British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 64–78 64

PHARMACOKINETICS

Pharmacokinetics of multiple doses of co-crystal of tramadol–celecoxib: findings from a four-way randomized open-label phase I clinical trial

Correspondence Dr Sebastián Videla MD, PhD, Clinical Investigation Department, Laboratorios Dr ESTEVE, S.A.U, Av Mare de Déu de Montserrat 221, Barcelona, 08041, Spain. Tel.: +34 93 446 6000; Fax: +34 93 446 6110; E-mail: svidela@esteve.es; sebastia.videla@upf.edu

Received 25 April 2017; **Revised** 19 August 2017; **Accepted** 3 September 2017

Sebastián Videla[1], Mounia Lahjou[2], Anna Vaqué[1], Mariano Sust[1], Marisol Escriche[1], Lluis Soler[1], Artur Sans[1], Eric Sicard[3,*], Neus Gascón[1], Gregorio Encina[1] and Carlos Plata-Salamán[1]

[1]*Laboratorios del Dr. Esteve, S.A.U., Barcelona, Spain,* [2]*Algorithme Pharma, Laval, QC, Canada, and* [3]*Alogrithme Pharma, Montreal, QC, Canada*

*Clinical Principal Investigator.

Keywords celecoxib, co-crystal, pain, pharmacokinetics, tramadol

AIM

We compared the pharmacokinetic (PK) profiles of co-crystal of tramadol–celecoxib (CTC) *vs.* each reference product (alone and in open combination) after single (first dose) and multiple dosing.

METHODS

Healthy adults aged 18–50 years received, under fasted conditions, 15 twice-daily doses of the following treatments (separated by ≥14-day washout): 200 mg immediate-release (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). The treatment sequence was assigned by computer-generated randomization. PK parameters were calculated using non-compartmental analysis. Parameters for CTC were adjusted according to reference product dose.

RESULTS

A total of 30 subjects (20 males, mean age 35 years) were included. Multiple-dose tramadol PK parameters for treatments 1, 2 and 4, respectively, were 551, 632 and 661 ng ml^{-1} [mean maximum plasma concentration (C_{max})]; 4796, 4990 and 5284 ng h ml^{-1} (area under the plasma concentration–time curve over the dosing interval at steady state); and 3.0, 2.0 and 2.0 h (median time to C_{max} at steady state). For treatments 1, 3 and 4, multiple-dose celecoxib PK parameters were 445, 536 and 396 ng ml^{-1}; 2803, 3366 and 2897 ng h ml^{-1}; and 2.0, 2.0 and 3.0 h. Single-dose findings were consistent with multiple-dose data. Types of adverse events were consistent with known reference product safety profiles.

CONCLUSION

After single (first dose) and multiple dosing, PK parameters for each active pharmaceutical ingredient in CTC were modified by co-crystallization compared with reference products alone or in open combination.

DOI:10.1111/bcp.13428

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Development of pharmaceutical co-crystals containing two active pharmaceutical ingredients (APIs) may confer each API with distinctive physicochemical, pharmacokinetic (PK) and clinical profiles compared with the reference products.
- Co-crystal of tramadol–celecoxib (CTC) is a novel API-API co-crystal under development for the treatment of pain.
- In a previous single-dose phase I study of CTC, the PK parameters of each API were modified by co-crystallization compared with the reference products (immediate-release tramadol or celecoxib) alone and in open combination.

WHAT THIS STUDY ADDS

- After multiple dosing, the PK profiles of tramadol and celecoxib from CTC are modified by co-crystallization compared with reference products alone or in open combination.
- The types of adverse event observed during multiple-dose treatment were as expected, based on the reference product labels.
- These observations are consistent with the CTC mechanistic effect that can translate into favourable PK changes.

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

Pain is a complex, multifaceted phenomenon, originating from various sources and involving multiple physiological pathways [4]. A multimodal approach to analgesia is often considered necessary [5, 6]. Combining drugs with complementary mechanisms of action can amplify pain relief when additive, supra-additive or 'synergistic' interactions occur [7, 8]. Multimodal therapy may also permit use of lower drug doses and thereby improve the safety and tolerability of treatment [9–11]. For example, combining non-steroidal anti-inflammatory drugs (NSAIDs) with opioids to treat acute pain can improve efficacy compared with opioids alone and also reduce opioid consumption [12, 13] and opioid-associated adverse events (AEs) [14, 15]. Traditionally, multimodal analgesia has involved the administration of multiple separate drug formulations in 'open' combination, or use of fixed-dose combinations (FDCs) in which component active pharmaceutical ingredients (APIs) are contained in a single formulation at a fixed ratio often representing the doses of the individual approved drugs [16].

A new approach to multimodal therapy is the development of 'co-crystal' drugs [17]. Within a co-crystal, the physicochemical properties of an API may be modified compared with other solid-state forms, although the API's molecular structure is unchanged. This may result in enhanced bioavailability and changes in other pharmacokinetic (PK) properties. For example, co-crystallization of carbamazepine with the co-former saccharin significantly improves its physical stability and dissolution. This translated to a higher mean maximum plasma concentration (C_{max}) and similar median time to C_{max} (T_{max}) compared with the marketed form of carbamazepine in preclinical models [18]. Similarly, co-crystallization of ibuprofen and nicotinamide enhances the solubility of ibuprofen [19, 20]. Although their physicochemical properties may be altered, APIs retain their biological activity within the co-crystal structure as they are not modified covalently [21].

Co-crystals containing two or more APIs represent the next generation in co-crystal technology and offer a novel approach to multimodal therapy [22]. A number of such co-crystals have been identified, although only one (a complex comprised of anionic forms of sacubitril and valsartan, sodium cations and water molecules) licensed for use in chronic heart failure (Entresto®; Novartis, Basel, Switzerland) [23] has so far been approved. As described in the label, the valsartan in Entresto is more bioavailable than the valsartan in other marketed tablet formulations – i.e. '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' [23].

Co-crystal-associated changes in physicochemical properties that may modify PK parameters do not necessarily lead to an improved clinical benefit over the single API. In the examples above, increases in exposure are reflected in dose

adjustments to maintain efficacy and safety. The first-in-class co-crystal of tramadol–celecoxib (CTC) presents a different concept supported by *in vitro* and phase I data after a single dose [24]; neither tramadol nor celecoxib from CTC show increased exposure levels compared with the individual authorized tramadol or celecoxib, but rather show a change in profile that may translate into clinical benefits *per se*. One aspect of CTC based on its individual API PK and pharmacodynamic profiles is the hypothesis of CTC-associated improved efficacy with reduced doses of each API. In this vein, to understand the safety of CTC, we will have to wait for the results of efficacy clinical trials. We will then know the real benefit–risk relationship for CTC and therefore its real therapeutic benefit.

CTC is in development by Esteve Pharmaceuticals (as E-58425) and Mundipharma Research (as MR308) for the treatment of acute pain. The final immediate-release (IR) tablet formulation of CTC combines racemic tramadol hydrochloride (*rac*-tramadol.HCl) and celecoxib at an intrinsic 1:1 molecular ratio (1:1.27 weight ratio) conferred by the co-crystal structure. CTC represents a rational approach to multimodal analgesia, combining four mechanisms of action. Tramadol is a weak mu-opioid receptor agonist and inhibits the reuptake of serotonin and noradrenaline, and its main active metabolite, (+)-O-desmethyl-tramadol (M1), has a much greater affinity for the mu-opioid receptor than tramadol itself [25], while celecoxib selectively inhibits cyclooxygenase-2 [26]. In a rat model of postoperative pain, a form of CTC co-crystal without additives in suspension ('CTC_{susp}') demonstrated synergistic analgesia (i.e. efficacy greater than that predicted by the addition of the individual analgesic effects of *rac*-tramadol.HCl and celecoxib alone). In addition, CTC_{susp} displayed comparable efficacy to the morphine and oxycodone in this model but with an improved safety profile [27]. Intrinsic dissolution studies have shown that the release profiles of tramadol and celecoxib from the co-crystal are modified compared with those from each reference drug [28]. Such effects have the potential to optimize the PK profiles, and thus efficacy and safety, of each API in CTC. In a single-dose phase I study of CTC, the PK characteristics of tramadol and celecoxib from CTC were modified by co-crystallization relative to IR tramadol or celecoxib alone and the open combination of these reference products [24]. These changes in PK parameters could translate into a real therapeutic benefit, to be determined in phase II and III clinical trials.

The main objective of the present phase I study was to compare the PK profile of CTC with that of each authorized reference product alone and in open combination after single (first dose) and multiple dosing. The safety and tolerability of CTC following single (first dose) and multiple dosing were also evaluated.

Methods

Study subjects

Males and nonpregnant, nonlactating females aged 18–50 years with a body mass index of ≥18.5 and <29.0 kg m^{-2} were eligible for inclusion in the study if they were non- or ex-smokers and in good general health, as determined by medical history, physical examination, electrocardiogram (ECG) and standard clinical laboratory tests. Individuals were excluded if they had a history of significant hypersensitivity to tramadol, celecoxib, opioids, sulphonamides or any related products; a history of severe hypersensitivity reaction to any drug; a significant history of drug dependency or alcohol abuse; a condition that may have affected the PK profile of the study drugs; or used systemic contraception, hormone replacement therapy, monoamine oxidase inhibitors or enzyme-modifying drugs within 4 weeks of the start of the study (see Appendix S1 for full inclusion and exclusion criteria).

Study design and treatments

This was a randomized, open-label, four-period, four-sequence, crossover, single- and multiple-dose study performed in a single centre in Canada. Four treatments were administered under fasting conditions (Figure 1). The order in which treatments were received by each subject was assigned from a computer-generated randomization list. The four treatments were: treatment 1: 2 × 100 mg IR CTC tablets (200 mg; equivalent to 88 mg *rac*-tramadol.HCl and 112 mg

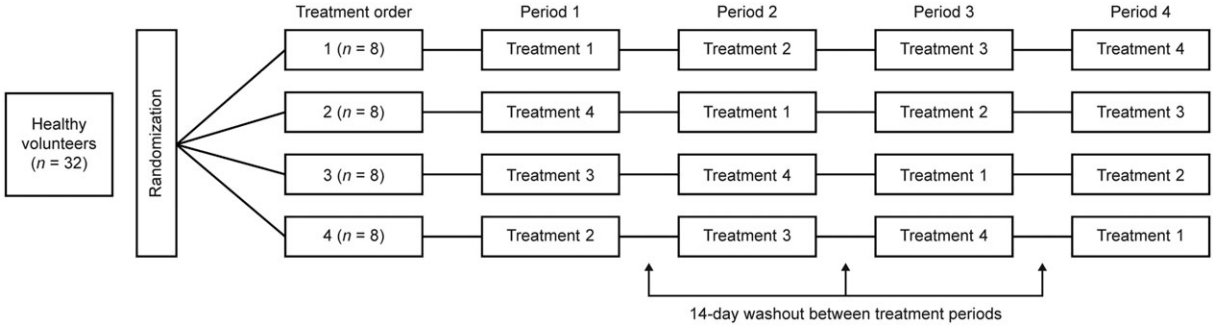

Figure 1

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 IR tramadol (2 × 50 mg capsules) plus 100 mg celecoxib (1 × 100 mg capsule). CTC, co-crystal of Ttramadol–celecoxib; IR, immediate-release

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®, Pfizer Manufacturing Deutschland GmbH, Karlsruhe, Germany); and treatment 4: open combination of 100 mg IR tramadol (*rac*-tramadol.HCl; 2 × 50 mg capsules) and 100 mg celecoxib (1 × 100 mg capsule).

Each treatment period was separated by a washout period of ≥14 days. Treatments were administered orally twice daily with 240 ml water (12 h apart, in the morning and evening) for 7 days, with a final dose in the morning of day 8 (15 doses in total). Morning doses were administered following a fast of at least 10 h and evening doses following a fast of at least 2 h. On days 1 and 8, fasting continued for at least 4 h following the first and 15th treatments. Standardized meals and snacks were provided postdose at approximately the same time throughout the study. Water was provided *ad libitum* until 1 h predose and allowed approximately 1 h after each dose. Volunteers were instructed not to take any non-investigator-approved prescription medications or over-the-counter products during the study and to avoid alcohol, and grapefruit-, pomelo- or xanthine-containing food or drink. Strenuous activity was restricted.

The study protocol was approved by an institutional review board (project number 2167, approved on 24 November 2011 by ETHIPRO; Montreal, QC, Canada) and the study was performed in compliance with Good Clinical Practice, the Declaration of Helsinki and relevant US, European and Canadian standards. Written informed consent was provided by all subjects.

PK sampling and analytical methods

For the single-dose part of the study, blood samples for PK measurements were collected prior to drug administration and at the following times postdose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h. For the multiple-dose part, samples were also collected: (i) within 5 min before the third (day 2), fifth (day 3), seventh (day 4), ninth (day 5), 11th (day 6), 13th (day 7) and 14th (day 7) drug administrations; and (ii) within 5 min before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72 h following the 15th (day 8) administration.

Blood samples were collected and centrifuged (1500 *g* for 10 min at 4°C) to obtain plasma, which was separated into duplicate tubes 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 solid phase extraction of tramadol, M1 and celecoxib and their internal standards (propranolol and E-6087, respectively) from 0.050 ml of human plasma. These compounds were identified and quantified over a theoretical concentration range of 4.00–640.00 ng ml^{-1} for tramadol, 1.00–160.000 ng ml^{-1} for M1 and 2.50–1000.00 ng ml^{-1} for celecoxib. Assay inter-run precision (coefficient of variation) and accuracy (nominal values) were 8.3% and 102.5%, respectively, for tramadol; 10.1% and 105.2% for M1; and 10.5% and 107.8% for celecoxib. Assay specificity was assessed by employing six independent sources of matrix and verifying for the absence of interference, compared with the respective limit of quantifications at the retention times and mass transitions of analytes and internal standards. Quantitation was carried out using peak area ratios, and back-calculated concentrations were determined using least squares regression analysis employing a weighted ($1/x^2$) linear regression.

Safety assessments

Safety was assessed by monitoring AEs and by evaluation of standard clinical laboratory parameters, physical and neurological examinations, and 12-lead ECG. AEs were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 15.1.

Data and statistical analyses

Sample size determination. As this was a descriptive study to characterize the PK of CTC following multiple doses, no hypothesis testing was planned. A sample size of 32 was estimated to be adequate based on judgements regarding PK properties and accounting for potential dropouts.

PK parameters. For the single-dose part of the study (first dose), the main PK parameters, calculated using noncompartmental analysis, were C_{max}, cumulative area under the plasma concentration–time curve (AUC_τ), measured concentration at the end of the dosing interval (C_t) and T_{max}. For the multiple-dose part of the study (last dose), the main PK parameters, calculated using noncompartmental analysis, were C_{max} at steady state ($C_{max,ss}$), C_t at steady state ($C_{\tau,ss}$), average plasma concentration during dosing interval (C_{avg}), AUC_τ at steady state ($AUC_{\tau,ss}$), trough concentration or predose concentration measured at a specific time (C_{pd}) and T_{max} at steady state ($T_{max,ss.}$). Additional PK parameters were calculated following the last drug administration in each study period and provided for information purposes only.

Statistical analyses of PK data were performed in SAS® version 9.0 (SAS Institute, Cary, NC, USA). Parameters were calculated, as above-mentioned, using noncompartmental analysis (non-adjusted and adjusted to the 100 mg doses of the reference products) with a log-linear terminal phase assumption. An analysis of variance (ANOVA) model was used to analyse all PK parameters with subject effect (nested within sequence), treatment, period and sequence as fixed factors. The natural logarithmic transformation of C_{max}, AUC_τ and C_t adjusted to dose for the single-dose part of the study, and of $C_{max,ss}$, $C_{\tau,ss}$, C_{avg} and $AUC_{\tau,ss}$ adjusted to dose for the multiple-dose part of the study were used for all statistical inference. Additional PK parameters were calculated following the last drug administration in each study period and provided for information purposes only. The 90% confidence interval (CI) for the exponential difference in least squares (LS) means between each comparison was calculated for the ln-transformed parameters. Subjects who provided evaluable PK data for a particular treatment

were included in the descriptive analysis of that treatment; those who provided evaluable PK data for both treatments under comparison were included in the PK and statistical analysis. An additional ANOVA model was used to determine if each analyte had reached steady state after multiple doses of CTC.

Safety. Safety data were analysed using descriptive statistics. Safety was assessed in subjects who received ≥1 dose of study treatment.

Results

Subjects

Thirty-two subjects were enrolled between 10 October and 23 December 2013. The majority were male (62.5%) and white (71.9%); mean age was 35 years (standard deviation: 9) (Table 1). Eight subjects withdrew/were withdrawn before the end of the study for personal reasons unrelated to clinical events (n = 4), personal reasons related to clinical events (n = 2) or a positive amphetamine test (n = 2). Twenty-nine, 30, 28 and 28 subjects received CTC, tramadol alone, celecoxib alone and the open combination of tramadol and celecoxib, respectively.

PK of tramadol, M1 and celecoxib after administration of CTC

PK parameters for tramadol, its M1 metabolite and celecoxib after single and multiple doses of CTC are summarized in Table 2. Plasma concentration–time profiles for these analytes during multiple dosing are shown in Figure 2. For tramadol, it was not proven statistically that steady state had been reached after the final dose of CTC. However, this finding was not considered clinically relevant. It was proven that steady state had been reached for M1 and celecoxib.

Table 1

Subject demographics (n = 32)

Characteristic	
Age, years	35 (9)
Gender, *n* (%)	
Male	20 (62.5)
Female	12 (37.5)
Race, *n* (%)	
White	23 (71.9)
Black	6 (18.8)
Asian	2 (6.3)
Other	1 (3.1)
Weight, kg	73.9 (10.8)
Height, cm	169.7 (9.0)
Body mass index, kg m^{-2}	25.57 (2.24)

Data are mean (standard deviation) unless otherwise stated

Comparison of tramadol PK after different treatments

Single dose (first dose). Figure 3A shows mean plasma concentration–time curves for tramadol after a single dose of each tramadol-containing treatment. Key single-dose PK parameters for tramadol are summarized and statistically compared in Table 3. After dose adjustment, for C_{max}, 90% CIs for the ratio of geometric LS means (CTC *vs*. tramadol alone or *vs*. tramadol plus celecoxib) were outside the equivalence range of 80–125%. For AUC_{τ} and C_t, 90% CIs were within this range for both treatment comparisons (Table 3). Median T_{max} for tramadol from CTC was delayed (3.5 h) relative to tramadol alone and the open combination of tramadol and celecoxib (1.75 and 2.00 h, respectively).

Multiple dose (last dose). Mean tramadol plasma concentration–time profiles after multiple dosing are shown in Figure 3B. Key multiple-dose PK parameters for tramadol are summarized and statistically compared in Table 4. After dose adjustment, for the comparison of $C_{max,ss}$ between CTC and the open combination, the 90% CI of the LS means ratio fell outside the 80–125% range. For all other statistical comparisons (including those of $C_{\tau,ss}$, C_{avg} and $AUC_{\tau,ss}$), 90% CIs were within this range. Median $T_{max,ss}$ for tramadol was delayed by 1 h with CTC compared with both of the other tramadol-containing treatments (3.0 *vs*. 2.0 h). Tramadol accumulation ratios were similar across treatments (Table 4).

Comparison of M1 PK after different treatments

Single dose (first dose). Dose-adjusted M1 C_{max} was lower after a single dose of CTC compared with tramadol alone or in open combination with celecoxib (Figure 4A; Table 5). Similar values for C_t and AUC_{τ} were observed across treatments. The 90% CIs of the LS means C_{max} ratio for M1 were outside the equivalence range for both treatment comparisons. All other statistical comparisons were within this range (Table 5). Median T_{max} for M1 from CTC was delayed at 4.00 h (*vs*. 2.03 h for tramadol alone and 3.00 h for tramadol plus celecoxib).

Multiple dose (last dose). Findings for M1 after multiple dosing (Figure 4B; Table 6) were similar to those observed with single-dose treatment. Similar M1 accumulation ratios were obtained with each treatment.

Comparison of celecoxib PK after different treatments

Single dose (first dose). Mean celecoxib plasma concentration–time curves after single doses of each celecoxib-containing treatment are shown in Figure 5A. Single-dose PK parameters for celecoxib are summarized and compared in Table 7. After dose adjustment, the 90% CI of the LS means ratio for celecoxib AUC_{τ} were within the 80–125% range for CTC *vs*. the open combination of

Table 2

Summary of pharmacokinetic parameters for tramadol, M1 and celecoxib following single and multiple doses of 200 mg CTC[a] (n = 29)

		Tramadol		M1		Celecoxib	
Parameter		**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**
Single dose	C_{max} (ng ml^{-1})	219.99	25.2	41.37	44.5	275.86	37.4
	T_{max} (h)[b]	3.00	41.3	4.00	48.2	2.00	53.6
	AUC_{τ} (ng h ml^{-1})	1767.33	26.8	360.13	42.1	1436.43	32.1
	C_{τ} (ng ml^{-1})	98.38	44.1	23.67	37.4	47.59	38.7
Multiple dose	$C_{max,ss}$ (ng ml^{-1})	484.02	22.4	67.31	37.3	487.08	28.6
	$T_{max,ss}$ (h)[d]	3.00	32.4	3.00	37.1	2.00	55.9
	$AUC_{\tau,ss}$ (ng h ml^{-1})	4200.73	31.6	653.70	36.4	3088.81	28.6
	$C_{\tau,ss}$ (ng ml^{-1})	243.13	45.1	43.03	37.3	124.10	40.7
	C_{avg} (ng ml^{-1})	350.06	31.6	54.47	36.4	257.40	28.6
	Fluctuation (%)[c]	77.42	56.8	44.48	48.5	144.10	26.1
	AUC_{0-last} (ng h ml^{-1})	7427.52	49.9	1204.01	36.8	5431.19	34.8
	$T_{½el}$ (h)	8.93	24.8	9.76	20.1	12.32	30.8
	AUC_{∞} (ng h ml^{-1})	7667.96	49.6	1271.11	35.3	5686.07	32.9
	$AUC_{0-last/\infty}$ (%)	96.30	3.8	94.45	5.6	95.10	5.9
	K_{el} (h-^{1})	0.08	22.9	0.07	20.1	0.06	29.5
	$C_{pd\ -\ 24}$ (ng ml^{-1})	225.95	41.4	43.05	37.6	170.44	33.2
	$C_{pd\ -\ 12}$ (ng ml^{-1})	226.40	45.4	42.27	35.5	138.18	39.2
	$C_{pd\ 0}$ (ng ml^{-1})	237.65	42.8	43.58	37.6	176.18	40.1
	$C_{pd\ 12}$ (ng ml^{-1})	243.13	45.1	43.03	37.3	124.10	40.7
	$RA_{(C\tau)}$	2.55	22.7	1.90	23.4	2.68	27.3
	$RA_{(AUC)}$	2.39	17.4	2.02	35.0	2.21	22.7

AUC_{∞}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration–time curve calculated from 0 to last observed quantifiable plasma concentration; $AUC_{0-last/\infty}$, relative percentage of AUC_{0-last} with respect to AUC_{∞}; AUC_{τ}, area under the plasma concentration–time curve over the dosing interval after single dosing; $AUC_{\tau,ss}$, area under the plasma concentration–time curve over the dosing interval at steady state; C_{avg}, average plasma concentration during dosing interval; C_{max}, maximum observed plasma concentration; $C_{max,ss}$, maximum observed plasma concentration at steady state; C_{pd}, trough concentration or predose concentration measured at a specified time following a repeated dose regimen; CV, coefficient of variation; C_{τ}, measured concentration at the end of the dosing interval; CTC, co-crystal of tramadol–celecoxib; $C_{\tau,ss}$, measured concentration at the end of the dosing interval at steady state; K_{el}, apparent elimination rate constant; M1, (+)-O-desmethyl-tramadol; $RA_{(C\tau)}$, accumulation ratio $C_{\tau,ss}/C_{\tau}$; $RA_{(AUC)}$, accumulation ratio $AUC_{\tau,ss}/AUC_{\tau}$; $T_{½el}$, terminal elimination half-life; T_{max}, time to reach maximum observed plasma concentration; $T_{max,ss}$, time to reach maximum observed plasma concentration at steady state

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Median values shown

[c]Calculated from $([C_{max,ss}–C_{\tau,ss}]/C_{avg})*100$

tramadol and celecoxib (Table 7). The 90% CIs for all other comparisons were outside this range. Median celecoxib T_{max} after single-dose CTC was 2.00 h, compared with 3.00 h for celecoxib alone and 4.00 h for tramadol plus celecoxib.

Multiple dose (last dose). PK findings for celecoxib after multiple dosing are shown in Figure 5B and Table 8. After dose adjustment, the 90% CIs of the LS means ratio for $C_{max,ss}$ and $C_{\tau,ss}$ were outside the equivalence range for CTC compared with tramadol plus celecoxib, as were those of $C_{max,ss}$, C_{avg} and $AUC_{\tau,ss}$ for CTC *vs.* celecoxib alone. Accumulation ratios for celecoxib were similar across treatments (Table 8).

Safety

The number of subjects who reported ≥1 AE after administration of CTC, tramadol alone, celecoxib alone and the open combination of tramadol and celecoxib was 29 (45%), 26 (87%), 11 (39%) and 20 (71%), respectively. At least one treatment-related AE was reported by 12 (41%), 25 (83%), 10 (36%) and 19 (68%) subjects. Most AEs (78%) were mild in severity. AEs experienced by two or more subjects are shown in Table 9. By system organ class, gastrointestinal and nervous system disorder events were the most frequently reported AEs. Constipation was the most common individual AE, occurring in seven subjects with CTC and 10, two and eight subjects with tramadol alone, celecoxib alone, and tramadol plus celecoxib, respectively. Other AEs included somnolence, headache, dizziness and, less commonly, nausea and vomiting, hiccups and insomnia. No serious AEs or deaths occurred during the study.

There were no notable findings from other safety assessments. All abnormal laboratory values, with one exception,

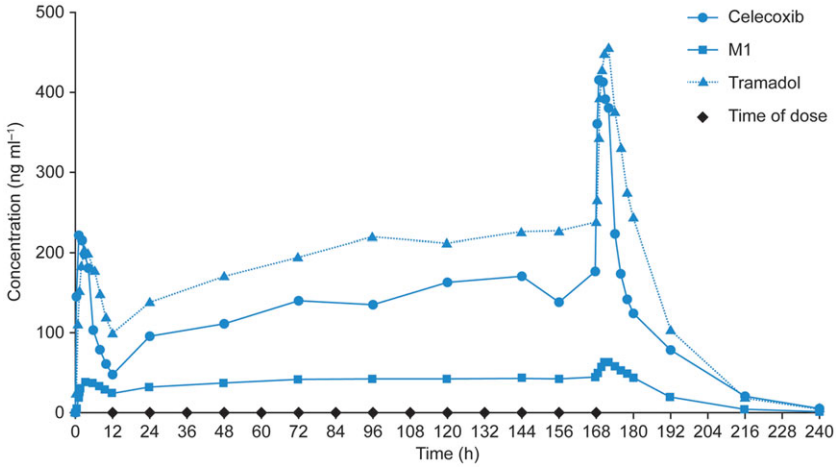

Figure 2

Mean plasma concentration–time curves for tramadol, M1 and celecoxib following multiple doses of 200 mg CTC (equivalent to 88 mg tramadol and 112 mg celecoxib). CTC, co-crystal of tramadol–celecoxib; M1, (+)-O-desmethyl-tramadol

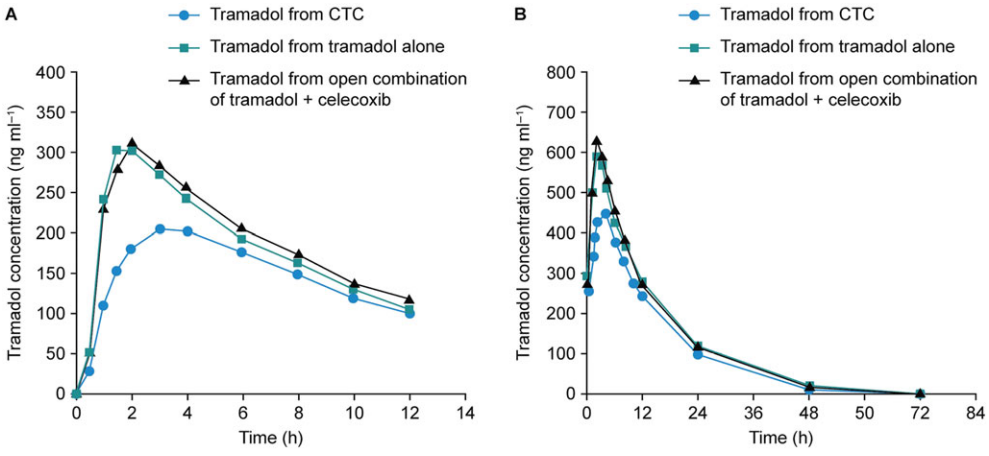

Figure 3

Mean plasma concentration–time curves for tramadol after single (A) and multiple (B) doses of CTC, tramadol alone and the open combination of tramadol and celecoxib. CTC, co-crystal of tramadol–celecoxib

were not considered to be clinically significant. One subject showed an abnormal alkaline phosphatase result at a poststudy visit that was considered clinically significant and reported as a mild AE. The last treatment administered to this subject was the open combination of celecoxib and tramadol.

Discussion

As pain is multifactorial, it is generally accepted that multimodal analgesia is optimal, targeting different physiological mechanisms [29]. This has led to an interest in the development of co-crystals as an innovative approach for multidrug delivery [22]. The present phase I study aimed to compare single- (after first dose) and multiple-dose (after last dose) PK profiles of CTC, a co-crystal of tramadol and celecoxib, with those of each reference product (IR tramadol and celecoxib) alone and in open combination. The study demonstrated that tramadol, its M1 metabolite and celecoxib accumulate within plasma after multiple doses of CTC to an extent similar to that observed after multiple doses of IR tramadol and celecoxib alone or in an open combination. Although it was not proven statistically that steady state was reached for tramadol after multiple doses of CTC, it can be assumed that this finding was not clinically relevant due to the high percentage of steady state reached for tramadol (based on C_{pd} values), the known elimination half-life of tramadol, the duration of treatment and the fact that the M1 metabolite of tramadol achieved steady state (as did celecoxib).

Table 3

Summary and statistical comparison of tramadol pharmacokinetic parameters following single doses of CTC, tramadol alone or the open combination of tramadol and celecoxib

Parameter	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 2: 100 mg tramadol (*n* = 30)		Treatment: 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% CI)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Treatment 1 *vs.* treatment 2	Treatment 1 *vs.* treatment 4
C_{max} (ng ml^{-1})	249.72[b]	25.7[b]	330.27	15.7	331.41	20.8	74.39 (69.95–79.11)	75.58 (71.16–80.29)
AUC_{τ} (ng h ml^{-1})	2011.47[b]	27.3[b]	2220.16	24.9	2299.81	23.8	90.35 (86.26–94.64)	88.20 (84.09–92.50)
C_t (ng ml^{-1})	113.04[b]	44.0[b]	102.38	45.7	113.73	38.7	112.43 (105.52–119.79)	100.08 (93.37–107.28)
T_{max} (h)[c]	3.50	40.8	1.75	39.7	2.00	29.3		

AUC_{τ}, area under the plasma concentration–time curve over the dosing interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_t, measured concentration at the end of the dosing interval; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; T_{max}, time to reach maximum observed plasma concentration

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for treatment 1 were adjusted according to reference dose

[c]Median values shown

Following multiple doses, and after dose adjustment, a co-crystal effect on both tramadol and celecoxib was observed. Tramadol $C_{max,ss}$ for CTC was lower compared with tramadol alone or in open combination with celecoxib, yet remained above levels required for efficacy [30]. Analysis of $C_{\tau,ss}$, C_{avg} and $AUC_{\tau,ss}$ for tramadol from CTC compared with the other tramadol-containing treatments suggested that similar levels of exposure between treatments were achieved. The reduction in tramadol $C_{max,ss}$ observed with CTC is consistent with a lower intrinsic dissolution rate (as observed *in vitro*) and, consequently, a slower absorption of tramadol. Indeed, $T_{max,ss,}$ was slightly prolonged for tramadol from CTC compared with other treatments. Similar observations were made for the M1 metabolite. Tramadol PK parameters following multiple doses of 100 mg of tramadol alone were comparable with those observed when given in open combination with celecoxib. Tramadol C_{max} and T_{max} values were also similar to those reported in the literature [25, 31].

After multiple dosing, celecoxib from CTC showed a reduced AUC. Lower $C_{max,ss}$ and similar $T_{max,ss}$ compared with celecoxib alone was obtained, indicating a lower rate and extent of exposure of celecoxib after co-crystal administration. However, when celecoxib from CTC was compared with the co-administration of celecoxib and tramadol, absorption was faster and $C_{max,ss}$ was greater, albeit without a concomitant increase in exposure. This observed reduction in the C_{max} of celecoxib when it was administered as a free combination with tramadol may be due to the effects of tramadol on gastrointestinal motility (slowing down), and this is minimized with CTC. Therefore, this suggests that co-crystallization of the two APIs improves the PK profile of celecoxib and avoids the apparent effects on dissolution and absorption that occur when the two drugs are co-administered. This is also consistent with changes in the intrinsic dissolution rate of celecoxib from CTC. As expected, intrasubject variabilities in measured PK parameters (quantified as the coefficient of variation) were greater for celecoxib than for tramadol. It is unlikely, however, that this greater variability reduces the certainty of conclusions drawn around the celecoxib data in the present study. Of note, all multiple-dose PK findings, including those for celecoxib, were consistent with the single-dose data collected in the present study and in a separate phase I study of CTC [24].

The potential clinical implications of the PK profile for CTC observed in the present study remain to be determined. However, in theory, a reduced tramadol C_{max} may translate into improved safety and tolerability. CTC was well tolerated in the present study, and the AEs observed were consistent with the safety profile of tramadol [30]. In aggregate, based on a descriptive analysis, a reduction in opioid-related AEs (e.g. dizziness, nausea, vomiting and severe constipation) was observed with CTC compared with other tramadol-containing treatments. This effect could potentially be attributed to the lower tramadol C_{max}, as there is a dose–response effect on the incidence of AEs for tramadol [32]. Also, the faster celecoxib T_{max} with CTC could translate into an earlier onset of analgesia and warrants further investigation. Our results demonstrate that simple co-administration of authorized tramadol and

Table 4

Summary and statistical comparison of tramadol pharmacokinetic parameters following multiple doses of CTC, tramadol alone or the open combination of tramadol and celecoxib

Parameter	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 2: 100 mg tramadol (*n* = 30)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometricLS means (90% CI)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Treatment 1 *vs.* treatment 2	Treatment 1 *vs.* treatment 4
$C_{max,ss}$ (ng ml^{-1})	551.19[b]	22.7[b]	631.97	23.8	661.24	25.2	87.55 (80.41–95.32)	84.42 (77.59–91.84)
$C_{\tau,ss}$ (ng ml^{-1})	279.89[b]	44.8[b]	257.13	44.1	274.51	43.3	108.38 (103.42–113.57)	103.62 (99.39–108.04)
C_{avg} (ng ml^{-1})	399.62[b]	31.9[b]	415.85	29.9	440.35	32.1	95.71 (92.47–99.06)	91.91 (88.50–95.45)
$AUC_{\tau,ss}$ (ng h ml^{-1})	4795.47[b]	31.9[b]	4990.17	29.9	5284.17	32.1	95.71 (92.47–99.06)	91.91 (88.50–95.45)
$T_{max,ss}$ (h)[c]	3.0	33.0	2.0	34.7	2.0	35.9		
AUC_{0-last} (ng h ml^{-1})	7502.19	50.1	8579.33	48.3	9003.85	46.5		
AUC_{∞} (ng h ml^{-1})	7749.40	49.6	8749.72	48.1	9350.52	49.3		
$AUC_{0-last/\infty}$ (%)	96.20	3.8	97.70	2.5	96.54	4.3		
Fluctuation (%)[d]	76.65	58.2	96.25	34.5	93.83	31.0		
K_{el} (h^{-1})	0.08	23.2	0.08	24.8	0.08	25.8		
$T_{½el}$ (h)	9.00	24.7	8.82	22.5	8.94	27.9		
$C_{pd\ -\ 24}$ (ng ml^{-1})	227.35	41.8	272.22	43.4	286.89	41.8		
$C_{pd\ -\ 12}$ (ng ml^{-1})	229.26	45.2	254.10	42.2	267.08	45.4		
$C_{pd\ 0}$ (ng ml^{-1})	239.42	43.1	267.08	40.6	277.22	43.3		
$C_{pd\ 12}$ (ng ml^{-1})	246.31	44.8	257.13	44.1	274.51	43.3		
$RA_{(C\tau)}$	2.56	22.9	2.65	30.0	2.48	26.1		
$RA_{(AUC)}$	2.40	17.6	2.25	18.4	2.28	17.4		

AUC_{∞}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration–time curve calculated from 0 to last observed quantifiable plasma concentration; $AUC_{0-last/\infty}$, relative percentage of AUC_{0-last} with respect to AUC_{∞}; $AUC_{\tau,ss}$, area under the plasma concentration–time curve over the dosing interval at steady state; C_{avg}, average plasma concentration during dosing interval; CI, confidence interval; $C_{max,ss}$, maximum observed plasma concentration at steady state; C_{pd}, trough concentration or predose concentration measured at a specified time following a repeated dose regimen; CTC, co-crystal of tramadol–celecoxib; $C_{\tau,ss}$, measured concentration at the end of the dosing interval at steady state; CV, coefficient of variation; K_{el}, apparent elimination rate constant; LS, least squares; $RA_{(C\tau)}$, accumulation ratio $C_{\tau,ss}/C_{\tau}$; $RA_{(AUC)}$, accumulation ratio $AUC_{\tau,ss}/AUC_{\tau}$; $T_{½el}$, terminal elimination half-life; $T_{max,ss}$, time to reach maximum observed plasma concentration at steady state

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for treatment 1 were adjusted according to reference dose

[c]Median values shown

[d]Calculated from $([C_{max,ss}–C_{\tau,ss}]/C_{avg})*100$

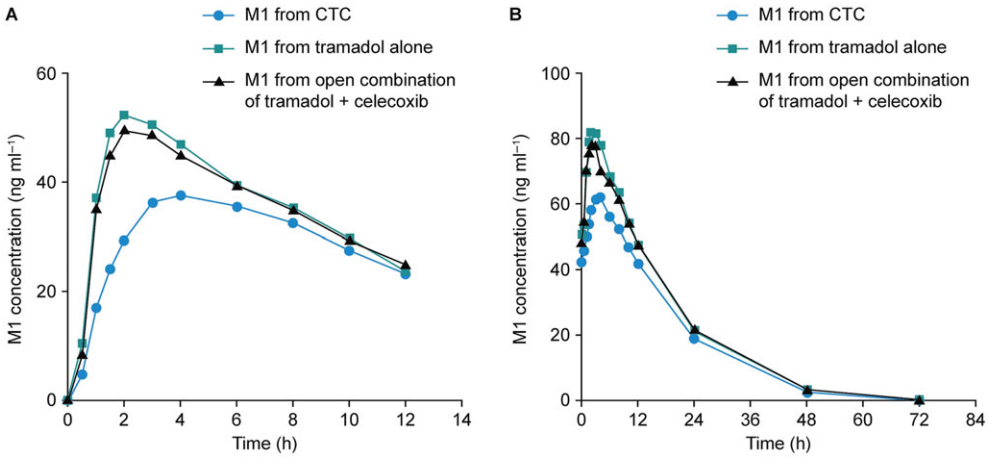

Figure 4

Mean plasma concentration–time profiles for M1 following single (A) and multiple (B) doses of CTC, tramadol alone and the open combination tramadol and celecoxib. CTC, co-crystal of tramadol–celecoxib; M1, (+)-O-desmethyl-tramadol

Table 5

Summary and statistical comparison of M1 pharmacokinetic parameters following single doses of CTC, tramadol alone or the open combination of tramadol and celecoxib

	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 2: 100 mg tramadol (*n* = 30)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% CI)	
Parameter	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Treatment 1 *vs.* treatment-2**	**Treatment 1 *vs.* treatment 4**
C_{max} (ng ml^{-1})	45.97[b]	44.6[b]	55.66	48.1	52.46	46.1	83.46 (76.81–90.67)	86.94 (79.97–94.52)
AUC_{τ} (ng h ml^{-1})	400.93[b]	42.3[b]	439.70	40.4	428.25	41.0	90.25 (85.86–94.86)	91.86 (86.14–97.97)
C_t (ng ml^{-1})	26.53[b]	37.9[b]	23.58	36.8	24.87	40.4	112.66 (107.27–118.33)	107.12 (100.14–114.59)
T_{max} (h)[c]	4.00	46.7	2.03	56.4	3.00	53.4		

AUC_{τ}, area under the plasma concentration–time curve over the dosing interval; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_t, measured concentration at the end of the dosing interval; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; M1, (+)-O-desmethyl-tramadol; T_{max}, time to reach maximum observed plasma concentration

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for treatment 1 were adjusted according to reference dose

[c]Median values shown

celecoxib does not replicate the PK profile of the co-crystal, and therefore its clinical effects are also likely to be different.

There were some limitations to the study. To have used noncompartmental analysis could limit the ability to determine C_{max} and T_{max} accurately. Another limitation was the requirement to perform dose adjustments prior to statistical comparison of treatments. This was due to the fact that the doses of APIs in CTC (88 mg tramadol and 112 mg celecoxib) differed from those in the commercially available formulations of tramadol and celecoxib. In addition, as treatments were given under fasting conditions, the effects of food on PK parameters were not evaluated. Another limitation arises from the fact that we do not know the role that the formulation of CTC played in the results obtained. In fact, we have no data based on comparative PK clinical trials in healthy volunteers between formulated CTC *vs*. unformulated CTC. However, based on our dissolution profile studies (internal data), unformulated CTC provides a unique dissolution profile, clearly different from the open combination, where CTC dissolves twice as fast as the open combination. This dissolution profile suggests that the outcomes obtained in the present study were due to CTC *per se*.

In conclusion, the study demonstrated that after single (first dose) and multiple dosing, the PK parameters of each API in CTC were modified by co-crystallization compared with reference products alone or in open combination. The potential implications of this unique profile should become clearer as clinical development progresses. A phase II trial comparing CTC with tramadol in patients with moderate to severe acute pain after oral surgery has been completed [33], and several phase III trials are ongoing.

Table 6

Summary and statistical comparison of M1 pharmacokinetic parameters following multiple doses of CTC, tramadol alone or the open combination of tramadol and celecoxib

	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 2: 100 mg tramadol (*n* = 30)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% confidence limits)	
Parameter	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Treatment 1 *vs.* treatment 2**	**Treatment 1 *vs.* treatment 4**
$C_{max,ss}$ (ng ml^{-1})	74.71[b]	36.6[b]	87.23	34.9	82.32	31.7	84.66 (78.18–91.67)	88.75 (82.34–95.66)
$C_{\tau,ss}$ (ng ml^{-1})	47.79[b]	36.7[b]	47.45	38.2	47.74	35.0	100.82 (95.01–106.99)	99.26 (93.97–104.85)
C_{avg} (ng ml^{-1})	60.33[b]	35.3[b]	65.97	34.6	63.48	31.3	91.20 (86.32–96.35)	93.53 (89.38–97.87)
$AUC_{\tau,ss}$ (ng h ml^{-1})	723.91[b]	35.3[b]	791.68	34.6	761.81	31.3	91.20 (86.32–96.35)	93.53 (89.38–97.87)
$T_{max,ss}$ (h)[c]	3.00	37.6	2.00	42.2	2.00	28.9		
AUC_{0-last} (ng h ml^{-1})	1178.39	36.4	1428.34	38.2	1402.01	35.3		
AUC_{∞} (ng h ml^{-1})	1246.81	35.0	1467.77	37.0	1447.35	33.7		
$AUC_{0-last/\infty}$ (%)	94.31	5.6	96.73	2.8	96.18	4.1		
Fluctuation (%)[d]	44.51	49.4	60.96	34.5	54.20	37.2		
K_{el} (h^{-1})	0.07	20.2	0.08	23.3	0.08	22.2		
$T_{½el}$ (h)	9.84	19.9	9.47	23.5	9.49	22.0		
$C_{pd\ -\ 24}$ (ng ml^{-1})	42.15	37.3	51.67	36.3	48.96	36.2		
$C_{pd\ -\ 12}$ (ng ml^{-1})	41.44	35.2	49.35	37.1	46.94	37.6		
$C_{pd\ 0}$ (ng ml^{-1})	42.43	36.4	50.81	38.1	47.99	34.8		
$C_{pd\ 12}$ (ng ml^{-1})	42.05	36.7	47.45	38.2	47.74	35.0		
$RA_{(C\tau)}$	1.89	23.8	2.10	25.9	2.07	31.8		
$RA_{(AUC)}$	2.02	35.6	1.98	30.0	2.00	36.9		

AUC_{∞}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration–time curve calculated from 0 to last observed quantifiable plasma concentration; $AUC_{0-last/\infty}$, relative percentage of AUC_{0-last} with respect to AUC_{∞}; $AUC_{\tau,ss}$, area under the plasma concentration–time curve over the dosing interval at steady state; C_{avg}, average plasma concentration during dosing interval; CI, confidence interval; $C_{max,ss}$, maximum observed plasma concentration at steady state; C_{pd}, trough concentration or predose concentration measured at a specified time following a repeated dose regimen; CTC, co-crystal of tramadol–celecoxib; $C_{\tau,ss}$, measured concentration at the end of the dosing interval at steady state; CV, coefficient of variation; K_{el}, apparent elimination rate constant; LS, least squares; M1, (+)-O-desmethyl-tramadol; $RA_{(C\tau)}$, accumulation ratio $C_{\tau,ss}/C_{\tau}$; $RA_{(AUC)}$, accumulation ratio $AUC_{\tau,ss}/AUC_{\tau}$; $T_{½el}$, terminal elimination half-life; $T_{max,ss}$, time to reach maximum observed plasma concentration at steady state

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for treatment 1 were adjusted according to reference dose

[c]Median values shown

[d]Calculated from $([C_{max,ss}–C_{\tau,ss}]/C_{avg})*100$

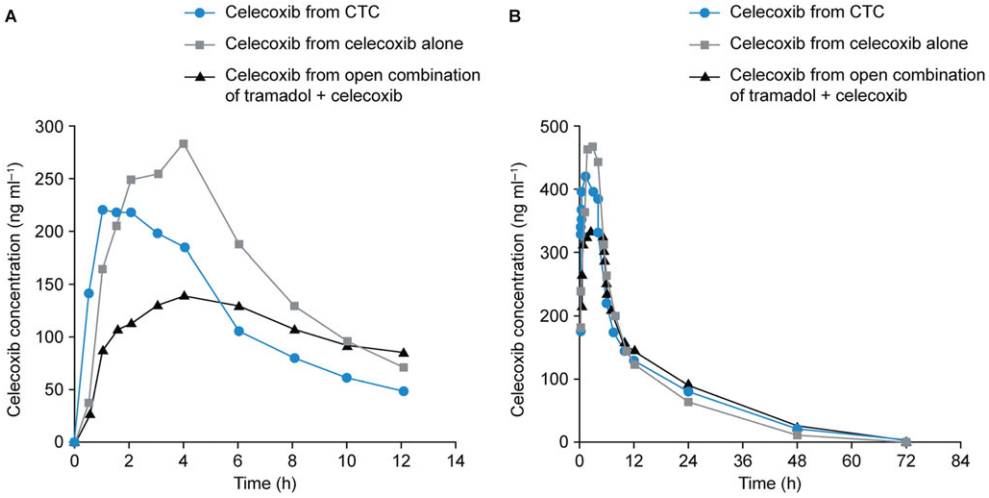

Figure 5

Mean plasma concentration–time profiles for celecoxib following single (A) and multiple (B) doses of CTC, celecoxib alone and the open combination tramadol and celecoxib. CTC, co-crystal of tramadol–celecoxib

Table 7

Summary and statistical comparison of celecoxib pharmacokinetic parameters following single doses of CTC, celecoxib alone or the open combination of tramadol and celecoxib

	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment-3: 100 mg celecoxib (*n* = 28)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% CI)	
Parameter	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Treatment 1 *vs.* treatment 3**	**Treatment 1 *vs.* treatment 4**
C_{max} (ng ml^{-1})	246.52[b]	38.8[b]	358.23	36.6	202.26	36.9	69.45 (59.52–81.03)	123.20 (101.83–149.06)
AUC_{τ} (ng h ml^{-1})	1287.36[b]	32.9[b]	1928.95	34.8	1255.78	30.0	67.26 (61.88–73.11)	102.68 (90.99–115.87)
C_t (ng ml^{-1})	42.79[b]	39.7[b]	71.97	37.5	83.03	60.7	58.58 (53.63–63.98)	54.17 (46.49–63.11)
T_{max} (h)[c]	2.00	51.9	3.00	45.3	4.00	72.5		

AUC_{τ}, area under the plasma concentration–time curve over the dosing interval after single dosing; CI, confidence interval; C_{max}, maximum observed plasma concentration; C_t, measured concentration at the end of the dosing interval; CTC, co-crystal of tramadol–celecoxib; CV, coefficient of variation; LS, least squares; T_{max}, time to reach maximum observed plasma concentration

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for Treatment-1 were adjusted according to reference dose

[c]Median values shown

Table 8

Summary and statistical comparison of celecoxib pharmacokinetic parameters following multiple doses of CTC, celecoxib alone or the open combination of tramadol and celecoxib

	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 3: 100 mg celecoxib (*n* = 28)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% CI)	
Parameter	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Mean**	**CV (%)**	**Treatment 1 *vs.* treatment 3**	**Treatment 1 *vs.* treatment 4**
$C_{max,ss}$ (ng ml^{-1})	444.76[b]	27.4[b]	536.21	32.6	396.28	34.4	85.06 (78.89–91.72)	115.66 (105.43–126.88)
$C_{\tau,ss}$ (ng ml^{-1})	112.65[b]	41.0[b]	123.45	40.9	144.52	32.1	91.37 (83.68–99.78)	76.26 (71.65–81.17)

(*continues*)

Table 8

(Continued)

Parameter	Treatment 1: 200 mg CTC[a] (*n* = 29)		Treatment 3: 100 mg celecoxib (*n* = 28)		Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)		Ratio of geometric LS means (90% CI)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Treatment 1 *vs.* treatment 3	Treatment 1 *vs.* treatment 4
C_{avg} (ng ml^{-1})	233.59[b]	28.4[b]	280.48	26.5	241.44	31.0	83.22 (79.11–87.54)	97.83 (93.07–102.83)
$AUC_{\tau,ss}$ (ng h ml^{-1})	2803.12[b]	28.4[b]	3365.80	26.5	2897.29	31.0	83.22 (79.11–87.54)	97.83 (93.07–102.83)
$T_{max,ss}$ (h)[c]	2.00	57.4	2.00	35.4	3.00	45.1		
AUC_{0-last} (ng h ml^{-1})	5544.34	34.5	5196.90	34.6	5564.37	34.3		
AUC_{∞} (ng h ml^{-1})	5810.35	32.4	5342.87	33.5	5823.14	34.1		
$AUC_{0-last/\infty}$ (%)	94.93	6.1	96.96	2.6	95.57	5.2		
Fluctuation (%)[d]	146.07	25.6	148.07	28.0	103.28	22.7		
K_{el} (h^{-1})	0.06	28.5	0.07	21.4	0.06	23.2		
$T_{½el}$ (h)	12.55	30.0	9.99	29.9	11.93	30.4		
$C_{pd\ -\ 24}$ (ng ml^{-1})	173.35	33.3	165.95	41.6	197.57	40.6		
$C_{pd\ -\ 12}$ (ng ml^{-1})	139.99	39.9	133.8	35.6	172.99	45.9		
$C_{pd\ 0}$ (ng ml^{-1})	180.81	39.3	181.68	39.6	216.32	39.1		
$C_{pd\ 12}$ (ng ml^{-1})	126.17	41.0	123.45	40.9	144.52	32.1		
$RA_{(C\tau)}$	2.71	27.4	1.74	24.8	1.99	32.4		
$RA_{(AUC)}$	2.24	22.6	1.82	23.1	2.45	35.3		

AUC_{∞}, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration–time curve calculated from 0 to last observed quantifiable plasma concentration; $AUC_{0-last/\infty}$, relative percentage of AUC_{0-last} with respect to AUC_{∞}; $AUC_{\tau,ss}$, area under the plasma concentration–time curve over the dosing interval at steady state; C_{avg}, average plasma concentration during dosing interval; CI, confidence interval; $C_{max,ss}$, maximum observed plasma concentration at steady state; C_{pd}, trough concentration or predose concentration measured at a specified time following a repeated dose regimen; CTC, co-crystal of tramadol–celecoxib; $C_{\tau,ss}$, measured concentration at the end of the dosing interval at steady state; CV, coefficient of variation; K_{el}, apparent elimination rate constant; LS, least squares; $RA_{(C\tau)}$, accumulation ratio $C_{\tau,ss}/C_{\tau}$; $RA_{(AUC)}$, accumulation ratio $AUC_{\tau,ss}/AUC_{\tau}$; $T_{½el}$, terminal elimination half-life; $T_{max,ss}$, time to reach maximum observed plasma concentration at steady state

[a]Equivalent to 88 mg tramadol and 112 mg celecoxib

[b]Parameters for treatment 1 were adjusted according to reference dose

[c]Median values shown

[d]Calculated from $([C_{max,ss}–C_{\tau,ss}]/C_{avg})*100$

Table 9

Adverse events reported in at least two subjects

System organ class	Adverse event	Treatment 1: 200 mg CTC[a] (*n* = 29)	Treatment 2: 100 mg tramadol (*n* = 30)	Treatment 3: 100 mg celecoxib (*n* = 28)	Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)
Gastrointestinal disorders	Constipation	7 / 8	10 / 10	2 / 2	8 / 8
	Severe constipation	0 / 0	2 / 2	0 / 0	4 / 4
	Dry lips	1 / 1	1 / 1	0 / 0	0 / 0
	Nausea	1 / 1	5 / 5	1 / 1	5 / 6
	Vomiting	0 / 0	2 / 2	0 / 0	2 / 2
General disorders and administration site conditions	Fatigue	0 / 0	1 / 1	1 / 1	1 / 1
	Feeling hot	0 / 0	1 / 1	0 / 0	1 / 1
		1 / 1	1 / 1	0 / 0	1 / 1

(*continues*)

Table 9

(Continued)

System organ class	Adverse event	Treatment 1: 200 mg CTC[a] (*n* = 29)	Treatment 2: 100 mg tramadol (*n* = 30)	Treatment 3: 100 mg celecoxib (*n* = 28)	Treatment 4: 100 mg tramadol + 100 mg celecoxib (*n* = 28)
Injury, poisoning and procedural complications	Vessel puncture site pain				
Nervous system disorders	Dizziness	0 / 0	6 / 7	0 / 0	4 / 5
	Headache	0 / 0	7 / 7	0 / 0	3 / 3
	Somnolence	5 / 7	7 / 12	6 / 6	8 / 11
Psychiatric disorders	Insomnia	1 / 1	1 / 1	0 / 0	2 / 2
Respiratory thoracic and mediastinal disorders	Hiccups	0 / 0	0 / 0	0 / 0	3 / 3

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

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 the clinical research organization Algorithme Pharma.

The authors acknowledge the following employees from Laboratorios del Dr. Esteve for their contribution to this study: Carmen Santano, Noemí Álvarez, Imma Cervera (Pharmaceutical Innovation); Esther Ortiz, Alberto Puyada (Clinical Investigation); Carmen Garcia (R&D Portfolio Management); Mercedes Encabo, Santiago Puig, Josep Maria Cendrós (ADME and Bioanalysis); and Fina Camacho (Quality Assurance). The study was funded by Laboratorios del Dr. Esteve, S.A.U. (Barcelona, Spain) and carried out by Algorithme Pharma, a clinical research organization (Laval, QC, Canada). Medical writing support was provided by Alice Wareham PhD (Aspire Scientific Ltd, Bollington, UK) and was funded by Mundipharma Research GmbH & Co. KG (Limburg, Germany). Monitoring support was provided by Vahe Bartekian and Vatché Bartekian (Vantage Biotrials, Montreal, QC, Canada).

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.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, *et al*. The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: G protein-coupled receptors. Br J Pharmacol 2015; 172: 5744–869.

3 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al*. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

4 Boya H. Pain pathways and analgesics. In: Musculoskeletal Research and Basic Science, ed Korkusuz F. Cham, Switzerland: Springer International Publishing, 2016; 641–50.

5 American Society of Anesthesiologists Task Force on Acute Pain. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on acute pain management. Anesthesiology 2012; 116: 248–73.

6 Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anaesthesiol 2010; 23: 697–703.

7 Moore RA, Derry CJ, Derry S, Straube S, McQuay HJ. A conservative method of testing whether combination analgesics produce additive or synergistic effects using evidence from acute pain and migraine. Eur J Pain 2012; 16: 585–91.

8 Raffa RB, Clark-Vetri R, Tallarida RJ, Wertheimer AI. Combination strategies for pain management. Expert Opin Pharmacother 2003; 4: 1697–708.

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

10 Mehlisch DR, Aspley S, Daniels SE, Southerden KA, Christensen KS. A single-tablet fixed-dose combination of racemic ibuprofen/paracetamol in the management of moderate to severe postoperative dental pain in adult and adolescent patients: a multicenter, two-stage, randomized, double-blind, parallel-group, placebo-controlled, factorial study. Clin Ther 2010; 32: 1033–49.

11 Moore RA, McQuay HJ, Tomaszewski J, Raba G, Tutunaru D, Lietuviete N, *et al*. Dexketoprofen/tramadol 25 mg/75 mg: randomised double-blind trial in moderate-to-severe acute pain after abdominal hysterectomy. BMC Anesthesiol 2016; 16: 1–14.

12 Camu F, Beecher T, Recker DP, Verburg KM. Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. Am J Ther 2002; 9: 43–51.

13 Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. Br J Anaesth 2003; 90: 166–72.

14 Malan TP Jr, Marsh G, Hakki SI, Grossman E, Traylor L, Hubbard RC. Parecoxib sodium, a parenteral cyclooxygenase 2 selective inhibitor, improves morphine analgesia and is opioid-sparing following total hip arthroplasty. Anesthesiology 2003; 98: 950–6.

15 Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005; 102: 1240–60.

16 Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharm Ther 2001; 26: 257–64.

17 European Medicines Agency. Reflection paper on the use of cocrystals of active substances in medicinal products. 2015. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500189927.pdf (last accessed 5 August 2016).

18 Hickey MB, Peterson ML, Scoppettuolo LA, Morrisette SL, Vetter A, Guzmán H, *et al*. Performance comparison of a co-crystal of carbamazepine with marketed product. Eur J Pharm Biopharm 2007; 67: 112–9.

19 Oberoi LM, Alexander KS, Riga AT. Study of interaction between ibuprofen and nicotinamide using differential scanning calorimetry, spectroscopy, and microscopy and formulation of a fast-acting and possibly better ibuprofen suspension for osteoarthritis patients. J Pharm Sci 2005; 94: 93–101.

20 Soares FLF, Carneiro RL. Evaluation of analytical tools and multivariate methods for quantification of co-former crystals in ibuprofen-nicotinamide co-crystals. J Pharm Biomed Anal 2014; 89: 166–75.

21 Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007; 59: 617–30.

22 Thipparaboina R, Kumar D, Chavan RB, Shastri NR. Multidrug co-crystals: towards the development of effective therapeutic hybrids. Drug Discov Today 2016; 21: 481–90.

23 Novartis. Summary of product characteristics for Entresto film-coated tablets. 2016. Available at http://www.medicines.org.uk/emc/medicine/31244 (last accessed 5 August 2016).

24 Videla S, Lahjou M, Vaqué A, Sust M, Encabo M, Soler L, *et al*. Single-dose pharmacokinetics of co-crystal of tramadol-Celecoxib: results of a four-way randomized open-label phase I clinical trial in healthy subjects. Br J Clin Pharmacol 2017; 83: 2718–28.

25 Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet 2004; 43: 879–923.

26 Pfizer. Summary of product characteristics for Celebrex 100 mg capsule. 2016. Available at http://www.medicines.org.uk/emc/medicine/14534 (last accessed 5 August 2016).

27 Merlos M, Portillo-Salido E, Brenchat A, Aubel B, Buxens J, Fisas À, Codony X, Romero L, Zamanilllo D, Vela J. Administration of tramadol and celecoxib in a 1:1 molecular ratio produces synergistic antinociceptive effects in postoperative pain models: preclinical rationale for clinical development of co-crystal of tramadol-celecoxib. 16th World Congress on Pain, 26–30 September 2016. Yokohama, Japan: Poster PW0290.

28 Almansa C, Mercè R, Tesson N, Farran J, Tomàs J, Plata Salamán CR. Co-crystal of tramadol hydrochloride-Celecoxib (ctc): a novel API-API co-crystal for the treatment of pain. Cryst Growth Des 2017; 17: 1884–92.

29 Raffa RB, Pergolizzi JV Jr, Tallarida RJ. The determination and application of fixed-dose analgesic combinations for treating multimodal pain. J Pain 2010; 11: 701–9.

30 Actavis. Summary of product characteristics for tramadol hydrochloride 50 mg capsules. 2015. Available at http://www.medicines.org.uk/EMC/medicine/24186/SPC (last accessed 05 August 2016).

31 Liao S, Hill J, Nayak R. Pharmacokinetics of tramadol following single and multiple oral doses in man [abstract]. Pharm Res 1992; (9 (Suppl.)): 308.

32 Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. Pain 1997; 69: 287–94.

33 Videla S, López-Cedrún J, Burgueño M, Juárez I, Aboul-Hosn S, Martín-Granizo R, *et al*. Co-crystal of tramadol-celecoxib: efficacy and safety results from a dose-finding, randomised, double-blind, multicentre, phase II clinical trial in patients with moderate to severe acute pain due to an oral surgical procedure. 16th World Congress on Pain, 26–30 September 2016. Yokohama, Japan: Poster PW0293.

Supporting Information

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

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13428/suppinfo

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