CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209777Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 209777	Submission Date(s): October 21, 2016; Jan 31, 2017
Brand Name	RoxyBond
Generic Name	Oxycodone Hydrochloride Abuse–Resistant Immediate-Release (ARIR) Tablet
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Inspirion Delivery Sciences, Inc. (IDS)
Relevant IND	IND 105,951
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Oral Immediate Release Tablets; 5, 15, and 30 mg
Indication	Management of moderate to severe pain where use of an opioid analgesic is appropriate.
Proposed Dosing Regimen	(b) (4)

This is an addendum to the original clinical pharmacology review in DARRTS dated 3/22/2017. OSI memorandums dated February 27, 2017 (for analytical site) and March 26, 2017 (for clinical site) recommended accepting the pharmacokinetic data obtained from the pivotal comparative BA/BE Study O-ARIR-003. The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated October 21, 2016 and January 31, 2017 and finds it acceptable provided that a mutual agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

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/s/

WEI QIU
03/27/2017

YUN XU
03/29/2017

CLINICAL PHARMACOLOGY REVIEW

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Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this submission dated October 21, 2016 and January 31, 2017 and finds it acceptable provided that OSI inspection finds the data from the pivotal comparative BA/BE study O-ARIR-003 acceptable, and a mutual agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Inspirion Delivery Sciences, Inc (IDS) submitted a 505(b)(2) NDA 209-777 for Oxycodone Hydrochloride Abuse-Resistant Immediate Release (ARIR) tablets, 5, 15, and 30 mg for the management of moderate to severe pain where use of an opioid analgesic is appropriate. The sponsor did not conduct clinical efficacy/safety studies using oxycodone ARIR tablets and proposed to rely on the agency's previous findings of safety and efficacy of the identified listed drug, Roxicodone (oxycodone) immediate release tablet (NDA 21-011) by establishing a pharmacokinetic bridge.

To rely on the Agency's previous finding of the safety and efficacy of Roxicodone tablet, the sponsor proposed to use the pivotal comparative bioavailability Study O-ARIR-003 conducted in healthy volunteers under naltrexone block to establish pharmacokinetic bridging to Roxicodone tablet under fasting condition using the highest strength (30 mg). The same study also evaluated food effect on oxycodone ARIR tablet using high-fat meal. A dose proportionality Study O-ARIR-006 was conducted in healthy volunteers under naltrexone block using all three strengths (5, 15, and 30 mg) to support the two lower strengths 5 mg and 15 mg. In addition, the sponsor conducted a human abuse-potential study (Study O-ARIR-002) to evaluate the abuse potential based on pharmacodynamics (e.g., decreased drug liking) and pharmacokinetics of oxycodone ARIR tablet in comparison with Roxicodone tablet when taken intranasally in nondependent but experienced opioid abusers. The to-be-marketed formulation was used in all these studies.

Comparable Bioavailability between Oxycodone ARIR tablet and Roxicodone Tablet

Oxycodone ARIR tablet (1 x 30 mg) showed equivalent AUCt and AUCinf values, similar Cmax values, and slightly longer median Tmax (1.8 h for oxycodone ARIR vs 1.0 h for Roxicodone tablet) but similar Tmax ranges in comparison to Roxicodone tablet (1 x 30 mg) under fasting condition.

Table 1: Mean ± SD (%CV) Oxycodone Pharmacokinetic Parameters for 30 mg Oxycodone ARIR Tablet (O-ARIR) Fasted versus 30 mg Roxicodone Tablet Fasted in Healthy Adults Subjects under Naltrexone Block and Statistical Analysis (Study O-ARIR-003)

PK Parameter	30 mg Oxycodone ARIR Tablet (1 x 30 mg) Fasted (N = 58)	30 mg Roxicodone Tablet (1 x 30 mg) Fasted (N = 54)
AUCt (ng.h/ml)	287.4 ± 65.80 (22.9)	300.3 ± 68.75 (22.9)
AUCinf (ng.h/mL)	292.7 ± 67.39 (23.0)	305.4 ± 70.08 (22.9)
Cmax (ng/mL)	57.8 ± 18.01 (31.1)	67.7 ± 23.76 (35.1)
T1/2 (h)	3.8 ± 0.68 (2.4 – 6.2)[a]	3.7 ± 0.58 (2.2 – 5.2)[a]
Tmax (h)[b]	1.8 (0.8 – 5.0)	1.0 (0.5 – 5.0)
Geometric Mean Ratio (Oxycodone ARIR Tablet Fasted/Roxicodone Tablet Fasted) % (90% CI)		
AUCt	95.6 (92.5 – 98.7)	
AUCinf	95.8 (92.8 – 98.9)	
Cmax	86.2 (78.8 – 94.3)	

[a] range; [b] tmax reported as median (range)
Source: Table 14.2.2-1 and 14.2.2-2 of study O-ARIR-003 report.

The total exposures of oxycodone (AUCt and AUCinf) for 30 mg oxycodone ARIR tablet and 30 mg Roxicodone tablet met the bioequivalent (BE) criteria. The point estimate of the geometric mean ratio (Oxycodone ARIR tablet /Roxicodone tablet) for oxycodone AUCt and AUCinf were 95.6% and 95.8%, respectively. The corresponding 90% confidence intervals (CIs) were 92.5 – 98.7% and 92.8 – 98.9%, respectively. All these 90% CIs fell within the 80 to 125% BE limit.

Oxycodone Cmax values were similar for 30 mg oxycodone ARIR tablet and 30 mg Roxicodone tablet. The point estimate of the geometric mean ratio (Oxycodone ARIR tablet /Roxicodone tablet) for oxycodone Cmax was 86.2% and the corresponding 90% CI was from 78.8% to 94.3%. Considering that the lower limit of the 90% CI for Cmax of 78.8% is very close to the 80% limit criterion and oxycodone ARIR tablet will be titrated, 1.2% lower CI for oxycodone Cmax is not anticipated to affect the efficacy of oxycodone ARIR tablet to a substantial degree after discussion with the review team.

Median (min, max) Tmax values were 1.8 (0.8, 5.0) hour for oxycodone ARIR tablet and 1.0 (0.5, 5.0) hour for Roxicodone tablet; oxycodone ARIR tablets had slightly longer median Tmax value than Roxicodone tablet but the ranges for Tmax were similar between the two products. Considering food caused a delay in Tmax (1.25 to 2.54 hour) for Roxicodone tablet as described in its labeling, and there is no food restriction for Roxicodone tablet administration, the slightly longer median Tmax value for oxycodone ARIR tablet under fasting condition will not be anticipated to affect the efficacy of oxycodone ARIR tablet to a substantial degree. Thus, the pharmacokinetic bridging between oxycodone ARIR tablet 30 mg and Roxicodone tablet 30 mg is established.

Food Effect:
High-fat meal increased oxycodone Cmax, AUCt, and AUCinf values by 18%, 23%, and 24%, respectively, following the administration of a single dose of 30 mg oxycodone ARIR tablet. Median Tmax (min, max) values were similar under fasting and fed conditions; 1.8 (0.8, 5.0) h under fasting and 2.0 (1.0, 6.1) h under fed condition. The

food effect on oxycodone AUC for oxycodone ARIR tablet is similar to that for Roxicodone tablet, the identified listed drug for this 505(b)(2) NDA. According to the approved Roxicodone tablet labeling, a high fat meal enhanced the extent (27% increase in AUC). In addition, food caused a delay in Tmax (1.25 to 2.54 hour). Roxicodone tablet labeling does not recommend a food restriction because of the limited extent of food effect. Therefore, no food restriction should be recommended for oxycodone ARIR tablet as well.

Table 2 Mean ± SD (%CV) Pharmacokinetic Parameters of Oxycodone for 30 mg Oxycodone ARIR tablet (1 x 30 mg) Fasted and High-Fat Fed Conditions in Healthy Adults Subjects under Naltrexone Block and Statistical Analysis (Study O-ARIR-003)

Parameter	30 mg Oxycodone ARIR Tablet (1 x 30 mg) Fed (N = 58)	30 mg Oxycodone ARIR Tablet (1 x 30 mg) Fasted (N = 58)
AUCt (ng.h/ml)	354.2 ± 82.49 (23.3)	287.4 ± 65.80 (22.9)
AUCinf (ng.h/mL)	361.9 ± 86.67 (23.9)	292.7 ± 67.39 (23.0)
Cmax (ng/mL)	68.0 ± 20.07 (29.5)	57.8 ± 18.01 (31.1)
T1/2 (h)	3.9 ± 0.64 (2.5 – 5.8)[a]	3.8 ± 0.68 (2.4 – 6.2)[a]
Tmax (h)[b]	2.0 (1.0 – 6.1)	1.8 (0.8 – 5.0)
Geometric Mean Ratio (Oxycodone ARIR Tablet Fed/Oxycodone ARIR Tablet Fasted) % (90% CI)		
AUCt	123.0 (119.1 – 127.0)	
AUCinf	123.5 (119.7 – 127.4)	
Cmax	118.5 (108.6 – 129.4)	

[a] range; [b] tmax reported as median (range)
Source: Table 14.2.2-1 and 14.2.2-2 of study O-ARIR-003 report.

Dose proportionality:
Following a single dose administration of 5, 15, and 30 mg oxycodone ARIR tablets to healthy volunteers under naltrexone block and fasting conditions, oxycodone Cmax and AUC values were dose proportional based on the analyses on log transformed parameters using a power model. The slopes of log-transformed Cmax, AUCt, and AUCinf values for oxycodone were 0.9769, 1.0081 and 0.9799, respectively, and they fell within the range of 0.80 to 1.25. In addition, the 90% CIs around the slope were within the predefined boundary (0.8755, 1.1245). Therefore, dose proportionality is demonstrated over the range of 5 mg to 30 mg for oxycodone ARIR tablet. As described in its label, dose proportionality was also demonstrated for Roxicodone tablet.

The PK bridging for two lower strengths 5 mg and 15 mg tablets between oxycodone ARIR and Roxicodone tablet can be justified by the established PK bridging for 30 mg tablet between oxycodone ARIR and Roxicodone tablet, dose proportionality for Roxicodone tablet (Roxicodone tablet approved labeling) and dose proportionality for oxycodone ARIR tablet over the range of 5 mg to 30 mg.

PK of Intranasal Ground Oxycodone ARIR Tablet vs Intranasal Crushed Roxicodone Tablet and Oral Intact Oxycodone ARIR Tablet:
In comparison to intranasal crushed Roxicodone tablet, intranasal ground oxycodone ARIR tablet had lower Cmax (28%) and slightly longer median Tmax (e.g., 1.7 h for crushed Roxicodone tablet intranasally and 2.3 h for ground oxycodone ARIR tablet intranasally), but similar total exposure (AUCt and AUCinf).

In comparison to orally intact oxycodone ARIR tablet, intranasal ground oxycodone ARIR tablet had lower Cmax (30%), longer median Tmax (e.g., 1.3 h for intact oxycodone ARIR tablet orally and 2.3 h for ground oxycodone ARIR tablet intransally), slightly greater total exposure (AUCt and AUCinf are 16-17% greater). The pharmacodynamics profiles such as dug liking VAS are under review by Controlled Substance Staff (CSS). The evaluation of the overall abuse potential is deferred to CSS.

***OSI Inspection**:*
OSI memo dated February 17, 2017 stated that the inspection at the clinical site for the pivotal BA/BE study O-ARIR-003 should be completed by March 24, 2017. Another OSI memo dated February 27, 2017 recommended to accept data without an on-site inspection of the analytical site.

As of today (March 22, 2017), OSI inspection of the clinical site for Study O-ARIR-003 is pending and an addendum to this review will be written if OSI audit finds significant issues affecting the acceptability of the data.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?

Inspirion Delivery Sciences, LLC (IDS) submitted an original 505(b)(2) NDA 209-777 for oxycodone ARIR, an abuse-resistant formulation of immediate-release oxycodone hydrochloride for the management of moderate to severe pain where the use of an opioid analgesic is appropriate on October 21, 2016. Oxycodone ARIR tablets incorporate an abuse-deterrent technology that is intended to make tablets difficult to manipulate and resist extraction in widely used solvents. Oxycodone ARIR was originally developed by Inspirion Delivery Technologies, LLC (IDT) and was transferred to IDS, which is a subsidiary of IDT, on August 2016.

The oxycodone ARIR tablet is composed of 3 strengths of oxycodone hydrochloride (5, 15, or 30 mg) to be administered every 4 to 6 hours as needed. IDS submitted the current 505(b)(2) NDA using Roxicodone tablet (NDA 21-011) as the listed drug and proposed to rely on the Agency's previous findings of safety and effectiveness for Roxicodone tablet by establishing a pharmacokinetic bridge. No efficacy/safety study has been conducted with oxycodone ARIR tablets.

At early phase of the drug development, a Pre-IND was held on November 24, 2009. The Sponsor was advised that the proposed BE study between test and reference product should be conducted with the highest strength (30 mg) under fasting condition. In addition, food effect must be employed the highest strength of the proposed product. The sponsor was asked provide data to support a biowaiver for lower strengths or dose proportionality if a biowaiver cannot be granted. On February 19, 2013, the Sponsor requested guidance on the PK comparison of oxycodone ARIR tablet to the listed drug Roxicodone tablet to support the clinical development program for their anticipated

505(b)(2) submission. In an email dated September 5, 2013, the Agency's response is shown below:

> You submitted data from a single-dose bioequivalence (BE) study for your proposed oxycodone product using Roxicodone as the reference drug product. We generally agree that the observed PK data would be acceptable for the purposes of bridging to FDA's prior findings of safety and efficacy for Roxicodone.
>
> The AUC for oxycodone met BE criteria, however, the lower limit of the confidence interval for Cmax (i.e., 78.8%) slightly missed the 80% criterion to establish BE. Additionally, Tmax is about 0.6 hr longer than the reference drug product (2.1 hr for your proposed drug product compared with 1.5 hour for the reference drug product, Roxicodone). Considering that a lower limit of the confidence interval for Cmax of 78.8% is very close to the 80% lower limit criterion, and that your proposed drug product will be used in titration, we do not anticipate that the slightly missed lower limit of the confidence interval for Cmax, nor the slightly longer Tmax, will affect the efficacy of your proposed drug product to a substantial degree.
>
> In addition, as we mentioned in the pre-IND meeting, you will still need to submit a biowaiver request for lower strengths if you plan to develop them.

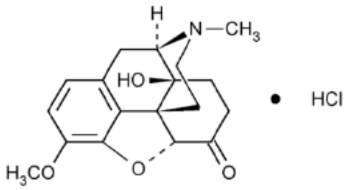
In this NDA submission, the sponsor included two pilot comparative bioavailability and dose proportionality studies (O-ARIR-001 and O-ARIR-004), a pivotal comparative bioavailability study and a dose proportionality study (O-ARIR-003 and O-ARIR-006), and one human abuse potential study (O-ARIR-002) with pharmacokinetic and pharmacodynamics measures. This clinical pharmacology review focuses on the pivotal studies (O-ARIR-003 and O-ARIR-006) and the pharmacokinetics in human abuse potential study (O-ARIR-002). The final to-be-marketed formulation was used in these studies (O-ARIR-002, O-ARIR-003, and O-ARIR-006).

Both Studies (O-ARIR-003 and O-ARIR-006) were randomized, open-label, crossover studies conducted in healthy volunteers with naltrexone blockade. Study O-ARIR-003 assessed comparative bioavailability of 30 mg oxycodone ARIR tablet and 30 mg Roxicodone tablet under fasting condition plus food effect on 30 mg oxycodone ARIR tablet. Study O-ARIR-006 assessed dose proportionality using 5, 15, and 30 mg oxycodone ARIR tablets under fasting condition. Study O-ARIR-002 was a randomized, double-blind, double-dummy, active and placebo-controlled crossover study in healthy opioid experienced nondependent recreational abusers.

2. *What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?*

Table 3 Physical-Chemical Properties of Oxycodone Hydrochloride

Drug Name	Oxycodone Hydrochloride
Chemical Name	(5α)-4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, hydrochloride (9CI)

Structure	 • HCl
Molecular Formula	$C_{18}H_{21}NO_4 \cdot HCl$
Molecular Weight	351.82 g/mol
Melting Point	270°C - 272°C
Appearance	White [redacted] powder
Solubility	One gram of oxycodone hydrochloride dissolves in 10 mL of water. It is slightly soluble in ethanol and almost insoluble in ether or chloroform.

The oxycodone ARIR tablet is a round, colored, and coated tablet. [redacted]

[redacted] All oxycodone ARIR tablets are approximately the same size. The quantitative compositions for each strength of oxycodone ARIR tablets are presented in **Table 4**.

Table 4 Components and Composition of Oxycodone ARIR Tablets

[redacted]

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3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Oxycodone is a pure agonist opioid whose principle therapeutic action is analgesic. Oxycodone (b) (4) is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

4. What are the proposed dosage(s) and route(s) of administration?

Oxycodone ARIR tablet is an abuse-resistant formulation of immediate-release oxycodone hydrochloride for oral administration. There are three available strengths, 5, 15, and 30 mg, same as the listed drug Roxicodone. Patients who have not been receiving opioid analgesics should be started in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of oxycodone for the listed drug Roxicodone tablet?

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower presystemic and/or first-pass metabolism of oxycodone. The relative oral bioavailability of ROXICODONE TABLET 15 mg and 30 mg tablets, compared to the 5 mg ROXICODONE TABLET tablets, is 96% and 101% respectively. ROXICODONE TABLET 15 mg tablets and 30 mg tablets are bioequivalent to the 5 mg ROXICODONE TABLET tablet. Dose proportionality of oxycodone has been established using the ROXICODONE TABLET 5 mg tablets at doses of 5 mg, 15 mg (three 5 mg tablets) and 30 mg (six 5 mg tablets) based on extent of absorption (AUC). It takes approximately 18 to 24 hours to reach steady state plasma concentrations of oxycodone with ROXICODONE TABLET.

Food Effect

A single-dose food effect study was conducted in normal volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance the extent

(27% increase in AUC), but not the rate of oxycodone absorption from the oral solution. In addition, food caused a delay in Tmax (1.25 to 2.54 hour). Similar effects of food are expected with the 15 mg and 30 mg tablets.

Distribution
Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk.

Elimination
Metabolism
A high portion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism, and is catalyzed by CYP3A4. Oxymorphone is formed by the O demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6. Free and conjugated noroxycodone, free and conjugated oxycodone, and oxymorphone are excreted in human urine following a single oral dose of oxycodone. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

Excretion
Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of ROXICODONE TABLET was 3.5 to 4 hours.

Specific Populations
Age: Geriatric Population
Population pharmacokinetic studies conducted with ROXICODONE TABLET, indicated that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65.

Hepatic Impairment
In a clinical trial supporting the development of ROXICODONE TABLET, too few patients with decreased hepatic function were evaluated to study these potential differences. However, because oxycodone is extensively metabolized in the liver, its clearance may decrease in hepatic impaired patients.

Renal Impairment
This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.

2. Were the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?

The activity is primarily due to the parent compound oxycodone. Oxycodone concentrations were measured in all pharmacokinetic studies.

2.3 Intrinsic Factors

1. What is the pediatric plan?

Division agreed that oxycodone ARIR tablet does not trigger the requirements of PREA and pediatric studies will not be required in response to the request for waiver of pediatric studies in patients from birth to less than 18 years of age, previously submitted to IND 105951 in SN 0003 (January 17, 2014). The Division's advice was conveyed to the sponsor on March 11, 2014.

2.4 General Biopharmaceutics

1. *What is the relative bioavailability of oxycodone following a single dose administration of the proposed oxycodone ARIR tablet in comparison to the listed drug, Roxicodone tablet under fasting condition?*

The 30 mg oxycodone ARIR tablet (1 x 30 mg) showed equivalent AUCt and AUCinf values, similar Cmax, and slight longer median Tmax (from 1 h to 1.8 h) in comparison to 30 mg Roxicodone tablet (1 x 30 mg) under fasting condition. The ranges of the Tmax values were similar.

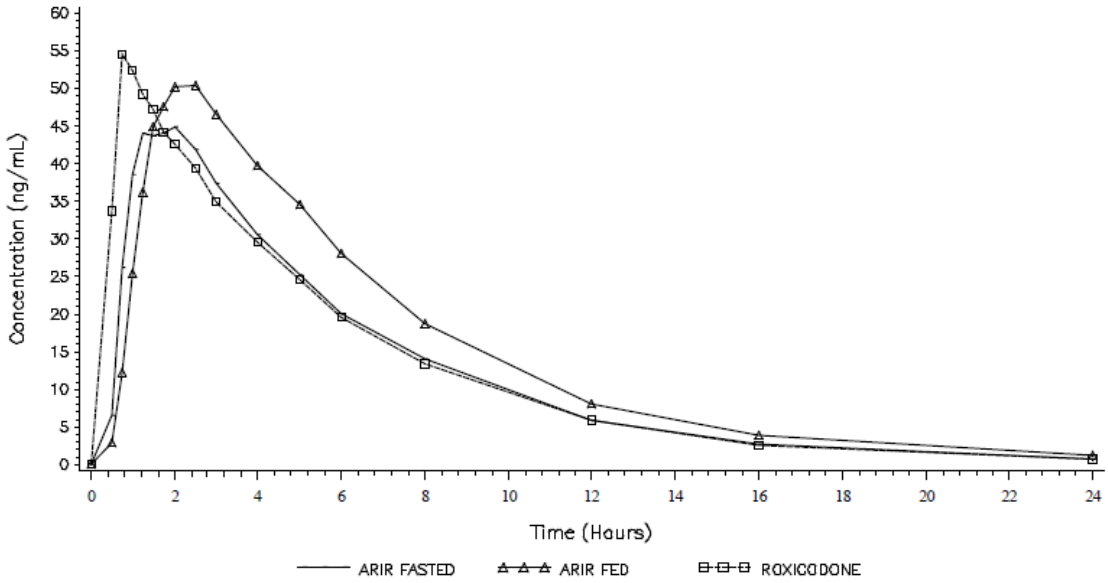
In the pivotal comparative bioavailability/bioequivalence study O-ARIR-003, the relative bioavailability of 30 mg oxycodone ARIR tablet in comparison with 30 mg Roxicodone tablet was assessed under fasting condition. The same study also evaluated the effect of food on the bioavailability of 30 mg oxycodone ARIR tablet. Study O-ARIR-003 was a randomized, open-label, single dose, 3-period, 3-treatment, 6-sequence cross over study in healthy volunteers under naltrexone block. Subjects were randomized to receive 30 mg oxycodone ARIR tablet under fasting condition, 30 mg Roxicodone tablet under fasting condition, and 30 mg oxycodone ARIR tablet under fed condition over 3 periods.

A single dose of 30 mg oxycodone ARIR tablet was administered to subjects following a 10-hour overnight fast or after a high fat/high-calorie meal. A single dose of 30 mg Roxicodone tablet was given following a 10-hour overnight fast. There was an at least 4 days of washout period between treatment. In order to block the adverse effects of oxycodone, 50 mg naltrexone was administered approximately 12 h and 1.5 h pre dose and 12 hour post dose. Blood samples for pharmacokinetic determination were collected from each subject at pre-dose, and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 hours post-dose.

The mean oxycodone plasma concentration-time profiles are shown in **Figure 1**. Descriptive statistics and results of the statistical analyses for oxycodone ARIR tablet versus Roxicodone tablet (both in fasted states) are summarized in **Table 1**. The total exposures (AUCt and AUCinf) of oxycodone following the administration of 30 mg oxycodone ARIR tablet met the bioequivalent criteria to that from 30 mg Roxicodone tablet under fasting conditions because the 90% confidence intervals for the geometric mean ratios of these AUC values were within 80% to 125% range (92.5% to 98.7% for AUC0-t and 92.8% to 98.9% for AUCinf). Oxycodone Cmax values were similar because the 90% confidence interval for the geometric mean ratio of Cmax values was 78.8% to 94.3%, which is slightly outside the BE range of 80% to 125%. Median Tmax value for

the 30 mg oxycodone ARIR tablet was 0.8 h longer than the 30 mg Roxicodone tablet but the ranges are similar.

Figure 1 Mean Oxycodone plasma concentration (ng/mL) time profiles for oxycodone ARIR tablet (1 x 30 mg) under Fasted and Fed Conditions and Roxicodone tablet (1 x 30 mg) under Fasted Condition



For acute analgesic products, partial AUCs at early time period have been used as additional evidence to support the performance of different formulations. Because of slightly longer median Tmax value for oxycodone ARIR tablet in comparison to Roxicodone tablet under fasted condition, partial AUCs of oxycodone at early time periods were compared. The results shows that the geometric mean ratios (oxycodone ARIR tablet/Roxicodone tablet) of AUC0-1h, AUC0-1.5h, AUC0-2h, AUC0-3h, and AUC0-4h were 44%, 63%, 75%, and 87%, respectively (**Table 5**). Both oxycodone ARIR tablet and Roxicodone tablet have the same dosing regimen, which is every 4 to 6 h as needed. With the shortest dosing interval (4 h), the 90% CI for AUC0-4h ratio was from 78.3% to 97.5%.

Table 5 Point Estimates and 90% Confidence Intervals for Partial AUCs from 0 to 4 Hours

	AUC0-1h (ng.h/mL)		AUC0-1.5h (ng.h/mL)		AUC0-2h (ng.h/mL)		AUC0-3h (ng.h/mL)		AUC0-4h (ng.h/mL)	
	LSM (SEM)	Ratio (90% CI)	LSM (SEM)	Ratio (90% CI)	LSM (SEM)	Ratio (90% CI)	LSM (SEM)	Ratio (90% CI)	LSM (SEM)	Ratio (90% CI)
Roxicodone tablet (ref)	3.21 (0.16)	43.8 (32.9, 58.4)	3.92 (0.16)	63.5 (46.0, 87.6)	4.30 (0.13)	74.6 (56.6, 98.2)	4.73 (0.10)	86.00 (70.0, 105.7)	4.96 (0.06)	87.4 (78.3, 97.5)
Oxycodone ARIR (test)	2.39 (0.15)		3.46 (0.16)		4.01 (0.13)		4.58 (0.10)		4.82 (0.06)	

Note: LSM = least square means; SEM = standard error of the mean
Data Source: Table 1.11.3-1 from NDA 209777, SN0009

Reviewer's Comment:
Studies O-ARIR-003 has shown that the proposed 30 mg oxycodone ARIR tablet had equivalent total exposures of oxycodone (AUCt and AUCinf), similar Cmax, and slightly

longer Tmax but similar range of Tmax values in comparison to 30 mg Roxicodone tablet.

Considering that the lower limit of the 90% CI for Cmax of 78.8% is very close to the 80% limit criterion and oxycodone ARIR tablet will be titrated, 1.2% lower CI for oxycodone Cmax is not anticipated to affect the efficacy of oxycodone ARIR tablet to a substantial degree after discussion with the review team. Median (min, max) Tmax values were 1.8 (0.8, 5.0) hour for oxycodone ARIR tablet and 1.0 (0.5, 5.0) hour for Roxicodone tablet; oxycodone ARIR tablet had slightly longer median Tmax value than Roxicodone tablet but the range for Tmax were similar between the two products. Considering food caused a delay in Tmax (1.25 to 2.54 hour) for Roxicodone tablet and there is no food restriction for Roxicodone tablet administration, the slightly longer median Tmax value for oxycodone ARIR tablet under fasting condition will not be anticipated to affect the efficacy of oxycodone ARIR tablet to a substantial degree.

Thus, the PK bridging between 30 mg oxycodone ARIR tablet and 30 mg Roxicodone tablet is established.

2. *How does food affect the bioavailability of oxycodone ARIR tablet?*

Food effect on oxycodone ARIR tablet was evaluated in the pivotal comparative bioavailability/bioequivalence study O-ARIR-003. As indicated previously, Study O-ARIR-003 was a randomized, open-label, single dose, 3-period, 3-treatment, 6-sequence cross over study in healthy volunteers under naltrexone block. For fed dose, following the overnight fast of at least 10 hours, subjects started the test meal 30 minutes prior to administration of the test product and were required to eat the meal in 30 minutes or less. The test meal was a standardized high-fat meal (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories). Oxycodone concentration-time profiles are shown in Figure 1 of this review. Descriptive statistics and results of the statistical analyses for oxycodone ARIR tablet fed versus oxycodone ARIR tablet fasting are summarized in Table 2 of this review.

High-fat meal increased oxycodone Cmax, AUCt, and AUCinf values by 18%, 23%, and 24%, respectively, following the administration of a single dose of 30 mg oxycodone ARIR tablet. Median (min, max) Tmax values were similar under fasting and fed conditions; 1.8 (0.8, 5.0) h under fasting and 2.0 (1.0, 6.1) h under high-fat fed condition. The food effect on oxycodone AUC for oxycodone ARIR tablet is similar to that for Roxicodone tablet, the identified listed drug for this 505(b)(2) NDA. According to the approved Roxicodone labeling, a high fat meal enhanced the extent (27% increase in AUC). In addition, food caused a delay in Tmax (1.25 to 2.54 hour) for Roxicodone tablet. Roxicodone tablet labeling does not recommend a food restriction because of the limited extent of food effect. Therefore, no food restriction should be recommended for oxycodone ARIR tablet as well.

3. *Is the dose proportionality established across the dose/strength range between 5 and 30 mg?*

Following a single dose administration of 5, 15, and 30 mg oxycodone ARIR tablets to healthy volunteers under naltrexone block and fasting conditions, oxycodone Cmax and

AUC values increased in a dose proportional fashion based on the analyses on log transformed parameters using a power model.

Dose proportionality Study O-ARIR-006 was an open-label, randomized, single-dose, 3-treatment, 3-period, 2-sequence crossover study. Subjects received 5 mg (Treatment A), 15 mg (Treatment B), and 30 mg (Treatment C) of oxycodone ARIR tablet under fasted conditions over 3 periods. All subjects received a single 15 mg dose of oxycodone ARIR tablet in Period 1 and then were randomized to receive the 5 or 30 mg of oxycodone ARIR tablet in periods 2 and 3. There was a 2-day washout between periods. All subjects were fasted overnight for at least 10 hours prior to study drug administration. To block the adverse effects of oxycodone, 50 mg naltrexone was administered approximately 12 and 1.25 h predose and 12 h postdose. Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, and 24 h post dose.

Mean oxycodone plasma concentration-time profiles are shown in **Figure 2**. Descriptive statistics of single dose of 5 mg, 15 mg and 30 mg oxycodone ARIR tablet and results of the statistical analyses for dose proportionality are summarized in **Table 6** and **Table 7**.

Figure 2 Mean Oxycodone Plasma Concentration-Time Profiles following the Administration of Single Doses of 5, 15, and 30 mg Oxycodone ARIR Tablet (n=51) (Study O-ARIR-006)

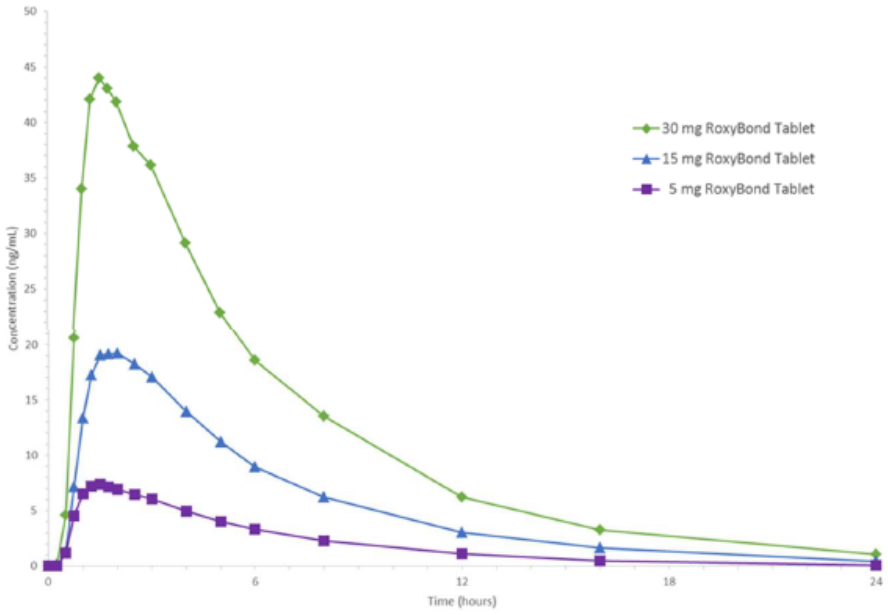


Table 6 Summary of PK Parameters of Oxycodone following A Single Dose Administration of 5 mg (Treatment A), 15 mg (Treatment B) and 30 mg (Treatment C) Oxycodone ARIR Tablet (Study O-ARIR-006)

Pharmacokinetic Parameter	Treatment*	N	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
AUC_{0-t} (ng·hr/mL)	Test A	51	45.5387 ± 15.4469 (33.9203)	17.5911	44.5793	84.7602
	Test B	51	127.5167 ± 38.0925 (29.8725)	62.1236	126.4218	208.2917
	Test C	51	277.0213 ± 89.6135 (32.3490)	127.9715	256.2492	559.2539
$AUC_{0-\infty}$ (ng·hr/mL)	Test A	51	48.9657 ± 16.1316 (32.9448)	19.7480	47.4850	89.6304
	Test B	50**	131.5798 ± 38.9669 (29.6146)	65.3109	128.5554	214.0704
	Test C	51	285.8070 ± 94.1490 (32.9415)	131.9821	260.6903	576.3756
AUC_{0-t}/ $AUC_{0-\infty}$	Test A	51	0.9274 ± 0.0222 (2.3931)	0.8780	0.9322	0.9699
	Test B	50**	0.9642 ± 0.0135 (1.3978)	0.9323	0.9644	0.9847
	Test C	51	0.9712 ± 0.0217 (2.2358)	0.8413	0.9742	0.9890
C_{max} (ng/mL)	Test A	51	8.3096 ± 2.1242 (25.5628)	4.2370	8.0980	12.9970
	Test B	51	21.9635 ± 5.8200 (26.4984)	12.5930	22.2590	37.9750
	Test C	51	48.5039 ± 15.9243 (32.8311)	25.9850	45.0020	95.1390
T_{max} (hr)	Test A	51	1.5595 ± 0.6554 (42.0284)	0.7500	1.5000	5.0000
	Test B	51	1.9804 ± 1.5140 (76.4480)	1.0000	1.7500	12.0000
	Test C	51	1.8539 ± 1.0149 (54.7454)	1.0000	1.5167	8.0000

Pharmacokinetic Parameter	Treatment*	N	Arithmetic mean ± SD (%CV)	Min.	Median	Max.
K_{el} (hr^{-1})	Test A	51	0.1864 ± 0.0420 (22.5567)	0.0692	0.1865	0.2981
	Test B	50**	0.1746 ± 0.0360 (20.6135)	0.1090	0.1645	0.2597
	Test C	51	0.1691 ± 0.0357 (21.1245)	0.0857	0.1625	0.2490
$T_{1/2}$ (hr)	Test A	51	3.9454 ± 1.1598 (29.3953)	2.3251	3.7173	10.0119
	Test B	50**	4.1308 ± 0.8200 (19.8514)	2.6689	4.2137	6.3618
	Test C	51	4.2870 ± 0.9527 (22.2238)	2.7841	4.2653	8.0860

Note: Data from Table 11.4.1.1 in report for Study O-ARIR-006

Dose proportionality was assessed by power model described by Gough et al 1995 and Smith et al., 2000. Results of power model analyses on log-transformed AUCt, AUCinf, and Cmax showed that the slopes (1.0081 for AUCt, 0.9799 for AUCinf, and 0.9769 for Cmax) fell within the range of 0.80 to 1.25 and the corresponding 90% CIs were contained within the predefined acceptance range of 08755 to 1.1245. Thus, oxycodone ARIR was dose proportional over the range of 5 to 30 mg.

Table 7 Summary of Dose Proportionality Analysis for Log-Transformed Oxycodone AUCt, AUCinf, and Cmax for 5 mg, 15 mg, and 30 mg Oxycodone ARIR Tablets Using Power Model (Study O-ARIR-006)

Parameters	Slope	90% CI	Acceptance Limits for 90% CI
AUC0-t (ng.h/mL)	1.0081	0.9888-1.0273	0.8755-1.1245
AUC0-inf (ng.h/mL)	0.9799	0.9608-0.9991	0.8755-1.1245
Cmax (ng/mL)	0.9769	0.9514-1.0024	0.8755-1.1245

Source: Table 11.4.1.2 and 11.4.1.3 in Study O-ARIR-006
Power model by (1) Gough et al., Assessment of Dose Proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK Joint Working Party. Drug Information Journal, 1995;29:1039-48 and (2) Smith et al., Confidence Interval criteria for assessment of dose proportionality. Pharmaceutical Research 2000;17(10):1278-83.

Reviewer's Comment:
Sponsor has established a PK bridge for the highest strength (30 mg) between oxycodone ARIR tablet and Roxicodone tablet under fasting condition in Study O-ARIR-003. Food has similar effect on AUC and Cmax for oxycodone ARIR tablet and Roxicodone, and it has minimal or no effct on Tmax for oxycodone ARIR tablet. Therefore, oxycodone ARIR tablet can be taken regardless of food, same as Roxicodone. In Study O-ARIR-006, dose proportionality is demonstrated over the range of 5 mg to 30 mg for oxycodone ARIR tablet. As described in its label, dose proportionality was also demonstrated for Roxicodone tablet. Therefore, the PK bridging for two lower strengths 5 and 15 mg between oxycodone ARIR tablet and Roxicodone tablet can be justified.

4. *What is the abuse potential of ground oxycodone ARIR tablet intranasally relative to crushed Roxicodone tablet intranasally and intact oxycodone ARIR tablet orally to recreational, nondependent opioid users?*

In comparison to intranasal crushed Roxicodone tablet, intranasal ground oxycodone ARIR tablet had lower Cmax (~ 28%) and slightly longer median Tmax (e.g., 1.7 h for crushed Roxicodone tablet intranasally and 2.3 h for ground oxycodone ARIR tablet intranasally), but similar total exposure (AUCt and AUCinf).

In comparison to oral intact oxycodone ARIR tablet, intranasal ground oxycodone ARIR tablet had lower Cmax (~ 30%), longer median Tmax (e.g., 1.3 h for intact oxycodone ARIR tablet orally and 2.3 h for ground oxycodone ARIR tablet intransally), slightly greater total exposure (AUCt and AUCinf are 16-17% greater).

Study O-ARIR-002 was a randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover study. Nondependent but experienced opioid abusers were randomized to receive each of the following 4 treatments in a randomized, 4-way crossover, double-blind, double-dummy, 1:1:1:1 ratio design. There was a minimum of 72 hours washout separating each treatment:
Treatment A: Ground placebo oxycodone ARIR tablet (high volume, 587 mg) administered intranasally + placebo tablet matching oxycodone ARIR tablet swallowed intact
Treatment B: Crused 30 mg Roxicodone tablet (low volume, 100 mg) administered intranasally + placebo tablet matching oxycodone ARIR tablet swallowed intact
Treatment C: Ground 30 mg oxycodone ARIR tablet (high volume, 587 mg) administered intranasally + placebo tablet matching oxycodone ARIR tablet swallowed intact
Treatment D: Placebo powder matching Roxicodone tablet (low volume, 100 mg) administered intranasally + oxycodone ARIR 30 mg tablet swallowed intact

Mean plasma oxycodone concentrations over time profiles are shown in **Figure 3**. The descriptive statistics of the PK parameters and statistical analyses are shown in **Table 8** and **Table 9**, respectively.

Figure 3 Mean Plasma Oxycodone Concentrations (ng/mL) Time Profile (Study O-ARIR-002) (N = 31)

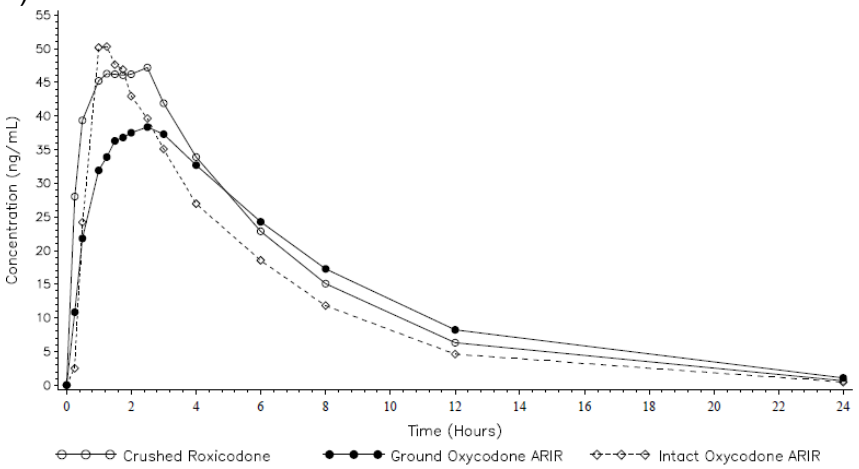


Table 8 Summary of PK Parameters for Oxycodone following the administration of intranasal Crushed Roxicodone tablet 30 mg, intranasal Ground oxycodone ARIR tablet, and oral intact oxycodone ARIR tablet (Study O-ARIR-002)

Parameter	Treatment	Mean ± SD	%CV	Median	Range	n
C_{max} (ng/mL)	Crushed Roxicodone	56.5 ± 11.5	20.4	55.0	42.6 - 83.3	30
	Ground Oxycodone ARIR	42.7 ± 13.5	31.7	42.9	12.0 - 65.9	30
	Oral Oxycodone ARIR	58.4 ± 13.1	22.4	57.6	35.6 - 94.3	31
T_{max} (hr)	Crushed Roxicodone	2.0 ± 1.1	nc	1.7	0.6 - 6.1	30
	Ground Oxycodone ARIR	2.3 ± 0.9	nc	2.3	1.1 - 4.1	30
	Oral Oxycodone ARIR	1.5 ± 0.6	nc	1.3	0.6 - 3.1	31
AUC_{0-t} (ng•hr/mL)	Crushed Roxicodone	338.6 ± 72.1	21.3	323.5	199.0 - 472.0	30
	Ground Oxycodone ARIR	331.4 ± 97.2	29.3	347.5	65.4 - 475.0	30
	Oral Oxycodone ARIR	273.2 ± 62.3	22.8	259.0	172.0 - 449.0	31
$AUC_{0-\infty}$ (ng•hr/mL)	Crushed Roxicodone	345.3 ± 71.1	20.6	331.0	209.0 - 482.0	30
	Ground Oxycodone ARIR	340.5 ± 98.5	28.9	350.5	70.8 - 516.0	30
	Oral Oxycodone ARIR	279.5 ± 61.7	22.1	263.0	180.0 - 452.0	31
k_e (hr^{-1})	Crushed Roxicodone	0.2060 ± 0.0361	nc	0.2005	0.1610 - 0.3060	30
	Ground Oxycodone ARIR	0.1830 ± 0.0375	nc	0.1780	0.1010 - 0.2580	30
	Oral Oxycodone ARIR	0.2171 ± 0.0430	nc	0.2050	0.1500 - 0.3030	31
$t_{1/2}$ (hr)	Crushed Roxicodone	3.5 ± 0.5	nc	3.5	2.3 - 4.3	30
	Ground Oxycodone ARIR	4.0 ± 1.0	nc	3.9	2.7 - 6.9	30
	Oral Oxycodone ARIR	3.3 ± 0.6	nc	3.4	2.3 - 4.6	31

nc = not calculated

Table 9 Bioequivalence Comparison for Oxycodone after Intranasal Administration of Crushed Roxicodone tablet and Ground Oxycodone ARIR tablet and Oral Administration of Oxycodone ARIR tablet (Study O-ARIR-002) (N = 31)

	LS Means (Back-transformed)			Ratio (%)	90% CI	
Parameter/ Comparison	Ground Oxyco-done ARIR	Crushed Roxi-codone	Intact Oxyco-done ARIR	(Test: Reference)	Lower	Upper
Ln(C_{max})						
Ground Oxycodone ARIR vs Crushed Roxicodone	40.04	55.56	-	72.06	64.80	80.15
Ground Oxycodone ARIR vs Intact Oxycodone ARIR	40.04	-	56.97	70.28	63.24	78.11
Oral Oxycodone ARIR vs Crushed Roxicodone	-	55.56	56.97	102.53	92.26	113.95
Ln(AUC_{0-t})						
Ground Oxycodone ARIR vs Crushed Roxicodone	309.21	330.77	-	93.48	83.74	104.35
Ground Oxycodone ARIR vs Intact Oxycodone ARIR	309.21	-	265.38	116.52	104.46	129.96
Oral Oxycodone ARIR vs Crushed Roxicodone	-	330.77	265.38	80.23	71.93	89.49
Ln($AUC_{0-\infty}$)						
Ground Oxycodone ARIR vs Crushed Roxicodone	318.82	337.91	-	94.35	84.99	104.74
Ground Oxycodone ARIR vs Intact Oxycodone ARIR	318.82	-	271.98	117.22	105.67	130.04
Oral Oxycodone ARIR vs Crushed Roxicodone	-	337.91	271.98	80.49	72.55	89.29

For the comparison of ground oxycodone ARIR tablet versus crushed Roxicodone tablet, both administered intranasally, ground intranasal oxycodone ARIR tablet had lower Cmax (~ 28%) and slightly longer median Tmax (e.g., 1.7 h for crushed Roxicodone tablet intranasally and 2.3 h for ground oxycodone ARIR tablet intranasally), but similar total exposure (AUCt and AUCinf). For the comparison of ground oxycodone ARIR tablet administered intranasally versus oral oxycodone ARIR tablet, ground intranasal oxycodone ARIR tablet had lower Cmax (~ 30%), longer median Tmax (e.g., 1.3 h for intact oxycodone ARIR tablet orally and 2.3 h for ground oxycodone ARIR tablet intransally), slightly greater total exposure (AUCt and AUCinf are 16-17% greater).

The pharmacodynamics profiles in this study, such as dug liking VAS score, are under review by CSS. The evaluation of the overall abuse potential is deferred to CSS.

2.5 Analytical Section

1. *Do the bioanalytical methods adequately validated for determining plasma concentrations of oxycodone?*

A validated LC-MS/MS method was used for the determination of oxycodone in human plasma in Studies O-ARIR-002, O-ARIR-003, and O-ARIR-006. The accuracy and precision for Studies 002, 003, and 006 are summarized in **Table 10**.

Table 10 Summary of Accuracy and Precision Data for Oxycodone

Study	LLOQ Calibration Range	QC	QC Precision (%CV)	QC % Accuracy
Study O-ARIR-002 (Bioanalytical Report 1407495)	LLOQ: 0.398 ng/mL Calibration Range: 0.398 to 99.629 ng/mL	1.200, 10.500, 37.500, and 74.999 ng/mL	2.8 to 4.6%	97.8 to 102.1%
Study O-ARIR-003 (Bioanalytical Report SAI-1212217)	LLOQ: 0.400 ng/mL Calibration Range: 0.400 to 100.059 ng/mL	1.204, 37.634, and 75.269 ng/mL	2.8 to 3.7%	97.7 to 102.8%
Study O-ARIR-006 (Bioanalytical Report SAI-1408517)	LLOQ: 0.397 ng/mL Calibration Range: 0.397 to 99.351 ng/mL	1.186, 5.187, 37.051, and 74.102 ng/mL	2.6 to 4.2%	100.7 to 106.3%

Note: The bioanalytical reports are in the following locations in the NDA:

SAI-1212217 for Study O-ARIR-003: See module 5.3.1.2 under the leaf for the study see section 16.2.5 "Compliance and/or Drug Concentration Data Listing."

SAI-1407495 for Study O-ARIR-002: See module 5.3.4.1 under the leaf for the study see section 16.2.5 "Compliance and/or Drug Concentration Data Listing."

SAI-1408517 for Study O-ARIR-006: See module 5.3.1.1. The report is bookmarked under this section as a stand-alone report.

2.6 OSI Inspection

An OSI inspection was requested for the pivotal BA/BE study O-ARIR-003. OSI memo dated February 17, 2017 stated that the inspection at the clinical site for the pivotal BA/BE study O-ARIR-003 should be completed by March 24, 2017. Another OSI memo dated February 27, 2017 recommended to accept data without an on-site inspection of the analytical site.

As of today (March 22, 2017), OSI inspection of the clinical site for study O-ARIR-003 is pending and an addendum to this review will be written if OSI audit finds significant issues affecting the acceptability of the data.

3 Detailed Labeling Recommendations

As of March 22, labeling negotiation is still ongoing. Majority of the labeling languages in Roxicodone label can be used to support this product. However, the following changes are recommended for pharmacokinetics in Section 12.3. (Deletion is shown by (b) (4), addition is shown by blue underline)

(b) (4)

[Note: This paragraph should be removed and replaced with the PK finding between RoxyBond and Roxicodone (e.g., equivalent AUCt and AUCinf, similar Cmax because lower end of 90% CI was 78.8% and missed 80-125% BE limit slightly, slightly longer median Tmax (1.8 h for RoxyBond and 1.0 for Roxicodoned…). See added paragraph below.]

The activity of RoxyBond tablets is primarily due to the parent drug oxycodone. RoxyBond tablets are designed to provide immediate-release of oxycodone.

Oxycodone pharmacokinetics are similar between RoxyBond and oxycodone immediate-release tablets. In the fasted state, the extent of absorption (AUC) is equivalent, the rate of absorption (Cmax) is similar, and median Tmax is slightly longer (1.0 to 1.8 h).

Table (b) (4) **Pharmacokinetic Parameters (Mean ± SD)**				
Dose\Parameters	**AUC_{0-t} (ng·hr/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**Half-Life (hr)**
Single Dose Pharmacokinetics Study				
RoxyBond 5 mg tab (fasted)	45.5±15.4	8.3±2.1	1.5[a] (0.7 to 5.0)	3.9±1.2
RoxyBond 15 mg tab (fasted)	127.5±38.1	22.0±5.8	1.7[a] (1.0 to 12.0)	4.1±0.8
RoxyBond 30 mg tab (fasted)	277.0±89.6	48.5±15.9	1.5[a] (1.0 to 8.0)	4.3±1.0
Single Dose Food-Effect Study				
RoxyBond 30 mg tab (fasted)	287.4±65.8	57.8±18.0	1.8[a] (0.8 to 5.0)	3.8±0.7
RoxyBond 30 mg tab (fed)	354.2±82.5	68.0±20.1	2.0[a] (1.0 to 6.1)	3.9±0.6

[a] Median (range)

[Note: recommended the sponsor to add (b) (4) *to Table* (b) (4)*.]*

[Note: recommend the sponsor to remove (b) (4) *and place it to Section 9.2 Abuse.]*

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of RoxyBond was 3.8 to (b) (4) 4.3 hours.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA/BLA Number	209777	Brand Name	Oxycodone ARIR tablet
OCP Division (I, II, III, IV, V)	II	Generic Name	Oxycodone Hydrochloride Tablet
Medical Division	DAAAP	Drug Class	Opioid analgesic
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Management of moderate to severe pain where use of an opioid analgesic is appropriate
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	Oral tablet
Pharmacometrics Reviewer		Dosing Regimen	
Date of Submission	Oct 21, 2016	Route of Administration	oral
Estimated Due Date of OCP Review	March 21, 2017	Sponsor	Inspirion Delivery Sciences, Inc.
Medical Division Due Date	March 28, 2017	Priority Classification	Priority
PDUFA Due Date	April 21, 2017		

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	x	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2		O-ARIR-003 and O-ARIR-006
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		(1)		O-ARIR-006
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -	x	1		O-ARIR-002 –drug liking
Phase 2:				
Phase 3:				
PK/PD -				

Phase 1 and/or 2, proof of concept:				
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)		O-ARIR-003
replicate design; single / multi dose:				
Food-drug interaction studies	x	(1)		Same as above
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				
Literature References				
Total Number of Studies		3		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the final formulation was used in support of the NDA
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable,	x			

	does it have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		Division agreed that oxycodone ARIR does not trigger the requirements of PREA and pediatric studies will not be required in response to the request for waiver of pediatric studies, previously submitted to IND 105951 in SN 0003 (January 17, 2014).
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet	x			

	basic requirements for approvability of this product?				
19	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___

Request for OSI inspection on Study O-ARIR-003 was sent out on November 28, 2016 and OSI review is requested by March 14, 2017.

Title of the Study O-ARIR-003: A 3-Way Crossover Relative Bioavailability Study of Oxycodone ARIR (Abuse Resistant Immediate Release) 30 mg Tablets in Fasted State Versus Roxicodone 30 mg Tablets in Fasted State Versus Oxycodone ARIR 30 mg Tablets in Fed State

Study Clinical Site: CRI Lifetree
3838 South 700 East, Suite 202
Salt Lake City, UT 84106
T: 801-269-8200

Study Analytical Site: (b) (4)
(b) (4)

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

This NDA submission is fillable from clinical pharmacology perspective.

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

For study O-ARIR-003, provide comparison of partial AUCs (point estimate and 90% confidential intervals) at every time points from time 0 to 4h (e.g., AUC0-1 h, AUC0-1.5 h, AUC0-2h, AUC0-3h, and AUC0-4h, etc.) between test and the reference treatments. Provide justification that the delayed Tmax of your product under fast condition compared to Roxicodone will not affect efficacy, especially onset of action of your product.

For a 505(b)(2) application, you need to establish a scientific bridge or link to the listed drug Roxicodone. You propose to establish a link to 30 mg strength Roxicodone by conducting a BE study with your 30 mg strength product. In addition, you conducted a dose proportionality study across 5, 15 and 30 mg of your product. However, there is no direct BE study at 5 and 15 mg strengths between your proposed product and Roxicodone. Provide justification how a link to Roxicodone is established with these two strengths.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Inspirion Delivery Sciences, Inc (IDS) submitted a 505(b) (2) NDA for Oxycodone ARIR Tablet, 5, 15, and 30 mg for the management of moderate to severe pain where use of an opioid analgesic is appropriate.

Sponsor plans to rely on the agency's finding of the safety and efficacy of oxycodone as reflected in the approved product of Roxicodone® (NDA 21-011), an immediate-release tablet.

The PK studies supporting this NDA include a pivotal comparative BA/BE study O-ARIR-003 and a dose proportionality study O-ARIR-006. Study O-ARIR-003 showed that oxycodone AUC values met BE criteria. The lower limit of the 90% CI for Cmax (i.e., 78.8%) slightly missed the 80% criterion to establish BE. Median Tmax value is prolonged from 1 h to 1.8 h. Agency agreed previously that considering that a lower limit of the confidence interval for Cmax of 78.8% is very close to the 80% lower limit criterion, and that the proposed drug product will be used in titration, the slightly missed lower limit of the confidence interval for Cmax and the slightly longer Tmax will not be anticipated to affect the efficacy of the proposed drug product to a substantial degree.

Preliminary analysis on the early exposure (e.g., partial AUCs) for the comparison of the proposed product and listed drug product under fasting condition suggested that the early exposures for the proposed product are lower than the listed drug product.

	Oxycodone ARIR Fast	**Roxicodone Fast**	**Ratio (Test/Reference)**
AUC0-1 h (ng.h/mL)	13.8 (11.4)	32.6 (21.0)	0.42
AUC0-2 h (ng.h/mL)	57.2 (25.8)	79.6 (32)	0.72
AUC0-3 h (ng.h/mL)	98.6 (31)	119 (36.7)	0.83

In the same study, it was shown that high-fat meal increased AUC by 23% and increased Cmax by 18%. Median Tmax values were not affected. This food effect is similar to the food effect for Roxicodone. According to Roxicodone labeling, AUC is increased by 27%, Cmax is not changed, and Tmax is delayed from 1.25 h to 2.54 h.

In Study O-ARIR-006, it was demonstrated that the proposed product is dose proportional over the range of 5 to 30 mg. See more details in the attached filing slides.

4.2 Individual Study Synopsis

4.2.1 Study O-ARIR-003

2 SYNOPSIS

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to part of the Dossier:**	**(For National Authority Use only)**
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		
Title of Study: A 3-Way Crossover Relative Bioavailability Study of Oxycodone ARIR (Abuse-Resistant Immediate Release) 30 mg Tablets in Fasted State Versus Oxycodone ARIR 30 mg Tablets in Fed State		
Investigators and/or Study Centers: 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 Period: **Date of first subject randomized:** 27 December 2012 **Date of last subject completed:** 29 January 2013	**Phase of Development:** 1 (Bioequivalence)	
Objective: This study assessed the relative bioavailability of Oxycodone ARIR 30 mg tablets when administered to healthy adult subjects under fasted and fed conditions compared with that of Roxicodone 30 mg tablets following a single oral dose administered under fasted conditions.		
Study Design: This study was an open-label, single-dose, randomized, 3-period, 3-treatment, 6-sequence crossover study. Subjects randomly received an Oxycodone ARIR 30 mg tablet and a Roxicodone 30 mg tablet under fasted conditions and an Oxycodone ARIR 30 mg tablet under fed conditions. Each treatment was separated by a minimum 4-day washout period between doses. At study check-in, the subjects reported to the clinical site at least 14 hours prior to Day 1 dosing and were required to stay for 24 hours after Day 1 dosing. In order to block the major effects of oxycodone, subjects were given Naltrexone (1 x 50 mg tablet) with 240 mL of water at approximately 12 hours (± 30 minutes) prior to oxycodone administration, within 1.5 (± 15 minutes) hours of oxycodone administration, and approximately 12 hours (± 30 minutes) after oxycodone administration.		
Number of Subjects (planned and analyzed): **Planned:** Approximately 70 subjects were planned; 75 enrolled; and 58 completed the study. **Analyzed:** The Safety population comprised 75 subjects and the per-protocol population comprised 58 subjects.		
Diagnosis and Main Criteria for Inclusion: **Inclusion:** 1. Informed of the nature of the study and agreed to and were able to read, review and sign the informed consent document prior to any screening visit procedures. Completed the screening process up to 28 days prior to Period I dosing. 2. Healthy male and female subjects 18-45 years of age, inclusive, at the time of dosing. 3. Body Mass Index (BMI) between 18.0-32.0 kg/m^2, inclusive, at the time of dosing.		

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

4. Judged by an investigator to be in good health as documented by the medical history, physical examination, (including, but not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory, and central nervous systems), vital sign assessments, 12-lead electrocardiogram (ECG), clinical laboratory assessments, and by general observations. Any abnormalities or deviations outside the normal ranges for any clinical testing (laboratory tests, ECG, vital signs) could be repeated at the discretion of the investigator and judged to be not clinically significant for study participation.
5. If female, subject was:

   a. Surgically sterilized via hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; or

   b. Of childbearing potential and using at least one of the following methods of birth control: total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to Screening); oral or transdermal contraception; intrauterine device; double-barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring all with spermicidal jelly or cream). (*The subject must have used the chosen oral or transdermal contraceptive for at least 90 days before the Screening Visit. The subject agree d to continue using their selected method of birth control during the study and for 30 days after study completion)*; or

   c. Of non-childbearing potential (ie, postmenopausal for at least 1 year).

6. If male, the subject had a vasectomy or used one of the following methods of birth control: double-barrier method (see above) with partner or total abstinence from sexual intercourse. *The subject agreed to continue using their selected method of birth control with their sexual partner during the study and for 30 days after study completion).*

Exclusion:

1. Reports receiving any investigational drug within 30 days prior to Period I dosing.
2. Reports any presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, hepatic, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease as determined by the clinical investigator(s).
3. Presence of any clinically significant results from laboratory tests, vital signs assessments, and ECG, as judged by the investigator.
4. When confirmed upon additional testing, demonstrates a reactive screen for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody.
5. Demonstrates a positive drug screen.
6. Reports a clinically significant illness during the 28 days prior to Period I dosing (as determined by the clinical investigators).
7. Reports a history of allergic response(s) to oxycodone hydrochloride, naltrexone, or related drugs.
8. Reports a history of clinically significant allergies including food or drug allergies.

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

9. Reports a history of drug or alcohol addiction or abuse within the past year.
10. Reports donating blood within 30 days prior to Period I dosing. All subjects were advised not to donate blood for four weeks after completing the study.
11. Reports donating plasma (eg, plasmapheresis) within 30 days prior to Period I dosing. All subjects were advised not to donate plasma for 4 weeks after completing the study.
12. Reports an intolerance of direct venipuncture or IV catheter placement.
13. Reports difficulty fasting or consuming standardized and high fat meals.
14. Reports difficulty swallowing tablets or capsules whole.
15. Pregnant, lactating, breastfeeding, or intends to become pregnant over the course of the study.
16. Demonstrates a positive pregnancy screen.
17. Reports smoking or using tobacco products or is currently using nicotine products (patches, gums, etc.). Thirty (30) days abstinence was required.
18. Receipt of Oxycodone ARIR in a previous Inspirion Delivery Technologies, LLC study.

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

1 x 30 mg tablet of test product was given orally as a single dose with approximately 240 mL (8 fluid ounces) of room temperature water (Oxycodone ARIR 30 mg Tablets by Inspirion Delivery Technologies, LLC). One dose of test product was administered under fasted conditions and another dose of test product was administered under fed conditions. The lot number for test product was C005012.

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

1 x 30 mg tablet of reference product was given orally as a single dose with approximately 240 mL (8 fluid ounces) of room temperature water after an overnight fast of at least 10 hours (Roxicodone 30 mg Tablets). The lot number for reference product was A120033A. Naltrexone (1 x 50 mg tablet) was administered with 240 mL of water at approximately 12 hours (± 30 minutes) prior to oxycodone administration, within 1.5 (± 15 minutes) hour of oxycodone administration, and approximately 12 hours (± 30 minutes) after oxycodone administration. The lot numbers for naltrexone were 34007240A and N11835.

Duration of Treatment:

One dose at the beginning of each of 3 study periods separated by at least a 4-day washout period.

CRITERIA FOR EVALUATION:

Pharmacokinetic: Pharmacokinetic and statistical analyses were performed for oxycodone plasma data. Data from subjects in the Per Protocol population was included in the analyses of oxycodone plasma concentration data. The Per Protocol population was defined as all subjects who completed at least 2 treatment periods of the study, with 1 of those periods representing the results for Oxycodone ARIR fasted, provided adequate data for estimates of area under the plasma concentration versus time curve (AUC) and C_{max} pharmacokinetic parameters in both periods, and who did not have any major protocol deviations. Subjects who experienced emesis were treated according to the investigator's discretion.

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to part of the Dossier:**	**(For National Authority Use only)**
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

Pharmacokinetic parameters for oxycodone plasma concentration were calculated using standard non-compartmental approaches as indicated below:

AUC_{0-t}	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
AUC_{0-inf}	The area under the plasma concentration versus time curve from time 0 to infinity. AUC_{0-inf} is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable plasma concentration to the terminal rate constant.
AUC_{0-t}/AUC_{0-inf}	The ratio of AUC_{0-t} to AUC_{0-inf}
C_{max}	Maximum measured plasma concentration over the time span specified.
T_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
K_{el}	Apparent first-order terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis in the terminal log-linear phase (three or more non-zero plasma concentrations).
$T_{½}$	The apparent first-order terminal half-life was calculated as $0.693/K_{el}$.

No value of K_{el}, AUC_{0-inf} or $T_{½}$ was reported for cases that did not exhibit a terminal log-linear phase in the concentration versus time profile.

Safety: Safety measurements included clinical laboratory testing, physical examinations, measurements of vital signs and continuous pulse oximetry, electrocardiograms, and queried or spontaneously volunteered adverse events.

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

STATISTICAL METHODS:

Descriptive Statistics:

Descriptive statistics (mean, median, standard deviation, standard error of the mean, coefficient of variation, minimum, maximum, and number of subjects) were computed for each pharmacokinetic parameter and sampling time concentration for the Test and Reference products.

Analyses of Variance:

Analysis of variance (ANOVA) models of $\log_e$ transformed parameter values for the AUC_{0-t}, AUC_{0-inf}, and C_{max} parameters for the PP population are provided. The models included terms for sequence, group, sequence-by-group interaction, treatment, group-by-treatment interaction and period nested in group as fixed effects and subject nested within sequence-by-group as a random effect. Sequence, group, and sequence-by-group interaction were tested using subject nested within sequence-by-group as the error term. A 10% level of significance was used to test the sequence effect. The Group effect was defined as cohort 1, cohort 2, etc as subjects that were dosed on the same day. If the group-by-treatment interaction was not significant it was removed from the model. If the interaction was significant, an investigation was conducted and if a true interaction was implausible, the term was to be dropped from the statistical model. If any least squares (LS) means or LS mean differences were not estimable for treatment comparisons, the sequence effect would be dropped from the model if sequence was not significant and no evidence of carry-over was seen by reviewing pre-dose concentrations. Thus, if sequence was removed, the model would include terms for group, period nested in group, and treatment as fixed effects and subject nested in group as a random effect. Each ANOVA included calculation of LS means, the difference between adjusted formulation means, and the standard error associated with this difference. The statistical analyses were done using Proc Mixed in SAS.

In agreement with the two one-sided tests for bioequivalence, 90% confidence intervals (CIs) for the difference (test minus reference) in the mean between treatments were constructed for the $\log_e$-scale values of each parameter. CIs were based on the LS means estimation using the mean square error from the ANOVA models. The endpoints of the CIs were back-transformed to obtain CIs for the test-to-reference ratio of geometric means of each parameter on the original scale and expressed as a percentage.

The two comparisons presented are as follows:

- Oxycodone ARIR Fasted (test) vs. Roxicodone (reference);
- Oxycodone ARIR Fed (test) vs. Oxycodone ARIR Fasted (reference).

Analyses of T_{max} were provided comparing the medians by ranking the values within subject and an ANOVA model performed on the ranks including the same model terms as defined for AUC and C_{max}. The median and range was provided for T_{max} for each treatment, and the difference between

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to part of the Dossier:	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

medians for the two treatment comparisons of interest is provided.

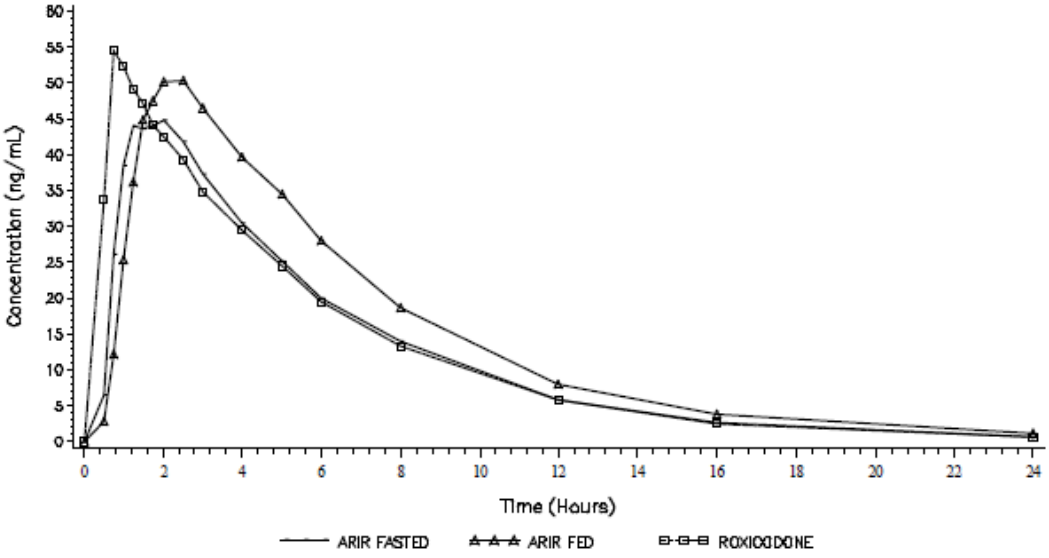
Analyses of K_{el} and $T_{1/2}$ are also provided including the same ANOVA terms as AUC and C_{max} and the LS means for each treatment, LS mean differences in each treatment comparison and the standard error associated with the LS mean are provided as well as the test-to-reference ratio of the treatment LS means.

SUMMARY AND CONCLUSIONS

Pharmacokinetic Results:

Mean plasma oxycodone concentration over time by treatment are shown in Figure 1.

Figure 1. Mean Plasma Oxycodone Concentrations (ng/mL) Time Profile by Treatment (PP Population, N=58)



Pairwise comparisons of Oxycodone ARIR 30 mg with Roxicodone 30 mg (both administered in the fasted state) indicated small, but statistically significant ($p < 0.0001$), differences in AUC_{0-t} and AUC_{0-inf} of approximately 4%. The 90% confidence intervals were within 80% to 125% (92% to 99% for AUC_{0-t} and 93% to 99% for AUC_{0-inf}), indicating bioequivalence in total exposure to oxycodone for Oxycodone ARIR and Roxicodone. For C_{max}, the maximum exposure for Oxycodone ARIR was 14% less than with Roxicodone. The difference in formulations was statistically

significant ($p = 0.0031$). The 90% confidence interval for C_{max} was 79% to 94%, which is slightly outside the 80% to 125% interval for bioequivalence. There was a statistically significant difference in ranked T_{max} ($p < 0.0001$), with median T_{max} being approximately 0.5 hour later for Oxycodone ARIR. There were 3% to 4% differences in K_{el} and $T_{1/2}$ that were statistically significant ($p = 0.0116$ and 0.0042, respectively).

Table 1. Summary of ANOVA Results for Comparison of Oxycodone ARIR and Roxicodone, Both Administered in the Fasted State (PP Population, N=58)

Parameter	O-ARIR Fasted[a] (Test)	Roxicodone Fasted[a] (Reference)	O-ARIR Fasted[b] (Test)	Roxicodone Fasted[b] (Reference)	LSM Ratio[c]	CV%[d]	90% Confidence Interval[e] Lower	Upper
$\ln(AUC_{0-t})$	5.5953	5.6409	269.2	281.7	95.6%	10.3%	92.5%	98.7%
$\ln(AUC_{0-inf})$	5.6128	5.6561	273.9	286.0	95.8%	10.1%	92.8%	98.9%
$\ln(C_{max})$	4.0096	4.1579	55.1	63.9	86.2%	28.9%	78.8%	94.3%
T_{max} (hr)	2.1035	1.4915	--	--	0.48 hr[f] difference	--	--	--
K_{el} (hr^{-1})	0.1869	0.1932	--	--	96.8%	--	--	--
$T_{1/2}$ (hr)	3.8140	3.6704	--	--	103.9%	--	--	--

[a] LS means of log transformed parameters for areas and peak concentrations. LS arithmetic means for other parameters.
[b] Geometric LS means (back-transformed)
[c] Ratio calculated as back-transformation of the LS mean difference for areas and peak concentrations, and as ratio of Test LS mean divided by Reference LS mean for other parameters.
[d] Estimated intra-subject coefficient of variation.
[e] Confidence interval on the Test-to-Reference ratio.
[f] Median difference.

Comparison of Oxycodone ARIR 30 mg administered in the fasted and fed states indicated 23% higher values for AUC_{0-t} and AUC_{0-inf} when Oxycodone ARIR was administered in the fed state (Table 2). The difference was statistically significant ($p < 0.0001$), and the 90% confidence limits, 119% - 127%, were slightly outside the 80% - 125% bioequivalence limits. In the fed state, C_{max} and median T_{max} were 15% higher and 0.5 hour longer, respectively, with the differences being significant ($p = 0.0031$ and < 0.0001 for C_{max} and T_{max}, respectively). There were 2% differences in K_{el} and $T_{1/2}$ that were statistically significant ($p = 0.0116$ and 0.0042, respectively), but not clinically meaningful.

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to part of the Dossier:**	**(For National Authority Use only)**
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		

Table 2. Summary of ANOVA Results for Comparison of Oxycodone ARIR Administered in the Fasted and Fed States (PP Population, N=58)

Parameter	O-ARIR Fed[a] (Test)	O-ARIR Fasted[a] (Reference)	O-ARIR Fed[b] (Test)	O-ARIR Fasted[b] (Reference)	LSM Ratio[c]	CV%[d]	90% Confidence Interval[e] Lower	Upper
$\ln(AUC_{0-t})$	5.8023	5.5953	331.1	269.2	123.0%	10.3%	119.1%	127.0%
$\ln(AUC_{0-inf})$	5.8236	5.6128	338.2	273.9	123.5%	10.1%	119.7%	127.3%
$\ln(C_{max})$	4.1796	4.0096	65.3	55.1	118.5%	28.9%	108.6%	129.4%
T_{max} (hr)	2.3397	2.1035	--	--	0.50 hr[f] difference	--	--	--
K_{el} (hr^{-1})	0.1829	0.1869	--	--	97.9%	--	--	--
$T_{1/2}$ (hr)	3.8972	3.8140	--	--	102.2%	--	--	--

[a] LS means of log transformed parameters for areas and peak concentrations. LS arithmetic means for other parameters.
[b] Geometric LS means (back-transformed)
[c] Ratio calculated as back-transformation of the LS mean difference for areas and peak concentrations, and as ratio of Test LS mean divided by Reference LS mean for other parameters.
[d] Estimated intra-subject coefficient of variation.
[e] Confidence interval on the Test-to-Reference ratio.
[f] Median difference.

Safety Results:

All 3 study treatments were well tolerated with all AEs being mild or moderate in severity and typical of opioid related AEs. The overall incidence of treatment-emergent AEs was higher in the Oxycodone ARIR (fasted) treatment than the Oxycodone ARIR (fed) and Roxicodone treatments (19.7% vs 17.2% and 11.3%). All adverse events were considered either mild (N = 74) or moderate (N = 11) in severity and all were resolved. For the treatment-emergent AEs considered by the investigator to be related to the study drug, the overall incidence of AEs was usually higher in the Oxycodone ARIR (fasted) treatment than the Oxycodone ARIR (fed) and Roxicodone treatments. No serious adverse events or deaths were reported during the study. No clinically significant laboratory results or abnormalities were identified at Screening. A review of vital signs did not reveal any potential abnormalities that should have been investigated as possible AEs.

Conclusions:

Based on fasted AUC_{0-t} and AUC_{0-inf}, Oxycodone ARIR 30 mg was bioequivalent to Roxicodone 30 mg. The small differences (<15%) for the other pharmacokinetic parameters including C_{max}, while statistically significant, are probably not clinically significant. With multiple dosing, AUC would be the most important parameter since pain relief is due to continued presence of oxycodone, and the results of this study indicate that efficacy would be equivalent for both Oxycodone ARIR and Roxicodone.

Name of Sponsor/Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to part of the Dossier:**	**(For National Authority Use only)**
Name of Finished Product: Oxycodone ARIR 30 mg Tablets		
Name of Active Ingredient: Oxycodone hydrochloride		
Values for AUC_{0-t} and AUC_{0-inf} were approximately 23% higher when Oxycodone ARIR 30 mg was administered in the fed state. In the fed state, C_{max} and T_{max} were 15% higher and 0.5 hour longer, respectively. Although there were differences due to administration with and without food, the differences were moderate (less 30%). The 30 mg Oxycodone ARIR tablet was well tolerated with adverse events typical of those seen with opioid drugs. Opioid-related adverse events were more common with Oxycodone ARIR when consumed in a fasted state compared with a fed state.		
Date of the Report: 09 December 2014		

4.2.2 Study O-ARIR-006

CLINICAL STUDY REPORT

Oxycodone ARIR Tablets, CII **Study No. O-ARIR-006** (b) (4)

ANALYTICAL LABORATORY: (b) (4)

BIOSTATISTICS:

STUDY DURATION: The time from first subject dosed to when the last subject completed was about 5 days.

STUDY TYPE: Open-label, single-dose, randomized, three-treatment, three-period, two-sequence, crossover study under fasted conditions.

OBJECTIVE: The objective of this pharmacokinetic study was to evaluate the dose proportionality of three test formulations of Oxycodone ARIR tablets (5 mg, 15 mg, and 30 mg) (oxycodone hydrochloride immediate-release tablet) CII (manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC) under fasted conditions in healthy adult subjects.

METHODOLOGY: This was an open-label, randomized, single-dose, three-treatment, three-period, two-sequence, crossover study to evaluate the pharmacokinetic dose proportionality of three test formulations containing oxycodone, under fasted conditions. The study was conducted with 54 (51 completing) healthy, adult subjects in accordance with Protocol No. O-ARIR-006 (Revision 1). In each period of the study, a single Oxycodone ARIR (oxycodone hydrochloride immediate-release) tablet, CII (5 mg, 15 mg, or 30 mg) was administered to subjects following an overnight fast of at least 10 hours. Test product A was Oxycodone ARIR tablets, 5 mg (oxycodone hydrochloride immediate-release tablet) CII (manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC), Test product B was Oxycodone ARIR tablets, 15 mg (oxycodone hydrochloride immediate-release tablet) CII (manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC), and Test product C was Oxycodone ARIR tablets, 30 mg (oxycodone hydrochloride immediate-release tablet) CII (manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC). All subjects received the 15 mg tablet in the first period of the study and then randomly received either the 5 mg tablet or the 30 mg tablet in the second and third study periods according to a two-sequence randomization schedule. Subjects were confined at the clinical facility from at least 13 hours before oxycodone dosing in Period I until after the 24-hour blood sample collection in Period III (about 120 hours after oxycodone dosing in Period I). The interval between doses was 2 days.

TEST PRODUCT C: Oxycodone ARIR Tablets, 30 mg (Oxycodone Hydrochloride Immediate-Release Tablet) CII
Manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC
Lot No.:C005012
Manufacture Date: 11/09/2012

NALTREXONE: Naltrexone Hydrochloride Tablets, USP 50 mg
Manufactured By: Barr Laboratories, Inc.;
Manufactured For: Teva Pharmaceuticals USA
Lot No.: 34011022A
Expiration Date: 08/2015

ROUTE OF ADMINISTRATION: Oral

DURATION OF TREATMENT: This was a randomized, single-dose, three-treatment, three-period, two-sequence crossover study. In each period of the study, a single Oxycodone ARIR (oxycodone hydrochloride immediate-release) tablet, CII (5 mg, 15 mg, or 30 mg) was administered to subjects following an overnight fast of at least 10 hours. All subjects received the 15 mg tablet in the first period of the study and then randomly received either the 5 mg tablet or the 30 mg tablet in the second and third study periods according to a two-sequence randomization schedule. Each dose was separated by a 2 day interval. The study began dosing on 09/05/14 and was completed on 09/10/14.

PRIMARY EFFICACY ANALYSIS: Not applicable.

SECONDARY EFFICACY ANALYSIS: Not applicable.

SAFETY ANALYSIS: Adverse events were collected and tabulated. No formal statistical analyses were performed.

STATISTICAL METHODS: Eighteen (18) blood samples were collected from each subject during each period of the study: up to 90 minutes before dosing (0 hr), then at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, and 24.0 hours post-dose for measurement of plasma oxycodone concentrations. The analytical data were used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $T_{½}$. The t in AUC_{0-t} is the time at which the last measurable concentration was recorded. The Statistical Analysis System (SAS®, Version 9.4) was used for all pharmacokinetic and statistical calculations.

Dose proportionality of log transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} values for oxycodone was evaluated from a power model. The model is:

$$\log(PKparameter_{ijk}) = \alpha' + \beta_i \log(\text{dose}_j) + S_i + P_k + \varepsilon'_{ijk},$$

where the subject effect is denoted S and the period effect P.

A two-stage approach was used whereby the model was first fit using an analysis of variance, including terms for dose and subject-by-dose interaction. The test of the subject-by-dose interaction assessed the departure from a common slope for each subject. If this interaction term was found not to be statistically significant, then a common slope model was used. Otherwise, the separate estimates of slope for each subject were summarized across subjects as a single sample to obtain estimates and 90% confidence intervals for the average value of β, the slope.

Dose proportionality was concluded based on the criteria that β fell within the range of 0.8000 to 1.2500 and the 90% confidence interval (CI) around β was within the pre-defined boundary limits defined by the equation below.

$$1 + [(\ln(\theta_L)/\ln(r)] < \beta < 1 + [(\ln(\theta_H)/\ln(r)]$$

$\theta_L = 0.8$, the standard lower limit for bioequivalence

$\theta_H = 1.25$, the standard upper limit for bioequivalence

r = ratio of highest to lowest dose

Applying the above values and r = 6 the acceptance limits for a 6-fold dose range is 0.8755, 1.1245.

SUMMARY OF RESULTS: Estimates of slope (β), and their associated 90% confidence intervals based on ANOVA (ln-transformed); and statistical comparisons are provided in Tables 2.1 to 2.3 for oxycodone.

Fifty-four (54) subjects were enrolled in the study, and all subjects were healthy adults. Fifty-four (54) subjects were dosed in Period I, 51 subjects were dosed in Periods II and III, and 51 subjects completed at least two periods of the study. Subjects 24, 45 and 47 did not complete at least two periods of the study; therefore, plasma samples from these participants were not sent for bioanalysis. The plasma samples from 51 subjects were assayed for oxycodone.

Subject 39, listed below, had a measurable pre-dose (0 hour sample) plasma concentration in Period III that was greater than 5% of the respective C_{max}. As per Section 5.7.1 of the protocol and recommended in the Attachment of the FDA Guidance for Industry *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Consideration*, March 2003, the data set (n = 1) for this subject was excluded from the primary statistical analysis for that period.

Subject	Period(s)	Treatment(s)	Pre-Dose Concentration (ng/mL)	C_{max} (ng/mL)	% Ratio Pre-dose/ C_{max}	Period Included in PK/Statistical Analysis
39	III	A	0.568	8.8	6.45455	No

Subject 39 had one dataset (Period I, Test B) for which the terminal elimination phase was not well characterized (adjusted R^2<0.8). Therefore, the terminal elimination rate constant (K_{el}) was not estimated, and no value for AUC_{0-inf} is reported for this dataset.

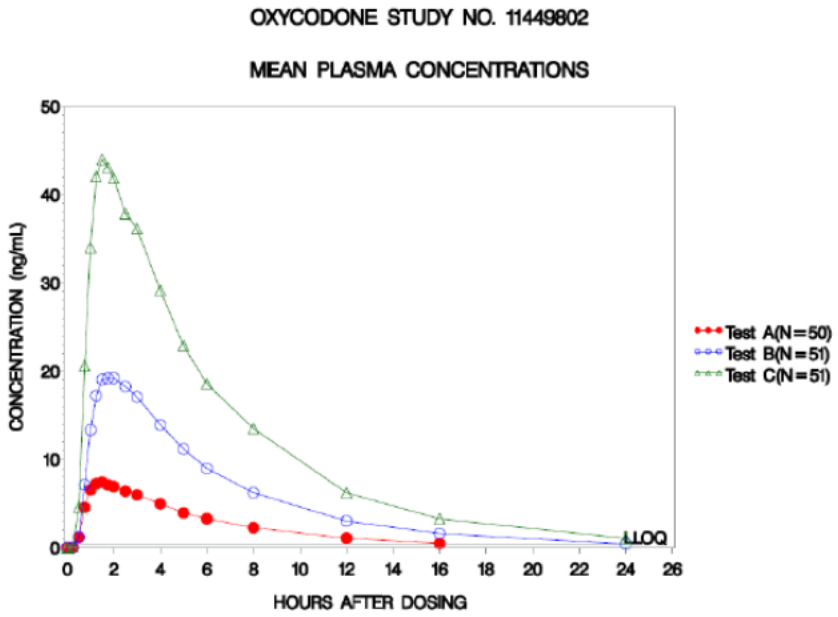
There are 152 sets of data (50 Test A, 51 Test B, 51 Test C) from 51 subjects eligible for pharmacokinetic and statistical analyses of oxycodone for this study.

For ln-transformed AUC_{0-t} and AUC_{0-inf}, the subject-by-dose interaction term was not statistically significant at the 5% significance level (p=0.9646 and p=0.8512, respectively) and the common slope model (without the subject-by-dose interaction term in the ANOVA model) was utilized as the primary analysis to evaluate dose proportionality for these parameters. These results are presented in Table 2.1.

For ln-transformed C_{max} the subject-by-dose interaction term was statistically significant at the 5% significance level (p=0.0002); therefore, the common slope model was not used as the primary analysis to evaluate dose proportionality for this parameter. The separate estimates of slope for each subject were summarized across subjects as a single sample to obtain the average value of β (the slope) and its associated 90% confidence interval. This method was used as the primary analysis for determining dose proportionality for C_{max}. These results are presented in Table 2.2.

Sensitivity analyses for C_{max} were performed assuming a common slope for all subjects, both with and without the subject-by-dose interaction term included in the ANOVA model, and the results are presented below in Table 2.3.

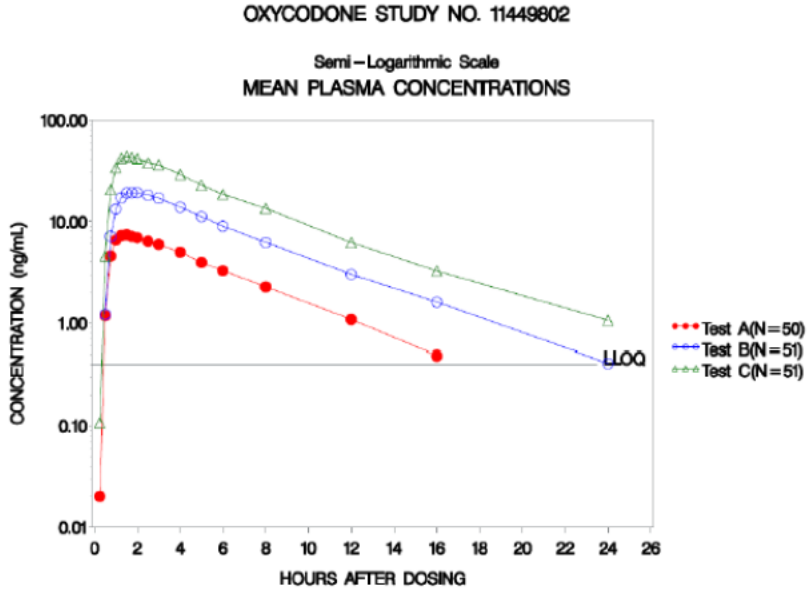
Figure 2.1 Mean Plasma Concentration versus Time Plot (Linear): Oxycodone



Mean concentration values below LLOQ (<0.397) in the terminal phase are not plotted

CLINICAL STUDY REPORT
Oxycodone ARIR Tablets, CII Study No. O-ARIR-006 (b) (4)

Figure 2.2 Mean Plasma Concentration versus Time Plot (Semi-Log): Oxycodone



Mean concentration values below LLOQ (<0.397) in the terminal phase are not plotted

Table 2.1 Summary of Ln-Transformed AUC Primary Study Results Based on Plasma Oxycodone Concentrations: Common Slope Model (Without Subject-by-Dose Interaction Term in the ANOVA Model)

Study No.: 11449802

Plasma PK and Dose Proportionality (DP) Parameters of Oxycodone

Parameter	Slope (ß)	90% Confidence Interval	ISCV(%)	P-value Sequence	Acceptance Limits	DP Outcome
AUC_{0-t} (ng·hr/mL)	1.0081	0.9888-1.0273	10.5	0.4220	0.8755-1.1245	Pass
$AUC_{0-\infty}$ (ng·hr/mL)	0.9799	0.9608-0.9991	10.4	0.3571	0.8755-1.1245	Pass

Table 2.2 Summary of Ln-Transformed C_{max} Primary Study Results Based on Plasma Oxycodone Concentrations: Separate Estimates of Slope for Each Subject

Study No.: 11449802

Plasma PK and Dose Proportionality (DP) Parameters of Oxycodone

Parameter	Slope (ß)	90% Confidence Interval	Acceptance Limits	DP Outcome
C_{max} (ng/mL)	0.9769	0.9514-1.0024	0.8755-1.1245	Pass

Table 2.3 Summary of Ln-Transformed C_{max} Study Results Based on Plasma Oxycodone Concentrations: Common Slope Model (With and Without Subject-by-Dose Interaction Term in the ANOVA Model) – Supplemental Analysis

Study No.: 11449802

Plasma PK and Dose Proportionality (DP) Parameters of Oxycodone

Parameter	Slope (ß)	90% Confidence Interval	ISCV(%)	P-value Sequence	Acceptance Limits	DP Outcome
With Subject-by-Dose Interaction Term						
C_{max} (ng/mL)	1.0055	0.9108-1.1001	15.5	0.8901	0.8755-1.1245	Pass
Without Subject-by-Dose Interaction Term						
C_{max} (ng/mL)	0.9752	0.9482-1.0023	14.7	0.2323	0.8755-1.1245	Pass

CLINICAL STUDY REPORT

Oxycodone ARIR Tablets, CII Study No. O-ARIR-006 (b) (4)

SAFETY: Fifty-nine (59) adverse events (8 Test A, 29 Test B, 20 Test C, 2 Naltrexone) were reported by 27 of the 54 subjects who participated in this study. Fifty-eight (58) reported adverse events were considered "mild" and all resolved spontaneously by study completion. One (1) adverse event was considered moderate severity and resolved spontaneously by study completion. The most frequently reported adverse event was nausea (Test B: 6 subjects; Test C: 1 subject). See Appendix 16.2.7 for a listing of adverse events by subject.

CONCLUSION: Based on the common slope model utilized for ln-transformed AUC_{0-t} and AUC_{0-inf} in the analysis of oxycodone, the slopes (1.0081 and 0.9799, respectively) fall within the range of 0.8000 to 1.2500 and the corresponding 90% confidence intervals are contained within the pre-defined acceptance range of 0.8755 to 1.1245. For ln-transformed C_{max}, based on the method of using separate estimates of slope for each subject, the average slope (0.9769) falls within the range of 0.8000 to 1.2500 and the corresponding 90% confidence interval is contained within the pre-defined acceptance range of 0.8755 to 1.1245. Therefore, the 5-, 15-, and 30-mg strengths of Oxycodone ARIR tablets (oxycodone hydrochloride immediate-release tablet) CII (manufactured by: Cerovene, Inc; Inspirion Delivery Technologies, LLC) have been demonstrated to be pharmacokinetically dose proportional.

There were no serious adverse events reported during this study.

4.2.3 Study O-ARIR-002

2. SYNOPSIS

Name of Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	**Volume:**	
Name of Active Ingredient: Oxycodone	**Page:**	
Title of Study: A Randomized, Double-Blind, Double-Dummy, Active- and Placebo-Controlled, Four-Way Crossover Study to Assess the Relative Abuse Potential of Intranasal Administration of Ground Oxycodone ARIR Tablets (Abuse Deterrent) versus an Equivalent Dose of Crushed Roxicodone® in Nondependent Recreational Opioid Users		
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: 10 February 2014 (first subject screened) **Study Completion Date:** 01 August 2014 (last subject contact)		**Phase of Development:** 1
Objectives: The primary objective was to assess the relative abuse potential of ground Oxycodone ARIR to crushed Roxicodone® when administered intranasally to nondependent, recreational opioid users with intranasal experience. The secondary objectives were: 1. To assess the abuse potential of intact Oxycodone ARIR administered orally relative to ground Oxycodone ARIR administered intranasally to nondependent, recreational opioid users. 2. To assess the abuse potential of ground and intact Oxycodone ARIR relative to placebo when administered intranasally and orally respectively to non-dependent, recreational opioid users. 3. To assess the relative bioavailability of oxycodone in plasma from ground and intact Oxycodone ARIR compared with one another and crushed Roxicodone when administered intranasally (ground Oxycodone ARIR and crushed Roxicodone) and orally (intact Oxycodone ARIR) to non-dependent, recreational opioid users. 4. To assess the safety of ground and intact Oxycodone ARIR compared with crushed Roxicodone and placebo following intranasal and oral administration in non-dependent, recreational opioid users.		
Methodology: This was a randomized, double-blind, double-dummy, active- and placebo-controlled, single-dose, four-way crossover, single-center study. The study consisted of a Screening Period, Qualification Period, Treatment Period and Follow-up Period. The Screening Period was completed as an outpatient visit. The Qualification Period consisted of a 4-night inpatient, double-blind qualifying session during which a Naloxone Challenge Test and Drug Discrimination Test were administered. Subjects who successfully passed the Naloxone Challenge Test and Drug Discrimination Test underwent a 72-hour washout period and then entered the Treatment Period. Subjects could remain in the clinical unit between the Qualification Period and Treatment Period or to facilitate subject schedules and clinical availability, could be discharged following the Qualification Period and return for the Treatment Period within 40 days. The		

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

Treatment Period consisted of an 11-night inpatient treatment session with a minimum 72-hour washout period between treatments. A post-treatment Follow-up Period was performed 7-10 days after the last dose of the Treatment Period and consisted of safety assessments.

Naloxone Challenge Test: During the Naloxone Challenge Test an initial dose of naloxone hydrochloride (HCl) 0.2 mg was administered by intravenous (IV) bolus. The subject was observed for signs or symptoms of withdrawal through assessment of the Clinical Opiate Withdrawal Scale (COWS) score. If no evidence of withdrawal occurred within 30 seconds as assessed by a COWS score <5, an additional 0.6 mg of naloxone HCl was administered by IV bolus. The subject was observed for 5 minutes for signs and symptoms of withdrawal through an additional assessment of the COWS. Subjects who did not experience symptoms of withdrawal, ie, were not opioid dependent, proceeded to the Drug Discrimination Test.

Drug Discrimination Test: Subjects remained as inpatients to complete the Drug Discrimination Test. In a 3-way crossover, 1:1:1 ratio, double-blind, randomized design, subjects received a single, intranasal dose each of Roxicodone (15 mg crushed tablet), Roxicodone (30 mg crushed tablet) and placebo powder (microcrystalline powder). Each dose was separated by at least a 24-hour period.

At completion of the Qualification Period, the study data from each subject were obtained and the Investigator made a blinded assessment as to whether the subject was able to distinguish active from placebo and between the high and low active dose and is eligible to continue in the trial. The non-blinded pharmacist confirmed the Investigators assessment by breaking the blind for the Drug Discrimination Test for each subject. Subjects were eligible for the Treatment Period, if they showed the following:

Drug Liking (bipolar VAS 0-100 point scale): The 0-100 point bipolar VAS is anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100):

- A minimum E_{max} score of 75 mm in response to Roxicodone 30 mg in the first 2 hours following dosing.
- A ≥20 mm difference in E_{max} between the crushed Roxicodone 30 mg and placebo in the first 2 hours following dosing.
- A ≥15 mm difference in E_{max} between the crushed Roxicodone 30 mg and crushed Roxicodone 15 mg in the first 2 hours following dosing.
- A crushed Roxicodone 15 mg E_{max} score that is greater by any amount (ie, > 0 mm) than placebo in the first 2 hours following dosing.
- A placebo response ≥ 40 and ≤ 60 mm during the first 2 hours following dosing.

Additional criteria included:

- The ability to tolerate crushed 15 mg Roxicodone and crushed Roxicodone 30 mg administered intranasally as assessed by no emesis within 2 hours following dosing, ability to insufflate the entire volume of crushed treatments, and as otherwise judged by the Investigator.

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

- Acceptable response to other study assessments, as determined by the Investigator.
- Ability to successfully complete the study as judged by the Investigator.

Treatment Period: Subjects received each of 4 treatments in a randomized, four-way crossover, double-blind, double-dummy, 1:1:1:1 ratio design.

Treatment	Tampered Intranasal Dose (Weight ≈ mg)	Intact Oral Dose
Treatment A – Placebo	Ground placebo Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
Treatment B – Crushed Roxicodone	Crushed 30 mg Roxicodone tablet (low volume, 100 mg)	Placebo tablet matching Oxycodone ARIR
Treatment C – Ground Oxycodone ARIR	Ground 30 mg Oxycodone ARIR tablet (high volume, 587 mg)	Placebo tablet matching Oxycodone ARIR
Treatment D – Intact Oxycodone ARIR	Placebo powder (microcrystalline cellulose) matching Roxicodone (low volume, 100 mg)	Intact 30 mg Oxycodone ARIR

The inpatient Treatment Period encompassed an 11-night stay for dosing, followed with a minimum 72-hour washout separating each treatment.

After completion of the Treatment Period, subjects returned in 7-10 days as an outpatient, to complete a 1-day Follow-up visit.

Number of Subjects (Planned and Analyzed):

Planned: A sufficient amount of subjects were screened to complete at least 28 subjects in the Treatment Period.

Analyzed: Of 214 subjects who entered the study and underwent the Naloxone Challenge Test, all 214 subjects passed the Naloxone Challenge Test. Three subjects withdrew from the study following the Naloxone Challenge Test. Of the 211 subjects who entered the Drug Discrimination Test, 180 subjects were withdrawn from the study prior to the Treatment Phase (158 subjects failed the Drug Discrimination Test; 11 experienced emesis within 2 hours of dosing in the Drug Discrimination Test and were withdrawn due to protocol-mandated criterion; 5 withdrew consent; 3 experienced AEs other than emesis; 2 had protocol deviations; and 1 was non-compliant and withdrawn due to Investigator decision.). Of the 31 subjects who entered the Treatment Period, 29 completed the study (2 subjects withdrew consent during the Treatment Phase, both citing family emergencies). An additional 5 subjects participated in the Naloxone Challenge Test, Drug Discrimination Test, and first treatment period cohort (08 March 2014) and completed the trial prior to FDA feedback, which changed the method of study drug dosing. Data from these 5 subjects are not included in the analysis, but are included in a subgroup analysis and in the listings.

Diagnosis and Main Criteria for Inclusion: Experienced opioid users, male or female, between

Name of Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	**Volume:**	
Name of Active Ingredient: Oxycodone	**Page:**	

18-55 years of age, inclusive, who were not currently physically dependent on opioids comprised the study. Subjects were opioid users who were not physically dependent on opioids based on DSM-IV-TR criteria and a Naloxone Challenge Test but had experience in the use of opioids for non-therapeutic purposes on at least 10 occasions within the previous year and at least once in the 12 weeks prior to the Screening Period. Subjects had experience with intranasal drug administration, defined as intranasal use on at least 3 occasions within the past year and at least once in the 12 weeks prior to the Screening Period. Main exclusion criteria for the study included previous or current participation in treatment for substance-related disorders (except nicotine and caffeine); history or presence of drug or alcohol dependence excluding nicotine and caffeine; and positive urine drug screen (UDS) at Screening, the Qualification Period, or any admission for the Treatment Periods (subjects testing positive for opiates, amphetamines, cocaine, and benzodiazepines at Screening could be enrolled if the UDS at check-in to the Qualification Period was negative).

Test Product, Dose and Mode of Administration:

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

- Naloxone HCl Injection, USP, 0.4 mg/mL, 1 mL single dose vial: Code NDC #00409-1215-01, Lot#39-540-EV.
- Naloxone HCl Injection, USP, 0.4 mg/mL, 10 mL multidose vial: Code NDC #00409-1219-01, Lot#22-148-EV and Lot #30-080-EV.

Drug Discrimination Test: Single dose of 15 mg crushed Roxicodone, 30 mg crushed Roxicodone, and crushed placebo administered intranasally with doses separated by 24 hours.

- Roxicodone, USP, 15 mg: NDC #23635-0581-10, Lot #AI30033A.
- Roxicodone, USP, 30 mg: NDC #23635-0582-10, Lot #G130386A.
- Placebo powder (microcrystalline powder). Lot #PN13825901.

Treatment Period: Oxycodone ARIR is an IR oral formulation of oxycodone. Oxycodone ARIR was provided at a tablet dose strength of 30 mg; the dose of Oxycodone ARIR used was 1 tablet crushed and administered intranasally or 1 tablet swallowed intact. Lot #C005012.

Duration of Treatment: The Treatment Period consisted of 4 treatments. During the treatment period subjects received a single treatment with 1 of the 4 study drugs; study periods were separated by at least 72 hours.

Reference Therapy, Dose and Mode of Administration:

Treatment Period:

- Roxicodone, USP, 30 mg is an IR oral formulation of oxycodone. Roxicodone was provided at a tablet dose strength of 30 mg; the dose of Roxicodone was 1 tablet crushed and administered intranasally: NDC #23635-0582-10, Lot #F13036A. (Of note, 1 subject [Subject 01-072] who participated in the 08 March 2014 cohort and was not included in any of the analyses received crushed Roxicodone 30 mg during the Treatment Period from the Roxicodone 30 mg lot used in the Drug Discrimination Test.)

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

- Matching placebo to the Oxycodone ARIR tablet was provided as identical to the Oxycodone ARIR tablet but contained no oxycodone; the dose of placebo tablet was 1 tablet ground and administered intranasally and 1 tablet swallowed intact. Lot #PB02013.
- Placebo power (microcrystalline cellulose) was used to match Roxicodone. Lot #PN13825901.

Criteria for Evaluation:

Pharmacokinetic Assessments: Pharmacokinetic parameters were calculated for plasma oxycodone concentration data using non-compartmental methods. The following PK parameters were calculated:

- $AUC_{0-0.5h}$: Area under the plasma concentration vs time curve from 0 to 30 minutes.
- AUC_{0-1h}: Area under the plasma concentration vs time curve from 0 to 1 hour.
- AUC_{1-2h}: Area under the plasma concentration vs time curve from 1 to 2 hour.
- AUC_{0-2h}: Area under the plasma concentration vs time curve from 0 to 2 hours.
- AUC_{0-8h}: Area under the plasma concentration vs time curve from 0 to 8 hours.
- AUC_{0-12h}: Area under the plasma concentration vs time curve from 0 to 12 hours.
- AUC_{0-24h}: Area under the plasma concentration vs time curve from 0 to 24 hours.
- AUC_{0-t}: Area under the plasma concentration vs time curve from 0 to last measurable concentration.
- $AUC_{0-\infty}$: Area under the plasma concentration vs time curve extrapolated to infinity. It is calculated as the sum of AUC_{0-t} plus C_t/k_e where C_t is the last measurable plasma concentration and k_e is the elimination rate constant.
- Percent extrapolation for $AUC_{0-\infty}$: $(AUC_{\infty}-AUC_{0-t})/AUC_{0-\infty}$.
- C_{max}: Maximum measured plasma concentration occurring at T_{max}.
- T_{max}: Time to achieve maximum plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
- $t_{½}$: Apparent first-order terminal elimination half-life were calculated as $\ln(2)/k_e$ $(0.693/k_e)$.
- k_e: First order rate constant associated with the terminal (log-linear) portion of the curve.

Pharmacodynamic Assessments: Abuse potential was assessed during the Treatment Period using the following instruments:

- Drug Liking measured using the Bipolar Visual Analog Scale (VAS) – Primary Parameter of Interest.
- Drug Effects Questionnaire (DEQ; VAS for Any Drug Effects, Good Effects, High, Bad Effects, Sick, Nausea, Sleepy and Dizzy)
- Ease of Snorting measured using VAS
- Overall Drug Liking measured using VAS
- Take Drug Again measured using VAS
- Pupillometry
- Nasal Effect Asssessments (intranasal irritation, burning, need to blow nose, runny nose/nasal

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

discharge, facial pain/pressure, and nasal congestion) – using Likert Scale (Exploratory).

The following PD endpoints were calculated for Drug Liking, DEQ, and pupillometry:

- Peak effect (E_{max})
- Time of peak effect (TE_{max})
- Area under the effect curve to 0.5 hour ($AUE_{0-0.5h}$)
- Area under the effect curve to 1 hour (AUE_{0-1h})
- Area under the effect curve from 1 to 2 hour (AUE_{1-2h})
- Area under the effect curve to 2 hours (AUE_{0-2h})
- Area under the effect curve to 8 hours (AUE_{0-8h})
- Area under the effect curve to 12 hours (AUE_{0-12h})
- Area under the effect curve to 24 hours (AUE_{0-24h})
- Area under the effect curve to time of observed maximum plasma oxycodone concentration (AUE_{0-Tmax}).

Safety Assessments: Safety was evaluated based on adverse events (AEs), Nasal Effects Assessment, clinical laboratory assessments, vital signs, 12-lead electrocardiogram, and physical examinations.

Statistical Methods:

Sample Size Determination: It was planned that 36 subjects would be enrolled into the Treatment period and assuming an approximately 22% dropout from the Treatment period it was estimated that 28 subjects would complete the study. Enough subjects were to be enrolled to ensure 28 completed subjects. Sample size considerations were based on providing an adequate number of subjects to show the reduction of abuse potential as measured by Drug Liking (bi-polar VAS) E_{max} between crushed Roxicodone and ground Oxycodone ARIR at approximately 90% power. The sample size estimations were made using a Type I error rate at α=0.05 (two-sided), a paired means test and correlation of 0.1. Assuming a difference of 17.5 mm and a 20 standard deviation, 28 subjects were adequate to detect a difference with at least 90% power. Accounting for adjustments for non-normality using a $\log_e$ transformation is expected to reduce the power by 3% to 10%, but a power of 80% is still considered acceptable for this study. In addition, a sample size of 28 subjects provides 90% power to show the test-to-reference ratio confidence interval for $\log_e$-transformed pharmacokinetic parameters is within 80.00% and 125.00% bioequivalence criteria if the ratio is within 5% of the reference and the coefficient of variation (CV) is not larger than 31%, assuming a 0.5 correlation.

General Considerations: Unless otherwise specified, all significance testing was 2-tailed using α = 0.05. Tests were declared statistically significant if the calculated α was $\leq$ 0.05. The pairwise comparison between crushed Roxicodone and the placebo control for Drug Liking E_{max} was used for validation of the appropriateness of the positive control, and a significant result for this test was required to proceed with further testing.

Analysis Populations:

Qualification Safety Population: This population comprised all subjects who received at least one

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

dose of study medication, which included all medication prespecified in the protocol, naloxone, Roxicodone, Oxycodone ARIR, and their matching placebos, during the Qualification Period, excluding subjects in the 08 March 2014 cohort. This population will be analyzed as treated.

Safety Population: This population comprised all randomized subjects who received at least one dose of study medication during the Treatment Period, excluding subjects in the 08 March 2014 cohort. This population was analyzed as treated.

Pharmacodynamic (PD) Population: This population comprised all subjects who completed all 4 treatment periods with at least one PD assessment in each treatment period, excluding subjects in the 08 March 2014 cohort. This was the primary population for PD analyses and was analyzed as randomized.

Intent-to-Treat (ITT) Population: This population comprised all subjects in the Safety Population with at least one assessment during the Treatment Period, excluding subjects in the 08 March 2014 cohort. This was the secondary population for PD analyses and was analyzed as randomized.

Pharmacokinetic (PK) Population: This population comprised all subjects with any available C_{max} and AUC data, excluding subjects in the 08 March 2014 cohort.

Pharmacokinetic Analyses: Oxycodone pharmacokinetic parameters for each treatment were calculated for the PK population. Relative bioavailability of oxycodone was evaluated for the partial AUC values, $AUC_{0\text{-}0.5h}$ to $AUC_{0\text{-}24h}$, and also for $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$, and C_{max} by calculating the ratio of the geometric means and the 90% confidence interval of the log-transformed values.[3] The SAS mixed effect linear model procedure (PROC MIXED) was used to construct the ANOVA models. The models included terms for sequence, period, and treatment as fixed effects and subject nested within sequences as a random effect. The endpoints of the CIs were back-transformed to obtain CIs for the test-to-reference ratio of geometric means of each parameter on the original scale. Least-squares geometric means for C_{max} and AUCs were provided for each treatment and each treatment comparison along with 90% CIs for the treatment comparisons. The comparisons included ground Oxycodone ARIR versus crushed Roxicodone (C to B), intact Oxycodone ARIR versus crushed Roxicodone (D to B), and ground Oxycodone ARIR versus intact Oxycodone ARIR (C to D).

In addition, ANOVA models were also used for the non-transformed pharmacokinetic parameters, $t_{1/2}$, k_e, and T_{max} as the dependent variables with sequence, period, and treatment as fixed effects and subjects nested within sequences as a random effect. The same comparisons listed for AUC and C_{max} were provided.

Pharmacodynamic Analyses: The primary comparison was crushed Roxicodone to ground Oxycodone ARIR 30 mg administered intranasally (Treatment B vs Treatment C) for Drug Liking. All other comparisons were secondary. The comparison of crushed Roxicodone to ground placebo was made to confirm study validity.

Each of the 6 comparisons were made:

- Treatment B vs Treatment C – Primary Comparison
- Treatment B vs Treatment A – Validity Comparison

- Treatment C vs Treatment A
- Treatment D vs Treatment A
- Treatment B vs Treatment D
- Treatment C vs Treatment D

The PD endpoints or applicable time points were analyzed using a mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. Least-squares (LS) means along with 95% confidence intervals (CIs) were provided for each treatment. LS mean differences along with 95% CIs were provided for the pairwise treatment comparisons defined above. The parameters or time points defined above were analyzed as defined in separate models.

- Drug Liking – All PD parameters analyzed
- DEQ VAS (for Any Drug Effects, Good Effects, High, Bad Effects, Sick, Nausea, Sleepy and Dizzy) – All PD parameters analyzed
- Ease of Snorting – 5 minute time point analyzed
- Overall Drug Liking – E_{max} analyzed
- Take Drug Again – E_{max} analyzed
- Nasal Effects Assessment – All PD parameters analyzed
- Pupillometry – All PD parameters analyzed

The distribution of the residuals from each parametric model was examined to determine whether substantial departures from normality were apparent using the Shapiro Wilk test (tested at α=0.01). If the residuals were not normally distributed, a non-parametric analysis (the same procedure after ranked transformation) was applied. In addition, the Hodges-Lehmann estimate for the differences in two paired medians was provided and the 95% CI of the median difference.

The percent reduction in peak effect (E_{max}) was calculated for Drug Liking. The percent reduction was calculated as:

$$reduction = \frac{c_i - t_i}{abs(c_i - p_i)} \times 100\%, i = 1, 2, \ldots, n,$$

where c_i, t_i, and p_i were the E_{max} values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the ith subject; and n is the sample size. Additionally, the percent reduction was calculated for the comparison between crushed Roxicodone and intact Oxycodone ARIR (B vs D), and between intact Oxycodone ARIR and ground Oxycodone ARIR (D vs C). The percent reduction was calculated if data for the active control, test product, and placebo were available. In cases where one of those values was not available percent reduction was set to missing. In cases where the control was equal to placebo, the percent reduction was set to the largest percentage observed in the study (negative or positive depending on the difference of c_i-t_i) for that comparison; if no large percentage existed (or it was less than 101%) then the percent reduction was set to 101% (and set

to negative or positive depending on the difference of c_i-t_i), a large value so that the subject was still counted in the analysis and would not markedly impact the descriptive statistical results. An exploratory calculation was also be presented for percent reduction in E_{max} for Drug Liking as:

$$\%reduction = \begin{cases} \frac{c_i - t_i}{c_i - 50} \times \left(1 - \frac{p_i - 50}{50}\right) 100\%, i = 1, 2, \dots, n, \ \ if\ p_i > 55; \\ \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n, \ \ if\ p_i \leq 55. \end{cases}$$

where c_i, t_i, and p_i were the E_{max} values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the *i*th subject; and *n* was the sample size. Additionally, the percent reduction was calculated for the comparison between crushed Roxicodone and intact Oxycodone ARIR (B vs D), and between intact Oxycodone ARIR and ground Oxycodone ARIR (D vs C). The percent reduction was calculated if data for the active control, test product, and placebo were available. In cases where one of those values was not available percent reduction was set to missing. In cases where the control was equal to 50, the percent reduction was set to the largest percentage observed in the study (negative or positive depending on the difference of c_i-t_i) for that comparison; if no large percentage existed (or it was less than 101%) then the percent reduction was set to 101% (and set to negative or positive depending on the difference of c_i-t_i), a large value so that the subject was still counted in the analysis and would not markedly impact the descriptive statistical results.

Percent reduction for partial AUE PD parameters for Drug Liking was also calculated using the following formula:

$$\%reduction = \frac{c_i - t_i}{abs(c_i - p_i)} \times 100\%, i = 1, 2, \dots, n$$

where c_i, t_i, and p_i were the AUE values for the control (crushed Roxicodone [Treatment B]), test (ground Oxycodone ARIR [Treatment C]), and Placebo (Treatment A) respectively; from the *i*th subject; and *n* was the sample size. Additionally, the percent reduction was calculated for the comparison between crushed Roxicodone and intact Oxycodone ARIR (B vs D), and between intact Oxycodone ARIR and ground Oxycodone ARIR (D vs C). The percent reduction was calculated if data for the active control, test product, and placebo were available. In cases where the control was equal to placebo, the percent reduction was set to the largest percentage observed in the study (negative or positive depending on the difference of c_i-t_i) for that comparison; if no large percentage existed (or it was less than 101%) then the percent reduction was set to 101% (and set to negative or positive depending on the difference of c_i-t_i), a large value so that the subject was still counted in the analysis and would not markedly impact the descriptive statistical results.

Name of Company: Inspirion Delivery Technologies, LLC	**Individual Study Table Referring to Part of the Dossier**	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	**Volume:**	
Name of Active Ingredient: Oxycodone	**Page:**	

The percent reduction in peak effect (E_{max}) and AUE parameters was calculated for Drug Liking and summarized using descriptive statistics (n, arithmetic mean, SD, median, minimum, maximum, first and third quartile limits, and CV). In addition, the number and percent of subjects was provided for the categories of no change (% change of -1 to 1%), reduction (% change > 1%), or increase (% change < -1%). Categories incremented by 10% (ie, 0% to 10% reduction, 10% to 20% reduction, etc. up to >100% reduction, as well as 0% t-o 10% increase, 10% to 20% increase, etc. up to >100% increase) was provided for each comparison, crushed Roxicodone to ground Oxycodone ARIR, crushed Roxicodone to intact Oxycodone ARIR, and intact Oxycodone ARIR to ground Oxycodone ARIR.

The percent reduction in Drug Liking E_{max} and AUE parameters was used to define a responder at several cutoffs. A responder was defined as a subject who had at least a prespecified level of reduction, where levels from 10% to 90% in 10% increments were presented. The number and percent of subjects considered as responders and non-responders were presented for each comparison, crushed Roxicodone to ground Oxycodone ARIR, crushed Roxicodone to intact Oxycodone ARIR, and intact Oxycodone ARIR to ground Oxycodone ARIR. The binominal test of proportions was utilized to test the null hypothesis that 50% or fewer subjects were responders.

A contingency table of the percent reduction in Drug Liking E_{max} of the comparison of crushed Roxicodone relative to ground Oxycodone ARIR percent reduction calculation vs Roxicodone E_{max} categories was presented. The 10% categories were used for the percent reduction and Roxicodone E_{max} were split into categories incremented by 10, ie, 51-60, 61-70, 71-80, 81-90, and 91-100, where additional range categories are included prior to 51 if needed.

A graph for the percent reduction profile was provided for each comparison for Drug Liking E_{max}, where the y-axis contained the cumulative percentage of subjects and the x-axis contained the percent reduction in 10% increments of >0, ≥10, up to >100.

Pharmacokinetic/Pharmacodynamic Analyses: Correlation plots for drug liking that show the regression lines and R2 using logarithmic regression and the means of each parameter and treatment are provided for the following: E_{max} vs Abuse Quotient (C_{max}/T_{max}); E_{max} vs C_{max}; E_{max} vs T_{max}; AUE [0-0.5h, 0-1h, 0-2h, 0-8h, 0-12h, and 0-24h] vs Abuse Quotient (C_{max}/T_{max}); AUE [0-0.5h, 0-1h, 0-2h, 0-8h, 0-12h, and 0-24h] vs C_{max}; AUE [0-0.5h, 0-1h, 0-2h, 0-8h, 0-12h, and 0-24h] vs T_{max}; and AUE vs AUC [0-0.5h, 0-1h, 0-2h, 0-8h, 0-12h, and 0-24h].

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

SUMMARY – CONCLUSIONS

Pharmacokinetic Results

For the comparison of ground Oxycodone ARIR versus crushed Roxicodone, both administered intranasally, the overall exposure to oxycodone was similar. However, C_{max} was lower and occurred later for ground Oxycodone ARIR. The partial AUC values from $AUC_{0\text{-}0.5h}$ to $AUC_{0\text{-}12h}$ were not contained within 80% to 125%, indicating significantly lower exposure to oxycodone during the first 12 hours after administration of ground Oxycodone ARIR, and the differences were most marked for $AUC_{0\text{-}0.5h}$ and $AUC_{0\text{-}1h}$, with LS mean ratio values indicating that within the first 0.5 hour and first 1.0 hour after intranasal administration, the amounts of oxycodone from ground Oxycodone ARIR were only 38% and 50%, respectively, of the amounts of oxycodone from crushed Roxicodone.

For the comparison of ground Oxycodone ARIR administered intranasally versus oral Oxycodone ARIR, the AUC intervals for $AUC_{0\text{-}8h}$ through $AUC_{0\text{-}\infty}$ were bioequivalent or nearly bioequivalent. C_{max} for intranasal administration was 70% of the C_{max} for intact oral administration, T_{max} was 0.84 hours longer, and the LS mean ratios for $AUC_{0\text{-}0.5h}$, $AUC_{0\text{-}1h}$, and $AUC_{0\text{-}2h}$ were 275.00, 96.63, and 75.91, respectively, reflecting distinct differences in the plasma concentration profiles. Overall, the results indicate that after the initial brief lag for orally administered Oxycodone ARIR there is a lower maximum oxycodone concentration, a later T_{max}, and lower exposure from 0 to 2 hours for intranasally administered ground Oxycodone ARIR.

For the comparison of oral Oxycodone ARIR versus crushed Roxicodone administered intranasally, the 90%CI was within 80% to 125% for only C_{max}. The T_{max} was slightly shorter for oral Oxycodone ARIR. The exposures to oxycodone for the first 0.5 and 1.0 hours after oral Oxycodone ARIR were only 14% and 52%, respectively, of the exposures after intranasal administration of crushed Roxicodone. For partial and full AUC values from $AUC_{0\text{-}2}$h to $AUC_{0\text{-}\infty}$, the LS mean ratios were similar, ranging from 80.49 to 83.60, indicating a consistent approximately 20% difference in bioequivalence from 2 hours onward.

Small, not clinically significant, differences of 18% or less were noted in k_e and $t_{1/2}$ between treatments.

Pharmacodynamic Results

Study Validity: Study validity was confirmed with the comparison of LS mean for E_{max} for Drug Liking being significantly higher for crushed Roxicodone than crushed placebo (82.67 vs 53.16 mm, $p < 0.0001$). The differences between crushed Roxicodone and crushed placebo were also statistically significantly higher ($p < 0.0001$) for all AUE intervals. That is, subjects were successfully able to distinguish between placebo and 30 mg Roxicodone.

Table 2-1 presents an overall summary of the results for the primary endpoint, Drug Liking, as well as each of the secondary endpoints for the primary comparison of the study, crushed Roxicodone vs ground Oxycodone ARIR. Drug Liking E_{max} was significantly lower for ground Oxycodone ARIR than for crushed Roxicodone ($p < 0.0001$) as were all other PD parameters. TE_{max} was

significantly longer for ground Oxycodone ARIR than crushed Roxicodone with the LS median difference of -0.52 hours ($p = 0.0148$). Results for the secondary endpoints supported results for Drug Liking. Overall Drug Liking and Take Drug Again Assessment both suggested significantly lower abuse potential for ground Oxycodone ARIR than crushed Roxicodone ($p < 0.0001$). Each of the positive effects for the DEQ, that is Any Effects, Good Effects, and High were significantly lower for ground Oxycodone ARIR than crushed Roxicodone; no differences were seen in the negative DEQ effects including Sleepy, Bad Effects, Sick, Nausea, and Dizzy. Ground Oxycodone ARIR was significantly more difficult to snort than crushed Roxicodone ($p < 0.0001$) and produced significantly worse nasal effects for all 5 assessments (Irritation, Burning, Runny Nose/Nasal Discharge, Facial Pain/Pressure, and Nasal Congestion; $p < 0.0001$).

Most subjects had a reduction in Drug Liking E_{max} with ground Oxycodone ARIR compared with crushed Roxicodone. Twenty-five subjects (86.2%) had a reduction in Drug Liking for ground Oxycodone ARIR compared with crushed Roxicodone. Twenty subjects (69%) had at least a 30% reduction on E_{max} and 31% had at least a 50% reduction. Findings for AUE parameters were consistent with findings for E_{max}. Most subjects also had a reduction in Drug Liking AUE parameters especially at the time points within 2 hours (93.1% to 96.6% of subjects had a reduction in Drug Liking $AUE_{0\text{-}0.5h}$, $AUE_{0\text{-}1h}$, and $AUE_{0\text{-}2h}$), but also from 8 through 24 hours (72.4% through 75.9% of subjects had a reduction in Drug Liking $AUE_{0\text{-}8h}$, $AUE_{0\text{-}12h}$, and $AUE_{0\text{-}24h}$).

Table 2-1: Least Square Means and P-Values for the Primary Endpoint, Drug Liking, and Secondary Endpoints for the Primary Comparison, Crushed Roxicodone vs Ground Oxycodone ARIR (PD Population, N = 29)

Endpoint	Crushed Roxicodone vs Ground Oxycodone ARIR
Drug Liking (0 through 100 bipolar VAS)	
E_{max}[a] (mm)	82.67 vs 70.74, $p < 0.0001$
$AUE_{0\text{-}0.5h}$ (h·mm)[b]	6.89 vs 1.03, $p < 0.0001$
$AUE_{0\text{-}1h}$ (h·mm)[a]	19.20 vs 6.09, $p < 0.0001$
$AUE_{1\text{-}2h}$ (h·mm)[a]	23.71 vs 14.87, $p = 0.0004$
$AUE_{0\text{-}2h}$ (h·mm)[a]	42.91 vs 20.96, $p < 0.0001$
$AUE_{0\text{-}8h}$ (h·mm)[b]	113.17 vs 65.02, $p = 0.0005$
$AUE_{0\text{-}12h}$ (h·mm)[b]	121.53 vs 66.17, $p = 0.0008$
$AUE_{0\text{-}24h}$ (h·mm)[b]	127.49 vs 58.06, $p = 0.0007$
$AUE_{0\text{-}Tmax}$ (h·mm)[b]	36.89 vs 20.67, $p = 0.0063$
TE_{max} (h)[b]	1.58 vs 2.29, $p = 0.0148$
% subjects with reduction in Drug Liking with ground Oxycodone ARIR	86.2%
Overall Drug Liking[b] (mm)	80.78 vs 63.84, $p < 0.0001$
Take Drug Again Assessment[b] (mm)	82.07 vs 61.83, $p < 0.0001$

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

Drug Effects Questionnaire (E_{max}) (0 through 100 unipolar VAS) (mm)	
Any Effects[a]	64.55 vs 38.26, $p < 0.0001$
Good Effects[a]	68.15 vs 39.97, $p < 0.0001$
High[a]	66.10 vs 38.34, $p < 0.0001$
Sleepy[a]	30.76 vs 23.21, $p = 0.1010$
Bad Effects[b]	12.73 vs 15.73, $p = 0.4688$
Sick[b]	7.73 vs 6.39, $p = 0.9077$
Nausea[b]	7.36 vs 6.38, $p = 0.8909$
Dizzy[b]	9.78 vs 6.86, $p = 0.6269$
Ease of Snorting[b] (0 = very easy through 100 = very difficult unipolar VAS) (mm)	9.03 vs 72.06, $p < 0.0001$
Nasal Effects Assessment (4-pt Likert scale 0=none through 3=severe)	
Irritation[a]	0.35 vs 1.55, $p < 0.0001$
Burning[a]	0.41 vs 1.39, $p < 0.0001$
Runny Nose/Nasal Discharge[a]	0.35 vs 1.17, $p < 0.0001$
Facial Pain/Pressure[a]	0.21 vs 1.30, $p < 0.0001$
Nasal Congestion[a]	0.42 vs 1.86, $p < 0.0001$
Pupillometry[a] (mm)	2.84 vs 2.46, $p = 0.0575$

[a] Normality assumption test met, no change to final analysis.
[b] Normality assumption not met, rank transformation applied to the data.

Intact Oxycodone ARIR vs Ground Oxycodone ARIR. The E_{max} for Drug Liking was significantly ($p < 0.0001$) lower for ground Oxycodone ARIR than intact Oxycodone ARIR. For percent reduction in peak effect between ground and intact Oxycodone ARIR, 75.9% of subjects had a reduction in Drug Liking E_{max} with ground Oxycodone ARIR compared with intact Oxycodone ARIR. E_{max} for Overall Drug Liking and Take Drug Again Assessment was lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0014$). For DEQ Any Effects, E_{max} and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0268$); exceptions were $AUE_{0\text{-}0.5h}$ ($p = 0.0738$) and $AUE_{0\text{-}1h}$ ($p = 0.5640$). For Good Effects, E_{max} and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0276$). For High, E_{max} and most AUE parameters were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR ($p \leq 0.0358$). For Bad Effects, $AUE_{0\text{-}05h}$ and $AUE_{0\text{-}Tmax}$ values for were significantly lower for ground Oxycodone ARIR than intact Oxycodone ARIR and T_{max} was significantly longer for intact Oxycodone ARIR than ground Oxycodone ARIR. No other significant treatment differences were observed for any of the negative DEQ Effects including Sleepy, Sick, Nausea, and Dizzy.

Crushed Roxicodone vs Intact Oxycodone ARIR. E_{max} for Drug Liking was not significantly

different (p = 0.5301) for crushed Roxicodone and intact Oxycodone ARIR. Slightly more than half of subjects (55.2%) had a reduction in Drug Liking E_{max} with intact Oxycodone ARIR compared with crushed Roxicodone. However, for $AUE_{0\text{-}0.5h}$ and $AUE_{0\text{-}1h}$, 93.1% of subjects had a reduced Drug Liking for intact Oxycodone ARIR compared with crushed Roxicodone. All AUE parameters at later time points also showed reduced Drug Liking in ≥ 69.0% of subjects with intact Oxycodone compared with crushed Roxicodone. E_{max} for Overall Drug Liking and Take Drug Again Assessment was not significantly different between intact Oxycodone ARIR and crushed Roxicodone. For DEQ Any Effects, neither E_{max} (p = 0.7328) nor any of the AUE parameters from 8 hours through 24 hours (p ≥ 0.0709) were significantly different. For Good Effects, E_{max} was not significantly different (p = 0.4474), however, $AUE_{0\text{-}0.5h}$, $AUE_{0\text{-}1h}$, $AUE_{0\text{-}2h}$, $AUE_{0\text{-}8h}$, and $AUE_{0\text{-}Tmax}$ were significantly lower for intact Oxycodone ARIR than crushed Roxicodone (p ≤ 0.0489). For High, E_{max} was not significantly different (p = 0.9536), however, $AUE_{0\text{-}0.5h}$, $AUE_{0\text{-}1h}$, $AUE_{0\text{-}2h}$, and $AUE_{0\text{-}Tmax}$ were significantly lower for intact Oxycodone ARIR than crushed Roxicodone (p ≤ 0.0071). For the negative DEQ Effects of Sleepy, Bad Effects, Sick, Nausea, and Dizzy there were no significant treatment differences except that T_{max} for Bad Effects was significantly longer for intact Oxycodone ARIR than crushed Roxicodone (p = 0.0172).

Pharmacodynamic/Pharmacokinetic Results

Correlation between E_{max} and C_{max} was excellent (R^2 = 0.9660) and the correlation between E_{max} and AQ (R^2 = 0.8820) and AUC vs AUE at 0-0.5h (R^2 = 0.8737), 0-1h (R^2 = 0.9874) and 0-2h (R^2 = 0.9752) was very strong to excellent. These correlations suggest that a higher C_{max}, AQ, and AUE (at earlier time points) may be associated with greater Drug Liking. Less correlation was observed between E_{max} and T_{max} (R^2 = 0.5314) and little correlation was observed for AUE vs T_{max} at all time intervals (R^2 values for all time intervals ≤ 0.2157). Correlation between AUE and C_{max} was weakest at the early time points (ie, R^2 for $AUE_{0\text{-}0.5h}$ vs C_{max} = 0.1267), but increased as the time interval increased (ie, R^2 for $AUE_{0\text{-}24h}$ vs C_{max} = 0.7538). Correlation between AUE and AQ showed the same pattern as for AUE and C_{max} with the weakest correlation observed at the early time points (ie, R^2 for $AUE_{0\text{-}0.5h}$ vs AQ = 0.0389), but increased as the time interval increased (ie, R^2 for $AUE_{0\text{-}24h}$ vs AQ = 0.6001). The weaker correlation observed with T_{max} and AUE vs AQ and AUE vs C_{max} at the earlier time points may have been a reflection of the initial brief lag observed in the plasma concentrations seen following orally administered Oxycodone ARIR.

Safety

During the Treatment Period, the most frequently occurring AE was generalised pruritus (occurring in 23.3% of subjects with crushed Roxicodone, 12.9% of subjects with intact Oxycodone ARIR, 6.7% of subjects with ground Oxycodone ARIR, and 0% of subjects with placebo). Nausea (13.3%, 6.5%, 13.3%, and 0%, respectively) and vomiting (6.7%, 6.5%, 10.0%, and 0%, respectively) were the only other AEs that occurred in more than 10% of subjects with any treatment. Each of these AEs are common opioid-related AEs.

Most AEs that occurred during the Treatment Period were considered by the Investigator to be treatment-related. No subjects were withdrawn from the study during the Treatment Period due to AEs. All AEs that occurred during the Treatment Period and all AEs during the Qualification

Name of Company: Inspirion Delivery Technologies, LLC	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Oxycodone ARIR Tablets 30 mg	Volume:	
Name of Active Ingredient: Oxycodone	Page:	

Period except nausea in 1 subject were mild or moderate in severity. Fifteen subjects discontinued from the study during the Qualification Phase due to an AE: 11 experienced emesis within 2 hours of dosing during the Drug Discrimination Test and were withdrawn from the study according to protocol-mandated criterion; and 4 subjects were withdrawn due to adverse events including elevated liver enzymes (prior to participating in the Drug Discrimination Test), back pain, headache, and epitaxis. There were no SAEs or deaths.

Although few subjects reported AEs in the Respiratory, Thoracic, and Mediastinal System Organ Class, subjects reported significantly more severe nasal effects with the ground Oxycodone ARIR treatments (active and placebo) than with crushed Roxicodone, on the Nasal Effect Assessment that included irritation, burning, runny nose/nasal discharge, facial pain/pressure, and nasal congestion. The difficulties subjects had with insufflation of the Oxycodone ARIR tablets may be desirable for this type of product as this may serve as a nuisance to an abuser who wants to snort the drug. The occurrence of adverse nasal effects may be desirable in terms of reducing the desirability for tampering this product.

Conclusions

This study demonstrates that physical manipulation and intranasal administration of Oxycodone ARIR resulted in significantly less drug liking relative to crushed intranasal Roxicodone and intact oral Oxycodone ARIR. This decrease in drug liking suggests that the intranasal abuse potential of Oxycodone ARIR is significantly lower than the reference listed drug Roxicodone and provides a disincentive for abusers to manipulate and snort Oxycodone ARIR. The pharmacokinetic results supported the pharmacodynamic/abuse potential results with substantially lower peak plasma concentrations (C_{max}) in the ground intranasal Oxycodone ARIR arm compared with the crushed intranasal Roxicodone and intact Oxycodone ARIR arms. The finding that crushed intranasal Oxycodone ARIR compared to intact Oxycodone ARIR taken orally produced significantly lower E_{max} in Drug Liking demonstrates the ability of the abuse-deterrent features of the ARIR technology to alter the intended release profile when manipulated and may deter abusers from intentional manipulation and abuse via illicit routes of administration.

Date of the Report: 05 December 2014

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

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WEI QIU
03/22/2017

YUN XU
03/22/2017

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	**209777**	**Brand Name**	**Oxycodone ARIR tablet**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Oxycodone Hydrochloride Tablet**
Medical Division	**DAAAP**	**Drug Class**	**Opioid analgesic**
OCP Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Management of moderate to severe pain where use of an opioid analgesic is appropriate**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Oral tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission	**Oct 21, 2016**	**Route of Administration**	**oral**
Estimated Due Date of OCP Review	**March 21, 2017**	**Sponsor**	**Inspirion Delivery Sciences, Inc.**
Medical Division Due Date	**March 28, 2017**	**Priority Classification**	**Priority**
PDUFA Due Date	**April 21, 2017**		

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	**x**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**x**	**2**		**O-ARIR-003 and O-ARIR-006**
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		**(1)**		**O-ARIR-006**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -	**x**	**1**		**O-ARIR-002 –drug liking**
Phase 2:				
Phase 3:				
PK/PD -				

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

Phase 1 and/or 2, proof of concept:				
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)**		**O-ARIR-003**
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**(1)**		**Same as above**
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				
Literature References				
Total Number of Studies		**3**		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Sponsor stated that the final formulation was used in support of the NDA
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable,	x			

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

	does it have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			Sponsor submitted plasma concentration time dataset as well as pharmacokinetic parameter datasets in SAS transport format.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	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	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x		Division agreed that oxycodone ARIR does not trigger the requirements of PREA and pediatric studies will not be required in response to the request for waiver of pediatric studies, previously submitted to IND 105951 in SN 0003 (January 17, 2014).
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet	x			

	basic requirements for approvability of this product?				
19	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___

Request for OSI inspection on Study O-ARIR-003 was sent out on November 28, 2016 and OSI review is requested by March 14, 2017.

Title of the Study O-ARIR-003: A 3-Way Crossover Relative Bioavailability Study of Oxycodone ARIR (Abuse Resistant Immediate Release) 30 mg Tablets in Fasted State Versus Roxicodone 30 mg Tablets in Fasted State Versus Oxycodone ARIR 30 mg Tablets in Fed State

Study Clinical Site: CRI Lifetree
3838 South 700 East, Suite 202
Salt Lake City, UT 84106
T: 801-269-8200

Study Analytical Site: (b) (4)
(b) (4)

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

This NDA submission is fillable from clinical pharmacology perspective.

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

For study O-ARIR-003, provide comparison of partial AUCs (point estimate and 90% confidential intervals) at every time points from time 0 to 4h (e.g., AUC0-1 h, AUC0-1.5 h, AUC0-2h, AUC0-3h, and AUC0-4h, etc.) between test and the reference treatments. Provide justification that the delayed Tmax of your product under fast condition compared to Roxicodone will not affect efficacy, especially onset of action of your product.

For a 505(b)(2) application, you need to establish a scientific bridge or link to the listed drug Roxicodone. You propose to establish a link to 30 mg strength Roxicodone by conducting a BE study with your 30 mg strength product. In addition, you conducted a dose proportionality study across 5, 15 and 30 mg of your product. However, there is no direct BE study at 5 and 15 mg strengths between your proposed product and Roxicodone. Provide justification how a link to Roxicodone is established with these two strengths.

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

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Inspirion Delivery Sciences, Inc (IDS) submitted a 505(b) (2) NDA for Oxycodone ARIR Tablet, 5, 15, and 30 mg for the management of moderate to severe pain where use of an opioid analgesic is appropriate.

Sponsor plans to rely on the agency's finding of the safety and efficacy of oxycodone as reflected in the approved product of Roxicodone® (NDA 21-011), an immediate-release tablet.

The PK studies supporting this NDA include a pivotal comparative BA/BE study O-ARIR-003 and a dose proportionality study O-ARIR-006. Study O-ARIR-003 showed that oxycodone AUC values met BE criteria. The lower limit of the 90% CI for Cmax (i.e., 78.8%) slightly missed the 80% criterion to establish BE. Median Tmax value is prolonged from 1 h to 1.8 h. Agency agreed previously that considering that a lower limit of the confidence interval for Cmax of 78.8% is very close to the 80% lower limit criterion, and that the proposed drug product will be used in titration, the slightly missed lower limit of the confidence interval for Cmax and the slightly longer Tmax will not be anticipated to affect the efficacy of the proposed drug product to a substantial degree.

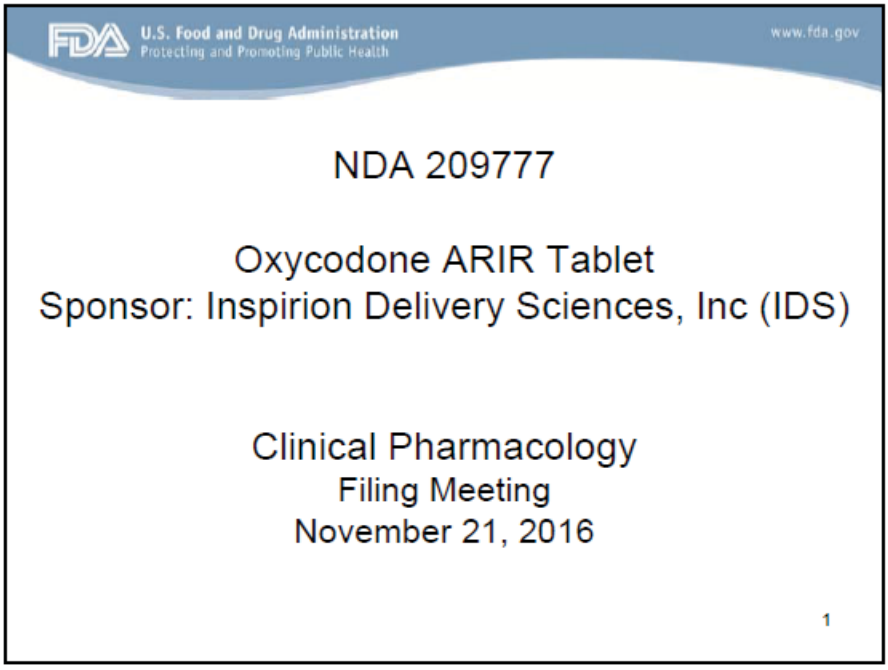
Preliminary analysis on the early exposure (e.g., partial AUCs) for the comparison of the proposed product and listed drug product under fasting condition suggested that the early exposures for the proposed product are lower than the listed drug product.

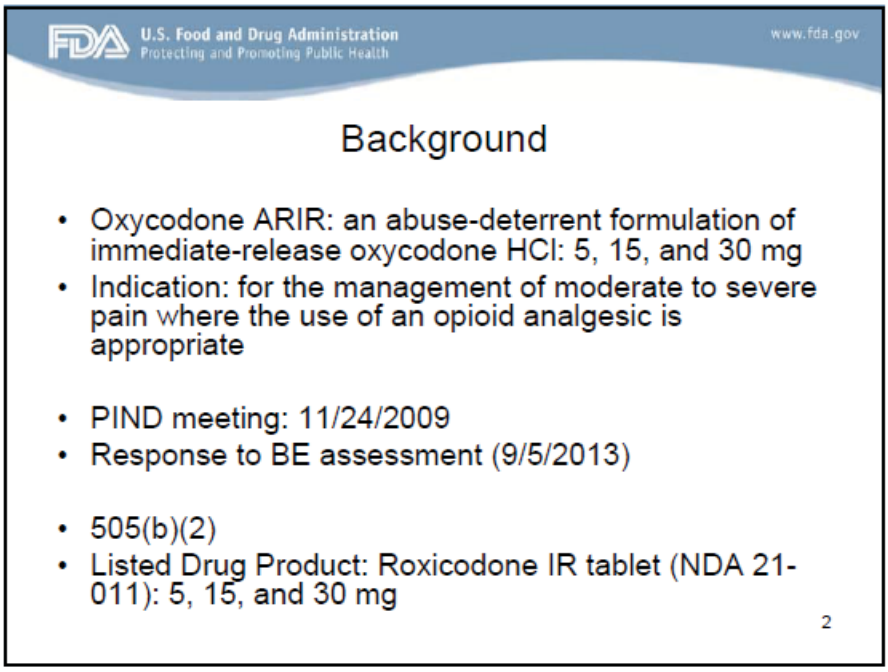
	Oxycodone ARIR Fast	**Roxicodone Fast**	**Ratio (Test/Reference)**
AUC0-1 h (ng.h/mL)	13.8 (11.4)	32.6 (21.0)	0.42
AUC0-2 h (ng.h/mL)	57.2 (25.8)	79.6 (32)	0.72
AUC0-3 h (ng.h/mL)	98.6 (31)	119 (36.7)	0.83

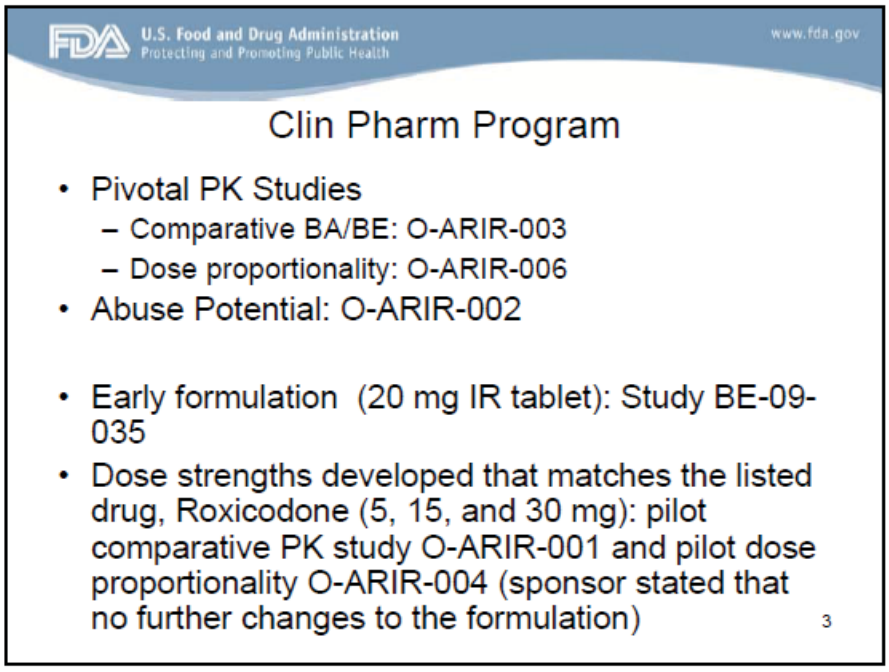
In the same study, it was shown that high-fat meal increased AUC by 23% and increased Cmax by 18%. Median Tmax values were not affected. This food effect is similar to the food effect for Roxicodone. According to Roxicodone labeling, AUC is increased by 27%, Cmax is not changed, and Tmax is delayed from 1.25 h to 2.54 h.

In Study O-ARIR-006, it was demonstrated that the proposed product is dose proportional over the range of 5 to 30 mg. See more details in the attached filing slides.

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



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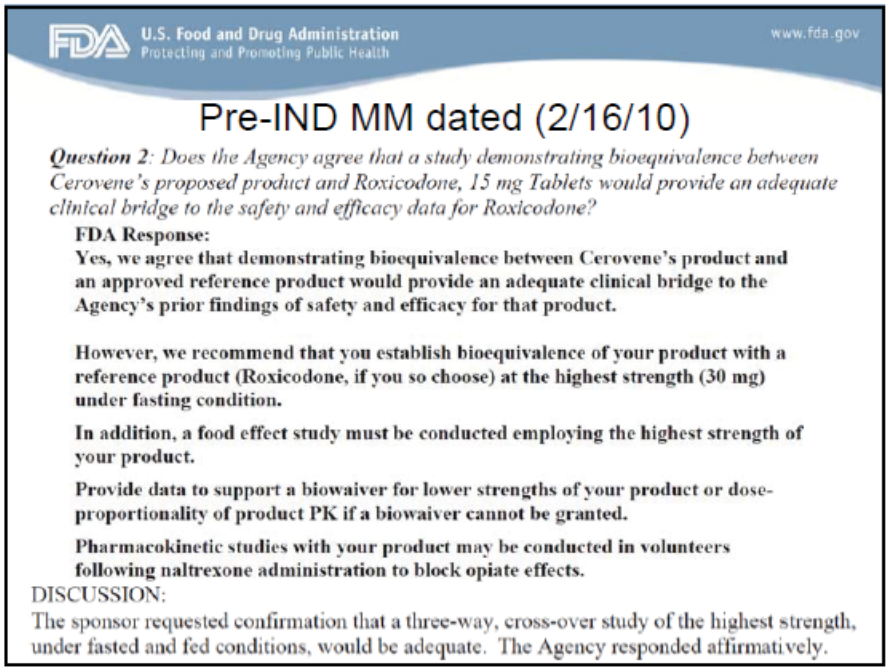
Clin Pharm Program
• Pivotal PK Studies
– Comparative BA/BE: O-ARIR-003
– Dose proportionality: O-ARIR-006
• Abuse Potential: O-ARIR-002
• Early formulation (20 mg IR tablet): Study BE-09-035
• Dose strengths developed that matches the listed drug, Roxicodone (5, 15, and 30 mg): pilot comparative PK study O-ARIR-001 and pilot dose proportionality O-ARIR-004 (sponsor stated that no further changes to the formulation)
3


U.S. Food and Drug Administration
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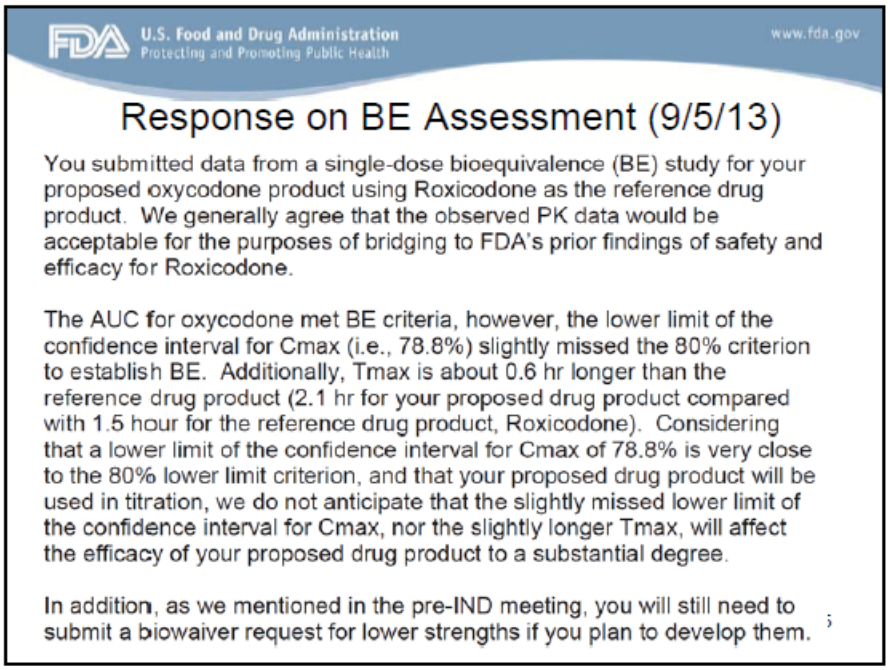
Pre-IND MM dated (2/16/10)
Question 2: Does the Agency agree that a study demonstrating bioequivalence between Cerovene's proposed product and Roxicodone, 15 mg Tablets would provide an adequate clinical bridge to the safety and efficacy data for Roxicodone?
FDA Response:
Yes, we agree that demonstrating bioequivalence between Cerovene's product and an approved reference product would provide an adequate clinical bridge to the Agency's prior findings of safety and efficacy for that product.
However, we recommend that you establish bioequivalence of your product with a reference product (Roxicodone, if you so choose) at the highest strength (30 mg) under fasting condition.
In addition, a food effect study must be conducted employing the highest strength of your product.
Provide data to support a biowaiver for lower strengths of your product or dose-proportionality of product PK if a biowaiver cannot be granted.
Pharmacokinetic studies with your product may be conducted in volunteers following naltrexone administration to block opiate effects.
DISCUSSION:
The sponsor requested confirmation that a three-way, cross-over study of the highest strength, under fasted and fed conditions, would be adequate. The Agency responded affirmatively.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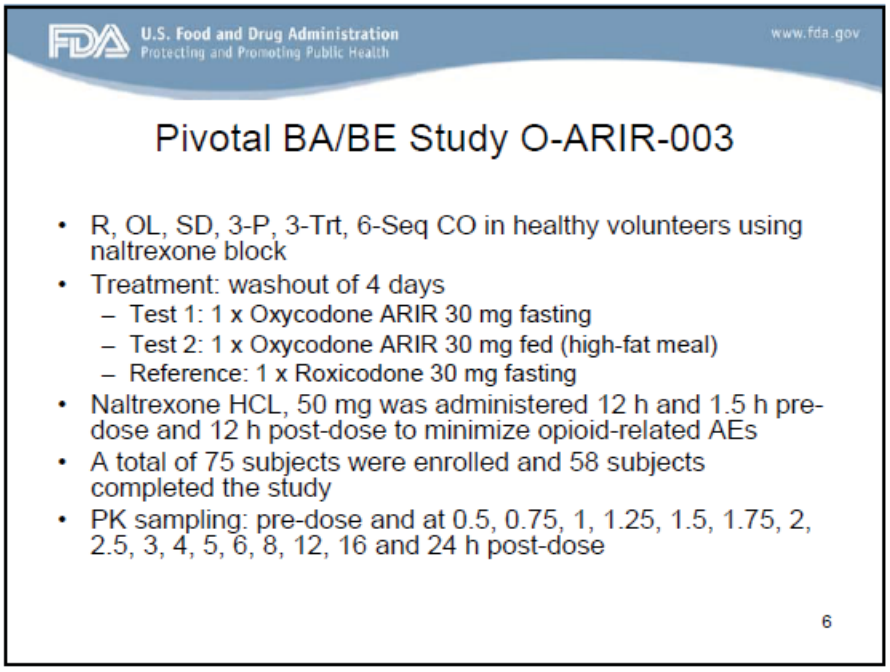
Response on BE Assessment (9/5/13)
You submitted data from a single-dose bioequivalence (BE) study for your proposed oxycodone product using Roxicodone as the reference drug product. We generally agree that the observed PK data would be acceptable for the purposes of bridging to FDA's prior findings of safety and efficacy for Roxicodone.
The AUC for oxycodone met BE criteria, however, the lower limit of the confidence interval for Cmax (i.e., 78.8%) slightly missed the 80% criterion to establish BE. Additionally, Tmax is about 0.6 hr longer than the reference drug product (2.1 hr for your proposed drug product compared with 1.5 hour for the reference drug product, Roxicodone). Considering that a lower limit of the confidence interval for Cmax of 78.8% is very close to the 80% lower limit criterion, and that your proposed drug product will be used in titration, we do not anticipate that the slightly missed lower limit of the confidence interval for Cmax, nor the slightly longer Tmax, will affect the efficacy of your proposed drug product to a substantial degree.
In addition, as we mentioned in the pre-IND meeting, you will still need to submit a biowaiver request for lower strengths if you plan to develop them.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Pivotal BA/BE Study O-ARIR-003
• R, OL, SD, 3-P, 3-Trt, 6-Seq CO in healthy volunteers using naltrexone block
• Treatment: washout of 4 days
– Test 1: 1 x Oxycodone ARIR 30 mg fasting
– Test 2: 1 x Oxycodone ARIR 30 mg fed (high-fat meal)
– Reference: 1 x Roxicodone 30 mg fasting
• Naltrexone HCL, 50 mg was administered 12 h and 1.5 h pre-dose and 12 h post-dose to minimize opioid-related AEs
• A total of 75 subjects were enrolled and 58 subjects completed the study
• PK sampling: pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 h post-dose
6

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Figure 11.4.1-1: Mean Plasma Oxycodone Concentrations (ng/mL) Time Profile by Treatment (PP Population, N=58)

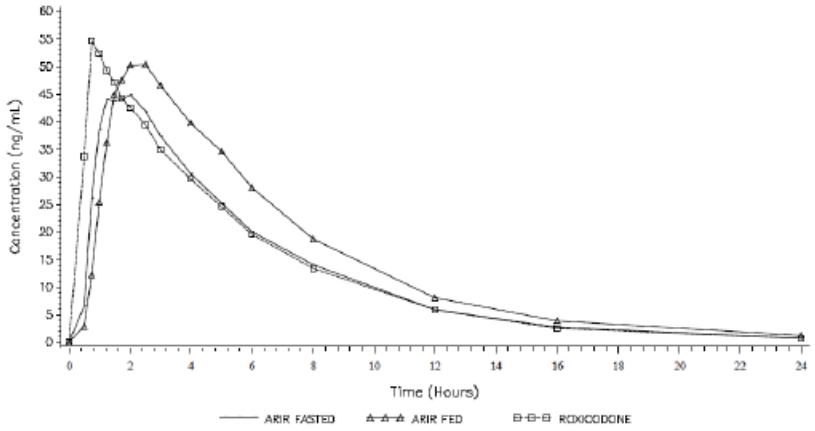

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Table 11.4.1-1: Pharmacokinetic Parameters for Oxycodone ARIR Fasted versus Roxicodone Fasted (PP Population, N=58)

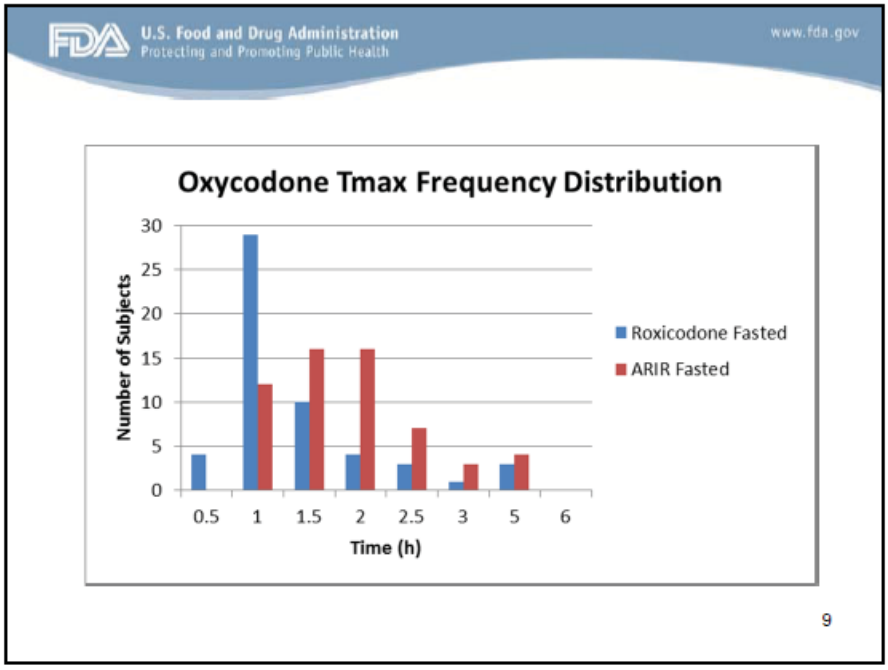
Parameter	Unit	O-ARIR (Fasted)[a] (N = 58)	Roxicodone (Fasted)[a] (N = 54)
AUC_{0-t}	ng•hr/mL	287.4 (22.9)	300.3 (22.9)
AUC_{0-inf}	ng•hr/mL	292.7 (23.0)	305.4 (22.9)
C_{max}	ng/mL	57.8 (31.1)	67.7 (35.1)
T_{max}	hr	1.8 (0.8, 5.0)[b]	1.0 (0.5, 5.0)[b]
K_{el}	hr^{-1}	0.1871 (0.1112, 0.2840)[c]	0.1932 (0.1322, 0.3117)[c]
$T_{1/2}$	hr	3.8 (2.4, 6.2)[c]	3.7 (2.2, 5.2)[c]

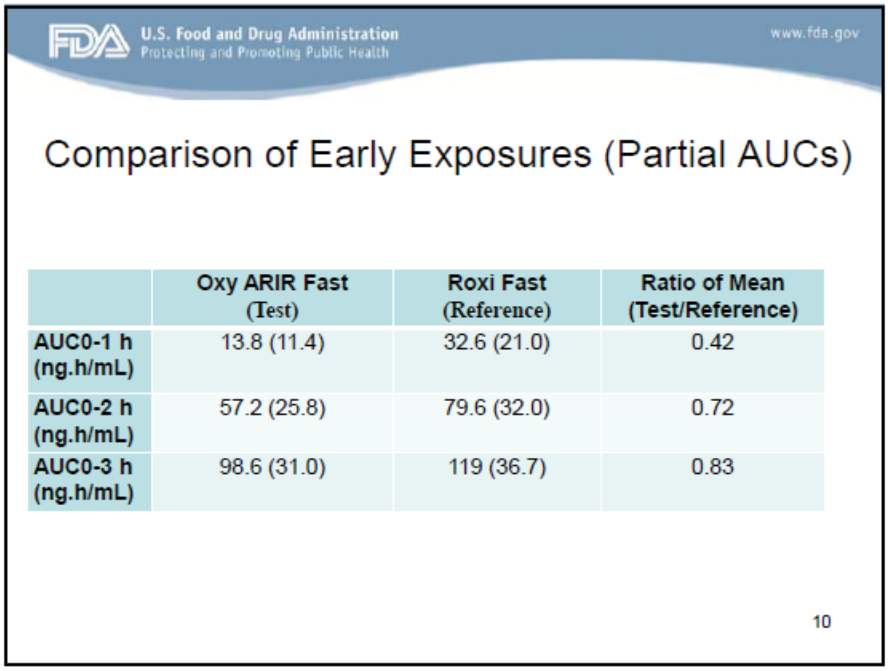
Table 11.4.1-2: Summary of ANOVA Results for Comparison of Oxycodone ARIR and Roxicodone, Both Administered in the Fasted State (PP Population, N=58)

Parameter	O-ARIR Fasted[a] (Test)	Roxicodone Fasted[a] (Reference)	O-ARIR Fasted[b] (Test)	Roxicodone Fasted[b] (Reference)	LSM Ratio[c]	CV%[d]	90% Confidence Interval[e] Lower	Upper
$ln(AUC_{0-t})$	5.5953	5.6409	269.2	281.7	95.6%	10.3%	92.5%	98.7%
$ln(AUC_{0-inf})$	5.6128	5.6561	273.9	286.0	95.8%	10.1%	92.8%	98.9%
$ln(C_{max})$	4.0096	4.1579	55.1	63.9	86.2%	28.9%	78.8%	94.3%
T_{max} (hr)	2.1035	1.4915	--	--	0.48 hr[f] difference	--	--	--
K_{el} (hr^{-1})	0.1869	0.1932	--	--	96.8%	--	--	--
$T_{1/2}$ (hr)	3.8140	3.6704	--	--	103.9%	--	--	--

- Equivalent AUC, 14% lower Cmax (lower end of 90%CI slightly less than 80%)
- Median Tmax values prolonged from 1.0 h to 1.8 h

8





	Oxy ARIR Fast (Test)	Roxi Fast (Reference)	Ratio of Mean (Test/Reference)
AUC0-1 h (ng.h/mL)	13.8 (11.4)	32.6 (21.0)	0.42
AUC0-2 h (ng.h/mL)	57.2 (25.8)	79.6 (32.0)	0.72
AUC0-3 h (ng.h/mL)	98.6 (31.0)	119 (36.7)	0.83

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Table 11.4.1-3: Pharmacokinetic Parameters for Oxycodone ARIR Fed versus Oxycodone ARIR Fasted (PP Population, N=58)

Parameter	Unit	O-ARIR (Fed)[a] (N = 58)	O-ARIR (Fasted)[a] (N = 58)
AUC_{0-t}	ng•hr/mL	354.2 (23.3%)	287.4 (22.9%)
AUC_{0-inf}	ng•hr/mL	361.9 (23.9%)	292.7 (23.0%)
C_{max}	ng/mL	68.0 (29.5%)	57.8 (31.1%)
T_{max}	hr	2.0 (1.0, 6.1)[b]	1.8 (0.8, 5.0)[b]
K_{el}	hr^{-1}	0.1824 (0.1204, 0.2810)[c]	0.1871 (0.1112, 0.2840)[c]
$T_{1/2}$	hr	3.9 (2.5, 5.8)[c]	3.8 (2.4, 6.2)[c]

Table 11.4.1-4: Summary of ANOVA Results for Comparison of Oxycodone ARIR Administered in the Fasted and Fed States (PP Population, N=58)

Parameter	O-ARIR Fed[a] (Test)	O-ARIR Fasted[a] (Reference)	O-ARIR Fed[b] (Test)	O-ARIR Fasted[b] (Reference)	LSM Ratio[c]	CV%[d]	90% Confidence Interval[c] Lower	Upper
$\ln(AUC_{0-t})$	5.8023	5.5953	331.1	269.2	123.0%	10.3%	119.1%	127.0%
$\ln(AUC_{0-inf})$	5.8236	5.6128	338.2	273.9	123.5%	10.1%	119.7%	127.4%
$\ln(C_{max})$	4.1796	4.0096	65.3	55.1	118.5%	28.9%	108.6%	129.4%
T_{max} (hr)	2.3397	2.1035	--	--	0.50 hr difference	--	--	--
K_{el} (hr^{-1})	0.1829	0.1869	--	--	97.9%	--	--	--
$T_{1/2}$ (hr)	3.8972	3.8140	--	--	102.2%	--	--	--

- Food increased AUC by 23%, Cmax 18%, similar median Tmax
- Roxicodone PI: AUC increased by 27% and no change in Cmax, Tmax delayed from 1.25 to 2.54 h
- In two other NDAs for IR Oxy: median Tmax for Roxicodone under fed condition was about 1.5 h

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Pivotal Dose Proportionality Study O-ARIR-006

- R, OL, SD, 3-P, 3-Trt CO in healthy volunteers under fasting condition using naltrexone block
- Treatment: washout of 2 days
  - 1 x Oxycodone ARIR 15 mg (Period 1), then randomized to receive
  - 1 x Oxycodone ARIR 5 mg
  - Or 1 x Oxycodone ARIR 30 mg
- Naltrexone HCL, 50 mg was administered 12 h and 1.5 h pre-dose and 12 h post-dose to minimize opioid-related AEs
- A total of 54 subjects were enrolled and 51 subjects completed the study

12

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Table 2.7.1-10.	Summary of Dose Proportionality Analysis for Log-Transformed Oxycodone AUC_{0-t} and $AUC_{0-\infty}$ (Study O-ARIR-006)					
Parameter (Units)	**Slope**	**90% CI**	**ISCV (%)**	***P*-value Sequence**	**Acceptance Limits**	**DP Outcome**
AUC_{0-t} (ng•h/mL)	1.0081	0.9888-1.0273	10.5	0.4220	0.8755-1.1245	Pass
$AUC_{0-\infty}$ (ng•h/mL)	0.9799	0.9608-0.9991	10.4	0.3571	0.8755-1.1245	Pass

Table 2.7.1-11.	Summary of Dose Proportionality Analysis for Log-Transformed Oxycodone C_{max} (Study O-ARIR-006)			
Parameter (Units)	**Slope**	**90% CI**	**Acceptance Limits**	**DP Outcome**
C_{max} (ng/mL)	0.9769	0.9514-1.0024	0.8755-1.1245	Pass

- Oxycodone ARIR is dose proportional over the range of 5 to 30 mg

13

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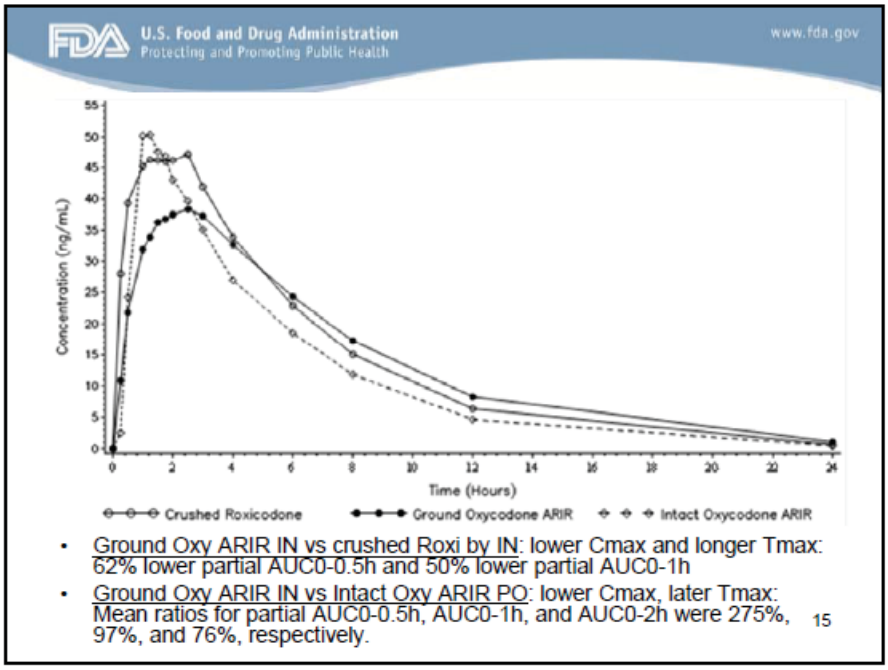
Human Abuse Potential Study O-ARIR-002

- R, DB, DD, active- and Plcb-C, SD, 4-Way CO in experienced but not dependent opioid abusers (N = 31)
- Relative PK, PD effects (e.g., drug liking), safety
- Treatment: washout of 3 days
  - Trt A: Ground Placebo Oxy ARIR tablet (high volume, 587 mg) IN + Placebo tablet matching Oxy ARIR swallowed intact
  - Trt B: Crushed 30-mg Roxicodone tablet (low volume, 100 mg) IN + Placebo tablet matching Oxy ARIR swallowed intact
  - Trt C: Ground 30-mg Oxy ARIR tablet (high volume, 587 mg) IN + Placebo tablet matching Oxy ARIR swallowed intact
  - Trt D: Placebo powder matching Roxicodone (low volume, 100 mg) IN + Oxy ARIR 30-mg tablet swallowed intact

14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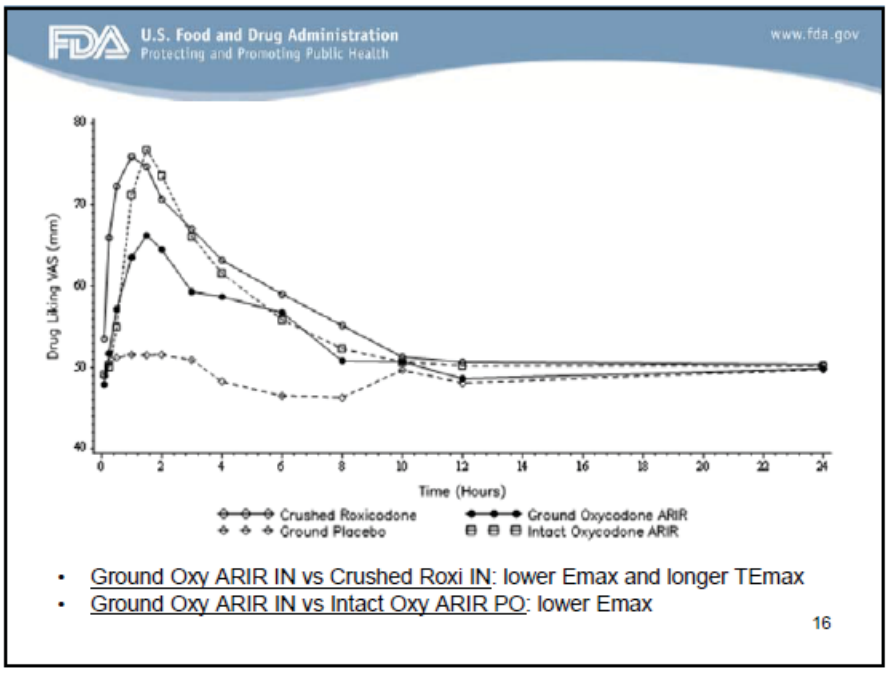
Concentration (ng/mL)
Time (Hours)
Crushed Roxicodone
Ground Oxycodone ARIR
Intact Oxycodone ARIR
• Ground Oxy ARIR IN vs crushed Roxi by IN: lower Cmax and longer Tmax: 62% lower partial AUC0-0.5h and 50% lower partial AUC0-1h
• Ground Oxy ARIR IN vs Intact Oxy ARIR PO: lower Cmax, later Tmax: Mean ratios for partial AUC0-0.5h, AUC0-1h, and AUC0-2h were 275%, 97%, and 76%, respectively.
15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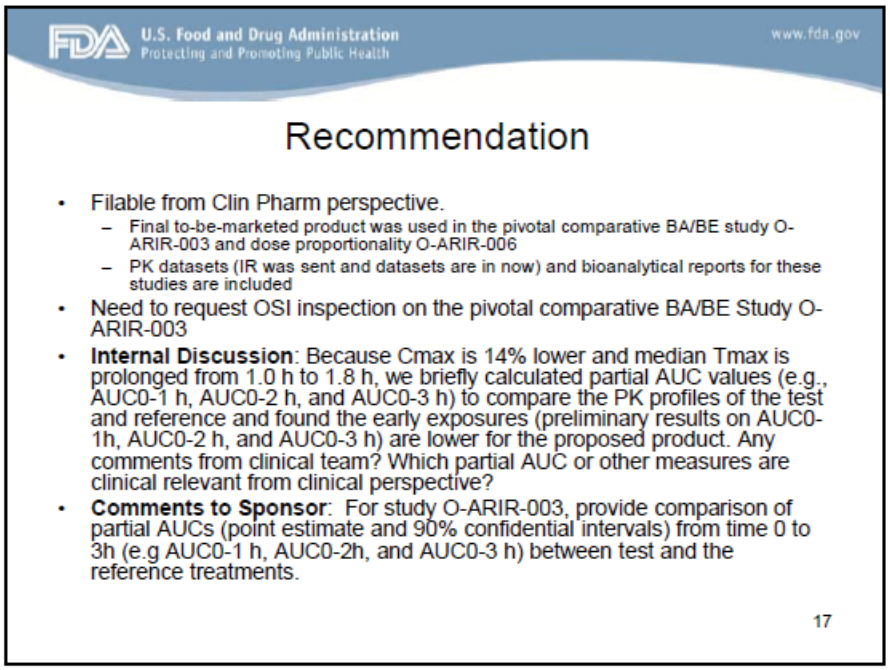
Drug Liking VAS (mm)
Time (Hours)
Crushed Roxicodone
Ground Placebo
Ground Oxycodone ARIR
Intact Oxycodone ARIR
• Ground Oxy ARIR IN vs Crushed Roxi IN: lower Emax and longer TEmax
• Ground Oxy ARIR IN vs Intact Oxy ARIR PO: lower Emax
16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Recommendation
• Filable from Clin Pharm perspective.
– Final to-be-marketed product was used in the pivotal comparative BA/BE study O-ARIR-003 and dose proportionality O-ARIR-006
– PK datasets (IR was sent and datasets are in now) and bioanalytical reports for these studies are included
• Need to request OSI inspection on the pivotal comparative BA/BE Study O-ARIR-003
• Internal Discussion: Because Cmax is 14% lower and median Tmax is prolonged from 1.0 h to 1.8 h, we briefly calculated partial AUC values (e.g., AUC0-1 h, AUC0-2 h, and AUC0-3 h) to compare the PK profiles of the test and reference and found the early exposures (preliminary results on AUC0-1h, AUC0-2 h, and AUC0-3 h) are lower for the proposed product. Any comments from clinical team? Which partial AUC or other measures are clinical relevant from clinical perspective?
• Comments to Sponsor: For study O-ARIR-003, provide comparison of partial AUCs (point estimate and 90% confidential intervals) from time 0 to 3h (e.g AUC0-1 h, AUC0-2h, and AUC0-3 h) between test and the reference treatments.
17

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

/s/

WEI QIU
12/07/2016

YUN XU
12/07/2016