CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

IND:	29,038 SDN 693, 753
Date Received:	9/17/2010, 9/4/2012
Product Name:	OxyContin Tablets
Active Ingredient:	Oxycodone HCl
Sponsor:	Purdue Pharma
Type of Submission:	Abuse Liability Clinical Study Reports
Reviewer:	Srikanth C. Nallani, Ph.D.

Background:

Purdue Pharma LP conducted five clinical studies to evaluate the abuse potential of their developmental tamper resistant formulation of oxycodone extended release tablets (OTR). These studies were submitted to IND 029038 on September 16, 2010.

1. **OTR-1016** entitled "A Randomized, Open-Label, Single-Dose, Crossover Study of the Effects of Various Tampering Methods on Exposure to Oxycodone in Fasting Healthy Subjects".
2. **OTR-1018** entitled "A Single-Center, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Oxycodone HCl Tamper Resistant Tablets".
3. **OTR-1019** entitled "Relative Attractiveness of Oxycodone TR: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations".
4. **OTR-1021** entitled "A Randomized, Single-Blind, 3-Way Crossover Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Crushed Intranasal Oxycodone Tamper Resistant Tablets (OTR) and OxyContin® in Healthy Adults".
5. **OTR-1022** entitled "Single-Center, Randomized, Cross-Over Study in Recreational Opioid Users to Evaluate the Safety of Crushed and Intranasally Administered OTR and OC Placebo Tablets".

Studies OTR-1016, OTR-1018 and OTR-1021 are reviewed in this memo with particular focus on pharmacokinetic disposition of oxycodone following administration of intact oxycodone extended release formulations (OxyContin tablets (OC) or tamper resistant tablets (OTR)) or administration of tablet contents following various methods of abuse (chewing, grinding followed by intranasal administration). Sponsor compares systemic exposure (Cmax and AUC) of oxycodone in blood following several treatments.

1. Study OTR-1016

Study Title:

A Randomized, Open-Label, Single-Dose, Crossover Study Of The Effects Of Various Tampering Methods On Exposure To Oxycodone In Fasting Healthy Subjects

OBJECTIVES:

The objectives of this study were as follows:

Primary: To characterize the pharmacokinetic (PK) profiles and metrics for each treatment.

Secondary: To assess the safety and tolerability of the oxycodone treatments administered under naltrexone blockade.

METHODOLOGY:

Part A: Randomized, open-label, single-dose, 8-treatment, 5-period, incomplete block, crossover study in fasting healthy adult male and female subjects.

Parts B and C: Randomized, open-label, single-dose, 4-period, 2-treatment replicated design in fasting healthy adult male and female subjects.

Part A: Subjects were randomized to a treatment sequence. All sequences included the immediate-release oxycodone reference solution. All treatments were administered orally with a total fluid volume of 240 mL in the fasted state.

Test Treatments:

Part A:

Treatment A: OTR 40 mg tablet swallowed intact

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment C: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, and swallowed

Treatment D: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, chewed, and swallowed

Treatment E: OTR 40 mg tablet pre-softened in water, chewed, and swallowed

Treatment F: OxyContin® 40 mg tablet (OC formulation) swallowed intact

Treatment G: OxyContin® 40 mg tablet chewed and swallowed

Reference Treatment:

Treatment H: Immediate-release 40 mg oxycodone solution

There were 5 Periods for Part A. Study drug was administered in each period according to the random allocation schedule (RAS).

Part B:

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment G: OxyContin® 40 mg tablet chewed and swallowed (Under vigorous chewing conditions as established in Part A)

Part C:

Treatment B: OTR 40 mg tablet chewed and swallowed

Treatment G: OxyContin® 40 mg tablet chewed and swallowed (Under normal chewing conditions with duration times established in the chewing qualification session prior to Part C.)

Reference Treatment:

Parts B and C: none

Study drugs (OTR, OC, and IR oxycodone solution) were prepared and administered as follows:

1. For intact dosing (Part A), the OTR and OxyContin® tablets were swallowed whole with 240 mL of water.

2. Particle size reduction of OTR tablets by crushing via mortar and pestle (Part A only) was performed per standardized procedures. Following particle size reduction, subjects directly swallowed or chewed and swallowed the tablet contents as described below.

3. Pre-softening of OTR tablets (Part A only) was performed per standardized procedures. Following tablet softening in water, subjects chewed and swallowed the softened tablet as described below. Just prior to administration of the softened tablet, the water used to soften the tablet was administered, followed by administration of a rinse of the tablet softening container. Upon completion of chewing, subjects received the remaining volume of water.

4. For each 'chewed and swallowed' treatment in Parts A and B, subjects were required to chew the administered intact tablet (OC or OTR), crushed tablet (OTR), or softened tablet (OTR) vigorously for up to (b) (4). Chewing stopped once (b) (4) whichever occurred first. During chewing, subjects were allowed to swallow accumulated saliva and small particulates ad libitum.

Subjects informed site staff upon completion of chewing/particle size reduction if this occurred prior to the end of the (b) (4) chewing period, and immediately after chewing stopped, the remaining dosing solution was administered.

Otherwise chewing stopped at the end of (b) (4) and the remaining tablet or tablet fragments were swallowed with the remaining dosing solution.

For Part B, the duration of chewing in minutes and seconds following vigorous chewing for each subject was recorded.

5. For each 'chewed and swallowed' treatment in Part C, subjects were required to chew the administered intact tablet (OC or OTR), using "normal" non-vigorous chewing techniques. Chewing duration data from the chewing qualification session was used to obtain the maximum duration of chewing (in minutes and seconds) for each subject for

Part C. Once the subject reached his/her maximum chewing duration time, they were instructed to swallow the dose followed by 240 mL of water.

6. For immediate-release oxycodone solution administration (Part A only), subjects received study drug in the appropriate volume of the oxycodone oral solution, followed by dosing cup rinses with an additional quantity of water sufficient to bring the total volume administered to 240 mL.

7. Study drug (test or reference treatment) was administered following a 10-h overnight fast. Subjects continued fasting from food for 4 h following dosing.

8. Subjects were standing or in an upright sitting position while receiving their dose of study drug. Following dosing, subjects remained in an upright position for a minimum of 4 h.

Fasting was not required for non-dosing study days.

Subjects received naltrexone HCl 50 mg tablets with 240 mL of water at -13, -1, 11, 23, and 35 h relative to each study drug dosing.

Endpoints/Criteria for Evaluation:

Pharmacokinetic:

Plasma concentrations of oxycodone were analyzed to determine the following PK metrics: area under the plasma concentration-time curve from h 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration-time curve extrapolated to infinity (AUCinf), maximum observed plasma concentration (Cmax), time to maximum plasma concentration (tmax), apparent plasma terminal phase half-life ($t_{1/2Z}$), lag time was estimated as the timepoint immediately prior to the first measurable plasma concentration value (t_{lag}), and apparent terminal phase rate constant (λZ).

Safety:

Safety was assessed using recorded adverse events (AEs), clinical laboratory test results, vital signs results, pulse oximetry, physical examinations, and electrocardiograms.

Bioanalytical Methods:

Plasma concentrations of oxycodone were quantified by using a validated liquid chromatography tandem mass spectrometric method ((b) (4) SOP TM.664,(b) (4) Report # 4141.090806.1).

Statistical Analysis:

For Part A, oxycodone AUCt, AUCinf, and Cmax, a mixed-model analysis of variance (SAS PROC MIXED) was used to compare logarithmic-transformed (base e) values for each comparison. The 90% confidence intervals were estimated for the ratios (test/reference) of exponentiated LS means from all 28 pairwise treatment comparisons. Additionally, a secondary analysis on normalized metrics (indexed by subjects' own metric values from the Immediate-release 40 mg oxycodone solution treatment) was also performed.

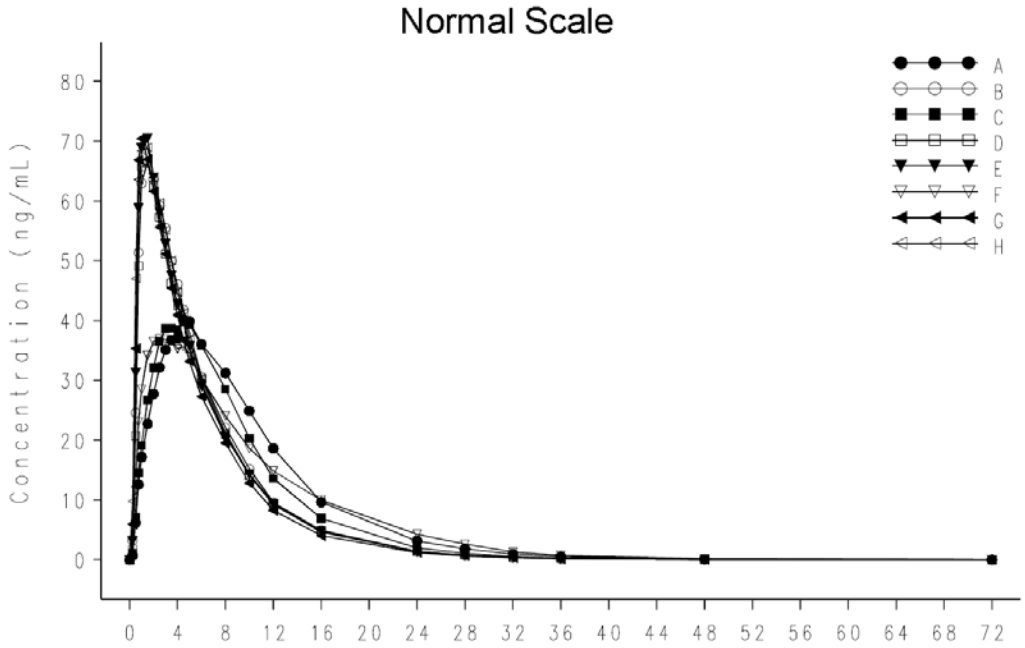
For Part B, the relative bioavailability of the controlled release oxycodone formulations (OTR 40 mg and OxyContin® 40 mg) following vigorous chewing (as conducted in Part A) was evaluated.

For Part C, the relative bioavailability of the controlled release oxycodone formulations (OTR 40 mg and OxyContin® 40 mg) under "normal" non-vigorous chewing conditions was evaluated. This would attempt to determine release of oxycodone from the formulations following chewing in a manner that would be considered accidental or inadvertent.

The analyses for Parts B and C were performed using a linear mixed model appropriate for a replicated crossover design.

Pharmacokinetic Analysis Results:

Mean Plasma Profile of Oxycodone following administration of different oxycodone treatments



The following table describes the mean pharmacokinetic parameters of oxycodone following administration of treatments A – H in part A of the study.

Table: Summary of Mean Oxycodone Pharmacokinetic Metrics: Part A

PK Metric	Units		Treatment A	B	C	D	E	F	G	H
AUC_t	(ng*h/mL)	Mean	472	456	423	437	446	454	424	462
		SD	148	114	108	175	142	107	103	139
		N	32	31	30	29	31	35	30	56
AUC_{inf}	(ng*h/mL)	Mean	474	458	424	438	453	457	426	464
		SD	149	114	108	176	150	108	103	140
		N	32	31	30	29	31	34	30	56
C_{max}	(ng/mL)	Mean	42.6	74.1	43.3	72.6	77.2	40.5	79.1	79.1
		SD	11.7	19.1	10.2	22.2	19.4	10.7	22.4	21.9
		N	32	31	30	29	31	35	30	56
t_{max}[a]	(h)	Median	4.50	1.50	3.75	1.50	1.50	2.50	1.00	1.00
		Min, Max	3.00, 8.00	0.533, 5.03	2.50, 6.02	0.750, 3.50	0.750, 4.50	0.750, 5.00	0.750, 3.00	0.500, 4.00
		N	32	31	30	29	31	35	30	56
λ_z	(1/h)	Mean	0.152	0.163	0.157	0.151	0.161	0.148	0.162	0.158
		SD	0.0512	0.0498	0.0584	0.0520	0.0492	0.0495	0.0429	0.0515
		N	32	31	30	29	31	34	30	56
$t_{½z}$	(h)	Mean	5.57	5.44	5.33	5.96	5.60	5.47	5.11	5.66
		SD	3.47	4.78	2.70	4.80	4.96	2.91	3.37	4.57
		N	32	31	30	29	31	34	30	56
t_{lag}[a]	(h)	Median	0	0	0	0	0	0	0	0
		Min, Max	0, 0.250	0, 0	0, 0.250	0, 0	0, 0	0, 0.250	0, 0	0, 0.250
		N	32	31	30	29	31	35	30	56

Table: Summary of Mean Oxycodone Pharmacokinetic Metrics: Part B

PK Metric	Units		Treatment B	Treatment G
AUC_t	(ng*h/mL)	Mean	398	428
		SD	99.6	89.3
		N	25	25
AUC_{inf}	(ng*h/mL)	Mean	400	436
		SD	99.7	104
		N	25	25
C_{max}	(ng/mL)	Mean	70.0	81.2
		SD	17.4	20.5
		N	25	25
t_{max}[a]	(h)	Median	1.50	1.00
		Min, Max	0.625, 3.75	0.500, 4.50
		N	25	25
λ_z	(1/h)	Mean	0.157	0.155
		SD	0.0534	0.0513
		N	25	25
$t_{½z}$	(h)	Mean	6.11	6.16
		SD	5.59	5.52
		N	25	25
t_{lag}[a]	(h)	Median	0	0
		Min, Max	0, 0.142	0, 0
		N	25	25

Table: Summary of Mean Oxycodone Pharmacokinetic Metrics: Part C

PK Metric	Units		Treatment B	Treatment G
AUC_t	(ng*h/mL)	Mean	415	433
		SD	111	118
		N	26	25
AUC_{inf}	(ng*h/mL)	Mean	416	435
		SD	112	118
		N	26	25
C_{max}	(ng/mL)	Mean	57.0	74.2
		SD	12.7	17.4
		N	26	25
t_{max}[a]	(h)	Median	2.38	1.13
		Min, Max	1.00, 4.75	0.625, 2.50
		N	26	25
λ_z	(1/h)	Mean	0.130	0.138
		SD	0.0554	0.0596
		N	26	25
$t_{½z}$	(h)	Mean	7.94	7.40
		SD	6.58	5.99
		N	26	25
t_{lag}[a]	(h)	Median	0	0
		Min, Max	0, 0.125	0, 0
		N	26	25

The sponsor utilized the immediate release oral tablet, treatment H, as reference in assessing/comparing the pharmacokinetic parameters of oxycodone following various methods of abuse. However, the proper reference is an intact OTR formulation (treatment A). Since the goal of this PK study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact extended-release product should be used as reference. Use of IR tablets as a reference, which produces a much rapid plasma levels of oxycodone, would confound the PK results of physical manipulation which may defeat the control release properties of Oxycontin TR (see table below). Hence, from a clinical pharmacology perspective, bioavailability comparisons are appropriate using Treatment A or the intact extended-release tablet as reference. Note that the OTR tablet (Treatment A) is bioequivalent to Oxycontin tablet (Treatment F) when swallowed intact.

Summary of PK parameters of oxycodone compared to reference treatment A (OTR tablet swallowed intact): Part A results.

			LS Mean[a]				
Treatment Comparison	**PK Parameter**	**n**	**Test**	**n**	**Reference**	**Test/Reference[b] (%)**	**90% Confidence Interval[c]**
A vs. F	C_{max}	32	41.1	35	39.3	105	(97.93 , 111.83)
	AUC_t	32	453	35	455	99.4	(95.24 , 103.72)
	AUC_{inf}	32	455	34	459	99.0	(94.86 , 103.34)
B vs. A	C_{max}	31	**70.5**	32	**41.1**	**171**	**(160.08 , 183.60)**
	AUC_t	31	424	32	453	93.8	(89.72 , 97.99)
	AUC_{inf}	31	426	32	455	93.7	(89.65 , 97.90)
C vs. A	C_{max}	30	42.7	32	41.1	104	(96.74 , 111.26)
	AUC_t	30	415	32	453	91.8	(87.74 , 96.00)
	AUC_{inf}	30	418	32	455	91.9	(87.85 , 96.12)
D vs. A	C_{max}	29	**69.7**	32	**41.1**	**169**	**(158.03 , 181.78)**
	AUC_t	29	414	32	453	91.4	(87.37 , 95.61)
	AUC_{inf}	29	415	32	455	91.3	(87.31 , 95.57)
E vs. A	C_{max}	31	**72.9**	32	**41.1**	**177**	**(165.50 , 189.84)**
	AUC_t	31	417	32	453	92.0	(88.05 , 96.17)
	AUC_{inf}	31	422	32	455	92.8	(88.79 , 96.97)
G vs. A	C_{max}	30	**80.6**	32	**41.1**	**196**	**(182.97 , 209.93)**
	AUC_t	30	441	32	453	97.4	(93.21 , 101.82)
	AUC_{inf}	30	442	32	455	97.3	(93.08 , 101.66)

[a] Least squares means from ANOVA, calculated by transforming the natural log (ln) means back to the linear scale, i.e., geometric means.
[b] Ratio of metric means (expressed as a percent), transformed back to the linear scale.
[c] 90% confidence interval for ratio of metric means (expressed as a percent), transformed back to the linear scale.

Part A:
Treatment A: OTR 40 mg tablet swallowed intact
Treatment B: OTR 40 mg tablet chewed and swallowed
Treatment C: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, and swallowed
Treatment D: OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, chewed, and swallowed
Treatment E: OTR 40 mg tablet pre-softened in water, chewed, and swallowed
Treatment F: OxyContin® 40 mg tablet swallowed intact
Treatment G: OxyContin® 40 mg tablet chewed and swallowed

Sponsor's choice of Reference Treatment:

Treatment H: Immediate-release 40 mg oxycodone solution

Comparison of OTR formulation and Oxycontin under rigorous conditions of abuse (Chewing) indicates that the rate and extent of oxycodone released and absorbed is bioequivalent (See table below).

Table - Statistical Results of Oxycodone Pharmacokinetic Metrics (Treatment Comparison): Part B

Treatment Comparison	Metric	Units	LS Means[a] N[b]	(Test)	N[b]	(Reference)	Test/ Reference (%)[c]	90% Confidence Interval (%)[d]
B vs. G	C_{max}	ng/mL	25 (48)	68.3	25 (44)	79.0	86.5	(81.74 , 91.49)
	AUC_t	ng*h/mL	25 (48)	388	25 (44)	412	94.2	(89.64 , 99.07)
	AUC_{inf}	ng*h/mL	25 (46)	389	25 (43)	415	93.6	(89.29 , 98.17)

Note: Under ***vigorous*** chewing conditions: Treatment B = OTR 40 mg tablet chewed and swallowed; Treatment G = OxyContin® 40 mg tablet (OC formulation) chewed and swallowed.

Reviewer's comments: Bioequivalence of oxycodone systemic exposure indicates that under rigorous chewing condition, the OTR formulation did not show better tamper-resistant performance compared to the OxyContin® 40 mg tablet (OC formulation) based on PK data.

Comparison of OTR formulation and Oxycontin under normal non-rigorous conditions of abuse (Chewing) indicates that the extent of oxycodone released and absorbed, as seen by Cmax, was lower with OTR formulation (See table below).

Table - Statistical Results of Oxycodone Pharmacokinetic Metrics (Treatment Comparison): Part C

Treatment Comparison	Metric	Units	LS Means[a] N[b]	(Test)	N[b]	(Reference)	Test/ Reference (%)[c]	90% Confidence Interval (%)[d]
B vs. G	C_{max}	ng/mL	26 (47)	54.9	25 (49)	71.9	76.4	(72.19 , 80.89)
	AUC_t	ng*h/mL	26 (47)	398	25 (49)	414	96.3	(93.31 , 99.40)
	AUC_{inf}	ng*h/mL	26 (44)	402	25 (49)	415	96.8	(93.85 , 99.88)

Note: Under ***"normal" non-vigorous*** chewing conditions: Treatment B = OTR 40 mg tablet chewed and swallowed; Treatment G = OxyContin® 40 mg tablet chewed and swallowed.

Reviewer's comments: Under "normal" non-vigorous chewing conditions, Cmax of the OTR formulation does not meet the bioequivalent criteria to that of the OxyContin® tablet (OC formulation), but it is only about 23.6% lower.

Conclusions:

Part A:

Utilizing intact Oxycontin extended release (OTR) as reference under fasting conditions:

- OTR 40 mg is bioequivalent to OC 40 mg when swallowed intact
- Immediate release oxycodone 40 mg oral treatment results in highest Cmax
- Chewing OTR 40 mg or OC 40 mg results in disruption of the extended release characteristics of both the products with early peak plasma concentrations noted compared to intact OTR or OC treatments.

Part B and C:

- It should be noted that chewing disrupts ER characteristics of OTR and OC treatments (Part A)
- Upon chewing vigorously (part B), OTR and OC products are bioequivalent with respect to oxycodone Cmax and AUC.
- Upon chewing normally (part C), OTR formulation resulted in a lower Cmax (76.4%) compared to chewed OC formulation

Reviewer's comments:

Use of intact oxycodone extended release formulation is indicated in the product label (OC or OTR formulation). Hence, pharmacokinetic profile of the approved extended release product serves as a reference for subsequent manufacturing changes as well as approval of generic drugs. Since the goal of the PK study is to understand whether the extended-release product can withstand physical tampering, PK results from an intact oxycodone extended-release product should be used as reference. However, the Sponsor used the IR formulation as reference in study OTR-1016. Use of IR formulation as a reference, which produces a much rapid plasma levels of oxycodone, would confound the PK results of physical manipulation which may defeat the control release properties of Oxycontin OTR. Hence, from a clinical pharmacology perspective, bioavailability comparisons are appropriate using the intact extended-release tablet as reference instead of IR formulation after oral administration.

After oral administration, the extents of drug absorption (in term of AUC) are comparable among different formulations (OTR, OC and IR solution formulations) with different chewing methods including swallowing intact. However, the rates of absorption (in term of Cmax and Tmax) are different. Disrupted ER characteristics of the OTR or OC formulation after several chewing methods can be characterized by shorter Tmax and higher Cmax compared to swallowing intact.

The sponsor tested various chewing methods for the OTR formulation before swallowing. Only Treatment C (particle size reduced by crushing via mortar and pestle, and swallowed) showed comparable Tmax and Cmax to Treatment A (swallowing intact). The ER characteristics of the OTR formulation was mostly disrupted for the rest of the chewing methods, including Treatment B (chewed and swallowed), Treatment D (particle size reduced by crushing via mortar and pestle, chewed, and swallowed), and Treatment E (tablet pre-softened in water, chewed, and swallowed). This was demonstrated by shorter Tmax and higher Cmax compared to swallowing intact OTR tablet, and comparable Tmax and Cmax to the IR oxycodone solution.

There is no substantial evidence that the OTR formulation demonstrated better tamper-resistant characteristics than the OC formulation after chewing and swallowing based on PK data. The Cmax value met the bioequivalence criteria between the two formulations after vigorously chewing, while the Cmax value for OTR is only about 23.6% lower than that of OC formulation after "normal" non-vigorous chewing conditions.

2. Study OTR-1018

Study Title:

A Single-Center, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Oxycodone HCl Tamper Resistant Tablets

Objectives:

Qualification Phase

To ensure that subjects with self-reported recreational opioid experience including intranasal administration, were also able to report positive subjective effects of the drugs in a controlled laboratory setting.

To ensure that no safety issues arose, if subjects needed to receive an opioid antagonist rescue during the study.

Treatment Phase

To evaluate intranasal abuse potential and pharmacodynamic effects of coarsely and finely crushed OTR compared to OC, oxycodone Active Pharmaceutical Ingredient (API), and OC placebo in healthy, adult recreational opioid users with a history of intranasal abuse.

To evaluate the safety and tolerability of intranasally administered crushed OTR in healthy, adult recreational opioid users with a history of intranasal abuse.

To determine the comparative pharmacokinetics of intranasally administered crushed OTR compared to OC and Oxy API.

Study Design

This was a randomized, double-blind, placebo-controlled crossover study to evaluate the relative pharmacodynamic, pharmacokinetic, and safety profile of intranasally administered crushed OTR tablets (fine powder [OTR_F] and coarse powder [OTR_C]) compared to crushed OC tablets (fine powder), Oxy API powder, and OC placebo (fine powder) in recreational opioid users with a history of intranasal use. The procedures for crushing to "coarse" and/or "fine" powder for OTR and for OC were standardized, and particle size distributions were assessed.

The study design is summarized below. The study consisted of 4 phases: Screening, Qualification, Treatment, and Follow-up.

Treatments administered

During the double-blind *Qualification Phase*, the following single intranasal doses were administered to each subject:

- 30 mg Oxy API powder
- lactose powder placebo

During the double-blind *Treatment Phase*, the following single intranasal doses were administered to each subject in a randomized, full crossover manner:

- Treatment A: finely crushed OC placebo
- Treatment B: 30 mg Oxy API powder
- Treatment C: 30 mg finely crushed OTR tablets
- Treatment D: 30 mg coarsely crushed OTR tablets
- Treatment E: 30 mg finely crushed OC tablets

Dosing Sequence	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5
1	A	B	E	C	D
2	B	C	A	D	E
3	C	D	B	E	A
4	D	E	C	A	B
5	E	A	D	B	C
6	D	C	E	B	A
7	E	D	A	C	B
8	A	E	B	D	C
9	B	A	C	E	D
10	C	B	D	A	E

Sponsor indicates that insufflation was incomplete for OTR_F and OTR_C for approximately one-third of subjects (10 out of 30). This may have been due to the inability to completely insufflate OTR when crushed into a coarse or fine powder. Incomplete dosing was more likely to occur with OTR_F (10 subjects) and OTR_C (9 subjects) compared with OC (2 subjects), Oxy API (0 subjects), and placebo (3 subjects), due to granules falling from the subjects' nostrils.

Study Endpoints

Pharmacodynamic Endpoints **(results are discussed by Dr. James Tolliver of the Controlled Substances Staff)**

For the purpose of study validation, the primary pharmacodynamic measures were Drug Liking VAS, Overall Drug Liking VAS, Subjective Drug Value, and ARCI MBG. Measurements were carried out at 6 and 23 hours post-dose for the Qualification Phase and at 8 and 24 hours post-dose for the Treatment Phase.

Safety Endpoints

The safety endpoints of this study were as follows:

- Concomitant medications
- Type, incidence, and severity of AEs
- Vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation)
- 12-lead ECG (heart rate and PR, QRS, QT, and QTc intervals)
- Clinical laboratory tests (haematology, chemistry, and urinalysis)
- Physical examination

Pharmacokinetic Endpoints

Blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post dose. The plasma samples were analyzed by [redacted] (b) (4) using validated methods [redacted] (b) (4) SOP TM.664, [redacted] (b) (4) Report # 3351.061505.2). The limit of quantification was 0.100 ng/mL. Plasma concentration data for oxycodone were listed for each subject and time point, and summarized using descriptive statistics at each time point. Pharmacokinetic parameters were calculated using non-compartmental methods and summarized by treatment.

The pharmacokinetic endpoints of this study were as follows:

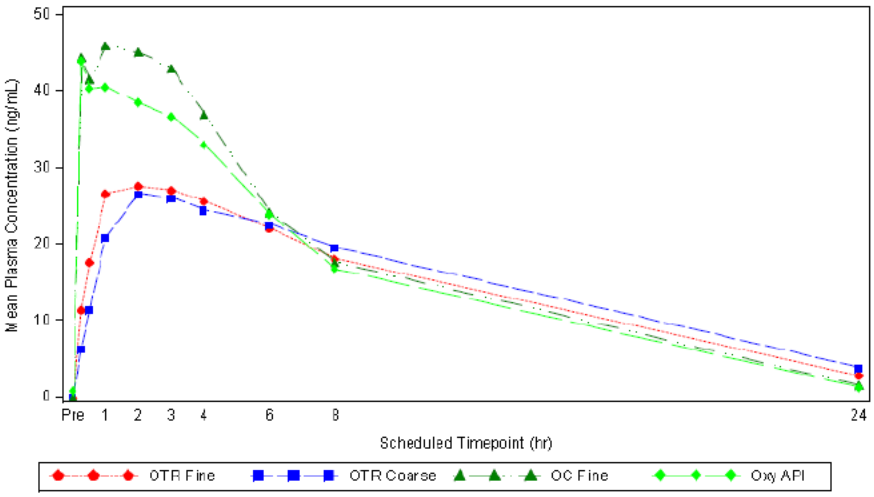
- Cmax: maximum plasma concentration
- Tmax: time to maximum plasma concentration
- AUC_{last}: area under the concentration time curve from time zero to last assessment
- $AUC_{0-\infty}$: area under the concentration time curve from time zero to infinity
- Plasma concentrations over time for oxycodone

Pharmacokinetic Results:

Range of PK parameters following Complete and Incomplete Dosing of OTR

Range (Minimum – Maximum)	Cmax (ng/mL)	AUClast (ng/mL*h)
OTR_F		
Incomplete (n=10)	20.0 – 34.8	141 – 432
Complete (n=19)	19.1 – 44.9	162 – 534
OTR_C		
Incomplete (n=9)	6.93 – 46.2	41.2 – 427
Complete (n=19)	12.7 – 55.6	131 – 726

Mean Oxycodone Plasma Concentration Curves (ng/mL)



Summary of PK parameters for OTR coarse, OTR fine, OC fine, oxycodone API

Parameter	N	Nobs	Mean	SD	Geometric Mean	CI 90%Lower	CI 90%Upper
Coarsely crushed OTR tablet							
AUCINF	27	28	376.4	182.4	320.4	65.3	687.4
AUCLAST	28	28	328.4	151.8	285.0	69.7	587.0
CMAX	28	28	29.8	12.2	27.0	9.1	50.5
TMAX	28	28	3.1	1.9	2.4	-0.1	6.2
Finely crushed OTR tablet							
AUCINF	29	29	339.2	101.2	323.3	167.1	511.4
AUCLAST	29	29	311.5	86.6	299.1	164.1	458.9
CMAX	29	29	29.4	7.7	28.4	16.3	42.5
TMAX	29	29	2.1	1.1	1.9	0.2	3.9
Finely crushed Oxycontin tablet							
AUCINF	28	28	384.6	101.8	371.6	211.2	558.0
AUCLAST	28	28	374.2	93.2	362.7	215.5	532.9
CMAX	28	28	59.6	16.2	57.5	32.0	87.3
TMAX	28	28	1.3	1.0	0.9	-0.4	3.0
Oxycodone API powder							
AUCINF	29	29	350.2	69.6	343.4	231.8	468.7
AUCLAST	29	29	342.1	67.0	335.6	228.1	456.1
CMAX	29	29	52.1	13.0	50.6	30.0	74.2
TMAX	29	29	1.2	1.2	0.8	-0.8	3.2

Conclusions:

- Insufflation was incomplete for finely ground OTRF and coarsely ground OTRC for approximately one-third of subjects.
- Higher variability is noted in the pharmacokinetics of oxycodone following intranasal administration of OTR coarse/fine treatments.
- Without the intact tablet as reference and because of incomplete insufflation in OTR treatment arms, the PK comparison of the various treatments via intranasal administration has limited utility.

Reviewer's comments

- The Cmax value for Treatment C (Finely Crushed 30 mg OTR) and Treatment D (Coarsely Crushed 30 mg OTR) is approximately 40-50% lower than that of Treatment A (30 mg Oxy API powder) and Treatment E (30 mg finely crushed OC tablets). If the Drug Liking VAS score measured in the study also favors the OTR formulation, the results may be used to support that the OTR formulation has a better tamper-resistant characteristics compared to the OC and API formulation by nasal administration after crushing. In addition, the reason for incomplete insufflation of the coarse or fine OTR powder is not clear. Hence, input from CSS will be necessary to conclude if incomplete insufflation is in itself a valid advantage.

3: <u>Study OTR-1021 Synopis:</u>

Study Title:

A Randomized, Single-Blind, Single-Dose, Single-Center, 3-Treatment, 3-Period Crossover Study In Fasted Healthy Adult Subjects.

Objective:

The objective of this study was to compare the safety, tolerability, and PK of Finely Crushed OTR, Coarsely Crushed OTR, and Finely Crushed OC tablets administered as 10 mg intranasally.

Study Design:

Single intranasal doses of the following study drugs were administered in a randomized, single-blinded, 3-way crossover study:

- Treatment A: Finely Crushed 10 mg OTR
- Treatment B: Coarsely Crushed 10 mg OTR
- Treatment C: Finely Crushed 10 mg OC

Treatments were administered in alternating nares (left-right-left) and were separated by a 48-hour washout. Detailed procedures for crushing the OTR (coarse and fine crush) and OC (fine crush) tablets were described in the Pharmacy Manual.

Treatment Sequences

Sequence	Period 1	Period 2	Period 3
	Treatment		
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

Subjects were healthy men and women aged 18 to 55 years, inclusive, with no clinically significant medical history, who were deemed suitable to participate in this clinical study by the PI. The washout period separating dose administrations was 48 hours. When a subject prematurely discontinued from the study, an additional subject may have been enrolled following Sponsor (or designee) approval to ensure that up to approximately 20 subjects completed the study. Additional subjects were assigned the next sequential randomization number.

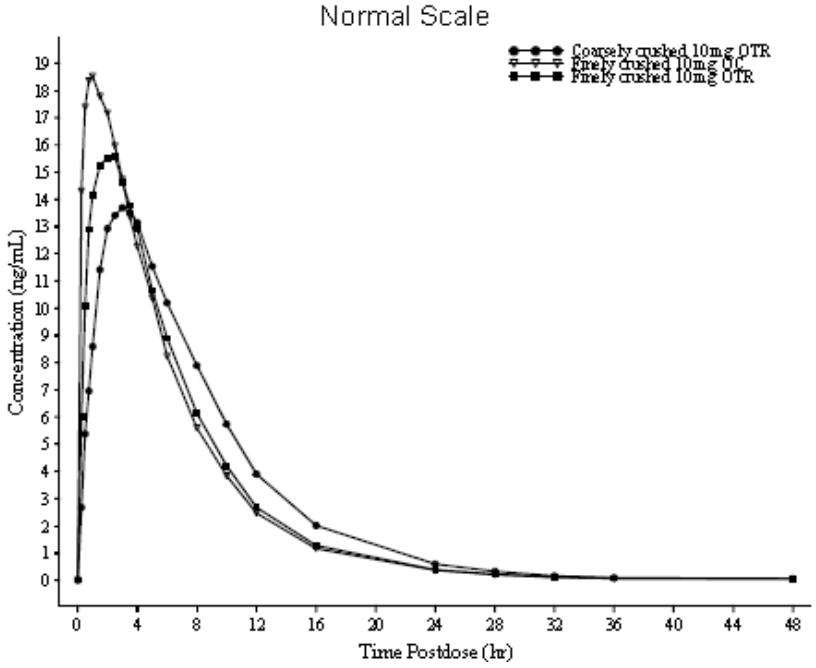
Blood samples for determining oxycodone plasma concentrations were obtained for each subject predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, and 48 hours post study-drug administration during each of the study periods. The first 48-hour samples may have been obtained up to 10 minutes early and served as the predose samples for the remaining treatments. Plasma concentrations of oxycodone were quantified by a validated liquid chromatography tandem mass spectrometric method. The

PK metrics used in this study were those typically used to assess rate and extent of drug absorption (ie, bioavailability). Assessments of bioavailability were based on comparisons of area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration (AUC_t), area under the plasma concentration-time curve extrapolated to infinity (AUC_{inf}), and maximum observed plasma concentration (C_{max}). Other standard PK metrics (time to maximum plasma concentration [t_{max}], apparent terminal phase rate constant [λ_Z], and apparent plasma terminal phase half-life [$t_{1/2Z}$]) were estimated and presented as mean ± standard deviation.

Summary of Mean Oxycodone Pharmacokinetic Metrics: Full Analysis Population

PK Metric	Units		Finely Crushed 10 mg OTR	Coarsely Crushed 10 mg OTR	Finely Crushed 10 mg OC
AUC_t	(ng*h/mL)	Mean	123	133	127
		SD	29.2	45.0	29.4
		N	29	29	30
AUC_{inf}	(ng*h/mL)	Mean	124	134	128
		SD	29.3	45.1	29.4
		N	29	29	30
C_{max}	(ng/mL)	Mean	17.1	15.5	22.2
		SD	3.65	5.41	4.87
		N	29	29	30
t_{max}[a]	(h)	Median	2.00	3.00	1.00
		Min, Max	0.750, 3.50	1.00, 8.13	0.250, 2.50
		N	29	29	30
λ_z	(1/h)	Mean	0.161	0.160	0.160
		SD	0.0257	0.0236	0.0277
		N	29	29	30
$t_{½z}$	(h)	Mean	4.43	4.45	4.46
		SD	0.786	0.796	0.810
		N	29	29	30
t_{lag}	(h)	Mean	0	0	0
		SD	0	0	0
		N	29	29	30

Mean Plasma Concentrations of Oxycodone following intranasal administration of different oxycodone formulations



The 90% CIs for oxycodone Cmax for the comparison of Finely Crushed 10 mg OTR versus Finely Crushed 10 mg OC and Coarsely Crushed 10 mg OTR versus Finely Crushed 10 mg OTR were not entirely contained within the 80 to 125% range, while the 90% CI for oxycodone Cmax for the comparison of Coarsely Crushed 10 mg OTR versus Finely Crushed 10 mg OC was entirely outside of the 80 to 125% range (See table below).

Table: Statistical Results of Oxycodone Pharmacokinetic Metrics (Treatment Comparison): Full Analysis Population

Treatment			LS Means[a]				Test/	90% Confidence
Comparison	Metric	Units	N	(Test)	N	(Reference)	Reference (%)[b]	Interval (%)[c]
A vs. C	C_{max}	ng/mL	29	16.8	30	21.7	77.6	(69.27 , 87.02)
	AUC_t	ng*h/mL	29	121	30	124	97.4	(86.45 , 109.73)
	AUC_{inf}	ng*h/mL	29	122	30	125	97.4	(86.56 , 109.50)
B vs. A	C_{max}	ng/mL	29	14.5	29	16.8	86.3	(76.91 , 96.78)
	AUC_t	ng*h/mL	29	124	29	121	103	(91.34 , 116.12)
	AUC_{inf}	ng*h/mL	29	125	29	122	103	(91.64 , 116.10)
B vs. C	C_{max}	ng/mL	29	14.5	30	21.7	67.0	(59.76 , 75.07)
	AUC_t	ng*h/mL	29	124	30	124	100	(89.04 , 113.01)
	AUC_{inf}	ng*h/mL	29	125	30	125	100	(89.29 , 112.94)

[a] Least squares means from ANOVA, calculated by transforming the natural log (ln) means back to the linear scale, ie, geometric means.

[b] Ratio of metric means (expressed as a percent), transformed back to the linear scale.

[c] 90% confidence interval for ratio of metric means (expressed as a percent), transformed back to the linear scale.

[d] Intersubject variability, intrasubject variability, and intrasubject coefficient of variation (expressed as a percent) for ln-transformed metric from ANOVA. They are same for all treatment comparisons (by metric).

These results demonstrate that the 3 treatments were not equivalent with regard to oxycodone Cmax. In contrast, the 90% CIs for oxycodone AUC_t and AUC_{inf} were entirely contained within the 80 to 125% range for all treatment comparisons, indicating bioequivalence.

Reviewer's comments

The Cmax value for both Treatment A (Finely Crushed 10 mg OTR) and Treatment B (Coarsely Crushed 10 mg OTR) is lower that of Treatment C (Finely Crushed 10 mg OC), which are 22.4% and 33% lower, respectively. This trend is consistent with the PK results from Study OTR-1018. However, without Drug Liking VAS score measured, it is difficult to make a conclusion whether the 22.4% and 33% lower Cmax for the OTR formulation can be interpreted as better tamper-resistant characteristics by nasal administration after crushing.

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/s/

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09/19/2012

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