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# PHARMACOKINETICS

# Single-dose pharmacokinetics of co-crystal of tramadol–celecoxib: Results of a four-way randomized open-label phase I clinical trial in healthy subjects

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## AIMS

Co-crystal of tramadol–celecoxib (CTC) is a novel co-crystal molecule containing two active pharmaceutical ingredients under development by Esteve (E-58425) and Mundipharma Research (MR308). This Phase I study compared single-dose pharmacokinetics (PK) of CTC with those of the individual reference products [immediate-release (IR) tramadol and celecoxib] alone and in open combination.

## METHODS

Healthy adults aged 18–55 years were orally administered four treatments under fasted conditions (separated by 7-day wash-out period): 200 mg IR CTC (equivalent to 88 mg tramadol and 112 mg celecoxib; Treatment 1); 100 mg IR tramadol (Treatment 2); 100 mg celecoxib (Treatment 3); and 100 mg IR tramadol and 100 mg celecoxib (Treatment 4). Treatment sequence was assigned using computer-generated randomization. PK parameters were calculated using noncompartmental analysis with parameters for CTC adjusted according to reference product dose (100 mg).

## RESULTS

Thirty-six subjects (28 male, mean age 36 years) participated. Tramadol PK parameters for Treatments-1, –2 and –4, respectively, were 263, 346 and 349 ng ml$^{-1}$ (mean maximum plasma concentration); 3039, 2979 and 3119 ng h ml$^{-1}$ (mean cumulative area under the plasma concentration–time curve); and 2.7, 1.8 and 1.8 h (median time to maximum plasma concentration). For Treatments 1, 3 and 4, the respective celecoxib PK parameters were 313, 449 and 284 ng ml$^{-1}$; 2183, 3093 and 2856 ng h ml$^{-1}$; and 1.5, 2.3 and 3.0 h. No unexpected adverse events were reported.

## CONCLUSION

PK parameters of each API in CTC were modified by co-crystallization compared with marketed formulations of tramadol, celecoxib, and their open combination.

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pharmaceutical co-crystals are usually composed of an active pharmaceutical ingredient (API) with a neutral guest compound (excipient, conformer) in a crystal lattice.
- A new generation of co-crystals containing two APIs are now in development (API–API co-crystals).
- Co-crystal of tramadol–celecoxib (CTC) is the first API–API co-crystal to show synergistic analgesic effects in preclinical studies.

## WHAT THIS STUDY ADDS

- Co-crystallizing tramadol and celecoxib modifies the PK profile of each API compared with the reference products (immediate-release tramadol or celecoxib) alone or in open combination.
- CTC is a different concept from previously reported co-crystals of increases of the blood levels of an API from the levels of the API itself, but without clinical benefit since the dose needs to be adjusted in a proportional way. By contrast, in CTC, none of the three active therapeutic moieties (tramadol (+)-enantiomer mu agonist and inhibitor of 5-hydroxytryptophan reuptake, tramadol (–)-enantiomer inhibitor of NE reuptake, and celecoxib inhibitor of cyclooxygenase-2) show an increased exposure levels compared to the individual moieties, but rather they show a change in their profile that translates into clinical benefits.

## Tables of Links

| TARGETS | |
|---|---|
| **G protein-coupled receptors** [2] | **Enzymes** [3] |
| μ receptor | cyclooxygenase |
| 5-HT receptor | |

| LIGANDS |
|---|
| tramadol |
| celecoxib |

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

## Introduction

Unrelieved pain is a recognized global healthcare problem, with the International Association for the Study of Pain (IASP) declaring that 'access to pain management is a fundamental human right' [4, 5]. Despite major advances in management, the burden of acute pain – which results from tissue and nerve damage and is normally moderate to severe in intensity and of short duration (<12 weeks) [6, 7] – remains great. For example, over half of patients experience severe or intolerable levels of pain after surgery or trauma [5]. The consequences of poorly controlled acute pain include an increased risk of progression to chronic pain. Surveys have consistently shown that chronic pain affects between one in four and one in three adults [8]. The impact of chronic pain is far reaching and includes both direct and indirect economic costs. One study reported that the estimated costs associated with chronic pain in the USA exceeded 550 billion USD in 2010, similar to the combined costs for heart disease, cancer and diabetes [9].

Multimodal therapy – i.e. combined use of two or more analgesic drugs targeting different pain pathways, or different points within a pathway – is a viable strategy for improving pain management as it may result in additive or even synergistic analgesia [10]. Coadministration of two different drugs in open combination is a simple way to achieve multimodal therapy, although this approach increases the pill burden for patients and the costs of treatment, and, since in general it uses the approved doses of the individual agents, this may result in more adverse events. Fixed-dose combination (FDC) drugs containing two active pharmaceutical ingredients (APIs) are also available; however, the creation of new FDCs can be difficult due to issues with stability and solubility. Moreover, FDCs using similar amounts of approved individual APIs may result in more adverse events while often only producing sub-additive analgesia.

The development of co-crystal drugs containing two or more APIs is a new approach that has been extensively investigated in recent years as a means to circumvent these problems and potentially provide benefits above those offered by other multimodal strategies [11]. The European Medicines Agency recently published a reflection paper in which co-crystals were defined as 'crystalline structures made up of two or more components in a definite stoichiometric ratio…' [12]. In the pharmaceutical setting, at least one of the components is an API while the other(s) may be a nonactive coformer or excipient, or another API. API–API co-crystals may enhance the physiochemical properties, pharmacokinetic (PK) profile and ultimately the efficacy and/or safety of each API, without requiring chemical modifications [11].

Co-crystal of tramadol–celecoxib (CTC) is a novel, patented, first-in-class, API–API co-crystal that contains the analgesic drugs tramadol and celecoxib and is under development by Esteve Pharmaceuticals (as E-58425) and Mundipharma Research (as MR308). CTC contains racemic tramadol hydrochloride (*rac*-tramadol.HCl) and celecoxib at an intrinsic 1:1 molecular ratio (1:1.27 weight ratio) and is formulated as an immediate-release (IR) tablet. Four different mechanisms of action for analgesia in central and

peripheral pathways are captured by inclusion of tramadol and celecoxib in CTC. Tramadol (+)-enantiomer acts as a mu agonist and inhibitor of 5-hydroxytryptophan reuptake, tramadol (–)-enantiomer as inhibitor of norepinephrine reuptake [13], and celecoxib as inhibitor of cyclooxygenase-2 [14].

When administered alone in its conventional form, tramadol is absorbed quickly and rapidly distributed with an elimination half-life ($T_{½el}$) of 5–6 h. The main active metabolite of tramadol, (+)-O-desmethyl-tramadol (M1), has a much greater affinity for the mu-opioid receptor than tramadol itself [13]. Celecoxib reaches peak plasma concentrations 2–3 h after administration of its commercially available formulation and is primarily eliminated by metabolism with an elimination half-life of 8–12 h [14]. Intrinsic dissolution rate studies have demonstrated the potential of a form of CTC co-crystal without additives to improve the dissolution profiles of both tramadol and celecoxib [15], the latter of which is a Biopharmaceutics Classification System Class II compound. When CTC was administered in suspension ('$CTC_{susp}$') in a rat postoperative pain model, it exerted a synergistic analgesic effect compared with its reference products (i.e. it showed efficacy greater than that expected by adding together the analgesic effects observed with *rac*-tramadol.HCl and celecoxib alone). This synergistic effect on efficacy was achieved without an increase in adverse effects [16].

*In vitro* data have shown that the co-crystal structure of CTC modifies the physicochemical properties and intrinsic dissolution profiles of each of the APIs (tramadol and celecoxib) [15] and preclinical pharmacological studies also show that the intrinsic 1:1 molecular ratio of CTC is the optimal ratio for best efficacy and safety [16]. Hence, the unique characteristics of CTC are hypothesized to translate into clinical benefits in efficacy and safety.

The main objective of this Phase I study was to compare the single-dose PK profile of CTC with that of the individual authorized reference products (IR tramadol or celecoxib alone) and the open combination of IR tramadol and celecoxib. Secondary objectives included evaluation of the safety and tolerability of CTC after single-dose administration.

# Methods

## *Study subjects*

Healthy adults aged 18–55 years with body mass index ≥18.5 and <29.0 kg $m^{-2}$ were eligible for the study if they were non- or ex-smokers and in good health as determined by medical history review, physical examination, electrocardiogram (ECG) and clinical laboratory tests. Key exclusion criteria included: pregnancy or lactation in females; history of severe hypersensitivity reactions to any drug; conditions known to interfere with the PK profile of the study drugs; and a significant history of drug dependency or alcohol abuse. Full inclusion and exclusion criteria can be found in Appendix S1.

## *Study design and treatments*

This was a Phase I, randomized, open-label, four-period, four-sequence, crossover study carried out in a single centre in Canada. Four single-dose treatments were administered orally under fasted conditions. The treatment sequence for each participant was assigned by a computer-generated randomization list. Each treatment period was separated by a 7-day wash-out period (Figure 1). The four treatments were: Treatment 1: 2 × 100 mg IR CTC tablets (200 mg; equivalent to 88 mg *rac*-tramadol.HCl and 112 mg celecoxib: proposed marketed formulation); Treatment 2: 2 × 50 mg IR tramadol capsules (*rac*-tramadol.HCl; 100 mg; Adolonta, Grünenthal GmbH, Germany); Treatment 3: 1 × 100 mg celecoxib capsule (100 mg; Celebrex, Henrick Marck Nachf. GmbH & Co., KG, Germany); and Treatment 4: open combination of 100 mg tramadol (*rac*-tramadol.HCl; 2 × 50 mg IR capsules) and 100 mg celecoxib (1 × 100 mg capsule). Tablets and capsules were swallowed whole. Subjects fasted overnight for at least 10 h prior to drug administration and for at least 4 h post-dose, after which controlled food intake was allowed. Subjects were also required to fast at least 12 h prior to the last blood sample. Alcohol, grapefruit-, pomelo- or xanthine-containing food or drink, and noninvestigator-approved prescription medications or over-the-counter products were to be avoided during the study.

The study protocol was approved by an institutional review board (project number 1975, approved on 17 December

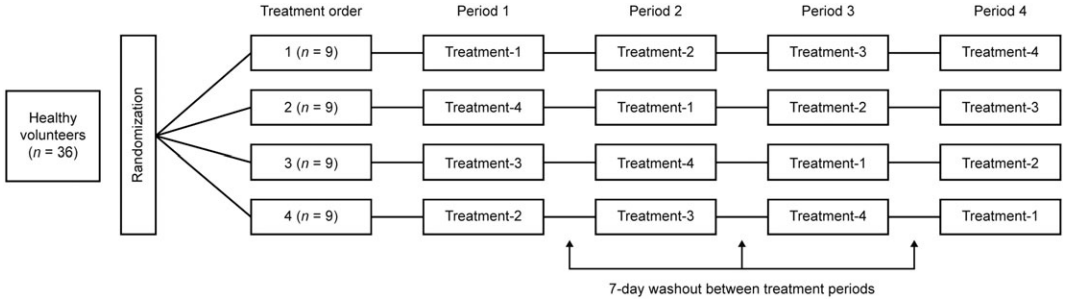



**Figure 1**

Study design. Treatment 1, 2 × 100 mg CTC tablets; Treatment 2, 2 × 50 mg IR tramadol capsules; Treatment 3, 1 × 100 mg celecoxib capsule; Treatment 4, 100 mg tramadol (2 × 50 mg IR capsules) plus 100 mg celecoxib (1 × 100 mg capsule). CTC, co-crystal of tramadol–celecoxib; IR, immediate release

2010 by ETHIPRO, Montreal, Quebec, Canada) and was conducted in accordance with Good Clinical Practice, the requirements of the Declaration of Helsinki and relevant US, European and Canadian regulations/directives. All subjects provided written informed consent.

## PK sampling and analytical methods

For treatments-1, –2 and –4, blood samples for determination of tramadol and M1 were collected prior to drug administration and at the following times postdose: 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 6, 8, 10, 12, 16, 24 and 36 h. For determination of celecoxib concentrations for treatments-1, –3 and –4, samples were collected pretreatment and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 12, 16, 24, 36 and 48 h postdose.

Blood samples were centrifuged (1500 *g* for 10 minutes at 4°C) and collected plasma then divided into half and frozen until assayed. Samples from all subjects who received at least one study treatment were assayed. Plasma concentrations of tramadol, M1 and celecoxib were measured using validated high-performance liquid chromatography with tandem mass spectrometry methods. Sample pretreatment involved the liquid–liquid extraction of tramadol and O-desmethyl tramadol from 0.100 ml of human plasma; tramadol-D6, O-desmethyl tramadol-D6 and celecoxib-D7 were used as internal standards. These compounds were identified and quantified over a theoretical concentration range of 2.00 ng $ml^{-1}$ to 800.00 ng $ml^{-1}$ for Tramadol, 0.500 ng $ml^{-1}$ to 200.000 ng $ml^{-1}$ for O-desmethyl tramadol and 3.00 ng $ml^{-1}$ to 1200.00 ng $ml^{-1}$ for celecoxib. Assay specificity was evaluated using six independent matrix sources to verify the absence of interference, compared with respective limits of quantitation at retention time, and mass transitions of analytes and internal standards. Quantitation was made using peak area ratios, and back-calculated concentrations were determined using least squares regression analysis employing a weighted (1/×2) linear regression (y = mx + b).

## Safety assessments

Safety assessments, including the reporting and recording of adverse events (AEs), measurement of standard clinical laboratory parameters, physical examination (including vital signs) and 12-lead ECG, were performed throughout the study. AEs were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, version 12.1.

## Data and statistical analyses

*Sample size determination.* The PK profile of celecoxib is known to be more variable than that of tramadol. Based on previous findings, the intrasubject variation following a single dose of celecoxib was estimated to be around 27% for $C_{max}$ and around 11% for $AUC_{\tau}$. Statistically, given that the expected ratio of geometric least squares (LS) means should fall within 95% and 105%, it was estimated that 32 subjects would be sufficient to provide an adequate assessment of the pharmacokinetic and safety profiles of CTC and evaluate possible drug interactions between tramadol and celecoxib. Therefore, the inclusion of 36 subjects was deemed sufficient to take into account the possibility of drop-outs and variations around the estimated intrasubject coefficient of variation to perform a confirmatory study (pivotal Phase I study).

*PK.* Calculated PK parameters included maximum plasma concentration ($C_{max}$), time to maximum measured plasma concentration ($T_{max}$), cumulative area under the plasma concentration–time curve ($AUC_{\tau}$), area under the plasma concentration–time curve extrapolated to infinity ($AUC_{\infty}$), relative percentage of $AUC_{\tau}$ with respect to $AUC_{\infty}$ ($AUC_{\tau/\infty}$), apparent elimination rate constant ($K_{el}$), $T_{½el}$, apparent volume of distribution ($V_D/F$) and apparent plasma clearance (Cl/F). The natural logarithmic (ln) transformation normalized by the dose of $C_{max}$, $AUC_{\tau}$ and $AUC_{\infty}$, as well as the rank-transformation of $T_{max}$, were used for all statistical inference.

A noncompartmental approach with a log-linear terminal phase assumption was used to estimate the PK parameters. AUC was determined using the trapezoidal rule and the terminal phase was estimated by maximizing the coefficient of determination from the log-linear regression model. All ln-transformed PK parameters were statistically analysed using an analysis of variance model. The fixed factors included in this model were treatment, treatment period and treatment sequence as well as the left-over interaction terms between the three factors. A random factor was added for the subject effect (nested within the sequence). The sequence, period and treatment effects were assessed at the 5% two-sided level. Furthermore, the 90% confidence intervals (CIs) for the exponential of the difference in LS means between CTC and the other treatments was calculated for the ln-transformed parameters. All subjects who provided evaluable PK data for a particular treatment were included in the descriptive analysis of that treatment. For each treatment-group comparison, subjects who provided measurable PK data for both treatments were included in the PK and statistical analyses. Statistical analyses of PK data were generated using Kinetic, a validated software developed at Algorithme Pharma and SAS® version 9.1 or higher (SAS Institute, Cary, NC, USA).

*Safety.* Safety data were analysed using descriptive statistics. Safety was assessed in all subjects who received at least one dose of any study treatment.

# Results

## Subjects

Thirty-six subjects were enrolled between 23 March and 29 April 2011, of whom most were male (78%) and white (86%). Mean age was 36 years. Other demographic data are shown in Table 1. All subjects provided measurable PK data for at least two treatments and were therefore included in the PK evaluation and statistical analyses. Plasma samples collected from one subject during the first treatment period were excluded from analysis because a gastrointestinal AE occurring after administration of study treatment (open combination of tramadol and celecoxib) may have influenced PK findings. All subjects were included in the safety analysis. Four subjects withdrew or were withdrawn before study

## Table 1

Subject demographics ($n$ = 36)

| Characteristic | |
|---|---|
| **Age, years** | 36 (9.0) |
| **Sex, *n* (%)** | |
| **Male** | 28 (77.8) |
| **Female** | 8 (22.2) |
| **Race; *n* (%)** | |
| **White** | 31 (86.1) |
| **Black** | 3 (8.3) |
| **American Native** | 1 (2.8) |
| **Other** | 1 (2.8) |
| **Weight, kg** | 72.4 (11.8) |
| **Height, cm** | 171.4 (8.6) |
| **Body mass index, kg m$^{-2}$** | 24.53 (2.9) |

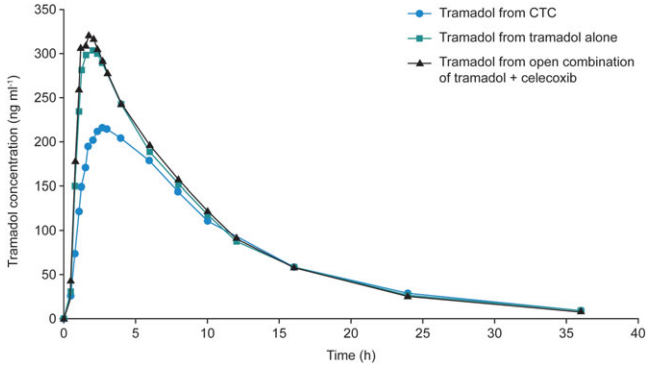
Data are mean (standard deviation) unless otherwise stated

end, due to positive alcohol test, un-cooperative behaviour, withdrawn consent or decreased haemoglobin levels (one subject each). These subjects did not receive treatment during study period 4; therefore, the statistical analysis only included 34 subjects for Treatment 1 and 35 subjects for Treatments-2, –3 and –4.

## *PK*

*PK of tramadol, M1 and celecoxib after administration of CTC.* PK parameters for tramadol, M1 and celecoxib after single-dose administration of CTC are summarized in Table 2. Plasma concentration–time profiles for each of these analytes after administration of CTC are shown in Figures 2–4, alongside the profiles observed with the reference products alone or in open combination.

*Tramadol PK.* Following PK parameters adjusted according to reference dose, mean tramadol $C_{max}$ after a single dose of CTC was lower than with tramadol alone or the open combination of tramadol and celecoxib (263.23 *vs.* 345.78 and 349.38 ng ml$^{-1}$, respectively; Table 3). In contrast, similar values were obtained for mean $AUC_{\tau}$ and $AUC_{\infty}$ for all three treatments. For tramadol $AUC_{\tau}$ and $AUC_{\infty}$, but not $C_{max}$, 90% CIs of the LS means ratios for CTC compared with tramadol alone or tramadol plus celecoxib were within the equivalence range of 80–125%. Median $T_{max}$ for




## Figure 2

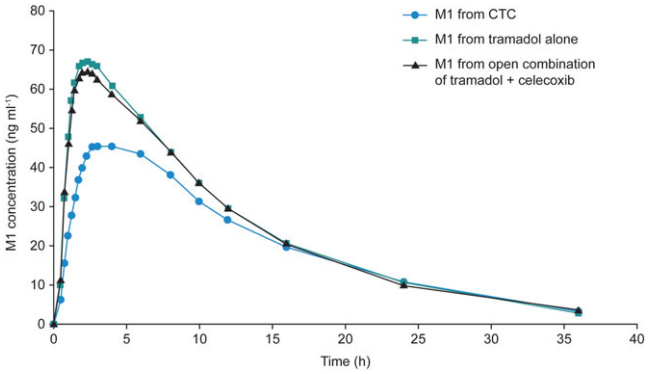
Mean plasma concentration *vs.* time profiles for tramadol following a single dose of CTC (Treatment 1), tramadol alone (Treatment 2) or the open combination of tramadol and celecoxib (Treatment 4). CTC, co-crystal of tramadol–celecoxib

## Table 2

Summary of pharmacokinetic parameters for tramadol, M1 and celecoxib following a single dose of CTC

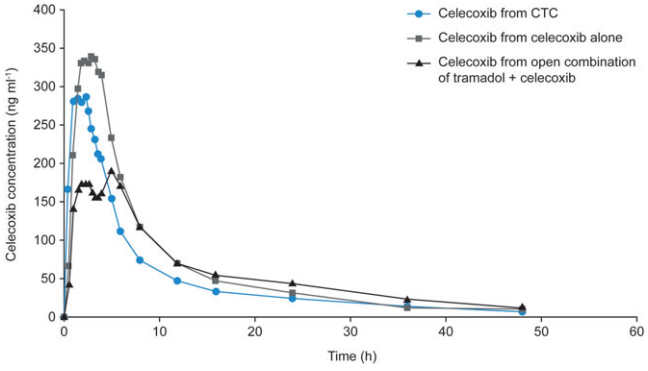
| | Tramadol ($n$ = 34) | | M1 ($n$ = 34) | | Celecoxib ($n$ = 34) | |
|---|---|---|---|---|---|---|
| **Parameter** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Mean** | **CV (%)** |
| **$C_{max}$ (ng ml$^{-1}$)** | 231.65 | 20.2 | 48.821 | 43.0 | 350.93 | 28.9 |
| **$T_{max}$ (h)**[a] | 2.67 | 1.00–6.00 | 4.00 | 2.00–8.00 | 1.50 | 1.00–5.00 |
| **$AUC_{\tau}$ (ng h ml$^{-1}$)** | 2674.50 | 29.5 | 713.428 | 31.1 | 2444.73 | 24.3 |
| **$AUC_{\infty}$ (ng h ml$^{-1}$)** | 2778.50 | 31.2 | 752.219 | 30.1 | 2756.08 | 24.8 |
| **$K_{el}$ (h$^{-1}$)** | 0.10 | 17.2 | 0.09 | 18.6 | 0.05 | 41.8 |
| **$T_{½el}$ (h)** | 6.96 | 18.1 | 7.82 | 17.7 | 16.91 | 45.7 |
| **Cl/F (l h$^{-1}$)** | 35.06 | 34.8 | 134.81 | 48.7 | 43.50 | 28.8 |
| **$V_d$/F (l)** | 339.86 | 27.1 | 1567.51 | 60.5 | 1028.33 | 45.7 |

[a]For $T_{max}$, median and range are presented. $AUC_{\infty}$, area under the plasma concentration–time curve extrapolated to infinity; $AUC_{\tau}$, cumulative area under the plasma concentration–time curve; Cl/F, apparent plasma clearance; $C_{max}$, maximum plasma concentration; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; $K_{el}$, apparent elimination rate constant; M1, (+)-O-desmethyl-tramadol; $T_{½el}$, terminal elimination half-life; $T_{max}$, time to maximum plasma concentration; $V_d$/F, apparent volume of distribution




## Figure 3

Mean plasma concentration *vs.* time profiles for M1 following a single dose of CTC (Treatment 1), tramadol alone (Treatment 2) or the open combination of tramadol and celecoxib (Treatment 4)]. CTC, co-crystal of tramadol–celecoxib




## Figure 4

Mean plasma concentration *vs.* time profiles for celecoxib following a single dose of CTC (Treatment 1), celecoxib alone (Treatment 3) or the open combination of tramadol and celecoxib (Treatment 4). CTC, co-crystal of tramadol–celecoxib

tramadol after single-dose CTC was slightly delayed (at 2.67 h *vs.* 1.75 h) for both tramadol alone and tramadol plus celecoxib.

*M1 PK.* After PK parameters had been adjusted according to reference dose, mean M1 $C_{max}$ after a single dose of CTC was lower than after treatment with tramadol alone or tramadol plus celecoxib (55.48 *vs.* 73.54 and 68.34 ng $ml^{-1}$, respectively; Table 4). For M1 $AUC_{\tau}$ and $AUC_{\infty}$, similar values were obtained with all three tramadol-containing treatments. As observed with tramadol, 90% CIs of the LS means ratios for M1 (CTC *vs.* tramadol alone or tramadol plus celecoxib) were within 80–125% for $AUC_{\tau}$ and $AUC_{\infty}$ but not for $C_{max}$. Median $T_{max}$ for M1 was 4.00 h with CTC compared to 2.33 h for tramadol and 2.00 h for tramadol plus celecoxib.

*Celecoxib PK.* As shown in Figure 4, a pronounced decrease in celecoxib $C_{max}$ was observed with the open combination

## Table 3

Summary and statistical comparison of key tramadol pharmacokinetic parameters following single doses of CTC (Treatment 1), tramadol alone (Treatment 2) or the open combination of tramadol and celecoxib (Treatment 4)

| | Treatment 1200 mg CTC[a] (*n*=34[b]) | | Treatment 2100 mg tramadol (*n* = 35) | | Treatment 4100 mg tramadol + 100 mg celecoxib (*n* = 35) | | Ratio of geometric LS means (90% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Treatment 1 *vs.* Treatment 2** | **Treatment 1 *vs.* Treatment 4** | **Treatment 2 *vs.* Treatment 4** |
| **$C_{max}$ (ng $ml^{-1}$)** | 263.23[c] | 20.2[c] | 345.78 | 23.2 | 349.38 | 23.9 | 75.85 (72.11–79.79) | 76.35 (72.58–80.32) | 100.66 (95.74–105.82) |
| **$AUC_{\tau}$ (ng h $ml^{-1}$)** | 3039.21[c] | 29.5[c] | 2979.01 | 31.9 | 3119.37 | 28.4 | 100.55 (97.11–104.10) | 98.21 (94.85–101.69) | 97.68 (94.38–101.10) |
| **$AUC_{\infty}$ (ng h $ml^{-1}$)** | 3157.38[c] | 31.2[c] | 3060.66 | 33.4 | 3202.99 | 29.7 | 101.41 (97.83–105.12) | 99.27 (95.77–102.91) | 97.89 (94.48–101.43) |
| **$T_{max}$ (h)[d]** | 2.67 | 1.00–6.00 | 1.75 | 1.00–4.00 | 1.75 | 0.75–2.67 | – | – | – |

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib.
[b]Three subjects did not receive treatment during study period 4; therefore, the analysis only included 34 subjects for Treatment 1 and 35 for Treatments-2 and -4.
[c]Parameters for Treatment 1 were adjusted according to reference dose.
[d]Median and minimum-maximum values shown. $AUC_{\infty}$, area under the plasma concentration–time curve extrapolated to infinity; $AUC_{\tau}$, cumulative area under the plasma concentration–time curve; CI, confidence interval; $C_{max}$, maximum plasma concentration; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; $T_{max}$, time to maximum plasma concentration

**Table 4**

Summary and statistical comparison of key M1 pharmacokinetic parameters following single doses of CTC (Treatment 1), tramadol alone (Treatment 2) or the open combination of tramadol and celecoxib (Treatment 4)

| | Treatment 1200 mg CTC[a] (*n*=34[b]) | | Treatment 2100 mg tramadol (*n* = 35) | | Treatment 4100 mg tramadol + 100 mg celecoxib (*n* = 35) | | Ratio of geometric LS means (90% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Treatment 1 *vs.* Treatment 2** | **Treatment 1 *vs.* Treatment 4** | **Treatment 2 *vs.* Treatment 4** |
| **$C_{max}$ (ng ml$^{-1}$)** | 55.48[c] | 43.0[c] | 73.54 | 42.3 | 68.34 | 35.5 | 76.28 (72.38–80.39) | 78.13 (74.13–82.35) | 102.43 (97.25–107.88) |
| **$AUC_{\tau}$ (ng h ml$^{-1}$)** | 810.71[c] | 31.1[c] | 851.78 | 33.6 | 844.07 | 30.2 | 95.79 (92.60–99.09) | 95.98 (92.78–99.30) | 100.20 (96.90–103.61) |
| **$AUC_{\infty}$ (ng h ml$^{-1}$)** | 854.79[c] | 30.1[c] | 881.26 | 32.6 | 876.28 | 29.4 | 97.32 (94.02–100.72) | 97.67 (94.37–101.10) | 100.37 (97.01–103.84) |
| **$T_{max}$ (h)[d]** | 4.00 | 2.00–8.00 | 2.33 | 1.00–4.00 | 2.00 | 0.75–6.00 | – | – | – |

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib.
[b]Three subjects did not receive treatment during study period 4; therefore, the analysis only included 34 subjects for Treatment 1 and 35 for Treatments-2 and -4.
[c]Parameters for Treatment 1 were adjusted according to reference dose.
[d]Median and minimum-maximum values shown. $AUC_{\infty}$, area under the plasma concentration–time curve extrapolated to infinity; $AUC_{\tau}$, cumulative area under the plasma concentration–time curve; CI, confidence interval; $C_{max}$, maximum plasma concentration; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; M1, (+)-O-desmethyl-tramadol; $T_{max}$, time to maximum plasma concentration

of tramadol plus celecoxib *vs.* celecoxib alone. After PK parameters adjusted according to reference dose, mean celecoxib $C_{max}$ with CTC (313.33 ng ml$^{-1}$) was lower than with celecoxib alone (448.87 ng ml$^{-1}$) but higher than with tramadol plus celecoxib (284.35 ng ml$^{-1}$; Table 5). For $C_{max}$, the ratio of LS means for the open combination of tramadol plus celecoxib *vs.* celecoxib alone was 163.92% (90% CI: 146.56–183.35). Mean celecoxib $AUC_{\tau}$ was lower with CTC than celecoxib alone or tramadol plus celecoxib (2182.79 *vs.* 3093.36 and 2855.97 ng h ml$^{-1}$, respectively), as was $AUC_{\infty}$. For celecoxib $C_{max}$, 90% CIs of the LS means ratios (CTC *vs.* celecoxib alone or tramadol plus celecoxib) were within 80–125%; CIs for $AUC_{\tau}$ and $AUC_{\infty}$ were outside this range. Median $T_{max}$ for celecoxib after a single dose of CTC was significantly earlier at 1.50 h *vs.* 2.33 h for celecoxib alone and 3.00 h for tramadol plus celecoxib.

### *Safety*

Twenty-nine (80.6%) subjects each reported one or more AE. The number of subjects who reported AEs after administration of each treatment was 15 (44.1%), 14 (40.0%), 12 (34.3%) and 22 (61.1%) for CTC, tramadol alone, celecoxib alone and tramadol plus celecoxib, respectively. AEs considered to be treatment-related occurred in 12 (35.3%), 14 (40.0%), 8 (22.9%) and 22 (61.1%) subjects, respectively. The most commonly reported AEs were somnolence, dizziness and nausea (Table 6). Most AEs were mild to moderate in intensity. No serious AEs or deaths were reported. Two subjects had abnormal laboratory values; one had elevated hepatic enzyme levels (at a poststudy visit) and one decreased haemoglobin levels (pretreatment period 4; the subject was discontinued from the study). No clinically significant on-study vital sign abnormalities were recorded. One subject had an abnormal poststudy ECG measurement that was subsequently classified as an on-study AE (ventricular extrasystoles).

## Discussion

The multifactorial nature of pain makes the concept of employing multiple mechanisms of analgesia within a single molecule an attractive one [17]. CTC is an API–API co-crystal of tramadol and celecoxib in development for the treatment of acute pain. This Phase I study compared the single-dose PK profile and evaluated the safety and tolerability of CTC compared with each reference product alone and with these products in open combination. The four-way design of this trial also allowed for intra- and interindividual heterogeneity to be assessed.

After adjusting for the different doses of tramadol in 200 mg CTC (88 mg) and reference tramadol (100 mg), tramadol from CTC showed a similar AUC but a lower $C_{max}$ compared with tramadol taken alone or in open combination with celecoxib. In addition, tramadol $T_{max}$ was slightly prolonged with CTC relative to the other tramadol-containing treatments. Similar observations were made for the main metabolite of tramadol M1. Observed PK parameters for tramadol alone were similar to those seen following coadministration of tramadol and celecoxib in this study, and are also comparable to those reported in the literature

## Table 5

Summary and statistical comparison of key celecoxib pharmacokinetic parameters following single doses of CTC (Treatment 1), celecoxib alone (Treatment 3) or the open combination of tramadol and celecoxib (Treatment 4)

| | Treatment 1200 mg CTC[a] (*n*=34[b]) | | Treatment 3100 mg celecoxib (*n* = 35) | | Treatment 4100 mg tramadol + 100 mg celecoxib (*n* = 35) | | Ratio of geometric LS means (90% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Mean** | **CV (%)** | **Treatment 1 *vs.* Treatment 3** | **Treatment 1 *vs.* Treatment 4** | **Treatment 3 *vs.* Treatment 4** |
| **$C_{max}$ (ng ml$^{-1}$)** | 313.33[c] | 28.9[c] | 448.87 | 33.4 | 284.35 | 43.0 | 71.84 (64.16–80.44) | 117.76 (105.15–131.89) | 163.92 (146.56–183.35) |
| **$AUC_t$ (ng h ml$^{-1}$)** | 2182.79[c] | 24.3[c] | 3093.36 | 23.1 | 2855.97 | 27.4 | 71.53 (68.45–74.76) | 78.97 (75.56–82.53) | 110.39 (105.68–115.32) |
| **$AUC_\infty$ (ng h ml$^{-1}$)** | 2460.79[c] | 24.8[c] | 3195.32 | 22.7 | 3121.09 | 25.9 | 76.42 (73.20–79.78) | 79.20 (75.79–82.76) | 103.64 (99.37–108.09) |
| **$T_{max}$ (h)[d]** | 1.50 | 1.00–5.00 | 2.33 | 1.00–5.00 | 3.00 | 1.00–12.00 | – | – | – |

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib.
[b]Three subjects did not receive treatment during study period 4; therefore, the analysis only included 34 subjects for Treatment 1 and 35 for Treatments-3 and -4.
[c]Parameters for Treatment 1 were adjusted according to reference dose.
[d]Median and minimum-maximum values shown. $AUC_\infty$, area under the plasma concentration–time curve extrapolated to infinity; $AUC_\tau$, cumulative area under the plasma concentration–time curve; CI, confidence interval; $C_{max}$, maximum plasma concentration; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; $T_{max}$, time to maximum plasma concentration

[13]. The reduction in tramadol $C_{max}$ observed with CTC is consistent with a slowed dissolution (and hence absorption) of tramadol; that is, a co-crystal mechanistic effect.

After PK parameters were adjusted according to reference dose, celecoxib from 200 mg CTC (celecoxib dose, 112 mg) showed a reduced AUC and a lower $C_{max}$ compared with 100 mg celecoxib alone. Of note, the open combination of tramadol and celecoxib was associated with a markedly reduced celecoxib $C_{max}$ compared with celecoxib alone (313.33 *vs.* 448.87 ng ml$^{-1}$). Compared with the open combination, the $C_{max}$ of celecoxib from CTC was increased (284.35 *vs.* 313.33 ng ml$^{-1}$). These observations may be due to the effects of coadministration on the dissolution and absorption profiles of celecoxib that are not present when the two APIs are co-crystallized. Differences in $T_{max}$, which was faster with CTC (1.50 h) than with celecoxib alone (2.33 h) or tramadol plus celecoxib (3.00 h), also suggest that co-crystallization improves the PK profile of celecoxib, consistent with an enhancement of its dissolution that is, again a co-crystal mechanistic effect.

The modified tramadol and celecoxib PK profiles observed with CTC relative to the individual reference products may have clinical implications. For example, lower $C_{max}$ levels may be predicted to improve the safety profile of a drug. The most common AEs reported after use of IR tramadol (affecting >10% of subjects) are nausea and dizziness; in addition, headache, somnolence, vomiting, constipation, dry mouth, sweating and fatigue are other common tramadol-related side effects [18]. Consistent with this, somnolence, dizziness and nausea were the most commonly reported AEs in the current study. The proportion of subjects affected by these AEs was slightly lower after treatment with CTC compared with tramadol alone or tramadol plus celecoxib. There is a dose–response effect on AE incidence with IR tramadol [19]. Although our study with a single dose was not designed to assess the difference in AEs, the lower tramadol $C_{max}$ observed with CTC may have been responsible for the accompanying trend toward a lower incidence of AEs. This is supported by the fact that the accompanying Phase I study of CTC that used single and multiple doses resulted in a lower incidence of AEs with the repeated dosing [cosubmitted manuscript by our group]. With respect to celecoxib, the faster $T_{max}$ observed with CTC relative to celecoxib alone could reflect an improvement in the dissolution of this inherently poorly soluble drug. There are many examples in the literature of attempts to improve the dissolution of celecoxib and tested techniques include the production of spherical crystals, solid dispersions and nanoparticles [20–22]. It is interesting to hypothesize whether the faster celecoxib $T_{max}$ observed with CTC may have implications for speed of analgesic onset. Changes in the PK profile of each API may explain the synergistic analgesic effects observed with $ctc_{susp}$ in a rat pain model [16].

There is a growing number of reports in the literature of co-crystals exhibiting different characteristics to the reference products alone, both *in vitro* and *in vivo*. The solubility of meloxicam was improved when produced as a co-crystal with aspirin, and an increase in dissolution rate for a paracetamol/aceclofenac co-crystal was noted compared with each of the individual components [23, 24]. A co-crystal of metformin and dichloroacetate demonstrated synergistic

## Table 6

Summary of adverse events reported in at least two subjects

| System organ class | Adverse event | Treatment 1200 mg CTC[a] (*n* = 34) | Treatment 2100 mg tramadol (*n* = 35) | Treatment 3100 mg celecoxib (*n* = 35) | Treatment 4100 mg tramadol + 100 mg celecoxib (*n* = 36) |
|---|---|---|---|---|---|
| **Nervous system disorders** | Dizziness | 4 / 5 | 4 / 4 | 1 / 1 | 7 / 8 |
| | Headache | 1 / 1 | 1 / 1 | 1 / 1 | 1 / 1 |
| | Somnolence | 8 / 8 | 10 / 10 | 5 / 5 | 10 / 11 |
| **Gastrointestinal disorders** | Abdominal pain | 0 | 2 / 2 | 0 | 0 |
| | Nausea | 3 / 4 | 4 / 6 | 0 | 5 / 7 |
| **Respiratory, thoracic and mediastinal disorders** | Nasal congestion | 1 / 1 | 1 / 1 | 1 / 1 | 0 |
| | Dysphonia | 0 | 1 / 1 | 1 / 1 | 0 |
| | Rhinitis | 0 | 0 | 1 / 1 | 1 / 1 |
| | Rhinorrhoea | 0 | 0 | 1 / 1 | 1 / 1 |
| **Injury, poisoning and procedural complications** | Vessel puncture site pain | 0 | 0 | 2 / 2 | 1 / 1 |
| | Vessel puncture site reaction | 3 / 3 | 1 / 1 | 1 / 1 | 0 |
| **General disorders and administration site conditions** | Fatigue | 0 | 2 / 2 | 0 | 0 |
| | Feeling abnormal | 0 | 1 / 1 | 0 | 1 / 1 |
| **Psychiatric disorders** | Euphoric mood | 1 /1 | 2 / 2 | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | Rash | 0 | 0 | 1 / 1 | 1 / 1 |

Data shown are number of subjects/number of events.
[a]Equivalent to 88 mg tramadol and 112 mg celecoxib.
AE, adverse event; CTC, co-crystal of tramadol–celecoxib

antileukaemic activity when tested *in vitro* [25]. Improvements in the solubility and dissolution of baicalein when tested as a co-crystal with nicotinamide translated into a 2.5-fold greater $C_{max}$ and 2.8-fold greater AUC when administered to rats [26]. Data on the one multidrug co-crystal to have been approved to date, Entresto (Novartis, Basel, Switzerland; that by chemical analysis is a complex comprised of anionic forms of sacubitril and valsartan plus sodium cations, and water molecules) show that one of the component APIs (valsartan) has improved bioavailability compared with reference valsartan, that is, according to the Entresto label, '26 mg, 51 mg and 103 mg of valsartan in Entresto is equivalent to 40 mg, 80 mg and 160 mg of valsartan in other marketed tablet formulations, respectively'. Therefore, the amount of valsartan in Entresto is adjusted based on the doses used of valsartan alone.

It is important to recognize that changes in dissolution, absorption and bioavailability profiles do not necessarily mean that there is an improved clinical or therapeutic benefit; for instance, in the examples that result in increased exposures compared to the individual drugs, there is no better clinical benefit *per se* since to maintain efficacy and to manage safety issues, the dose needs to be adjusted in a proportional way, as commented above.

CTC presents a different and unique case. Neither tramadol nor celecoxib from CTC show increased exposure levels compared to the individual tramadol or celecoxib, but rather they both show a change in their PK profiles that may translate into clinical benefits. Essentially, data collected in the current study demonstrates that co-crystallization improves the PK properties of both constituent APIs in CTC. The intrinsic CTC structure contains the two enantiomers of tramadol, its HCl counterpart and celecoxib. The various moieties are linked via ionic and hydrogen bonding where chloride ions establish three key intermolecular contacts with the adjacent molecules [15]. The different ionic and hydrogen bonds confer upon CTC the ability to release both tramadol and celecoxib at rates and profiles that are different from a combination approach or from the individual APIs. The Phase I data are consistent with the *in vitro* data that showed that the intrinsic dissolution rate of tramadol HCl is slowed down (which leads to a more sustained release, longer $T_{max}$ and a reduction of $C_{max}$) while that of celecoxib is accelerated (which leads to a faster rate of absorption).

There are some limitations to this study. The intrinsic 1:1 molecular ratio of tramadol to celecoxib in CTC means that the 200-mg dose used is equivalent to 88 mg tramadol and 112 mg celecoxib. As such, PK parameters adjusted according to reference dose calculations had to be performed to compare the PK properties of CTC and the approved doses of reference tramadol and celecoxib (both 100 mg). Furthermore, since this was the first four-way clinical trial in the CTC clinical development programme, the changes in PK parameters observed (arising from the co-crystal nature of CTC) need to be reproduced in other studies before they can be confirmed. In fact, the results of another Phase I study of CTC that used

single and multiple doses are now available and support the current findings [Co-submitted manuscript by our group].

In summary, the results of this Phase I study in healthy volunteers suggest that the PK profiles of both APIs in CTC (tramadol and celecoxib) are modified by co-crystallization (compared with marketed formulations of tramadol and celecoxib and their open combination). It is possible that these PK effects may have favourable clinical implications although studies in patients experiencing pain are required to test this hypothesis fully. A randomized placebo-controlled Phase II trial comparing CTC with tramadol alone in patients with acute pain after oral surgery has now been completed [27] and Phase III trials are ongoing.

## Competing Interests

S.V., A.V., M.S., M.E., A.S., N.G., G.E. and C.P. are employees of Laboratorios del Dr Esteve, S.A.U. L.S. was an employee of Laboratorios del Dr Esteve, S.A.U. when the study was performed. M.L. and E.S. are employees of Algorithme Pharma.

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## Contributors

S.V., M.L., A.V., M.S., L.S., N.G., G.E. and C.P. were involved in the conception and design of the study and the analysis and interpretation of data. A.S., M.E. and E.S. were involved in the acquisition of data. All authors revised the article critically for important intellectual content and gave final approval of the version to be published.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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**Appendix S1** Selection of study population: full inclusion and exclusion criteria