

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
208090Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 208090	Submission Date(s): 12/12/2014
Brand Name	Xtampza
Generic Name	Oxycodone Extended-release capsules
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Collegium Pharmaceutical Inc.
Relevant IND(s)	75,786
Submission Type; Code	Original NDA; 505(b)(2)
Formulation; Strength(s)	Xtampza capsule contains either 9, 13.5, 18, 27, or 36 mg of oxycodone (equivalent to 10, 15, 20, 30, or 40 mg of oxycodone HCl, respectively)
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Proposed Dosage Regimen	Titrate to effect with a twice a day regimen.

This is an addendum to the clinical pharmacology review from 9/8/2015.

The food-effect of Xtampza was discussed at the Advisory committee meeting on September 11, 2015. The committee discussed the potential safety risks and the potential effects on efficacy associated with the extent of the food effect, as well as potential fluctuations in plasma oxycodone levels that may occur if the product is not taken consistently with the same amount of food. In addition, the committee was asked to review and discuss whether the data characterizing the abuse-deterrent properties support the likelihood that this drug product will have a meaningful effect on abuse, and whether potential benefits to the public from abuse-deterrent properties outweigh potential risks to patients from the effect of food. The committee was asked to vote on whether this product should be approved for marketing in the United States. The Advisory Committee recommended unanimous approval probably based on the following reasons:

- The sponsor conducted their clinical studies per Agency recommendations during the clinical development program:
 - Attempted reformulation of the product.

- Evaluated the food-effect in several PK studies, including single dose studies and multiple dose study.
- Evaluated the food-effect on efficacy and safety in a Phase 3 clinical trial recommended by the Division and no obvious evidence that switching meal type had an impact on the safety and efficacy profile.
- The target population is patient with chronic pain who needs around the clock pain management. Although the recommendation to take the product with food is not consistent with most opioid ER product label, the committee believes that this patient population may comply well with the label recommendation to take the drug with food. In addition, the committee believes that the benefits of being able to sprinkle the contents of this product on applesauce or in a feeding tube will be very helpful for patients who cannot swallow an entire tablet or capsule.
 - AC recommended that the product be labeled so patients take it consistently with food.
- The committee thought the product, although not perfect, is an incremental improvement in terms of abuse-deterrent characteristics.

The potential effect of naltrexone block on the food effect was mentioned by the Sponsor in the meeting. The Division commented that based on current data, there is no convincing evidence to support that naltrexone block can affect the food effect of Xtampza. To address this question, a four-way cross-over food effect study with and without naltrexone block will be the best solution. However, whether naltrexone block will affect the food effect of Xtampza did not affect the committee's decision. The committee believes that the available data, including the multiple dose PK study, the Phase 3 clinical trial, and the abuse deterrent studies are adequate to make the decision.

After the Advisory committee meeting, a required office level briefing in Office of Clinical Pharmacology was held on September 15, 2015. It was agreed that this NDA is acceptable from clinical pharmacology perspective based on totality of the data. The labeling recommendation with regard to food was also discussed. It was agreed that the Xtampza should be labeled as taken with food; however, the amount and type of the food does not need to be specified in the label.

Labeling Recommendations: The following labeling changes are recommended in the proposed product label. Additions are indicated in bold font, and deletions are indicated as strikethrough text:

Highlights

Dosage and Administration

- Instruct patients to take XTAMPZA ER capsules (b) (4)

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

XTAMPZA ER is administered twice daily, every 12 hours [REDACTED] (b) (4)

2.3 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at 1/3 to 1/2 the usual starting dose followed by careful dose titration. Monitor closely for adverse events such as respiratory depression [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

2.6 Administration of XTAMPZA ER

Instruct patients to always take XTAMPZA ER capsules with food [REDACTED] (b) (4)

[REDACTED] (b) (4)

12.3 Pharmacokinetics

The activity of XTAMPZA ER is primarily due to the parent drug oxycodone. XTAMPZA ER is designed to provide delivery of oxycodone over 12 hours.

[REDACTED] (b) (4)

Reviewer Note: The above information is pertinent information, in part [REDACTED] (b) (4)

[REDACTED] could be misleading [REDACTED] (b) (4)

[REDACTED]

(b) (4)

Absorption

(b) (4)

Table 7: (b) (4) Oxycodone PK Parameters, Administration of Capsule Contents and Intact Capsules (36 mg oxycodone base)*

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-1NF} (hr•ng/mL)*(hr)
Treatment	Sprinkle Administration Study		
Intact XTAMPZA ER Capsules (fed)	55.3 (13.6)	4.5 (1.5 – 9.0)	540 (143)
Sprinkled XTAMPZA ER Capsule Contents (fed)	48.1 (12.0)	4.5 (2.5 – 9.0)	528 (130)

(b) (4)

Values shown for C_{max} and AUC_{0-1NF} are mean (standard deviation); values shown for T_{max} are median (minimum - maximum).

(b) (4)

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/s/

SRIKANTH C NALLANI
09/24/2015

YUN XU
09/24/2015

CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

1.1 Recommendation

The sponsor's plan to label Xtampza use with food will be discussed at the Advisory Committee meeting to be held on September 11, 2015. Additional product labeling, review recommendations may be made from a clinical pharmacology perspective after the AC meeting by an addendum to this review.

1.2 Phase IV Commitments

None identified.

1.3 Summary of Clinical Pharmacology Findings

Collegium Pharmaceutical, Inc. submitted a 505(b)(2) NDA 208090 for marketing Xtampza for pain management where continued use of an opioid is indicated. Xtampza (or Oxycodone DETERx) is an extended release (ER) microsphere-in-capsule opioid formulation developed by Collegium Pharmaceutical, Inc. (or Collegium) for the treatment of chronic pain that has been developed to deter abuse of currently marketed oxycodone ER opioid products. Unlike most opioid products, Xtampza is intended for every 12 hour administration with food. Xtampza contains oxycodone base in microspheres, whereas the reference drug OxyContin ER tablets uses oxycodone HCl salt. The microspheres contain oxycodone (b) (4) The microspheres are formed (b) (4)

(b) (4) Microspheres are encapsulated to produce capsules that contain oxycodone in an amount equivalent to 10 mg, 15 mg, 20 mg, 30 mg, or 40 mg oxycodone HCl. (b) (4)

Initial PK studies during drug development indicated that bioavailability of Xtampza under fasting condition is very variable and low compared to OxyContin, with improved bioavailability only after administration with high-fat food. Hence, Collegium changed their clinical plan to support use of Xtampza with food. Collegium originally attempted establishing bioequivalence of their product with OxyContin under fed state without any additional clinical trials.

In light of Xtampza's lower bioavailability compared to OxyContin under fasting condition and the increased systemic exposure with a high-fat meal, Agency advised the sponsor to reformulate the product so the product does not have the noted significant food-effect. After several attempts to reformulate Collegium arrived at a final formulation that was still susceptible to significantly increased bioavailability with food. Hence, Agency advised Collegium to revise the 505(b)(2) program to include additional clinical studies to document safety and efficacy of Xtampza when taken with food. In this regard, several bioavailability studies were conducted to address safety and efficacy of Xtampza when taken with food comprised of different fat content, or following physical manipulation, and when taken with alcohol. In addition, one clinical efficacy study was also conducted to support the plan to label the use of Xtampza with food.

Relative bioavailability of Xtampza was compared to OxyContin after single doses (Studies CP-OXYDET-15 and -25) or multiple doses (Study CP-OXYDET-18). Studies CP-OXYDET-15 and -18 also evaluated food-effect on PK of Xtampza and OxyContin. Xtampza bioavailability after oral abuse was evaluated in three studies (CP-OXYDET-17, -24, and -25) that evaluated chewing and crushing of the capsule contents. Xtampza bioavailability after intranasal abuse was evaluated in two studies (CP-OXYDET-19, -21). PK and PD of intranasal abuse or oral abuse of Xtampza were also evaluated in studies CP-OXYDET-21 and CP-OXYDET-24, respectively. Alcohol interaction susceptibility of Xtampza was evaluated in PK study CP-OXYDET-26. To evaluate flexibility of dosing in elderly or patients with nasogastric tube, a relative bioavailability study was conducted to compare intact Xtampza with capsule contents sprinkled over applesauce. Most of the relative bioavailability studies described above, except for studies CP-OXYDET-21 and CP-OXYDET-24, were conducted in healthy volunteers following naltrexone-block.

As shown in the table below, Xtampza has low and variable bioavailability, across different studies, when administered under fasting condition. When taken with high-fat high-calorie (HFHC) meal bioavailability of Xtampza increased up to two-fold in different studies.

Table: Mean (SD) PK parameters of oxycodone following single dose administration of Xtampza 40 mg capsule in different studies that were conducted with or without naltrexone-block.

Study Number	Fasted			HFHC Meal		
	Cmax (ng/mL)	AUClast (hr•ng/mL)	AUCINF (hr•ng/mL)	Cmax (ng/mL)	AUClast (hr•ng/mL)	AUCINF (hr•ng/mL)
Naltrexone-blocked studies						
-15	31.5 (9.52)	343 (127)	373 (134)	51.9 (14.3)	498 (155)	518 (156)
-17	30.7 (7.09)	343 (85.6)	369 (89.5)	62.3 (13.0)	552 (123)	561 (124)
-19	ND	ND	ND	47.5 (7.89)	493 (110)	499 (110)
-25	ND	ND	ND	67.5 (17.6)	569 (139)	581 (138)
26	24.7 (9.41)	358 (120)	398 (114)	54.8 (14.6)	512 (105)	531 (105)
-27	22.3 (6.60)	317 (99.5)	339 (98.9)	55.3 (13.6)	529 (142)	540 (143)
Non-naltrexone blocked studies						
-21	ND	ND	ND	41.0 (9.95)	470 (93.1)	477 (89.6)
-24	30.9 (9.91)	408 (113)	469 (107)	41.9 (12.4)	511 (155)	553 (131)

Single dose PK of Xtampza under fasting and fed state and comparison with OxyContin

In relative bioavailability study CP-OXYDET-15 conducted in naltrexone-blocked healthy volunteers (n= 45), pharmacokinetics of Xtampza 40 mg capsule was determined when taken with high-fat high-calorie (HFHC) meal, with a medium-fat medium-calorie (MFMC) meal, and with a low-fat low-calorie (LFLC) meal, as well as in the fasted state, compared with OxyContin 40 mg dosed with an HFHC meal and in the fasted state.

As shown in the table below, bioavailability of Xtampza increases with fat and calorie content in a meal. In food-effect study CP-OXYDET-15, medium-fat medium-calorie meal increased Xtampza bioavailability by 84%. In other studies, up to 2-fold increase in Cmax was noted when Xtampza was administered with high-fat high-calorie meal.

Table: Statistical Analysis Evaluating Food-effect on Bioavailability of Xtampza. Least squares geometric mean (LSGM) of PK parameter, ratio and 90% confidence intervals of treatment to reference from Study CP-OXYDET-15.

Parameter	Fasted (Reference) LSGM	LFLC LSGM	Ratio % ^a (90% CI)	MFMC LSGM	Ratio % ^a (90% CI)	HFHC LSGM	Ratio % ^a (90% CI)
Cmax (ng/mL)	29.84	35.9	120 (112 – 128)	54.9	184.2 (172 – 196)	49.75	166.7 (156 – 177)
AUClast (ng h/mL)	317.9	372.6	117 (111 – 123)	440.7	138 (132 -145)	472.6	148.6 (141 – 156)
AUCinf (ng h/mL)	337.8	384.02	113.7 (108 -119)	451.2	133.6 (127 – 139)	485.5	143.7 (137 – 150)

LFLC: Low-fat Low-calorie; MFMC: Medium-fat Medium calorie; HFHC: High-fat High-calorie.

^aRatio to fasted Xtampza treatment and 90% CI. Bold face numbers indicate significant increase in PK parameter as indicated by the 90% CI beyond the 80 – 125 limits.

In the relative bioavailability study CP-OXYDET-15, it was observed that bioavailability of Xtampza 40 mg capsule is lower compared to OxyContin 40 mg tablet both under fasting and fed condition.

Table: Statistical analysis evaluating bioavailability/bioequivalence of Xtampza to OxyContin under fasting or fed condition. Least squares geometric mean (LSGM) of PK parameter, ratio and 90% confidence intervals of treatment to reference from Study CP-OXYDET-15.

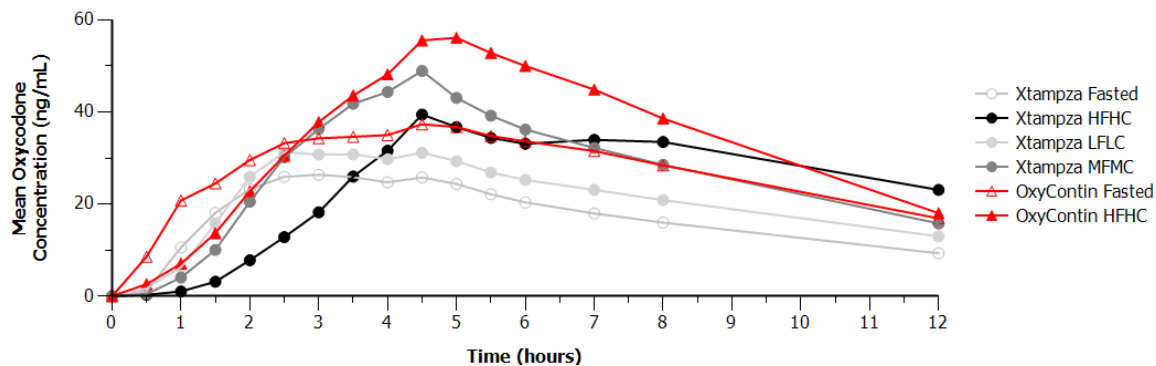
Parameter	Xtampza Fasted (Test)	OxyContin Fasted (Ref)	T/F Fast Ratio % ^a (90% CI)	Xtampza HFHC (Test)	OxyContin HFHC (Ref)	T/F HFHC Ratio % ^b (90% CI)	OxyContin Fed/Fasted Ratio %
	LS GM			LS GM			
Cmax (ng/mL)	29.84	40.3	74 (69 – 78)	49.75	61.1	81.3 (76 – 87)	151 (142 – 161)
AUClast (ng.h/mL)	317.9	444.4	71 (68 – 75)	472.6	521.1	90.7 (86 – 95)	117 (111 – 122)
AUCinf (ng.h/mL)	337.8	455.2	74.2 (71 – 78)	485.5	530.7	91.5 (87 – 90)	116.6 (111 – 122)

Following OxyContin 40 mg tablet administration under fasting conditions, peak plasma concentrations of oxycodone (mean 42.3 ng/mL) were noted after a median 4.5 hours (Range 1.5 – 8 h). Variability in C_{max} and AUC_{0-inf} of oxycodone following OxyContin administration under fasting condition were 25% and 29%, respectively (See table below). Following Xtampza 40 mg capsule administration under fasting condition, peak plasma concentrations of oxycodone (mean 31.5 ng/mL) were noted after a median 2.5 hours (Range 1 – 5.5 h). Variability in C_{max} and AUC_{0-inf} of oxycodone following Xtampza administration under fasting condition were 30% and 36%, respectively. A Tlag or delay in oxycodone absorption for up to 4 hours was noted when Xtampza was taken with MFMC or HFHC food. Such a delay in first noted plasma level was not observed with OxyContin.

Relative to OxyContin fasted, Xtampza fasted treatment has 26% lower C_{max} and 28% lower AUC. OxyContin fed treatment bioavailability was 52% higher with regard to C_{max} without significant increase in AUC compared to fasting state.

The data presented in Table above indicates that Xtampza exhibited higher C_{max} and AUC values after dosing with either MFMC or HFHC meal relative to the fasted state. Therefore, additional statistical analysis was conducted to understand the impact of food administration on Xtampza pharmacokinetics (See figure and table below).

Figure: Pharmacokinetic profile of mean oxycodone in healthy subjects receiving Xtampza 40 mg capsule, and OxyContin 40 mg tablet after fasting or different fed conditions.

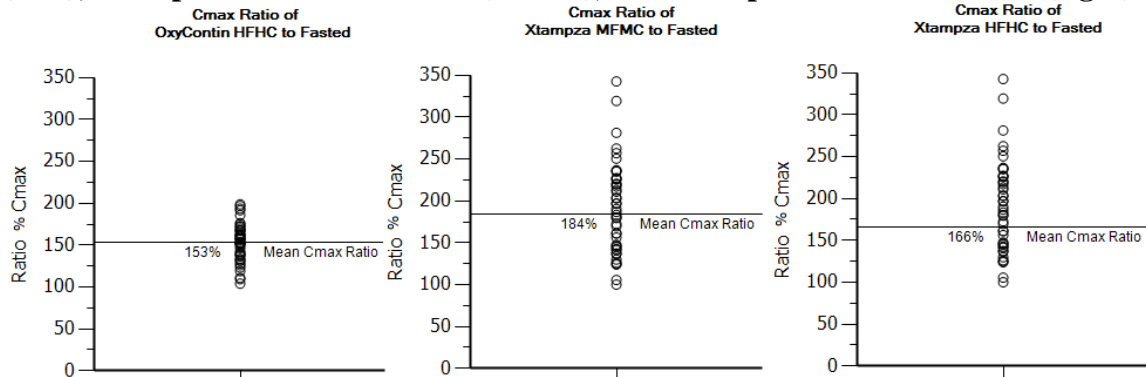


LFLC: Low-Fat Low-calorie; MFMC: Medium-fat Medium Calorie; HFHC: High-fat High-calorie

In addition to the above statistical analysis, variability in food-effect in terms of peak plasma oxycodone concentration was also compared between OxyContin and Xtampza with respect to the fasted data. The C_{max} data of each individual following a drug treatment (Xtampza or OxyContin) under a given fed condition was compared to the observed C_{max} following the same drug treatment under fasting. The individual C_{max} ratios and the mean ratio of C_{max} for each comparison (also noted in the table above) are shown in the figure below. As described in the table above, Xtampza MFMC and HFHC treatments produced a mean 84% and 66% higher C_{max} ratio, respectively compared to fasting state. However, greater degree of variability in food-effect was noted in Xtampza treatments compared to OxyContin. While a limited number of subjects receiving OxyContin with HFHC had a 2-fold increase in C_{max}, significant number of subjects receiving Xtampza had increase in C_{max} as high as 3-fold compared to fasted state. This

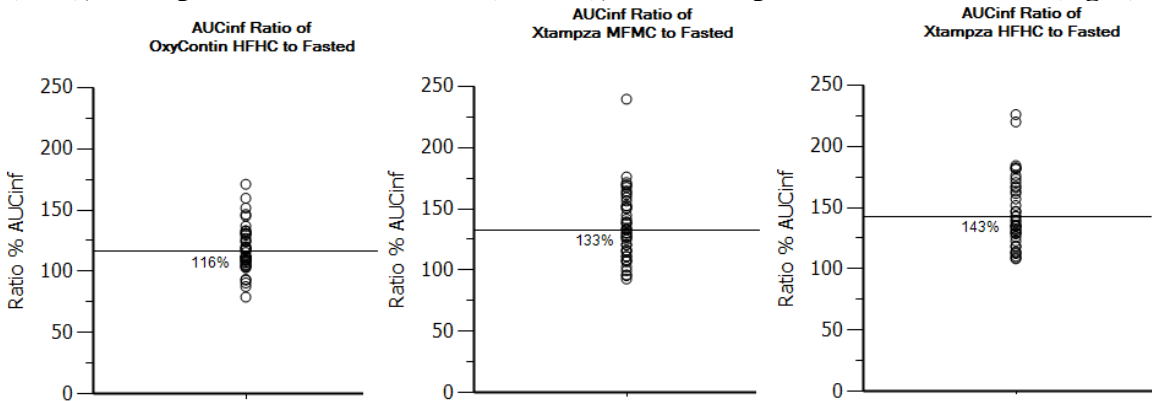
observation is mainly because of the low and variable bioavailability with Xtampza under fasting condition.

Figure: Ratio % of Cmax for each individual receiving OxyContin fed Vs. fasted (Left), Xtampza MFMC Vs. fasted (middle), and Xtampza HFHC Vs. fasted (right).



HFHC- High-Fat High-Calorie, MFMC- Medium-fat Medium-calorie.
Horizontal reference lines indicate mean Cmax ratio for each treatment comparison.

Figure: Ratio % of AUCinf for each individual receiving OxyContin fed Vs. fasted (Left), Xtampza MFMC Vs. fasted (middle), and Xtampza HFHC Vs. fasted (right).



Multiple dose PK of Xtampza and comparison with OxyContin

Multiple dose PK of Xtampza was compared with OxyContin in Study CP-OXYDET-18 which was an open-label, randomized, active-controlled, NTX-blocked, cross-over comparison study. The study goal was to assess the safety and PK of multiple-dose administration of 40 mg Oxycodone DETERx compared with OxyContin OP 40 mg under 2 different fed states. Subjects were randomized to receive each of the following 4 treatments in random order:

Treatment A: OxyContin OP 40 mg with a HFHC meal for all doses

Treatment B: OxyContin OP 40 mg in the fasted state for all morning doses and with a HFHC calorie meal for all evening doses

Treatment C: Oxycodone DETERX 40 mg with a HFHC meal for all doses

Treatment D: Oxycodone DETERx 40 mg in the fasted state for all morning doses and with a HFHC meal for all evening doses.

Blood samples were collected predose each day and at multiple timepoints on Day 5.

Statistical analyses of AM and PM trough concentrations indicated that steady-state concentrations were achieved by Day 2 for all treatment arms.

Figure: Mean $\pm$ SD Concentrations of Oxycodone after Oxycodone DETERx and OxyContin OP (Fed AM/Fed PM), PK Population (5 day BID).

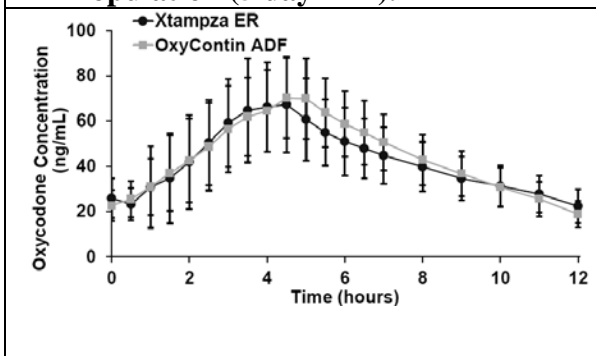
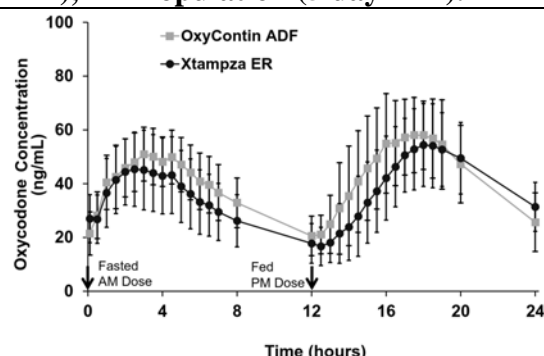


Figure: Mean $\pm$ SD Concentrations of Oxycodone after Oxycodone DETERx and OxyContin OP (Fasted AM/Fed PM), PK Population (5 day BID).



As indicated in the figure above and table below, the pharmacokinetic profile of Xtampza following multiple dose administration was similar to OxyContin profile (also see table below). However, it should be noted that BA/BE guidance generally recommends single-dose PK studies to assess BA and BE because they are generally more sensitive than steady-state studies in assessing rate and extent of release of the drug substance from the drug product into the systemic circulation.

As shown in the table below, Xtampza C_{max} and AUC (highlighted in blue box) were 54% and 32% higher, on average, when comparing systemic exposure following fasted AM dosing with fed AM dosing at steady-state. OxyContin C_{max} and AUC (highlighted in red box) were 40% and 20% higher, on average, when comparing systemic exposure following fasted AM dosing with fed AM dosing at steady-state.

C_{min} values for Xtampza fed/fed treatment were almost 20% and 30% higher compared to fasted/fed AM and fasted/fed PM dosing, respectively. The C_{min} values for Oxycontin fed/fed dosing were only 10% and 13% higher compared to fasted/fed AM and fasted fed dosing, respectively.

Table: Descriptive statistics of oxycodone PK following multiple dose administration of OxyContin or Xtampza for five days.

Treatment		C _{max} (ng/mL)	T _{max} (hr)	C _{min} (ng/mL)	C _{ave} (ng/mL)	AUC _{tau} (hr•ng/mL)	AUC ₀₋₂₄ (hr•ng/mL)	%PTF
Oxycodone DETERx Fed/Fed (AM dosing)	N	35	35	35	35	35	NA	35
	Mean (SD) ^a	77.7 (23.6)	3.5 (1 - 5.5)	21.3 (7.09)	42.6 (9.66)	511 (116)	NA	134 (35.8)
OxyContin OP Fed/Fed (AM dosing)	N	37	37	37	37	37	NA	37
	Mean (SD) ^a	77.1 (17.8)	4.5 (1 - 6.5)	21.2 (6.39)	44.3 (9.81)	532 (118)	NA	127 (18.9)
Oxycodone DETERx Fasted/Fed (AM dosing)	N	36	36	36	36	36	NA	36
	Mean (SD) ^a	49.6 (15.1)	2.5 (1 - 5)	17.8 (7.32)	32.1 (10.3)	385 (124)	NA	101 (19.6)
Oxycodone DETERx Fasted/Fed (PM dosing)	N	36	36	36	36	36	NA	36
	Mean (SD) ^a	62.4 (12.9)	6 (2 - 8)	15.2 (6.57)	39.4 (8.99)	473 (108)	NA	122 (21.5)
Oxycodone DETERx Fasted/Fed (24-hr profile)	N	36	36	36	36	NA	36	36
	Mean (SD) ^a	63.7 (13.9)	17.3 (1 - 20)	15.1 (6.48)	35.7 (9.14)	NA	858 (219)	140 (27.5)
OxyContin OP Fasted/Fed (AM dosing)	N	36	36	36	36	36	NA	36
	Mean (SD) ^a	54.9 (10.5)	3 (1 - 5)	19.2 (7.35)	37 (8.39)	444 (101)	NA	99.3 (27.1)
OxyContin OP Fasted/Fed (PM dosing)	N	36	36	36	36	36	NA	36
	Mean (SD) ^a	71.3 (14.7)	5 (1.5 - 8)	18.7 (5.6)	42.7 (8.58)	512 (103)	NA	125 (27.7)
OxyContin OP Fasted/Fed (24-hr profile)	N	36	36	36	36	NA	36	36
	Mean (SD) ^a	72 (13.9)	16.5 (3 - 20)	17.7 (6.15)	39.9 (8.26)	NA	957 (198)	139 (34.4)

^a Values shown for T_{max} are median (minimum - maximum).

AUC = area under the plasma concentration vs time curve; AUC_{tau} = AUC from time 0 to the end of the dosing interval; AUC₀₋₂₄ = AUC summed for 2 dosing intervals; C_{ave} = average plasma concentration; C_{max} = maximum observed plasma concentration; NA = not applicable; PK = pharmacokinetic; %PTF = percentage of peak-trough fluctuation within a dosing interval; SD = standard deviation; T_{max} = time to reach maximum plasma concentration
Source: Study CP-OXYDET-18 Pharmacokinetic Report, Table 2 and Table 3.

Additional differences as calculated by the sponsor's BE analysis is described in the table below.

Table: Bioequivalence analysis of steady-state oxycodone PK with Xtampza and Oxycontin.

Test	Reference	PK Parameter	GM Ratio (% of Reference)	90% CI Lower Bound	90% CI Upper Bound
12-Hour Profiles					
Oxycodone DETERx: Fed/Fed: AM Dose	OxyContin OP: Fed/Fed: AM dose	C _{max}	99.60 ^a	93.60	105.97
		C _{min}	95.70	87.39	104.80
		AUC _{tau}	95.60	92.71	98.57
Oxycodone DETERx: Fasted/Fed: AM Dose	OxyContin OP: Fasted/Fed: AM Dose	C _{max}	87.43	81.53	93.76
		C _{min}	92.66	81.04	105.95
		AUC _{tau}	83.91	78.42	89.78
Oxycodone DETERx: Fasted/Fed: PM Dose	OxyContin OP: Fasted/Fed: PM Dose	C _{max}	87.26	82.03	92.83
		C _{min}	77.51	68.88	87.22
		AUC _{tau}	91.73	87.31	96.36
OxyContin OP: Fasted/Fed: PM Dose	OxyContin OP: Fasted/Fed: AM Dose	C _{max}	129.1	122.21	137.05
		C _{min}	101.05	92.01	110.98
		AUC _{tau}	115.78	112.69	118.96
Oxycodone DETERx: Fasted/Fed: PM Dose	Oxycodone DETERx: Fasted/Fed: AM Dose	C _{max}	128.71	120.56	137.40
		C _{min}	84.21	79.72	88.95
		AUC _{tau}	125.70	119.57	132.16

PK of Xtampza capsule contents sprinkled over applesauce:

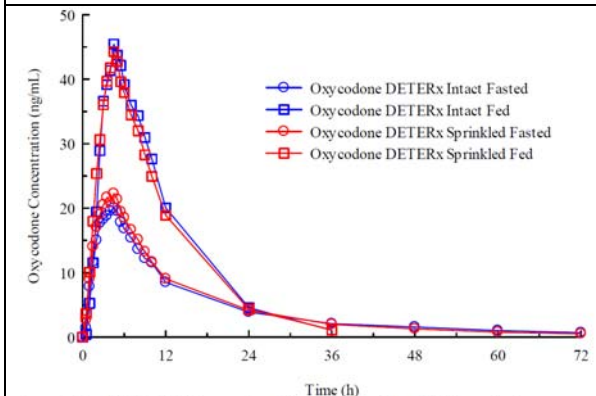
In order to allow Xtampza administration in patients with difficulty in swallowing capsules, Collegium conducted a study (CP-OXYDET-27) under fasting and fed condition where PK of intact product was compared to capsule contents sprinkled over applesauce. This study was conducted in healthy volunteers (n=43) receiving naltrexone block. As noted in other PK studies, systemic levels of oxycodone were low (Mean 22 ng/mL) when Xtampza capsules were given while fasting. The peak plasma levels of oxycodone following a high-fat meal administration were a mean of 55 ng/mL, thus a 2.5-fold increase in C_{max} was noted. However, the primary comparison for the study was successful in that Xtampza capsule contents sprinkled over applesauce were bioequivalent to intact capsule when administered with food.

Table: Statistical analysis comparing bioavailability of Xtampza 40 mg taken while fasting (Reference) or with other treatments.

Dependent	Test GLSM	Ref GLSM	Ratio%Ref (90% CI)	Test Treatment
C_{max}	53.48	21.30	251.1 (233.5 - 269.9)	Xtampza 40 mg Intact Fed
	23.15	21.30	108.7 (101.1 - 116.9)	Xtampza 40 mg Sprinkled onto Applesauce Fasted
	46.72	21.30	219.3 (204.0 - 235.9)	Xtampza 40 mg Sprinkled onto Applesauce Fed
AUC_{last}	505.09	300.42	168.1 (158.9 - 177.9)	Xtampza 40 mg Intact Fed
	309.36	300.42	103 (97.3 - 108.9)	Xtampza 40 mg Sprinkled onto Applesauce Fasted
	497.85	300.42	165.7 (156.6 - 175.3)	Xtampza 40 mg Sprinkled onto Applesauce Fed
AUC_{INF}	516.33	334.80	154.2 (145.8 - 163.1)	Xtampza 40 mg Intact Fed
	335.40	334.80	100.2 (94.7 - 106.0)	Xtampza 40 mg Sprinkled onto Applesauce Fasted
	509.16	334.80	152.1 (143.7 - 160.9)	Xtampza 40 mg Sprinkled onto Applesauce Fed

Bold numbers indicate significant difference.

Figure: PK Profile of Xtampza intact and capsule contents sprinkled over applesauce under fasting and fed condition.



Source: Study CP-OXYDET-27 Pharmacokinetic Report, Figure 1 or Figure 2 (with error bars).

Table: PK Parameters of Xtampza intact and capsule contents sprinkled over applesauce under fasting and fed condition.

Treatment	N	C _{max} (ng/mL)	T _{max} (hr)	AUC _{last} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)	t _{1/2} (hr)
Intact Oxycodone DETERx Fasted	43	22.3 (6.60)	4.00 (1.00 – 10.0)	317 (99.5)	339 (98.9)	15.6 (9.86)
Intact Oxycodone DETERx HFHC	43	55.3 (13.6)	4.50 (1.50 – 9.00)	529 (142)	540 (143)	5.68 (0.84)
Sprinkled Oxycodone DETERx Fasted	43	24.6 (8.66)	4.00 (1.50 – 6.00)	330 (117)	373 (130)	16.0 (9.62)
Sprinkled Oxycodone DETERx HFHC	43	48.1 (12.0)	4.50 (2.50 – 9.00)	516 (127)	528 (130)	5.82 (0.89)

* Values shown for T_{max} are median (minimum - maximum).

Pharmacokinetics of Xtampza when administered in conditions of physical manipulation (chewing/crushing/alcohol) followed by oral abuse:

In relative bioavailability study (or Category 2 PK only Abuse Liability Study) CP-OXYDET-17, pharmacokinetics of Xtampza taken intact in naltrexone-blocked healthy volunteers under fasting or HFHC condition was compared with Xtampza taken orally after different physical manipulations. This study was an open-label, randomized, active-controlled, cross-over comparison study (two 7x7 Williams square randomization design). Subjects were randomized to receive each of the seven treatments in random order (N = 38 to 42 depending on treatment arm):

- Xtampza (Oxycodone DETERx) 40 mg (capsule intact) with a HFHC meal
- Xtampza 40 mg (capsule contents crushed) with a HFHC meal
- Xtampza 40 mg (capsule contents chewed) with a HFHC meal
- **Xtampza 40 mg (capsule intact) in the fasted state (Used as reference by Agency)**
- Xtampza 40 mg (capsule contents crushed) in the fasted state
- Xtampza 40 mg (capsule contents chewed) in the fasted state
- Oxycodone Solution 40 mg (Used as reference by Collegium) in the fasted state

As shown by the descriptive statistics in the table below, systemic exposure of oxycodone was lowest following intact Xtampza capsule administration in fasted state. As noted previously, C_{max} and AUC of Xtampza increased when given intact with High-fat High Calorie meal. Although a slight delay in T_{max} was noted in all Xtampza treatments taken with food, a T_{lag} (as noted in study CP-OXYDET-15) was not observed in this study in any of the individual subjects.

Table: Study CP-OXYDET-17: Summary of Oxycodone DETERx (Xtampza) PK parameters following intact, chewed or crushed ingestion in fasted or fed (HFHC) state.

Treatment		C _{max} (ng/mL)	T _{max} (hr)	AUC _{last} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)	t _{1/2} (hr)
Oxycodone DETERx Intact HFHC	N	42	42	42	42	42
	Mean (SD) ^a	62.3 (13.0)	4.0 (1.5 - 6)	552 (123)	561 (124)	7.25 (2.40)
Oxycodone DETERx Crushed HFHC	N	42	42	42	41	41
	Mean (SD) ^a	57.6 (12.6)	4.5 (2.5 - 6)	537 (140)	553 (134)	5.44 (1.05)
Oxycodone DETERx Chewed HFHC	N	38	38	38	38	38
	Mean (SD) ^a	55.6 (10.9)	4.5 (2.5 - 8)	550 (112)	559 (113)	5.99 (1.44)
Oxycodone DETERx Intact Fasted	N	40	40	40	39	39
	Mean (SD) ^a	30.7 (7.09)	3.0 (1 - 5)	343 (85.6)	369 (89.5)	13.8 (10.0)
Oxycodone DETERx Crushed Fasted	N	40	40	40	40	40
	Mean (SD) ^a	34.0 (9.93)	3.0 (1 - 8)	394 (131)	410 (129)	11.6 (6.18)
Oxycodone DETERx Chewed Fasted	N	41	41	41	41	41
	Mean (SD) ^a	41.1 (15.2)	2.5 (0.5 - 4.5)	403 (108)	422 (113)	12.4 (8.94)
Oxycodone IR Solution Fasted	N	40	40	40	40	40
	Mean (SD) ^a	115 (27.3)	0.75 (0.5 - 2)	480 (77.9)	489 (80.2)	4.48 (0.458)

^a Values shown for T_{max} are median (minimum - maximum).

AUC = area under the plasma concentration vs time curve; AUC_{INF} = AUC to from time 0 to infinity;

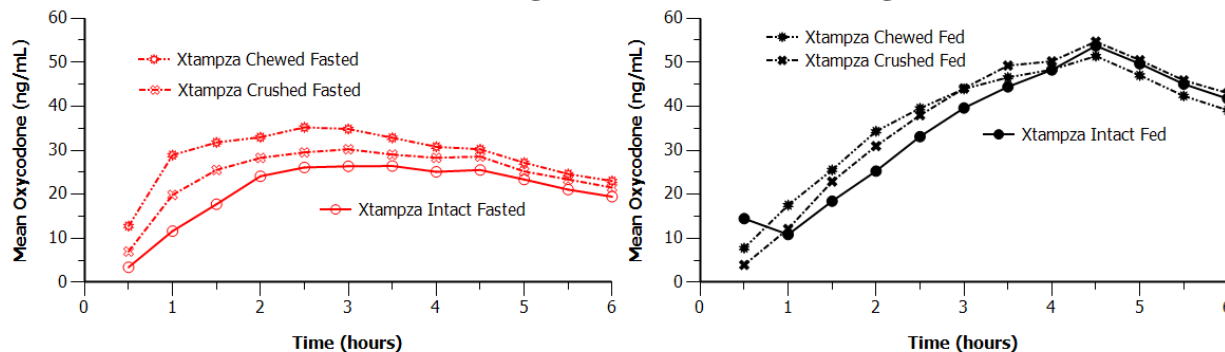
AUC_{last} = AUC from time 0 to the time of the last measurable plasma concentration; C_{max} = maximum observed plasma concentration; HFHC = high-fat, high-calorie; IR = immediate-release; PK = pharmacokinetic;

SD = standard deviation; t_{1/2} = apparent terminal half-life; T_{max} = time to reach maximum plasma concentration.

Source: Study CP-OXYDET-17 Pharmacokinetic Report, Table 3.

As shown in the figure (left side) below, average pharmacokinetic profile of oxycodone appears to be higher following crushing and chewing Xtampza capsule contents compared to intact product taken under fasting condition. However, the impact of crushing and chewing is limited compared to intact Xtampza when taken with a high-fat meal. Peak plasma concentrations of oxycodone following all treatments (intact or manipulated) when taken with high-fat meal are higher than any of the treatments (intact or manipulated) taken while fasting.

Figure: Pharmacokinetic profile of oxycodone following administration of Xtampza intact, chewed or crushed under fasting (Left) or Fed HFHC (Right) conditions.



Note: Open symbols with red line (left figure) indicate fasted state. Closed symbols with black line (right figure) indicate fed state. Oxycodone PK profile following oxycodone solution administration is not depicted in the figure.

Table: Statistical analysis showing effect of different manipulations (chewing or crushing) (Study CP-OXYDET-17) on Oxycodone IR or Xtampza PK Parameters compared to fasted intact Xtampza.

	Xtampza Crushed Fasted	Xtampza Chewed Fasted	Xtampza Intact Fed	Xtampza Crushed Fed	Xtampza Chewed Fed	Oxycodone IR Fasted
Cmax						
Ratio % ^a	110.4	127.7	204.4	188.6	169.6	376.7
90% CI Lower	100.3	116.1	185.8	171.4	154.0	342.4
90% CI Upper	121.5	140.5	225.0	207.5	186.8	414.3
AUClast						
Ratio % ^a	106.4	115.9	162.6	155.9	143.5	140.9
90% CI Lower	92.9	101.3	142.0	136.1	125.1	123.1
90% CI Upper	122.0	132.7	186.2	178.5	164.5	161.2
AUCinf						
Ratio % ^a	109.2	113.7	153.9	149.1	155.2	135.7
90% CI Lower	103.1	107.5	145.4	140.9	146.5	128.2
90% CI Upper	115.7	120.3	162.9	157.8	164.4	143.6

FDA analysis of data submitted to CP-OXYDET-17.

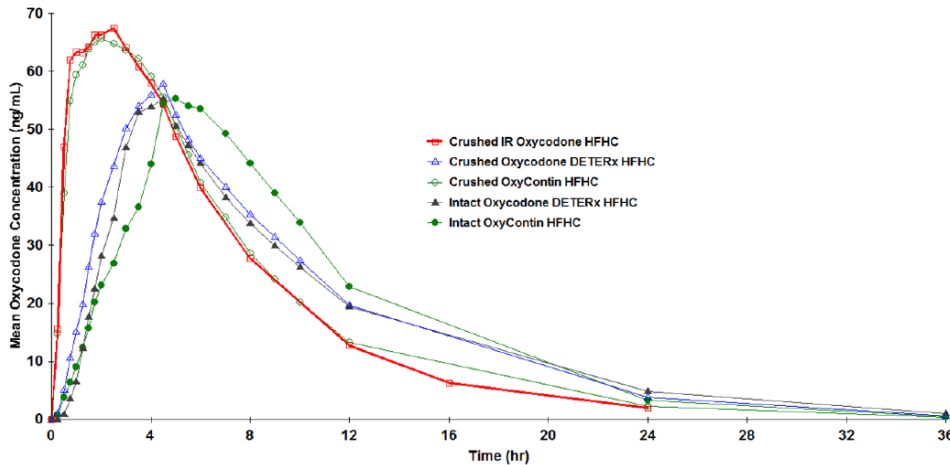
^aRatio to intact Xtampza fasted treatment and 90% Confidence Interval. Bold face numbers indicates significant increase in PK parameter as indicated by the 90% CI beyond the 80 – 125 limits.

Additional statistical analysis showed that crushing Xtampza did not impact PK under fasting condition, while after chewing Xtampza Cmax increased by 28% under fasting condition. The analysis also showed that the two-fold increase in Cmax noted when

Xtampza is taken with food overshadowed any additional impact of crushing or chewing Xtampza under fed state.

In a separate study the effect of crushing Xtampza followed by administration with food was evaluated in study CP-OXYDET-25. Additional comparisons involved OxyContin intact and crushed taken with food and crushed IR oxycodone taken with food. As seen in study -17, oral abuse of Xtampza in fed-state resulted in systemic exposure comparable to intact product.

Figure: Oxycodone PK Profile following intact and crushed administration of Xtampza and OxyContin, compared to Crushed IR oxycodone after high-fat meal.



HFHC = high-fat, high-calorie, IR = immediate-release; PK = pharmacokinetic.

Source: Study CP-OXYDET-25 Pharmacokinetic Report, Figure 1 or Figure 2 (with error bars).

Table: Summary of Oxycodone PK Parameters following intact or crushed Xtampza, OxyContin, or IR oxycodone administration with high-fat meal.

Treatment		C _{max} (ng/mL)	T _{max} (hr)	AUC _{last} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)	t _{1/2} (hr)
Crushed IR Oxycodone	N	40	40	40	40	40
	Mean (SD) ^a	79.4 (17.1)	1.75 (0.50 - 4.00)	548 (140)	561 (146)	4.25 (0.654)
Crushed Oxycodone DETERx	N	38	38	38	38	38
	Mean (SD) ^a	62.9 (12.6)	4.00 (2.00 - 7.00)	587 (151)	597 (149)	5.00 (0.641)
Crushed OxyContin OP	N	39	39	39	39	39
	Mean (SD) ^a	78.4 (12.9)	1.75 (0.50 - 5.00)	579 (130)	587 (132)	4.49 (0.743)
Intact Oxycodone DETERx	N	38	38	38	38	38
	Mean (SD) ^a	67.5 (17.6)	3.50 (1.25 - 6.00)	569 (139)	581 (138)	5.74 (0.942)
Intact OxyContin OP	N	40	40	40	39	39
	Mean (SD) ^a	64.9 (13.8)	5.00 (2.00 - 10.00)	598 (146)	611 (145)	4.29 (0.647)

^a Values shown for T_{max} are median (minimum - maximum).

Source: Study CP-OXYDET-25 Pharmacokinetic Report, Table 2

In study CP-OXYDET-26, for each Xtampza dose cohort (40 mg and 10 mg), effect of alcohol co-ingestion was evaluated in healthy subjects (n= 37 – 44) receiving naltrexone-block. PK analysis and comparisons were conducted between the following treatments:

- Treatment A: Xtampza 10 mg or 40 mg, coingested with 40% alcohol, Fasted
- Treatment B: Xtampza 10 mg or 40 mg, coingested with 20% alcohol, Fasted
- Treatment C: Xtampza 10 mg or 40 mg, coingested with 0% alcohol, Fasted
- Treatment D: Xtampza 10 mg or 40 mg, coingested with 0% alcohol, Fed

As noted previously in studies CP-OXYDET-15 and -17, significant food-effect was noted on Cmax of Xtampza 10 mg and 40 mg (See Tables below). A two fold increase in Cmax was noted when Xtampza (10 or 40 mg) was given with food in healthy subjects on naltrexone-block. Compared to fasted state, high-fat meal resulted in a delay in Tmax as noted in previous studies. A delay in appearance of oxycodone concentration in plasma or Tlag was noted in this study.

Table: Summary of Pharmacokinetic Parameters, Cohort 1 (top table- 40 mg) and Cohort 2 (bottom table – 10 mg Oxycodone DETERx or Xtampza).

Parameter*	Oxycodone DETERx 40% Alcohol Fasted	Oxycodone DETERx 20% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fed
Tlag (hr)	0.75 (36) [0.50 – 1.27]	0.75 (39) [0.50 – 1.75]	0.75 (42) [0.50 – 2.00]	0.75 (43) [0.50 – 2.50]
Cmax (ng/mL)	44.1 ± 15.6 (36)	31.9 ± 11.9 (39)	24.7 ± 9.41 (42)	54.8 ± 14.6 (43)
Tmax (hr)	1.75 (36) [0.75 – 08.0]	3.00 (39) [1.00 – 12.00]	3.50 (42) [1.75 – 8.00]	4.50 (43) [1.50 – 6.00]
AUC(0-t) (hr×ng/mL)	430 ± 158 (36)	421 ± 169 (39)	358 ± 120 (42)	512 ± 105 (43)
AUC(inf) (hr×ng/mL)	456 ± 158 (30)	457 ± 177 (31)	398 ± 114 (27)	531 ± 105 (40)
λz (1/hr)	0.0833 ± 0.0530 (30)	0.0699 ± 0.0310 (31)	0.0720 ± 0.0355 (27)	0.1166 ± 0.0190 (40)
t½ (hr)	10.5 ± 5.66 (30)	12.5 ± 6.69 (31)	12.7 ± 07.3 (27)	6.12 ± 1.11 (40)
CL/F (L/hr)	95.6 ± 66.7 (30)	90.0 ± 33.3 (31)	99.5 ± 36.6 (27)	70.8 ± 17.6 (40)
Vz/F (L)	1,268 ± 685 (30)	1,596 ± 1038 (31)	1,790 ± 1,107 (27)	629 ± 209 (40)
Fr (%)	87.1 ± 28.6 (28)	86.4 ± 29.5 (30)	73.4 ± 20.6 (24)	—†

CV = coefficient of variation; HFHC = high-fat, high-calorie; Max = maximum; Min = minimum; n = number of subjects used in the calculation; SD = standard deviation

*Arithmetic mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†Not applicable as Oxycodone DETERx 0% Alcohol Fed was the reference treatment.

Source: Appendix 16.6.1, Table 2

Parameter*	Oxycodone DETERx 40% Alcohol Fasted	Oxycodone DETERx 20% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fed
Tlag (hr)	1.00 (27) [0.50 – 3.57]	1.00 (34) [0.50 – 2.50]	1.00 (38) [0.50 – 2.00]	1.27 (36) [0.50 – 3.50]
Cmax (ng/mL)	12.4 ± 3.81 (27)	8.09 ± 2.34 (34)	6.41 ± 2.33 (38)	15.1 ± 3.61 (36)
Tmax (hr)	2.50 (27) [0.75 – 9.00]	2.75 (34) [1.00 – 6.00]	3.00 (38) [1.00 – 5.00]	4.00 (36) [1.75 – 8.00]
AUC(0-t) (hr×ng/mL)	118 ± 43.3 (27)	98.0 ± 36.2 (34)	88.9 ± 30.0 (38)	132 ± 37.2 (36)
AUC(inf) (hr×ng/mL)	137 ± 43.5 (23)	122 ± 36.5 (21)	114 ± 29.3 (16)	143 ± 37.9 (35)
λz (1/hr)	0.0833 ± 0.0471 (23)	0.0745 ± 0.0283 (21)	0.0699 ± 0.0293 (16)	0.1246 ± 0.0369 (35)
t½ (hr)	10.4 ± 4.59 (23)	10.8 ± 4.90 (21)	11.4 ± 04.3 (16)	5.97 ± 1.55 (35)
CL/F (L/hr)	73.9 ± 30.1 (23)	81.1 ± 27.6 (21)	83.0 ± 19.7 (16)	68.7 ± 26.9 (35)
Vz/F (L)	1,031 ± 497 (23)	1,240 ± 583 (21)	1,360 ± 0,566 (16)	561 ± 151 (35)
Fr (%)	96.0 ± 22.9 (23)	83.0 ± 16.5 (19)	78.5 ± 22.2 (16)	—†

CV = coefficient of variation; HFHC = high-fat, high-calorie; Max = maximum; Min = minimum; n = number of subjects used in the calculation; SD = standard deviation

*Arithmetic mean ± standard deviation (N) except Tlag and Tmax for which the median (N) [Range] is reported.

†Not applicable as Oxycodone DETERx 0% Alcohol Fed was the reference treatment.

Source: Appendix 16.6.1, Table 9

Ratios of Cmax were calculated using individual Cmax data following different treatments of alcohol or food compared to fasting state. While on average a two-fold

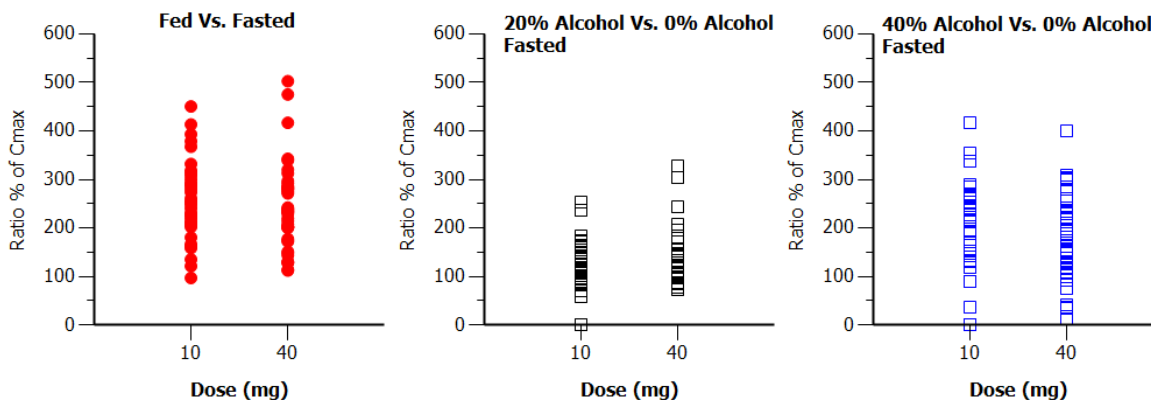
increase in Cmax was noted when Xtampza (10 or 40 mg) was taken with food, some individuals showed up to 5-fold increase in Cmax (See full red circles in left figure below).

Table: Statistical Analysis Evaluating Food-effect on Bioavailability of Xtampza. Least squares geometric mean (LSGM) of PK parameter, ratio and 90% confidence intervals of treatment to reference from Study CP-OXYDET-26.

Treatment	Parameter	Fasted (Reference) LSGM	HFHC (Test) LSGM	Fed/Fasted Ratio % ^a (90% CI)
Xtampza 10 mg	Cmax (ng/mL)	6.1	14.83	244 (219- 273)
	AUClast (ng.h/mL)	84.28	128.57	152 (107 – 216)
	AUCinf (ng.h/mL)	107.59	139.93	132 (122 – 144)
Xtampza 40 mg	Cmax (ng/mL)	23.35	52.62	226 (197 – 258)
	AUClast (ng.h/mL)	337.78	498.37	148 (111 – 196)
	AUCinf (ng.h/mL)	352.59	516.39	142 (128 – 158)

HFHC: High-fat High-calorie. ^aRatio to fasted Xtampza treatment and 90% CI. Bold face numbers indicate significant increase in PK parameter as indicated by the 90% CI beyond the 80 – 125 limits.

Figure: Ratio of Cmax in individual subjects comparing fed-state (full red circles-left), 20% alcohol fasted (black open squares-center), and 40% alcohol (blue open squares-right) to fasted state (CP-OXYDET-16).



Compared to Xtampza 40 mg taken intact while fasting, alcohol-effect with 20% and 40% alcohol was a 30% and 74% mean increase in Cmax, respectively. As shown in the figure above, few individuals had Cmax ratios around 4-fold increase in Cmax with alcohol treatment compared to no alcohol treatment, which is within the range of approved opioid ER products in alcohol dose dumping study.

Table: Statistical Analysis showing effect of alcohol on Cmax and AUC of oxycodone when Xtampza 40 mg (Cohort 1-top table) or 10 mg (Cohort 2-bottom table) is taken fasting (CP-OXYDET-26).

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*			Within-Subject CV (%)
			Test	Reference	Estimate	90% Confidence Interval		
Oxycodone DETERx 40% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Cmax	40.61	23.35	173.91	156.19 →	193.65	29.12
		AUC(0-t)	399.90	337.78	118.39	106.16 →	132.03	29.56
		AUC(inf)	424.98	352.59	120.53	105.55 →	137.64	28.83
Oxycodone DETERx 20% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Cmax	30.30	23.35	129.76	116.70 →	144.28	29.12
		AUC(0-t)	392.60	337.78	116.23	104.37 →	129.44	29.56
		AUC(inf)	423.74	352.59	120.18	105.25 →	137.22	28.83

AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; CV = coefficient of variation; LS = least squares.

Source: Appendix 16.6.1, Table 4.

Test	Reference	Parameter	LS Geometric Means		LS Geometric Mean Ratio (%)*			Within-Subject CV (%)
			Test	Reference	Estimate	90% Confidence Interval		
Oxycodone DETERx 40% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Cmax	11.92	6.10	195.36	176.39 →	216.37	23.71
		AUC(0-t)	113.33	84.28	134.47	122.60 →	147.48	21.39
		AUC(inf)	129.27	107.59	120.15	108.60 →	132.94	16.24
Oxycodone DETERx 20% Alcohol Fasted	Oxycodone DETERx 0% Alcohol Fasted	Cmax	7.87	6.10	128.99	117.56 →	141.53	23.71
		AUC(0-t)	92.77	84.28	110.06	101.21 →	119.70	21.39
		AUC(inf)	109.60	107.59	101.87	91.70 →	113.16	16.24

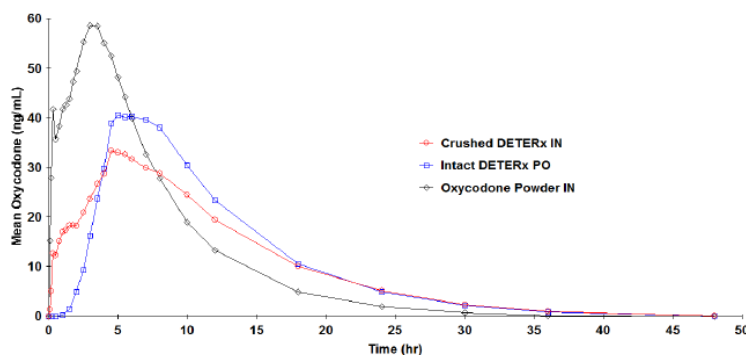
AUC = area under the plasma concentration-time curve; Cmax = maximum plasma concentration; CV = coefficient of variation; LS = least squares.

Source: Appendix 16.6.1, Table 11.

Pharmacokinetics of Xtampza when administered in conditions of physical manipulation (chewing/crushing) followed by intranasal abuse:

Potential for Xtampza abuse after physical manipulation by intranasal route was evaluated in PK only study CP-OXYDET-19 and PK/PD study CP-OXYDET-21. While study -19 was conducted in healthy volunteers following naltrexone-block, study-21 was conducted in opioid-experienced, non-dependent subjects without naltrexone-block to facilitate pharmacodynamic evaluation of intranasal abuse. Both the studies are similar in terms of treatment phase; however, study-21 required a qualification phase to recruit opioid-experienced, non-dependent subjects. Both studies indicate that following intranasal administration of crushed Xtampza, systemic absorption was comparable (AUC) or lower (Cmax) compared to Xtampza taken intact with high-fat meal. Treatment arm of intact Xtampza under fasting condition was not maintained as the product will be required to be administered with food.

Figure: Oxycodone PK Profile following intranasal abuse of crushed Xtampza or IR oxycodone compared with intact Xtampza taken orally with high-fat meal. (Study CP-OXYDET-19)



IN = intranasal; PO = by mouth (per os); PK = pharmacokinetic.
Source: Study CP-OXYDET-19 Pharmacokinetic Report, Figure 1 or Figure 2 (with error bars).

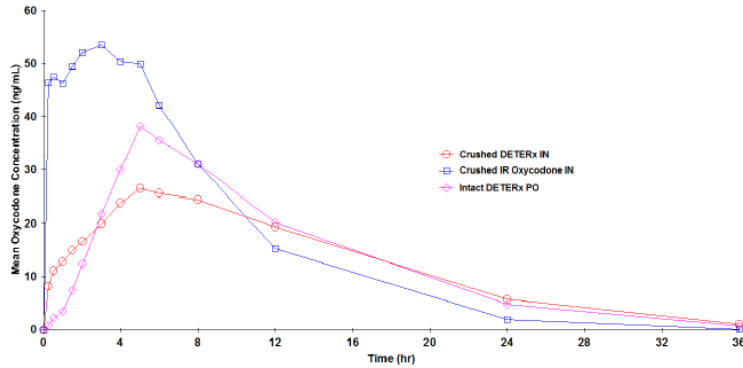
Table: Bioequivalence analysis of Oxycodone PK parameters following intranasal abuse compared to intact product taken oral with high-fat meal (highlighted). (Study CP-OXYDET-19)

Test	Reference	PK Parameter	GM Ratio (% of Reference)	90% CI Lower Bound	90% CI Upper Bound
Crushed Oxycodone DETERx IN	Oxycodone Powder IN	C _{max}	59.04	55.37	62.96
		AUC _{last}	88.07^a	81.95	94.66
		AUC _{INF}	88.59	82.48	95.15
Intact Oxycodone DETERx PO	Oxycodone Powder IN	C _{max}	74.20	67.27	81.85
		AUC _{last}	95.56	89.20	102.37
		AUC _{INF}	95.99	89.64	102.79
Crushed Oxycodone DETERx IN	Intact Oxycodone DETERx PO	C _{max}	79.57	72.14	87.77
		AUC _{last}	92.16	86.03	98.74
		AUC _{INF}	92.29	86.19	98.83

^a Boldface indicates bioequivalence between the test and reference conditions.
AUC = area under the plasma concentration vs time curve; AUC_{INF} = AUC to from time 0 to infinity;
AUC_{last} = AUC from time 0 to the time of the last measurable plasma concentration; CI = confidence interval;
C_{max} = maximum observed plasma concentration; GM = geometric mean; IN = intranasal; PK = pharmacokinetic;
PO = by mouth (per os).

Source: Study CP-OXYDET-19 Pharmacokinetic Report, Table 3.

Figure: Oxycodone PK Profile following intranasal abuse of crushed Xtampza or IR oxycodone compared with intact Xtampza taken orally with high-fat meal. (Study CP-OXYDET-21)



IN = intranasal; IR = immediate-release; PD = pharmacodynamic; PO = by mouth (per os).
 Source: Study CP-OXYDET-21 Pharmacokinetic Report, Figure 1 or Figure 2 (with error bars).

Table: Bioequivalence analysis of Oxycodone PK parameters following intranasal abuse compared to intact product taken oral with high-fat meal (highlighted). (Study CP-OXYDET-21)

Test	Reference	PK Parameter	GM Ratio (% of Reference)	90% CI Lower Bound	90% CI Upper Bound
Crushed Oxycodone DETERx IN	Crushed IR Oxycodone IN	C _{max}	48.72	45.63	52.02
		AUC _{last}	77.32	73.31	81.56
		AUC _{INF}	78.95	74.67	83.49
Intact Oxycodone DETERx PO	Crushed IR Oxycodone IN	C _{max}	66.74	62.69	71.05
		AUC _{last}	82.99	79.40	86.75
		AUC _{INF}	85.69^a	81.79	89.77
Crushed Oxycodone DETERx IN	Intact Oxycodone DETERx PO	C _{max}	73.02	68.35	78.00
		AUC _{last}	93.24	88.41	98.35
		AUC _{INF}	94.00	88.07	100.34

Boldface indicates bioequivalence between the test and reference conditions.
 AUC = area under the plasma concentration vs time curve; AUC_{INF} = AUC to from time 0 to infinity;
 AUC_{last} = AUC from time 0 to the time of the last measurable plasma concentration; CI = confidence interval;
 C_{max} = maximum observed plasma concentration; GM = geometric mean; IN = intranasal; IR = immediate-release;
 PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth (per os).
 Source: Study CP-OXYDET-21 Pharmacokinetic Report, Table 5.

Impact of naltrexone on bioavailability of Xtampza:

Collegium indicates that the abuse liability study CP-OXYDET-24 is representative of the limited food-effect with Xtampza. As noted above, majority of studies summarized were Phase 1 studies in healthy volunteers for which a naltrexone-block was provided prior to study drug administration in order to avoid opioid-related AEs. Naltrexone is an orally administered opioid antagonist typically, but not always, co-administered with opioids in Phase 1 healthy volunteer PK studies for safety reasons. While very few of the numerous opioid BA studies conducted with or without NTX have been published, a review of available published literature demonstrates that NTX can affect opioid BA. For example, Sathyan et al. in 2007 performed a study on the BA of OROS® hydromorphone, demonstrating that with NTX block, the hydromorphone C_{max} increased by 39% and the t_½ decreased by 4.5 hours, under fasting conditions (Sathyan et al., 2007). Bashaw et al. in 1995 performed a study on the BA of controlled-release morphine. Compared with morphine given alone, the apparent absorption half-life of morphine was decreased from 0.94 to 0.58 hours (*P* = 0.01), C_{max} was increased from 28.17 ng/mL to 32.26 ng/mL (*P* = 0.04), and AUC_{0-24h} increased from 215 hr•ng/mL to 265 hr•ng/mL (*P* < 0.01) during NTX blockade (Bashaw, Kaiko, Grandy, Reder, Goldenheim, 1995). Thus, the sponsor concludes that “it is apparent that NTX can alter the BA of several opioids”.

While Bashaw et. al. 1995 indicate the limited effect of naltrexone on morphine ER PK under fasting condition, they go on to mention that the observed difference is minimal and hence naltrexone can be used to block opioid effects in bioavailability studies.

Sathyan et. a. 2007 indicates some effect of naltrexone on OROS Hydromorphone ER PK under fasting condition. Hence, there is no evidence of naltrexone-effect on opioid bioavailability in fed state, or on the extent of food effect. As such, Xtampza bioavailability is low and variable under fasting condition across different studies.

Xtampza PK is variable under fed condition across different studies. Accordingly, the observed difference in food-effect may be due to between study variability.

Table: Mean (SD) PK parameters of oxycodone following single dose administration of Xtampza in different studies that were conducted with or without naltrexone-block. (Table represented from page 3 above)

Study Number	Fasted			HFHC Meal		
	C _{max} (ng/mL)	AUC _{clast} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)	C _{max} (ng/mL)	AUC _{clast} (hr•ng/mL)	AUC _{INF} (hr•ng/mL)
Naltrexone-blocked studies						
-15	31.5 (9.52)	343 (127)	373 (134)	51.9 (14.3)	498 (155)	518 (156)
-17	30.7 (7.09)	343 (85.6)	369 (89.5)	62.3 (13.0)	552 (123)	561 (124)
-19	ND	ND	ND	47.5 (7.89)	493 (110)	499 (110)
-25	ND	ND	ND	67.5 (17.6)	569 (139)	581 (138)
26	24.7 (9.41)	358 (120)	398 (114)	54.8 (14.6)	512 (105)	531 (105)
-27	22.3 (6.60)	317 (99.5)	339 (98.9)	55.3 (13.6)	529 (142)	540 (143)
Non-naltrexone blocked studies						
-21	ND	ND	ND	41.0 (9.95)	470 (93.1)	477 (89.6)
-24	30.9 (9.91)	408 (113)	469 (107)	41.9 (12.4)	511 (155)	553 (131)

Conclusion

In summary, Xtampza relative bioavailability is lower compared to OxyContin under fasting condition and taking Xtampza with food increases bioavailability. Based on the increase in fat and calorie content, bioavailability of Xtampza increased in terms of both C_{max} and AUC. Across different bioavailability studies conducted in naltrexone-blocked healthy subjects, an average 2-fold increase in exposure is noted when Xtampza is taken with some type of food, particularly high-fat high-calorie or medium-fat medium-calorie meal. It appears that due to the low bioavailability in fasting condition, some subjects could have up to a 5-fold increase in C_{max} when taken with high-fat high calorie meal. The impact of food on Xtampza bioavailability overshadows any possible effects of chewing, crushing, and possibly alcohol related dose dumping that may be noted if Xtampza were taken fasting.

In the current submission, the sponsor evaluated food-effect on the reformulated OxyContin and showed that an average increase of 52% C_{max} is noted compared to reformulated OxyContin taken while fasting. However, the variability in C_{max} increase with food-effect was much higher for Xtampza compared to OxyContin (see results above for study CP-OXYET-15). This observed variability in food-effect with Xtampza is due to low and variable PK of Xtampza in fasted-state which is not noted with OxyContin in fasted or fed-state. In addition, food has much less effect on AUC for OxyContin compared to Xtampza.

Currently available oxycodone extended-release tablet, OxyContin, does not have labeling restrictions with regard to diet. The original OxyContin product (withdrawn NDA 020553) did not exhibit clinically significant food-effect on bioavailability. The reformulation OxyContin product was found to be bioequivalent to originally approved OxyContin under fasting and fed conditions.

Collegium is proposing to label the oxycodone extended release capsules to be taken with food. In support of their argument that the observed variability in food-effect may not cause clinically significant safety or efficacy concerns, the sponsor has conducted a clinical trial CP-OXYDET-008.

The proposed labeling of Xtampza requiring dosing with food is different from current clinical practice for oxycodone products which do not have dietary restriction. The sponsor's plan to label Xtampza use with food will be discussed at the Advisory Committee meeting to be held on September 11, 2015. Additional product labeling, review recommendations may be made from a clinical pharmacology perspective after the AC meeting by an addendum.

1.4 General Biopharmaceutics:

The final formulation, Formulation J, was arrived at through a step-wise development program during which twelve formulations of Xtampza/Oxycodone DETERx were evaluated human subjects over the course of development. (b) (4)

The evolution of the tested formulations was based on the stage of both formulation and manufacturing process development.

Table: Composition of Xtampza/Oxycodone DETERx Capsules (Formulation J)

Ingredient	% w/w	Composition (mg/capsule)				
		10 mg ^a capsule	15 mg ^a capsule	20 mg ^a capsule	30 mg ^a capsule	40 mg ^a capsule
(b) (4)						(b) (4)
Oxycodone Base						
Myristic Acid						
Yellow Beeswax						
Carnauba Wax						
Stearoyl polyoxyl-32 glycerides						
(b) (4)						
Colloidal Silicon Dioxide						
Magnesium Stearate						
Total						
Hypromellose Capsule Shells						
Total Capsule Weight (mg)						

^a Capsule strengths expressed in oxycodone HCl equivalent during IND development stage and in the NDA. Commercial strengths will be named to reflect base content (9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg).
 Source: Module 3.2.P.1.
 w/w = weight for weight

2 Analytical:

For each clinical PK study, plasma levels of oxycodone in human plasma were determined using a validated, commercially available liquid chromatography-tandem mass spectrometry method (LC-MS/MS). The method validation report for each study is included as an appendix to the PK study report for each clinical study. Samples were prepared for analysis using a solid phase extraction procedure and analyzed using a triplequadrupole mass spectrometer.

Method validation results are listed below:

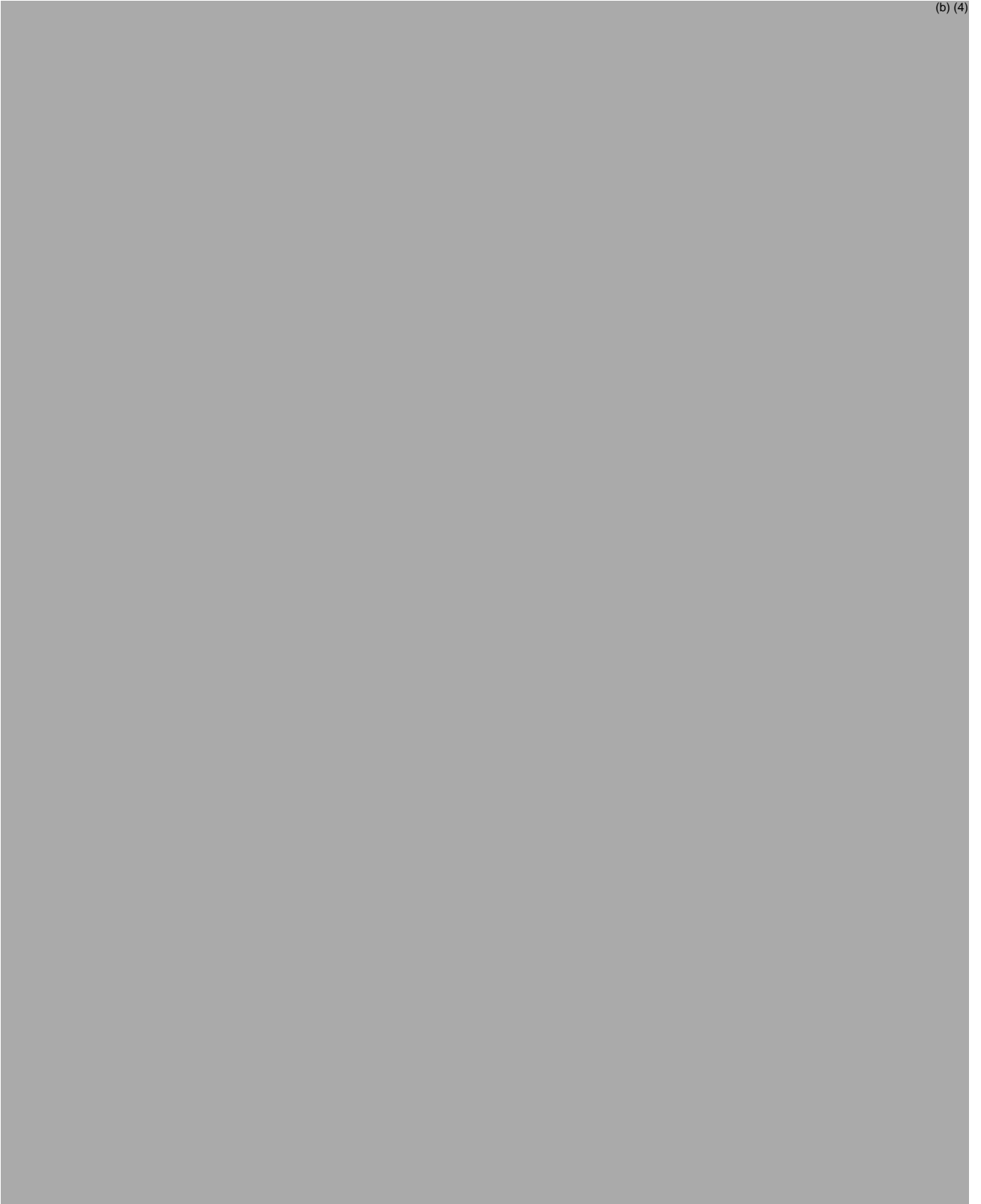
- Linearity range: 0.500 – 100 ng/mL
- Lower limit of quantitation: 0.500 ng/mL
- Overall recovery of drug (% mean) near the low, medium, and high quality control concentrations: 57% at 1.20 ng/mL, 66% at 15.0 ng/mL, 62% at 75.0 ng/mL

The LC-MS/MS method for the determination of oxycodone in human plasma (EDTA) met the requirements as specified in the validation protocol. Stability was demonstrated for oxycodone in human plasma (EDTA) samples and solutions for 24 hours at ambient temperature (short-term stability), for 51 hours at ambient temperatures (total of all thaw cycles), under 6 freeze/thaw cycles (-20°C, ambient temperature), and for 133 days at -20°C.

3 Appendices

3.1 Proposed labeling

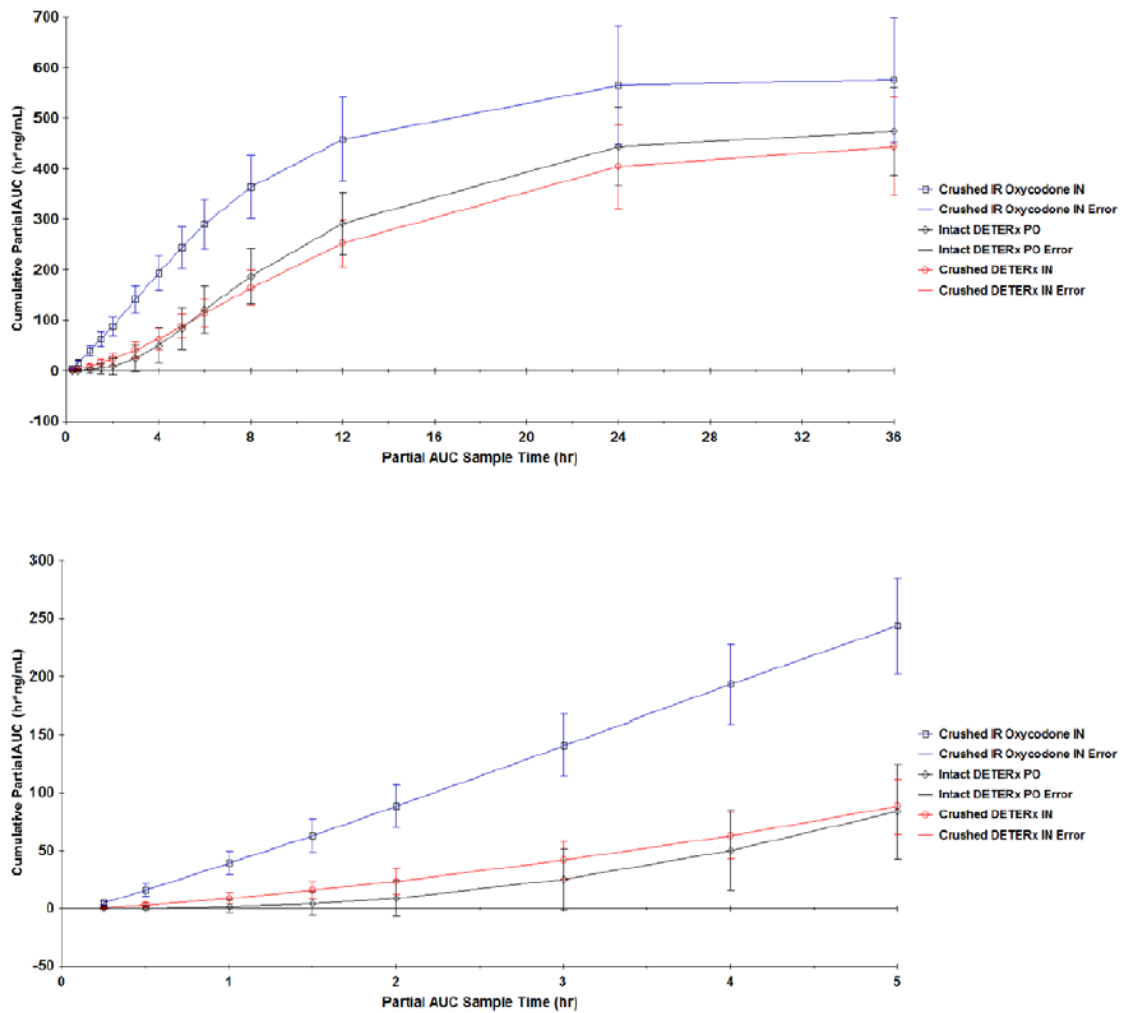
(b) (4)



23 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Mean $\pm$ SD Cumulative PAUC Values: All Treatments: PD Population (PD Population, N = 36)

(top panel: all data, 0 – 36 hr, bottom panel: expanded time scale, 0 – 5 hr)



IN = intranasal; *IR* = immediate-release; *PAUC* = partial area under the curve; *PD* = pharmacodynamic; *PO* = per os; *SD* = standard deviation.

Source: CP-OXYDET-21 Complete clinical study report

Summary Statistics: Oxycodone PK Parameters: PK Population

Treatment		T _{lag} (hr)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{last} (hr*ng/mL)	AUC _{INF} (hr*ng/mL)	AUC _{extrap} (%)	λz (1/hr)	t _{1/2} (hr)	Vz/F (L)	CL/F (L/hr)	Fr_IR (%)	Fr_PO (%)
Crushed Oxycodone DETERX IN	n	36	36	36	36	31	31	31	31	31	31	31	23
	Mean	0.00	29.8	5.78	440	459	3.64	0.121	6.02	779	91.8	79.3	95.7
	SD	0.00	6.58	2.40	101	106	4.40	0.0257	1.52	199	23.0	14.0	12.4
	Min	0.00	15.5	1.58	215	219	0.908	0.0739	4.01	415	54.2	35.7	71.9
	Median	0.00	29.2	5.08	416	436	1.74	0.124	5.57	739	91.8	80.7	93.4
	Max	0.00	43.5	12.10	712	738	20.5	0.173	9.38	1200	182	107	120
CV%	.	22.1	41.5	22.9	23.0	120.6	21.2	25.2	25.6	25.0	17.6	12.9	
Crushed Oxycodone IR IN	n	36	36	36	36	36	36	36	36	36	36	NA	27
	Mean	0.00	60.9	2.48	568	577	1.59	0.180	3.92	405	72.3	NA	117
	SD	0.00	11.9	1.75	124	124	0.838	0.0231	0.523	79.1	15.0	NA	13.2
	Min	0.00	44.7	0.28	359	362	0.462	0.126	3.00	268	42.2	NA	88.6
	Median	0.00	56.6	2.58	573	584	1.45	0.176	3.94	396	68.4	NA	113
	Max	0.00	94.5	6.05	944	949	4.05	0.231	5.50	580	111	NA	146
CV%	.	19.5	70.5	21.8	21.5	52.7	12.9	13.3	19.5	20.7	NA	11.3	
Intact Oxycodone DETERX PO	n	33	33	33	33	27	27	27	27	27	27	27	NA
	Mean	1.05	40.7	5.30	473	476	2.61	0.140	5.03	622	86.7	86.7	NA
	SD	0.60	8.87	1.49	93.1	90.5	2.35	0.0174	0.705	102	15.4	9.96	NA
	Min	0.00	27.6	1.58	329	345	0.705	0.100	4.15	454	58.8	68.7	NA
	Median	1.07	38.4	5.08	449	466	1.38	0.141	4.90	619	85.8	88.4	NA
	Max	2.08	66.9	8.08	666	680	11.5	0.167	6.92	925	116	113	NA
CV%	.	56.8	21.8	28.1	19.7	19.0	90.1	12.4	14.0	16.4	17.8	11.5	NA

WinNonlin Source: Worksheet: Sheet1: \Collegium\CP-OXYDET-21\PK Analysis 02-21-14\Table 4 PK Parameters PK Pop pwo (24-Feb-2014)

CV = coefficient of variation; Fr_IR = bioavailability relative to crushed IR oxycodone IN; Fr_PO = bioavailability relative to intact Oxycodone DETERX PO; IN = intranasal; IR = immediate-release; n = number of observations; NA = not applicable; PO = per os; SD = standard deviation; “.” = missing or not estimable.

Source: Table 4 CP-OXYDET-14 study report.

Least Square Mean Differences for PD Parameters for the Primary Endpoint Drug Liking – PD Population (N = 36)

	Least Square Mean Difference						
	E _{max} (mm)	AUE _{0-1h} (h-mm)	AUE _{0-2h} (h-mm)	AUE _{0-4h} (h-mm)	AUE _{0-8h} (h-mm)	AUE _{0-24h} (h-mm)	TE _{max} (h)
IR Oxycodone IN v Oxycodone DETERX IN ^a	20.69 ^c	22.39 ^{c,f}	43.23 ^{c,f}	72.66 ^{c,f}	99.90 ^{c,f}	97.96 ^{c,f}	-0.75 ^{d,f}
Oxycodone DETERX IN v Oxycodone DETERX PO ^b	-5.99 ^d	0.14 ^{e,f}	0.00 ^{e,f}	-7.52 ^{e,f}	-28.36 ^{d,f}	-45.25 ^{d,f}	-1.00 ^{e,f}
IR Oxycodone IN v Oxycodone DETERX PO ^a	14.70 ^c	22.55 ^{c,f}	43.20 ^{c,f}	64.06 ^{c,f}	68.37 ^{c,f}	52.29 ^{d,f}	-2.50 ^{c,f}

AUE = area under the effect curve; E_{max} = maximum (peak) effect; IN = intranasal; IR = immediate-release; PO = per os; PD = pharmacodynamic; TE_{max} = time to peak effect

Source: Table 14.2.1.1

^aPositive values for E_{max} and AUE indicate less drug liking for Oxycodone DETERX IN and Oxycodone DETERX PO than IR oxycodone IN; negative values for TE_{max} indicate longer period of time to reach peak effect with Oxycodone DETERX IN and Oxycodone DETERX PO than IR oxycodone IN.

^bNegative values for E_{max} and AUE indicate less drug liking for Oxycodone DETERX IN compared with Oxycodone DETERX PO; positive value for TE_{max} indicate longer period of time to reach peak effect with Oxycodone DETERX PO v Oxycodone DETERX IN.

^cp ≤ 0.0001

^dp ≤ 0.05

^enot significant

^fMedian differences using Hodges-Lehman estimates are reported due to the ranked analysis.

See detailed review of PD analysis by Dr. Anna Sun, statistics reviewer assisting Dr. James Tolliver, CSS reviewer.

Table S-1: Statistical Analysis of PD Parameters for the Primary Endpoint Drug Liking – PD Population (N = 38)

	LS Mean (SEM) Difference ^a for E _{max} , AUE _{0-2h} , AUE _{0-4h} , and AUE _{0-8h} and P-Value						
	E _{max} (mm)	AUE _{0-1h} (h·mm)	AUE _{0-2h} (h·mm)	AUE _{0-4h} (h·mm)	AUE _{0-8h} (h·mm)	AUE _{0-24h} (h·mm)	TE _{max} (h)
Primary Comparisons							
Chewed Oxycodone DETERx HFHC vs Crushed IR Oxycodone Fasted ^c	10.84 (2.246) < 0.0001	14.00 (1.212) < 0.0001	29.47 (2.537) < 0.0001	38.05 (6.295) < 0.0001	25.50 (11.605) 0.0293	17.77 (22.888) 0.3847	-2.00 (0.505) < 0.0001
Chewed Oxycodone DETERx Fasted vs Crushed IR Oxycodone Fasted ^c	7.73 (2.235) 0.0007	11.03 (1.594) < 0.0001	17.41 (2.523) < 0.0001	16.88 (6.261) 0.0077	7.76 (11.544) 0.5023	-3.75 (25.618) 0.5123	-1.00 (0.255) < 0.0001
Secondary Comparisons							
Chewed Oxycodone DETERx HFHC vs Intact Oxycodone DETERx HFHC ^d	1.79 (2.246) 0.4264	0.00 (0.130) 0.7309	3.88 (2.537) 0.1276	10.01 (6.295) 0.1134	2.57 (11.605) 0.8249	3.26 (19.776) 0.7924	0.00 (0.510) 0.6083
Chewed Oxycodone DETERx Fasted vs Intact Oxycodone DETERx HFHC ^d	4.89 (2.247) 0.0307	2.65 (0.895) < 0.0001	15.95 (2.537) < 0.0001	31.19 (6.295) < 0.0001	20.31 (11.606) 0.0818	21.69 (21.304) 0.0755	-1.00 (0.510) 0.0224
Chewed Oxycodone DETERx Fasted vs Intact Oxycodone DETERx Fasted ^d	4.52 (2.246) 0.0457	1.97 (0.926) < 0.0001	11.13 (2.537) < 0.0001	17.41 (6.295) 0.0063	15.21 (11.605) 0.1917	16.64 (21.396) 0.1670	0.00 (0.383) 0.5819
Other Relevant Comparisons							
Intact Oxycodone DETERx HFHC vs Crushed IR Oxycodone Fasted ^c	12.63 (2.246) < 0.0001	14.25 (1.191) < 0.0001	33.36 (2.537) < 0.0001	48.07 (6.295) < 0.0001	28.07 (11.605) 0.0166	24.13 (23.156) 0.2579	-2.50 (0.510) < 0.0001
Intact Oxycodone DETERx Fasted vs Crushed IR Oxycodone Fasted ^c	12.25 (2.247) < 0.0001	13.97 (1.179) < 0.0001	28.54 (2.537) < 0.0001	34.29 (6.295) < 0.0001	22.97 (11.606) 0.0493	19.20 (23.503) 0.4637	-1.50 (0.255) < 0.0001

AUE = area under the effect curve; E_{max} = maximum (peak) effect; HFHC = high-fat, high-calorie; IR = immediate-release; LS = least square; PD = pharmacodynamic; SEM = standard error of the mean; TE_{max} = time to peak effect

^a No Change to Final Analysis, Assumption Tests Met.

^b Normality Assumption Not Met, Rank Transformation Applied to the Data.

^c Positive value for E_{max} and AUE indicate lower Drug Liking scores for Oxycodone DETERx treatment than crushed IR Oxycodone fasted; negative value for TE_{max} indicates longer time to reach peak effect with Oxycodone DETERx treatment than crushed IR Oxycodone fasted.

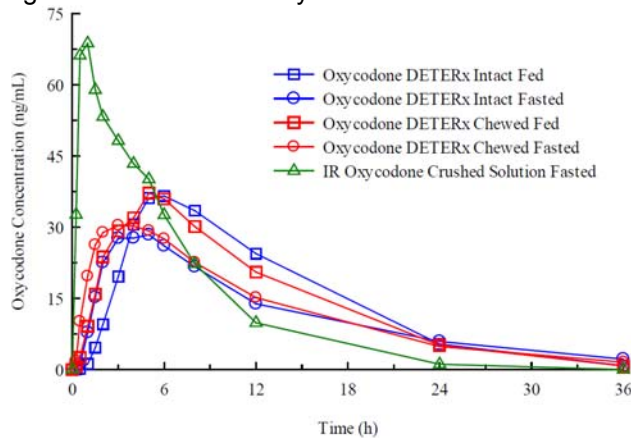
^d Positive value for E_{max} and AUE indicate higher Drug liking for the chewed Oxycodone DETERx treatment than intact Oxycodone DETERx treatment; negative value for TE_{max} indicates longer time to reach peak effect with chewed Oxycodone DETERx treatment than intact Oxycodone DETERx treatment.

Conclusions: This study demonstrates that administration of chewed Oxycodone DETERx in both the fed and fasted state resulted in less drug liking than crushed IR oxycodone in solution. Similarly, intact Oxycodone DETERx resulted in less drug liking than crushed IR oxycodone in solution. This decrease in drug liking for both chewed and intact oral administration in both the fasted and fed state suggests that the Oxycodone DETERx relative abuse potential is significantly lower when compared with a non abuse-deterrent formulation of crushed IR oxycodone in solution. Consistent patterns of response to most PD endpoints and parameters by treatment indicate a decreased abuse potential profile for Oxycodone DETERx relative to IR oxycodone.

Administration of chewed Oxycodone DETERx under fed or fasted conditions did not lead to any change in the PK profile compared with the corresponding intact Oxycodone DETERx treatment. See discussion of study results in summary of CPB findings.

Chewed Oxycodone DETERx under fed conditions demonstrated a similar C_{max} to that of intact Oxycodone DETERx under fed conditions (40.3 ± 12.2 ng/mL and 41.9 ± 12.4 ng/mL, respectively). Chewed Oxycodone DETERx under fasted conditions demonstrated a numerically higher C_{max} than intact Oxycodone DETERx under fasted conditions (35.5 ± 12.5 ng/mL and 30.9 ± 9.91 ng/mL, respectively), but is bioequivalent to intact Oxycodone DETERx fasted. Oxycodone DETERx chewed vs. intact treatments were bioequivalent with respect to C_{max}, AUC(0-t), and AUC(inf) and had comparable values for T_{max}, AQ, and Fr as well as the PAUC vs. time profiles. Administration of crushed IR oxycodone as a solution under fasted conditions resulted in a higher C_{max} at a shorter T_{max}, and thus a greater AQ, than after all methods of administration of Oxycodone DETERx. This was further supported by the comparisons of PAUCs. The results indicate that there is no dose dumping when Oxycodone DETERx is administered after chewing. Chewed Oxycodone DETERx under fasted conditions was bioequivalent to intact Oxycodone DETERx under both fasted and fed (HFHC) conditions for AUC(0-t) and AUC(inf), but not for intact Oxycodone DETERx fed C_{max}. Chewed Oxycodone DETERx fed was bioequivalent to intact Oxycodone DETERx Fed; similarly, chewed Oxycodone DETERx fasted and chewed Oxycodone DETERx fed were bioequivalent for all 3 bioequivalence comparison parameters. Administration of Oxycodone DETERx under fed conditions resulted in higher exposure compared with fasted conditions for both intact and chewed dosing. Total exposure after administration of crushed IR oxycodone in solution fasted, measured by AUC(0-t) and AUC(inf), was comparable to that from intact and chewed Oxycodone DETERx.

Figure: Mean Plasma Oxycodone Concentration following different Xtampza treatments.



IR = immediate-release; PAUC = partial area under the plasma concentration-time curve

Source: Figure 17 CP-OXYDET-24 study report.

Table 5: Descriptive Statistics of Oxycodone Cumulative PAUC.

Sampling Time (hr)*	Oxycodone DETERx Intact Fed	Oxycodone DETERx Intact Fasted	Oxycodone DETERx Chewed Fed	Oxycodone DETERx Chewed Fasted	IR Oxycodone Crushed Solution Fasted
0.00					
0.25	0.00 ± 0.00 (37)	0.00 ± 0.00 (40)	0.09 ± 0.25 (40)	0.27 ± 0.51 (44)	5.21 ± 4.32 (44)
0.50	0.02 ± 0.08 (37)	0.13 ± 0.24 (40)	0.47 ± 0.95 (40)	1.73 ± 1.86 (44)	17.86 ± 10.58 (44)
1.00	0.35 ± 1.10 (37)	2.34 ± 1.98 (40)	3.39 ± 3.95 (40)	9.05 ± 6.64 (44)	51.84 ± 20.86 (44)
1.50	1.79 ± 3.77 (37)	7.97 ± 4.97 (40)	9.49 ± 8.49 (40)	20.30 ± 12.05 (44)	83.29 ± 29.36 (44)
2.00	5.29 ± 7.37 (37)	17.48 ± 8.80 (40)	19.54 ± 13.88 (40)	33.98 ± 17.56 (44)	111.58 ± 36.97 (44)
3.00	19.92 ± 16.67 (37)	42.60 ± 16.96 (40)	46.00 ± 24.75 (40)	63.69 ± 27.81 (44)	162.70 ± 48.62 (44)
4.00	45.10 ± 27.28 (37)	69.94 ± 25.88 (40)	76.96 ± 35.96 (40)	93.97 ± 37.63 (44)	208.24 ± 56.97 (44)
5.00	78.28 ± 38.53 (37)	97.88 ± 34.53 (40)	111.29 ± 47.40 (40)	123.63 ± 46.33 (44)	250.06 ± 63.12 (44)
6.00	114.59 ± 47.60 (37)	124.74 ± 42.12 (40)	147.72 ± 56.63 (40)	151.97 ± 53.44 (44)	286.39 ± 67.51 (44)
8.00	184.76 ± 61.14 (37)	172.07 ± 55.06 (40)	213.87 ± 69.76 (40)	201.78 ± 66.12 (44)	341.33 ± 74.86 (44)
12.00	300.66 ± 80.98 (37)	242.48 ± 74.28 (40)	315.27 ± 83.99 (40)	276.67 ± 85.74 (44)	405.55 ± 85.76 (44)
24.00	478.72 ± 136.27 (37)	360.17 ± 104.76 (40)	468.86 ± 109.85 (40)	396.31 ± 116.99 (44)	467.59 ± 105.73 (44)
36.00	510.84 ± 155.36 (37)	408.22 ± 113.31 (40)	497.96 ± 123.44 (40)	432.79 ± 123.31 (44)	467.59 ± 105.73 (44)

*Arithmetic mean ± standard deviation (N). | IR = immediate-release; PAUC = partial area under the plasma concentration-time curve

Source: Listing 10.

difference in T_{max} values when comparing crushed OxyContin HFHC to intact OxyContin HFHC was -3.25 hr (i.e., T_{max} for crushed OxyContin was shorter), and was statistically different.

- Crushed OxyContin HFHC was BE to crushed IR oxycodone HFHC with respect to C_{max} , AUC_{last} , and AUC_{INF} .
- The abuse quotient values for crushed OxyContin HFHC and crushed IR oxycodone HFHC (which were similar) were much higher than that for intact OxyContin HFHC.
- Intact Oxycodone DETERx HFHC was BE to intact OxyContin HFHC.
- The PK parameters and statistical analyses for the Alternate PK Population were nearly identical to those derived for the PK Population. Overall interpretations were not affected by inclusion of subjects or exclusion of aberrant data points in the Alternate PK Population.

See clinical pharmacology summary for reviewer comments on this study.

Pharmacokinetic Conclusions:

The primary objective of this study was to evaluate the PK and relative bioavailability of Oxycodone DETERx 10 mg and 40 mg coingested with 0%, 20%, and 40% alcohol.

The PK results of the study showed:

- Overall bioavailability was greater for 0% Alcohol Fed compared with 0% Alcohol Fasted. This finding is consistent with other single-dose food effect studies with Oxycodone DETERx; the product is to be taken with food.
- Oxycodone DETERx coingestion with alcohol does not promote dose dumping. There is no dose dumping with the addition of alcohol to the fasted state versus the baseline state (fed with 0% alcohol). Administration of Oxycodone DETERx 40 mg or 10 mg with 40% and 20% alcohol under fasted conditions resulted in a rate and extent of exposure that was lower than that for 0% alcohol under fed conditions.
- Within each dosage strength cohort (40 mg and 10 mg) for all treatments, the rate of increase (see PAUC data) during the initial 2 to 3 hours was comparable, indicating that there was no dose dumping with alcohol coingestion.
- Administration of Oxycodone DETERx 40 mg or 10 mg with 40% and 20% alcohol under fasted conditions lead to an increase in the rate and extent of exposure, as measured by C_{max} , T_{max} , and AUC, compared with administration with 0% alcohol under fasted conditions; C_{max} and AUC in each of the above treatments were demonstrably lower than the Oxycodone DETERx 0% Alcohol Fed treatments, with the AQ being similar.
- Although the numeric increases in the mean PAUC over time over the initial 2 to 3 hours for the Oxycodone DETERx 40 mg or 10 mg with 40% and 20% alcohol under fasted conditions appear to be greater than for the corresponding Oxycodone DETERx 0% Alcohol Fasted treatment, overall, the PK profiles are comparable when the standard deviations are taken into account.

Overall Conclusions:

Consistent with previous single-dose food effect PK studies, administration of Oxycodone DETERx 40 mg or 10 mg under fasted conditions leads to a peak and overall exposure that is lower than that observed under fed conditions. As Oxycodone DETERx is to be taken with food, the baseline PK profile is established in the presence of food. The effect of co-ingestion of alcohol (40% or 20%) under fasted conditions is to increase the peak and overall exposure relative to 0% alcohol; however, the observed exposures remain lower than the baseline (control) exposure - administration under fed conditions with 0% alcohol.

3.2.12 Office of Clinical Pharmacology Filing Review:

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	208090		Brand Name	Xtampza
OCP Division (I, II, III, IV, V)	DCP2		Generic Name	Oxycodone Extended Release Capsules
Medical Division	DAAAP		Drug Class	Opioid
OCP Reviewer	Srikanth C. Nallani, Ph.D.		Indication(s)	Chronic Pain Management
OCP Team Leader	Yun Xu, Ph.D.		Dosage Form	Capsule
Pharmacometrics Reviewer	None		Dosing Regimen	B.I.D.
Date of Submission	12/12/2014		Route of Administration	Oral
Estimated Due Date of OCP Review	9/7/2015		Sponsor	Collegium Pharmaceuticals
Medical Division Due Date	10/9/2015		Priority Classification	Priority
PDUFA Due Date	10/12/2015			
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	CP-OXYDET-14 (Formulation Selection)
multiple dose:	X	1	1	CP-OXYDET-18 (Multiple dose relative BA/food-effect study)
Patients-				
single dose:				
multiple dose:	X	1	-	CP-OXYDET-08 Phase 3 study with PK assessments
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	Alcohol Interaction Study CP-OXYDET-26
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2	5	Abuse liability studies IN - CP-OXYDET-21 PK-PD IN CP-OXYDET-19 PK OralCP-OXYDET-17 PK OralCP-OXYDET-24 PK-PD Oral CP-OXYDET-25 PK
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	CP-OXYDET-14
replicate design; single / multi dose:				
Food-drug interaction studies	X	3	3	CP-OXYDET-14 CP-OXYDET-15 CP-OXYDET-16 CP-OXYDET-27 (Sprinkles on applesauce)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X	1	1	iPSP submitted and granted as of 11/16/2014.
Literature References				
Total Number of Studies		12	12	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	RLD

3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	X			
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-			X	

	response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Y			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

List of studies submitted include the tabulated (see next page) nine biopharmaceutics and clinical pharmacology studies. Additionally, One alcohol interaction study (CP-OXYDET-26), food effect study (CP-OXYDET-16), and PK data from clinical trial CP-OXYDET-08 were also submitted to the NDA. Most of the clinical pharmacology information as it relates to ADME is referred from the approved drug Oxycontin (NDA 022272).

Study	Description	Oxycodone DETERx Conditions	Oxycodone DETERx Meal States	Comparators
Relative Bioavailability and Food-Effect Studies (Naltrexone-Blocked)				
14	Relative oral BA and food-effect study of multiple Oxycodone DETERx formulations prepared at laboratory scale (formulation selection)	Intact	Fed Fasted	OxyContin OP (same fed/fasted regimen)
15	Relative oral BA and food-effect examining 3 meal types	Intact	Low-, medium-, or high-fat, calorie Fasted	OxyContin OP (high-fat, high-calorie or fasted)
18	Multiple-dose relative oral BA and food-effect study	Intact	Fed AM, fasted PM Fed AM, fed PM	OxyContin OP (same fed/fasted regimen)
Product Manipulation Studies (Naltrexone-Blocked)				
17	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Crushed Chewed	Fed Fasted	IR oxycodone solution (fasted)
19	Relative PK of intact (oral) vs manipulated (IN) Oxycodone DETERx	Intact (oral) Crushed (IN)	Fed	Crushed IR oxycodone (IN; fed)
25	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Crushed	Fed	Intact OxyContin OP (fed) Crushed OxyContin OP (fed) Crushed IR oxycodone (fed)
27	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Capsule contents (sprinkled on applesauce)	Fed Fasted	n/a
Clinical Abuse Potential Studies (Not Naltrexone-Blocked)				
21	Relative PK and drug likeability of intact (oral) vs manipulated (IN) Oxycodone DETERx	Intact Crushed	Fed	Crushed IR oxycodone (IN; fed) Placebo (fed)
24	Relative oral PK and drug likeability of intact (oral) vs manipulated (oral) Oxycodone DETERx	Intact Chewed	Fed Fasted	IR oxycodone in solution (fasted) Placebo (fed)

BA = bioavailability; IN = intranasal; IR = immediate release; PK = pharmacokinetics.

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist

Date

Yun Xu, Ph.D.

Team Leader/Supervisor

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
09/07/2015

YUN XU
09/08/2015

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	208090	Brand Name	Xtampza
OCP Division (I, II, III, IV, V)	DCP2	Generic Name	Oxycodone Extended Release Capsules
Medical Division	DAAAP	Drug Class	Opioid
OCP Reviewer	Srikanth C. Nallani, Ph.D.	Indication(s)	Chronic Pain Management
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Capsule
Pharmacometrics Reviewer	None	Dosing Regimen	B.I.D.
Date of Submission	12/12/2014	Route of Administration	Oral
Estimated Due Date of OCP Review	9/7/2015	Sponsor	Collegium Pharmaceuticals
Medical Division Due Date	10/9/2015	Priority Classification	Priority
PDUFA Due Date	10/12/2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		CP-OXYDET-14 (Formulation Selection)
multiple dose:	X	1		CP-OXYDET-18 (Multiple dose relative BA/food-effect study)
Patients-				
single dose:				
multiple dose:	X	1		CP-OXYDET-08 Phase 3 study with PK assessments
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:	X	1		Alcohol Interaction Study CP-OXYDET-26
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		Abuse liability studies IN - CP-OXYDET-21 PK-PD IN CP-OXYDET-19 PK OralCP-OXYDET-17 PK OralCP-OXYDET-24 PK-PD Oral CP-OXYDET-25 PK
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		CP-OXYDET-14
replicate design; single / multi dose:				
Food-drug interaction studies	X	3		CP-OXYDET-14 CP-OXYDET-15 CP-OXYDET-16 CP-OXYDET-27 (Sprinkles on applesauce)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X	1		iPSP submitted and granted as of 11/16/2014.
Literature References				
Total Number of Studies		12		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	RLD
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	X			
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-response			X	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

	relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Y			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

List of studies submitted include the tabulated (see next page) nine biopharmaceutics and clinical pharmacology studies. Additionally, One alcohol interaction study (CP-OXYDET-26), food effect study (CP-OXYDET-16), and PK data from clinical trial CP-OXYDET-08 were also submitted to the NDA. Most of the clinical pharmacology information as it relates to ADME is referred from the approved drug Oxycontin (NDA 022272).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study	Description	Oxycodone DETERx Conditions	Oxycodone DETERx Meal States	Comparators
Relative Bioavailability and Food-Effect Studies (Naltrexone-Blocked)				
14	Relative oral BA and food-effect study of multiple Oxycodone DETERx formulations prepared at laboratory scale (formulation selection)	Intact	Fed Fasted	OxyContin OP (same fed/fasted regimen)
15	Relative oral BA and food-effect examining 3 meal types	Intact	Low-, medium-, or high-fat, calorie Fasted	OxyContin OP (high-fat, high-calorie or fasted)
18	Multiple-dose relative oral BA and food-effect study	Intact	Fed AM, fasted PM Fed AM, fed PM	OxyContin OP (same fed/fasted regimen)
Product Manipulation Studies (Naltrexone-Blocked)				
17	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Crushed Chewed	Fed Fasted	IR oxycodone solution (fasted)
19	Relative PK of intact (oral) vs manipulated (IN) Oxycodone DETERx	Intact (oral) Crushed (IN)	Fed	Crushed IR oxycodone (IN; fed)
25	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Crushed	Fed	Intact OxyContin OP (fed) Crushed OxyContin OP (fed) Crushed IR oxycodone (fed)
27	Relative oral PK of intact vs manipulated Oxycodone DETERx	Intact Capsule contents (sprinkled on applesauce)	Fed Fasted	n/a
Clinical Abuse Potential Studies (Not Naltrexone-Blocked)				
21	Relative PK and drug likeability of intact (oral) vs manipulated (IN) Oxycodone DETERx	Intact Crushed	Fed	Crushed IR oxycodone (IN; fed) Placebo (fed)
24	Relative oral PK and drug likeability of intact (oral) vs manipulated (oral) Oxycodone DETERx	Intact Chewed	Fed Fasted	IR oxycodone in solution (fasted) Placebo (fed)

BA = bioavailability; IN = intranasal; IR = immediate release; PK = pharmacokinetics.

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist

Date

Yun Xu, Ph.D.

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SRIKANTH C NALLANI
02/09/2015

YUN XU
02/09/2015

3.2 Individual Study Synopses:

3.2.1 Study CP-OXYDET-14 Synopsis:

Title of Study: A Study to Assess the Safety and Pharmacokinetics of Single Dose Administration of Four Formulations of Oxycodone DETERx™ Compared with OxyContin®	
Investigators and Study Centers: Gregory Tracey, MD, Frontage Clinical Research Center, 241 Main Street, Hackensack, NJ 07601	
Publication (reference): Not applicable.	
Study Period: 8 weeks	Phase of Development: 1
Date of First Subject Enrolled: 31 March 2011	
Date of Last Subject Completed Visit: 25 May 2011	
Objectives: The objectives of this study were to assess the safety and pharmacokinetics of four formulations of Oxycodone DETERx in the fed and fasted states relative to a marketed formulation of oxycodone (OxyContin, NDA Reference 22.272) in the fed and fasted states	
Methodology: There were to be two parallel groups investigating 2 formulations each of Oxycodone DETERx in the fed and fasted states versus OxyContin in the fed and fasted states. Following Screening (Visit 1), subjects in each group were to be randomized to receive each of 6 treatments in random order:	
Group A • Oxycodone DETERx Formulation I in the Fed State • Oxycodone DETERx Formulation I in the Fasted State • Oxycodone DETERx Formulation J in the Fed State • Oxycodone DETERx Formulation J in the Fasted State • OxyContin in the Fed State • OxyContin in the Fasted State Group B • Oxycodone DETERx Formulation K in the Fed State • Oxycodone DETERx Formulation K in the Fasted State • Oxycodone DETERx Formulation L in the Fed State • Oxycodone DETERx Formulation L in the Fasted State • OxyContin in the Fed State • OxyContin in the Fasted State	
All dosing meals in the study were to follow the recommendation as described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. Following an overnight fast of at least 10 hours, subjects in the fed arms were to start a standardized, high-fat, high-calorie meal 30 minutes prior to the scheduled dosing time and were to complete the meal prior to dosing. For all Treatment Periods, subjects were to remain in the clinic during each Treatment Period until 36 hours after dosing. There were to be at least five days between each treatment. Subjects were to receive 50 mg naltrexone 13 hours prior and 1 hour prior to each dose of study medication in each Treatment Period.	
PK samples were to be collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 18.0, 24.0, 30.0 and 36.0 hours post-dose.	

Number of Subjects (planned and analyzed): Up to 36 subjects (18 per group) were to be enrolled and dosed with study drug. Thirty-six were actually enrolled, and all received at least 1 dose of study medication and are therefore included in the safety dataset. Analysis was based on the following populations:

Datasets Used	N
Safety	36
PK	
Group A: Formulation I Fed	15
Group A: Formulation I Fasted	14
Group A: Formulation J Fed	15
Group A: Formulation J Fasted	15
Group A: OxyContin Fed	14
Group A: OxyContin Fasted	15
Group B: Formulation K Fed	16
Group B: Formulation K Fasted	18
Group B: Formulation L Fed	18
Group B: Formulation L Fasted	18
Group B: OxyContin Fed	18
Group B: OxyContin Fasted	17

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Subject must provide written informed consent and privacy authorization prior to participation in the study. Subject must have the ability to read and/or follow written and oral instructions.
2. Subject is male or female 18-50 years of age (inclusive) at the time of consent.
3. Subject does not have any dietary restrictions and is able to consume a complete high-fat, high-calorie meal prior to dosing.
4. Female subject has a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at admission for each period.
5. Female subject of childbearing potential will use an acceptable method of birth control. Acceptable birth control includes total abstinence from sexual intercourse for a minimum of 1 complete menstrual cycle prior to the Screening Visit, a vasectomized partner that had a vasectomy a minimum of 6 months prior to the Screening Visit, contraceptives (oral, parenteral, or transdermal) used for a minimum of 12 weeks prior to the start of dosing in Period 1, intrauterine device used for a minimum of 12 weeks prior to the start of dosing in Period 1, or double barrier method including condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream throughout the study. Subjects taking birth control pills must have taken the same type pill for at least 12 weeks prior to the Screening Visit and must not change their dosing regimen during the study. Subjects who discontinued the use of birth control pills must have discontinued usage at least eight weeks prior to the start of dosing in Period 1. Subjects considered not of childbearing potential must be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) or greater than one year post menopausal, defined as a complete cessation of menstruation for at least one year.
6. Subject must be in general good health based on screening physical examination (defined as the absence of any clinically relevant abnormalities), medical history, 12-lead ECG, and clinical laboratory values (hematology, serum chemistry and urinalysis).

Exclusion Criteria:

1. Female subject who is pregnant, planning a pregnancy, or breastfeeding.
2. Subject has a Body Mass Index (BMI) > 33 kg/m².
3. Subject has any clinically significant unstable medical abnormality or chronic disease of the cardiovascular, gastrointestinal, respiratory (e.g., chronic obstructive pulmonary disease), hepatic, or renal systems.
4. Subject has any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG, or clinical laboratory measurements, as determined by the Investigator.
5. Subject has history of alcohol and/or drug abuse in Investigator's judgment. A negative urine drug screen is required at the Screening Visit and at admission for each period.
6. Subject who cannot refrain from taking medications (prescription or over-the-counter), supplements, or herbs for 24 hours prior to admission to the clinic (Period 1) and for the duration of the study. Note: contraceptives are the only exception (see Inclusion Criteria #5).
7. Subject who cannot refrain from using caffeine or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who cannot tolerate stopping caffeine without symptoms are excluded.
8. Subject currently uses tobacco products or smokes cigarettes. Subject must have stopped using tobacco products or smoking cigarettes ≥ 30 days prior to Screening Visit.
9. Subject who cannot refrain from strenuous activity for 3 days prior to admission to the clinic (Period 1) and for the duration of the study.
10. Subject has a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion.
11. Subject is known to be allergic to any of the test product(s) or any components in the test product(s)
12. Subject has participated in any investigational study within 30 days prior to Screening Visit or is currently participating in another clinical trial.
13. Subject has experienced significant blood loss within 60 days or has donated plasma within 72 hours prior to the start of dosing.
14. Subject tests positive at screening for HIV or is known to be seropositive for HIV.
15. Subject tests positive at screening for hepatitis B surface antigen, hepatitis C antibody or has a history of a positive result.
16. Subject is a staff member or relative of a staff member.
17. Subject is not able to meet the study attendance requirements.

Test Product, Dose and Mode of Administration, Batch Number:

Oxycodone DETERx 40 mg oxycodone HCl equivalent; Capsules for Oral Administration:

- Formulation I; Batch OXY-03312011- Form I
- Formulation J; Batch OXY-04012011- Form J
- Formulation K; Batch OXY-03312011- Form K
- Formulation L; Batch OXY-03312011- Form L

Reference Therapy, Dose and Mode of Administration, Batch Number:

OxyContin® 40 mg oxycodone HCl; Tablets for Oral Administration
Batch WBT41 (NDA Reference 22,272, "OxyContin OP")

Duration of Treatment: For each Treatment Period, subjects were to receive 1 single dose.

Criteria for Evaluation:

Efficacy: No efficacy variables were assessed in this PK study.

Safety: The incidence of treatment-emergent Adverse Events (AEs) was to be assessed in each Treatment Period. Other safety parameters were to include the monitoring of vital signs in each Treatment Period. Hematologic, biochemical, and urinalysis variables were to be assessed during screening and prior to discharge from the study.

Pharmacokinetics: During each Treatment Period, serial blood samples for PK evaluation were to be collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 18.0,

24.0, 30.0, and 36.0 hours post-dose. Maximum observed concentration ($C_{\max}$), time to maximum concentration ($T_{\max}$), area under the curve (AUC_{last} , AUC_{INF}), λ_z , and half-life ($t_{1/2}$) for oxycodone were to be calculated using standard noncompartmental PK methods.

Statistical Methods: The sample size was adequate to conduct a bioequivalence analysis between the products in each group. Summary statistics by treatment received were to be calculated for the oxycodone pharmacokinetic parameters. Two one-sided confidence intervals for $C_{\max}$, AUC_{last} , and AUC_{INF} were to be calculated:

- For all formulations with fed as test treatment and fasted as reference treatment;
- For all DETERx formulations administered in the fed state with OxyContin as the reference treatment; and
- For all DETERx formulations administered in the fasted state with OxyContin as the reference treatment.

Summary:

Safety:

There were no Serious Adverse Events (SAEs) or deaths reported during the study. The type and incidence of AEs reported during the study were consistent with prior studies of Oxycodone DETERx. All treatments were well tolerated and there was no evidence of a difference in the safety profile or adverse effects by treatment. The safety profiles of Oxycodone DETERx were similar irrespective of fasted or fed states and all treatment conditions were well tolerated. The most commonly reported AEs in Group A were vomiting, nausea, somnolence, dizziness, headache, constipation, and diarrhea. The most commonly reported AEs in Group B were nausea, headache, and dizziness. Numerical differences in AEs by formulation were noted, but the numbers were too small to ascertain if these represented evidence of clinically relevant differences. There were no severe AEs. In Group A, one AE (vomiting in the OxyContin fasted arm) was considered moderate, and all other AEs were considered mild. In Group B, two AEs (hyperkalemia in the OxyContin fed arm and panic attack in DETERx Formulation L fed arm) were considered moderate, and all other AEs were considered mild. AEs by relationship and severity do not suggest any particular trend. None of the AEs were definitely related. AEs considered to be probably related (constipation, vomiting, somnolence, nausea, headache, and hot flush) and possibly related (abdominal distention, abdominal pain, diarrhea, epigastric discomfort, vomiting, increased alanine aminotransferase, increased blood creatinine, dizziness, headache, somnolence, malaise, and dysuria) were those anticipated with the use of oxycodone. AEs considered to be possibly related (nausea, stomach discomfort, vomiting, fatigue, dizziness, and headache) were those anticipated with the use of oxycodone. AEs by relationship and severity do not suggest any particular trend.

Pharmacokinetics:

- After administration with a high-fat/high-calorie meal, Fed to Fasting OxyContin $C_{\max}$ LSMeans ratios were 134% and 123% for Groups A and B, respectively; AUC values (fed versus fasting) were bioequivalent.
- Similar to that observed with OxyContin, Oxycodone DETERx formulations also exhibited higher $C_{\max}$ values after dosing with a high-fat/high-calorie meal, relative to fasting. Fed to Fasting $C_{\max}$ LSMeans ratios for Formulations I, J, K and L were 202%, 167%, 188% and 203%, respectively. Fed to Fasting AUC_{INF} LSMeans ratios for Formulations I, J, K and L were 151%, 154%, 181% and 123%, respectively.
- After administration with a high-fat/high-calorie meal, all four Oxycodone DETERx formulations were bioequivalent (BE) with OxyContin with respect to extent of absorption (AUC_{last} and AUC_{INF}). Formulation K $C_{\max}$ was BE to OxyContin $C_{\max}$ after administration of a high-fat/high-calorie meal. $C_{\max}$ values for Formulations I, J and L did not meet BE criteria after administration of a high-fat/high-calorie meal.
- None of the four Oxycodone DETERx formulations were bioequivalent to OxyContin when administered in the fasting state.
- Of the four formulations tested, Formulation J had the lowest within subject variability (ANOVA CV) for $C_{\max}$ (fed to fasting comparison).

- With the exception of Formulation J, Fasting, female exposure was generally higher than that observed for male subjects. On average, across all groups, including OxyContin, C_{max} and AUC_{INF} were approximately 25% higher in females compared to males.
- Formulation J was selected for future clinical development based upon the observations that it exhibited the lowest within subject variability for C_{max} (based upon ANOVA CV, fed to fasting comparison) and the lowest C_{max} LSMean ratio (Fed to Fasting).

Conclusions:

The objectives were to assess the safety and pharmacokinetics of four formulations of Oxycodone DETERx in the fed and fasted states relative to a marketed formulation of oxycodone (OxyContin, NDA 22,272) in the fed and fasted states. Formulation J was selected for future clinical development based upon the observations that it exhibited the lowest within subject variability for C_{max} (based upon ANOVA CV, fed to fasting comparison) and the lowest C_{max} LSMean ratio (Fed to Fasting).

The safety profiles of all formulations of Oxycodone DETERx were similar to OxyContin; all formulations were well tolerated. AEs were those anticipated in an opioid study with concomitant administration of naltrexone. Possibly and probably related AEs were those anticipated with the use of oxycodone. No clinically significant changes in vital signs were observed. No deaths or AEs were reported during this study.

Date of the Report: FINAL 19 Jul 2011

3.2.2 Study CP-OXYDET-15 Synopsis:

Title of Study: An Assessment of the Pharmacokinetics and Safety of Single Dose Administration of Oxycodone DETERx™ 40 mg in the Fasted State, with a High-Fat, High-Calorie Meal, with a Medium-Fat, Medium-Calorie Meal, and with a Low-Fat, Low-Calorie Meal Compared with OxyContin® 40 mg in the Fasted State and with a High-Fat, High-Calorie Meal	
Investigators: Michael McDonnell, MD - INC Research Toronto, Inc., Toronto, ON, Canada.	
Study Center: INC Research Toronto, Inc. 720 King Street West, 7th Floor Toronto, ON M5V 2T3 Canada	
Publication (Reference): Not applicable	
Study Period: 19SEP2012 to 09NOV2012	Phase of development: 1
Objectives: The primary objective was to assess the safety and pharmacokinetics (PK) of Oxycodone DETERx in various fed and fasted states relative to a marketed formulation of oxycodone (OxyContin OP; herein “OxyContin”) in the fed and fasted states.	
Methodology: This was an open-label, randomized, active-controlled, naltrexone-blocked, crossover comparison study designed to assess the safety and PK of Oxycodone DETERx 40 mg when dosed with a high-fat, high-calorie (HFHC) meal, with a medium-fat, medium-calorie (MFMC) meal, and with a low-fat, low-calorie (LFLC) meal, as well as in the fasted state, compared with OxyContin 40 mg dosed with an HFHC meal and in the fasted state. Subjects were randomized to receive each of 6 treatments: • Oxycodone DETERx 40 mg in the fasted state • Oxycodone DETERx 40 mg with an LFLC meal • Oxycodone DETERx 40 mg with an MFMC meal • Oxycodone DETERx 40 mg with an HFHC meal • OxyContin 40 mg in the fasted state • OxyContin 40 mg with an HFHC meal For both the fed and fasted arms, subjects received 1 dose of the assigned treatment following an overnight fast of at least 10 hours. For the fed arms, subjects had to complete the meal prior to dosing. The HFHC meal followed the recommendation described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. The MFMC meal contained approximately 400 calories with approximately 20% of the total caloric content from fat. The LFLC meal followed the recommendation described in the FDA Guidance for Industry: A Food Labeling Guide, dated October 2009 (low calorie is defined as 120 calories or less per 100 g; low-fat is defined as 3 g of fat or less per 100 g and not more than 30% of calories from fat) and contained approximately 107 calories with approximately 22% of the total caloric content from fat. Subjects also received 50 mg naltrexone hydrochloride (HCl) approximately 13 hours and 1 hour prior to each dose of study medication in each Treatment Period. There were at least 5 days between each dose of study drug.	
Number of Subjects (planned and analyzed): Up to 48 subjects were planned to be randomized to the Treatment Phase. Forty-eight (48) subjects were enrolled and assigned to treatment sequences, and 45 subjects received all planned doses. All 48 randomized subjects were included in the Safety Population. A total of 45 to 46 subjects per treatment were included in the PK Population and the Alternate PK Population.	
Diagnosis and Main Criteria for Inclusion: Healthy adult males and females, 18 to 50 years of age (inclusive), representative of American demographics.	

Test Product, Dose, Mode of Administration, and Batch No.: Oxycodone DETERx 40 mg, oral administration. Batch number: 3101451 (capsule batch number: 3100363R), expiry date: 31 May 2013.
Reference Product, Dose, and Mode of Administration: Commercially available OxyContin 40 mg oxycodone HCl (NDC 59011-440-10, imprinted with "OP"), expiry date: 31 March 2014, oral administration.
Adjunctive Product, Dose, Mode of Administration: Commercially available naltrexone 50 mg, expiry date: 31 December 2014, oral administration.
Duration of Treatment: Each subject participated in the study for approximately 7 weeks. Screening was performed up to 2 weeks prior to first dosing. The Open-label Treatment Phase was approximately 5 weeks, containing 6 Treatment Periods, separated by a washout of at least 5 days. Each subject received 1 treatment in each Treatment Period.
Criteria for Evaluation: <u>PHARMACOKINETICS:</u> For Treatment Periods OxyContin HFHC and OxyContin Fasted, blood sampling continued for 48 hours after dosing. For Treatment Periods Oxycodone DETERx Fasted, Oxycodone DETERx HFHC, Oxycodone DETERx MFMC, and Oxycodone DETERx LFLC, blood sampling continued for 96 hours after dosing. C_{max}, T_{max}, T_{lag}, AUC_{last}, AUC_{0-inf}, $AUC_{%extrap}$, λ_z, $t_{1/2}$, CL/F, Vd/F, and PAUC for oxycodone were calculated using non-compartmental PK methods. <u>SAFETY:</u> The incidences of treatment-emergent adverse events (TEAEs) were assessed in each Treatment Period. Other safety parameters included the monitoring of vital signs and oxygen saturation in each Treatment Period. Hematologic, biochemical, and urinalysis variables were assessed at Screening, prior to discharge in Treatment Period 3 (hemoglobin only), and prior to discharge from the study. Statistical Methods: <u>PHARMACOKINETICS:</u> Plasma concentrations and PK parameters were listed and summarized by treatment. A mixed model was fitted on log-transformed AUC_{last}, AUC_{0-inf}, and C_{max} with sequence, treatment, and period number as fixed effects and subject as the random effect. From this model, geometric least square mean (LSMean) estimates with 90% confidence intervals (CIs) for each treatment were estimated, as well as estimates and 90% CIs for differences between each of the 4 Oxycodone DETERx treatments and each of the 2 OxyContin treatments. These estimates were exponentiated to produce geometric LSMean estimates for each of the treatments, and estimated mean ratios with their 90% CIs were calculated. These ratios were expressed as a percentage relative to the reference treatment. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios were entirely within the 80.00% to 125.00% limits. T_{max} was compared among the treatments using the non-parametric Wilcoxon rank-sum test. Significant differences in T_{max} values for the treatment comparisons were concluded if the p-value from the Wilcoxon signed-rank test was <0.05. <u>SAFETY:</u> Safety data were listed and summarized by treatment.
SUMMARY – CONCLUSIONS
<u>PHARMACOKINETIC RESULTS:</u> Oxycodone plasma concentrations were higher when dose administration occurred after a meal compared with when dose administration occurred in the fasted state.

Oxycodone Pharmacokinetic Parameters - PK Population

Parameter Statistics		Oxycodone DETERx				OxyContin	
		Fasted (N=45)	LFLC (N=46)	MFMC (N=45)	HFHC (N=45)	Fasted (N=46)	HFHC (N=46)
C _{max} (ng/mL)	n	45	46	45	45	46	46
	Mean	31.46	37.50	58.01	51.85	42.30	63.11
	SD	9.5225	9.5713	18.880	14.362	10.448	12.860
	%CV	30.3	25.5	32.5	27.7	24.7	20.4
T _{max} (hr)	n	45	46	45	45	46	46
	Min	1.00	1.50	1.03	2.50	1.50	1.50
	Median	2.500	2.500	3.500	4.500	4.500	4.750
	Max	5.50	7.00	8.00	12.0	8.00	8.00
T _{lag} (hr)	n	45	46	45	45	46	46
	Min	0.00	0.00	0.00	0.00	0.00	0.00
	Median	0.5000	0.5000	1.000	1.500	0.000	0.2500
	Max	1.50	1.50	2.00	4.00	0.500	1.00
t _{1/2} (hr)	n	43	46	45	40	46	45
	Mean	14.63	8.750	6.886	5.648	4.602	4.157
	SD	14.793	4.9272	5.0401	1.1931	0.67671	0.85130
	%CV	101	56.3	73.2	21.1	14.7	20.5
AUC _{last} (ng•hr/mL)	n	45	46	45	45	46	46
	Mean	343.4	396.9	468.5	498.3	470.1	544.8
	SD	127.01	125.42	160.31	155.86	139.19	146.26
	%CV	37.0	31.6	34.2	31.3	29.6	26.8
AUC _{0-inf} (ng•hr/mL)	n	43	46	45	40	46	45
	Mean	373.2	410.0	478.6	518.0	480.3	552.6
	SD	133.84	125.63	159.13	156.59	137.94	148.55
	%CV	35.9	30.6	33.2	30.2	28.7	26.9

CV = coefficient of variation; HFHC = high-fat, high-calorie; LFLC = low-fat, low-calorie; Max = maximum; MFMC = medium-fate, medium-calorie; Min = minimum; N = number of subjects in treatment group; n = number of subjects used in the calculations; SD = standard deviation.

Oxycodone DETERx median T_{max} values were generally slightly earlier than those for OxyContin, except for the median T_{max} after the Oxycodone DETERx HFHC treatment. An increase in lag time was observed after treatment with Oxycodone DETERx HFHC and, to a lesser extent, after Oxycodone DETERx MFMC as a result of the food regimen.

The apparent terminal half-lives observed in this study reflected continued absorption from the extended-release dosage forms rather than true elimination of oxycodone; t_{1/2} values reported for all treatments were longer than the reported t_{1/2} following immediate-release oxycodone (3.2 hr). In this study, the mean t_{1/2} was shorter after administration with HFHC meals. The mean t_{1/2} was shortest after OxyContin HFHC and longest after Oxycodone DETERx Fasted.

Bioequivalence was concluded for the Oxycodone DETERx LFLC and OxyContin Fasted treatments, for the Oxycodone DETERx MFMC and OxyContin HFHC treatments, and for the Oxycodone DETERx MFMC and Oxycodone DETERx HFHC treatments. Although bioequivalence could not be concluded for any of the other treatments tested in this study because of C_{max} differences, the extent of absorption (AUC) across several treatment arms was equivalent. AUC_{0-inf} was equivalent across the Oxycodone DETERx MFMC, OxyContin Fasted, Oxycodone DETERx HFHC, and OxyContin HFHC treatments. AUC_{0-inf} was also equivalent across the OxyContin Fasted, Oxycodone DETERx MFMC, and Oxycodone DETERx LFLC treatments and across the Oxycodone DETERx LFLC and Oxycodone DETERx Fasted treatments.

SAFETY RESULTS:

There were no deaths and no serious adverse events (SAEs) in this study. None of the subjects were discontinued by the Investigator because of TEAEs. The overall safety profiles of the Oxycodone DETERx and OxyContin formulations were similar, except that gastrointestinal disorders and nervous system disorders were slightly more frequently observed following Oxycodone DETERx administration than following OxyContin administration.

Between 6.5% (3 subjects after OxyContin HFHC) and 29.8% (14 subjects after Oxycodone DETERx Fasted) of the subjects receiving the various treatments reported TEAEs during the study.

Most of the TEAEs were of mild intensity; of the 82 TEAEs, only 8 were of moderate intensity and only 1 was of severe intensity. Seven of the TEAEs of moderate intensity and the TEAE of severe intensity were reported by 3 subjects in the Oxycodone DETERx Fasted treatment, and 1 TEAE of moderate intensity was reported by 1 subject in the Oxycodone DETERx LFLC treatment. Reported TEAEs of moderate or severe intensity were vomiting (4 adverse events [AEs]), headache (2 AEs, 1 of which was severe), nausea (1 AE), abdominal pain (1 AE), and asthenia (1 AE).

Approximately 80% (65 of 82) of the reported TEAEs were considered probably or possibly related to the study drug. The most frequently reported treatment-related TEAEs were somnolence (12 subjects), nausea (5 subjects), headache (5 subjects), dizziness (4 subjects), and vomiting (3 subjects).

Nausea and vomiting were only reported after treatment with Oxycodone DETERx. Dizziness, headache, and somnolence were reported after treatment with Oxycodone DETERx as well as after treatment with OxyContin. Dizziness and headache were reported in similar frequencies after Oxycodone DETERx treatment and after OxyContin treatment. Somnolence was reported more frequently after Oxycodone DETERx treatment than after OxyContin treatment: 5, 4, 3, and 7 subjects following the Oxycodone DETERx Fasted, LFLC, MFMC, and HFHC treatments, respectively, versus 2 subjects following both the HFHC and Fasted OxyContin treatments.

There were no subjects with clinically significant results for clinical laboratory, vital signs, physical examination, oxygen saturation, or electrocardiogram (ECG) assessments.

OVERALL CONCLUSIONS:

- Oxycodone plasma concentrations were higher when dose administration occurred after a meal compared with dose administration in the fasted state.
- Oxycodone plasma concentrations and exposure were generally higher after OxyContin treatment than after Oxycodone DETERx when comparing similar fed or fasted treatments.
- Oxycodone DETERx median T_{max} values were generally slightly earlier than those for OxyContin, except for the median T_{max} after the Oxycodone DETERx HFHC treatment.
- An increase in lag time was observed after treatment with Oxycodone DETERx HFHC and, to a lesser extent, after Oxycodone DETERx MFMC as a result of the food regimen.
- The apparent terminal half-lives observed in this study reflected continued absorption from the extended-release dosage forms rather than true elimination of oxycodone. In this study, the mean $t_{1/2}$ was generally shorter after administration of study drug with HFHC meals. The mean $t_{1/2}$ was shortest after OxyContin HFHC and longest after Oxycodone DETERx Fasted.
- Bioequivalence was concluded for the Oxycodone DETERx LFLC and OxyContin Fasted treatments, for the Oxycodone DETERx MFMC and OxyContin HFHC treatments, and for the Oxycodone DETERx MFMC and Oxycodone DETERx HFHC treatments. Although bioequivalence could not be concluded for any of the other treatments tested in this study because of C_{max} differences, the extent of absorption (AUC) for several treatments was equivalent. AUC_{0-inf} was equivalent across the Oxycodone DETERx MFMC, OxyContin Fasted, Oxycodone DETERx HFHC, and OxyContin HFHC treatments. AUC_{0-inf} was also equivalent across the OxyContin Fasted, Oxycodone DETERx MFMC and Oxycodone DETERx LFLC treatments and across the Oxycodone DETERx LFLC and Oxycodone DETERx Fasted treatments.
- The overall safety profiles of the Oxycodone DETERx and OxyContin formulations were similar, except that gastrointestinal disorders and nervous system disorders were slightly more frequently observed following Oxycodone DETERx administration than following OxyContin administration.
- There were no subjects with clinically significant results for clinical laboratory, vital sign, physical examination, oxygen saturation, or ECG assessments.

Date of the report: 22NOV2013

3.2.3 Study CP-OXYDET-17 Synopsis:

Title of Study: An Assessment of the Safety and Pharmacokinetics of Multiple Dose Administration of Oxycodone DETERx™ 40 mg Compared with OxyContin® 40 mg Under Two Different Fed States
Principal Investigator: Michael McDonnell, BSc, MD, FRCPC – INC Research Toronto, Inc., Toronto, ON, Canada
Sub-Investigators:  (b) (6)
Investigators' curricula vitae are available in Appendix 16.1.4 . Form FDA 1572 is available in Appendix 16.1.4 .
Study Center: INC Research Toronto, Inc. 720 King Street West, 7 th Floor Toronto, ON M5V 2T3 Canada
Project Managers:  (b) (6) INC Research Toronto, Inc.
Biostatistician:  (b) (6)
Medical Writer:  (b) (6)

Objective:

The primary objective was to assess the safety and pharmacokinetics (PK) of Oxycodone DETERx in various fed and fasted states relative to a marketed formulation of oxycodone (OxyContin) following multiple dose administration.

Methodology: This was an open-label, randomized, active-controlled, naltrexone-blocked, crossover comparison study designed to assess the safety and PK of multiple dose administration of 40 mg Oxycodone DETERx compared with OxyContin 40 mg dosed under 2 different fed states.

Subjects were randomized to receive each of 4 treatments:

- A: OxyContin 40 mg with a high-fat, high-calorie (HFHC) meal for all doses
- B: OxyContin 40 mg fasted for all morning doses and with an HFHC meal for all evening doses
- C: Oxycodone DETERx 40 mg with an HFHC meal for all doses
- D: Oxycodone DETERx 40 mg fasted for all morning doses and with an HFHC meal for all evening doses

The schedule of assessments is included in [Table 1](#).

All pre-dose meals in the study were to follow the recommendation as described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. Subjects receiving either study drug with an HFHC meal for all doses were planned to receive the assigned treatment twice daily (morning and evening) for 4 days (Days 1 to 4) followed by a morning dose only on Day 5. Subjects receiving either study drug with an HFHC meal prior to all evening doses were planned to receive the assigned treatment twice daily (morning and evening) for 5 days (Days 1 to 5). For all arms, subjects began an overnight fast of at least 10 hours prior to the scheduled dosing time. For the fed doses, subjects started consuming an HFHC meal 30 minutes prior to administration of the study drug.

Subjects were planned to receive 50 mg naltrexone 13 hours prior to the first dose of study drug in each Treatment Period and 1 hour prior to each dose of study drug on all dosing days. A subject who vomited after receiving the naltrexone dose 1 hour prior to the scheduled study drug dosing was not dosed with study drug.

Subjects were planned to be discharged from the clinic 12 hours post-last dose (from last dosing of study drug on Day 5). Subjects were only discharged if the Investigator deemed it was safe. An interval of approximately 7 days between treatments was planned to provide a washout of study drug before the subjects were crossed over to the next treatment.

See the protocol in [Appendix 16.1.1](#) for additional study information. The Ontario Institutional Review Board contact information and documentation of approvals are provided in [Appendix 16.1.3](#).

The study was terminated early in Period 1 due to an error in the evening HFHC meals (more than double the amount of food planned in the protocol) that was served to all 36 enrolled subjects (further details can be found in the deviation report in the Trial Master File). As a result of the meal error, 14 of the 36 enrolled subjects were unable to complete the meal and did not receive the Day 1 evening dose of study drug.

Therefore, analysis of the primary endpoint was no longer possible, and the study was stopped on Day 2 of Period 1.

Protocol Deviations

Protocol deviations are presented for all individuals in [Appendix 16.2.2](#) and are summarized by category in [Table 14.1.3](#).

The study was terminated early on Day 2 of Period 1 due to an error in the evening HFHC meals that were served to all 36 enrolled subjects. The subjects received more than double the amount of food (HFHC meal) planned in the protocol (further details can be found in the deviation report in the Trial Master File). As a consequence, the PK data collected in this Treatment Period were invalid and the study was terminated early.

All other protocol deviations concerned late or missing assessments or missing or incorrect documentation of assessment times or results.

SUMMARY – CONCLUSIONS**PHARMACOKINETIC RESULTS:**

PK results were not analyzed due to early termination of the study.

Table 1 Schedule of Assessments

	Screening Phase	Treatment Phase			
Visit:	1	Period 1	Period 2	Period 3	Period 4
Days:	-14 to -1	0-6	13-19	26-32	39-45
Informed Consent	X				
Demography	X				
Medical History	X	X			
Prior Medications	X	X			
Physical Exam	X				X
Weight and Height	X				
12-lead ECG	X				
HIV/HBV/HCV Screen	X				
Serum Pregnancy	X				
Urine Pregnancy		X ¹	X ¹	X ¹	X ¹
Vital Signs	X	X ²	X ²	X ²	X ²
Oxygen Saturation		X ³	X ³	X ³	X ³
Randomization		X			
Serum Chemistry	X				X ⁴
Hematology	X			X ⁴	X ⁴
Urinalysis	X				X ⁴
Urine Drug Screen	X	X ¹	X ¹	X ¹	X ¹
Cotinine	X	X	X	X	X
Breath Alcohol	X	X	X	X	X
Naltrexone Dosing		X ⁵	X ⁵	X ⁵	X ⁵
Study Drug		X ⁶	X ⁶	X ⁶	X ⁶
Pharmacokinetics		X ⁷	X ⁷	X ⁷	X ⁷
Adverse Events	X ⁸	← Monitored Throughout →			
Concomitant Medications	X	← Monitored Throughout →			
End-of-Study					X ⁹

ECG=electrocardiogram; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

Note: The “days” noted above reflect that there are approximately 7 days between each treatment.

1. Urine pregnancy test for all women and urine drug screen occurred upon check-in to the clinic. The results were to be negative for the subject to continue.

3.2.4 Study CP-OXYDET-17 Synopsis:

Title of Study: An Open-label, Randomized, Seven-Period, Crossover Study to Evaluate the Effect of Tampering on Oxycodone DETERx™ Compared with Oxycodone Solution	
Principal Investigator: Investigator: (b) (4)	
Study center: Frontage Clinical Services, 241 Main Street, Hackensack, NJ 07601 USA	
Publications (reference): None	
Studied period (years): Date first subject enrolled: 05-Dec-2012 Date last subject completed: 01-Feb-2013	Phase of development: I
Objectives: The primary objective of this study was to assess the safety and pharmacokinetics (PK) of Oxycodone DETERx intact, crushed, and chewed in the fed and fasted states relative to an oxycodone solution administered in the fasted state.	
Methodology: This was an open-label, randomized, active-controlled, naltrexone-blocked, cross-over comparison study designed to assess the safety and PK of Oxycodone DETERx 40 mg when dosed with a high-fat, high-calorie (HFHC) meal as well as in the fasted state, compared with an oxycodone solution administered in the fasted state. Eligible healthy adult male and female subjects, 18-50 years of age, inclusive, were randomly assigned to receive each of the following seven treatments according to a randomization schedule prepared prior to the start of the study: • Oxycodone DETERx 40 mg (capsule intact) in the Fasted State • Oxycodone DETERx 40 mg (capsule intact) with a HFHC Meal • Oxycodone DETERx 40 mg (capsule contents crushed) in the Fasted State • Oxycodone DETERx 40 mg (capsule contents crushed) with a HFHC Meal • Oxycodone DETERx 40 mg (capsule contents chewed) in the Fasted State • Oxycodone DETERx 40 mg (capsule contents chewed) with a HFHC Meal • Oxycodone IR Solution 40 mg (Reference) in the Fasted State During each Period, eligible subjects were admitted to the study site the evening prior to dosing and began an overnight fast of at least 10 hours. All subjects received an oral dose of 50 mg naltrexone hydrochloride (HCl) with approximately 240 mL noncarbonated, room temperature water approximately 13 hours and 1 hour prior to their scheduled dose of study drug. Subjects in the fasted arms were administered their assigned dose of study drug at approximately 0800 hours with approximately 240 mL noncarbonated, room temperature water. Subjects in the fed arms consumed a HFHC breakfast, beginning 30 minutes prior to study drug administration, which they completed within approximately 20 minutes. The HFHC meal followed the recommendation described in the Food and Drug Administration (FDA) Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002.³⁰ Subjects assigned to receive Oxycodone IR Solution were administered study drug as a 240 mL solution and did not receive additional water.	

Following administration of Oxycodone DETERx in the fasted state (Oxycodone DETERx Intact Fasted, Oxycodone DETERx Crushed Fasted, and Oxycodone DETERx Chewed Fasted), serial blood samples for PK evaluation were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 12.0, 24.0, 36.0, 48.0, 60.0, and 72.0 hours post-dose.

Following administration of Oxycodone DETERx in the fed state (Oxycodone DETERx Intact HFHC, Oxycodone DETERx Crushed HFHC, and Oxycodone DETERx Chewed HFHC), serial blood samples for PK evaluation were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 12.0, 24.0, 36.0, and 48.0 hours post-dose.

Following administration of Oxycodone IR Solution, serial blood samples for PK evaluation were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours post-dose.

There was a washout period of at least 5 days between each dose of study drug.

The incidence of treatment-emergent adverse events (TEAEs) was assessed in each Treatment Period. Adverse events were collected from the first dose of study drug to discharge from the study. Serious adverse events were collected from the time of informed consent to 30 days post last dose. Other safety parameters included the monitoring of vital signs during each Treatment Period. Hematologic, biochemical, and urinalysis variables were assessed at screening and prior to discharge from the study. All safety assessments may have been repeated if deemed to be in the best interest of the subject, per Investigator discretion.

Number of subjects (planned and analyzed):

It was planned that 44 eligible subjects would be enrolled. Forty-four subjects were enrolled and randomized to receive study drug, 40 (90.9%) subjects completed the study and 40 (90.9%) subjects received all doses as planned. Forty-two (95.5%) subjects were included in the PK analysis populations.

Diagnosis and main criteria for inclusion:

Eligible subjects were healthy male or non-pregnant female volunteers who provided written informed consent, 18-50 years of age, inclusive, with a body mass index $>33 \text{ kg/m}^2$.

Test product, dose and mode of administration, batch number:

Oxycodone DETERx 40 mg oxycodone HCl equivalent was administered to subjects orally intact, chewed and crushed under fed and fasted conditions. Batch No. 3105260, Expiry/Retest Date: May 2013.

Duration of treatment:

All subjects underwent a Screening Phase of up to 3 weeks and a Treatment Phase of up to approximately 5 weeks.

Reference therapy, dose and mode of administration, batch number:

Oxycodone HCl Oral Solution, 100 mg/5 mL, was administered orally as 40 mg to subjects under fasted conditions. Lot No. 35300812, Expiry Date: Jan 2014.

Other drug, dose and route of administration, batch number:

Naltrexone HCl (Barr Laboratories, Pomona, NY 10970) 50 mg was administered orally. Lot No. 3400725A. Expiration date: January 2015.

Criteria for evaluation:

Pharmacokinetics:

T_{lag} , C_{max} , T_{max} , AUC_{last} , AUC_{INF} , $AUC_{\%extrap}$, λ_z , $t_{1/2}$, apparent CL/F, apparent Vd/F, Fr, Partial AUC, $PAUC_{IR}$, and AQ for plasma oxycodone were calculated using noncompartmental PK methods using WinNonlin version 5.3 (Pharsight Corporation, St. Louis, MO).

Safety:

The incidence of TEAEs was assessed in each Treatment Period. Adverse events were collected from the first dose of study drug to discharge from the study. Serious adverse events were collected from the time of informed consent to 30 days post last dose. Other safety parameters included the monitoring of

vital signs and oxygen saturation during each Treatment Period. Hematologic, biochemical, and urinalysis variables were assessed at screening and prior to discharge from the study.

Statistical methods:

Analysis of variance (ANOVA) was performed on the ln-transformed AUC_{last} , AUC_{INF} , and C_{max} . The ANOVA model included sequence, treatment (i.e. food status), and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance; all other main effects were tested using the residual error (error mean square). Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. These calculations were done using SAS[®] (version 9.3 for Windows, SAS Institute, Inc., Carey, NC) generalized linear model procedure.

Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC_{last} , AUC_{INF} , and C_{max} . These ratios were expressed as a percentage relative to the reference (oxycodone solution) treatment. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios fell entirely within the 80.0-125% limits.

Bioequivalence CI calculations were performed for all treatments versus Oxycodone DETERx 40 mg (capsule intact) in the fasted state; all treatments versus Oxycodone DETERx 40 mg (capsule intact) with a HFHC Meal; and all treatments versus Oxycodone IR Solution in the fasted state.

T_{max} was analyzed using nonparametric analysis. The 25% Quantile (Q1), 50% Quantile (Median), and 75% Quantile (Q3) was calculated from the Walsh Averages of the treatment differences. Wilcoxon Signed Rank Test was used to compare the test treatments versus reference treatments (using the same comparisons as shown above). T_{max} was not transformed; results are reported.

Safety and tolerability were assessed through TEAEs, vital signs measurements, oxygen saturation, and hematologic, biochemical, and urinalysis laboratory parameters.

Safety summaries are provided for all subjects in the safety population. Adverse event data, clinical laboratory test results, physical examination findings, ECG, vital signs data, and blood oxygen saturation data are presented descriptively using summary tables and listings. Change and shift from

baseline in clinical laboratory results are presented descriptively using summary tables and listings. Physical examination findings are listed by subject, and summarized.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

- The PK parameters and statistical analyses for the Alternate PK Population were nearly identical to those derived for the PK Population. Overall interpretations were not affected by inclusion of subjects or exclusion of aberrant data points in the Alternate PK Population.
- The AUC of the fasting Oxycodone IR Solution was bioequivalent (BE) to that of the intact Oxycodone DETERx capsule when administered with a HFHC meal.
- The Oxycodone IR Solution represents the worst case scenario, i.e., total loss of controlled-release characteristics. Relative to Intact Oxycodone DETERx administered with a HFHC meal, the Oxycodone IR Solution point estimate for C_{max} was 184%.
- When administered with a HFHC meal, both the crushed and chewed contents of the Oxycodone DETERx capsules were BE to the intact Oxycodone DETERx capsules demonstrating that crushing or chewing the contents of the Oxycodone DETERx capsules does not alter oxycodone exposure.
- The Oxycodone DETERx Crushed Fasting treatment was BE to the Oxycodone DETERx Intact Fasting treatment. Thus, crushing does not alter the exposure of oxycodone when administered in the fasting state.
- The Oxycodone DETERx Chewed Fasting AUC values were BE to the Oxycodone DETERx Intact Fasting values.

- C_{max} values were not BE; the Oxycodone DETERx Chewed Fasting C_{max} was lower than both the Oxycodone DETERx Intact HFHC (point estimate 63.56%) and the Oxycodone IR Solution (reference) (point estimate 34.63%) treatments. Thus, the C_{max} observed after chewing in the fasted state remained lower than that of Oxycodone DETERx Intact HFHC and was low relative to the Oxycodone IR Solution.
- Mean (SD) AQ values for Oxycodone DETERx Chewed Fasted, Oxycodone DETERx Chewed HFHC, Oxycodone DETERx Crushed Fasted, Oxycodone DETERx Crushed HFHC, Oxycodone DETERx Intact Fasted and Oxycodone DETERx Intact HFHC were 24.99 (25.84), 13.96 (4.49), 13.61 (9.11), 14.43 (4.50), 10.97 (5.54), and 19.70 (8.71), respectively. The AQ value for the Oxycodone IR Solution dose was the highest of all treatments: 167.81 (75.86). Statistical comparisons demonstrated that Oxycodone DETERx Crushed Fasted was not different from Oxycodone DETERx Intact Fasted; similarly, Oxycodone DETERx Chewed Fasted was not different from Oxycodone DETERx Intact HFHC. Although all other comparisons were statistically significant ($p < 0.05$), the differences between the Oxycodone DETERx manipulated and intact treatments were small in comparison to the Oxycodone IR Solution.
- The Oxycodone DETERx $PAUC_{IR}$ (using median solution T_{max}) values were small compared with Oxycodone IR Solution. Oxycodone DETERx Intact Fasted and HFHC treatment $PAUC_{IR}$ values were only 3.3% and 2.0% of the Oxycodone IR Solution $PAUC_{IR}$, respectively. When the Oxycodone DETERx capsule contents were crushed, the $PAUC_{IR}$ values for HFHC and Fasted treatments increased to only 5.8% and 10.2% of the Oxycodone IR Solution $PAUC_{IR}$, respectively. Chewing the Oxycodone DETERx capsule contents provided the highest $PAUC_{IR}$ values, but these were still much less than that of the Oxycodone IR Solution (11.3% and 18.5%, respectively).

CONCLUSIONS:

The data from this study demonstrated that the potential for Oxycodone DETERx abuse by chewing or crushing the contents of Oxycodone DETERx capsules may be very low; crushing or chewing Oxycodone DETERx did not significantly increase C_{max} or total exposure, which may be considered key determinants of facilitating abuse.

Up to seven single oral doses of oxycodone 40 mg, administered as an Oxycodone DETERx capsule (intact, crushed or chewed) under fed or fasted conditions, or as an immediate-release solution administered under fasted conditions, were safe and well-tolerated in this healthy, naltrexone-blocked adult population.

Date of the report: 27 November 2013

3.2.5 Study CP-OXYDET-18 Synopsis:

Title of Study: An Assessment of the Safety and Pharmacokinetics of Multiple Dose Administration of Oxycodone DETERx™ 40 mg Compared With OxyContin® 40 mg Under Two Different Fed States	
Principal Investigator: Gregory J. Tracey, M.D.	
Subinvestigator: (b) (4)	
Study center(s): Frontage Clinical Services, Inc., 241 Main Street, Hackensack, NJ 07601 USA	
Publications (reference): None	
Studied period (years): Date first subject enrolled: 19DEC2012 Date last subject completed: 02MAR2013	Phase of development: I
Objective: The primary objective of this study was to assess the safety and pharmacokinetics (PK) of Oxycodone DETERx in various Fed and Fasted states relative to a marketed formulation of oxycodone (OxyContin) following multiple-dose administration.	
Methodology: This was an open-label, randomized, active-controlled, naltrexone-blocked, crossover comparison study designed to assess the safety and PK of multiple-dose administration of Oxycodone DETERx 40 mg compared with OxyContin 40 mg dosed under 2 different Fed states. Eligible healthy adult men and women 18 to 50 years of age, inclusive, were randomly assigned to receive each of the following 4 treatments according to a randomization schedule prepared prior to the start of the study: • Treatment A: OxyContin 40 mg with a High-Fat, High-Calorie (HFHC) Meal for all doses • Treatment B: OxyContin 40 mg in the Fasted state for all morning doses and with a HFHC Meal for all evening doses • Treatment C: Oxycodone DETERx 40 mg with a HFHC Meal for all doses • Treatment D: Oxycodone DETERx 40 mg in the Fasted state for all morning doses and with a HFHC Meal for all evening doses There was a washout period of approximately 7 days between each treatment (i.e., between the last dose in one Treatment Period and the first dose in the next Treatment Period). During each Period, eligible subjects were admitted to the study site the evening prior to dosing and began an overnight fast of at least 10 hours. All subjects received 50 mg of naltrexone hydrochloride (HCl) orally approximately 13 hours and 1 hour prior to administration of study drug. Subjects receiving Treatments A and C were administered the assigned treatment twice daily (morning and evening) for 4 days (Days 1 through 4), followed by a morning dose only on Day 5. Subjects receiving Treatments B and D were administered the assigned treatment twice daily (morning and evening) for 5 days (Days 1 through 5). In the Fasted arms of the study, dosing of study drug must have taken place within the allotted time after an overnight fast of at least 10 hours. For the Fed doses, subjects started consuming a HFHC meal 30 minutes prior to administration of the study drug. Blood samples for the measurement of oxycodone concentrations were taken at regular intervals pre and post study drug dose. Pharmacokinetic profiles of oxycodone after each study treatment were derived from plasma concentration data.	
Number of subjects (planned and analyzed): It was planned that up to 40 eligible subjects would be enrolled. Forty-five subjects were enrolled in the study and randomized to receive study drug. Thirty-two subjects (71.1%) received all planned doses and completed the study. Thirteen subjects (28.9%) discontinued from the study prematurely.	

Duration of treatment:

Subjects received study drug for 5 consecutive days in each Treatment Period. All subjects underwent a Screening Phase of up to 21 days and a Treatment Phase of up to approximately 6 weeks.

Reference therapy, dose and mode of administration, batch number:

Oxycodone HCl (OxyContin[®]; Purdue Pharma LP, Stamford, CT) 40 mg administered orally under Fed and Fasted conditions. Lot No. WLH51.

Other drug, dose and route of administration, batch number:

Naltrexone HCl (Barr Laboratories, Inc., Pomona, NY) 50 mg administered orally. Lot No. 34007251A.

Criteria for evaluation:**Study populations:**

- The PK Population included subject treatments with sufficient quantifiable data in at least 2 Treatment Groups and who did not experience emesis during the 12-hour dosing intervals on Day 5.
- The Alternate PK Population included subject treatments in the PK Population and those subjects who experienced emesis after time to reach maximum plasma concentration (T_{max}). Eligibility for inclusion in this population was determined by an experienced Pharmacokineticist. The PK Analysis Plan permitted subjects with apparently aberrant PK data to be excluded from the Alternate PK Population after consulting with the Sponsor.
- The Safety Population consisted of all subjects who received at least 1 dose of study drug and for whom there was at least 1 posttreatment safety observation.

PK variables:

- C_{max} : maximum observed plasma concentration
- T_{max} : time to reach maximum plasma concentration
- C_{min} : minimum observed plasma concentration
- T_{min} : time to reach minimum plasma concentration
- AUC_{TAU} : area under the plasma concentration vs. time curve from time zero to the end of the dosing interval (12 hours postdose)
- AUC_{0-24} : area under the plasma concentration vs. time curve, summed for 2 dosing intervals for Treatments B and D
- C_{ave} : average plasma concentration; AUC_{TAU} divided by the dosing interval
- CL_{ss}/F : steady state apparent clearance; $Dose/AUC_{TAU}$
- %PTF: Percentage of peak-trough fluctuation within a dosing interval, calculated as $100 \cdot (C_{max} - C_{min})/C_{ave}$
- Swing: $(C_{max} - C_{min})/C_{min}$

Safety variables:

- Treatment-emergent adverse events (TEAEs)
- Vital sign and oxygen saturation measurements
- Physical examinations
- Clinical laboratory evaluations

Statistical methods:

Plasma concentration-time data were summarized by treatment with descriptive statistics at each scheduled time point. For descriptive summaries and PK parameter derivation, plasma concentrations that were below the lower limit of quantification were set to a value of zero. Concentration-time data for individual subjects were analyzed by noncompartmental methods using actual blood collection times (as specified in the protocol) in WinNonlin[®] version 5.3 (Pharsight Corp., St. Louis, MO).

To test for steady state, regression analysis was used to test the slope of trough value vs. time for each Treatment Group. The models contained effect for study day (slope) and intercept. Because of potential diurnal effects, AM and PM troughs were tested separately. For Fed/Fed Treatments (Treatments A and C), the regression model contained Days 2 through 5, 3 through 5, and 4 through 5. For Fasted/Fed Treatments (Treatments B and D), the model contained Days 2 through 6, 3 through 6, and 4 through 6. Note that the model for Days 5 through 6 was run only for AM troughs. The results of each model (intercept, slope, and *P* value) were to be presented for each Treatment Group and dosing time (AM or PM).

Analysis of variance (ANOVA) was performed on the ln-transformed C_{max} , C_{min} , AUC_{TAU} , and AUC_{0-24} . The ANOVA model included sequence, treatment (and food status), and period as fixed effects and subject nested within sequence as a random effect. Thirty-one subjects received Treatment Period 1 study drug on 7JAN2013 (Group 1), and a second set of 9 subjects (Group 2) received Treatment Period 1 study drug on 20JAN2013. Because of this, effects for Group and Treatment by Group interaction were added to the initial model. The interaction term was tested first. If it was found to be statistically significant, then both Group effect and Treatment by Group interaction were to remain in the final model. If the interaction term was not found to be statistically significant, then Group effect was to be tested. If Group effect was not found to be statistically significant, then it was not to be included in the final model. If Group effect was statistically significant, then it was to remain in the final model for the analysis of all subjects. Additionally, secondary analyses were to be completed excluding subjects in Group 2 due to the small sample size of Group 2. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance; all other main effects were tested using the residual error (error mean square). Because Group effect and Treatment by Group interaction were not statistically significant for any of the comparisons, neither was included in the final statistical model. Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. These calculations were performed using SAS[®] (SAS Institute, Inc., Cary, NC) MIXED procedure.

Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed C_{max} , C_{min} , AUC_{TAU} , and AUC_{0-24} . These ratios were expressed as a percentage relative to the reference treatment. Consistent with the two 1-sided tests for bioequivalence, 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios were entirely within the 80.00% to 125.00% limits.

The T_{max} was analyzed using nonparametric analysis. The 25% quantile, 50% quantile (median), and 75% quantile were calculated from the Walsh Averages of the treatment differences. The Wilcoxon signed rank test was used to compare the test treatments vs. reference treatments (using the same comparisons as shown above). The T_{max} was not transformed; the results are reported.

Safety summaries are provided for all subjects in the Safety Population. Adverse event data, clinical laboratory test results, physical examination findings, electrocardiogram (ECG) and vital sign data, and blood oxygen saturation data are presented descriptively using summary tables and listings. Change and shift from baseline in clinical laboratory results are presented descriptively using summary tables and listings. Physical examination findings are listed by subject and are summarized.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Pharmacokinetic analyses yielded the following observations regarding Oxycodone DETERx and OxyContin when administered in the Fed and Fasted states:

- Analysis of trough concentrations indicated that steady state concentrations were achieved by Day 2 for all treatment arms.
- Dosing Oxycodone DETERx capsules with food (AM Fed and PM Fed Treatment) produced steady state oxycodone profiles that were bioequivalent (BE) to those of OxyContin. The Oxycodone DETERx median T_{max} was slightly shorter than that of OxyContin when Oxycodone DETERx was taken as directed (“take with food”); the median T_{max} values were 3.5 and 4.5 hours for Oxycodone DETERx and OxyContin, respectively. Although this was a statistically significant difference, the sponsor opines that this difference may not be clinically

significant. Steady state fluctuations were comparable between the 2 treatments; mean (standard deviation [SD]) Oxycodone DETERx and OxyContin fluctuations were 134% (35.8%) and 127% (18.9%), respectively. Reviewer comments are included in the summary of clinical pharmacology findings above.

- Alternating Fasted and Fed doses produced BE steady state (Day 5) concentration-time profiles for Oxycodone DETERx and OxyContin. The AUC_{0-24} and C_{max} BE 90% CIs were 84.04% to 92.84% and 82.38% to 93.72%, respectively. The median difference in T_{max} values was 0.00 hours and was not statistically significant ($P = 0.7249$). Steady state fluctuations were nearly identical between the 2 treatments; mean (SD) Oxycodone DETERx and OxyContin fluctuations were 140% (27.5%) and 139% (34.4%), respectively.
- When comparing the Oxycodone DETERx and OxyContin AM (Fasted) doses from the alternating Fasted/Fed Treatments, C_{max} was BE (90% CI, 81.53%–93.76%), but bioequivalence with respect to AUC_{TAU} could not be concluded (90% CI, 78.42%–89.78%). The median difference in T_{max} values between OxyContin and Oxycodone DETERx was –0.50 hours but was not statistically significant ($P = 0.0625$). Steady state fluctuations were nearly identical between the 2 treatments; mean (SD) Oxycodone DETERx and OxyContin fluctuations were 101% (19.6%) and 99.3% (27.1%), respectively.
- Comparing the Oxycodone DETERx and OxyContin PM (Fed) doses from the alternating Fasted/Fed Treatments, AUC_{TAU} and C_{max} were BE (90% CIs, 87.31%–96.36% and 82.03%–92.83%, respectively). The median difference in T_{max} values was 0.50 hours but was not statistically significant ($P = 0.0690$). Steady state fluctuations were nearly identical between the 2 treatments; mean (SD) Oxycodone DETERx and OxyContin fluctuations were 122% (21.5%) and 125% (27.7%), respectively.
- When comparing PM (Fed) doses with AM (Fasted) doses for OxyContin from the alternating Fasted/Fed Treatments, AUC_{TAU} was BE (90% CI, 112.69%–118.96%) but C_{max} was not (90% CI, 122.21%–137.05%). The median difference in T_{max} values was 1.25 hours and was statistically significant ($P < 0.0001$). For Oxycodone DETERx, bioequivalence could not be demonstrated for AUC_{TAU} or C_{max} (90% CIs, 119.57%–132.16% and 120.56%–137.40%, respectively). The median difference in T_{max} values was 3.25 hours and was statistically significant ($P < 0.0001$).
- The PK parameters and statistical analyses for the Alternate PK Population were nearly identical to those derived for the PK Population. Overall interpretations were not affected by exclusion of the 1 subject-treatment who was excluded because of an adverse event (diarrhea) that affected absorption of the second dose on Day 5.

CONCLUSION:

The data from this study demonstrate that when study drug was taken as directed (i.e., with food) and as intended (i.e., multiple dosing as in the treatment of chronic pain), Oxycodone DETERx and OxyContin were BE. Additionally, when the proposed dosing instruction for Oxycodone DETERx was not adhered to (dosing alternated between Fasted and Fed administration), the steady state PK profiles of Oxycodone DETERx and OxyContin were similar; over the AM and PM dosing intervals, bioequivalence was established for C_{max} (AM and PM) and AUC_{TAU} (PM); AUC_{TAU} (AM) 90% CIs were just below the 80.00% limit (78.42%–89.78%).

Multiple-dose administration of Oxycodone DETERx in either the Fed or Fasted state was well tolerated in this population of healthy, naltrexone-blocked adults.

Date of the report: 29MAY2014

3.2.6 Study CP-OXYDET-19 Synopsis:

Title of Study: An Assessment of the Safety and Pharmacokinetics of Intranasal (“Snorted”) Administration of Crushed Oxycodone DETERx™ 40 mg, Oral Administration of Intact Oxycodone DETERx™ 40 mg, and Intranasal Oxycodone Powder 40 mg	
Principal Investigator: Glen Apseloff, M.D., F.C.P.	
Subinvestigators: [REDACTED] (b) (4)	
Study center(s): Ohio Clinical Trials, Inc., 1380 Edgehill Road, Columbus, OH 43212 USA	
Publications (reference): None	
Studied period (years): Date first subject enrolled: 04APR2013 Date last subject completed: 08MAY2013	Phase of development: I
Objective: The primary objective of this study was to compare the safety and pharmacokinetics (PK) of crushed Oxycodone DETERx following intranasal (IN) administration, intact Oxycodone DETERx capsules following per os (PO) administration, and oxycodone powder following IN administration.	
Methodology: This was an open-label, randomized, active-controlled, naltrexone-blocked, crossover study. Eligible healthy adult male and female subjects, 18 to 55 years of age, inclusive, were randomly assigned to receive each of the following 3 treatments according to a randomization schedule prepared prior to the start of the study: • Crushed Oxycodone DETERx 40 mg dosed IN after a High-Fat, High-Calorie (HFHC) meal • Intact Oxycodone DETERx 40 mg dosed PO after a HFHC meal • Oxycodone powder 40 mg dosed IN after a HFHC meal Subjects received 1 dose of the assigned treatment following a HFHC breakfast. Subjects fasted overnight for at least 10 hours prior to the start of the meal and must have completed the meal before dosing. Prior to receipt of any oxycodone formulation, subjects underwent a naloxone challenge test. The test was administered on Admission to the clinic on Day 0 of Treatment Period 1 to identify subjects with physical dependence on opioids. In the naloxone challenge, each subject received a subcutaneous bolus dose of 0.8 mg of naloxone hydrochloride (HCl) and was observed over the course of 20 minutes for signs and/or symptoms of withdrawal using the Clinical Opiate Withdrawal Scale. Only subjects with no signs and/or symptoms of withdrawal were eligible to continue in the study. For safety reasons, naltrexone (HCl) 50 mg was administered 1 hour prior to dosing with study drug on each dosing day to block the pharmacodynamic effects of the oxycodone. To determine whether subjects tolerated naltrexone, naltrexone was administered approximately 13 hours prior to dosing with study drug in each Treatment Period. Blood samples for the measurement of oxycodone concentrations were taken at regular intervals pre and post study drug dose. Pharmacokinetic profiles of oxycodone after each study treatment were derived from plasma concentration data. A washout period of at least 7 days (–4 hours) occurred between treatments.	
Number of subjects (planned and analyzed): Enrollment of approximately 15 subjects was considered adequate to conduct a pilot analysis of the treatment regimens assessed in this study. Fifteen subjects were enrolled and randomized to receive study drug. Thirteen subjects (86.7%) received all planned doses and completed the study; 2 subjects (13.3%) discontinued from the study prematurely.	

Diagnosis and main criteria for inclusion: Eligible subjects were healthy male or nonpregnant female volunteers who provided written informed consent, were 18 to 50 years of age (inclusive), had a body mass index of 33 kg/m² or less, and had a history of insufflating opioids recreationally but were not dependent on opioids and had not required treatment for addiction.
Test product, dose and mode of administration, batch number: Crushed 40-mg Oxycodone DETERx capsules administered IN. Capsule Lot No. 3100363R; Bottle Lot No. 3105260.
Duration of treatment: Subjects received a single dose of study drug in each Treatment Period. All subjects underwent a Screening Phase of up to 21 days and a Treatment Phase of approximately 2.5 weeks.
Reference therapy, dose and mode of administration, batch number: Intact 40-mg Oxycodone DETERx capsules administered PO. Capsule Lot No. 3100363R; Bottle Lot No. 3105260. Oxycodone HCl powder (b) (4) 40 mg administered IN. Lot No. 12EW684. Other therapy, dose and mode of administration, batch number: Naltrexone HCl (Teva Pharmaceutical Industries Ltd, North Wales, PA) 50 mg administered PO. Lot No. 34007242A.
Criteria for evaluation: Study populations: • The PK Population included subject treatments with sufficient quantifiable data within the 2 IN treatment groups in subjects who did not experience emesis within 6 hours after administration of PO Oxycodone DETERx or within 2.5 hours of Oxycodone DETERx or oxycodone powder dosed IN. • The Alternate PK Population included all subject treatments in the PK Population as well as those subjects who did not complete at least 2 IN treatments or who experienced emesis after the time to reach maximum plasma concentration (T_{max}). Eligibility for inclusion in this population was determined by an experienced Pharmacokineticist. The PK Analysis Plan permitted subjects with apparently aberrant PK data to be excluded from the Alternate PK Population after consulting with the Sponsor. • The Safety Population consisted of all subjects who received at least 1 dose of study drug and for whom there was at least 1 posttreatment safety observation.
PK variables: • C_{max}: maximum observed plasma concentration • T_{max}: time to reach maximum plasma concentration • T_{lag}: time prior to the first measurable plasma concentration value • AUC_{last}: area under the plasma concentration vs. time curve from time zero to the time of the last measurable plasma concentration • AUC_{INF}: area under the plasma concentration vs. time curve from time zero to infinity • AUC_{%extrap}: percentage of AUC_{INF} that is due to extrapolation from C_{last} to infinity (where C_{last} is the last measurable concentration) • AQ: abuse quotient; estimated as C_{max}/T_{max} • PAUC: partial AUC; AUC from time zero to all blood sample time points • λ_z: terminal elimination rate constant • t_{1/2}: terminal elimination half-life • CL/F: apparent clearance; Dose/AUC_{0-∞}

- Vz/F: apparent volume of distribution; Dose/(AUC_{0-∞} × λz)
- Fr: relative bioavailability; calculated as AUC_∞ (test product)/AUC_∞ (reference product) × 100

Safety variables:

- Treatment-emergent adverse events (TEAEs)
- Vital sign and oxygen saturation measurements
- Physical and nasal cavity examinations
- Clinical laboratory evaluations

Statistical methods:

Plasma concentration-time data were summarized by treatment with descriptive statistics at each scheduled time point. For descriptive summaries and PK parameter derivation, plasma concentrations that were below the lower limit of quantification were set to a value of zero. Concentration-time data for individual subjects were analyzed by noncompartmental methods using actual blood collection times (as specified in the protocol) in WinNonlin[®] version 5.3 (Pharsight Corp., St. Louis, MO).

A minimum of 3 data points, excluding C_{max}, were included in the estimate of λz. When assessing terminal elimination phases, the R² value was used as a measure of the goodness of fit of the data points to the determined line. The R² value decreases as the data points move farther away from the regression line. Acceptable R² values were assessed on a case-by-case basis depending on the concentration data for the analyte(s) in question, but generally, required values are at least 0.9.

Analysis of variance (ANOVA) was performed on the ln-transformed AUC_{last}, AUC_∞, and C_{max} values. The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. These calculations were done using SAS (SAS Institute, Inc., Cary, NC) General Linear Model procedure.

Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed C_{max}, AUC_{last}, and AUC_∞. These ratios were expressed as a percentage relative to the reference treatment. Consistent with the two 1-sided tests for bioequivalence, 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios were entirely within the 80.00% to 125.00% limits.

The T_{max} was analyzed using nonparametric analyses. The 25% quantile, 50% quantile (median), and 75% quantile were calculated from the Walsh averages of the treatment differences. The Wilcoxon signed rank test was used to compare the test treatments vs. reference treatments (using the same comparisons as shown above). The T_{max} was not transformed; results were reported.

Safety summaries are provided for all subjects in the Safety Population. Adverse event data, clinical laboratory test results, physical examination and nasal assessment findings, baseline electrocardiogram results, vital sign measurements, and blood oxygen saturation data are presented descriptively using summary tables and listings. Change and shift from baseline in clinical laboratory results are presented descriptively using summary tables.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

The PK of crushed Oxycodone DETERx administered IN compared with the standard route of administration (PO administration of the intact capsules as in the treatment of patients with chronic pain, “intact Oxycodone DETERx PO”) and with an active control (IN administration of drug powder as in the nonmedical use by recreational opioid abusers, “oxycodone powder IN”) may be summarized as follows:

- The PK parameters and statistical analyses for the Alternate PK Population were nearly identical to those derived for the PK Population. Overall interpretations were not affected by the exclusion of 2 subjects who did not complete at least 2 IN treatments.

- Crushed Oxycodone DETERx IN, intact Oxycodone DETERx PO, and oxycodone powder IN were all bioequivalent with respect to AUC_{last} and AUC_{INF} .
- The C_{max} values for crushed Oxycodone DETERx IN were lower than those observed for either intact Oxycodone DETERx PO or oxycodone powder IN. Relative to Oxycodone DETERx PO, the crushed Oxycodone DETERx IN C_{max} point estimate was 79.57%, indicating that IN administration of crushed Oxycodone DETERx capsule contents resulted in approximately 80% of the peak exposure of intact Oxycodone DETERx PO. Relative to oxycodone powder IN, the crushed Oxycodone DETERx IN C_{max} point estimate was 59.04%, indicating that IN administration of crushed Oxycodone DETERx capsule contents resulted in approximately 60% of the peak exposure of oxycodone powder IN.
- The relative bioavailability of crushed Oxycodone DETERx IN compared with intact Oxycodone DETERx PO was approximately 92%. The relative bioavailability of oxycodone powder IN compared with intact Oxycodone DETERx PO was approximately 105%.
- The relative bioavailability of crushed Oxycodone DETERx IN compared with oxycodone powder IN was approximately 88%.
- The mean $PAUC_{(0-3hr)}$ value ($PAUC$ from time zero to the 3-hr median T_{max} of oxycodone powder) of crushed Oxycodone DETERx IN was higher than that of intact Oxycodone DETERx PO but was much lower than that of oxycodone powder IN. Mean (standard deviation) $PAUC_{(0-3hr)}$ values for crushed Oxycodone DETERx IN, intact Oxycodone DETERx PO, and oxycodone powder IN were 50.0 (21.9), 11.9 (12.6), and 133 (22.0) hr • ng/mL, respectively.
- The AQ values for crushed Oxycodone DETERx IN and intact Oxycodone DETERx PO were comparable. Mean (SD) AQ values were 8.46 (3.61) and 8.37 (2.88) ng/mL/hr, respectively. These data showed that IN administration of crushed Oxycodone DETERx capsule contents did not increase the AQ relative to intact Oxycodone DETERx PO.
- The AQ values for crushed Oxycodone DETERx IN and intact Oxycodone DETERx PO were much lower than those for oxycodone powder IN. The mean (SD) AQ value for oxycodone powder IN was 42.49 (51.85) ng/mL/hr. On average, the AQ value for crushed Oxycodone DETERx IN was approximately 5-fold lower than that for oxycodone powder IN.

SAFETY RESULTS:

All 15 enrolled subjects were exposed to at least 1 dose of study drug. The safety profiles for each group that received Oxycodone DETERx were similar to those for the group that received oxycodone powder; in all groups, study drug was well-tolerated, although local nasal irritation and adverse events (AEs) were reported for subjects in the 2 groups that received IN study drug. There were more spontaneously reported nasal-related AEs and a greater number of episodes of need to blow nose post insufflation of crushed Oxycodone DETERx compared with oxycodone powder. Adverse events reported as possibly or probably related to study drug administration were those anticipated with the use of oxycodone. No clinically significant changes in vital signs or oxygen saturation were observed. No deaths or serious AEs were reported during this study. No subject withdrew from the study due to AEs, nasal-related AEs, or lack of nasal tolerability.

CONCLUSION:

Data from this study demonstrated that administration of crushed Oxycodone DETERx IN resulted in a lower mean peak plasma concentration than both intact Oxycodone DETERx PO and oxycodone powder IN; the C_{max} for crushed Oxycodone DETERx IN was approximately 80% of intact Oxycodone DETERx PO and 60% of oxycodone powder IN. The extent of absorption was similar for all treatment groups, with crushed Oxycodone DETERx IN equivalent to intact Oxycodone DETERx PO and oxycodone powder IN with respect to AUC_{last} and AUC_{INF} . The AQ values for crushed Oxycodone DETERx IN and intact Oxycodone DETERx PO were comparable and showed that IN administration of crushed Oxycodone DETERx capsule contents did not increase the AQ relative to intact Oxycodone DETERx PO. In contrast, the AQ value for crushed Oxycodone DETERx IN was approximately 5-fold lower (on average) than that for oxycodone powder IN. Therefore, crushing and insufflating (snorting) DETERx capsule contents did not produce the relatively high plasma concentrations over a short duration that abusers seek in order to rapidly achieve a euphoric effect when manipulating and administering dosage forms via the nasal route.

3.2.7 Study CP-OXYDET-21 Synopsis:

Title of Study: Assessment of the Relative Human Abuse Potential of Intranasal Oxycodone DETERx®	
Investigator and Study Center: This study was conducted at a single site in the United States of America (USA): Lynn R. Webster, MD, CRI Lifetree, Salt Lake City, Utah.	
Publication (reference): None	
Study Start Date: 09 October 2013 (date of first screening)	Phase of Development: 1
Study Completion Date: 09 December 2013 (date of last contact)	
Objectives: The primary objective of this study was to evaluate the abuse potential and pharmacokinetic (PK) profile of crushed Oxycodone DETERx 40 mg following intranasal (IN) administration, intact Oxycodone DETERx 40 mg following oral (PO) administration, and crushed immediate-release (IR) oxycodone 40 mg following IN administration.	
Methodology: This was a randomized, double-blind, double-dummy, positive- and placebo-controlled, single-dose, 4-treatment, 4-period crossover comparison study designed to evaluate the abuse potential and PKs of crushed 40 mg Oxycodone DETERx IN, intact 40 mg Oxycodone DETERx PO, and crushed 40 mg IR oxycodone IN. The primary comparison of interest was between crushed 40 mg Oxycodone DETERx IN and crushed 40 mg of IR oxycodone IN. Subjects who successfully completed the Screening Phase returned to the research clinic as inpatients to complete the Drug Discrimination Phase. The Drug Discrimination Phase comprised a Naloxone Challenge Test to confirm that subjects were not opioid tolerant and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single 20 mg dose of crushed IR oxycodone dosed IN and placebo. Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a two-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, IN dose of the following treatments: • Crushed IR Oxycodone 20 mg Dosed IN • Crushed Placebo Dosed IN All doses were administered following a high-fat, high-calorie (HFHC) meal. Each dose was separated by at least 24 hours. Following an overnight fast of at least 10 hours, subjects started a standardized, HFHC breakfast 30 minutes prior to the scheduled administration of study drug and completed the meal within 20 minutes. Predose meals in the Drug Discrimination Phase followed the recommendation as described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. Subjects were discharged from the research clinic approximately 24 hours after the second dose, if deemed safe by the Investigator. Subjects who were eligible to continue the study returned to the research clinic to begin the Double-blind Treatment Phase. A minimum of 5 days separated the second treatment in the Drug Discrimination Test and the first treatment in the Double-blind Treatment Phase.	

During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1 ratio to receive 1 of 4 sequences of 4 single dose treatments in a double-blind, double-dummy design. Each treatment was separated by a minimum of 5 days.

Subjects received each of the 4 treatments in random order: crushed Oxycodone DETERx 40 mg dosed IN; intact Oxycodone DETERx 40 mg dosed PO; crushed IR Oxycodone 40 mg dosed IN; and placebo. All doses were administered following a HFHC meal. All predose meals in the Double-blind Treatment Phase followed the recommendation as described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. Following an overnight fast of at least 10 hours, subjects started a standardized, HFHC breakfast 30 minutes prior to the scheduled administration of study drug and completed the meal within 20 minutes. Subjects received the assigned treatment once in the morning. For all Treatment Periods, subjects remained in the clinic until approximately 36 hours after dosing. Subjects were only discharged if the Investigator deemed it was safe; subjects could be asked to stay resident in the research clinic for a longer period of time, if necessary. A minimum of 5 days between treatments provided a washout of study drug before the subjects were crossed over to another treatment.

Number of Subjects (Planned and Analyzed):

Planned: Thirty-six completed subjects were planned for this study. A sample size of 36 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥ 11.2 points in $E_{\max}$ for the bipolar Drug Liking visual analog scale (VAS), at the 2-sided significance level of 0.05, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 20 points.

Analyzed: Sixty-four subjects entered the Drug Discrimination Phase and underwent the Naloxone Challenge Test; all subjects passed the test and proceeded to the Drug Discrimination Test. Of the 64 subjects who entered the Drug Discrimination Test, 15 failed the Drug Discrimination Test, 6 experienced an adverse event (AE), i.e., emesis, which required withdrawal according to protocol-mandated criteria, 3 withdrew due to subject decision and 1 was withdrawn due to a protocol violation. Of the 39 subjects who entered the Double-blind Treatment Phase, 36 completed the study.

Diagnosis and Main Criteria for Inclusion:

For a subject to enroll in the study, all of the following inclusion and exclusion criteria had to be met:

Inclusion Criteria:

1. Subject must provide written informed consent prior to participation in the study.
2. Subject must have the ability to read and/or follow written and oral instructions.
3. Subject is male or female 18-55 years of age (inclusive) at the time of consent.
4. Subject is a recreational opioid user. A recreational opioid user is defined as a user of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Phase (Visit 1).
5. Subject is not dependent on and has not developed a tolerance to opioids based on Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-IV-TR) criteria and naloxone challenge.

6. Subject must have a history of IN drug administration of at least 3 times within the last year prior to Screening Phase (Visit 1).
7. Subject must have a history of tolerating a 40 mg dose of oxycodone IN.
8. Subject does not have any dietary restrictions and is able to consume a complete HFHC meal, in the allotted time, prior to dosing.
9. Female subject has a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test upon admission to the clinic at the start of the Drug Discrimination Phase and at admission for each period.
10. Female subject of childbearing potential will use an acceptable method of birth control. Acceptable birth control includes total abstinence from sexual intercourse for a minimum of 1 complete menstrual cycle prior to the Screening Visit, a vasectomized partner that had a vasectomy a minimum of 6 months prior to the Screening Visit, contraceptives (oral, parenteral, or transdermal) used for a minimum of 12 weeks prior to the start of dosing in Period 1, intrauterine device used for a minimum of 12 weeks prior to the start of dosing in Period 1, or dual method including condoms, sponges, diaphragms, or vaginal rings with spermicidal jellies, films, foams, creams, or suppositories throughout the study. Subjects taking birth control pills must have taken the same type pill for at least 12 weeks prior to the Screening Visit and must not change their dosing regimen during the study. Subjects considered not of childbearing potential must be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) or greater than one year postmenopausal, defined as a complete cessation of menstruation for at least one year.
11. Male subjects must use an acceptable method of contraception with female partners. Acceptable contraception includes a vasectomy, a minimum of 6 months prior to the Screening Visit; use of a dual method with female partners who are not using contraception including condoms, sponges, diaphragms, or vaginal rings with spermicidal jellies, films, foams, creams, or suppositories throughout the study; female partner who is using contraceptives (oral, parenteral, or transdermal) or an intrauterine device; or agreement to total abstinence from sexual intercourse during the study.
12. Subject must be in general good health based on screening physical examination (defined as the absence of any clinically significant abnormalities), medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory values (hematology, serum chemistry and urinalysis) as determined by the Investigator.
13. Subject must have a negative urine drug screen and alcohol breath test prior to dosing in the Drug Discrimination Phase and in each Treatment Period with the exception of tetrahydrocannabinol (THC), which must be negative or positive from the start of the study through End-of-Study (e.g., subjects with negative tests cannot become positive at a later admit and subjects with positive tests cannot become negative at a later admit). Subjects positive for THC must pass a targeted neurological exam showing that they are not cognitively impaired.

Exclusion Criteria:

1. Female subject who is pregnant, planning a pregnancy, or breastfeeding.
2. Subject has a body mass index (BMI) > 33.0 kg/m².

3. Subject has any clinically significant unstable medical abnormality or chronic disease of the neurological, cardiovascular, endocrine, hematologic, metabolic, gastrointestinal, hepatic, or renal systems.
4. Subject has a known history or current respiratory disease (e.g., asthma, chronic obstructive pulmonary disease, exercise-induced asthma, bronchitis, obstructive sleep apnea). Subject with childhood asthma and/or mild exercise-induced asthma, and/or a remote history of bronchitis, may be approved for participation at the discretion of the Investigator.
5. Subject has a known anatomical nasal abnormality that may compromise his/her ability to insufflate drugs (e.g., deviated nasal septum, erosions, perforated nasal septum, malformations, and/or a significant nasal piercing).
6. Subject has an abnormal nasal exam (e.g., infection, rhinorrhea).
7. Diagnosis of drug and/or alcohol dependence, excluding caffeine and/or nicotine, as assessed by the Investigator using DSM-IV-TR criteria.
8. Subject has participated in, is currently participating in, or is seeking treatment for drug- and/or alcohol-related disorders, excluding caffeine and nicotine.
9. Subject has any condition for which an opioid is contraindicated (e.g., significant history of respiratory depression, acute or chronic bronchial asthma or hypercarbia, or suspected or confirmed paralytic ileus).
10. Subject who cannot refrain from taking medications (prescription [14 days] or over-the-counter [48 hours]), supplements, or nutraceuticals for 48 hours and herbs for 14 days prior to admission to the clinic (Drug Discrimination Phase) and for the duration of the study.
11. Subjects who consumed Seville oranges, grapefruit, pomegranate, pomelo, and star fruit juice/products, drinks/foods containing quinine, or any foods containing poppy seeds within 1 week prior to the start of the Drug Discrimination Phase and throughout the study.
12. Subject who cannot refrain from using caffeine or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who cannot tolerate stopping caffeine without symptoms will be excluded.
13. Subject is a heavy smoker (>20 cigarettes per day on average in the past 30 days prior to Screening), chews tobacco, uses a nicotine transdermal patch, uses any other nicotine-containing products, and/or is unable to abstain from smoking for at least 5 hours during any day.
14. Subject who cannot refrain from strenuous activity for 3 days prior to admission to the clinic (Drug Discrimination Phase) and for the duration of the study.
15. Subject has a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion.
16. Subject is known to be allergic or have hypersensitivity to any of the test product(s) or any components in the test product(s)
17. Subject has participated in any investigational study within 30 days prior to the first dosing of study drug or is currently participating in another clinical study.
18. Subject has donated blood or experienced significant blood loss (50 to 499 mL whole blood within 30 days or >499 mL whole blood within 60 days) or has donated plasma within 7 days prior to the start of dosing.

19. Subject tests positive at screening for human immunodeficiency virus (HIV) or is known to be seropositive for HIV.
20. Subject tests positive at screening for hepatitis B surface antigen, hepatitis C antibody or has a history of a positive result.
21. Subject is a staff member or relative of a staff member.
22. Subject is not able to meet the study attendance requirements.
23. The Investigator believes the subject is not suitable for the study for reasons not otherwise **Additional Exclusion Criteria to be Evaluated after Clinic Admission to be Eligible to Participate in the Double-blind Treatment Phase (Visits 3-6)**

1. Physical dependence on opioids, as determined by the Naloxone Challenge Test (i.e., subject has a Clinical Opiate Withdrawal Scale [COWS] score of ≥ 5) (precludes entry into the Drug Discrimination Test).
2. Inability to discriminate between opioid (IR oxycodone 20 mg IN) and placebo during the Drug Discrimination Test. Ability to discriminate is defined for Drug Liking as follows (inclusive):
 - A minimum E_{max} of 65 points for Drug Liking in response to active treatment;
 - A ≥ 15 -point difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
 - A placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.
3. Intolerant to study treatments in the Drug Discrimination Test (e.g., emesis within first 6 hours after dosing precludes entry into Double-blind Treatment Phase).
4. Inability to completely insufflate the entire volume of test doses administered during Drug Discrimination Test.
5. Unacceptable response to other study assessments or inability to successfully complete the study as judged by the Investigator (e.g., inability to consume a HFHC meal within 20 minutes or emesis following the meal).

Test Product, Dose and Mode of Administration:

Naloxone Challenge Test: An initial dose of naloxone hydrochloride 0.2 mg was administered by intravenous (IV) bolus followed by an additional 0.6 mg of IV naloxone if no evidence of withdrawal occurred within 30 seconds.

- Naloxone HCl Injection, USP, 0.4 mg/mL multiple-use (10 mL) vials: Lot No. 22-148-EV, Expiry Date: 01 October 2014.

Drug Discrimination Test: Single dose of crushed IR Oxycodone 20 mg dosed IN and crushed placebo dosed IN with doses separated by 24 hours. Four 5 mg tablets of IR oxycodone were used.

- IR Oxycodone, USP, 5 mg: Lot #BVM0089A, Expiry Date: April 2016.
- Placebo, Lactose powder NF, Lot #73056/D, Expiry Date: September 2016.

Double-blind Treatment Phase: Subjects were randomized in a 1:1:1:1 ratio to receive 1 of 4 sequences of the following 4 single dose treatments. For the crushed IR oxycodone 40 mg IN treatment used in the Double-blind Treatment Phase, four 10 mg tablets of IR oxycodone were used.

Treatment	Crushed IN Dose (Weight ≈ mg)	PO Intact Dose (Capsules)
A	Crushed Oxycodone DETERx 40 mg (420 mg)	1 DETERx Placebo
B	Crushed Placebo DETERx (420 mg)	1 DETERx 40 mg
C	Crushed IR Oxycodone 40 mg (400 mg)	1 DETERx Placebo
D	Crushed Placebo DETERx (420 mg)	1 DETERx Placebo

IN = intranasal; IR = immediate-release; mg = milligram; PO = oral

Oral study drugs were administered with 240 mL of room temperature, noncarbonated water immediately prior to administration of IN study drugs. Subjects self-administered IN study drugs, out of a scintillation vial (held by a site staff member) through a short black straw (held by the subject) over colored construction paper taped to a light box lit with a black light, and insufflated through one or both nares. All study drugs were administered in a low lit room by unblinded staff members. Each dose of the assigned treatment IN was insufflated as rapidly as possible, but within a maximum of 4 minutes.

Oxycodone DETERx 40 mg capsules were supplied by the Sponsor as bottles of 100 Batch No. 3101451, Expiry/Retest Date: May 2014.

Duration of Treatment: For each Treatment Period of the Double-blind Treatment Phase, subjects received one single dose.

Reference Therapy, Dose and Mode of Administration: IR Oxycodone, USP (5 mg and 10 mg) is an oral formulation of oxycodone. IR oxycodone was provided at a tablet dose strength of 5 mg

for the Drug Discrimination Test (4 tablets for total dose of 20 mg) and 10 mg for the Double-blind Treatment Phase (4 tablets for total dose of 40 mg); the dose of IR oxycodone was crushed and administered intranasally. Oxycodone HCl, 5 mg tablets were procured by the study site from Sun Pharmaceuticals (Cranberry, NJ 08512 USA), Lot #BVM0089A, Expiry Date: April 2016. Oxycodone HCl, 10 mg was procured by the study site from KVK Tech Newtown, PA 18940 USA, Lot No. 11656A, Expiry Date: July 2016. These doses were prepared at the clinical site according to a crushing procedure that was outlined in a separate Pharmacy Manual. A report detailing the post study appearance and particle size analysis of the nasal treatments was also prepared.

Oxycodone DETERx 40 mg placebo capsules were supplied by the Sponsor and shipped to the study site in blister packaging, Lot No. 3101503R, Expiry/Retest Date: May 2014.

Criteria for Evaluation:

Pharmacokinetic Assessments: Prior to administration of the first discrimination dose of study drug/placebo, a 4 mL blood sample for PK evaluation was collected.

During each Treatment Period of the Double-blind Treatment Phase, 4 mL serial blood samples for PK evaluation were collected predose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours post dose.

C_{max} , T_{max} , T_{lag} , AUC_{last} , AUC_{INF} , $AUC_{\%extrap}$, abuse quotient (AQ, C_{max}/T_{max}), partial AUC (0-all blood sample time points), λ_z , $t_{1/2}$, CL/F, Vd/F, and Fr for oxycodone were calculated using noncompartmental PK methods.

Pharmacodynamic Assessments: Pharmacodynamic (PD) assessments included subjective and objective assessments as follows:

Subjective assessments included Drug Effects Questionnaire (DEQ) drug liking, feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy; Ease of Snorting; Overall (Global) Drug Liking; Addiction Research Center Inventory-Morphine Benzodrine Group (ARCI/MBG); Take Drug Again Assessment; and Price Value Assessment Questionnaire (PVAQ). The DEQ was assessed during each Treatment Period of the Double-blind Treatment Phase at the following times: 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. Predose assessments were limited to DEQ for nausea, feel sick, and ARCI/MBG. The Ease of Snorting assessment was performed within 5 minutes post dose. Data were collected at 8.0 and 24.0 hours post dose for Take Drug Again Assessment and Overall (Global) Drug Liking. PVAQ was captured at 24 hours post dose.

Pupil diameter (pupillometry), an objective assessment, was measured during each Treatment Period of the Double-blind Treatment Phase at predose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours post dose.

The following PD endpoints were derived: maximum (peak) effect (E_{max}) from 0 to 24 hours post dose; time of maximum (peak) effect (TE_{max}); minimum (peak) effect (E_{min}) for bipolar scales only from 0 to 24 hours post dose; time of minimum (peak) effect (TE_{min}) for bipolar scales only; area under the effect curve (AUE) to 1 hour (AUE_{0-1h}), AUE_{0-2h} , AUE_{0-4h} , AUE_{0-8h} , AUE_{0-24h} . For Overall (Global) Drug Liking and the Take Drug Again Assessment, the E_{max} and mean response (E_{mean}) were calculated. The percentage of drug insufflated (mg%) was calculated.

Safety Assessments: Safety was evaluated based on AEs, clinical laboratory assessments, vital signs, oxygen saturation, 12-lead ECG, nasal cavity assessment, Nasal Effects Assessment, and physical examinations.

Statistical Methods:

Analysis Populations:

Pharmacodynamic Population: Subjects who completed all 4 Treatment Periods with at least one PD assessment in each Treatment Period. This was the primary population for PD analyses.

Pharmacokinetic Population: Subjects in the PD Population who had sufficient quantifiable plasma concentration data to provide C_{max} and AUC data, and who did not experience emesis within 12 hours of dosing for DETERx (intact PO and crushed IN) or within 2 x median T_{max} (5 hours) of dosing for crushed IR oxycodone IN. Subjects with apparently aberrant PK data could have been excluded from the PK Population, but no data were excluded.

Drug Discrimination Safety Population: All subjects who received at least one dose of study drug during the Drug Discrimination Phase and for whom there was at least one post-treatment safety observation.

Safety Population: All subjects randomized into the Double-blind Treatment Phase who received at least one dose of study drug during the Double-blind Treatment Phase and for whom there was at least one post-treatment safety observation in this phase.

Pharmacokinetic Analyses: C_{max} , T_{max} , T_{lag} , AUC_{last} , AUC_{INF} , $AUC_{\%extrap}$, $AQ (C_{max}/T_{max})$, partial AUC (from time 0 to all blood sample time points), λ_z , $t_{1/2}$, Cl/F , apparent V_d/F , and Fr for oxycodone were calculated using noncompartmental PK methods. Analysis of variance (ANOVA) was performed on the ln-transformed AUC_{last} , AUC_{0-INF} , and C_{max} . The ANOVA model included sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Each ANOVA included calculation of least square (LS) Mean, the difference between treatment LS Mean, and the standard error associated with the difference. Ratios of LS Mean and the 90% confidence intervals (CIs) were calculated using the exponentiation of the difference and lower and upper confidence limits between treatment LS Mean from the analyses on the ln-transformed AUC_{last} , AUC_{0-INF} , and C_{max} . These ratios were expressed as a percentage relative to the reference product (crushed IR oxycodone 40 mg IN - Treatment C). Crushed Oxycodone DETERx 40 mg IN (Treatment A) was compared to the reference for this test. In addition, the same analysis was performed for crushed Oxycodone DETERx 40 mg IN (Treatment A) v intact Oxycodone DETERx 40 mg PO (Treatment B). T_{max} was analyzed using nonparametric analysis (Walsh averages and appropriate quantile of the Wilcoxon Signed Rank Test statistic). T_{max} was not transformed. Plots are presented for the mean ($\pm$ standard deviation) plasma concentration versus time, and for individual subject plasma concentration data versus time on linear and semi-logarithmic axes.

Pharmacodynamic Analyses: For PD statistical analyses, significance testing for the primary comparisons and Drug Liking primary endpoint, E_{max} , were 1-tailed using a nominal $\alpha = 0.025$, however, all p-values presented are 2-tailed and the direction of the difference, which had to be positive, is equivalent to the 1-tailed test. Significance testing for all other endpoints and comparisons are 2-tailed using $\alpha = 0.05$, unless otherwise specified. The parameters of interest that were collected in this study included the following:

- Drug Liking – bipolar VAS scale (Primary)
- Overall (Global) Drug Liking – bipolar VAS scale:

- Take Drug Again – bipolar VAS scale;
- DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy) – unipolar VAS scale;
- Ease of Snorting – unipolar VAS scale;
- PVAQ;
- ARCI/MBG;
- Pupillometry

The following PD endpoints were calculated for each parameter of interest as appropriate:

- E_{max} during 24 hours after dosing;
- TE_{max} ;
- E_{min} for bipolar scales only during 24 hours after dosing;
- TE_{min} for bipolar scales only;
- AUE_{0-1h} ;
- AUE_{0-2h} ;
- AUE_{0-4h} ;
- AUE_{0-8h} ;
- AUE_{0-24h} ;
- For Overall (Global) Drug Liking and the Take Drug Again Assessment, the E_{max} and E_{mean} averaging the 8 and 24 hour assessments; and
- The percentage of drug insufflated (mg%).

The primary analysis was based on the pairwise comparison between crushed IR oxycodone 40 mg IN (control - Treatment C) and crushed Oxycodone DETERx 40 mg IN (Treatment A) for Drug Liking E_{max} . The Drug Liking E_{max} comparison between crushed IR oxycodone 40 mg IN (Treatment C) and Placebo (Treatment D) was used for validation of the appropriateness of the positive control.

Secondary comparisons were performed between crushed Oxycodone DETERx 40 mg IN (Treatment A) and intact Oxycodone DETERx 40 mg PO (Treatment B), between intact Oxycodone DETERx 40 mg PO (Treatment B) and DETERx Placebo (Treatment D), between crushed Oxycodone DETERx 40 mg IN (Treatment A) and DETERx Placebo (Treatment D), and between crushed IR oxycodone 40 mg IN (Treatment C) and intact Oxycodone DETERx 40 mg PO (Treatment B).

The following treatment comparisons were made for each of the PD endpoints:

- Treatment C v Treatment A (Primary Comparison);
- Treatment C v Treatment D (Validity);
- Treatment A v Treatment B;
- Treatment B v Treatment D;
- Treatment A v Treatment D; and
- Treatment C v Treatment B.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results: The results of this study showed the following:

- C_{max} values for crushed Oxycodone DETERx IN were lower than those observed for either intact Oxycodone DETERx PO or crushed IR oxycodone IN. Relative to intact Oxycodone DETERx PO, the crushed Oxycodone DETERx IN C_{max} point estimate was 73.02% (73.73% for the PK Population) indicating that IN administration of crushed Oxycodone DETERx capsule contents resulted in approximately 73% of the peak exposure of intact Oxycodone DETERx PO. Relative to crushed IR oxycodone IN, the crushed Oxycodone DETERx IN C_{max} point estimate was 48.72% (48.70% for the PK Population), indicating that IN administration of crushed Oxycodone DETERx capsule contents resulted in approximately 49% of the peak exposure of crushed IR oxycodone IN.
- Crushed Oxycodone DETERx IN was bioequivalent (BE) to intact Oxycodone DETERx PO with respect to AUC_{last} and AUC_{INF} for both the PD and PK Populations.
- Intact Oxycodone DETERx PO was BE to crushed IR oxycodone IN with respect to AUC_{INF} for both the PD and PK populations. The lower bound of the 90% CIs for AUC_{last} fell just below the bioequivalence criteria (90% CIs were 79.40-86.75% and 78.80-85.52% for the PD and PK populations, respectively).
- AUC values for crushed Oxycodone DETERx IN were lower than those for crushed IR oxycodone IN; AUC_{last} and AUC_{INF} point estimates were 77.32% and 78.95% (for the PD Population) and 77.27% and 79.02% (for the PK population).
- The mean cumulative $PAUC_{(0-3h)}$ value of crushed Oxycodone DETERx IN was higher than that of intact Oxycodone DETERx PO, but was much less than that of crushed IR oxycodone IN. For the PD Population, mean $\pm$ SD cumulative $PAUC_{(0-3h)}$ for crushed Oxycodone DETERx IN, crushed IR oxycodone IN, and intact Oxycodone DETERx PO were 41.4 ± 16.2 , 141 ± 26.4 and 25.0 ± 26.1 h*ng/mL, respectively. For the PK Population, these values were 41.4 ± 16.2 , 141 ± 26.4 and 24.6 ± 26.5 h*ng/mL, respectively.
- The mean cumulative $PAUC_{(0-5h)}$ value of crushed Oxycodone DETERx IN was similar to that of intact Oxycodone DETERx PO, and was much less than that of crushed IR oxycodone IN. For the PD Population, mean $\pm$ SD cumulative $PAUC_{(0-5h)}$ for crushed Oxycodone DETERx IN, crushed IR oxycodone IN, and intact Oxycodone DETERx PO were 88.0 ± 24.0 , 243 ± 41.7 and 83.7 ± 41.2 h*ng/mL, respectively. For the PK Population, these values were 88.0 ± 24.0 , 243 ± 41.7 and 83.6 ± 41.8 h*ng/mL, respectively.
- The AQ values for crushed Oxycodone DETERx IN and intact Oxycodone DETERx PO were comparable. For the PD Population, mean $\pm$ SD AQ values were 6.24 ± 3.72 and 8.60 ± 4.67 ng/mL/h, respectively. For the PK Population, mean $\pm$ SD AQ values were 6.24 ± 3.72 and 8.66 ± 4.71 ng/mL/h, respectively. These data show that IN administration of crushed Oxycodone DETERx capsule contents does not increase the AQ relative to intact Oxycodone DETERx PO.
- The AQ values for crushed Oxycodone DETERx IN and intact Oxycodone DETERx PO were much lower than that of crushed IR oxycodone IN. The mean $\pm$ SD AQ value for crushed IR oxycodone IN was 69.6 ± 84.1 ng/mL/h for both PD and PK Populations. Thus, on average, the AQ value for crushed Oxycodone DETERx IN was approximately 11-fold lower than that of crushed IR oxycodone IN.

3.2.8 Study CP-OXYDET-24 Synopsis:

Title of Study: Assessment of the Oral Human Abuse Potential of Oxycodone DETERx®	
Investigator and Study Center: This study was conducted at a single site in the United States of America (USA): Lynn R. Webster, MD, PRA Healthsciences, Salt Lake City, Utah.	
Publication (reference): None	
Study Start Date: 22 January 2014 (date of first screening)	Phase of Development: 1
Study Completion Date: 17 June 2014 (date of last contact)	
Objectives: The primary objective of this study was to evaluate the abuse potential and pharmacokinetics (PK) of intact Oxycodone DETERx 40 mg under fed (high-fat, high-calorie [HFHC] meal) and fasted conditions, chewed Oxycodone DETERx 40 mg under fed and fasted conditions, and crushed immediate-release (IR) oxycodone 40 mg under fasted conditions.	
Methodology: This was a randomized, double-blind, triple-dummy, active- and placebo-controlled, single-dose, 6-treatment, 6-period crossover comparison study designed to evaluate the oral abuse potential and PKs of intact Oxycodone DETERx HFHC, intact Oxycodone DETERx fasted, chewed Oxycodone DETERx HFHC, chewed Oxycodone DETERx fasted, and crushed IR oxycodone fasted. All active doses of oxycodone were 40 mg. The primary comparisons of interest were between chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted and between chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted. Subjects who successfully completed the Screening Phase returned to the research clinic as inpatients to complete the Drug Discrimination Phase. The Drug Discrimination Phase comprised a Naloxone Challenge Test to confirm that subjects were not opioid tolerant and a Drug Discrimination Test to ensure that subjects could differentiate between the effects of a single 20 mg dose of crushed IR oxycodone dosed per os (PO) in solution and crushed placebo in solution. Subjects who successfully completed the Naloxone Challenge Test remained as inpatients to complete the Drug Discrimination Test. In a two-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, PO dose of the following treatments: • IR Oxycodone 20 mg Dosed PO Crushed, in Solution • Placebo Dosed PO Crushed, in Solution Both doses were administered fasted. Subjects were administered each test dose with 250 mL of room temperature, non-carbonated water. Site staff performed a thorough mouth check after each test dose had been taken. Each dose was separated by at least 24 hours. Subjects were discharged from the research clinic approximately 24 hours after the second dose, if deemed safe by the Investigator. Subjects who were eligible to continue the study returned to the research clinic to begin the Double-blind Treatment Phase. A minimum of 5 days separated the second treatment in the Drug Discrimination Test and the first treatment in the Double-blind Treatment Phase. During the Double-blind Treatment Phase, subjects were randomized in a 1:1:1:1:1:1 ratio to receive a single dose of 6 treatments in a double-blind, triple-dummy design. Each treatment was separated by a minimum of 5 days.	

Subjects received each of 6 treatments in random order:

- A. Chewed DETERx placebo plus intact Oxycodone DETERx 40 mg plus placebo IR solution following HFHC meal (treatment referred to as intact Oxycodone DETERx HFHC or Oxycodone DETERx Intact Fed)
- B. Chewed DETERx Placebo plus intact Oxycodone DETERx 40 mg plus placebo IR solution fasted (treatment referred to as intact Oxycodone DETERx fasted or Oxycodone DETERx Intact Fasted)
- C. Chewed Oxycodone DETERx 40 mg plus intact DETERx placebo plus placebo IR solution following HFHC meal (treatment referred to as chewed Oxycodone DETERx HFHC or Oxycodone DETERx Chewed Fed)
- D. Chewed Oxycodone DETERx 40 mg plus intact DETERx placebo plus placebo IR solution fasted (treatment referred to as chewed Oxycodone DETERx fasted or Oxycodone DETERx Chewed Fasted)
- E. Chewed DETERx placebo plus intact DETERx placebo plus crushed IR Oxycodone 40 mg in solution fasted (treatment referred to as crushed IR oxycodone fasted or IR Oxycodone Crushed Solution Fasted)
- F. Chewed DETERx placebo plus intact DETERx placebo plus placebo IR in solution following HFHC meal (treatment referred to as placebo HFHC)

Fed doses were administered following a HFHC meal. All predose meals in the Double-blind Treatment Phase followed the recommendations described in the Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. Following an overnight fast of at least 10 hours, subjects started a standardized, HFHC breakfast 30 minutes prior to the scheduled administration of study drug and completed the meal in 20 minutes. Subjects received the assigned treatment once in the morning.

For all Treatment Periods, subjects remained in the clinic until approximately 36 hours after dosing. Subjects were only discharged if the Investigator deemed it was safe; subjects could be asked to reside in the research clinic for a longer period of time, if necessary. A minimum of 5 days between treatments provided a washout of study drug before the subjects were crossed over to another treatment.

Number of Subjects (Planned and Analyzed):

Planned: Thirty-six completed subjects were planned for this study. A sample size of 36 completed subjects was estimated to provide at least 90% power to detect treatment differences of ≥ 11.2 points in $E_{\max}$ for the bipolar Drug Liking visual analog scale (VAS), at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming standard deviation differences of 20 points.

Analyzed: A total of 111 subjects entered the Drug Discrimination Phase and underwent the Naloxone Challenge Test; 110 subjects passed the test. Three subjects withdrew consent prior to the Drug Discrimination Test. Of the 107 subjects who participated in the Drug Discrimination Test, 24 failed the Drug Discrimination Test (i.e., they were unable to discriminate between opioid and placebo based on Drug Liking scores); 7 were considered Drug Discrimination failures as per the Sponsor; 3 experienced an adverse event (AE) that required withdrawal according to a protocol-mandated criterion (i.e., emesis within the first 6 hours after dosing during the Drug Discrimination Phase); 7 subjects withdrew consent, and 2 subjects were withdrawn due to protocol deviations. Of the 64 subjects who entered the Double-blind Treatment Phase, 38 completed the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

For a subject to enroll in the study, all of the following inclusion criteria had to be met:

1. Subject must provide written informed consent prior to participation in the study.
2. Subject must have the ability to read and/or follow written and oral instructions.
3. Subject is male or female 18-55 years of age (inclusive) at the time of consent.
4. Subject is a recreational opioid user. A recreational opioid user is defined as a user of opioids for non-medical purposes (i.e., for psychoactive effects) on at least 10 occasions within the last year and at least once in the 12 weeks before the Screening Phase (Visit 1).
5. Subject is not dependent on and has not developed a tolerance to opioids based on Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision (DSM-IV-TR) criteria and naloxone challenge.
6. Subject must have a history of tolerating a 40 mg dose of oxycodone.
7. Subject does not have any dietary restrictions and is able to consume a complete HFHC meal, in the allotted time, prior to dosing.
8. Female subject has a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test upon admission to the clinic at the start of the Drug Discrimination Phase and at admission for each period.
9. Female subject of childbearing potential will use an acceptable method of birth control. Acceptable birth control includes total abstinence from sexual intercourse for a minimum of 1 complete menstrual cycle prior to the Screening Visit, a vasectomized partner that had a vasectomy a minimum of 6 months prior to the Screening Visit, contraceptives (oral, parenteral, or transdermal) used for a minimum of 12 weeks prior to the start of dosing in Period 1, intrauterine device used for a minimum of 12 weeks prior to the start of dosing in Period 1, or dual method including condoms, sponges, diaphragms, or vaginal rings with spermicidal jellies, films, foams, creams, or suppositories throughout the study. Subjects taking birth control pills must have taken the same type pill for at least 12 weeks prior to the Screening Visit and must not change their dosing regimen during the study. Subjects considered not of childbearing potential must be surgically sterile (total hysterectomy, bilateral salpingo-oophorectomy, or tubal ligation) or greater than one year postmenopausal, defined as a complete cessation of menstruation for at least one year.
10. Male subjects must use an acceptable method of contraception with female partners. Acceptable contraception includes a vasectomy, a minimum of 6 months prior to the Screening Visit; use of a dual method with female partners who are not using contraception including condoms, sponges, diaphragms, or vaginal rings with spermicidal jellies, films, foams, creams, or suppositories throughout the study; female partner who is using contraceptives (oral, parenteral, or transdermal) or an intrauterine device; or agreement to total abstinence from sexual intercourse during the study.
11. Subject must be in general good health based on screening physical examination (defined as the absence of any clinically significant abnormalities), medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory values (hematology, serum chemistry and urinalysis) as determined by the Investigator.

12. Subject must have a negative urine drug screen and alcohol breath test prior to dosing in the Drug Discrimination Phase and in each Treatment Period with the exception of tetrahydrocannabinol (THC), which must be negative or positive from the start of the study through End-of-Study (e.g., subjects with negative tests cannot become positive at a later admit and subjects with positive tests cannot become negative at a later admit). Subjects who are positive for THC must pass a targeted neurological exam showing that they are not cognitively impaired.

Exclusion Criteria:

For a subject to enroll in the study, none of the following exclusion criteria could be met:

1. Female subject who is pregnant, planning a pregnancy, or breastfeeding.
2. Subject has a Body Mass Index (BMI) > 33.0 kg/m².
3. Subject has any clinically significant unstable medical abnormality or chronic disease of the neurological, cardiovascular, endocrine, hematologic, metabolic, gastrointestinal, hepatic, or renal systems.
4. Diagnosis of drug and/or alcohol dependence, excluding caffeine and/or nicotine, as assessed by the Investigator using DSM-IV-TR criteria.
5. Subject has participated in, is currently participating in, or is seeking treatment for drug- and/or alcohol-related disorders, excluding caffeine and nicotine.
6. Subject has any condition for which an opioid is contraindicated (e.g., significant history of respiratory depression, acute or chronic bronchial asthma or hypercarbia, or suspected or confirmed paralytic ileus).
7. Subject who cannot refrain from taking medications (prescription [14 days] or over-the-counter [48 hours]), supplements, or nutraceuticals for 48 hours and herbs for 14 days prior to admission to the clinic (Drug Discrimination Phase) and for the duration of the study.
8. Subjects who consumed Seville oranges, grapefruit, pomegranate, pomelo, and star fruit juice/products, drinks/foods containing quinine, or any foods containing poppy seeds within 1 week prior to the start of the Drug Discrimination Phase and throughout the study.
9. Subject who cannot refrain from using caffeine or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who cannot tolerate stopping caffeine without symptoms will be excluded.
10. Subject is a heavy smoker (>20 cigarettes per day on average in the past 30 days prior to Screening), chews tobacco, uses a nicotine transdermal patch, uses any other nicotine-containing products, and/or is unable to abstain from smoking for at least 5 hours during any day.
11. Subject who cannot refrain from strenuous activity for 3 days prior to admission to the clinic (Drug Discrimination Phase) and for the duration of the study.
12. Subject has a disorder or history of a condition (e.g., malabsorption, gastrointestinal surgery) that may interfere with drug absorption, distribution, metabolism, or excretion.
13. Subject is known to be allergic or have hypersensitivity to any of the test product(s) or any components in the test product(s).

14. Subject has participated in any investigational study within 30 days prior to the first dosing of study drug or is currently participating in another clinical study.
15. Subject has donated blood or experienced significant blood loss (50 to 499 mL whole blood within 30 days or >499 mL whole blood within 60 days) or has donated plasma within 7 days prior to the start of dosing.
16. Subject tests positive at screening for human immunodeficiency virus (HIV) or is known to be seropositive for HIV.
17. Subject tests positive at screening for hepatitis B surface antigen, hepatitis C antibody or has a history of a positive result.
18. Subject is a staff member or relative of a staff member.
19. Subject is not able to meet the study attendance requirements.
20. The Investigator believes the subject is not suitable for the study for reasons not otherwise specified.

Additional Exclusion Criteria to be Evaluated after Clinic Admission to be Eligible to Participate in the Double-blind Treatment Phase (Visits 3-6)

1. Physical dependence on opioids, as determined by the Naloxone Challenge Test (i.e., subject has a Clinical Opiate Withdrawal Scale [COWS] score of ≥ 5) (precludes entry into the Drug Discrimination Test).
2. Inability to discriminate between opioid (crushed IR oxycodone 20 mg PO solution) and crushed placebo solution during the Drug Discrimination Test. Ability to discriminate is defined for Drug Liking as follows (inclusive):
 - A minimum E_{max} of 65 points for Drug Liking in response to active treatment;
 - A ≥ 15 -point difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
 - A placebo response ≥ 40 and ≤ 60 points for Drug Liking during the first 2 hours following drug administration.
3. Intolerant to study treatments in the Drug Discrimination Test (e.g., emesis within first 6 hours after dosing precludes entry into Double-blind Treatment Phase).
4. Unacceptable response to other study assessments or inability to successfully complete the study as judged by the Investigator with input from the Sponsor.

Test Product, Dose, and Mode of Administration:

Naloxone Challenge Test: An initial dose of naloxone hydrochloride 0.2 mg was administered by intravenous (IV) bolus followed by an additional 0.6 mg of IV naloxone if no evidence of withdrawal occurred within 30 seconds.

Drug Discrimination Test: Single dose of IR Oxycodone 20 mg dosed PO, crushed in solution and placebo dosed PO, crushed in solution with doses separated by 24 hours.

- IR oxycodone, USP, 20 mg (KVK Tech, Newtown, PA): Lot No. 11663A, Expiry Date: July 2016.
- Placebo, microcrystalline cellulose (PCCA, Houston, TX): Lot No. C143993, Expiry Date: 18 May 2015.

Double-blind Treatment Phase: Subjects were randomized in a 1:1:1:1:1:1 ratio to receive 1 of 6 treatment sequences of the following 6 single dose treatments.

Treatment	Chewed	Intact Capsules	IR Solution	Fed/Fasted
A	DETERx placebo	Oxycodone DETERx	Placebo	HFHC
B	DETERx placebo	Oxycodone DETERx	Placebo	Fasted
C	Oxycodone DETERx	DETERx placebo	Placebo	HFHC
D	Oxycodone DETERx	DETERx placebo	Placebo	Fasted
E	DETERx placebo	DETERx placebo	IR oxycodone	Fasted
F	DETERx placebo	DETERx placebo	Placebo	HFHC

HFHC=high-fat, high-calorie; IR=immediate-release

Intact study drug/placebo was administered prior to chewed study drug/placebo. Subjects swallowed the intact capsule directly from the dosing container. Intact doses of study drug/placebo were administered with 50 mL of either crushed oxycodone IR in solution or placebo in solution. Following dosing, 2 additional 50 mL rinses of room temperature, non-carbonated water were administered from the dosing container. For the chewed capsule treatments, dosing staff opened the capsule and poured the capsule contents (beads) into a small dosing cup immediately prior to dosing. Subjects were instructed to pour the study drug capsule contents from the dosing cup onto their tongue and to chew the study drug/placebo capsule contents for 2 minutes without swallowing or talking while chewing. Following dosing, 2 additional 50 mL rinses of room temperature, non-carbonated water were administered from the dosing container. Detailed procedures for intact study drug, chewed study drug, and crushed study drug administration were provided in a separate Chewing and Visual Oral Cavity Inspection Procedure.

Oxycodone DETERx 40 mg capsules were supplied by the Sponsor (Collegium Pharmaceutical, Inc., Canton, MA) as bottles of 100 Batch No. 3101451, Expiry/Retest Date: July 2014.

For the crushed IR oxycodone 40 mg in solution treatment in the Double-blind Treatment Phase, two 20 mg tablets of the following were used: Oxycodone HCl, 20 mg (KVK Tech, Newtown, PA), Lot No. 11663A, Expiry Date: July 2016.

Duration of Treatment: For each Treatment Period of the Double-blind Treatment Phase, subjects received one single dose.

Reference Therapy, Dose, and Mode of Administration: IR Oxycodone, USP is an oral formulation of oxycodone. IR oxycodone was provided at a tablet dose strength of 20 mg with 1 tablet used for the Drug Discrimination Test (total dose of 20 mg) and 2 tablets used for the Double-blind Treatment Phase (total dose of 40 mg); the dose of IR oxycodone was crushed and administered PO in solution. Oxycodone HCl, 20 mg tablets were procured by the study site from KVK Tech (Newtown, PA 18940 USA), Lot No. 11663A, Expiry Date: July 2016. These doses were prepared at the clinical site according to a crushing procedure that was outlined in a separate Pharmacy Manual.

Oxycodone DETERx 40 mg placebo capsules were supplied by the Sponsor and shipped to the study site in blister packaging, Lot No. 3101503R, Expiry/Retest Date: July 2014.

Criteria for Evaluation:

Pharmacokinetic Assessments: Prior to administration of the first discrimination dose of study drug/placebo, a 3-mL blood sample for PK evaluation was collected.

During each Treatment Period of the Double-blind Treatment Phase, 3 mL serial blood samples for PK evaluation were collected predose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 24.0, and 36.0 hours post dose.

C_{max} , T_{max} , T_{lag} , $AUC_{(0-t)}$, AUC_{INF} , $AUC_{\%extrap}$, abuse quotient (AQ, C_{max}/T_{max}), partial AUC (0-all blood sample time points), λ_z , $t_{1/2}$, CL/F , V_z/F , and Fr for oxycodone were calculated using noncompartmental PK methods.

Pharmacodynamic Assessments: Pharmacodynamic (PD) assessments included subjective and objective assessments as follows:

Subjective assessments included Drug Effects Questionnaire (DEQ) drug liking, feeling high, any drug effects, good effects, bad effects, feel sick, nausea, sleepy, and dizzy; Overall (Global) Drug Liking; Addiction Research Center Inventory-Morphine Benzedrine Group (ARCI/MBG); Take Drug Again Assessment; and Price Value Assessment Questionnaire (PVAQ). The DEQ was assessed during each Treatment Period of the Double-blind Treatment Phase at the following times: 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0 and 24.0 hours post dose. Predose assessments were limited to DEQ for nausea, feel sick, and ARCI/MBG. Data were collected at 8.0 and 24.0 hours post dose for Take Drug Again Assessment and Overall (Global) Drug Liking. PVAQ was captured at 24 hours post dose.

Pupil diameter (pupillometry), an objective assessment, was measured during each Treatment Period of the Double-blind Treatment Phase at predose and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 hours post dose.

The following PD endpoints were derived: maximum (peak) effect (E_{max}) from 0 to 24 hours post dose; time to maximum (peak) effect (TE_{max}); minimum (peak) effect (E_{min}) for bipolar scales only from 0 to 24 hours post dose; time to minimum (peak) effect (TE_{min}) for bipolar scales only; area under the effect curve (AUE) to 1 hour (AUE_{0-1h}), AUE_{0-2h} , AUE_{0-4h} , AUE_{0-8h} , AUE_{0-24h} . For Overall (Global) Drug Liking and the Take Drug Again Assessment, the E_{max} and mean response (E_{mean}) averaging the 8 and 24 hour assessments were calculated.

Safety Assessments: Safety was evaluated based on adverse events (AEs), clinical laboratory assessments, vital signs, oxygen saturation, 12-lead ECG, and physical examinations.

Statistical Methods:

Analysis Populations:

Pharmacodynamic Population: Subjects who completed all 6 Treatment Periods with at least one PD assessment in each Treatment Period. This was the primary population for PD analyses.

Pharmacokinetic Population: The PK Population consists of subjects who completed at least two active Treatment Periods, who have sufficient quantifiable plasma concentration data to provide C_{max} and AUC data, and who did not experience emesis within 12 hours of dosing for Oxycodone DETERx or within 2 x median T_{max} ($2 \times 1.07 = 2.14$ h) of dosing for IR oxycodone. Subjects with apparently aberrant PK data may have been excluded from the PK Population after consulting with the Sponsor.

Alternate PK Population: An Alternate PK Population was defined in the Pharmacokinetic Analysis Plan (PKAP) as consisting of subjects in the PK Population as well as subjects with at least two complete PK profiles and selected subjects who experienced emesis after T_{max} (selected by an experienced Pharmacokineticist). Subjects with apparently aberrant PK data may be included in or excluded from the Alternate PK Population after consulting with the Sponsor. NB. The Pharmacokineticist did not identify any subjects who should have been included in an Alternate PK Population.

Drug Discrimination Safety Population: All subjects who received at least one dose of study drug during the Drug Discrimination Phase and for whom there was at least one post-treatment safety observation.

Safety Population: All subjects randomized into the Double-blind Treatment Phase who received at least one dose of study drug during the Double-blind Treatment Phase and for whom there was at least one post-treatment safety observation in this phase.

Pharmacokinetic Analyses: All PK parameters were calculated using non-compartmental analysis. Only those plasma concentrations equal to or greater than the validated lower limit of quantitation (LOQ), 0.5 ng/mL, were used in the analysis. Plasma concentrations < LOQ were taken as 0 for the calculation of the descriptive statistics for plasma concentrations at each sampling time. For the PK analysis, plasma concentrations < LOQ that occurred from pre-dose to the first concentration $\geq$ LOQ were treated as 0 and those that occurred thereafter were treated as missing. Actual sampling times were used for all PK analyses. Protocol times were used to calculate mean plasma concentrations for graphical displays.

The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were taken directly from the data. If the plasma concentration at the first sampling time, 0.25 h, was < LOQ, then T_{lag} , the absorption lag time, was estimated as the time of the first concentration $\geq$ LOQ. The elimination rate constant, λ_z , was calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The slope was determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration $\geq$ LOQ and not including C_{max} , were selected for the determination of λ_z ; the regression had to have a coefficient of determination (r^2) of ≥ 0.9000 . The range of data used for each subject and treatment was determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Elimination half-life ($t_{1/2}$) was calculated according to the following equation:

$$t_{1/2} = \frac{0.693}{\lambda_z}$$

Area under the curve from zero to the final sample with a concentration $\geq$ LOQ [$AUC(0-t)$] was calculated using the linear trapezoidal method and extrapolated to infinity [$AUC(\text{inf})$] using the following equation:

$$AUC(\text{inf}) = AUC(0-t) + \frac{C_{tf}}{\lambda_z},$$

where C_{tf} is the final concentration $\geq$ LOQ. The percentage of $AUC(\text{inf})$ extrapolated was calculated using the following equation:

$$\%AUC \text{ Extrapolated} = 100\% \times \frac{C_{tf} / \lambda_z}{AUC(\text{inf})}$$

The partial areas under the curve [$PAUC(0-t_i)$], from 0 to all sampling points (t_i), were calculated using the linear trapezoidal method.

The clearance (CL/F) and volume of distribution (V_z/F), uncorrected for bioavailability (F), were calculated according to the following equation:

$$CL / F = \frac{Dose}{AUC(\text{inf})} \text{ and } V_z / F = \frac{Dose}{AUC(\text{inf}) \times \lambda_z},$$

respectively, where Dose represents the dose of oxycodone

(b) (4)

The relative bioavailability (Fr) of each treatment relative to the reference was calculated using the following equation:

$$Fr = 100\% \times \frac{AUC(\text{inf})_{TEST}}{AUC(\text{inf})_{REF}},$$

where REF is IR Oxycodone Crushed Solution Fasted.

The abuse quotient (AQ) was calculated as

$$AQ = \frac{C \text{ max}}{T \text{ max}}.$$

The following treatment comparisons were made for ln-transformed AUC(0-t), AUC(inf), and Cmax:

- Treatment A vs. Treatment E
- Treatment B vs. Treatment E
- Treatment C vs. Treatment E
- Treatment D vs. Treatment E
- Treatment C vs. Treatment A
- Treatment B vs. Treatment A
- Treatment D vs. Treatment A

Treatment D vs. Treatment B

Treatment D vs. Treatment C

where,

Treatment A = Intact Oxycodone DETERx 40 mg dosed PO with a HFHC meal

Treatment B = Intact Oxycodone DETERx 40 mg dosed PO fasted

Treatment C = Chewed Oxycodone DETERx 40 mg dose PO with a HFHC meal

Treatment D = Chewed Oxycodone DETERx 40 mg dosed PO fasted

Treatment E = IR Oxycodone Crushed in Solution 40 mg dosed PO fasted

Primary Analysis: The PK parameters for oxycodone — C_{max} , $AUC(0-t)$, and $AUC(inf)$ — were compared among treatments using an analysis of variance (ANOVA) statistical model with sequence, treatment, and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data. Confidence intervals (90% [CI]) were constructed for the least squares geometric mean ratios (GMR) of all 3 parameters for the treatments being compared using the natural log-transformed data and the 2 one-sided t-tests procedure. The GMRs and associated 90% CI were exponentiated back to the original scale. Bioequivalence was to be concluded if the 90% CIs of the GMRs for a specific comparison fell entirely within 80.0% to 125.00%.

Secondary Analysis: T_{max} was analyzed using a nonparametric analysis without transformation. The 25% Quantile (Q1), 50% Quantile (Median), and 75% Quantile (Q3) were calculated from the Walsh averages of the treatment differences. The Wilcoxon Signed Rank Test was used to compare T_{max} among the different treatments.

Pharmacodynamic Analyses: For PD statistical analyses, significance testing for the primary comparisons and the Drug Liking primary endpoint, E_{max} , were 1-tailed using a nominal $\alpha = 0.025$; however, all p-values presented are 2-tailed and the direction of the difference, which had to be positive, is equivalent to the 1-tailed test. Significance testing for all other endpoints and comparisons was 2-tailed using $\alpha = 0.05$, unless otherwise specified. The parameters of interest that were collected in this study included the following:

- Drug Liking – bipolar VAS scale (Primary);
- Overall (Global) Drug Liking – bipolar VAS scale;
- Take Drug Again – bipolar VAS scale;
- DEQ (any drug effects, high, good effects, bad effects, sick, nausea, sleepy, and dizzy) – unipolar VAS scale;
- PVAQ;
- ARCI/MBG;
- Pupillometry

The following PD endpoints were calculated for each parameter of interest as appropriate:

- E_{max} during 24 hours after dosing
- TE_{max}
- E_{min} for bipolar scales only during 24 hours after dosing
- TE_{min} for bipolar scales only
- AUE_{0-1h}
- AUE_{0-2h}
- AUE_{0-4h}
- AUE_{0-8h}
- AUE_{0-24h}
- For Overall (Global) Drug Liking and the Take Drug Again Assessment, the E_{max} and E_{mean} average of the 8 and 24 hour assessments.

The primary analysis was based on the pairwise comparisons between crushed IR oxycodone fasted (control - Treatment E) and chewed Oxycodone DETERx HFHC (Treatment C) and chewed Oxycodone DETERx fasted (Treatment D) for Drug Liking E_{max} . The Drug Liking E_{max} comparison between crushed IR oxycodone fasted (Treatment E) and placebo HFHC (Treatment F) was used for validation of the appropriateness of the positive control.

Secondary comparisons were done between chewed Oxycodone DETERx HFHC (Treatment C) and chewed Oxycodone DETERx fasted (Treatment D) compared with intact Oxycodone DETERx HFHC (Treatment A), as well as between chewed Oxycodone DETERx fasted (Treatment D) and intact Oxycodone DETERx fasted (Treatment B). Other relevant comparisons were done between intact Oxycodone DETERx HFHC (Treatment A) and crushed IR oxycodone fasted (Treatment E), between intact Oxycodone DETERx fasted (Treatment B) and crushed IR oxycodone fasted (Treatment E), between intact Oxycodone DETERx HFHC (Treatment A) and placebo HFHC (Treatment F), between intact Oxycodone DETERx fasted (Treatment B) and placebo HFHC (Treatment F), between chewed Oxycodone DETERx HFHC (Treatment C) and placebo HFHC (Treatment F), and between chewed Oxycodone DETERx fasted (Treatment D) and placebo HFHC (Treatment F).

The following treatment comparisons were made for each of the PD endpoints:

- Treatment E vs. Treatment C (Primary Comparison);
- Treatment E vs. Treatment D (Primary Comparison);
- Treatment E vs. Treatment F (Validity);
- Treatment C vs. Treatment A (Secondary Comparison);
- Treatment D vs. Treatment A (Secondary Comparison);
- Treatment D vs. Treatment B (Secondary Comparison);
- Treatment E vs. Treatment A;
- Treatment E vs. Treatment B;
- Treatment A vs. Treatment F;
- Treatment B vs. Treatment F;
- Treatment C vs. Treatment F;
- Treatment D vs. Treatment F.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results: The results of this study showed the following:

- Oxycodone DETERx Chewed under fed or fasted conditions did not lead to any change in the PK profile compared with the corresponding Oxycodone DETERx Intact treatment.
- Oxycodone DETERx Chewed vs. Intact treatments were bioequivalent with respect to C_{max} , $AUC(0-t)$, and $AUC(inf)$ and had comparable values for T_{max} , AQ, and Fr as well as the PAUC vs. time profiles.
- IR Oxycodone Crushed in solution under fasted conditions resulted in a higher C_{max} at a shorter T_{max} , and thus a greater AQ, than after all methods of administration of Oxycodone DETERx. This was further supported by the comparisons of PAUCs.
- The results indicate that there is no dose dumping when Oxycodone DETERx is administered after chewing.
- Oxycodone DETERx Chewed Fasted was bioequivalent to Oxycodone DETERx Intact under both fasted and fed (HFHC) conditions for $AUC(0-t)$ and $AUC(inf)$, but not for Oxycodone DETERx Intact Fed C_{max} . Oxycodone DETERx Chewed Fed was bioequivalent to Oxycodone Intact Fed; similarly, Oxycodone DETERx Chewed Fasted and Oxycodone Chewed Fed were bioequivalent for all 3 bioequivalence comparison parameters.

- Oxycodone DETERx under fed conditions resulted in higher exposure compared with fasted conditions for both intact and chewed dosing although DETERx Intact fasted was bioequivalent to DETERx Intact fed on AUC(inf), although Oxycodone DETERx Intact Fasted was bioequivalent to Oxycodone DETERx Intact Fed for AUC(inf).
- Total exposure after administration of IR Oxycodone Crushed Solution Fasted, measured by AUC(0-t) and AUC(inf), was comparable to that from Oxycodone DETERx Intact and Chewed.

Pharmacodynamic Results: An abuse potential assessment is typically conducted by comparing an investigational drug to a drug of known abuse and placebo. The primary endpoint of interest for this study was the 0-100 mm bipolar VAS score for Drug Liking; larger values indicate greater liking. The primary parameter was E_{max} . Study validity was evaluated with the comparison of Drug Liking E_{max} for crushed IR oxycodone fasted to placebo HFHC. LS mean $\pm$ SEM E_{max} for Drug Liking was significantly higher for crushed IR oxycodone fasted than placebo HFHC (81.56 ± 1.915 vs 54.70 ± 1.915 mm, $p < 0.0001$), which confirms validity of the study. The difference of LS means between the crushed IR oxycodone fasted and placebo HFHC was also significantly higher for all AUE parameters ($p < 0.0001$), further supporting study validity.

Primary Comparisons for the Primary Endpoint

Table S-1 presents an overall summary of the statistical analysis of PD Parameters for the Primary Endpoint Drug Liking. The LS Mean E_{max} for Drug Liking was significantly lower for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted ($p < 0.0001$). Specifically, Drug Liking E_{max} for chewed Oxycodone DETERx HFHC was approximately 87% of E_{max} for crushed IR oxycodone fasted. The primary PD analysis comparing chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted was corroborated by the supporting analysis of the AUE parameters through 8 hours with significantly less liking of chewed Oxycodone DETERx HFHC and crushed IR oxycodone fasted ($p \leq 0.0293$). TE_{max} was significantly longer for chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted (LS mean $\pm$ SEM: 3.31 ± 0.421 vs 1.36 ± 0.421 hours; median difference $\pm$ SEM: -2.00 ± 0.505 hours, $p < 0.0001$) indicating that central exposure took longer to achieve with chewed Oxycodone DETERx HFHC than crushed IR oxycodone fasted.

The LS Mean E_{max} for Drug Liking was significantly lower for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted ($p = 0.0007$). Specifically, Drug Liking E_{max} for chewed Oxycodone DETERx fasted was approximately 91% of E_{max} for crushed IR oxycodone fasted. The primary PD analysis comparing chewed Oxycodone DETERx fasted and crushed IR oxycodone fasted was corroborated by the supporting analysis of the AUE parameters at the earlier time points with significantly less liking of chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted ($p \leq 0.0077$) for the AUE parameters through 4 hours. TE_{max} was significantly longer for chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted (LS mean $\pm$ SEM: 3.77 ± 0.421 vs 1.36 ± 0.421 hours, $p < 0.0001$) indicating that central exposure took longer to achieve with chewed Oxycodone DETERx fasted than crushed IR oxycodone fasted.

3.2.9 Study CP-OXYDET-25 Synopsis:

Title of Study: An Evaluation of the Effect of Tampering on Oxycodone DETERx® Compared with OxyContin®	
Principal Investigator: Investigator: (b) (4)	
Study center: Frontage Clinical Services, 241 Main Street, Hackensack, NJ 07601 USA	
Publications (reference): None	
Studied period (years): Date first subject enrolled: 17-Jan-2014 Date last subject completed: 17-Feb-2014	Phase of development: I
Objectives: The primary objective of this study was to assess the safety and pharmacokinetics (PK) of intact and crushed Oxycodone DETERx in the fed state relative to a marketed intact and crushed oxycodone extended-release formulation in the fed state and a crushed immediate-release (IR) formulation in the fed state.	
Methodology: This is an open-label, randomized, 5-treatment, 5-period, active-controlled, cross-over comparison study designed to assess the safety and PK of intact and crushed Oxycodone DETERx 40 mg when dosed with a high-fat, high-calorie (HFHC) meal, compared with intact and crushed OxyContin administered with a HFHC meal and with crushed IR oxycodone administered with a HFHC meal. Eligible healthy adult male and female subjects, 18-50 years of age, inclusive, were randomly assigned to receive each of the following five treatments according to a randomization schedule prepared prior to the start of the study: • Oxycodone DETERx 40 mg (capsule intact) with a HFHC Meal • Oxycodone DETERx 40 mg (capsule contents crushed) with a HFHC Meal • OxyContin 40 mg (tablet intact) with a HFHC Meal • OxyContin 40 mg (tablet crushed) with a HFHC Meal • IR oxycodone 40 mg (tablet crushed) with a HFHC Meal Subjects received one dose of the assigned treatment following an overnight fast of at least 10 hours. Subjects consumed a HFHC breakfast, beginning 30 minutes prior to study drug administration, which they completed within approximately 20 minutes. The HFHC meal followed the recommendation described in the Food and Drug Administration (FDA) Guidance for Industry: Food Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. For Treatment Periods with intact Oxycodone DETERx and crushed Oxycodone DETERx, blood sampling continued for duration of 36 hours after dosing. For Treatment Periods with intact OxyContin and crushed OxyContin, blood sampling continued for duration of 36 hours after dosing. For Treatment Period of crushed IR oxycodone, blood sampling continued for duration of 24 hours after dosing. There were at least 5 days between each treatment to provide sufficient washout time between treatments. Subjects received an oral dose of 50 mg naltrexone approximately 13 hours prior to and 1 hour prior to each dose of study drug in each Treatment Period.	

Following administration of intact Oxycodone DETERx and crushed Oxycodone DETERx, serial blood samples for PK evaluation were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0 and 36.0 hours post-dose. Following Treatment Periods of intact OxyContin and crushed OxyContin, serial blood samples for PK evaluation were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0 and 36.0 hours post-dose. Following Treatment Period of crushed IR oxycodone, serial blood samples for PK evaluation were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours post-dose.

The incidence of treatment-emergent adverse events (TEAEs) was assessed in each Treatment Period. Adverse events were collected from the first dose of study drug to 14 days following the subject's last study drug dose or until the last study visit, whichever is later. Serious adverse events were collected from the time of informed consent to 30 days post last dose. Other safety parameters included the monitoring of vital signs and oxygen saturation during each Treatment Period. Hematologic, biochemical, and urinalysis variables were assessed at screening and prior to discharge from the study. All safety assessments may have been repeated if deemed to be in the best interest of the subject, per Investigator discretion.

Number of subjects (planned and analyzed):

It was planned that 42 eligible subjects would be enrolled. Forty-two subjects were enrolled and randomized to receive study drug, 38 (90.5%) subjects completed the study and 37 (88.1%) subjects received all doses as planned. The PK Population included 38, 38, 40, 39 and 40 subjects who completed treatments A, B, C, D, and E, respectively. The Alternate PK Population included 38, 39, 41, 39 and 39 subjects who completed treatments A, B, C, D, and E, respectively.

Diagnosis and main criteria for inclusion:

Eligible subjects were healthy male or non-pregnant female volunteers who provided written informed consent, 18-50 years of age, inclusive, with a body mass index ≤ 33 kg/m².

Test product, dose and mode of administration, batch number:

Oxycodone DETERx 40 mg manufactured by Patheon Pharmaceuticals, Inc. (Cincinnati, OH) [Lot No. 3101451, Manufacturing Date: May 2012] was administered to subjects orally intact and crushed under fed conditions.

OxyContin® manufactured by Purdue Pharma, L.P. (Stamford, CT) [containing 40 mg oxycodone HCl, Lot No. WSH21, Expiration Date: SEP 2015] was administered to subjects orally intact and crushed under fed condition.

Reference therapy, dose and mode of administration, batch number:

IR oxycodone 40 mg (2 x 20 mg) tablets manufactured by KVK-TECH, Inc. (Newtown, PA) [Lot No. 11800A, Expiration Date: OCT2016] were administered orally, crushed, to subjects under fed conditions.

Duration of treatment:

All subjects underwent a Screening Phase of up to 3 weeks and a Treatment Phase of up to approximately 3.5 weeks. Total study duration was approximately 6.5 weeks.

Criteria for evaluation:

Pharmacokinetics:

T_{lag} , C_{max} , T_{max} , AUC_{last} , AUC_{INF} , $AUC_{\%extrap}$, λ_z , $t_{1/2}$, apparent CL, apparent Vd, Fr, Partial AUC, and AQ for plasma oxycodone were calculated using noncompartmental PK methods using WinNonlin version 6.3 (Pharsight Corporation, St. Louis, MO).

Safety:

The incidence of TEAEs was assessed in each Treatment Period. Adverse events were collected from the first dose of study drug to 14 days following the subject's last study drug dose or until the last study visit, whichever is later. Serious adverse events were collected from the time of informed consent to 30 days post last dose. Other safety parameters included the monitoring of vital signs and oxygen

saturation during each Treatment Period. Hematologic, biochemical, and urinalysis variables were assessed at screening and prior to discharge from the study.

Statistical methods:

Analysis of variance (ANOVA) was performed on the ln-transformed AUC_{last} , AUC_{INF} , and C_{max} . The ANOVA model included sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term, at a 10% level of significance; all other main effects was tested using the residual error (error mean square). Each ANOVA included calculation of least square mean (LSM), the difference between treatment LSM, and the standard error associated with the difference. These analyses were calculated using SAS® Version 9.3 (SAS Institute, Inc., Cary, NC), General Linear Model procedure.

Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed AUC_{last} , AUC_{INF} , and C_{max} . These ratios were expressed as a percentage relative to the reference (IR oxycodone) treatment. Consistent with the two one-sided tests for bioequivalence (BE), 90% confidence intervals (CIs) for the ratios were derived. Bioequivalence was concluded if the 90% CIs of the estimated mean ratios fell entirely within the 80.0-125% limits. The primary analyses were a comparison of crushed Oxycodone DETERx vs. crushed IR oxycodone and crushed OxyContin vs. crushed IR oxycodone. Secondary analyses included crushed Oxycodone DETERx vs. intact Oxycodone DETERx, crushed OxyContin vs. intact OxyContin, intact Oxycodone DETERx vs. crushed IR oxycodone and intact OxyContin vs. crushed IR oxycodone, and intact Oxycodone DETERx vs. intact OxyContin, and crushed Oxycodone DETERx vs. crushed OxyContin. T_{max} was analyzed using nonparametric analysis. The 25% Quantile (Q1), 50% Quantile (Median), and 75% Quantile (Q3) were calculated from the Walsh averages of the treatment differences. Wilcoxon Signed Rank Test was used to compare the test treatments versus reference treatment. T_{max} was not transformed; results are reported.

Plots are presented for the mean ($\pm$ standard deviation) plasma concentration versus time, and for individual subject plasma concentration data versus time on linear and semi-logarithmic axes.

Safety and tolerability were assessed through TEAEs, vital signs measurements, oxygen saturation, hematologic, biochemical, and urinalysis laboratory parameters.

Safety summaries are provided for all subjects in the Safety Population. Adverse event data, clinical laboratory test results, physical examination findings, ECG, vital signs data, and blood oxygen saturation data are presented descriptively using summary tables and listings. Change and shift from baseline in clinical laboratory results are presented descriptively using summary tables and listings. Physical examination findings are listed by subject and summarized.

SUMMARY – CONCLUSIONS

PHARMACOKINETICS RESULTS:

- Administration of crushed Oxycodone DETERx HFHC was BE to intact Oxycodone DETERx HFHC with no significant difference in T_{max} when comparing the 2 treatments.
- Comparing crushed and intact Oxycodone DETERx HFHC to crushed IR oxycodone HFHC, the treatments were equivalent with respect to AUC, but not C_{max} . Relative to crushed IR oxycodone HFHC, the crushed and intact Oxycodone DETERx HFHC C_{max} point estimates were 77.41% and 82.41%, respectively. The median difference in T_{max} when comparing intact or crushed Oxycodone DETERx HFHC to crushed IR oxycodone HFHC was 2 hours (i.e., T_{max} for crushed IR oxycodone was shorter), and was statistically different.
- Abuse quotient values were comparable for crushed and intact Oxycodone DETERx HFHC treatments, and were much lower than for crushed IR oxycodone HFHC.
- Crushed OxyContin HFHC was equivalent to intact OxyContin HFHC with respect to AUC, but not with respect to C_{max} . The C_{max} point estimate was 121.15%. The median

3.2.10 Study CP-OXYDET-26 Synopsis:

Title of the Study: Effect of Coingestion of Alcohol on the Pharmacokinetics of Oxycodone DETERx [®]	
Principal Investigator: Gregory Tracey, MD	
Study Center: Frontage Clinical Services, Clinical Research Center 241 Main Street Hackensack, New Jersey 07601 USA	
Publications (reference): None	
Studied Period: 08 July 2014 to 06 September 2014	Clinical Phase: I
Objectives: The primary objective of this study was to evaluate the pharmacokinetics (PK) and relative bioavailability of Oxycodone DETERx 10 mg and 40 mg coingested with water (0% alcohol), 20% alcohol, and 40% alcohol.	
Rationale: The primary rationale for the study was to determine whether Oxycodone DETERx, when coingested with alcohol, would demonstrate “dose dumping,” that is, a tendency to exhibit more rapid and/or extensive exposure to the drug than would otherwise occur. A prior <i>in vitro</i> study demonstrated that no alcohol-induced dose dumping occurred in fed media or in fasted media when compared with the fed baseline. The intent of the present study was to validate the <i>in vitro</i> result in the natural physiological conditions of an <i>in vivo</i> study.	
Methodology: This was a phase I, randomized, open-label, negative-controlled, 2 Treatment Cohort, single-dose, 4 treatment x 4 Treatment Period, naltrexone-blocked, crossover, single-center comparison study. Subjects were enrolled in either of 2 Treatment Cohorts. In each cohort, subjects received a total of 4 treatments, separated by a washout period of at least 7 days between treatments, as follows: Treatment Cohort 1 • Treatment A: Oxycodone DETERx 40 mg, coingested with 40% alcohol, Fasted • Treatment B: Oxycodone DETERx 40 mg, coingested with 20% alcohol, Fasted • Treatment C: Oxycodone DETERx 40 mg, coingested with 0% alcohol, Fasted • Treatment D: Oxycodone DETERx 40 mg, coingested with 0% alcohol, Fed Treatment Cohort 2 • Treatment A: Oxycodone DETERx 10 mg, coingested with 40% alcohol, Fasted • Treatment B: Oxycodone DETERx 10 mg, coingested with 20% alcohol, Fasted • Treatment C: Oxycodone DETERx 10 mg, coingested with 0% alcohol, Fasted • Treatment D: Oxycodone DETERx 10 mg, coingested with 0% alcohol, Fed The order in which subjects in either cohort received their 4 treatments was randomized equally to one of 4 sequences, as follows: • ADBC (40% alcohol fasted, 0% alcohol fed, 20% alcohol fasted, 0% alcohol fasted) • BACD (20% alcohol fasted, 40% alcohol fasted, 0% alcohol fasted, 0% alcohol fed) • CBDA (0% alcohol fasted, 20% alcohol fasted, 0% alcohol fed, 40% alcohol fasted) • DCAB (0% alcohol fed, 0% alcohol fasted, 40% alcohol fasted, 20% alcohol fasted)	

Each treatment was administered following a minimum 10-hour overnight fast. For Fed Treatment Periods, subjects began to consume a high-fat, high-calorie (HFHC) meal 30 minutes prior to dosing, which was completed within 20 minutes, i.e., at least 10 minutes prior to dosing with study drug. The nutritional composition of the HFHC meal followed the recommendation described in the Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002.

For treatments administered with 0% alcohol, study drug was administered with 240mL of refrigerated, non-carbonated water. For treatments administered with 40% or 20% alcohol, study drug was administered with 240mL of refrigerated 40% or 20% alcohol. The same brand of alcohol was used throughout the study. All water and alcohol treatment arms were administered as four (4) sequential 60mL aliquots, administered over a 20-minute interval, at approximately 5-minute intervals (e.g., 60 mL given every 5 minutes). All 4 aliquots were consumed within 20 minutes of administration of study drug. All aliquots of water and alcohol were flavored with the same zero calorie flavoring for each subject and Treatment Period and were refrigerated to reduce the risk of vomiting.

For fed Treatment Periods, serial blood sampling for PK analysis was conducted pre-dose and at specified intervals in the 36 hours after dosing. For fasted Treatment Periods, serial blood sampling was conducted pre-dose and at specified intervals in the 72 hours after dosing. A dose-to-dose washout period of at least 7 days was provided between each Treatment Period.

Naltrexone (Adjunctive Drug)

For each of the 4 Treatment Periods, subjects were administered naltrexone 50mg to block the pharmacodynamic effects of the study drug according to the following schedule:

- 13 hours ($\pm$ 30 minutes) prior to dosing
- 1 hour ($\pm$ 5 minutes) prior to dosing
- 12 hours ($\pm$ 30 minutes) post-dose.

Pharmacokinetic Endpoints

The study assessed the following PK endpoints:

- T_{lag} - Absorption lag time;
- C_{max} - Maximum plasma concentration;
- T_{max} - Time of maximum plasma concentration;
- $AUC_{(0-t)}$ - Area under the plasma concentration-time curve from 0 to the final time with a concentration $\geq$ limit of quantitation (LOQ);
- $AUC_{(inf)}$ - Area under the plasma concentration-time curve to infinity;
- $AUC_{\%extrap}$ - Percentage of $AUC_{(inf)}$ that is due to extrapolation from C_{last} to infinity (where C_{last} is the last measurable concentration);
- λ_z - Terminal elimination rate constant;
- $t_{1/2}$ - Terminal half-life ($0.693 / \lambda_z$);
- Fr - Relative bioavailability = $AUC_{(inf)}$ (test product) / $AUC_{(inf)}$ (reference product) * 100 (where the reference product is Oxycodone DETERx 0% Alcohol Fed);
- CL/F - Total clearance uncorrected for bioavailability (F);
- Vz/F - Volume of distribution uncorrected for bioavailability (F);
- AQ - Abuse quotient (C_{max} / T_{max});
- PAUC - Partial area under the plasma concentration-time curve.

PK Sampling Times

For all fed Treatment Periods, blood samples for plasma PK analysis of oxycodone were drawn pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0, and 36.0 hours post-dose.

For all fasted Treatment Periods, blood samples for plasma PK analysis of oxycodone were drawn pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 24.0, 36.0, 48.0, 60.0, and 72.0 hours post-dose.

Safety Assessment:

Safety was assessed in each of the study's Treatment Periods in terms of the incidence of treatment emergent adverse events (TEAEs).

Non-serious adverse events (AEs) were collected from the start of the first administration of study drug in Treatment Period 1 until the last study visit. If the Investigator became aware of non-serious AEs after the last study visit, but within 14 days after the subject's last study drug dose, these AEs were also recorded. Serious Adverse Events (SAEs) were collected from the time of signing informed consent until the last study visit. If the Investigator became aware of SAEs after the last study visit, but within 30 days after the subject's last study drug dose, these SAEs were also recorded and reported.

Other safety parameters included monitoring of vital signs including oxygen saturation, hematologic, biochemical, and urinalysis parameters as well as physical exam findings assessed at Screening and prior to discharge from the study. At the discretion of the Investigator, any safety assessment could be repeated if deemed to be in the best interest of the subject.

Protocol Amendments:

The original protocol, dated 24 June 2014, was amended on 14 August 2014. Amendment 1 updated contact information for the medical monitor and specified, for reasons of safety, that for all Treatment Periods, ECG and vital sign data were to be collected in a semi-supine, rather than fully supine position.

Number of Subjects Planned and Analyzed:

A total of 88 healthy, non-smoking adult male and female volunteer subjects between the ages of 21 and 49 who were moderate, social drinkers (defined as consuming 7-21 units of alcohol/week) were enrolled and randomized in the study. Seventy-five (75) subjects (85.2%) received all planned doses of study drug; 66 (75.0%) completed the study. A total of 6 subjects (13.6%) from Treatment Cohort 1 and 16 subjects (36.4%) from Treatment Cohort 2 were discontinued from the study due to an AE, evidence of alcohol or substance abuse, the Investigator's concern for the subject's medical interests, or the subject's withdrawal of consent. All 88 enrolled subjects are included in the Safety Population. The PK Population included 43 (97.7%) subjects from Cohort 1 (36 men and 7 women ranging from 21 to 49 years of age) and 38 (86.4%) subjects from Cohort 2 (29 men and 9 women ranging from 22 to 49 years of age).

Demographics:

Subjects were representative of a healthy adult male and female population, ranging from 21 to 49 years of age. Overall mean (standard deviation [SD]) age was 34.8 (8.38) years and mean (SD) Body Mass Index (BMI) was 27.74 (2.848) kg/m². Racial composition was 51 (58.0%) Black and 37 (42.0%) White.

Criteria for Inclusion/Exclusion:

The primary inclusion and exclusion criteria for eligibility in the study are summarized below.

Primary inclusion criteria

- Subjects were male or female 21-50 years of age (inclusive) at the time of consent
- Subjects did not have any dietary restrictions or food allergies, were able to fast for at least 10 hours, and were able to consume the complete, assigned HFHC meal within the allotted time prior to dosing
- Subjects were moderate, social drinkers (7 to 21 units of alcohol per week, where 1 unit of alcohol equals 12 ounces of 5% beer, 5 ounces of 12% wine, or 1.5 ounces of 80-proof distilled spirits)
- Subjects weighed at least 70 kg (154 lbs.)
- Female subjects had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at admission for each Treatment Period
- Female subjects of childbearing potential had to use an acceptable form of birth control
- Subjects were in general good health based on screening physical examination (defined as the absence of any clinically relevant abnormalities), medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory values (hematology, serum chemistry and urinalysis)
- Subjects had negative urine drug screen, saliva alcohol test, and urine cotinine test at the Screening Visit and at admission for each Treatment Period.

Primary exclusion criteria

- Subjects with no previous history of alcohol consumption, i.e., was alcohol naive
- Female subjects who were pregnant, planning a pregnancy, or were breastfeeding
- Subjects with a BMI > 33 kg/m²
- Subjects with any clinically significant unstable medical abnormality or chronic disease of the

cardiovascular, gastrointestinal, respiratory (e.g., chronic obstructive pulmonary disease), hepatic, or renal systems

- Subjects with any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG, or clinical laboratory measurements, as determined by the Investigator.
- Subjects with a history of alcohol and/or drug abuse
- Subjects with current or prior enrollment in an alcohol or other drug treatment program or current legal issues relating to alcohol, or other drug use, including waiting trial or supervision by a parole or probation officer
- Subjects who were trying to quit alcohol use
- Subjects who could not refrain from taking medications (prescription, over-the-counter, or behind-the-counter), supplements, nutraceuticals, or herbs for 24 hours prior to admission to the clinic (Treatment Period 1) and for the duration of the study except for those allowed by protocol
- Subjects who had taken hepatic enzyme inducing drugs within the 3 months prior to admission to the clinic (Treatment Period 1)
- Subjects who could not refrain from eating and/or drinking the following foods starting 7 days prior to admission to the clinic (Treatment Period 1) and for the duration of the study: grapefruit, pomegranate, pomelo, and star fruit juice/products, and foods containing poppy seeds, Seville oranges, and/or drinks or foods containing quinine (i.e., tonic water)
- Subjects whose QTc interval was >450msec at Screening
- Subjects whose resting blood pressure was <110/45 mmHg at Screening or <100/45 mmHg prior to study drug administration on the day of dosing for any Treatment Period
- Subjects who were on a special diet during the 28 days prior to the first dose of study drug in Treatment Period 1 or during the study
- Subjects who could not refrain from using caffeine or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who could not tolerate stopping caffeine without symptoms were excluded
- Subjects who smoked cigarettes or used any other tobacco products. Subject must have stopped using tobacco products or smoking cigarettes at least 30 days prior to the Screening Visit.

Study, Reference and Adjunctive Drugs, Dose, and Mode of Administration:

Study Drug:

Treatment Cohort 1: Oxycodone DETERx 40 mg oxycodone HCl equivalent.

Lot/Batch No. 3106430, Retest date: 11/2014

Treatment Cohort 2: Oxycodone DETERx 10 mg oxycodone HCl equivalent.

Lot/Batch No. 3106391, Retest date: 11/2014

For each Treatment Period, study drug was administered to subjects enrolled in Cohort 1 as a single 40 mg oral capsule and to subjects enrolled in Cohort 2 as a single 10 mg oral capsule. All treatments were administered following a minimum 10-hour overnight fast. For 1 of the 2 treatments with 0% alcohol, administration of study drug was preceded by a HFHC meal started 30 minutes and fully consumed at least 10 minutes prior to treatment; the remaining 3 treatments were administered fasting (0% alcohol, 20% alcohol and 40% alcohol).

Adjunctive drug: Naltrexone 50 mg, administered 13 hours prior to dosing, 1 hour prior to treatment and 12 hours following treatment with study drug. Lot/Batch No. 1170X89847, Expiry Date: 11/2018

Duration of Treatment:

Following a Screening Visit conducted no more than 21 days prior to the first dose of study drug, subjects returned to the study center for 4 inpatient treatment visits, 1 of which included 2 nights of confinement to the center and 3 which included 4 nights of confinement. Each treatment visit began no sooner than 7 days after the start of the previous visit.

Criteria for Pharmacokinetic and Safety Evaluation:

Criteria for evaluation were the comparisons of PK endpoints and safety parameters for each treatment arm of the study.

Statistical Methods:

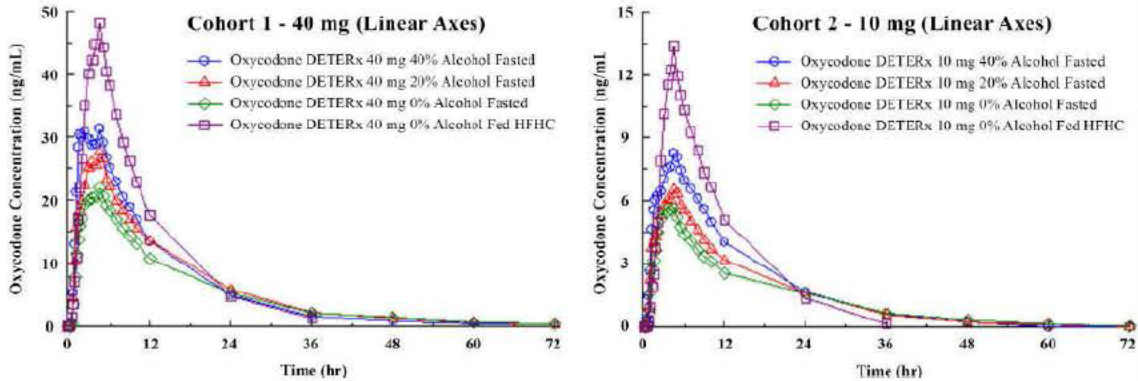
A total of 44 subjects were enrolled in each of the 2 Treatment Cohorts. Summary statistics by treatment and 2-one sided confidence intervals (CIs) for C_{max} , $AUC_{(0-t)}$, and $AUC_{(inf)}$ were calculated in order to compare treatments.

RESULTS:

Pharmacokinetic Results

Figure S-1 displays mean oxycodone plasma concentration for each of the 4 treatments in Cohort 1 (40 mg) on the left and Cohort 2 (10 mg) on the right.

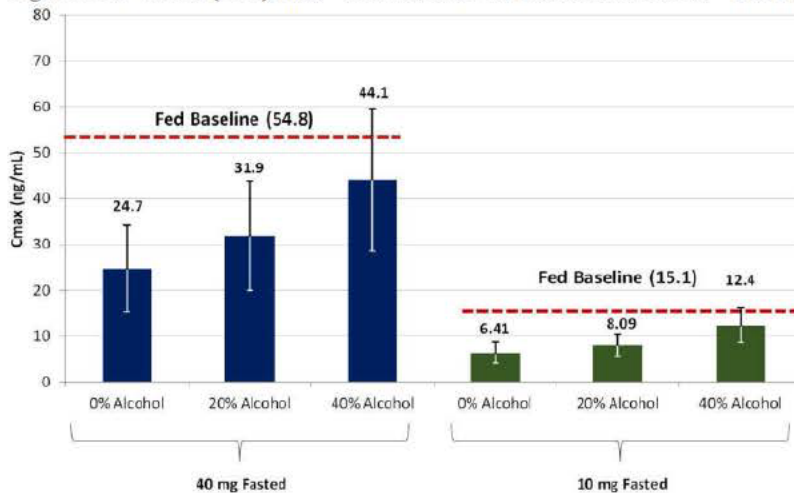
Figure S-1: Mean Oxycodone Plasma Concentration by Treatment – PK Population



Note: The range of oxycodone concentrations on the vertical axis is different for Cohort 1 (0 – 50 ng/mL) vs. Cohort 2 (0 – 15 ng/mL), reflecting the difference in dosage (40 mg vs. 10 mg) between the 2 groups.

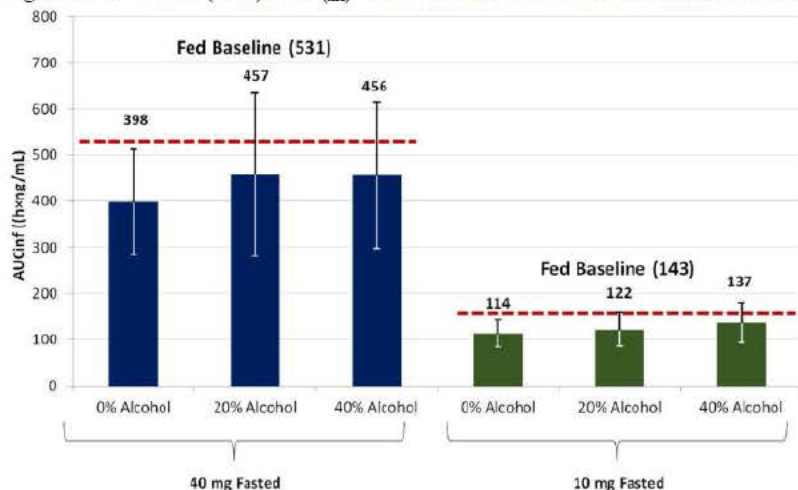
Figure S-1 demonstrates that in both Oxycodone DETERx cohorts the extent of drug exposure is greatest after the fed treatment without alcohol. Forty percent alcohol increased exposure more than the 20% or 0% alcohol, but in each case, the exposure was less than with coingestion of the standardized HFHC meal. The following figures illustrate that for all treatments in each of the cohorts, mean C_{max} (Figure S-2) and mean $AUC_{(inf)}$ (Figure S-3) were below the fed baseline values (0% alcohol fed state), marked with dashed lines.

Figure S-2: Mean ($\pm$ SD) C_{max} - Fed Baseline vs. Fasted Treatments – PK Population



C_{max} = maximum observed plasma concentration; PK = pharmacokinetic; SD = standard deviation

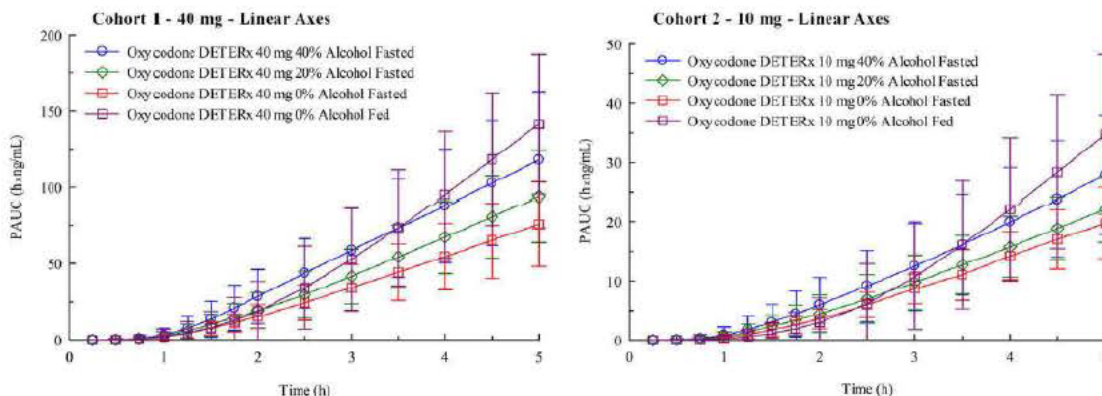
Figure S-3: Mean ($\pm$ SD) $AUC_{(inf)}$ - Fed Baseline vs. Fasted Treatments – PK Population



$AUC_{(inf)}$ = area under the plasma concentration-time curve from time = 0 (dosing) to infinity; PK = pharmacokinetic; SD = standard deviation

Figure S-4 illustrates the mean cumulative partial area under the concentration curve (PAUC) of oxycodone for the initial 5 hours after dosing for each of the 4 treatments in Cohort 1 (40 mg) on the left and Cohort 2 (10 mg) on the right.

Figure S-4: Mean ($\pm$ SD) Cumulative Partial AUC of Oxycodone – Initial 5 Hours by Treatment – PK Population



AUC = area under the plasma concentration-time curve; PK = pharmacokinetic; PAUC = partial AUC

Figure S-4 demonstrates that in each Oxycodone DETERx cohort, the initial rise of plasma drug exposure is comparable among treatments (i.e., for the first 2-3 hours). The absence of “dose dumping” is clearly reflected by the similarity of PAUC profiles among treatments.

The abuse quotient (AQ) – defined as C_{max}/T_{max} – is a proposed measure of the abuse potential of a drug. In both Cohort 1 and Cohort 2, the mean AQs of fasted treatments with 20% alcohol and 0% alcohol were lower than the AQ of the baseline 0% alcohol fed treatment. In both dose cohorts, the AQ for the fasted treatment with 40% alcohol was somewhat higher than the corresponding baseline AQ value.

For Cohort 1, mean ($\pm$ SD) AQ values for 40% alcohol fasted and 0% alcohol fed were 23.1 ($\pm$ 14.2) and 17.4 ($\pm$ 9.29) ng/mL/hr, respectively. For Cohort 2, the AQ values were 5.64 ($\pm$ 3.28) and 4.32 ($\pm$ 2.12) ng/mL/hr, respectively.

While mean C_{max} was considerably lower for the fasted treatments coingested with 40% alcohol, T_{max} was also shorter for these treatments than for the corresponding 0% alcohol fed treatments, resulting in a higher AQ. However, even though the AQ values for the 40% alcohol treatments were numerically higher than the AQs for the baseline treatment, when the standard deviations are taken into account, the AQ values are similar.

3.2.11 Study CP-OXYDET-27 Synopsis:

Title of the Study: Safety and Pharmacokinetics of Sprinkled Oxycodone DETERx [®] Microspheres onto Applesauce																
Principal Investigator: Gregory Tracey, MD																
Study Center: Frontage Clinical Services Clinical Research Center 241 Main Street Hackensack, New Jersey 07601 USA																
Publications (reference): None																
Studied Period: 24-June-2014 to 24-July-2014	Clinical Phase: I															
Objectives: The primary objective of this study was to assess the safety and PK profile of Oxycodone DETERx administered by sprinkling the capsule contents – microspheres – onto applesauce compared with the administration of the intact formulation under fed and fasted states.																
Methodology: This was an open-label, randomized, single-dose, 4-treatment, 4-period, naltrexone-blocked, cross-over comparison study designed to assess the safety and PK profile of Oxycodone DETERx administered by sprinkling the capsule contents – microspheres – onto applesauce compared with administration of the intact formulation under fed and fasted states. Each study subject received a single 40mg dose of DETERx during each of 4 different study visits, with an inter-visit washout period of at least 7 days. For each subject, 1 intact dose was administered following an overnight fast of at least 10 hours; 1 intact dose was administered 30 minutes after consuming a high-fat, high-calorie (HFHC) meal; 1 dose consisted of the full capsule contents sprinkled onto 1 teaspoon (approximately 5 g) of room temperature applesauce while the subject was fasted; and 1 dose was sprinkled onto applesauce after the subject consumed a HFHC meal. The HFHC meal followed the recommendations in the FDA Draft Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, dated December 2002. ¹ The study drug sprinkling procedure (study drug dose preparation) is provided in Appendix 16.1.1, Study Manual, Section 3 . In all Treatment Periods, no additional food was permitted for at least 4 hours following dosing though water was permitted <i>ad libitum</i> except during the period from 1 hour before until 1 hour after dosing. The following table summarizes the 4 study treatments.																
<table border="1"> <thead> <tr> <th>Treatment</th> <th>Intact/Sprinkled onto Applesauce</th> <th>Subject meal status</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>Intact capsule</td> <td>Minimum 10-hour overnight fast</td> </tr> <tr> <td>B</td> <td>Intact capsule</td> <td>HFHC meal</td> </tr> <tr> <td>C</td> <td>Capsule contents sprinkled onto applesauce</td> <td>Minimum 10-hour overnight fast</td> </tr> <tr> <td>D</td> <td>Capsule contents sprinkled onto applesauce</td> <td>HFHC meal</td> </tr> </tbody> </table>		Treatment	Intact/Sprinkled onto Applesauce	Subject meal status	A	Intact capsule	Minimum 10-hour overnight fast	B	Intact capsule	HFHC meal	C	Capsule contents sprinkled onto applesauce	Minimum 10-hour overnight fast	D	Capsule contents sprinkled onto applesauce	HFHC meal
Treatment	Intact/Sprinkled onto Applesauce	Subject meal status														
A	Intact capsule	Minimum 10-hour overnight fast														
B	Intact capsule	HFHC meal														
C	Capsule contents sprinkled onto applesauce	Minimum 10-hour overnight fast														
D	Capsule contents sprinkled onto applesauce	HFHC meal														
HFHC = high-fat, high-calorie																

Following a screening visit conducted no more than 21 days prior to the start of the first Treatment Period, subjects were randomized to one of 4 treatment sequences (ABDC, BCAD, CDBA or DACB) using a 4x4 Williams square design.

Naltrexone (Adjunctive Drug)

Prior to each of the 4 study treatments, subjects were administered two (2) 50mg doses of naltrexone, the first given 13 hours prior to treatment (± 30 minutes) to test for tolerance and the second given 1 hour prior to treatment (± 5 minutes) to block the effects of oxycodone.

Analysis Populations

The PK Population included all subjects who completed at least 2 Treatment Periods of the study, had data sufficient for the determination of PK parameters, and did not experience emesis within 12 hours of dosing with Oxycodone DETERx.

The Safety Population included all subjects who received at least one dose of study drug and for whom there was at least one post-treatment safety observation (e.g., treatment emergent adverse event [TEAE], vital signs, oxygen saturation, or hematologic, biochemical and urinalysis laboratory parameters or physical examination).

PK Endpoints

The study assessed the following PK endpoints:

- T_{lag} - Time of first quantifiable concentration;
- C_{max} - Maximum observed plasma concentration;
- T_{max} - Time to reach maximum plasma concentration;
- AUC_{0-t} - Area under the plasma concentration versus time curve from time zero to the time of the last measurable plasma concentration;
- AUC_{INF} - Area under the plasma concentration versus time curve from time zero to infinity;
- $AUC_{\%extrap}$ - Percentage of AUC_{INF} that is due to extrapolation from T_{last} to infinity;
- λ_z - Terminal elimination rate constant;
- $t_{1/2}$ - Terminal elimination half-life;
- $CL/F = Dose/AUC_{INF}$;
- $V_z/F = Dose/(AUC_{INF} * \lambda_z)$;
- F_r - Relative bioavailability = $AUC_{INF}(\text{test product})/AUC_{INF}(\text{reference product}) * 100$ (where the test product is Oxycodone DETERx sprinkled onto applesauce and the reference product is Oxycodone DETERx intact);
- C_{max}/T_{max} - Abuse quotient;
- PAUC - AUC from time zero (t_0) to all blood sample time points.

PK Sampling

For fed Treatment Periods, whether the study drug was administered intact or sprinkled on applesauce, blood samples for plasma PK analysis of oxycodone were drawn according to the following schedule:

- Within 60 minutes prior to study drug administration
- 0.50, 1.0, 1.5, 2.0, 2.5, and 3.0 hours post-dose (± 2 minutes)
- 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, and 10.0 hours post-dose (± 5 minutes)
- 12.0, 24.0, and 36.0 hours post-dose (± 15 minutes)

For fasted Treatment Periods, whether the study drug was administered intact or sprinkled on applesauce, blood samples for plasma PK analysis of oxycodone were drawn according to the following schedule:

- Within 60 minutes prior to study drug administration
- 0.50, 1.0, 1.5, 2.0, 2.5, and 3.0 hours post-dose (± 2 minutes)
- 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 9.0, and 10.0 hours post-dose (± 5 minutes)
- 12.0, 24.0, and 36.0 hours post-dose (± 15 minutes)
- 48.0, 60.0, and 72.0 hours post-dose (± 30 minutes)

Safety Assessment:

Safety was assessed in each of the study's Treatment Periods in terms of the incidence of TEAEs. Non-serious adverse events (AEs) were collected from the start of the first administration of the study drug in Treatment Period 1 until the last study visit. Had the Investigator become aware of non-serious adverse events after the last study visit, but within 14 days after the subject's last study drug dose, these adverse events would have been recorded. Serious Adverse Events (SAEs) would have been collected from the time of signing informed consent until the last study visit. Had the Investigator become aware of serious adverse events after the last study visit, but within 30 days after the subject's last study drug dose, the serious adverse event also would have been recorded and reported.

Other safety parameters included monitoring of vital signs including oxygen saturation, hematologic, biochemical, and urinalysis parameters as well as physical exam findings assessed at Screening and prior to discharge from the study. At the discretion of the Investigator, any safety assessment could be repeated if deemed to be in the best interest of the subject.

Protocol Amendments:

The original protocol, dated 17 June 2014, was amended on 26 June 2014. Amendment 1 clarified the timing of specific study procedures, removed less important PK sample collections thereby lowering total volume of blood collected, clarified the procedures for early termination and the handling of subjects experiencing nausea in response to naltrexone, brought inclusion/exclusion criteria into alignment with standard site policies, and corrected minor editorial errors. The original protocol, the amended protocol, and a summary of the changes specified by Amendment 1 are provided in [Appendix 16.1.1](#).

Number of Subjects Planned:

The study planned to enroll a total of 44 healthy, non-smoking adult male and female volunteer subjects between the ages of 18 and 50 to ensure a minimum of 36 subjects completing the study; 44 subjects between the ages of 20 and 50 were enrolled and randomized in the study; 43 subjects completed the study; 43 subjects were included in the PK analysis.

Criteria for Inclusion:

To be eligible for the study, subjects had to satisfy the study eligibility criteria detailed in [Section 9.2](#). Primary inclusion and exclusion criteria are summarized below.

Primary inclusion criteria

- Subjects were male or female 18-50 years of age (inclusive) at the time of consent
- Subjects did not have any dietary restrictions or food allergies, were able to fast for at least 10 hours, and able to consume the complete, assigned HFHC meal within the allotted time prior to dosing
- Female subjects had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at admission for each Treatment Period and females of childbearing potential used an acceptable form of contraception
- Subjects were in general good health based on screening physical examination (defined as the absence of any clinically relevant abnormalities), medical history, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory values (hematology, serum chemistry and urinalysis)
- Subjects had negative urine drug screens, saliva alcohol tests, and urine cotinine tests at the Screening Visit and at admission for each Treatment Period.

Primary exclusion criteria

- Female subjects who were pregnant, planning a pregnancy, or were breastfeeding
- Subjects with a Body Mass Index (BMI) > 33 kg/m²
- Subjects with any clinically significant unstable medical abnormality or chronic disease of the cardiovascular, gastrointestinal, respiratory (e.g., chronic obstructive pulmonary disease), hepatic, or renal systems
- Subjects with any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG, or clinical laboratory measurements, as determined by the Investigator.
- Subjects with a history of alcohol and/or drug abuse
- Subjects who could not refrain from taking medications (prescription, over-the-counter, or behind-the-

counter), supplements, nutraceuticals, or herbs for 24 hours prior to admission to the clinic (Treatment Period 1) and for the duration of the study except for those allowed by protocol

- Subjects who had taken hepatic enzyme inducing drugs within the 3 months prior to admission to the clinic (Treatment Period 1)
- Subjects who could not refrain from eating and/or drinking the following foods starting 7 days prior to admission to the clinic (Treatment Period 1) and for the duration of the study: grapefruit, pomegranate, pomelo, and star fruit juice/products, and foods containing poppy seeds, Seville oranges, and/or drinks or foods containing quinine (i.e., tonic water)
- Subjects who could not refrain from using caffeine or alcohol within 24 hours prior to each admission to the clinic. Heavy caffeine users who could not tolerate stopping caffeine without symptoms were excluded
- Subjects who smoked cigarettes or used any other tobacco products. Subjects must have stopped using tobacco products or smoking cigarettes at least 30 days prior to the Screening Visit.

Study, Reference and Adjunctive Drugs, Dose, and Mode of Administration:

Study Drug: Oxycodone DETERx 40 mg oxycodone HCl equivalent, Batch No. 3106430; Retest Date, November 2014. Depending on the Treatment Period, study drug was administered either as an intact capsule taken orally (PO) with 240 mL of non-carbonated, room temperature water, or opened with its complete contents sprinkled onto 1 teaspoon (approximately 5g) of room temperature applesauce and taken PO, followed by 240 mL of water.

Reference drug: None

Adjunctive drug: Naltrexone 50mg manufactured by Mallinckrodt, Inc., Batch No. 1170W88911, Expiry date: 08/2018

Duration of Treatment:

Following a Screening Visit conducted no more than 21 days prior to the first dose of study drug, subjects returned to the study center for 4 inpatient treatment visits, 2 of which included 2 nights of confinement to the center and 2 of which included 4 nights of confinement. Each treatment visit began no sooner than 7 days after the start of the previous visit. See [Table 3, Schedule of Assessments](#) for complete details.

Criteria for Evaluation:

Criteria for evaluation were the comparison of PK endpoints and safety parameters between fed and fasted treatment administered with intact capsules and capsule contents sprinkled on applesauce.

Analysis Methods:

Pharmacokinetic Analysis

Oxycodone PK parameters C_{max} , AUC_{0-t} , and AUC_{INF} were compared among treatments using an Analysis of Variance (ANOVA) statistical model with sequence, treatment and period as the fixed effects and subject within sequence as a random effect, using the natural logarithms of the data. Sequence was tested using subject within sequence as the error term, at a 10% level of significance; all other main effects were tested using the residual error (mean squared error).

Confidence intervals (CIs) (90%) were constructed for the least squares geometric mean ratios (GMR) – Oxycodone DETERx sprinkled fed-to-Oxycodone DETERx intact fed – of all 3 parameters using the natural log-transformed data and the two one-sided t-tests procedure. The GMRs and associated 90% CIs were exponentiated back to the original scale. Bioequivalence was concluded if the 90% CIs of the GMRs for a specific comparison fell entirely within the range 80.00% - 125.00%.

Statistical Analysis

A total of 44 subjects were enrolled in order to ensure a minimum of 36 evaluable subjects, i.e., subjects who completed the study with sufficient PK data to contribute to the final analysis. Thirty-six (36) evaluable subjects were determined to provide 80% power to detect an equivalence ratio between 0.8 and 1.25 if the true mean ratio was 1.10 or less and the coefficient of variation was 21% or less. Summary statistics by treatment and one-sided confidence intervals for C_{max} , AUC_{0-t} , and AUC_{INF} were calculated in order to compare the treatments.

Safety Analysis

Safety was analyzed in terms of the incidence of TEAEs coded by system organ class (SOC) and preferred term (PT) based on the MedDRA reporting system and further classified by severity and relationship to study drug. Other safety parameters included the monitoring of vital signs and oxygen saturation in each Treatment Period. Hematologic, biochemical, and urinalysis variables and physical examination results were assessed at the Screening Visit and prior to discharge from the study.

RESULTS:

Forty-four (44) healthy subjects (33 male, 11 female) were enrolled and randomized to treatment; 43 subjects (97.7%) completed the study as planned; 44 subjects (100.0%) were included in the Safety analysis and 43 (97.7%) were included in the PK analysis. One (1) subject (#1033) was discontinued from the study due to significant noncompliance after receiving only 1 of the 4 planned study treatments and was not included in the PK analysis.

Demographics: Subjects were representative of a healthy adult male and female population, ranging from 20 to 50 years of age. Overall mean (standard deviation [SD]) age was 35.0 (9.20) years and mean (SD) BMI was 26.67 (2.914) kg/m². Racial composition was 22 (50.0%) Black and 22 (50.0%) White.

Pharmacokinetic Results:

The mean (SD) values of C_{max} for the Oxycodone DETERx Intact Fed and the Sprinkled Fed treatments were similar: 55.3 (13.6) and 48.1 (12.0), respectively. Mean (SD) values of AUC_{0-t} were also similar between the Intact Fed and Sprinkled Fed treatments: 529 (142) and 516 (127), respectively, as were values of AUC_{INF}: 540 (143) and 528 (130), respectively.

Following a similar, although lower trend, mean (SD) values of C_{max} and the mean (SD) values of AUC_{0-t} and AUC_{INF} for the Intact Fasted and Sprinkled Fasted treatments were also similar [C_{max}: 22.3 (6.60) and 24.6 (8.66), respectively; AUC_{0-t}: 317 (99.5) and 330 (117), respectively; AUC_{INF}: 339 (98.9) and 373 (130), respectively].

Median T_{max} was 4.5 h for both fed treatments and 4.0 h for both fasted treatments, although the individual range of T_{max} from minimum to maximum was considerably smaller for the sprinkled fasted treatment (from 1.50 to 6.0 h) compared with the other 3 treatments. Summary statistics of PK parameters for the PK Population are displayed below:

Summary of Oxycodone Pharmacokinetic Parameters – PK Population

Parameter (units)	Statistic	Intact Fed N=43	Intact Fasted N=43	Sprinkled Fed N=43	Sprinkled Fasted N=43
C _{max} (ng/mL)	Mean (SD)	55.3 (13.6)	22.3 (6.60)	48.1 (12.0)	24.6 (8.66)
T _{max} (hr)	Median (Range)	4.50 (1.50 – 9.00)	4.00 (1.00 – 10.0)	4.50 (2.50 – 9.00)	4.00 (1.50 – 6.00)
AUC _{0-t} ^a (hr*ng/mL)	Mean (SD)	529 (142)	317 (99.5)	516 (127)	330 (117)
AUC _{INF} (hr*ng/mL)	Mean (SD)	540 (143)	339 (98.9)	528 (130)	373 (130)

^(a) t = 72 hours for fasted treatments and 36 hours for fed treatments; PK = pharmacokinetic; SD = standard deviation

Source: Appendix 16.6.1, Table 2

Bioequivalence Analysis Results:

The 90% confidence intervals (Cis) for C_{max} , AUC_{0-t} and AUC_{INF} are summarized below. Values demonstrating bioequivalence are shown in bold:

Summary of Bioequivalence Analysis – PK Population

Test	Reference	PK Parameter (unit)	Test Geo LSM	Test Geo LSM	Ratio (%Ref)	90% CI Lower Bound	90% CI Upper Bound
PRIMARY ANALYSIS							
Sprinkled Oxycodone DETERx HFHC	Intact Oxycodone DETERx HFHC	C_{max} (ng/mL)	46.67	53.48	87.27	81.21	93.78
		AUC_{0-t} (hr*ng/mL)	496.77	505.06	98.36	93.06	103.96
		AUC_{INF} (hr*ng/mL)	508.30	516.39	98.43	93.21	103.95
SECONDARY ANALYSES							
Sprinkled Oxycodone DETERx Fasted	Intact Oxycodone DETERx Fasted	C_{max} (ng/mL)	23.12	21.26	108.76	101.21	116.87
		AUC_{0-t} (hr*ng/mL)	308.64	299.31	103.12	97.56	109.00
		AUC_{INF} (hr*ng/mL)	340.33	328.26	103.68	96.89	110.93
Intact Oxycodone DETERx Fasted	Intact Oxycodone DETERx HFHC	C_{max} (ng/mL)	21.26	53.48	39.75	36.99	42.71
		AUC_{0-t} (hr*ng/mL)	299.31	505.06	59.26	56.07	62.64
		AUC_{INF} (hr*ng/mL)	328.26	516.39	63.57	59.71	67.67
Sprinkled Oxycodone DETERx Fasted	Sprinkled Oxycodone DETERx HFHC	C_{max} (ng/mL)	23.12	46.67	49.54	46.10	53.23
		AUC_{0-t} (hr*ng/mL)	308.64	496.77	62.13	58.78	65.67
		AUC_{INF} (hr*ng/mL)	340.33	508.30	66.95	62.90	71.27

Data Source: Appendix 16.6.1, Table 3 (primary analysis) and Table 4 (secondary analysis)

CI = confidence interval; Geo = geometric; HFHC = high-fat, high-calorie; LSM = least square mean; PK = pharmacokinetic; Ref = reference

The analysis demonstrates that intact and sprinkled treatments in the HFHC fed state (Primary Analysis) are bioequivalent and that intact and sprinkled treatments in the fasted state (Secondary Analysis) are bioequivalent. However, the secondary analyses comparing intact fasted vs. intact fed and sprinkled fasted vs. sprinkled fed treatments were not bioequivalent vs. sprinkled fed treatments were not bioequivalent.

Safety Results:

A total of 1 (2.3%), 1 (2.3%), 4 (9.3%) and 3 (7.0%) subjects experienced at least one treatment-related TEAE following administration of Oxycodone DETERx Intact HFHC, Oxycodone DETERx Sprinkled HFHC, Oxycodone DETERx Intact fasted, Oxycodone DETERx Sprinkled fasted, respectively. All TEAEs were considered by the Investigator to be of mild severity. The frequency of AEs was comparable between both fed treatments – whether intact or sprinkled – as well as between both fasted treatments – whether intact or sprinkled. No deaths or other SAEs occurred and no subjects discontinued from the study due to an AE.

All subjects had normal clinical laboratory test results at screening and prior to discharge from the study, or had results that were outside normal reference ranges provided by the laboratory, but were considered not clinically significant by the Investigator. There were no clinically significant findings or trends noted from vital signs evaluations, blood oxygen saturation levels, or physical examination findings.

PK Conclusions:

- Administration of Oxycodone DETERx sprinkled under fed or fasted conditions did not lead to any change in the PK profile compared with the corresponding Oxycodone DETERx Intact treatment.
- The T_{lag} was the same for Oxycodone DETERx Sprinkled administration, Fed and Fasted, and Intact Fasted treatments, but longer for Intact Fed. The Oxycodone DETERx Sprinkled Fed vs. Intact Fed treatments and the Oxycodone DETERx Sprinkled Fasted vs. Intact Fasted treatments were each bioequivalent with respect to C_{max} , AUC_{0-t} and AUC_{INF} , had identical values for T_{max} , and had comparable values for AQ and Fr as well as cumulative PAUC vs. time profiles.

- Administration of Oxycodone DETERx under fed conditions resulted in higher exposure compared with fasted conditions for both the sprinkled and intact treatments.

Bioequivalence Conclusions:

- The primary comparison of Intact Fed vs. Sprinkled Fed administration of Oxycodone DETERx demonstrated bioequivalence. The secondary comparison of Intact Fasted and Sprinkled Fasted administration also showed bioequivalence. The other secondary comparisons made between the Fed and Fasted state were not bioequivalent. The PK characteristics of Oxycodone DETERx were not influenced by the Intact vs. Sprinkled administration of the study drug while the Fed vs. Fasted state showed a difference in the PK parameters assessed.

Safety Conclusions:

- Based on the assessment of AEs, laboratory test results, vital signs, oxygen saturation and physical examination findings, Oxycodone DETERx 40 mg was demonstrated to be safe and generally well-tolerated in this healthy, naltrexone-blocked adult population, whether administered in the fed (HFHC) or fasted state and whether ingested as an intact capsule or opened and sprinkled onto applesauce.

Date of Report: 04 November 2014