drug-related treatment-emergent adverse reactions of somnolence, nausea, dizziness, and vomiting in the 6-h window following the first dose of CTC 200 mg or tramadol 50 mg [34]. As illustrated in the figure, percentages of patients reporting these drug-related adverse reactions were similar between the two arms for each reaction, at each timepoint (i.e., at 2, 4, and 6 h after the first dose of CTC 200 mg or tramadol 50 mg).

DISCUSSION

In the primary analysis of this phase 3 study, the tolerability profile of CTC 200 mg BID, especially in relation to opioid-associated adverse reactions, was shown to be similar to that of immediate-release tramadol 50 mg QID when analyzed over the whole 48-h treatment period [39]. This finding was expected, given that patients in the CTC 200 mg BID arm received a slightly lower total daily dose of tramadol than patients in the tramadol 50 QID arm (176 vs. 200 mg, respectively). However, what remained unclear was how the tolerability of CTC 200 mg compared with that of tramadol 50 mg following first-dose administration, when adverse reactions and treatment discontinuations may first occur, and when the administered dose of tramadol is higher in the CTC arm (88 vs. 50 mg with immediate-release tramadol). Reassuringly, data from this additional, post hoc adverse reaction analysis of the initial 6-h period following first study drug administration indicate that 88 mg of tramadol given in 200 mg of CTC has a similar tolerability profile to 50 mg of immediate-release tramadol alone—the lowest dose recommended for the management of moderate-to-severe acute pain [1, 45, 47]. The differentiated physiochemical properties of CTC related to its co-crystal structure, which have been shown to translate into a slower absorption and lower maximum plasma concentration of tramadol (compared with tramadol taken alone) [31, 32, 36–38], may explain why first-dose administration of CTC 200 mg did not result in an increase in drug-related adverse reactions compared with

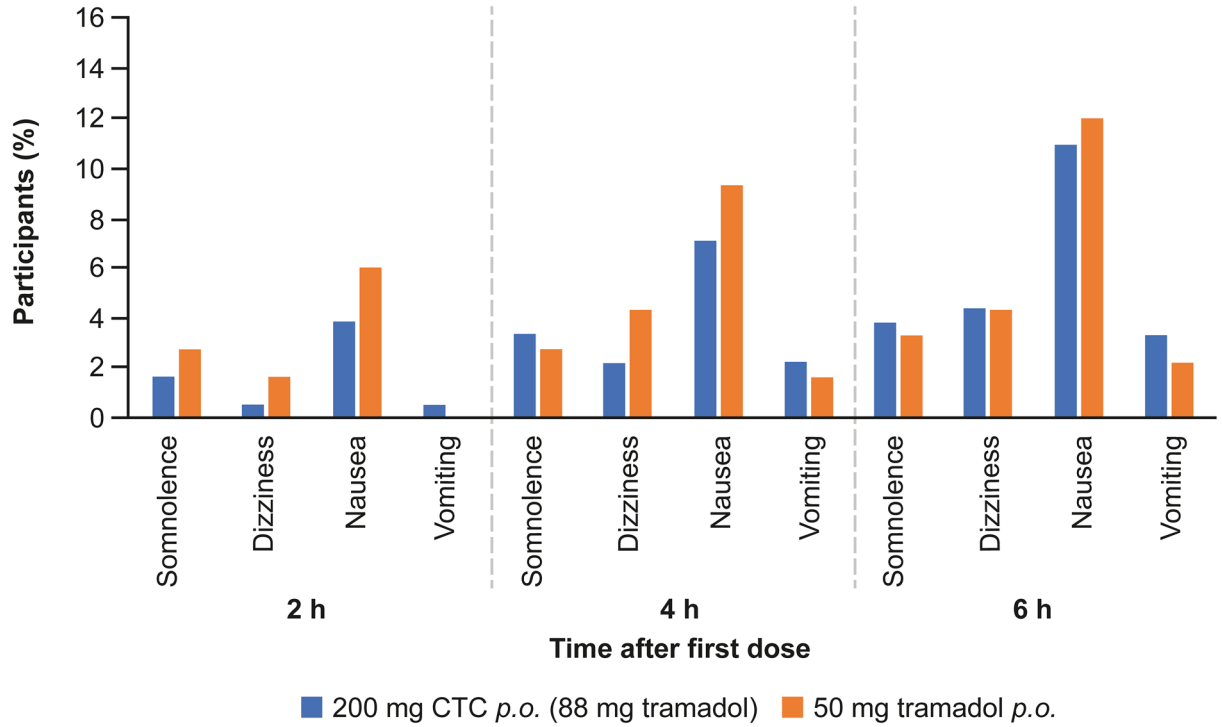

Fig. 1 Percentage[a] of participants reporting the most common opioid-related adverse reactions associated with CTC,[b] according to time after first study drug administration (post hoc analysis). Data are study drug-related treatment-emergent adverse reactions. [a]Denominator was total number of participants ($n = 183$) in each treatment group. [b]The most frequent adverse reactions observed with CTC are somnolence, dizziness, fatigue, nausea, and vomiting (very common ≥ 1/10) [34]. *CTC* co-crystal of tramadol-celecoxib, *h* hours, *p.o.* by mouth

tramadol 50 mg, despite the higher initial tramadol dose.

Importantly, these findings should be viewed in the context of the previously reported improved analgesic efficacy of CTC 200 mg versus tramadol 50 mg during the initial 6-h period following first-dose administration [39]. In the same phase 3 study on which this analysis was based [39], decreases in pain intensity difference from baseline (assessed on the 0–10 NRS) first became statistically significant for CTC 200 mg versus tramadol 50 mg at 3.5 h post first dose. Further, differences between CTC 200 mg and tramadol 50 mg for the time-weighted sum of pain intensity differences and time-weighted sum of pain relief scores were both statistically significant at 6 h. Thus, improvements in efficacy can be achieved with first-dose administration of CTC 200 mg versus tramadol 50 mg, without increasing the risk of drug-related adverse reactions.

CONCLUSIONS

In summary, previous data have shown that CTC, an API–API co-crystal containing the weak opioid tramadol and the COX-2 inhibitor celecoxib, shows promise in the management of moderate-to-severe acute pain with respect to improving efficacy versus immediate-release tramadol alone, while maintaining a similar tolerability profile over the complete treatment period [35, 39, 41, 46, 48, 49]. In this additional post hoc safety analysis, we demonstrate the similar tolerability of CTC 200 mg and tramadol 50 mg following first-dose administration, when adverse reactions may first occur. It is hoped that this finding will help to address any tolerability concerns practitioners may have over the initial dosing of CTC in relation to opioid-associated adverse reactions.

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Data Availability. The datasets generated during and/or analyzed during the current study are available upon reasonable request, please contact esteve@esteve.com.

Declarations

Conflict of interest. Adelaida Morte, Mariano Sust, Anna Vaqué, Jesús Cebrecos, and José María Giménez-Arnau are all employees of ESTEVE Pharmaceuticals S.A.

Ethical Approval. This article is based on a previously conducted study (ClinicalTrials.gov identifier, NCT03108482) and does not contain any new studies with human participants or animals performed by any of the authors. The protocol for the study on which this analysis was based was approved by an institutional review board (Atlanta, GA; IRB ID: 5724), and the study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

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