

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
207621Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA: 207621	Submission Date: 01/02/2015
Relevant IND(s):	107037
Submission Type; Code:	505 (b) (2)
Brand Name:	Troxyc ER
Generic Name:	Oxycodone with sequestered naltrexone
Reference Drugs:	Roxicodone® NDA 21011 & Revia® NDA 19932
Formulation; Strength(s):	Extended-release capsules; 10/1.2, 20/2.4, 30/3.6, 40/4.8, 60/7.2 and 80mg/9.6 mg (oxycodone/naltrexone)
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OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Pfizer
Proposed Indication:	 (b) (4)
Proposed Dosage Regimen:	BID

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1.0 Executive Summary

1.1 Recommendation

This submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement is reached between Agency and Sponsor regarding the labeling language.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

Pfizer submitted NDA 207621, for pellet filled capsules of extended release (ER) oxycodone with sequestered naltrexone (ALO-02) with trade name Troxyca ER, under section 505 (b) (2) of the Federal Food Drug and Cosmetic Act. The proposed indication for Troxyca ER is

(b) (4)
The referenced drugs for Troxyca ER for relying on the Agency's previous findings of safety and efficacy are Roxicodone (NDA 21011), oxycodone immediate-release (IR) tablets for oxycodone component and Revia® (NDA 19932) for naltrexone component.

In the proposed formulation ALO-02, the combination of oxycodone HCl and sequestered naltrexone HCl was selected to develop it as an abuse deterrent formulation to address the abuse of opioids associated with manipulation (i.e., crushing). The rationale for including naltrexone is that when ALO-02¹ is taken as directed by a physician for pain management program, the ER product will provide pain relief and the naltrexone remains sequestered. The ER dosage form incorporates an abuse deterrence feature whereby an

¹ In this review, for the proposed formulation Troxyca ER and ALO-02 were alternatively used.

immediate-release of naltrexone occurs upon manipulation by crushing. The opioid antagonistic properties of naltrexone once released will mitigate the euphoric potential of oxycodone.

The proposed dose strengths for ALO-02 (oxycodone hydrochloride/naltrexone hydrochloride) are 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg). The proposed dosing regimen is individualized dosing based on patient's prior analgesic treatment experience and risk factors for addiction, abuse and misuse by prescribers. For opioid-naïve patients, the therapy with Troxyca ER capsules should be initiated at the lowest dose of 10 mg oxycodone/1.2 mg naltrexone orally administered twice daily (BID) approximately every 12 hours. For an individual patient, the physicians should titrate Troxyca ER to a dose that provides adequate analgesia and minimizes adverse reactions.

In support of this NDA, sponsor submitted data from the following studies.

Clinical Pharmacology Studies:

- Relative bioavailability (BA) of ALO-02 to Roxycodone IR (B4531007):
- Effect of food on ALO-02 (B4531003)
- Effect of alcohol on ALO-02 (in vivo study) (B4531004)
- Single and multiple dose PK of ALO-02, QD vs BID dosing (B4531006)
- Abuse Potential Studies:
 - Oral relative abuse potential study (B4531008)
 - Intranasal relative abuse potential study (B4531009)
 - IV abuse potential study (simulated IV administration of ALO-02) (B4981002)
- Clinical Studies (with PK sampling):
 - Study B4531002- Pivotal Phase 3 study: A multicenter, 12-week, and double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 capsules in subjects with moderate-to-severe chronic low back pain. This study is intended to form the primary basis of efficacy claim in the NDA.
 - PK sampling at end of end of double-blind weeks 4, 8 and 12 (or early termination) to measure concentrations of oxycodone, noroxycodone, naltrexone and 6-β-naltrexol levels.
 - Study B4531001 (long-term safety study): A multicenter, 12-month, open-label, single-arm, safety study of ALO-02 capsules in subjects with moderate to severe chronic noncancer pain
 - PK sampling at end of weeks 1 and 4, at the end of months 2, 3, 6, 9, and 12 or early termination to measure concentrations of oxycodone, noroxycodone, naltrexone and 6-β-naltrexol levels.

1.3.1 Relative Bioavailability of ALO-02 compared to reference drugs:

- **Relative BA of ALO-02 versus Roxycodone for oxycodone component:**

The relative BA of ALO-02 using 40 mg strength was compared to the reference, IR oxycodone 20 mg tablet in the study B4531007. Based on dose normalized (dn) PK parameter geometric mean ratios, the AUC (dn) of ALO-02 was ~7% higher and C_{max} was 67% lower compared to oxycodone IR. Consistent with the ER PK profile, the dose normalized C_{max} for ALO-02 is 67% lower compared to IR oxycodone (reference) with test/reference adjusted geometric means ratio of 33% (90% CIs: 29%, 38%). This

may be in part due to slow initial oxycodone release and a prolonged Tmax of range 8-16 h (median, 12 h) for ALO-02 formulation compared to Tmax of 0.5 to 2.0 h (median, 1 h) for IR oxycodone. The dose normalized ratios (90% CIs) of adjusted geometric means for AUCinf(dn) and AUClast(dn) were 107% (97%, 119%) and 106% (95%, 118%), respectively, compared to IR oxycodone. In this study, naltrexone concentrations from intact ALO-02 were below limit of quantitation (BLQ) (<4 pg/mL). The 6-β-naltrexol concentrations were observed in 3 out of 13 subjects, with BLQ (<4 pg/mL) in other subjects. The maximum plasma 6-β-naltrexol concentration was 45 pg/mL observed at 96 h post dose.

- **Relative BA of ALO-02 versus Revia for naltrexone component:**

No formal relative BA study versus Revia was conducted. The relative BA of ALO-02 versus Revia under naltrexone blockade cannot be conducted in healthy volunteers since ALO-02 has sequestered naltrexone. For bridging the naltrexone exposures from ALO-02 capsule (10 mg/1.2 mg to 80 mg/9.6 mg) as intended (intact, orally) to Revia, to rely on the Agency's prior findings of systemic safety of Revia, Sponsor provided following justification:

1. The dose of naltrexone HCl in the highest ALO-02 80 mg/9.6 mg strength is 9.6 mg which is ~5-fold lower compared with Revia 50 mg tablets
2. When ALO-02 is used as intended (intact capsules taken orally), a relatively small extent of systemic naltrexone exposure is expected. The Phase 1 PK studies with ALO-02 showed no quantifiable naltrexone plasma concentrations. In two Phase 3 studies B4531001 and B4531002, the mean plasma naltrexone concentrations ranged between 1.7-11.6 pg/mL and 2.9- 24.9 pg/mL, respectively. The highest observed individual plasma naltrexone concentrations in Phase 3 studies were 331 pg/mL (B4531001) and 1090 pg/mL (B4531002), respectively. In comparison, the mean naltrexone Cmax following Revia 50 mg was 8550 pg/mL (Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9), which is over 300-fold higher compared with the highest mean concentration (24.9 pg/mL) and over 7-fold higher than the highest individual concentration (1090 pg/mL) observed following ALO-02 capsules.

Overall, since the highest amount of naltrexone that can be released from ALO-02 80 mg/9.6 mg strength is 9.6 mg, which is ~5-fold lower compared with approved 50 mg Revia tablets, and the naltrexone component in ALO-02 is sequestered, the proposed justification for not conducted formal relative BA study versus Revia is adequate.

1.3.2 Effect of food on ALO-02:

The effect of food on 40 mg ALO-02 capsules was evaluated in the study B4531003.

- **ALO-02 Fed vs Fasted:** Administration of 40 mg ALO-02 under fed conditions resulted in no change in AUC (geometric mean) and ~7% increase in Cmax (geometric mean) compared to fasted conditions. The ratios of adjusted geometric means for ALO-02 under fed relative to the reference (ALO-02 under fasted) were 99%, 100%, and 107% for AUCinf, AUClast, and Cmax respectively, with 90% CIs within 80-125% limits (96-103%, 97-104% and 98-116%, for AUCinf, AUClast, and Cmax respectively). The ALO-02 being an ER formulation, the oxycodone median Tmax under fasted was 12 h (range 12-16 h). Under fed conditions, the median Tmax is delayed by 2 h compared to fasted appearing at 14 h (range 12-24 h). There was no difference in the oxycodone half-life between fasted and fed treatments.

- **ALO-02 pellets sprinkled on applesauce vs Fasted:** Administration of 40 mg ALO-02 pellets sprinkled on applesauce (fasted) resulted in no change in AUC (geometric mean) and C_{max} (geometric mean) compared to fasted conditions. The ratios of adjusted geometric means for ALO-02 pellets sprinkled on applesauce relative to the reference (ALO-02 under fasted) were 101%, 101%, and 98% for AUC_{inf}, AUC_{last}, and C_{max} respectively, with 90% CIs within 80-125% limits (98-104%, 98-104% and 90-106%, for AUC_{inf}, AUC_{last}, and C_{max} respectively). The oxycodone median T_{max} under fasted is 12 h (range 12-16 h), whereas when ALO-02 pellets sprinkled on applesauce, the median T_{max} is delayed by 1 h appearing at 13 h (range 8-16 h). There was no difference in the oxycodone half-life between fasted and ALO-02 pellets sprinkled on applesauce treatments.
- In the food effect study, naltrexone concentrations from intact ALO-02 40 mg were BLQ (4 pg/mL) in all subjects. The 6-β-naltrexol concentrations were observed in 6, 10 and 6 subjects out of 24 subjects in ALO-02 fed, fasted, and ALO-02 pellets sprinkled on applesauce treatment arms, respectively, with BLQ (4 pg/mL) in other subjects. The maximum plasma 6-β-naltrexol concentration was 30 pg/mL observed at 120 h post dose in ALO-02 fed treatment arm.

The observed food effect PK results indicate that ALO-02 can be taken “without regards to meals”.

1.3.3 Single and Multiple Dose PK of ALO-02:

Single and multiple dose PK of ALO-02 capsules (40 mg and 80 mg) was evaluated in the study B4531006 in 12 healthy volunteers under naltrexone blockade. The ALO-02 40 mg was administered single dose on Day 1 for evaluating single dose PK and thereafter BID from Day 2 to Day 5 for evaluating its multiple-dose PK. The ALO-02 80 mg was administered QD from on Day 1 to Day 5, in which the single dose PK was evaluated on Day 1 and multiple dose PK was evaluated using Day 2 to Day 5 dosing.

Single dose PK:

- The single dose ALO-02 40 mg and 80 mg shows dose proportional PK based on AUC₂₄ and C_{max}. The dose normalized oxycodone geometric mean AUC₂₄ (dn) and C_{max} (dn) ratios and corresponding 90% CIs for ALO-02 40 mg and 80 mg were within 80%-125%. The ALO-02 treatments (40 mg and 80 mg) showed a median oxycodone T_{max} of ~ 12 h (range, 8 -12 h).

Multiple dose PK:

- ALO-02 80 mg QD vs 40 mg BID: The oxycodone steady state was reached within 48 h for both ALO-02 40 mg BID and 80 mg QD. The steady-state oxycodone concentration time profiles over the 24 h interval appeared flat with lower peak to trough values for ALO-02 40 mg BID treatment compared to ALO-02 80 mg QD treatment. The ALO-02 40 mg BID had higher C_{min} values (0 to 12h- 38 ng/mL and 12-24h -34 ng/mL) compared to ALO-02 80 mg QD (28 ng/mL).
- Oxycodone average concentrations (C_{av}) over the dosing interval were similar for QD and BID treatments. The C_{av} for ALO-02 80 mg QD was 47 ng/mL; ALO-02 40 mg BID was 45 ng/mL for 0 to 12h and 43 ng/mL for 12-24h.

- After multiple dosing (Day 2 to Day 5), the Day 5 plasma oxycodone exposures as measured by geometric mean AUC₂₄ and C_{max} values over the entire 24 hours interval were 6% and 15% higher, respectively for ALO-02 80 mg QD compared to 40 mg BID.

Accumulation ratio after multiple dosing:

After multiple dosing, the accumulation ratios for oxycodone (Day 5/ Day 1) based on AUC_τ and C_{max} were higher for the ALO-02 40 mg BID treatment compared to ALO-02 80 mg QD treatment. The accumulation ratios are as below:

- ALO-02 80 mg QD : AUC_τ - 1.3; C_{max}- 1.1
- ALO-02 40 mg BID: AUC₁₂ - 3.3; AUC₂₄ - 2.6 ; C_{max}- 1.9

The terminal elimination half-life for ALO-02 (40 mg BID and 80 mg QD) after multiple dosing is approximately 7 h.

1.3.4. Effect of Alcohol on ALO-02

The effect of 20% and 40% alcohol ALO-02 capsules was evaluated in the study B4531004. It was an open-label, single-dose, randomized, 3-period crossover study using the strength 20 mg/ 2.4 mg (referred to as 20 mg ALO-02) in naltrexone blocked 18 healthy subjects.

The administration of ALO-02 20 mg with 20% alcohol had no difference in PK parameters of oxycodone compared to water based on mean values. The ratios of adjusted geometric means for ALO-02 20 mg with 20% alcohol (test treatment) relative to the ALO-02 20 mg with water (reference treatment) were 97%, 98%, and 101% for AUC_{inf}, AUC_{last}, and C_{max}, respectively, with 90% CIs within the 80%-125% interval.

The administration of ALO-02 20 mg with 40% alcohol resulted in ~ 12% increase in AUC_{inf} and a 38% increase in C_{max} compared to the ALO-02 20 mg with water (reference) treatment. The ratios of adjusted geometric means for ALO-02 20 mg with 40% alcohol (test treatment) relative to ALO-02 20 mg with the water (reference treatment) were 112%, 115%, and 138% for AUC_{inf}, AUC_{last}, and C_{max} respectively, with the upper 90% CIs outside of the 80-125% limits (96-130%, 99-134% and 119-159%, for AUC_{inf}, AUC_{last} and C_{max}, respectively). The observed 38% increase in C_{max} with 40% alcohol treatment is due to one subject # 10011106 who had apparent 6.4 fold increase in C_{max} with 40% alcohol treatment compared to water treatment. This subject (# 10011106) had 2.7 fold and 6.4 fold increase in C_{max} with 20% alcohol and 40% alcohol treatments, respectively compared to the water treatment. The corresponding increase in AUC was 2.2 fold and 4.8 fold with 20% and 40 % alcohol treatments, respectively compared to water treatment. Further examination of this subject's concentrations showed that this subject's C_{max}, AUC values with 20% or 40% alcohol were within the range of exposures seen in other subjects, whereas the exposures following ALO-02 with water were the lowest, driving the ratios apparently to highest values. Additionally, there was no shift in T_{max} values in this subject among the treatments (6 h with water, 8 h with both 20% alcohol and 40% alcohol), which would have indicated dose dumping in this subject. The exact reason for the lower exposure in this subject is not known.

The greatest individual increase in C_{max} for ALO-02 with 40% alcohol in the subject # 10011106 was observed at 6.4-fold, slightly higher or comparable to those of the already approved extended-release opioid products (e.g. 2.7-fold for OPANA ER, 4.38-fold for NUCYNTA ER, 5-fold for EMBEDA ER); and much lower than that of PALLADONE (16-fold). Because of the reason that there is no change in the T_{max} values and subject's water

treatment C_{max} and AUC values were lowest compared to others, driving the ratios apparently to highest values, the alcohol interaction with the proposed product is not considered as an approvability issue.

There was no difference in the oxycodone half-life between water and alcohol treatments.

1.3.5 Dose linearity of oxycodone of ALO-02:

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For

ALO-02, the dose-linearity assessment of oxycodone was done using cross study comparison of Phase 1 PK studies (20, 40, 60 and 80 mg strengths) and based on prescribed daily dose (10, 20, 30, 40, 60, and 80 mg strengths in Phase 3 study (B4531001).

- Based on cross study comparison of Phase 1 single and multiple dose studies, the oxycodone component of ALO-02 demonstrated dose-linear increase in AUC and C_{max} values across the doses strengths for 20, 40, 60 and 80 mg. The dose normalized AUC_{inf} for 20, 40, 60 mg and dose normalized AUC_{tau} for 80 mg were 10, 13, 11 and 14 ng.hr/mL/mg, respectively. The dose normalized C_{max} for 20, 40, 60 mg 80 mg were 0.54, 0.66, 0.48 and 0.75 ng/mL/mg, respectively.
- Based on prescribed daily doses in Phase 3 study (B4531001), the mean steady state oxycodone concentrations increased dose linearly across the daily doses ranging from 10 mg to 200 mg. The mean steady-state concentrations of oxycodone for 10-40 mg, >40-80 mg, >80-120 mg, and >120 mg daily dose groups were 15 ng/mL, 35 ng/mL, 60 ng/mL and 83 ng/mL, respectively.

1.3.6 Naltrexone Sequestration:

In the proposed formulation, in theory, the naltrexone is supposed to be sequestered and not be released or leaked when used as intact capsules. However, small amount of naltrexone is released from the product when used as intact capsules in the Phase 1 and Phase 3 clinical trials.

1.3.6a Naltrexone and 6-β-naltrexol concentrations from intact ALO-02 capsules in the Phase 3 studies

The release or leakage of naltrexone from intact ALO-02 was assessed using the concentration data of naltrexone and 6-β-naltrexol in patients in Phase 3 studies (B4531002 and B4531001). Naltrexone and 6-β-naltrexol concentrations in Phase 3 trials were evaluated for two reasons.

- 1) To assess if there any relationship between the release of sequestered naltrexone and dose- strength (low to high strength of ALO-02 ,10 mg/1.2 mg to 80 mg/9.6) or prescribed ALO-02 daily dose
- 2) To assess if there is any relationship between naltrexone concentrations and the opioid withdrawal events.

The details of observed naltrexone and 6-β-naltrexol concentrations from intact ALO-02 capsules in Phase 3 study is described below.

While finalizing this review an information request (IR) was sent to the sponsor regarding the long term- storage stability of naltrexone concentrations for some subjects. This IR is not applicable to 6-β- naltrexol concentrations. A response from Sponsor is awaited. The numbers for naltrexone concentrations indicated in below may or may not change based the Sponsor's response to IR. Based on the sponsor's response, the language will be modified in the label accordingly. Below are the current proposed numbers and information for observed naltrexone and 6 β naltrexol concentrations.

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The subject 10271011 who had 1090 pg/mL of naltrexone level was on 12 mg daily dose of naltrexone present in ALO-02. This subject was not associated with withdrawal; COWS score for this subject was ≤ 2 at each time point. In comparison to the naltrexone concentration observed in this subject, the mean naltrexone Cmax following Revia 50 mg in a published study² was 8550 pg/mL. The 12 mg daily dose is approximately 1/4th of the dose compared to Revia 50 mg. The observed naltrexone concentration of 1090 pg/mL is approximately 1/8th of Cmax (8550 pg/mL) of Revia 50 mg. Although this particular subject had no with drawl event, the observed maximum naltrexone concentration of 1090 pg/ mL from intact ALO-02 capsules cannot be ignored. Also refer to Section 1.3.6d for naltrexone Cmax observed from crushed oral ALO-02 capsules.

In pivotal phase 3 trial, B4531002 the highest observed naltrexone and 6-β-naltrexol concentrations were 1090 pg/mL and 7320 pg/mL, respectively. The mean³ plasma concentrations of naltrexone were 5.3 pg/mL, 3.4 pg/mL, 2.9 pg/mL, and 3.0 pg/mL at randomization baseline, week 4, week 8, and week 12/early termination, respectively; the corresponding values for 6-β-naltrexol were 98 pg/mL, 86 pg/mL, 48 pg/mL, and 56 pg/mL, respectively. In long-term safety trial, B4531001, the highest observed naltrexone and 6-β-naltrexol concentrations were 331pg/mL and 4380 pg/mL, respectively. The mean^c steady-state concentrations of naltrexone were 1.7 pg/mL, 10 pg/mL, 9 pg/mL and 11.6 pg/mL for 10-40 mg dose group, > 40-80 mg dose group, > 80-120 mg dose group, and > 120 mg dose group, respectively; the corresponding values for 6-β-naltrexol were 44 pg/mL, 156 pg/mL, 162 pg/mL, and 227 pg/mL, respectively.

In both the Phase 3 studies, measurable plasma naltrexone or 6-β-naltrexol concentrations did not accumulate at any time during the study. There was no apparent correlation between plasma

² Literature: Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9)

³ Note that mean concentrations of naltrexone encompasses concentration values below LOQ value (4 pg/ml as in calculation of mean values, the BLQ values were considered as 'zero'

naltrexone or 6-β-naltrexol concentrations and the daily dose of naltrexone present in ALO-02. The R-squared values for naltrexone concentrations and daily dose of naltrexone present in ALO-02 were 0.022 and 0.026, respectively, for studies B4531002 and B4531001. The corresponding R-squared values for 6-β-naltrexol and the daily dose of naltrexone were 0.032 and 0.035.

Naltrexone concentrations in subjects with opioid withdrawal events:

The relationship between naltrexone or 6-β-naltrexol levels to opioid withdrawal events (exposure- response) has not been established. It is also speculated that the opioid tolerance level in a particular subject could affect an opioid withdrawal event.

In phase 3 studies, B4531001 and B4531002 15 out of 725 subjects had defined opioid withdrawal events. The relationship between opioid withdrawal events to naltrexone concentrations released from intact ALO-02 capsules in these subjects was assessed. It is noted that naltrexone and 6-β-naltrexol concentrations were taken around the time of each withdrawal event and not on the day of event (refer to the Table 2.2.1c.). Four subjects out of 15 subjects match the date of event and the date of sample collection. However, since ALO-02 capsules were being dosed to steady state, the concentrations taken around the time of each withdrawal event can be considered acceptable for comparison; known the naltrexone and 6-β-naltrexol half-lives of 4 h and 13 h, respectively. In most of events, the naltrexone concentrations are BLQ or lower. Of all subjects with withdrawal events, the highest naltrexone concentration was 139 pg/mL and the highest 6-β-naltrexol concentration was 1,740 pg/mL (subject 10151006). For, Revia (naltrexone tablets) is indicated for the blockade of the effects of exogenously administered opioids, the mean naltrexone C_{max} with 50 mg tablet in a published study⁴ was 8,550 pg/mL. The highest naltrexone concentration observed in subject with opioid withdrawal events (139 pg/mL) is much lower compared to Revia tablets 50 mg C_{max} (8,550 pg/mL). On the other hand, two subjects (10221015 and 10271011) in the study B4531002 who had concentrations >500 pg/mL of naltrexone were not associated with withdrawal; COWS scores for these subjects were ≤2 at each time point. Based on this, in the subjects who had defined opioid withdrawal events, it appears that opioid withdrawal events cannot be co-related the naltrexone concentrations.

Overall, the results suggest that 1) there was no co-relation between plasma naltrexone concentrations and prescribed ALO-02 daily dose or dose- strength 2) in the subjects who had defined opioid withdrawal events in the phase 3 trails, it appears that opioid withdrawal events cannot be co-related the naltrexone concentrations. However, based on the highest observed naltrexone concentration of 1090 pg/mL with in intact ALO-02, which is approximately 1/8th of C_{max} (8550 pg/mL) of 50 mg Revia tablets, the released naltrexone concentrations from intact ALO-02 capsules cannot be ignored. Also refer to Section 1.3.6d for naltrexone C_{max} from crushed ALO-02 capsules.

1.3.6b Naltrexone and 6-β-naltrexol concentrations from intact ALO-02 capsules in the Phase 1 studies

⁴ Literature: Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9)

In non-naltrexone blocked Phase 1 PK studies (B4531007 and B4531003), the naltrexone concentrations was undetected (BLQ, <4 pg/mL). The 6-β-naltrexol was observed in 19 out of 37 subjects at various time point samples ranging from 1 h to 120 h post dose with a maximum concentration of 45 pg/mL.

1.3.6c Naltrexone concentrations from crushed ALO-02 capsules in abuse deterrent studies:

The naltrexone exposure from crushed ALO-02 capsules was assessed in intranasal (IN) and oral abuse deterrent studies. The naltrexone BA of crushed ALO-02 was higher in IN route compared to the oral route, which can be related to the higher first-pass metabolism through oral route resulting in less oral BA. The mean naltrexone C_{max} for crushed -oral administered ALO-02 40/4.8 mg and 60/7.2 mg pellets was 1074 and 1810 pg/mL, respectively whereas for crushed intranasally taken ALO-02 30/3.6 mg, pellets it was 4372 pg/mL.

1.3.6d Maximum observed naltrexone and 6-β-naltrexol concentrations from intact or crushed ALO-02 capsules

The maximum naltrexone and 6-β-naltrexol concentrations from intact ALO-02 and crushed ALO-02 (oral and nasal routes) obtained in the clinical studies of ALO-02 are shown in the Table 1.3.6d. These concentrations were not normalized to dose. For comparison, the naltrexone exposure from 50 mg Revia Tablets is also shown. The subject (#10271011) who had maximum observed naltrexone concentrations of 1090 pg/mL was on 12 mg daily dose of naltrexone present in intact ALO-02. The highest naltrexone concentration released from intact ALO-02 capsules (1090 pg/mL) approximately closer to the naltrexone C_{max} after single dose of crushed and orally administered ALO-02, 1074 pg/mL (4.8 mg naltrexone). For this reason, the released naltrexone concentrations from intact ALO-02 capsules cannot be ignored.

The bioavailability of naltrexone from crushed ALO-02 via nasal route is higher compared to the crushed ALO-02 capsules via oral route, which can be due to higher first-pass metabolism of naltrexone through oral route.

Table 1.3.6d: Maximum naltrexone and 6-β-naltrexol concentrations from intact ALO-02 and crushed ALO-02 (oral and nasal routes)

	Study	Naltrexone Dose	Concentration (pg/mL)	
			Naltrexone	6-β-naltrexol
Intact ALO-02	Phase 1 ALO-02		BLQ	45
	Phase 3 studies ALO-02	2.4 to 19.2 mg daily dose (steady state)	1090 (12 mg daily dose)	7320 (14.4 mg daily dose)
Crushed ALO-02	Oral ALO-02 crushed	4.8 mg (single dose)	1074	1702
		7.2 mg (single dose)	1810	1855
	Nasal ALO-02 crushed	3.6 mg (single dose)	4372	3878
Literature ⁵	Naltrexone Oral Tablets	50 mg	8550	NA

1.3.7 Pharmacokinetics of oxycodone and naltrexone under ALO-02 abuse:

The abuse deterrent studies, B4531008, B4531009 and B4981002 were aimed at demonstrating the utility of naltrexone sequestered in the ALO-02 pellets to deter drug tampering and

⁵ Literature: Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9)

diversion. The B4531008 and B4531009 studies evaluated the relative abuse potential of ALO-02 compared to oxycodone hydrochloride IR and placebo when administered orally and intranasally, respectively. The ALO-02 dosage form incorporates an abuse deterrence feature whereby an immediate-release of naltrexone occurs upon manipulation by crushing. The opioid antagonistic properties of naltrexone once released will mitigate the euphoric potential of oxycodone. For these studies, the PK endpoints, i.e., naltrexone release from crushed and its comparison to intact ALO-02 capsules was reviewed. With regards to the PD endpoints, Emax for drug liking and high of crushed versus intact ALO-02 capsules and its statistical significance; refer to Control Substance Staff reviews in DARRTS.

1.3.7a Oral Abuse Potential Study:

- Study B4531008 evaluated the relative abuse potential of intact and crushed ALO-02 60 mg/7.2 mg compared to crushed IR oxycodone HCl 60 mg and placebo administered orally to non-dependent, recreational opioid users. Subjects received single dose of 6 treatments of placebo, ALO-02 40 mg/4.8 mg crushed, ALO-02 60 mg/7.2 mg intact and crushed, and oxycodone HCl IR 60 mg intact and crushed.
 - Oxycodone PK after crushed oral administration (ALO-02 versus IR oxycodone): The oxycodone and its metabolites (noroxycodone and oxymorphone) PK profiles and plasma exposures were similar between crushed ALO-02 capsules and crushed oxycodone IR tablets. When crushed, ALO-02 capsules lose its ER properties and the rate of absorption of oxycodone from ALO-02 was similar to IR oxycodone. The Cmax was achieved within a median Tmax of 0.6 -1 h post dose for crushed treatments. The mean t_{1/2} values ranged from 4.2-4.4 h, and appeared to be unrelated to the dose level or whether ALO-02 or IR oxycodone crushed was administered.
 - Naltrexone PK after crushed oral administration: Upon oral administration of crushed ALO-02 40 mg/4.8 mg and 60 mg/7.2 mg, the mean naltrexone Cmax of 1074 and 1810 pg/mL was achieved, respectively within a median Tmax of 0.5 h for both strengths, indicating the sequestered naltrexone was released and absorbed systemically. Across the 1.5-fold dose increment of naltrexone HCl in ALO-02 from 4.8 mg to 7.2 mg, the naltrexone Cmax and AUC_{inf} appeared to increase in a dose proportional manner by 1.69- and 1.63-fold, respectively. The mean t_{1/2} values were 5.4-5.6 h, respectively, and appeared to be unrelated to the dose level. For the intact ALO-02 60 mg/7.2 mg, naltrexone plasma exposure was BLQ, with the exception of a measurable concentration in 1 sample that was considered anomalous. This sample was the 1.5 h postdose sample (subject 10011090), in which an unusually high plasma concentrations for naltrexone (687 pg/mL) and 6-β naltrexol (11,300 pg/mL) was observed, while the concentrations of both naltrexone and 6-β naltrexol at all other time points were BLQ (<4 pg/mL).

1.3.7b Intranasal Abuse Potential Study:

- 3) Study B4531009 evaluated the relative abuse potential of crushed ALO-02 compared to crushed oxycodone HCl IR and placebo administered intranasally (IN) in non-dependent, recreational opioid users. Subjects received single dose of 4 treatments of placebo sugar spheres crushed, ALO-02 30 mg/3.6 mg crushed, placebo lactose tablets crushed, and oxycodone HCl IR 30 mg crushed.

- a. Oxycodone PK after crushed IN administration: Following IN administration, the oxycodone rate of absorption from the crushed ALO-02 (30 mg/3.6 mg) capsules was delayed (mean C_{max} at median T_{max} 1.6 h) compared to crushed oxycodone IR tablets (mean C_{max} at T_{max} 0.5 h). Oxycodone systemic exposure based on geometric mean AUC was 20% lower and C_{max} 30% lower for the crushed ALO-02 treatment compared to crushed oxycodone IR treatment. This difference is likely related to the formulation differences between ER ALO-02 and IR oxycodone such that part of the unabsorbed dose of ALO-02 from the nasal cavity may have been swallowed and entered the gastrointestinal tract, being subjected to a higher first-pass metabolism resulting in less oral BA. This possibility is consistent with the longer median T_{max} observed for ALO-02 (1.6 h) compared to IR oxycodone 30 mg (0.5 h). Mean t_{1/2} values were approximately similar, 4 h for both treatments given intranasally.
- b. Naltrexone PK after crushed IN administration: Following IN administration of crushed ALO-02 30 mg/3.6 mg capsules, individual naltrexone C_{max} was achieved within the range of 0.3 - 1.6 h postdose, with a median T_{max} - 0.3 h. The mean C_{max} was 4372 pg/mL, indicating the sequestered naltrexone was released and absorbed systemically. The mean t_{1/2} was 3.6 h.

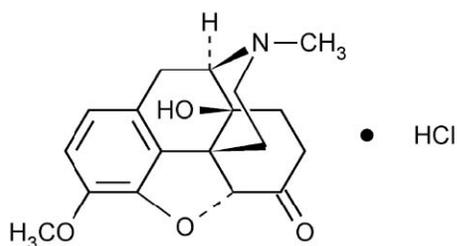
Overall, adequate information has been provided characterizing the clinical pharmacology aspects of Troxyca ER.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

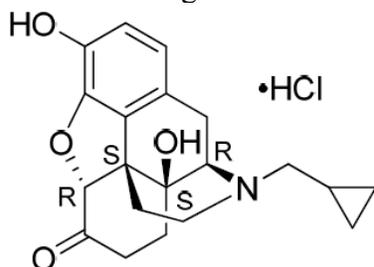
Oxycodone: Oxycodone Hydrochloride is described as 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride with an empirical formula of C₁₈H₂₁NO₄·HCl and a molecular weight of 351.82. The molecular structure of oxycodone is:



Physicochemical Properties: Oxycodone is a white to off-white crystalline solid. It is soluble up to 0.18 g/mL in water (pH 6.5-6.6); ~0.10 g/mL in water (pH>6.6).

Naltrexone: Naltrexone Hydrochloride is described as (5α)-17-(Cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride N-cyclopropylmethyl-14-

hydroxydihydromorphinone hydrochloride with an empirical formula of $C_{20}H_{23}NO_4 \cdot HCl$ and a molecular weight of 377.86. The molecular structure of naltrexone is:



Drug product

ALO-02 capsules are hard gelatin capsule shells filled with pellets [REDACTED] (b) (4). The pellets provide extended-release oxycodone HCl, with sequestered naltrexone HCl. The dosage strengths are differentiated by capsule shell size, color and printing. The qualitative and quantitative composition of the proposed commercial formulation (ALO-02 capsules) 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg of oxycodone HCl/naltrexone HCl is described in Table 2.1.1.

Table 2.1.1: Theoretical Composition of ALO-02 10 mg/1.2 mg Capsules

	Reference to Standard	Function(s)	Unit Formula ²	
			Unit (mg)	%
Pellet Composition				
Active Components:				
Oxycodone HCl	In house	Active	10.00	(b) (4)
Naltrexone HCl	In house	Active	1.20	
Inactive Components:				
Talc	USP/NF			(b) (4)
Ammonio methacrylate copolymer	USP/NF			
(b) (4)				
Sugar spheres	USP/NF			
(b) (4)				
Ethylcellulose	USP/NF			
(b) (4)				
Hydroxypropyl cellulose	USP/NF			
(b) (4)				
Polyethylene glycol	USP/NF			
(b) (4)				
Dibutyl sebacate	USP/NF			
Diethyl phthalate	USP/NF			
Sodium lauryl sulfate	USP/NF			
Methacrylic acid copolymer	(b) (4) USP/NF			
(b) (4)				
Magnesium stearate	USP/NF			
Ascorbic acid	USP/NF			
(b) (4)	In house			
	USP/NF			
	USP/NF			
	USP/NF			
Target Capsule Fill Weight		--		
Hard Gelatin Capsule Shell				
Capsule shells (size #4) silver opaque/yellow opaque	(b) (4) In house			
(b) (4)				
Black iron oxide (E172)	USP/NF			
Yellow iron oxide (E172)	USP/NF			
Titanium dioxide	USP/NF			
Gelatin	USP/NF			
(b) (4)				
Approximate weight of capsule shell		--		
Print Ink³				
Approximate weight of print ink on capsule shell		--		

(b) (4)

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

Oxycodone: Oxycodone is a (b) (4) agonist opioid whose principle therapeutic action is analgesic.
Naltrexone: Naltrexone is a (b) (4) opioid antagonist that reverses the subjective and analgesic effects of mu-opioid receptor agonists by competitively binding at mu-opioid receptors.

Troxyca ER is indicated for (b) (4)

2.1.3 What are the proposed dosage and route of administration?

The proposed Troxyca ER capsules are intended for twice-daily (BID) oral administration.

2.1.4 What is Troxyca ER to-be-marketed formulation?

Troxyca ER capsules are hard gelatin capsule shells filled with pellets (b) (4). The pellets provide extended-release oxycodone HCl, with sequestered naltrexone HCl. The dosage strengths, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg and 80 mg/9.6 mg of oxycodone HCl/naltrexone HCl are differentiated by capsule shell size, color and printing.

2.1.5 What are the core studies submitted in this NDA?

The following studies submitted in this NDA:

- Clinical Pharmacology Studies:
 - Relative bioavailability (BA) of ALO-02 to Roxycodone IR (B4531007):
 - Effect of food on ALO-02 (B4531003)
 - Effect of alcohol on ALO-02 (in vivo study) (B4531004)
 - Single and multiple dose PK of ALO-02, QD vs BID dosing (B4531006)
- Abuse Potential Studies:
 - Oral relative abuse potential study (B4531008):
 - Intranasal relative abuse potential study (B4531009)
 - IV abuse potential study (simulated IV administration of ALO-02) (B4981002)
- Clinical Studies (with PK sampling):
 - Study B4531002- Pivotal Phase 3 study: A multicenter, 12-week, and double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 capsules in subjects with moderate-to-severe chronic low back pain. This study is intended to form the primary basis of efficacy claim in the NDA.
 - PK sampling at end of end of double-blind weeks 4, 8 and 12 (or early termination) to measure concentrations of oxycodone, noroxycodone, naltrexone and 6-β-naltrexol levels.
 - Study B4531001 (long-term safety study): A multicenter, 12-month, open-label, single-arm, safety study of ALO-02 capsules in subjects with moderate to severe chronic noncancer pain

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical efficacy and safety studies, B4531002 (in chronic low back pain) and B4531001 (in chronic non-cancer pain), and clinical pharmacology studies characterizing the formulation form the basis to support the dosing claims for this NDA. In both the clinical studies, all strengths of ALO-02 oral capsules (oxycodone HCl/naltrexone HCl, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, and 80 mg/9.6 mg) were used based on subject's current average total daily opioid dose. The range of allowable total daily dose of ALO-02 capsules was 20 mg to 160 mg of the oxycodone component in a 24-hour time interval, administered twice daily approximately 12 hours apart. At the discretion of the investigator, ALO-02 capsules also administered once daily at 24-hour intervals. In both studies sparse PK sampling was conducted to measure oxycodone, noroxycodone, naltrexone and 6- β -naltrexol. The studies' details and PK sampling schedule is listed below:

- Study B4531002: pivotal Phase 3 study: A multicenter, 12-week, and double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 capsules in subjects with moderate-to-severe chronic low back pain. In this study, the PK sampling was conducted at end of open label titration (randomization baseline), end of double-blind weeks 4, 8 and 12 (or early termination) to measure concentrations of oxycodone, noroxycodone, naltrexone and 6- β -naltrexol levels.
- Study B4531001 - long-term safety (supportive study): A multicenter, 12-month, open-label, single-arm, safety study of ALO-02 capsules in subjects with moderate to severe chronic non-cancer pain. In this study, the PK sampling was conducted at end of weeks 1 and 4, at the end of months 2, 3, 6, 9, and 12 or early termination to measure concentrations of oxycodone, noroxycodone, naltrexone and 6- β -naltrexol levels. The PK population included all subjects who had at least one PK sample obtained during treatment and comprised 386 (97.7%) subjects. The number of subjects in each of average daily dose group, 10-40 mg >40-80 mg, > 80-120 mg and 120 mg are 126, 155, 57 and 43 subjects, respectively.

2.2.1 a Naltrexone release from ALO-02 Capsules:

In the proposed formulation, in theory, the naltrexone is supposed to be sequestered and not be released or leaked when used as intact Capsules. However, low concentrations of naltrexone and its metabolite 6- β -naltrexol appeared in the conducted phase 3 trials. In addition, the released naltrexone levels from ALO-02, should not show be a dose-linear relationship i.e., higher strength releasing higher naltrexone compared to the lower strength. To assess, if there any relationship between the release of sequestered naltrexone and dose- strength (low to high strength of ALO-02 ,10 mg/1.2 mg to 80 mg/9.6) or prescribed ALO-02 daily dose, the naltrexone and 6- β -naltrexol concentrations among different strengths were compared using the Phase 3 studies concentration data. The results show that there were no apparent relationship between plasma naltrexone concentrations and prescribed ALO-02 daily dose. The details of observed naltrexone and 6- β -naltrexol concentrations from intact ALO-02 capsules Phase 3 studies are as below.

While finalizing this review an information request (IR) was sent to the sponsor regarding the long term- storage stability of naltrexone concentrations for some subjects. This IR is not applicable to 6-β- naltrexol concentrations. A response from Sponsor is awaited. The numbers for naltrexone concentrations indicated in below may or may not change based the Sponsor's response to IR. Based on the sponsor's response, the language will be modified in the label accordingly.

Pivotal Phase 3 trial B4531002: The XY plot (X-categorical) of naltrexone and 6-β-naltrexol concentrations (pg/mL) versus ALO-02 dose was shown in the Figure 2.2.1a. The XY plot (X-categorical) of naltrexone and 6-β-naltrexol concentrations (pg/mL) versus each visit (end of open label titration or randomization base line, Week 4, Week 8 and at Week 12/Early Termination) is shown in the Figure 2.2.1b. The mean ± SD and maximum naltrexone and 6-β-naltrexol concentrations released from ALO-02 in the study B4531002 is shown in the Table 2.2.1a.

In this trial, 687 naltrexone samples were obtained from 350 subjects and 563 (82%) were BLQ (<4 pg/mL). Highest observed naltrexone and 6-β-naltrexol concentrations were 1090 pg/mL and 7320 pg/mL, respectively. The mean plasma concentrations of naltrexone were 5.3 pg/mL, 3.4 pg/mL, 2.9 pg/mL, and 3.0 pg/mL at randomization baseline, week 4, week 8, and week 12/early termination, respectively; the corresponding values for 6-β-naltrexol were 98 pg/mL, 86 pg/mL, 48 pg/mL, and 56 pg/mL, respectively. Note that the mean concentrations of naltrexone encompasses concentration values that are below the LOQ value of 4 pg/ml since in the calculation of 'mean values', the BLQ values were considered as 'zero'. The measurable plasma naltrexone or 6-β-naltrexol concentrations did not accumulate at any time during the study. There was no apparent correlation between plasma naltrexone or 6-β-naltrexol concentrations and the daily dose of naltrexone present in ALO-02. The R-squared values for naltrexone and 6-β-naltrexol concentrations and daily dose of naltrexone present in ALO-02 was much lower of 0.022 and 0.032, respectively,

Figure 2.2.1a Detectable plasma naltrexone and 6-β-naltrexol concentrations (pg/mL) versus total daily naltrexone dose in study B4531002

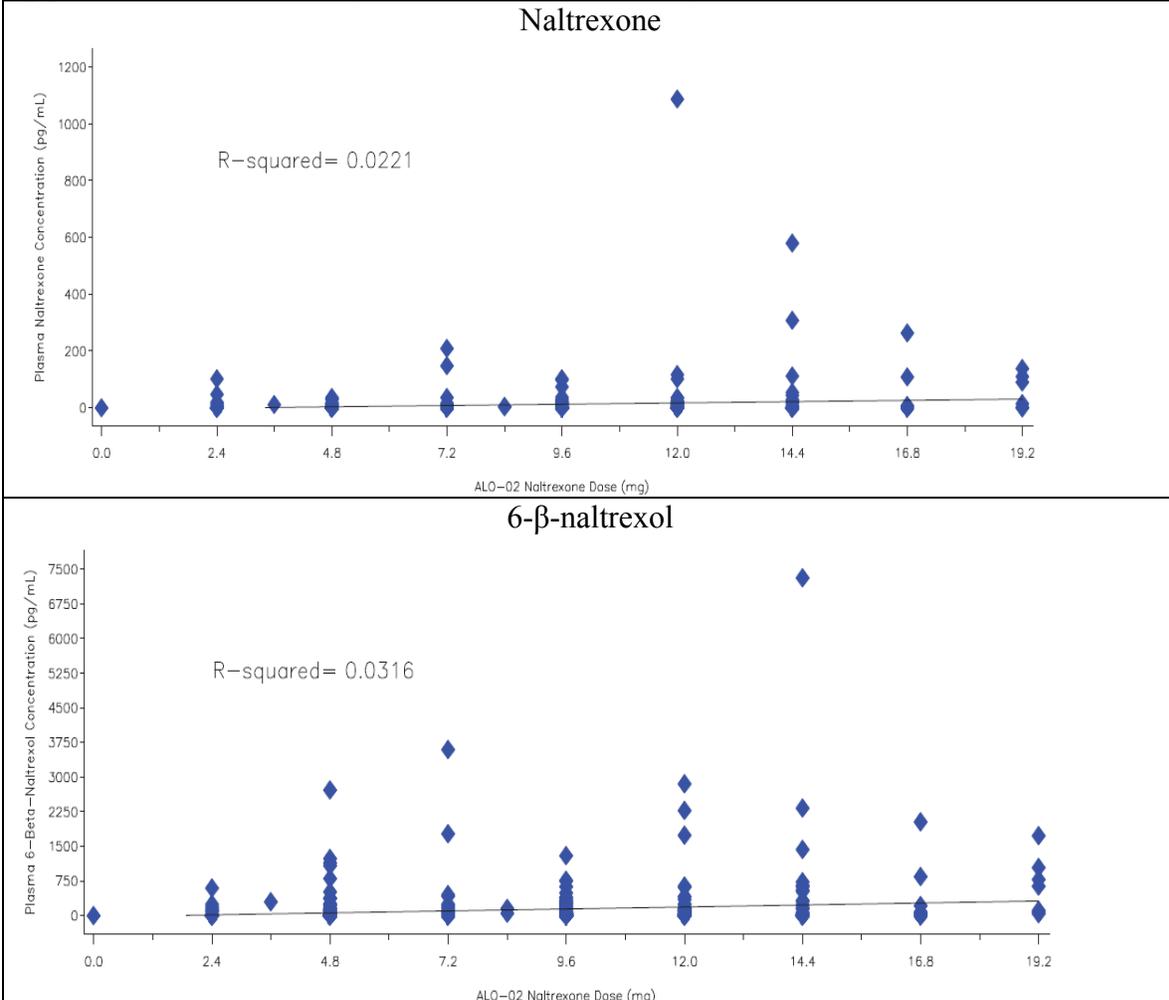


Figure 2.2.1b Detectable plasma naltrexone and 6-β-naltrexol concentrations (pg/mL) during different visits in study B4531002

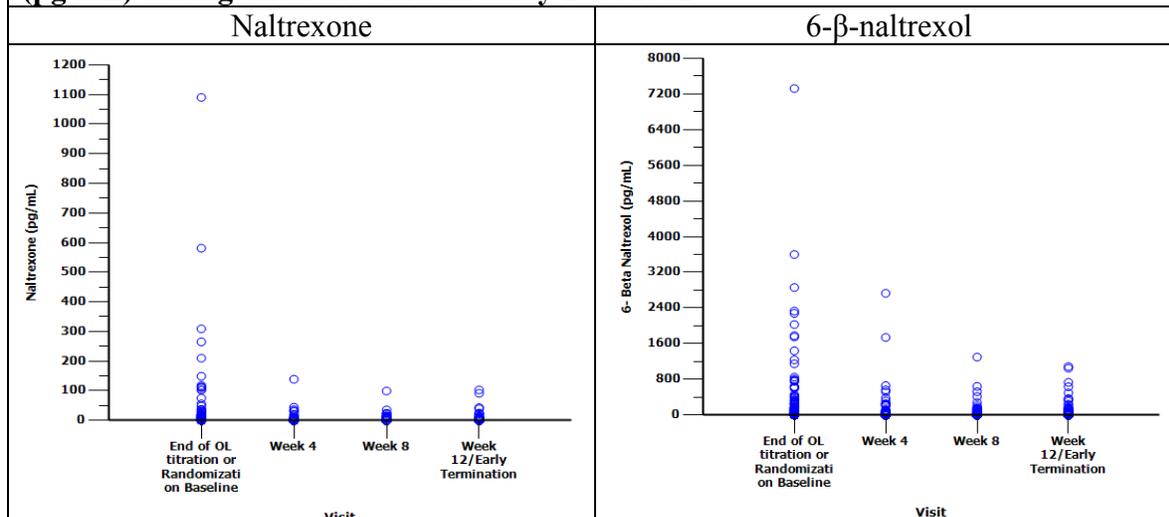


Table 2.2.1a Summary of plasma naltrexone and the 6-β-naltrexol concentrations in the pivotal 12 week efficacy study, B4531002

		Randomization Baseline or End of open label conversion and titration period*		Week 4 ALO-02 n= 115	Week 8 ALO-02 n= 107	Week 12/ Early Termination ALO-02 n= 137
		Placebo* n= 127	ALO-02 n= 139			
Naltrexone (pg/mL)	Range (BLQ- Maximum)	(BLQ-1090)	(BLQ-118)	(BLQ-139)	(BLQ-99)	(BLQ-103)
	Mean ± SD	25 ± 116	5 ± 17	3 ± 15	3 ± 11	3 ± 13
6-β-naltrexol (pg/mL)	Range (BLQ- Maximum)	(BLQ-7320)	(BLQ-2860)	(BLQ-2730)	(BLQ-1300)	(BLQ-1090)
	Mean ± SD	216 ± 800	98 ± 300	86 ± 315	48 ± 156	56 ± 163

BLQ- Below limit of quantitation; LOQ for both naltrexone and 6-β-naltrexol (pg/mL) is 4 pg/mL

*For the first 3 weeks of the Open-Label Conversion and Titration Period, a subject could have administered an IR oxycodone HCl at usual doses in conjunction with ALO-02, to manage the initial conversion from their previous therapy. For the remaining 3 weeks of the Open-Label Conversion and Titration Period, IR oxycodone HCl usage was not permitted, and the primary source of pain control was by means of maximizing the ALO-02 dose.

Long Term Safety Study (B4531001): For study B4531001, the XY plot (X-categorical) of naltrexone and 6-β-naltrexol concentrations (pg/mL) versus ALO-02 naltrexone daily dose is shown in the Figure 2.2.1c. The XY plot (X-categorical) of naltrexone and 6-β-naltrexol concentrations (pg/mL) versus ALO-02 average daily dose is shown in the Figure 2.2.1d. The mean ± SD and maximum naltrexone and 6-β-naltrexol concentrations of ALO-02 in the study B4531001 is shown in the Table 2.2.1b.

In this trial 1,720 samples were obtained from 375 subjects, and 1,324 (77%) were BLQ (<4 pg/mL). The highest observed naltrexone and 6-β-naltrexol concentrations were 331pg/mL and

4380 pg/mL, respectively. The mean steady-state concentrations of naltrexone were 1.7 pg/mL, 10 pg/mL, 9 pg/mL and 11.6 pg/mL for 10-40 mg dose group, $\geq 40-80$ mg dose group, $\geq 80-120$ mg dose group, and ≥ 120 mg dose group, respectively; the corresponding values for 6- β -naltrexol were 44 pg/mL, 156 pg/mL, 162 pg/mL, and 227 pg/mL. Note the mean concentrations of naltrexone encompasses concentration values that are below the LOQ value of 4 pg/mL since in the calculation of ‘mean values’, the BLQ values were considered as ‘zero’. The measurable plasma naltrexone or 6- β -naltrexol concentrations did not accumulate at any time during the study. Based on the individual subject data, there was no apparent relationship between plasma naltrexone or 6- β -naltrexol concentrations and the naltrexone daily dose.

Figure 2.2.1c: Detectable plasma naltrexone and 6- β -naltrexol concentrations (pg/mL) versus ALO-02 naltrexone daily dose in study B4531001

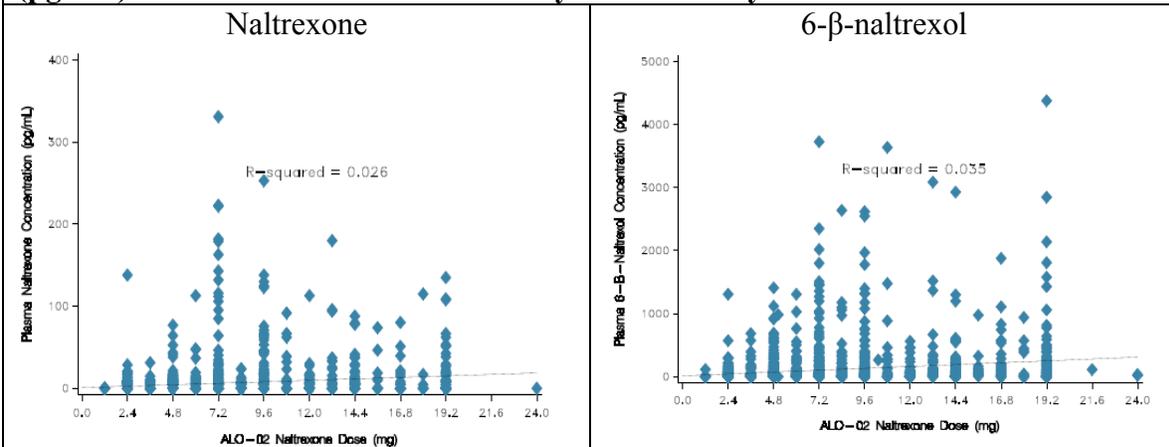


Figure 2.2.1d: Detectable plasma naltrexone and 6- β -naltrexol concentrations (pg/mL) versus different dose groups in study B4531001

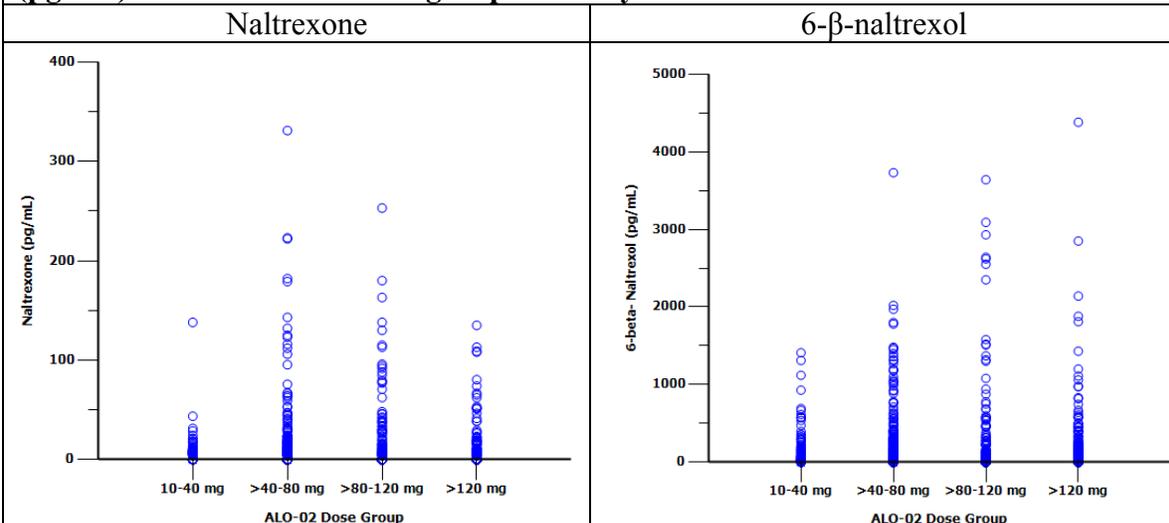


Table 2.2.1b. Summary of plasma naltrexone and the 6-β-naltrexol concentrations in the long-term safety study B4531001

		Average daily dose group			
		10-40 mg	>40-80 mg	>80-120 mg	>120 mg
Naltrexone (pg/mL)	Range (BLQ- Maximum)	(BLQ-138)	(BLQ-331)	(BLQ-180)	(BLQ-135)
	Mean ± SD	2 ± 8	10 ± 32	9 ± 22	12 ± 25
6-β-naltrexol (pg/mL)	Range (BLQ- Maximum)	(BLQ-1510)	(BLQ-3730)	(BLQ-3090)	(BLQ-4380)
	Mean ± SD	44 ± 134	156 ± 400	162 ± 410	227 ± 499

BLQ- Below limit of quantitation

Limit of quantitation for both naltrexone and 6-β-naltrexol (pg/mL) is 4 pg/mL

2.2.1 b Subjects with opioid withdrawal events and their naltrexone concentrations in Phase 3 studies:

The relationship between naltrexone or 6-β-naltrexol levels to opioid withdrawal events (exposure- response) has not been established. It is also to be noted that the opioid tolerance in a particular subject could affect an opioid withdrawal event.

In phase 3 studies, B4531001 and B4531002 15 subjects had defined opioid withdrawal events. Their naltrexone and 6-β-naltrexol concentrations in these subjects were taken around the time of each withdrawal event and not on the day of event (Table 2.2.1c). Four subjects' match the date of event and the date of sample collection were bolded in the Table (2.2.1c).

In most of events, the naltrexone concentrations are BLQ or lower. The highest naltrexone concentration was 139 pg/mL and the highest 6-β-naltrexol concentration was 1,740 pg/mL. For comparison, the mean naltrexone Cmax value was 8,550 pg/mL with Revia 50 mg tablet in a published study⁶. Two subjects (10221015 and 10271011) in the study B4531002 who had concentrations >500 pg/mL were not associated with withdrawal; COWS scores for these two subjects were ≤2 at each time point. Hence in the subjects who had defined opioid withdrawal events, it appears that opioid withdrawal events cannot be co-related the naltrexone concentrations.

⁶ Literature: Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9)

Table 2.2.1c. Subjects who had defined opioid withdrawal events in Phase 3 studies and the naltrexone and 6-β-naltrexol levels. Note naltrexone and 6-β-naltrexol concentrations taken around the time of each withdrawal event and not on the day of event)

Study	Subject ID	Date of Withdrawal or COWS Score ≥13	Date the Naltrexone or 6-β samples obtained	Naltrexone (pg/mL)	6-β-naltrexol (pg/mL)
B4531001	0003-0015	17 Apr 2012	02 Apr 2012	28.2	266
	0017-0013	22 Jul 2011	21 Jul 2011	BLQ	16.6
	0021-0009	03 Mar 2012	08 Mar 2012	22.3	62.4
	0027-0004	05 Jul 2011	5 Jul 2011	BLQ	BLQ
	0031-0010	13 Apr 2011	19 Apr 2011	BLQ	20.2
B4531002	10041014	19 Feb 2013	12 Feb 2013	BLQ	33.7
	10051005	23 Nov 2012	27 Nov 2012	4.3	50
	10151006	26 Oct 2012	Not available	Not available	
		13 Jan 2013	04 Jan 2013	139	1740
	10151010	16 Jan 2013	Not available	Not available	
	10171003	19 Sep 2012	12 Sep 2012	BLQ	45
			19 Sep 2012	6.9	149
	10171004	21 Sep 2012	14 Sep 2012	BLQ	122
	10561011	01 Mar 2013	19 Feb 2013	5	162
	10591008	08 Oct 2012	04 Oct 2012	BLQ	6.7
10661006	25 Oct 2012	25 Oct 2012	BLQ	47.1	
	10491003	22 Dec 2012	27 Dec 2012	BLQ	36.3

The PK dose linearity assessment for oxycodone and its metabolites under steady state conditions in the phase 3 trials is described in the section 2.2.5.2.

For final assessment of the safety and efficacy findings, refer to the Clinical review by Dr. Elizabeth Kilgore (reviewing Medical Officer). The pivotal efficacy-and-safety trial was randomized, double-blind, placebo-controlled clinical trial in patients with moderate to severe chronic low back pain. As per the clinical review, the mean change in the weekly diary NRS (Numerical Rating Scale) pain scores from randomization baseline to the end of study was statistically significantly superior for those treated with TROXYCA ER compared to the placebo group. With regards to safety, the major safety findings for Troxyca ER appear to be consistent with other ER opioids.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

ALO-02 analgesic activity is primarily due to the parent compound oxycodone. Another active component in the formulation is naltrexone which is sequestered in the inner core of ALO-02 pellets, which will be immediately released in the conditions of abuse such as manipulation or

diversion. In the Phase 1 and Phase 3 trails, low concentrations of naltrexone are released from the intact capsules.

The moieties oxycodone, its metabolites noroxycodone, oxymorphone and naltrexone and its metabolite 6- β -naltrexol was measured in the clinical trials.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. In the, randomized double-blind, placebo-controlled efficacy study (B4531002) the primary efficacy end point was mean change from randomization baseline in weekly average diary NRS-Pain score at final 2 weeks compared to placebo.

2.2.4 Exposure Response

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and response/efficacy. The pivotal efficacy study B4531002 provides evidence of efficacy for this product.

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety. The long term safety study B4531001 and the pivotal efficacy and safety study B4531001 provides evidence of safety for this product.

2.2.4.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of Oxycodone on QTc.

2.2.5 What are the general PK characteristics of the drug?

When administered orally, oxycodone is well absorbed. The oral bioavailability of IR oxycodone ranges from 60% to 87% with different formulations. Oxycodone HCl is extensively metabolized to noroxycodone, oxymorphone, and their glucuronide conjugates. The major circulating metabolite is noroxycodone. The formation of noroxycodone (N-demethylation) is mainly mediated by CYP3A4 and the formation of oxymorphone (O-demethylation) is mediated by CYP2D6. Oxymorphone is a known analgesic that is marketed in the US. However, although possessing analgesic activity, oxymorphone is present in plasma only in low concentrations (about 15% of administered dose), after oral administration of oxycodone. Oxycodone and its metabolites are excreted primarily via the kidney as both conjugated and unconjugated metabolites. Following intravenous administration, the volume of distribution (V_{ss}) 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. Precautions should be taken for special populations.

After single dose administration of Troxyca ER, the C_{max} of oxycodone appears at a T_{max} of 12 h. The apparent elimination half-life of oxycodone for Troxyca ER is ~7 h.

2.2.5.1 What are the single dose and multiple dose PK parameters?

See below in section 2.4.2

2.2.5.2. What are the characteristics of drug absorption? Are Troxyca ER PK parameters dose proportional?

From the IR Roxicodone® package insert, it is known that oxycodone oral bioavailability ranges from 60% to 87% with different formulations. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone (Roxicodone® package insert).

Dose proportionality:

[REDACTED] (b) (4)

The dose-linearity assessment of oxycodone of ALO-02 was done using 1) cross study comparison of Phase 1 PK studies (20, 40, 60 and 80 mg strengths) and 2) based on prescribed daily dose (10, 20, 30, 40, 60, and 80 mg strengths in phase 3 studies (B4531001).

Based on cross study comparison of Phase 1 single and multiple dose PK studies, the oxycodone component of ALO-02 demonstrated dose-linear increase in AUC and C_{max} values across the doses strengths for 20, 40, 60 and 80 mg (Table 2.2.5.2a). The dose normalized AUC_{inf} of 20, 40, 60 mg and dose normalized AUC_{tau} 80 mg were 10, 13, 11 and 14 ng.hr/mL/mg, respectively. The dose normalized C_{max} for 20, 40, 60 mg 80 mg were 0.54, 0.66, 0.48 and 0.75 ng/mL/mg, respectively. The oxycodone exposure, AUC and C_{max} dose normalized to 1 mg dose across Phase 1 studies in healthy volunteers was shown in the Figure 2.2.5.2a.

Based on prescribed daily doses in phase 3 study (B4531001), the mean steady state oxycodone concentrations increased dose linearly across the daily doses. The mean steady-state concentrations of oxycodone for 10-40 mg, >40-80 mg, >80-120 mg, and >120 mg daily dose groups were 15 ng/mL, 35 ng/mL, 60 ng/mL and 83 ng/mL, respectively Table 2.2.5.2b.

Table 2.2.5.2a: Dose linearity assessment of oxycodone from ALO-02 using cross-study comparison of phase 1 PK studies.

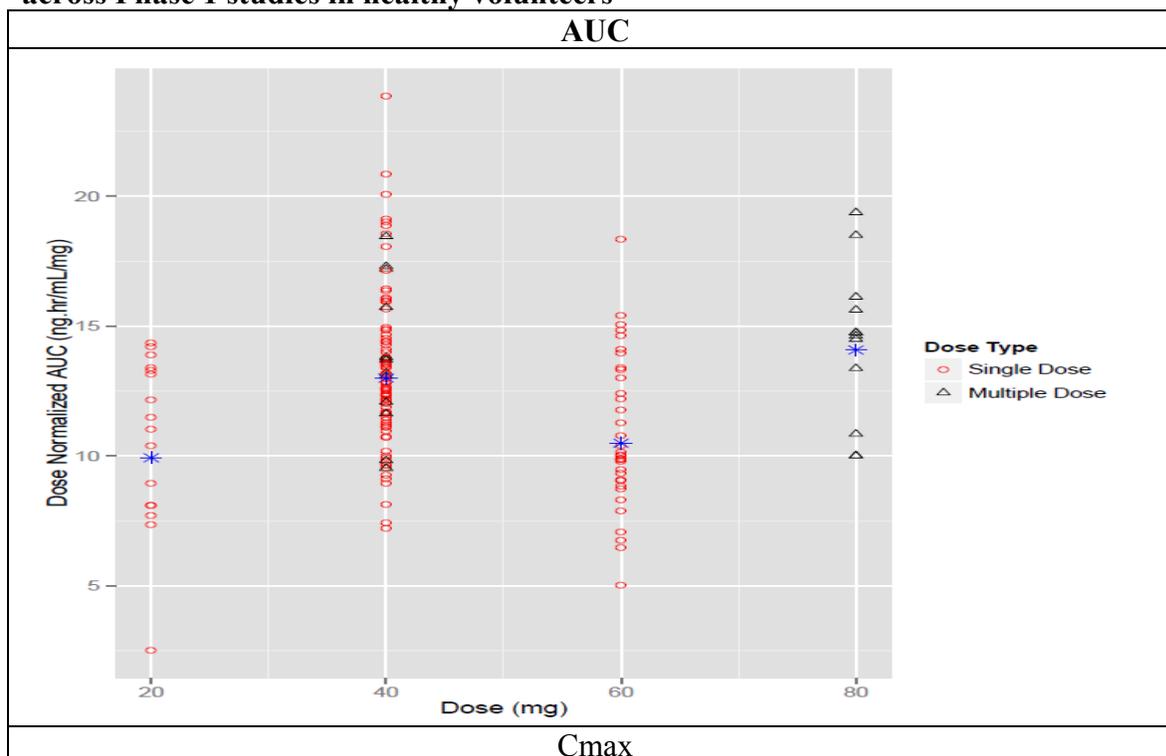
Strength	Study	Type of study	AUC _{0-t} (0-48 h)	AUC _{0-t} (dn) (0-48 h)(dn)	AUC _{inf} (SD) AUC _τ (MD)	AUC _{inf} (dn) (SD) AUC _τ (dn) (MD)	C _{max}	C _{max} (dn)
20 mg/2.4 mg	B4531004	alcohol effect (SD)	191	9.6	199	10.0	11	0.54
40 mg/4.8 mg	B4531007	relative BA (SD)	496	12.4	509	12.7	27	0.66
	B4531006	single and multiple dose (day1)	*	*			29	0.72
	B4531003	food effect (SD)	499	12.5	519	13.0	25	0.62
60 mg/7.2 mg	B4531008	abuse potential (SD)	^	^	629	10.5	29	0.48
80 mg/9.6 mg	B4531006	single and multiple dose (day1)	*	*	1126 (AUC _τ)	14.1 (AUC _τ dn)	60	0.75

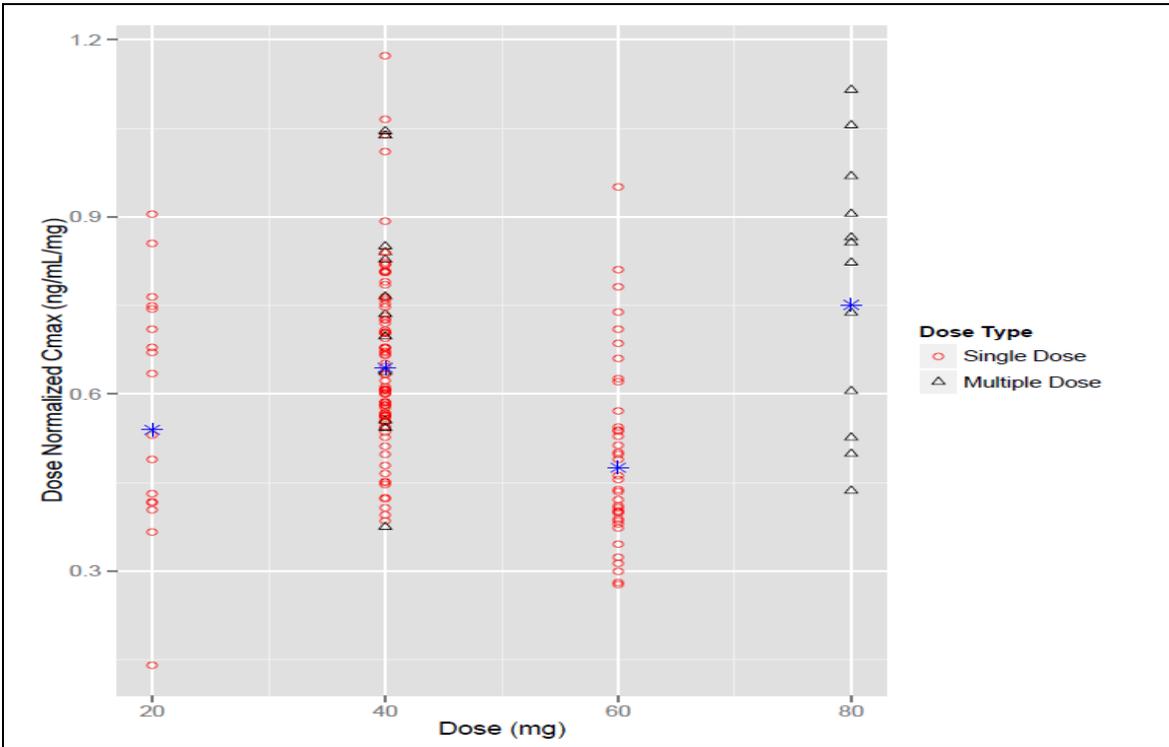
* AUC_t in single and multiple dose study was AUC (0-24h (day1) - hence not shown

^ AUC_t in abuse potential study was AUC (0-36h)- hence not shown

SD- Single dose; MD- Multiple dose

Figure 2.2.5.2a: Oxycodone exposure data (AUC and C_{max} dose normalized to 1 mg) across Phase 1 studies in healthy volunteers





Red circles represent dose normalized AUCinf (top) or Cmax (bottom) following single dose; black triangles represent dose normalized AUCtau (top) or Cmax (bottom) following multiple doses; geometric mean values for each dose group are represented by blue asterisk (*).

Table 2.2.5.2b: Dose linearity of oxycodone and noroxycodone using steady state concentrations among different daily dose groups in phase 3 study (B4531001).

	Oxycodone		
Prescribed Daily Dose Prior to PK Blood Sample	Mean ± SD	Median	Range (BLQ- Max)
10-40 mg (N= 888)	15.1 ± 11.8	12.8	BLQ - 70
>40-80 mg (N= 572)	35.4 ± 25.7	31.8	BLQ - 194
>80-120 mg (N= 229)	59.5 ± 40.7	53.4	BLQ - 264
>120 mg (N= 167)	82.8 ± 66.6	73.0	BLQ - 526

	Noroxycodone		
Prescribed Daily Dose Prior to PK Blood Sample	Mean ± SD	Median	Range (BLQ- Max)
10-40 mg (N= 887)	13.2 ± 12.3	10.7	BLQ - 94
>40-80 mg (N= 570)	35.2 ± 30.8	27.1	BLQ - 264
>80-120 mg (N= 229)	67.4 ± 55.9	53.9	BLQ - 403
>120 mg (N= 166)	96.3 ± 78.6	77.8	BLQ - 507

Naltrexone release is not linear across different dose strengths:

In the proposed formulation, in theory, the naltrexone is supposed to be sequestered and not be released or leaked when used as intact capsules. However, small amount of naltrexone is release from the product when used as intact capsules in the Phase 1 and Phase 3 clinical trials. To assess, if there any relationship between the release of sequestered naltrexone and dose-strength (low to high strength of ALO-02 ,10 mg/1.2 mg to 80 mg/9.6) or prescribed ALO-02 daily dose, the naltrexone and 6- β -naltrexol concentrations among different strengths were compared using the Phase 3 studies concentration data. The results show that there were no apparent relationship between plasma naltrexone concentrations and prescribed ALO-02 daily dose. The details were shown in the section 2.2.1

2.2.6. What are the pharmacokinetics characteristics of Troxyca ER under abuse?

The abuse deterrent studies, B4531008, B4531009 and B4981002 were aimed at demonstrating the utility of naltrexone sequestered in the ALO-02 pellets to deter drug tampering and diversion. For these studies, the PK endpoints, i.e., naltrexone release from crushed versus intact ALO-02 capsules was only reviewed. With regards to the PD endpoints, like Emax for drug liking and high and its statistical significance, refer to Control Substance Staff review in DARRTS.

2.2.6.1 Oral Abuse Potential Study:

The study B4531008 evaluated the oral abuse potential of ALO-02 in non-dependent, recreational opioid users. Subjects received single dose of following 6 treatments.

- Treatment A: Placebo
- Treatment B: Intact ALO-02 60 mg/7.2 mg
- Treatment C: Crushed ALO-02 60 mg/7.2 mg
- Treatment D: Crushed oxycodone HCl IR 60 mg
- Treatment E: Crushed ALO-02 40 mg/4.8 mg
- Treatment F: Crushed oxycodone HCl IR 40 mg

The mean oxycodone, naltrexone and 6- β -naltrexol plasma concentration-time profiles by treatment are presented in Figures 2.2.6.1a, 2.2.6.1b and 2.2.6.1c, respectively. The PK parameters for oxycodone and naltrexone are summarized descriptively in Table 2.2.6.1a and 2.2.6.1b, respectively.

Oxycodone PK after crushed oral administration:

The oxycodone and its metabolites (noroxycodone and oxymorphone) PK profiles and plasma exposures were similar between crushed ALO-02 capsules and crushed oxycodone IR tablets. When crushed, the ALO-02 capsules lose its ER properties and the rate of absorption of oxycodone from ALO-02 was similar to the IR oxycodone. The C_{max} was achieved within a median T_{max} of 0.6 -1 h post dose for all crushed treatments. The mean t_{1/2} values ranged from 4.2-4.4 h, respectively, and appeared to be unrelated to the dose level or whether ALO-02 or IR oxycodone crushed was administered.

Naltrexone PK after crushed oral administration:

Upon oral administration of crushed ALO-02 40 mg/4.8 mg and 60 mg/7.2 mg, the mean naltrexone C_{max} of 1074 and 1810 pg/mL was achieved, respectively within a median T_{max} of

0.5 h postdose for both strengths. Across the 1.5-fold dose increment of naltrexone HCl in ALO-02 (from 4.8 mg to 7.2 mg), the naltrexone C_{max} and AUC_{inf} values appeared to increase in a dose proportional manner by 1.69- and 1.63-fold, respectively. The mean t_{1/2} values were 5.4-5.6 h, respectively, and appeared to be unrelated to the dose level. For the intact ALO-02 60 mg/7.2 mg, naltrexone plasma exposure was BLQ, with the exception of a measurable concentration in 1 sample that was considered anomalous. In subject 10011090, unusually high plasma concentrations for naltrexone (687 pg/mL) and 6-β naltrexol (11,300 pg/mL) were observed at the 1.5 h postdose, while the concentrations of both naltrexone and 6-β naltrexol at all other time points were BLQ (<4 pg/mL).

Figure 2.2.6.1a Mean plasma oxycodone concentration-time profiles following oral administration of crushed and intact ALO-02 capsules and crushed oxycodone IR tablets

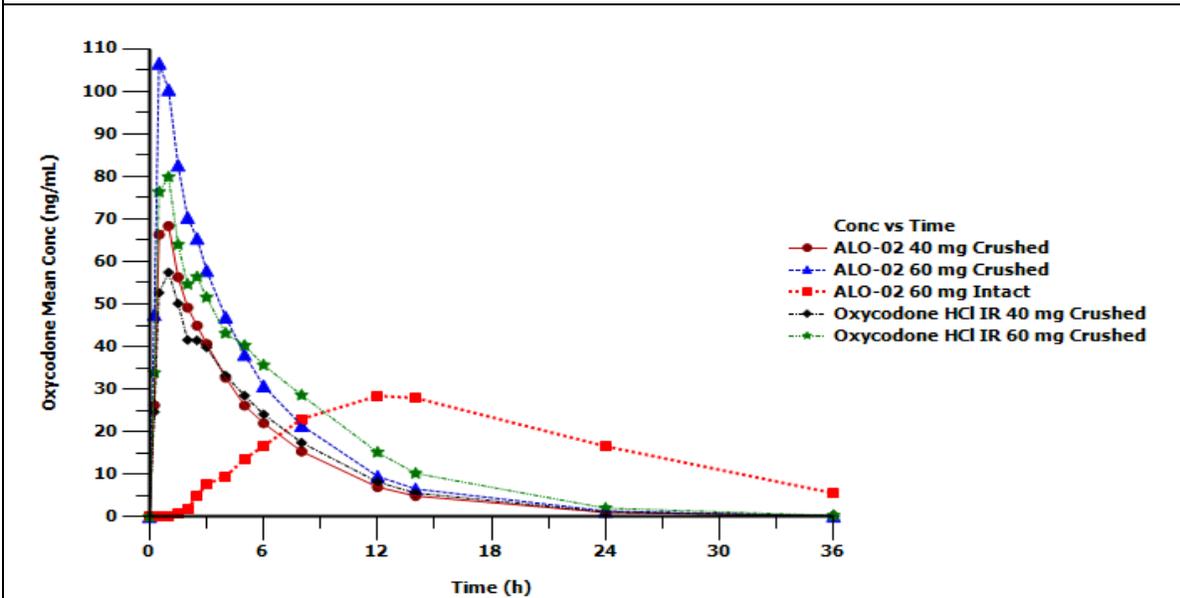


Figure 2.2.6.1.b : Mean plasma naltrexone concentration-time profiles following oral administration of crushed ALO-02 capsules

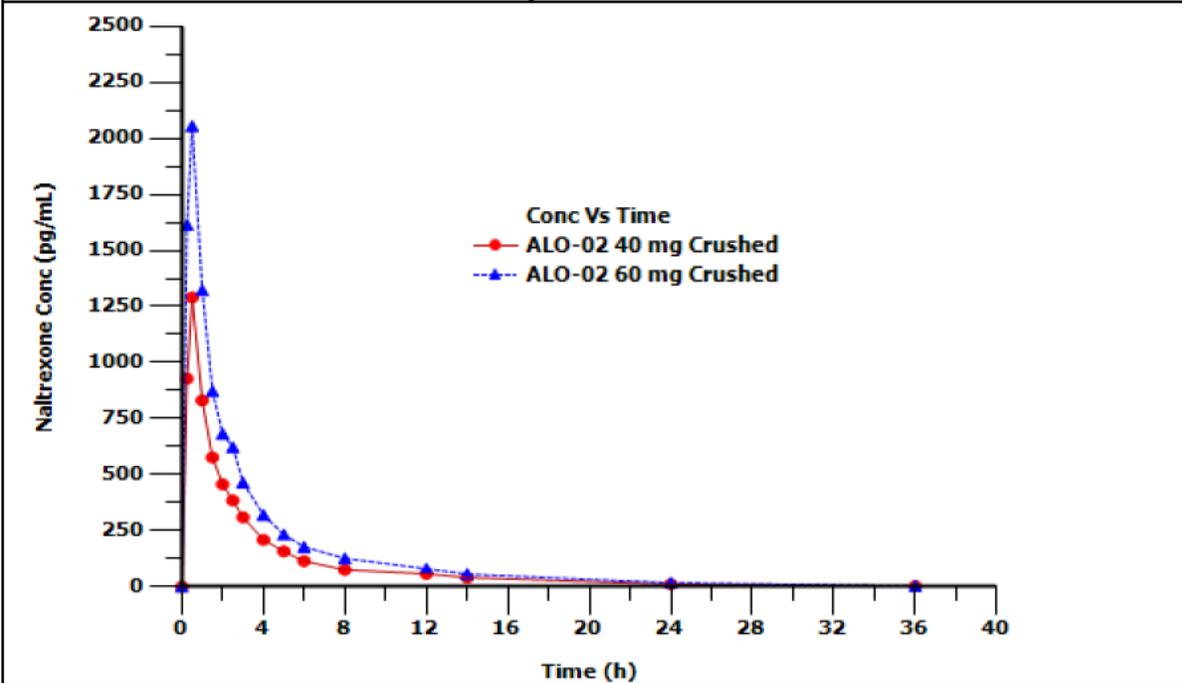


Figure 2.2.6.1c : Mean plasma 6-beta-naltrexol concentration-time profiles following oral administration of intact and crushed ALO-02 capsules

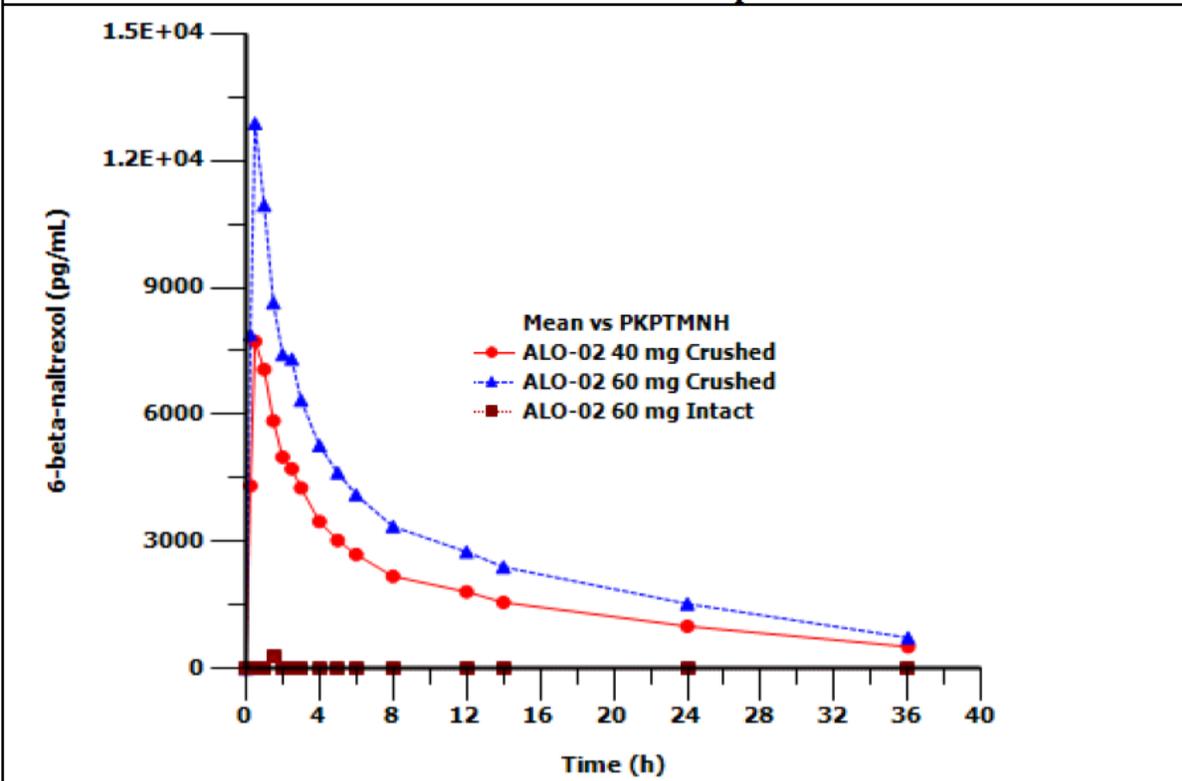


Table 2.2.6.1a Summary of plasma oxycodone pharmacokinetic parameters following oral administration of crushed and intact ALO-02 capsules and crushed oxycodone IR tablets.

PK Parameter (Units) ^a	Crushed ALO-02 40 mg/4.8 mg	Crushed Oxycodone IR 40 mg	Intact ALO-02 60 mg/7.2 mg	Crushed ALO-02 60 mg/7.2 mg	Crushed Oxycodone IR 60 mg
N, n	36, 36	37, 37	38, 35	37, 37	36, 36
AUC1h (ng.h/mL)	41.59 (44)	34.76 (46)	0.0009 (7078)	68.94 (31)	49.94 (39)
AUC2h (ng.h/mL)	100 (27)	86 (24)	0.65 (77)	153 (23)	115 (31)
AUC8h (ng.h/mL)	268 (26)	259 (23)	77 (26)	394 (24)	355 (28)
AUC12h (ng.h/mL)	308 (28)	305 (25)	177 (24)	450 (26)	435 (29)
AUC24h (ng.h/mL)	342 (30)	344 (28)	441 (27)	495 (28)	505 (32)
AUCinf (ng.h/mL)	348 (31)	351 (28)	629 (28)	504 (28)	517 (33)
AUCinf (dn) (ng h/mL/mg)	8.7 (31)	8.8 (28)	10.5 (28)	8.4 (28)	8.6 (33)
AUClast (ng.h/mL)	346.2 (31)	348.8 (28)	556.7 (27)	501.4 (29)	514.4 (33)
AUClast (dn) (ng h/mL/mg)	8.7 (31)	8.7 (28)	9.3 (27)	8.4 (28)	8.6 (33)
Cmax (ng/mL)	76 (29)	65 (24)	29 (31)	112 (26)	87 (31)
Cmax (dn) (ng/mL/mg)	1.91 (29)	1.63 (24)	0.48 (31)	1.86 (26)	1.45 (31)
Tmax (h)	1.03 (0.53-2.55)	1.03 (0.28-3.07)	12.1 (3.03-14.1)	0.58 (0.53 -1.6)	1.04 (0.30-2.6)
t1/2 (h)	4.4±0.7	4.3±0.7	9.3±1.6	4.4±0.6	4.2±0.5

Plasma concentrations at the 1.5 h time point for Subject 10011090 (intact ALO-02 60 mg/7.2 mg treatment) and Subject 10011134 (crushed ALO-02 60 mg/7.2 mg treatment) were considered anomalous, and were excluded from all PK calculation, and plots.

Abbreviations: CV=coefficient of variation; dn=dose normalized to 1 mg dose; IR=immediate release; N=number of subjects in the treatment and contributing to the mean; n=number of subjects with reportable AUCinf (dn) and t1/2; .

a. Geometric mean (%CV) for all except: median (range) for Tmax and arithmetic mean (±SD) for t1/2.

Table 2.2.6.1b: Summary of plasma naltrexone pharmacokinetic parameters following oral administration of crushed or intact ALO-02 capsules

PK Parameter (Units) ^a	Crushed ALO-02 40 mg/4.8 mg	Intact ALO-02 60 mg/7.2 mg	Crushed ALO-02 60 mg/7.2 mg
N, n	36, 33	38, NR	37, 35
AUC1h (ng.h/mL)	0.66 (80)	0 (0)	1.17 (72)
AUC2h (ng.h/mL)	1.22 (67)	0 (0)	2.01 (67)
AUC8h (ng.h/mL)	2.26 (57)	0 (0)	3.62 (57)
AUC12h (ng.h/mL)	2.49 (55)	0 (0)	3.98 (56)
AUC24h (ng.h/mL)	2.76 (56)	0 (0)	4.36 (57)
AUCinf (ng.h/mL)	2.9 (56)	NR	4.70 (54)
AUCinf (dn) (ng h/mL/mg)	0.60 (56)	NR	0.65 (54)
AUClast (ng.h/mL)	2.80 (57)	0 (0)	4.41 (57)
AUClast (dn) (ng.h/mL/mg)	0.58 (57)	0 (0)	0.61 (57)
Cmax (ng/mL)	1.07 (76)	0 (0)	1.81 (75)
Cmax (dn) (ng/mL/mg)	0.22 (76)	0 (0)	0.25 (75)
Tmax (h)	0.55	NR	0.55
t1/2 (h)	5.44±1.72	NR	5.57±2.09

Abbreviations: NR=not reported

2.2.6.2 Intranasal (IN) Abuse Potential Study:

The study B4531009 evaluated the IN abuse potential of ALO-02 in non-dependent, recreational opioid users. Subjects received single dose of following 4 treatments.

- Treatment A: Placebo (sugar spheres) crushed, weight matched to ALO-02 capsule fill weight
- Treatment B: Crushed ALO-02 30 mg/3.6 mg
- Treatment C: Placebo (lactose tablets) crushed, weight matched to oxycodone IR (3 × 10 mg)
- Treatment D: Oxycodone IR 30 mg (3 × 10 mg tablets crushed)

The mean oxycodone and naltrexone plasma concentration-time profiles by treatment are presented in Figures 2.2.6.2a and 2.2.6.2b, respectively. The PK parameters for oxycodone and naltrexone and 6-β-Naltrexol are summarized descriptively in Table 2.2.6.2a and 2.2.6.2b, respectively.

Oxycodone PK after crushed IN administration: Following IN administration, the oxycodone rate of absorption from the crushed ALO-02 (30 mg/3.6 mg) capsules was delayed (mean C_{max} achieved within a median T_{max} of 1.6 h) compared to crushed oxycodone IR tablets (mean C_{max} at T_{max} 0.5 h). Oxycodone systemic exposure based on geometric mean AUC_{last} and AUC_{inf} was 20% lower and C_{max} 30% lower for the crushed ALO-02 treatment compared to crushed oxycodone IR treatment. This difference is likely related to the formulation differences between ER ALO-02, and IR oxycodone such that part of the unabsorbed dose of ALO-02 from the nasal cavity may have been swallowed and entered the gastrointestinal tract, being subjected to a higher first-pass metabolism resulting in less oral BA. This possibility is consistent with the longer median T_{max} observed for ALO-02 (1.6 h) compared to IR oxycodone 30 mg (0.5 h). Mean t_{1/2} values were approximately similar, 4 h for both treatments given intranasally.

Naltrexone PK after crushed IN administration: Following IN administration of crushed ALO-02 30 mg/3.6 mg capsules, individual naltrexone C_{max} was achieved within 0.3 - 1.6 h postdose (median T_{max} - 0.3 h). The mean C_{max} was 4372 pg/mL. The mean t_{1/2} was 3.6 h.

Figure 2.2.6.2a Median plasma oxycodone concentration-time profiles following IN administration of crushed ALO-02 30 mg/3.6 mg capsules and crushed oxycodone IR 30 mg tablets

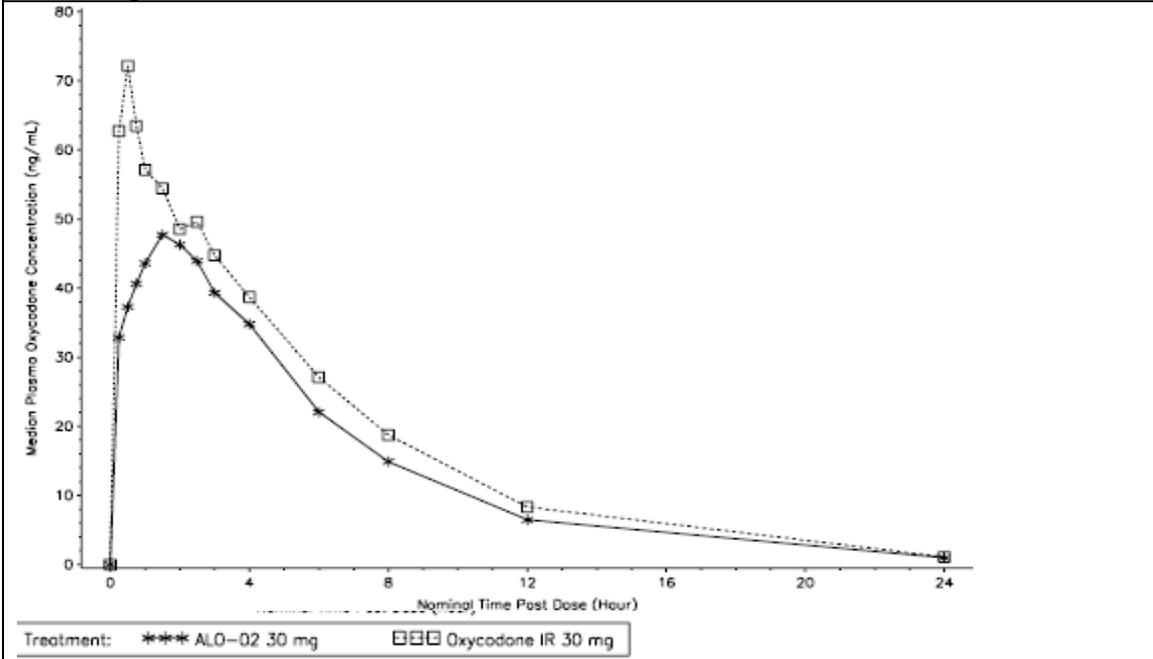


Figure 2.2.6.2b : Median plasma naltrexone concentration-time profiles following IN administration of crushed ALO-02 30 mg/3.6 mg capsules

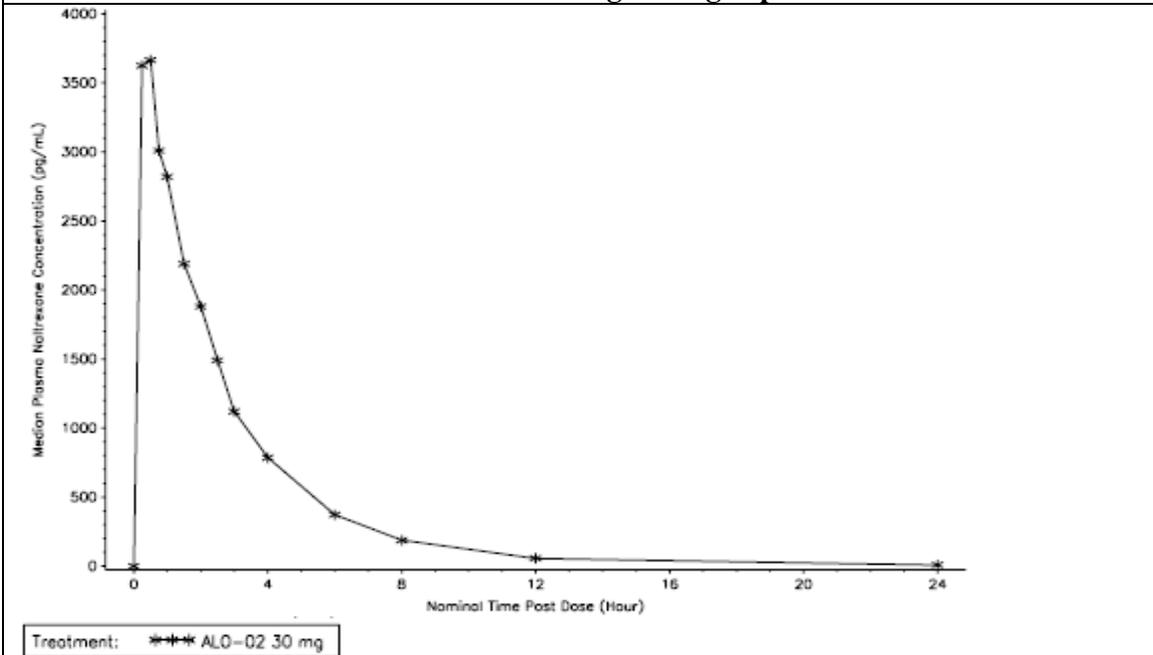


Figure 2.2.6.2c : Median plasma 6-beta-naltrexol concentration-time profiles following oral administration of crushed ALO-02 30 mg/3.6 mg capsules

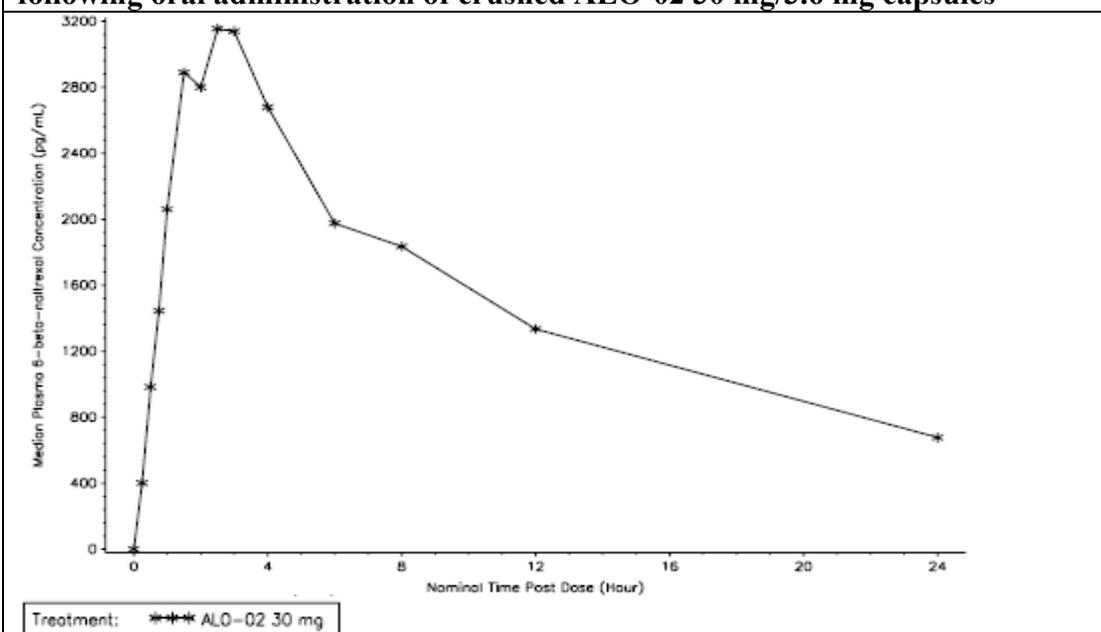


Table 2.2.6.2a: Summary of plasma oxycodone PK parameters following IN administration of crushed ALO-02 30 mg/3.6 mg capsules and crushed oxycodone IR 30 mg tablets

Parameter, Units a	ALO-02 30 mg/3.6 mg	Oxycodone IR 30 mg
N, n	30, 30	32, 32
AUC1h (ng.h/mL)	32.2 (30)	57.8 (25)
AUC2h (ng.h/mL)	78.3 (27)	113.3 (24)
AUC8h (ng.h/mL)	256.6 (25)	320.6 (22)
AUCinf (ng.h/mL)	346.8 (30)	432.7 (28)
AUClast (ng.h/mL)	339.7 (29)	422.6 (26)
Cmax (ng/mL)	56.4 (24)	80.4 (24)
Tmax (h)	1.59 (0.28-4.07)	0.48 (0.28-1.07)
t _{1/2} (h)	4.2 ± 0.7	4.1 ± 0.9

Abbreviations: AUC = area under the curve; CV = coefficient of variation; N = number of subjects receiving the treatment and contributing to the mean; n = number of subjects with reportable AUCinf and t_{1/2}; SD = standard deviation.

a. Geometric mean (%CV) for all except: median (range: min, max) for Tmax and arithmetic mean (± SD) for t_{1/2}.

Table 2.2.6.2b: Summary of plasma naltrexone and 6-β-Naltrexol PK parameters following IN administration of crushed ALO-02 30 mg/3.6 mg capsules

Parameter, Units a	Naltrexone	6-β-Naltrexol
N, n	30, 30	30, 11
AUC1h (ng.h/mL)	3.01 (28)	0.92 (54)
AUC2h (ng.h/mL)	5.48 (26)	3.45 (45)
AUC8h (ng.h/mL)	9.85 (30)	18.1 (26)
AUCinf (ng.h/mL)	10.71 (29)	NR
AUClast (ng.h/mL)	10.66 (29)	36.1 (25)
Cmax (ng/mL)	4.372 (31)	3.88 (32)
Tmax (h)	0.32 (0.28-1.57)	2.05 (0.77-4.07)
t½ (h)	3.58 ± 0.71	NR

Abbreviations: AUC = area under the curve; CV = coefficient of variation; N = number of subjects receiving the treatment and contributing to the mean; n = number of subjects with reportable AUCinf and t½; SD = standard deviation; NR= not reported;

a. Geometric mean (%CV) for all except: median (range: min, max) for Tmax and arithmetic mean (± SD) for t½.

2.3 Extrinsic Factors

2.3.1 What is the effect of food on the BA of Troxyca ER?

The food effect of ALO-02 was evaluated in the study B4531003. It was an open-label, single-dose, randomized, 3-period crossover study. Food effect was evaluated using the strength 40 mg/ 4.8 mg (referred to as 40-mg ALO-02) in non-naltrexone blocked 24 healthy subjects. Eligible subjects received the following 3 treatments:

- Treatment A: 1×40 mg ALO-02 with 240 mL of water under fasted conditions.
- Treatment B: 1×40 mg ALO-02 with 240 mL of water under fed conditions (standard high fat breakfast).
- Treatment C: 1×40-mg ALO-02 with the ALO-02 pellets sprinkled on approximately 1 tablespoon of applesauce. The contents of the spoon were swallowed without mixing and without delay, and were followed immediately with 240 mL of water under fasting conditions.

Lot and Formulation Identification (40 mg ALO-02):

- Lot # 668B-1104-T109
- Dosage Material Number: D1100311

PK blood samples during each study period:

- Oxycodone: 0, 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 24, 36, and 48 h
- Naltrexone and 6-β-naltrexol: 0, 1, 2, 4, 8, 12, 24, 48, and 120 h.

Analytes measured: oxycodone, naltrexone, and 6-β-naltrexol

- oxycodone: LLOQ- 0.1 ng/mL; calibration range: 0.1 to 50 ng/mL
- naltrexone and 6-β-naltrexol: LLOQ- 4 pg/mL; calibration range: 4 to 2000 pg/mL

Results:

The mean plasma oxycodone concentration-time profiles and the PK parameters following single doses of 40 mg ALO-02 administered under fasted, fed and ALO-02 pellets sprinkled on applesauce (fasted) is shown in the Figure 2.3.1a and Table 2.3.1a, respectively. The geometric means ratios (ALO-02 fed / ALO-02 fasted and ALO-02 pellets sprinkled on applesauce / ALO-02 fasted) and the 90% confidence intervals for AUC_t, AUC_{inf} and C_{max} are shown in Figure 2.3.1b

ALO-02 Fed vs Fasted: Administration of 40 mg ALO-02 under fed conditions resulted in no change in AUC (geometric mean) and ~7% increase in C_{max} (geometric mean) compared to fasted conditions. The ratios of adjusted geometric means for ALO-02 under fed relative to the reference (ALO-02 under fasted) were 99%, 100%, and 107% for AUC_{inf}, AUC_{last}, and C_{max} respectively, with 90% CIs within 80-125% limits (96-103%, 97-104% and 98-116%, for AUC_{inf}, AUC_{last}, and C_{max} respectively). The ALO-02 being an ER formulation, the oxycodone median T_{max} under fasted was 12 h with range of 12-16 h. Under fed conditions, the median T_{max} is delayed by 2 h compared to fasted appearing at 14 h with range of 12-24 h. There was no difference in the oxycodone half-life between fasted and fed treatments.

ALO-02 pellets sprinkled on applesauce vs Fasted: Administration of 40 mg ALO-02 pellets sprinkled on applesauce (fasted) resulted in no change in AUC (geometric mean) and C_{max} (geometric mean) compared to fasted conditions. The ratios of adjusted geometric means for ALO-02 pellets sprinkled on applesauce relative to the reference (ALO-02 under fasted) were 101%, 101%, and 98% for AUC_{inf}, AUC_{last}, and C_{max} respectively, with 90% CIs within 80-125% limits (98-104%, 98-104% and 90-106%, for AUC_{inf}, AUC_{last}, and C_{max} respectively). The oxycodone median T_{max} under fasted is 12 h with range of 12-16 h, whereas when ALO-02 pellets sprinkled on applesauce, the median T_{max} is delayed by 1 h appearing at 13 h with of range 8-16 h. There was no difference in the oxycodone half-life between fasted and ALO-02 pellets sprinkled on applesauce treatments.

Figure 2.3.1a: Mean plasma oxycodone concentration-time profiles following single oral doses of ALO-02 40 mg administered under fasted, fed and ALO-02 pellets sprinkled on applesauce (fasted)

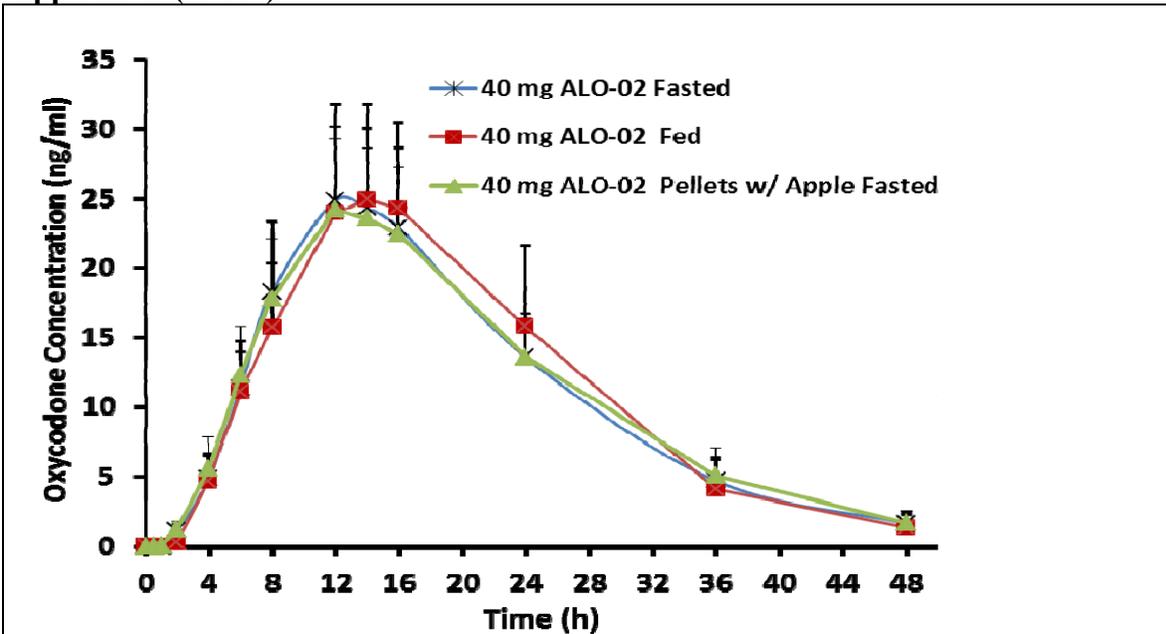
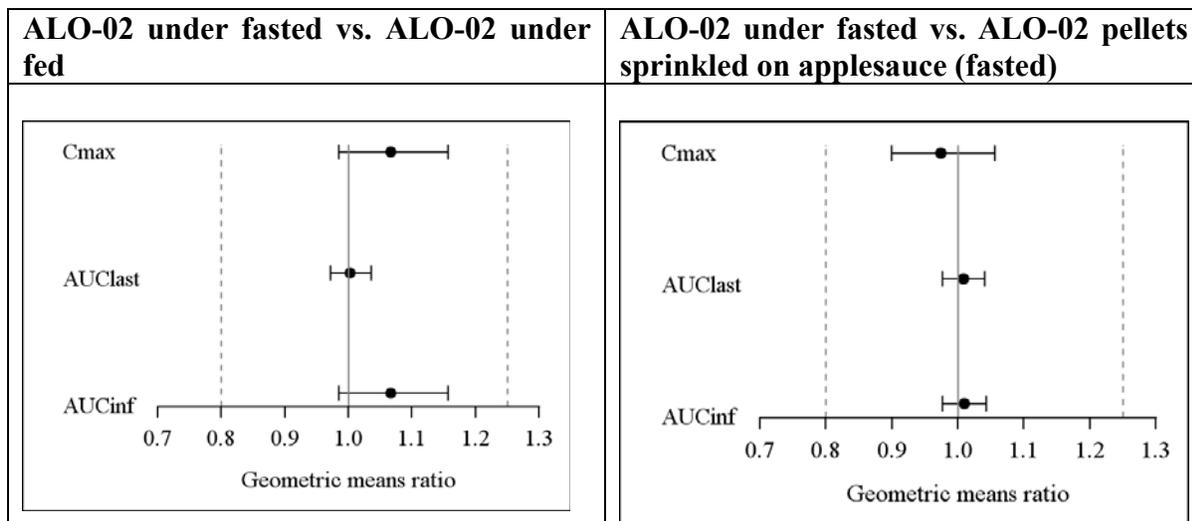


Table 2.3.1a: Summary of Oxycodone PK parameters after ALO-02 40 mg administration in fasted and fed conditions.

PK Parameter ^a	40 mg ALO-02 Fasted (n=24)	40 mg ALO-02 Fed (n=24)	40 mg ALO-02 Pellets Sprinkled on Applesauce (Fasted) (n=24)
AUC _{inf} (ng.hr/mL)	518.5 (24)	514.3 (23)	523.4 (21)
AUC _{last} (ng.hr/mL)	499.3 (23)	500.7 (23)	503.3 (19)
C _{max} (ng/mL)	24.9 (25)	14.8 (37)	13.3 (21)
C ₂₄ (ng/mL)	13.27 (23)	26.52 (22)	24.23 (21)
T _{max} (hr)	12 (12 -16)	14 (12-24)	13 (8 -16)
t _{1/2} (hr)	7.8 ± 1.6	6.7 ± 1.6	7.9 ± 1.693

^a Geometric mean (% CV) for all except median (range) for T_{max} and arithmetic mean (±SD) for t_{1/2}.

Figure 2.3.1b: Ratios of geometric means and the 90% confidence intervals for AUC and Cmax when ALO-02 administered under fasted versus ALO-02 administered under fed and ALO-02 administered under fasted versus ALO-02 pellets sprinkled on applesauce (fasted).



Naltrexone and 6-β-naltrexol concentrations (B4531007):

In the food effect study, plasma naltrexone concentrations for the 40 mg ALO-02 treatment were BLQ (4.00 pg/mL) in all subjects (Table 2.3.1.b). The 6-β-naltrexol concentrations were observed in 6 out of 24 subjects, 10 out of 24, and 6 out of 24 subjects in ALO-02 Fed, fasted and ALO-02 pellets sprinkled on applesauce treatment arms, respectively, with BLQ (4.00 pg/mL) in other subjects. The maximum plasma 6-β-naltrexol concentration was 30 pg/mL observed at 120 h post dose in ALO-02 fed treatment arm.

Table 2.3.1b: Observed 6-β-naltrexol concentrations following single oral doses of 40 mg ALO-02 capsules in descending order. Naltrexone levels were not detected (LOQ- 4 pg/mL)

ALO-02 Cap Fast			ALO-02 Cap Fed			ALO-02 Pellets w/ Apple Fast		
Subject#	Time postdose (h)	Conc (pg/ml)	Subject#	Time postdose (h)	Conc (pg/ml)	Subject#	Time postdose (h)	Conc (pg/ml)
10011001	2	17.1	10011007	120	29.5	10011023	4	23.3
10011001	4	13.9	10011008	120	16.1	10011007	4	22.5
10011001	1	13.2	10011018	120	13.2	10011007	8	22.3
10011020	48	12.1	10011024	120	11	10011007	12	20.4
10011007	120	12	10011021	48	10.4	10011007	24	20.1
10011007	48	9.9	10011019	48	10.1	10011007	2	19.5
10011001	8	9.6	10011016	48	9	10011007	0	19.2
10011001	12	7.5	10011001	120	7.9	10011023	1	18.4
10011014	2	6.6	10011009	120	7.3	10011023	2	18.2
10011014	0	6.5	10011010	48	6.8	10011007	1	17.2
10011014	4	6.5	10011021	48	4.8	10011007	48	15.4
10011014	1	6.1				10011023	8	12.9
10011024	120	5.6				10011007	120	11.8
10011024	1	4.9				10011023	12	11.1
10011014	8	4.6				10011002	4	9.6
10011014	12	4.6				10011002	8	8.5
10011024	0	4.6				10011023	24	8
10011007	8	4.5				10011012	2	7.6
10011024	4	4.5				10011002	2	7.5
10011007	24	4.4				10011012	8	7.3
10011024	2	4.4				10011002	12	7
10011011	120	4.3				10011024	120	6.2
10011001	24	4.2				10011012	4	6.1
10011007	12	4.1				10011012	12	6.1
						10011012	24	5.5
						10011001	120	4.9
						10011012	1	4.4
						10011002	24	4.1
Mean		7			11			12
SD		4			7			7
Range		4-17			5-30			4-23

Conclusions of ALO-02 food effect:

The observed no change in AUC and Cmax of ALO-02 under fed and ALO-02 pellets sprinkled on applesauce (fasted) compared to fasted conditions does not warrant any ALO-02 dosing recommendations in relation to food. The ALO-02 can be taken without regards to food.

2.3.2. Is there a potential for dose dumping in the presence of alcohol?

The effect of alcohol 20% and 40% on the bioavailability of ALO-02 was evaluated in vivo study in healthy volunteers (B4531004). It was an open-label, single-dose, randomized, 3-period crossover study using the strength 20 mg/ 2.4 mg (referred to as 20 mg ALO-02) in naltrexone blocked healthy subjects. The eligible subjects received the following 3 treatments:

- Treatment A: 1×20 mg ALO-02 with 240 mL of chilled (2⁰ to 8⁰ C) water under fasted conditions.
- Treatment B: 1×20 mg ALO-02 with 240 mL of chilled (2⁰ to 8⁰ C) aqueous solution of 20% alcohol under fasted conditions.

Treatment C: 1×20 mg ALO-02 with 240 mL of chilled (2⁰ to 8⁰ C) aqueous solution of 40% alcohol under fasted conditions.

Lot and Formulation Identification (20 mg ALO-02)

- Lot # 11-010707
- Dosage Material Number: D1100297

Naltrexone Block:

- To block opioid related unexpected adverse effects associated with oxycodone, all the subjects were given naltrexone at -12 h -1 h, and + 24 h.

PK blood samples during each study period:

- Oxycodone: 0, 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 24, 36, and 48 h

Analytes measured: oxycodone

- oxycodone: LLOQ- 0.1 ng/mL; calibration range: 0.1 to 50 ng/mL
- Since the study was conducted under naltrexone blockade, the naltrexone and 6-β-naltrexol release from ALO-02 capsules was not measured.

Results:

A total of 17 subjects were treated with ALO-02 20 mg and ALO-02 20 mg with 40% ethanol treatment and 16 subjects were treated with ALO-02 20 mg with 20% ethanol treatment were analyzed for PK parameters. The mean plasma oxycodone concentration-time profiles and the PK parameters following single oral doses of ALO-02 20 mg administered with water, 20% alcohol, and 40% alcohol is shown in the Figure 2.3.2a and Table 2.3.2a, respectively. The geometric means ratios (ALO-02 with 20% alcohol / ALO-02 with water and ALO-02 with 40% alcohol / ALO-02 with water) the 90% confidence intervals for AUC and C_{max} are shown in Figure 2.3.2 b. The line plot showing oxycodone C_{max} and AUC change in each individual when ALO-02 administered with water versus 20% alcohol and 40% alcohol is shown in Figure 2.3.2 c. The individual oxycodone C_{max} and AUC_{inf} values and the ratios following ALO-02 20 mg administered with 20% alcohol and 40% alcohol to water is shown in the Table 2.3.2b and Table 2.3.2c, respectively.

The administration of ALO-02 20 mg with 40% alcohol resulted in ~ 12% increase in AUC_{inf} and a 38% increase in geometric mean C_{max} values compared to the reference (water) treatment. The ratios of adjusted geometric means for the test treatment (ALO-02 20 mg with 40% alcohol) relative to the reference (ALO-02 20 mg with the water) were 112%, 115%, and 138% for AUC_{inf}, AUC_{last}, and C_{max} respectively, with the upper 90% CIs outside of the 80-125% limits (96-130%, 99-134% and 119-159%, for AUC_{inf}, AUC_{last}, and C_{max} respectively). The observed 38% increase in C_{max} with 40% alcohol treatment is due to one subject # 10011106 who had apparent 6.35 fold increase with 40% alcohol treatment compared to water treatment. The details of this is subject is shown below. In this subject, there was no difference in median T_{max} between ALO-02 with water [12 h (range 6 -14h)] and ALO-02 with alcohol treatments [20% alcohol- 12 h (range 6 -14 h) ; 40% alcohol- 8 h (range 6-14 h)], which

indicates any dose-dumping of ALO-02. There was no difference in the oxycodone half-life between water and alcohol treatments.

Figure 2.3.2a: Mean plasma oxycodone concentration-time profiles following single oral doses of ALO-02 20 mg administered with water, 20% alcohol, and 40% alcohol.

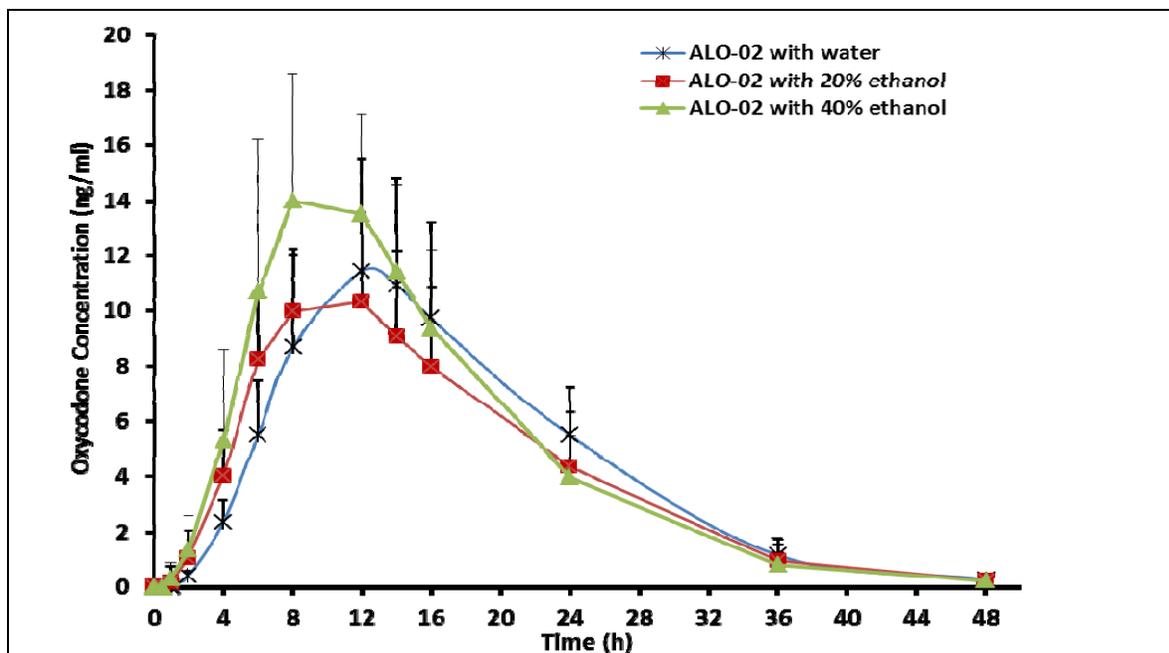


Table 2.3.2a: Plasma oxycodone PK parameter values following single oral doses of ALO-02 20 mg administered with water, 20% alcohol, and 40% alcohol

Parameter (Units) ^a	ALO-02 20 mg With Water (n=17)	ALO-02 20 mg With 20% Alcohol (n=16)	ALO-02 20 mg With 40% Alcohol (n=17)
AUC _{inf} (ng.hr/mL)	199.2 (46)	185.0 (40)	223.4 (27)
AUC _{last} (ng.hr/mL)	191.3 (46)	182.5 (40)	221.2 (27)
C _{max} (ng/mL)	10.8 (47)	10.7 (23)	14.8 (28)
C ₂₄ (ng/mL)	5.0 (51)	3.8 (71)	3.7 (43)
T _{max} (hr)	12 (6 -14)	12.0 (6 -14)	8.02 (6 -14)
t _{1/2} (hr)	5.6 ± 0.9	5.8 ± 1.0	5.9 ± 0.9

^a Geometric mean (% geometric CV) for all except median (range) for T_{max}; arithmetic mean (±SD) for t_{1/2}.

Subject 10011005 vomited shortly after the dose of ALO-02 20 mg with 20% alcohol (Treatment B) and samples were collected only up to 2 hours post dose. Hence, C_{max} and AUC_{inf} were not available.

Subject 10011001 missed Period 3 (ALO-02 with water) 36 h and 48 h post dose PK samples because the subject was discharged on Day 2 due to a family emergency. Hence AUC_{inf} was not reported.

Figure 2.3.2b: Ratios of geometric means and the 90% confidence intervals for AUC and C_{max} when ALO-02 administered with water versus ALO-02 administered with 20%

alcohol and ALO-02 administered with water versus ALO-02 administered with 40% alcohol

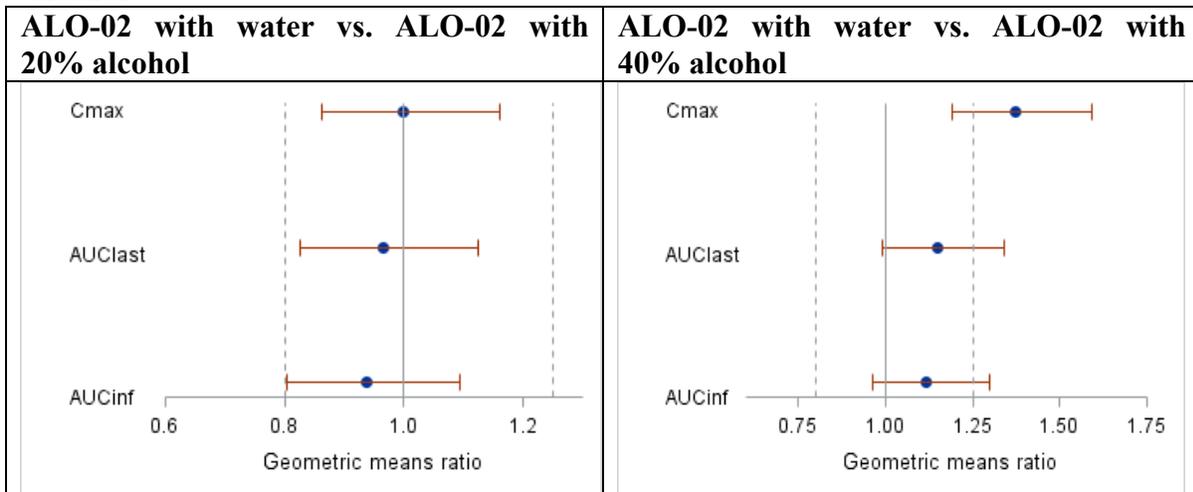
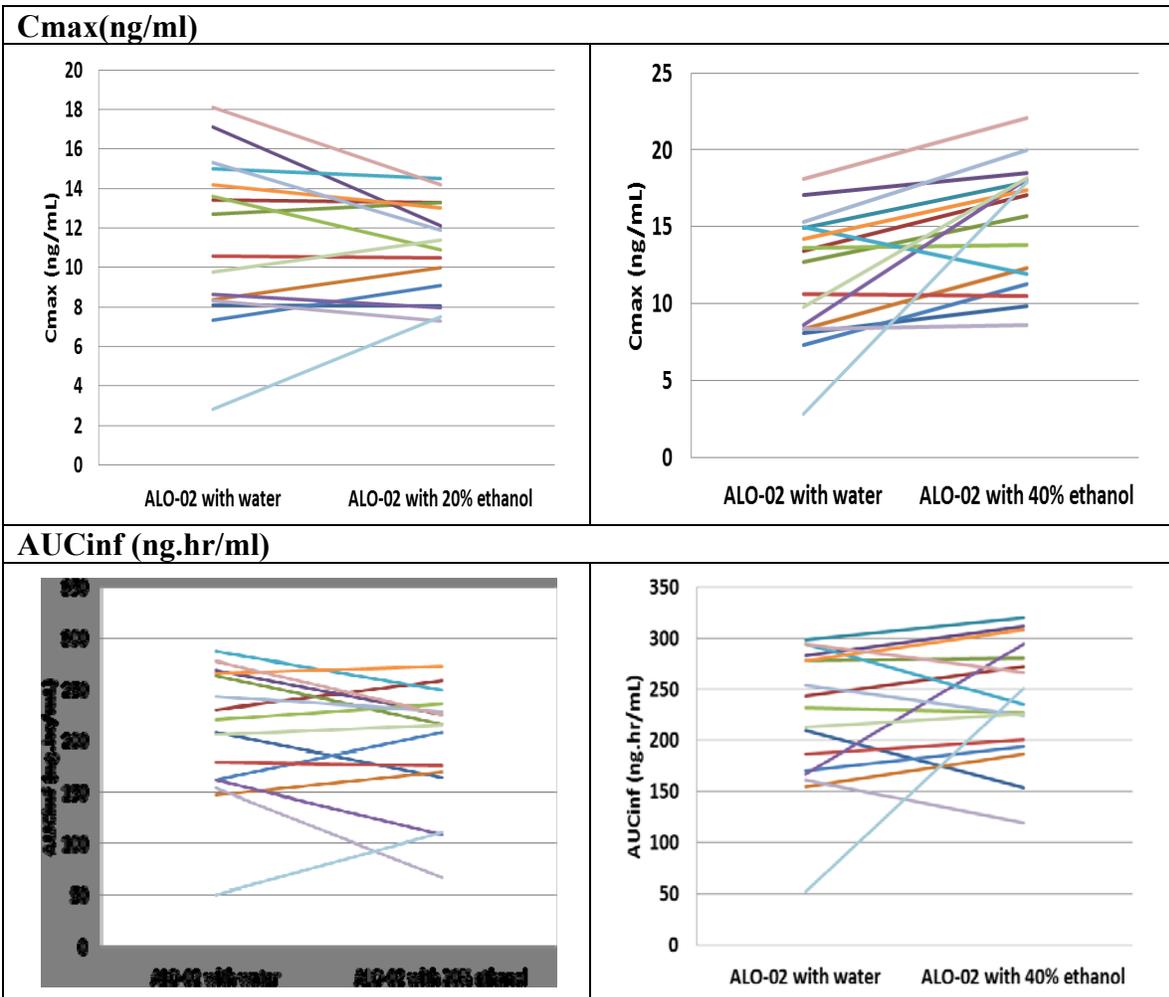


Figure 2.3.2c: Line plot showing oxycodone Cmax and AUC change in each individual following single dose of ALO-02 20 mg administered with water, 20% alcohol, and 40% alcohol.

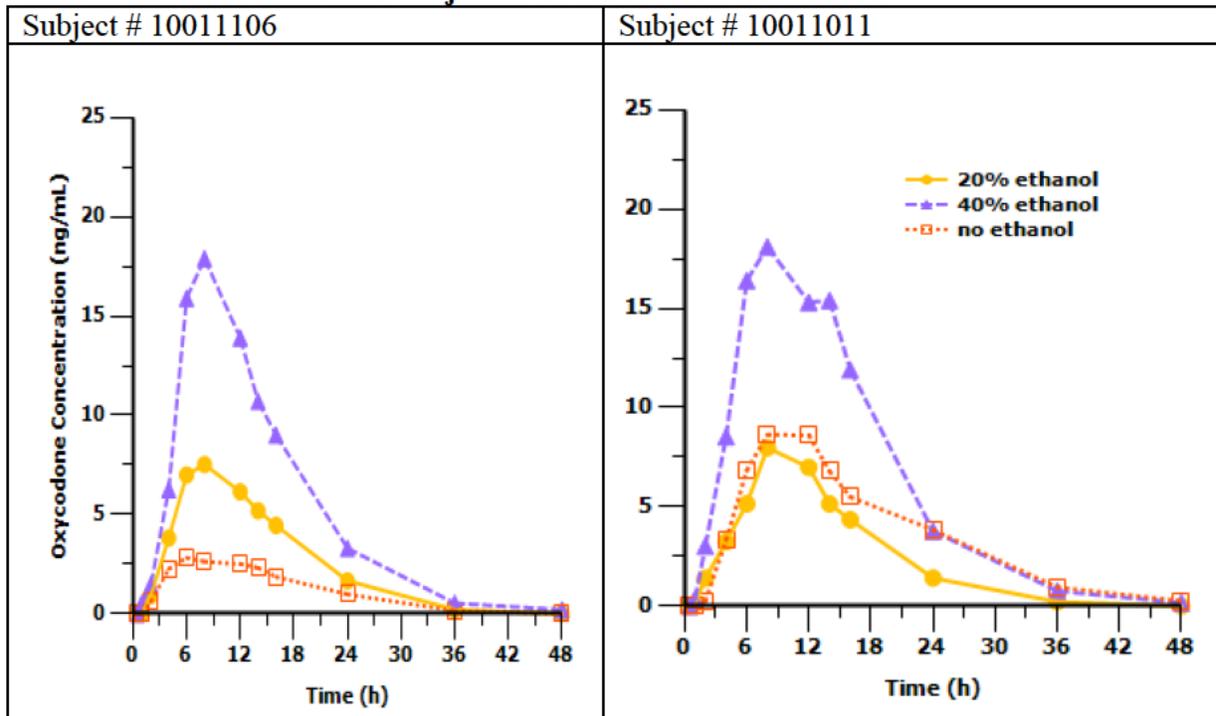


Subjects with high fold exposure in 20 and 40% alcohol treatments:

The individual oxycodone C_{max} and AUC ratios of ALO-02 administered 20% alcohol and 40% alcohol versus water treatments is shown in Table 2.3.2 b and Table 2.3.2 c, respectively. Of the 17 subjects, 2 subjects had more than 100% higher C_{max} or AUC_{inf} with alcohol treatments compared to the water. The details are as below.

- Subject # 10011106 had 2.7 fold (170%) and 6.4 fold (540%) increase in C_{max} with 20% and 40% alcohol treatment, respectively. The corresponding AUC_{inf} increase was 2.2 fold (120%) and 4.8 fold (380%), respectively (Tables 2.3.2 b and 2.3.2 c). Further examination of this subject's concentrations, this subject's C_{max}, AUC values with 20% or 40% alcohol were within the range of exposures seen in other subjects, whereas the exposures following ALO-02 with water were the lowest, driving the ratios apparently to highest values. This subject did not vomit during the study. Additionally, there was no shift in T_{max} values in this subject among the treatments (6 h with water, 8 h with 20% alcohol and 40% alcohol), which would have indicated dose dumping in this subject. The exact reason for the lower exposure in ALO-02 water treatment in this subject is not known. The concentration profile in this subject is shown in the Figure 2.3.2 d.
- Subject # 10011011 had 2.1 fold (110%) increase in C_{max} with 40% alcohol treatment (Figure 2.3.2 d)

Figure 2.3.2 d. Individual oxycodone C_{max} and AUC ratios of ALO-02 administered 20% alcohol and 40% alcohol in subjects # 10011106 and # 10011011



Looking at the individual C_{max} and AUC values, the greatest increase in C_{max} and AUC was observed at 6.4-fold and 4.8 fold, respectively in Subject #10011106. Based on this subject's C_{max}, AUC values with 20% or 40% alcohol within the range of exposures seen in other

subjects, and the exposures following ALO-02 with water the lowest, driving the ratios apparently to highest values, the observed alcohol effect may not be considered approvability issue. The greatest individual increase in Cmax was higher than those of the already approved extended-release opioid products (e.g. 2.7-fold for OPANA ER, 4.38-fold for NUCYNTA ER, 5-fold for EMBEDA ER); and much lower than that of PALLADONE (16-fold). Therefore, the alcohol interaction with the proposed product is not considered as an approvability issue.

Table 2.3.2b: Individual Oxycodone Cmax values and the ratios following ALO-02 20 mg administered with 20% alcohol and 40% alcohol to water. The ratios above 2 fold are bolded.

Subject ID	Cmax(ng/mL)			Cmax Ratio (20% / water)	Cmax Ratio (40% / water)
	ALO-02 with water	ALO-02 with 20% alcohol	ALO-02 with 40% alcohol		
10011001	8.09	8.07	9.83	1.00	1.22
10011002	13.4	13.3	17.1	0.99	1.28
10011003	12.7	13.3	15.7	1.05	1.24
10011004	17.1	12.1	18.5	0.71	1.08
10011005	14.9	\$	17.9	\$	1.20
10011007	8.35	9.97	12.3	1.19	1.47
10011008	7.32	9.11	11.3	1.24	1.54
10011009	10.6	10.5	10.5	0.99	0.99
10011010	13.6	10.9	13.8	0.80	1.01
10011011	8.63	7.98	18.1	0.92	2.10
10011012	15	14.5	11.9	0.97	0.79
10011013	14.2	13	17.4	0.92	1.23
10011014	15.3	11.9	20	0.78	1.31
10011016	18.1	14.2	22.1	0.78	1.22
10011017	9.78	11.4	18.2	1.17	1.86
10011018	8.32	7.3	8.61	0.88	1.03
10011106	2.82	7.52	17.9	2.67	6.35

Table 2.3.2c: Individual Oxycodone AUCinf values and the ratios following ALO-02 20 mg administered 20% alcohol, and 40% alcohol to water. The ratios above 2 fold are bolded.

Subject ID	AUCinf (ng hr/mL)			AUCinf Ratio (20% / water)	AUCinf Ratio (40% / water)
	ALO-02 with water	ALO-02 with 20% alcohol	ALO-02 with 40% alcohol		
10011001	*	164	146	*	*
10011002	231	259	262	1.12	1.14
10011003	264	216	267	0.82	1.01
10011004	269	226	298	0.84	1.11
10011005	285	\$	304	\$	1.07
10011007	147	170	181	1.15	1.23
10011008	162	209	187	1.29	1.15
10011009	179	176	191	0.98	1.06
10011010	221	236	220	1.07	0.99
10011011	162	108	282	0.67	1.75
10011012	287	249	227	0.87	0.79
10011013	266	273	299	1.03	1.12
10011014	243	229	214	0.94	0.88
10011016	278	226	258	0.81	0.93

10011017	206	215	220	1.05	1.07
10011018	154	67	117	0.44	0.76
10011106	50	111	242	2.20	4.79

§ Subject 10011005 vomited shortly after the dose of ALO-02 20 mg with 20% alcohol (Treatment B) and samples were collected only up to 2 hours post dose. Hence, C_{max} and AUC_{inf} were not available.

* Subject 10011001 missed Period 3 (ALO-02 with water) 36 h and 48 h post dose PK samples because the subject was discharged on Day 2 due to a family emergency. Hence AUC_{inf} was not reported.

2.4. General Biopharmaceutics

2.4.1. What is the relative bioavailability of Troxyca ER compared to the reference drugs, Roxicodone IR and Revia?

The bioavailability of ALO-02 capsules (40 mg) relative to reference IR roxicodone tablets (20 mg) was evaluated in the study B4531007. This was an open-label, single-dose, randomized, 2-way crossover study in healthy adult volunteers (n=14 subjects). Each subject received 2 treatments separated by at least a 7-day washout period as following:

Treatment A: 1×40 mg ALO-02 with 240 mL of water under fasted conditions (test).

Treatment B: IR oxycodone 20 mg tablets (Roxicodone: 1 × 15 mg tablet plus 1× 5 mg tablet) under fasted conditions (reference)

Lot and Formulation Identification:

	Lot #	Dosage Material Number:
ALO-02 40 mg	11-010734	D1100299
Roxicodone 5 mg tablet	160134A	NA
Roxicodone 15 mg tablet	061170A	NA

Analytes measured: oxycodone, naltrexone, and 6-β-naltrexol

- oxycodone: LLOQ- 0.1 ng/mL; calibration range: 0.1 to 50 ng/mL
- naltrexone and 6-β-naltrexol: LLOQ- 4 pg/mL; calibration range: 4 to 2000 pg/mL

PK blood samples during each study period:

- Oxycodone:
 - Treatment A: 0, 1, 2, 4, 6, 8, 12, 14, 16, 24, 36 and 48 h postdose
 - Treatment B: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 48 h
- Naltrexone and 6-β-naltrexol: 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h.

Results:

The plasma concentration-time profiles comparing 40 mg ALO-02 capsules and Roxicodone 20 mg tablets under fasted conditions are shown in figures 2.4.1. The corresponding PK parameters are shown in Table 2.4.1a. The geometric mean ratios and the 90% CIs for AUC_{0-t} and AUC_{0-∞} and C_{max} are shown in the Table 2.4.1b. The summary of results is shown below:

- Based on the dose normalized PK parameter geometric mean ratios (90% CIs), the adjusted geometric means were 107.2% (96.7%, 118.8%) for AUC_{inf}(dn) and 106.05% (95.4%, 118.0%) for AUC_{last}(dn).

- Consistent with the PK profile of the ER ALO-02 formulation, the dose normalized C_{max} for ALO-02 is lower than IR oxycodone (reference) with test/reference adjusted geometric means ratio of 33.0% (90% CI: 28.8%, 37.9%). This is in part due to the slow initial oxycodone release and a prolonged T_{max} (range 8-16 hours) for the ALO-02 formulation, compared to a T_{max} of 0.5 to 2.0 hours for the IR oxycodone.

Naltrexone and 6-β-naltrexol concentrations (B4531007):

- Plasma naltrexone concentrations from intact 40 mg ALO-02 capsules were BLQ (4.00 pg/mL) in all subjects. The 6-β-naltrexol concentrations were observed in 3 out of 13 subjects (Table 2.4.1c), with BLQ (4.00 pg/mL) in other subjects. The maximum plasma 6-β-naltrexol concentrations was 45 pg/mL observed at 96 h post dose.

Figure 2.4.1a: Mean ± SD plasma oxycodone concentration-time profiles following single oral doses of ALO-02 40 mg and Roxicodone 20 mg under fasted conditions.

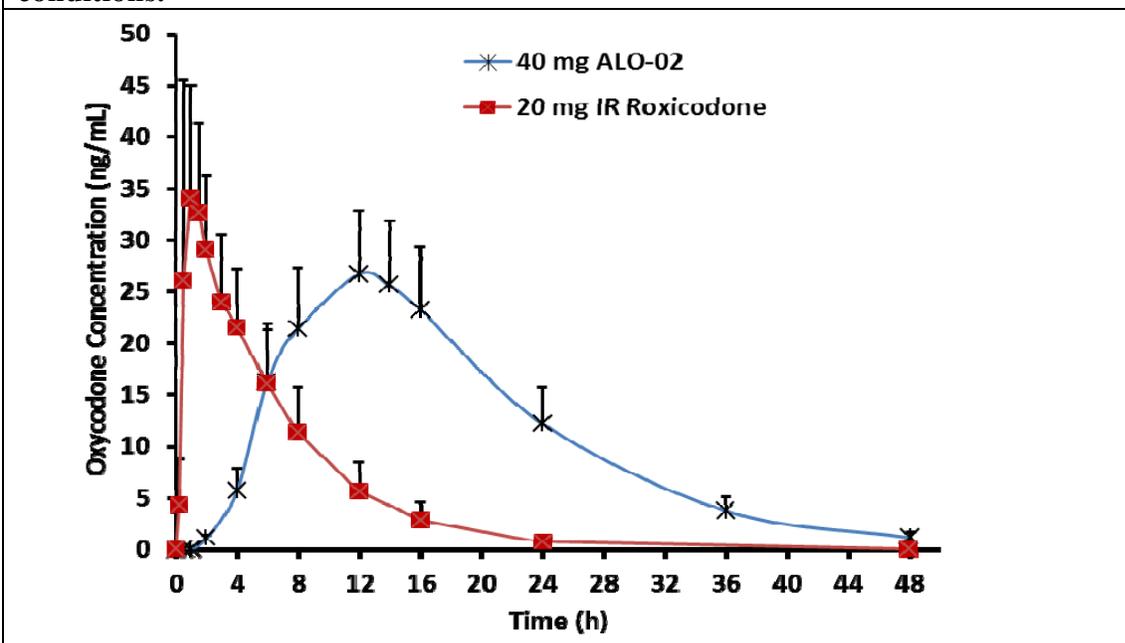


Table 2.4.1a. Plasma oxycodone PK parameters following single oral doses of ALO-02 40 mg capsules and IR oxycodone 20 mg tablets.

Parameter ^a	ALO-02 40 mg (Fasted) (N=13)*	IR Oxycodone 20 mg (Fasted) (N=13)*
AUC _{inf} (ng.hr/mL)	509 (29)	239 (23)
AUC _{inf} (dn) (ng.hr/mL/mg)	12.7 (29)	11.9 (23)
AUC _{last} (ng.hr/mL)	496 (29)	236 (23)
AUC _{last} (dn) (ng.hr/mL/mg)	12.4 (29)	11.8 (23)
C ₂₄ (ng/mL)	11.6 (37)	0.69 (61)
C _{max} (ng/mL)	27 (24)	40 (25)
C _{max} (dn) (ng/mL/mg)	0.67 (24)	2.0 (25)
T _{max} (h)	12 (8-16)	1 (0.5 -2)
t _{1/2} , (h)	7.2 ± 0.96	4.6 ± 1.2

^a Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean ±SD for t_{1/2}.

- *Subject 10011004 receiving IR oxycodone 20 mg treatment was excluded from the analysis. This subject had an approximately 5-fold lower oxycodone AUC_{inf} value compared with the mean value for the treatment as a whole (50.7 ng hr/mL versus 213.7 ng hr/mL) even though there was no clinical evidence (for example, vomiting) that would ordinarily exclude the data.
- *Subject 10011012 received only IR oxycodone 20 mg and discontinued from the study prior to receiving ALO-02 40 mg.

Table 2.4.1b: Geometric mean ratios and 90% CIs for dose-normalized plasma oxycodone pharmacokinetic parameters following single oral doses of 40 mg ALO-02 capsules and IR oxycodone 20 mg tablets

Parameter	Adjusted Geometric LS mean		Ratio [Test/Reference] (90% CI of ratio)
	Test (n=12) *	Reference (n=12) *	
AUC _{inf} (dn) ng.hr/mL/mg	12.75	11.90	107.17 (96.65, 118.83)
AUC _{last} (dn) ng.hr/mL/mg	12.45	11.74	106.05 (95.35, 117.96)
C _{max} (dn) ng/mL/mg	0.67	2.02	33.04 (28.80, 37.92)

*Subject 10011004 and 10011012 were excluded from BE analysis

Table 2.4.1c: Observed 6-β-naltrexol concentrations following single oral doses of intact 40 mg ALO-02 capsules. Naltrexone levels were not detected in any subject (LOQ- 4 pg/mL).

	Subject ID	Time post dose (h)	6-β-naltrexol (pg/mL)	Naltrexone
	10011001	72	20.3	Naltrexone levels were not detected in any subject with LOQ of 4 pg/mL.
	10011001	96	45.4	
	10011001	120	20.4	
	10011003	96	4.9	
	10011003	48	5.47	
	10011003	120	8.45	
	10011004	96	4.66	
	10011014	96	4.75	
	10011014	120	5.31	
Mean			13.3	
SD			13.7	
Range			(4.7- 45.4)	

Relative BA versus Revia for naltrexone component:

Sponsor has not conducted formal relative BA study versus Revia. The relative BA of ALO-02 versus Revia cannot be conducted in healthy volunteers under naltrexone blockade, since ALO-02 has sequestered naltrexone. To rely on the Agency’s prior findings of safety of Revia, for bridging the naltrexone exposures from ALO-02 capsule strengths 10 mg/1.2 mg - 80 mg/9.6 mg as intended (intact, orally), Sponsor provided following justification:

1. The dose of naltrexone HCl in the highest ALO-02 80 mg/9.6 mg strength is 5-fold lower compared with Revia 50 mg tablets.

- When ALO-02 is used as intended (intact capsules taken orally), a relatively small extent of systemic naltrexone exposure is expected. This is supported by the observed PK results from studies with ALO-02 that showed no quantifiable naltrexone plasma concentrations in Phase 1 studies, and the mean plasma naltrexone concentrations ranged between 1.7-11.6 pg/mL and 2.9- 24.9 pg/mL in the two Phase 3 studies, B4531001 and B4531002, respectively. The highest observed individual plasma naltrexone concentrations were 331 pg/mL and 1090 pg/mL in studies B4531001 and B4531002, respectively. In comparison, the mean naltrexone C_{max} following Revia 50 mg is 8550 pg/mL (Meyer et al, J Clin Psychiatry. 1984 Sep; 45 (9 Pt 2):15- 9), which is over 300-fold higher compared with the highest mean concentration (24.9 pg/mL) and over 7-fold higher than the highest individual concentration (1090 pg/mL) observed following ALO-02 capsules.

Since the highest amount of naltrexone that can be released from ALO-02 80 mg/9.6 mg strength is 9.6 mg, which is 5-fold lower compared with approved Revia 50 mg tablets, the proposed justification is for not conducted formal relative BA study versus Revia is adequate.

2.4.2. What are the single dose/multiple dose pharmacokinetics of Troxyca ER

The single and multiple dose PK of ALO-02 was evaluated in the study B4531006, which is an open-label, single-dose and multiple-dose, randomized, 3-period crossover study in 12 healthy volunteers. The sponsor’s synopsis of study B4531006 is provided in the end of this review.

Study Drug: ALO-02 capsules (oxycodone/ naltrexone), 40 mg/ 4.8 mg and 80 mg/ 9.6 (referred to as ALO-02 40 mg and 80 mg capsules), and OxyContin 40 mg tablets.

All study drugs were administered as a single dose on the morning of Day 1 to evaluate single dose PK. There was no PM dosing on Day 1. Thereafter, on Days 2-5, all study drugs were dosed to steady state according to the following treatment schedules:

- Treatment A: 1×ALO-02 40 mg capsule, BID at ~ 7 AM and 7 PM (Day 2-Day 5)
- Treatment B: 1×ALO-02 80 mg capsule, QD at ~ 7 AM (Day 2-Day 5)
- Treatment C: 1×OxyContin 40 mg tablet, BID at ~ 7 AM and 7 PM (Day 2-Day 5)

The drugs were administered under 8 h fasting conditions on Day 1 and Day 5. On days, 2, 3, 4, the study drugs were administered within 30 minutes of breakfast or snack in the afternoon.

Lot and Formulation Identification:

	Lot #	Dosage Material Number:
ALO-02 40 mg	11-009555	D1100299
ALO-02 80 mg	11-010736	D1100301

Naltrexone Block: To block opioid related unexpected adverse effects associated with oxycodone, all the subjects were given of naltrexone at -12 h on Day 1, and BID on Days 1, 2, 3, 4 and 5 and + 12 h on Day 5 (i.e., on Day 6).

PK blood samples during each study period:

Single dose: (Treatments A, B or C)

- Day 1: 0, 1, 2, 4, 6, 8, 12, 14, 16 h and 24 h (i.e., per dose sample on Day 2)

Multiple dose: (Day 2 – Day 5): Treatment B (ALO-02 80 mg QD), Treatment A (ALO-02 40 mg BID) or Treatment C (OxyContin 40 mg BID):

- Day 2, 3 and 4: 0 h
- Day 5
 - ALO-02 40 mg and OxyContin 40 mg: 0, 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 18, 24 (Day 6), 36 (Day 6), 48 h (Day 7) and 72 h (Day 8)
 - ALO-02 80 mg: 0, 0.5, 1, 2, 4, 6, 8, 12, 18, 24 (Day 6), 48 h (Day 7) and 72 h (Day 8)

Analytes measured: oxycodone, oxymorphone and noroxycodone

- Oxycodone, oxymorphone and noroxycodone: LLOQ- 0.1 ng/mL; calibration range: 0.1 to 50 ng/mL
- Since the study was conducted under naltrexone blockade, the naltrexone and 6- β -naltrexol release from ALO-02 capsules was not measured

Results:

The mean plasma oxycodone, noroxycodone and oxymorphone concentration-time profiles from 0 to 168h following administration of single dose and multiple doses of ALO-02 40 mg and ALO-02 80 mg were shown in the Figure 2.4.2a. The Day 1 (single dose, 0- 24 h) and Day 5 (multiple dose, 0- 72 h) mean plasma oxycodone concentration-time profiles of ALO-02 40 mg and ALO-02 80 mg were shown in the figure 2.4.2a and 2.4.2b, respectively. The PK parameters for oxycodone, noroxycodone and oxymorphone were shown in the Tables, 2.4.2a, 2.4.1c and 2.4.1d, respectively. The geometric mean ratios and 90% CIs of treatment comparisons for oxycodone on Day 1 and Day 5 were shown in the Table 2.4.2b

Single dose (Day 1):

- ALO-02 40 mg versus 80 mg:
 - The single dose of ALO-02 40 mg and 80 mg shows dose proportional PK for AUC₂₄ and C_{max}. The dose normalized oxycodone plasma exposures based on geometric mean AUC₂₄ (dn) and C_{max} (dn) ratios and 90% CIs of ALO-02 40 mg and 80 mg were within the bioequivalence limits (80%-125%).
 - The ALO-02 treatments (40 mg and 80 mg) showed a median oxycodone T_{max} of approximately 12 h.
 - The inter-subject variability for oxycodone exposure was similar between treatments with the percentage of coefficient of variation (%CV) values ranging between 21%-28% for AUC₂₄(dn) and 27%-31% for C_{max}(dn).

Multiple dose:

- The oxycodone steady state was reached within 48 hours for ALO-02 40 mg (BID) and 80 mg (QD). The steady-state oxycodone concentration time profiles over the 24 h interval appeared to be flat for ALO-02 40 mg BID treatment, with lower peak to trough values compared to ALO-02 80 mg.

- Oxycodone average concentrations over the dosing interval (C_{av}) for were similar for ALO-02 40 mg BID, or ALO-02 80 mg QD. Higher C_{min} values were observed for ALO-02 40 mg BID treatment group compared to ALO-02 80 mg QD

Comparison of PK after multiple dose:

- ALO-02 80 mg QD versus 40 mg BID (Day 2 to Day 5):
 - On Day 5, the plasma oxycodone exposures as measured by geometric mean AUC₂₄ and C_{max} values over the entire 24 hours interval were 6% and 15% higher, respectively for 80 mg QD compared to the 40 mg BID treatment. The overall plasma exposures as measured by geometric mean ratios and 90% CIs of AUC₂₄ and C_{max} (C_{max1} and C_{max2}) values over the entire 24 hours were within the bioequivalence limits of 80%-125% (Table 2.4.2d)

Accumulation ratio:

- After multiple dosing, the accumulation ratios for oxycodone (Day 5/ Day 1) based on AUC_τ and C_{max} were higher for the BID treatment (ALO-02 40 mg) compared to ALO-02 80 mg QD treatment. The accumulation ratios is as below:
 - ALO-02 80 mg QD : AUC_τ - 1.3; C_{max} - 1.1
 - ALO-02 40 mg BID: AUC₁₂ - 3.3; AUC₂₄ - 2.6 ; C_{max} - 1.9
- The elimination half-life for ALO-02 after multiple dosing is approximately 7 h.
- Metabolite to parent ratio (based on AUC₂₄):
 - Noroxycodone (all treatments):
 - single dose- 0.8 to 0.9
 - multiple dose- 1.2 to 1.4
 - Oxymorphone (all treatments):
 - single dose- 0.010 to 0.013
 - multiple dose- 0.012 to 0.013

Figure 2.4.2a Mean plasma oxycodone, noroxycodone and oxymorphone concentration-time profiles (0 to 168h) following administration of single dose and multiple doses of ALO-02 (40 mg and 80 mg). The ALO-02 40 mg was administered single dose on Day 1 and BID from Day 2 to Day 5. The ALO-02 80 mg was administered QD Day 1 to Day 5.

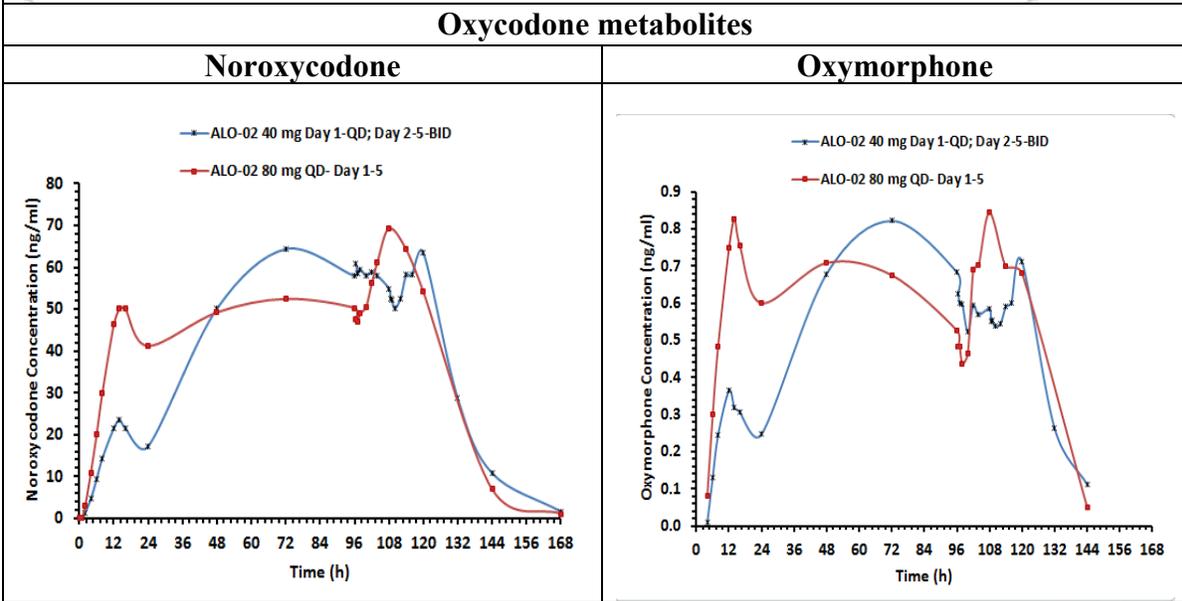
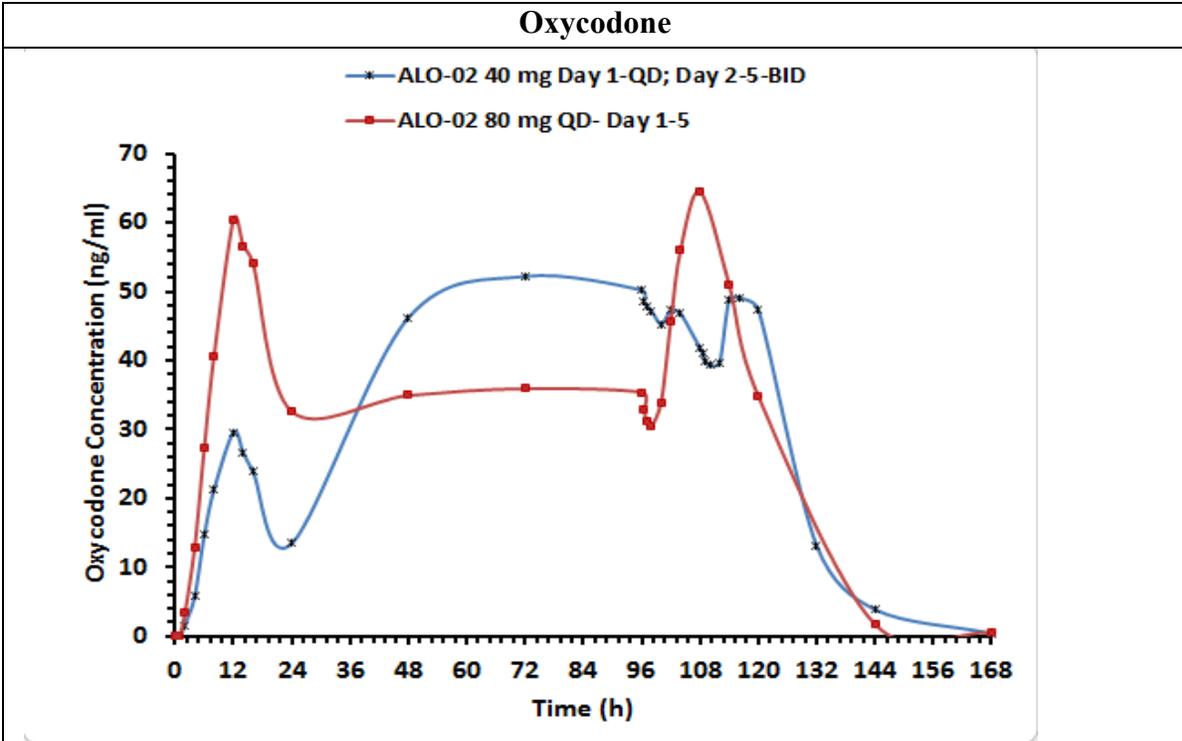


Figure 2.4.2b Mean plasma oxycodone concentration-time profiles on Day 1 (0- 24 h) and Day 5 (0- 72 h) following administration of single dose and multiple doses of ALO-02 40 mg and ALO-02 80 mg. The ALO-02 40 mg was administered single dose on Day 1 and BID from Day 2 to Day 5. The ALO-02 80 mg was administered QD Day 1 to Day 5.

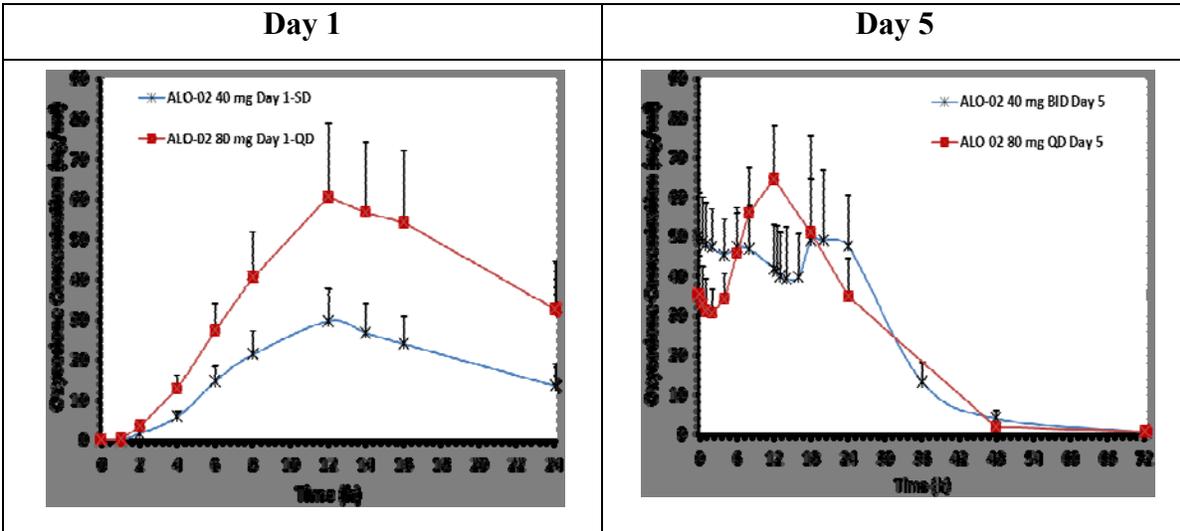


Table 2.4.2a: Summary of plasma oxycodone PK parameters. The ALO-02 40 mg was administered single dose on Day 1 and BID from Day 2 to Day 5 and ALO-02 80 mg was administered QD Day 1 to Day 5.

PK Parameter ^a	Day 1 (Single Dose, 0-24 hour interval)	
	ALO-02 80 mg (n=12)	ALO-02 40 mg (n=12)
AUC ₂₄ (ng•hr/mL)	860 (28)	404 (26)
AUC ₂₄ (dn) (ng•hr/mL/mg)	10.7 (28)	10.1 (26)
AUC ₁₂ (ng•hr/mL)	-	162 (23)
C _{max} (ng/mL)	60 (29)	29 (27)
C _{max} (dn) (ng/mL/mg)	0.75 (29)	0.72 (27)
T _{max} (hr)	12 (8-16.)	12 (8 -12)

PK Parameter ^a	Day 5 (Multiple dose)			
	ALO-02 80 mg (n=12) QD	ALO-02 40 mg (n=12) BID		
	0-24 h	0-24 h ^c	0-12 h	12-24 h
AUC ₂₄ (ng•hr/mL)	1126 (21)	1058 (25)		
AUC _τ (ng•hr/mL) ^b	1126 (21)	-	540(21)	515 (32)
C _{av} (ng/mL) ^d	47 (21)		45 (21)	43 (32)
C _{max} (ng/mL)	64 (22)	55 (41)	52 (22)	53 (45)
C _{max} (dn) (ng/mL/mg)	0.80 (21)	1.39 (41)		
C _{min} (ng/mL) ^e	28 (22)		38 (26)	34 (29)
PTF ^f	0.75 (16)		0.26 (57)	0.38 (57)
Rac ^g	1.31 (24)	2.62	3.33 (21)	
Rac,C _{max} ^h	1.06 (16)	1.89		
T _{max} (hr) ⁱ	11.9(8-12)		1.0 (0-12)	20 (12-24) i
t _{1/2} (hr)	6.6 ±1.7	6.9 ±1.7		

PK parameter definitions for Tables:

a	Geometric mean (%CV) for all except: median (range) for T _{max} , arithmetic mean and standard deviation for t _{1/2} .
b	τ = 12 for the BID treatment and 24 for the QD treatment
c	C _{max} of a given individual was the highest concentration observed across the entire 0-24 hour period and could represent either the morning (0-12 hour) or evening (12-24 hour) dosing interval.
d	C _{av} : Average concentration over the specified interval; AUC _{24/24} for the 24-hour interval for QD and AUC _τ /12 for the morning and evening intervals for BID treatments.
e	C _{min} : Lowest concentration observed during the specified interval. The specified intervals were from 0 to 24 hours following QD treatment and from 0 to 12 hours (AM interval), and 12 to 24 hours (PM interval) for the BID treatments
f	PTF: Peak-trough fluctuation, (C _{max} – C _{min})/C _{av}
g	Rac Accumulation ratios based on AUC _τ (AUC ₁₂) for the BID treatments and AUC _τ (AUC ₂₄) for the QD treatment; AUC _τ (Day 5)/ AUC _τ (Day 1)
h	Rac,C _{max} :C _{max} accumulation ratio based on C _{max} 24 for all treatments [C _{max} (Day 5)/ C _{max} (Day1)]
i	T _{max} : For Interval 2 (PM) of the BID treatments, T _{max} was based on the 1st dose administered on that day. For example, the median (range) T _{max} of 20 (12 -24) hours was really 8 (0-12) hours post second dose and the median (range) T _{max} of 16 (16-20) hours was really 4 (4 – 8) hours.

Table 2.4.2b: The geometric mean ratios and 90% CIs of treatment comparisons for oxycodone on Day 1 and Day 5.

Parameter	Test Vs Reference	Adjusted Geometric LS mean		Ratio % [Test/Reference] (90% CI of ratio)
		Test (n=12) ALO-02 80 mg QD	Reference (n=12) ALO-02 40 mg BID	
Day 1 (Single Dose, 0-24 hour Interval)				
AUC ₂₄ (dn) (ng•hr /mL/mg)	ALO-02 80 mg QD vs ALO-02 40 mg BID	10.70	10.10	105.98 (94.42, 118.96)
C _{max} (dn) (ng/mL/mg) ^a		0.751	0.716	104.90 (89.52, 122.91)
Day 5 (Single Dose, 0-24 hour Interval)				
AUC ₂₄ (dn) (ng•hr /mL/mg)	ALO-02 80 mg QD vs ALO-02 40 mg BID	1126	1058	106.4 (100.41, 112.76)
C _{max} (ng/mL/mg) ^a		63.60	55.40	114.79 (105.81, 124.54)
C _{max} (dn) (ng/mL/mg) ^a		0.795	1.39	57.35 (52.86, 62.21)

Abbreviations: CI = confidence interval, dn = dose normalized to 1 mg, vs = versus.

^a C_{max} was assessed over the entire day (24 hours interval) for all treatments and was referred to as C_{max24} or C_{max24}(dn)

Table 2.4.2c: Summary of plasma noroxycodone PK parameters. The ALO-02 40 mg was administered single dose on Day 1 and BID from Day 2 to Day 5 and ALO-02 80 mg was administered QD Day 1 to Day 5.

PK Parameter	Day 1 (Single Dose, 0-24 hour interval)	
	ALO-02 80 mg (n=12)	ALO-02 40 mg (n=12)
AUC ₂₄ (ng•hr/mL)	771 (31)	348 (25)
AUC ₂₄ (dn) (ng•hr/mL/mg)	9.6 (31)	8.7 (25)
AUC ₁₂ (ng•hr/mL)	-	112 (24)
C _{max} (ng/mL)	50 (33)	23 (27)
C _{max} (dn) (ng/mL/mg)	0.62 (33)	0.57 (27)
T _{max} (hr)	15.1 (12.0-16.1)	14.0 (14.0-16.1)

PK Parameter ^a	Day 5 (Multiple dose)			
	ALO-02 80 mg (n=12) QD	ALO-02 40 mg (n=12) BID		
	0-24 h	0-24 h	0-12 h	12-24 h
AUC ₂₄ (ng•hr/mL)	1379 (27)	1335 (24)		
AUC _τ (ng•hr/mL) ^b	1379 (27)	-	680 (20)	652 (28)
C _{av} (ng/mL) ^d	57 (27)		57 (20)	54 (28)
C _{max} (ng/mL)	68 (26)	69 (25)	65 (23)	66 (26)
C _{max} (dn)	0.85 (26)	1.73 (25)		

(ng/mL/mg)				
Cmin (ng/mL) ^e	43 (28)		48 (25)	45 (29)
PTF ^f	0.41 (24)		0.27 (40)	0.35 (39)
Rac g	1.8 (18)	3.8	6.1 (24)	
Rac,Cmax ^h	1.4 (16)	3.0 (31)		
Tmax (hr) ⁱ	12.0 (8.02-18.0)		3.0 (0.0-11.9)	20.0 (12-24)
t1/2 (hr)	8.3 ± 1.1	8.5 ± 1.1		

Table 2.4.2d: Summary of plasma oxymorphone PK parameters. The ALO-02 40 mg was administered single dose on Day 1 and BID from Day 2 to Day 5 and ALO-02 80 mg was administered QD Day 1 to Day 5.

PK Parameter	Day 1 (Single Dose, 0-24 hour interval)	
	ALO-02 80 mg (n=12)	ALO-02 40 mg (n=12)
AUC24 (ng•hr/mL)	11.0 (51)	4.6 (43)
AUC24(dn) (ng•hr/mL/mg)	0.14 (50)	0.11 (43)
AUC12 (ng•hr/mL)	-	1.58 (42)
Cmax (ng/mL)	0.81 (63)	0.35 (38)
Cmax(dn) (ng/mL/mg)	0.010 (63)	0.008 (38)
Tmax (hr)	14.0 (8.03-24.0)	12.1 (8.00-16.1)

PK Parameter ^a	Day 5 (Multiple dose)			
	ALO-02 80 mg (n=12) QD		ALO-02 40 mg (n=12) BID	
	0-24 h	0-24 h	0-12 h	12-24 h
AUC24 (ng•hr/mL)	14.7 (48))	13.21 (34)		
AUC _τ (ng•hr/mL) ^b	14.7 (48)	-	6.5 (36)	6.7 (34)
C _{av} (ng/mL) ^d	0.6 (48)		0.54 (36)	0.56 (34)
Cmax (ng/mL)	0.8 (52)	0.74 (37)	0.68 (39)	0.71 (38)
Cmax(dn) (ng/mL/mg)	0.01 (53)	0.02 (38)		
Cmin (ng/mL) ^e	0.37 (45)		0.43 (41)	0.42 (35)
PTF ^f	1.34 (24)	2.87	4.1 (36)	
Rac g	1.0 (25)	2.86	2.1 (39)	
Rac,Cmax ^h	11.9 (6-18.0)		8 (0.-12)	22 (12-24)
Tmax (hr) ⁱ	10.2 ± 1.6	10.5 ± 1.04		

2.5.2 What is the BCS Class classification for Troxyca ER?

Not Applicable.

2.5 Intrinsic Factors

2.5.1. Pediatrics

Troxyca ER has an 'agreed upon' iPSP. The iPSP was discussed in the three PERC meetings and recent PERC meeting was held on the August 19, 2015. For Troxyca ER

- Pediatric age group(s) to be waived: ages < 7 years of age.

- The reason is studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). The applicant provided following justification for the waiver
 - The Applicant submitted data from a commercial claims database which suggested that the numbers of patients in the birth to less than 7 year age range would be too small, making studies impractical. They also referenced a 2012 Public Workshop sponsored by the FDA where it was discussed that the number of patients in the less than seven year age range expected to need opioids for an extended period of time would be too small to make conducting studies in that age range feasible. Although the Division has continued to evaluate the feasibility of conducting pediatric chronic pain studies, we are currently granting waivers in children less than 7 years of age for the reasons stated by the Applicant.
- **Age groups included in the deferral request:** 7 to <17 years of age.
 - Planned Studies for ages 7 to <17 years: Open-label pharmacokinetic and safety study in patients 7 to <17 years of age who are anticipated to have pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
 - Timelines
 - Protocol Submission: April 2015
 - Study Completion: January 2019
 - Study Submission: July 2019

2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Clinical Center: Pfizer Clinical Research Unit

Bio-analytical Facility: (b) (4)

Oxycodone, Oxymorphone, and Noroxycodone:

The plasma concentrations of Oxycodone, Oxymorphone, and Noroxycodone were analyzed using validated HPLC-MS/MS assays. The range of calibrators and QCs used for studies were:

- Calibrators: 0.1, 0.2, 0.5, 2, 7.5, 20, 40, 50 ng/mL
- Quality controls: 0.1, 0.3, 3, and 37.5 ng/mL

Accuracy and Precision over the range:

- Accuracy (expressed as % bias) : $< \pm 15\%$ for all studies
- Precision (expressed as % CV) : $< 15\%$ for all studies

Internal standards: Oxycodone-d6, Oxymorphone-d3, and Noroxycodone-d3

Stability:

Processed-sample viability: Oxycodone: 164 h at 2 to 8°C
 Oxymorphone: 164 h at 2 to 8°C

Noroxycodone: 164 h at 2 to 8°C
Sample collection stability: Oxycodone, Oxymorphone and Noroxycodone: 2 h at room temperature and on wet ice

Storage stability: Oxycodone, and Noroxycodone: 960 days at -10 to -30°C

- Human plasma specimens were stored at -30 to -10°C until analysis and assayed within the following days of established stability data for each study:
 - B4531007: 165 days
 - B4531003: 180 days
 - B4531006: 78 days
 - B4531004: 221 days
 - B4531002: 221 days
 - B4531008: 221 days
 - B4531009: 221 days
 - B4531001: 960 days
 - B4531002: 819 days

Naltrexone and 6-β-Naltrexol:

The plasma concentrations of naltrexone and 6-β-naltrexol were analyzed using validated HPLC-MS/MS assays. The range of calibrators and QCs used for studies were:

- Calibrators: 4, 8, 24, 80, 200 700 1600 and 2000 pg/mL
- Quality controls: 4, 12, 120, and 1500 pg/mL

Accuracy and Precision over the range:

- Accuracy (expressed as % bias) : < ± 15% for all studies
- Precision (expressed as % CV) : < 15% for all studies

Internal standards: Naltrexone-D3 and 6-β-Naltrexol-D4

Stability:

Stability of standard stock solutions:

Naltrexone and 6-β-Naltrexol: 8 hours at room temperature
79 days at -10 to -30°C

Naltrexone-D3 and 6-β-Naltrexol-D4: 8 hours at room temperature

Stability of intermediate solutions:

Naltrexone and 6-β-Naltrexol 8 hours at room temperature
Naltrexone: 42 days at -10 to -30°C
6-β-Naltrexol: 16 days at -10 to -30°C

Reinjection reproducibility: 160 hours at 2 to 8°C

Sample collection stability: 2 hours at room temperature
2 hours on wet ice

Short-term matrix stability: 27 hours at room temperature

Freeze-thaw matrix stability: 5 cycles at -10 to -30°C
5 cycles at -60 to -80°C

Storage stability: 415 days at -10 to -30°C for naltrexone
812 days at -10 to -30°C 6-β-naltrexol

- Human plasma specimens were stored at -30 to -10°C until analysis and assayed within the following days of established stability data for each study
 - B4531007: 65 days
 - B4531003: 86 days
 - B4531002: 415 days
 - B4531008: 415 days
 - B4531009: 415 days
 - B4531001: 577 days
 - B4531002: 415 days

While finalizing this review an information request (IR) was sent to the sponsor regarding the long term- storage stability of naltrexone concentrations for some subjects. This IR is not applicable to 6-β- naltrexol concentrations. A response from Sponsor is awaited. The numbers for naltrexone concentrations indicated in below may or may not change based the Sponsor’s response to IR. Based on the sponsor’s response, the language will be modified in the label accordingly.

3.0 LABELING COMMENTS

The labelling comments have been made to the following sections in the Label:

Section 7: The Drug Interactions have been shown as a Table

Section 8.6: Hepatic Impairment

Section 8.7: Renal Impairment

Section 12.3

- Absorption, Food effect, Excretion, Elderly, Hepatic and Renal Impairment, Alcohol Interaction, Drug- Drug- Interactions for Oxycodone
- Absorption, Hepatic Impairment and Renal Impairment for Naltrexone

Below are the modified changes in the label.

8.6 Hepatic Impairment

Since oxycodone is extensively metabolized in the liver, its clearance may decrease in patients with hepatic impairment. (b) (4)
 (b) (4) Naltrexone is sequestered in the TROXYCA ER formulation and is not intended to be released when TROXYCA ER is used as directed. However, measurable naltrexone plasma concentrations have been observed in some patients in clinical trials with TROXYCA ER [see *Clinical Pharmacology (12.3)*]. (b) (4)
 (b) (4)

An increase in naltrexone AUC in patients with compensated and decompensated liver cirrhosis compared with subjects with normal liver function has been reported [see *Clinical Pharmacology (12.3)*]. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Dose initiation of TROXYCA ER should follow a conservative approach in patients with hepatic impairment. (b) (4)
 (b) (4) In patients with hepatic impairment, there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. Hence when administering TROXYCA ER to patients with hepatic impairment, monitor patients closely for signs of central nervous system or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naltrexone.
 (b) (4) and adjust the dose based on clinical response (b) (4)
 (b) (4)

¶

8.7 Renal Impairment

~~Elimination of oxycodone is reduced in patients with mild to severe renal impairment resulting in about 60% higher AUC.~~ [NS35]
Although naltrexone is sequestered in the TROXYCA ER formulation, measurable naltrexone plasma concentrations have been observed in some patients in clinical trials with TROXYCA ER [see *Clinical Pharmacology (12.3)*]. Since naltrexone and its primary metabolite are excreted primarily in urine, their plasma concentrations may be increased in patients with renal impairment.

Dose initiation of TROXYCA ER should follow a conservative approach in patients with renal impairment. In patients with renal impairment, there is a potential for differential increase in naltrexone exposure compared to oxycodone exposure. Hence when administering TROXYCA ER to patients with renal impairment, monitor patients closely for signs of central nervous system or respiratory depression due to elevated levels of oxycodone and for signs of withdrawal due to elevated levels of naltrexone. (b) (4)
(b) (4) and adjust the dose based on the clinical response (b) (4)

12.3 Pharmacokinetics

Absorption

In humans, 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 pre-systemic metabolism of oxycodone. Dose proportionality of oxycodone has been established using IR oxycodone 5, 15 and 30 mg tablets based on extent of absorption (AUC).

Following oral administration of TROXYCA ER capsules, oxycodone T_{max} is delayed to approximately 12 hours post dose (range, 8 - 16 h), AUC is equivalent (b) (4) and C_{max} is reduced by approximately 67% when compared with IR oxycodone tablets. It takes approximately 18 to 24 hours to reach steady-state plasma concentrations of oxycodone with IR oxycodone. With TROXYCA ER steady state was reached within 48 h (b) (4)

An analysis of pharmacokinetic results from Phase 1 single dose studies with TROXYCA ER capsules 20 mg/2.4 mg up to 80 mg/9.6 mg showed that oxycodone AUC and C_{max} increased in a dose proportional manner. Based on the prescribed daily doses in patients, the mean steady-state concentrations of oxycodone for 10-40 mg, >40-80 mg, >80-120 mg, and >120 mg daily dose groups were 15 ng/mL, 35 ng/mL, 60 ng/mL and 83 ng/mL, respectively.

After administration of crushed TROXYCA ER, the peak plasma levels of oxycodone occurred at 0.6-1.0 hours orally and 1.6 hours intranasally.

Food Effect: When single dose TROXYCA ER capsules are administered in fasted state or after a high-fat meal, or when the contents of TROXYCA ER capsules are sprinkled on one tablespoon of applesauce and administered in fasted state, oxycodone

pharmacokinetics are unaffected with similar AUC, C_{max}, and T_{max} values.

(b) (4)

(b) (4)

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 clearance of oxycodone is 0.8 L/min and the apparent elimination half-life following the administration of IR oxycodone is 3.5 to 4 hours.

Following oral administration of TROXYCA ER capsules, the apparent elimination half-life of oxycodone is approximately 7.2 hours and steady state is reached within 48 hours upon twice-daily dosing with TROXYCA ER capsules approximately 12 hours apart. Oxycodone and its metabolites are excreted primarily via the kidney.

(b) (4)

(b) (4) Populations

Elderly (≥65 years)

The effects of age on the pharmacokinetics of TROXYCA ER have not been investigated in a specific study in elderly patients (≥65 years). The safety and efficacy studies with TROXYCA ER did not include sufficient numbers of subjects aged 65 and older. The median age in these studies was 54 years and there were no significant differences in oxycodone concentrations between patients <54 years of age and patients ≥54 years of age. Population pharmacokinetic studies conducted with IR oxycodone indicated that the plasma concentrations of oxycodone did not appear to be increased in patients over the age of 65.

Hepatic Impairment

Since oxycodone is extensively metabolized in the liver, its clearance is expected to decrease in patients with hepatic impairment.

(b) (4)

Renal Impairment

(b) (4) Elimination of oxycodone is reported to be impaired in patients with

(b) (4)

(b) (4)

The mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance.

(b) (4)

(b) (4)

(b) (4)

Alcohol Interaction

Concomitant administration of TROXYCA ER 20 mg/2.4 mg with 20% alcohol did not affect C_{max} or AUC of oxycodone. With concomitant administration of 40% alcohol and TROXYCA ER 20 mg/2.4 mg there was an average 37% increase in C_{max} and 13% increase in AUC of oxycodone compared with TROXYCA ER administered with water. Out of 17 subjects, one subject had (b) (4) fold and (b) (4) fold (b) (4) increase in C_{max} following TROXYCA ER with 20% alcohol and 40% alcohol (b) (4) respectively compared to TROXYCA ER (b) (4). The corresponding increase in AUC in this subject were (b) (4) fold and (b) (4) fold with 20% and 40 % alcohol treatments, respectively compared to water (b) (4).

Drug-Drug Interactions

While no specific drug interaction studies have been performed with TROXYCA ER, an interaction with inhibitors and inducers of the CYP3A4 enzyme is expected based on the metabolism of oxycodone predominantly by CYP3A4. [see Drug Interactions (7).]

(b) (4)

(b) (4)

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxycodone via the cytochrome p450 isoenzyme CYP2D6.

(b) (4)

(b) (4)

Naltrexone Pharmacokinetics

Naltrexone blocks the effects of opioids by competitive binding at mu-opioid receptors. Naltrexone has few, if any intrinsic actions besides its opioid-blocking properties. However, it does produce some pupillary constriction by an unknown mechanism. Naltrexone, administered alone, is not associated with the development of tolerance or dependence, but it will precipitate withdrawal symptoms in subjects physically dependent on opioids.

Absorption

When TROXYCA ER capsules are administered in fasted state or after a high-fat meal, or when the contents of TROXYCA ER capsules are sprinkled on applesauce and administered in fasted state, naltrexone plasma concentrations remain undetectable (below limit of quantitation, 4 pg/mL) suggesting that administration of TROXYCA ER capsules with food or sprinkling of pellets on applesauce does not affect sequestration of naltrexone. The maximum plasma 6-β-naltrexol concentration was 30 pg/mL observed at 120 h post dose following Troxyca ER after a high-fat meal.

Following single dose administration of intact TROXYCA ER in Phase 1 studies, naltrexone was undetected (limit of quantitation, 4 pg/mL). (b) (4) The 6-β-naltrexol (limit of quantitation, 4 pg/mL) was observed in (b) (4) out of 37 subjects (b) (4)

[Redacted]

Special Populations

Hepatic Impairment

Since naltrexone is extensively metabolized, its clearance may decrease in hepatic failure patients. An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. (b) (4)

(b) (4) This study suggested increased bioavailability of naltrexone in liver cirrhosis, consistent with lesser metabolism of naltrexone to 6β-naltrexol, and appear to be related to the severity of liver disease[NS65].

Renal Impairment

Adequate studies of naltrexone tablets in patients with severe renal impairment have not been conducted. (b) (4) (b) (4)

(b) (4) since naltrexone and its primary metabolite are excreted primarily in urine, plasma concentrations of naltrexone may increase in patients with renal impairment.

4.0 Appendices

4.1 Sponsor’s Proposed Label

30 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.1 Study Designs:

Clinical Pharmacology Studies:

Study B4531003: An Open-Label, Single-Dose, Randomized, Three-Way Crossover Study in Healthy Volunteers to Estimate the Effects of Food and of Sprinkling ALO-02 Pellets on Applesauce on the Bioavailability of Oxycodone and Naltrexone/6-β-Naltrexol From n Extended Release Pellets-In-Capsule Formulation of Oxycodone 40 mg with Sequestered Naltrexone 4.8 mg.

Study B4531004: An Open-Label, Single-Dose, Randomized, Three-Way Crossover Study to Estimate the Effects of Alcohol 20% and 40% on the Bioavailability a Controlled Release Formulation of Oxycodone 20 mg with Sequestered Naltrexone 2.4 mg in Healthy Volunteers.

Study B4531006: An Open-Label, Single-Dose and Multiple-Dose, Randomized, Crossover Study to Evaluate Pharmacokinetics, Safety and Tolerability After Administration of ALO-02 40 mg Twice Daily Compared to ALO-02 80 mg Once Daily and to OxyContin 40 mg Twice Daily in Healthy Volunteers

Study B4531007: An Open-Label, Single-Dose, Randomized, Two-Way Crossover Study to Estimate the Relative Bioavailability of a Controlled-Release Formulation of Oxycodone (40 mg) With Sequestered Naltrexone Compared With Immediate-Release Oxycodone Tablets (20 mg) in Healthy Volunteers

Abuse Potential Studies:

Study B4531008: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, 6-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release and Placebo When Administered Orally to Non-Dependent, Recreational Opioid Users

Study B4531009: A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, 4-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release, and Placebo When Administered Intranasally to Non-Dependent, Recreational Opioid Users

Study B4981002: A Randomized, Single-Dose, Placebo-Controlled, Double-Blind, 3-Way Crossover Study to Determine the Relative Abuse Potential of Intravenous Oxycodone Hydrochloride Alone or in Combination with Intravenous Naltrexone Hydrochloride in Opioid Experienced Non-Dependent Subjects

Clinical Studies:

Study B4531002: A Multicenter, 12-Month, Open-Label, Single-Arm, Safety Study of Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules in Subjects With Moderate to Severe Chronic Noncancer Pain

Study B4531001: A Multicenter, 12-Week, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study to Determine the Efficacy and Safety of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride) Extended-Release Capsules in Subjects with Moderate-to-Severe Chronic Low Back Pain

4.2 Sponsor's Synopsis of Studies

B4531007, B4531003, B4531004 and B4531006

CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: Oxycodone Hydrochloride and Naltrexone Hydrochloride

Clinical Study Report Synopsis: [Protocol B4531007](#)

Protocol Title: An Open-Label, Single-Dose, Randomized, Two-Way Crossover Study to Estimate the Relative Bioavailability of a Controlled-Release Formulation of Oxycodone (40 mg) With Sequestered Naltrexone Compared With Immediate-Release Oxycodone Tablets (20 mg) in Healthy Volunteers

Investigator: Dr Sanela Tarabar

Study Center: One center in the United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 07 September 2012 to 15 October 2012

Date of Report: 4 March 2013

Phase of Development: Phase 1

Study Objectives:

Primary Objective:

- To estimate the relative bioavailability of oxycodone from a controlled-release formulation of oxycodone hydrochloride with sequestered naltrexone hydrochloride (ALO-02) compared with immediate-release (IR) oxycodone tablets (Roxicodone®) in healthy volunteers.

Secondary Objectives:

- To characterize the exposure levels of naltrexone and 6- β -naltrexol following single dose administration of ALO-02 40 mg capsules in healthy volunteers.
- To evaluate the safety and tolerability of oxycodone following single dose administration of ALO-02 40 mg capsules and IR oxycodone 20 mg tablets in healthy volunteers.

METHODS

Study Design: This was an open-label, single-dose, randomized, 2-way crossover study in healthy adult volunteers. Screening evaluation occurred within 28 days prior to the first dose of Period 1. Fourteen (14) subjects were enrolled and randomly assigned to 1 of 2 sequences. Each subject received the following 2 treatments separated by at least a 7-day washout period:

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Treatment A: ALO-02 40 mg capsules (oxycodone hydrochloride with sequestered naltrexone hydrochloride controlled-release capsule, 1 × 40 mg capsule) with 240 mL of water under fasted conditions (test treatment)

Treatment B: IR oxycodone 20 mg tablets (Roxicodone[®]: 1 × 15 mg tablet plus 1 × 5 mg tablet) with 240 mL of water under fasted conditions (reference treatment)

Diagnosis and Main Criteria for Inclusion: Subjects were healthy male and/or female between the ages of 18 and 55 years, with a body mass index (BMI) of 17.5 to 30.5 kg/m² and a total body weight >50 kg (110 lb).

Study Treatment: On the morning of Day 1 of each dosing period, following an overnight fast of at least 10 hours, investigator site personnel administered subjects 1 of the 2 single dose study treatments with 240 mL of ambient temperature water. Subjects swallowed the study medication whole, and did not chew the medication prior to swallowing.

The lot number, dosage material number, potency, and formulation of the investigational products are provided in Table S1.

Table S1. Study Drug Information

Study Drug	Lot Number	Dosage Material Number	Potency	Formulation
PF-05412527 (ALO-02) (b) (4) capsule	11-010734	D1100299	40 mg	Capsule
Roxicodone [®] 5 mg tablet	160134A	NA	5 mg	Tablet
Roxicodone [®] 15 mg tablet	061170A	NA	15 mg	Tablet

Abbreviations: ALO-02=oxycodone hydrochloride with sequestered naltrexone hydrochloride, NA=not available

Efficacy Evaluations: Efficacy evaluations were not performed in this study.

Pharmacokinetic Evaluations: Blood samples (4 mL) were collected to provide a minimum of 1.5 mL plasma for pharmacokinetic (PK) analysis of oxycodone at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 24, 36 and 48 hours postdose for Treatment A and at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 48 hours postdose for Treatment B in each dosing period. Blood samples (6 mL) were also collected to provide a minimum of 2 mL plasma for PK analysis of naltrexone and 6-β-naltrexol at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hours postdose for Treatment A in each dosing period. Plasma samples were analyzed for oxycodone, naltrexone and 6-β-naltrexol concentrations using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method in compliance with the sponsor's standard operating procedures.

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The PK parameters determined for this study were calculated for each subject and treatment, as applicable, using noncompartmental analysis of concentration-time data (Table S2).

Table S2. Pharmacokinetic Parameters Determined in the Study

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration	Linear/log trapezoidal method
AUC_{inf}^a	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}^* / k_{el})$, where C_{last}^* was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and where k_{el} was the terminal phase rate constant.
C_{24}	Concentration at 24 hours postdose	Observed directly from data
$t_{1/2}^a$	Terminal half-life	$\text{Log}_e(2) / k_{el}$, where k_{el} was the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
$AUC_{last}(dn)$	Dose-normalized AUC_{last}	AUC_{last} / dose
$AUC_{inf}(dn)^a$	Dose-normalized AUC_{inf}	AUC_{inf} / dose
$C_{max}(dn)$	Dose-normalized C_{max}	C_{max} / dose

Pharmacokinetic parameter values were calculated using eNCA version 2.2.3.

Abbreviations: dn=dose-normalized, eNCA=electronic noncompartmental analysis.

^a If data permitted.

Safety Evaluations: Safety evaluations included adverse events (AEs) and serious adverse events (SAEs) monitoring, potential cases of drug-induced liver injury monitoring, physical examinations, vital signs (blood pressure, heart rate and respiratory rate), 12-lead electrocardiogram (ECG) monitoring, and safety laboratory tests.

Statistical Methods:

Pharmacokinetics: The PK concentration population was defined as all enrolled subjects treated who had at least 1 concentration. The PK parameter analysis population was defined as all enrolled subjects treated who had at least 1 of the PK parameters of interest. Natural log-transformed values for dose-normalized PK parameters of interest [ie, oxycodone C_{max} (maximum plasma concentration), AUC_{last} (area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration), and AUC_{inf} (area under the plasma concentration-time from time 0 extrapolated to infinite time)] were analyzed using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences between the test

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(ALO-02 40 mg capsules) and reference (IR oxycodone 20 mg tablets) formulations and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios.

Relative bioavailability was estimated as the ratio of adjusted geometric means for ALO-02 relative to oxycodone for dose-normalized AUC_{inf} , AUC_{last} and C_{max} [$AUC_{inf}(dn)$, $AUC_{last}(dn)$ and $C_{max}(dn)$].

Safety: All subjects who received at least 1 dose of study medication were included in the safety analyses and listings. AEs, ECGs, vital signs, and safety laboratory data were listed or summarized descriptively in accordance with the sponsor's reporting standards.

RESULTS

Subject Disposition and Demography: A total of 14 subjects were assigned to study treatments and all but 1 subject completed the study. One (1) subject treated with IR oxycodone 20 mg discontinued from the study prior to receiving ALO-02 40 mg. Another subject treated with IR oxycodone 20 mg was deemed an influential outlier for having studentized (conditional) residual less than -3 and therefore was excluded from the PK analysis and results presented in this report. All subjects who were treated with study drug were analyzed for safety.

A total of 9 male and 5 female subjects were enrolled in this study. Half of the subjects were black. Subjects ranged in age from 26 to 51 years, with a mean BMI of 25.4 kg/m².

Efficacy Results: Efficacy evaluations were not done in this study.

Pharmacokinetic Results:

Analysis of Pharmacokinetics for Oxycodone: Following administration of single oral doses of ALO-02 40 mg compared to IR oxycodone 20 mg under fasted conditions, oral absorption of oxycodone from ALO-02 40 mg was consistent with that of an extended-release formulation with a slow initial oxycodone release and a prolonged T_{max} (time for C_{max}). C_{max} for ALO-02 40 mg was achieved within 8-16 hours postdose (median T_{max} =12 hours) compared to 0.5-2 hours postdose (median T_{max} =1 hour) for IR oxycodone 20 mg ([Table S3](#)).

The relative bioavailability of the test ALO-02 40 mg capsules was estimated to be approximately 7% higher than that of the reference IR 20 mg oxycodone tablets in the absence of the reference outlier, based on $AUC_{inf}(dn)$ and $AUC_{last}(dn)$. The ratios (90% CIs) of adjusted geometric means for $AUC_{inf}(dn)$ and $AUC_{last}(dn)$ of the ALO-02 40 mg (test) compared to IR oxycodone 20 mg tablets (reference) were 107.17% (96.65%, 118.83%) and 106.05% (95.35%, 117.96%), respectively. Consistent with the PK profile of the

extended-release ALO-02 formulation, C_{\max} was lower for the ALO-02 treatment than those observed for the IR oxycodone treatment with test/reference adjusted geometric means ratio of 33.04% (28.80%, 37.92%) for $C_{\max}(\text{dn})$ ([Table S4](#)).

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Oxycodone concentration at 24 hours postdose (C_{24}) was higher for ALO-02 40 mg (geometric mean value of 11.57 ng/mL) compared to those observed for IR oxycodone 20 mg (geometric mean value of 0.6119 ng/mL). Mean terminal half-life ($t_{1/2}$) values were 7.2 hours for ALO-02 40 mg compared to 4.6 hours for IR oxycodone 20 mg (Table S3).

Inter-subject variability for oxycodone exposure based on percent coefficient of variation (%CV) of geometric means AUC_{inf} , AUC_{last} and C_{max} was 29%, 29% and 24% for ALO-02 40 mg, and 23%, 23% and 25% for IR oxycodone 20 mg, respectively (Table S3).

Table S3. Summary of Plasma Oxycodone Pharmacokinetic Parameters Following Single Oral Doses of ALO-02 40 mg Capsules and IR Oxycodone 20 mg Tablets

Parameter, Unit	Parameter Summary Statistics ^a for Oxycodone by Treatment	
	ALO-02 40 mg	IR Oxycodone 20 mg
N, n	13, 13	13, 13
AUC_{inf} , ng hr/mL	508.8 (29)	238.8 (23)
$AUC_{inf}(dn)$, ng hr/mL/mg	12.71 (29)	11.93 (23)
AUC_{last} (ng hr/mL)	496.2 (29)	235.5 (23)
$AUC_{last}(dn)$, ng hr/mL/mg	12.41 (29)	11.78 (23)
C_{24} , ng/mL	11.57 (37)	0.6918 (61)
C_{max} , ng/mL	26.57 (24)	40.12 (25)
$C_{max}(dn)$, ng/mL/mg	0.6645 (24)	2.010 (25)
T_{max} , hr	12.0 (8.00-16.0)	1.00 (0.500-2.00)
$t_{1/2}$, hr	7.206±0.96	4.584±1.2

PK parameters are defined in [Table S2](#).

PK data for an outlier subject was excluded from the IR oxycodone 20 mg treatment in this table.

Abbreviations: ALO-02=oxycodone hydrochloride with sequestered naltrexone hydrochloride, %CV=percent coefficient of variation, dn=dose-normalized, hr=hour, IR=immediate-release, N=total number of subjects in the treatment group, n=number of subjects contributing to the mean, PK=pharmacokinetic, SD=standard deviation.

^a Geometric mean (geometric %CV) for all except: median (range) for T_{max} and arithmetic mean±SD for $t_{1/2}$.

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Table S4. Statistical Summary of Treatment Comparisons for Dose-Normalized Plasma Oxycodone Pharmacokinetic Parameters Following Single Oral Doses of ALO-02 40 mg Capsules and IR Oxycodone 20 mg Tablets

Parameter, Unit	Adjusted Geometric Means		Ratio ^a (%) Test/Reference	90% CI ^a for Ratio
	Test	Reference		
AUC _{inf} (dn), ng hr/mL/mg	12.75	11.90	107.17	(96.65, 118.83)
AUC _{last} (dn), ng hr/mL/mg	12.45	11.74	106.05	(95.35, 117.96)
C _{max} (dn), ng/mL/mg	0.6701	2.028	33.04	(28.80, 37.92)

Test treatment: ALO-02 40 mg capsules (oxycodone hydrochloride with sequestered naltrexone hydrochloride, 1 × 40 mg controlled-release capsule) under fasted conditions

Reference treatment: IR oxycodone 20 mg tablets (Roxicodone[®]: 1 × 15 mg tablet plus 1 × 5 mg tablet) under fasted conditions

PK parameters are defined in [Table S2](#).

PK data for an outlier subject was excluded from the IR Oxycodone 20 mg treatment in this table.

Abbreviations: ALO-02=oxycodone hydrochloride with sequestered naltrexone hydrochloride,

CI=confidence interval, dn=dose-normalized, hr=hour, IR=immediate-release, PK=pharmacokinetic. ^a

The ratios of adjusted means and 90% CIs are expressed as percentages (%).

Analysis of Pharmacokinetics for Naltrexone and 6-β-naltrexol: Plasma naltrexone concentrations for the ALO-02 40 mg treatment were below the lower limit of quantification (4.00 pg/mL) therefore PK parameters were not calculated or presented.

Overall plasma 6-β-naltrexol concentrations for the ALO-02 40 mg treatment were low, with more than 50% of subjects having concentration levels below the lower limit of quantification (4.00 pg/mL). As expected, the overall plasma concentrations for 6-β-naltrexol were low with individual C_{max} ranging between 0 pg/mL to 45.4 pg/mL and were achieved within 96 to 120 hours postdose (median T_{max}=108 hours).

AUC_{inf}, AUC_{last} and t_{1/2} for 6-β-naltrexol could not be calculated or accurately reported for any subjects treated with ALO-02 40 mg.

Safety Results: There were no severe AEs, SAEs, deaths, discontinuations, dose reductions, or temporary discontinuations due to AEs during this study. One (1) subject discontinued from the study due to a mild AE of gastroenteritis unrelated to study treatment. The most frequently reported AEs by preferred term were nausea and dizziness. The majority of AEs were mild in severity. No laboratory abnormalities were considered clinically significant or reported as AEs. None of the vital signs or ECG results were abnormal.

Conclusions:

- The relative bioavailability of the test ALO-02 40 mg capsules compared to that of the reference IR 20 mg oxycodone tablets, based on the ratios (90% CIs) of adjusted geometric means, was 107.17% (96.65%, 118.83%) for AUC_{inf}(dn) and 106.05% (95.35%, 117.96%) for AUC_{last}(dn).

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- Consistent with the PK profile of the extended-release ALO-02 formulation, C_{\max} was lower for the ALO-02 treatment (test) than those observed for the IR oxycodone treatment (reference) with test/reference adjusted geometric means ratio of 33.04% (90% CI: 28.80%, 37.92%) for $C_{\max}(\text{dn})$. This is in part due to the slow initial oxycodone release and a prolonged T_{\max} (range 8-16 hours) for the ALO-02 formulation, compared to a T_{\max} of 0.5 to 2.0 hours for the IR oxycodone formulation.
- Plasma naltrexone concentrations for the ALO-02 40 mg treatment were below the lower limit of quantification (4.00 pg/mL). Overall, plasma 6- β -naltrexol concentrations for the ALO-02 40 mg treatment were low (<50 pg/mL) with more than 50% of subjects in the ALO-02 treatment having concentration levels below the lower limit of quantification (4.00 pg/mL).
- Single oral doses of ALO-02 40 mg capsules and IR oxycodone 20 mg tablets were generally safe and well tolerated.

CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer Global Research & Development

Investigational Product: Oxycodone Hydrochloride and Naltrexone Hydrochloride

Clinical Study Report Synopsis: [Protocol B4531003](#)

Protocol Title: An Open-Label, Single-Dose, Randomized, Three-Way Crossover Study in Healthy Volunteers to Estimate the Effects of Food and of Sprinkling ALO-02 Pellets on Applesauce on the Bioavailability of Oxycodone and Naltrexone/6- β -Naltrexol From a Extended Release Pellets-In-Capsule Formulation of Oxycodone 40 mg with Sequestered Naltrexone 4.8 mg

Investigators: Dr. Arne G. Hansson

Study Center(s): 1 center in the United States.

Publications Based on the Study: None

Study Initiation and Completion Dates: 20 October 2011 and 03 January 2012

Date of Report: 08 June 2012

Phase of Development: Phase 1

Study Objective(s): The primary objectives of this study were: to estimate the bioavailability of oxycodone, naltrexone, and 6- β -naltrexol following the administration of single oral 40-mg capsules of oxycodone hydrochloride and naltrexone hydrochloride (ALO-02) under fed conditions (standard high-fat breakfast) versus under fasting conditions; and to estimate the bioavailability of oxycodone, naltrexone, and 6- β -naltrexol following the administration of single oral 40-mg doses of ALO-02 pellets sprinkled on applesauce versus intact ALO-02 capsules under fasting conditions.

The secondary objective of this study was to evaluate the safety and tolerability of single oral doses of 40-mg ALO-02 given to healthy subjects.

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METHODS

Study Design: This was an open-label, single-dose, randomized, 3-period crossover study in healthy volunteers. Eligible subjects were assigned to 1 of 6 treatment sequences to receive the following 3 treatments:

StudyDrug: ALO-02 extended-release (ER) capsules containing 40 mg of oxycodone hydrochloride (HCl) and 4.8 mg (12%) of sequestered naltrexone HCl (referred to as 40-mg ALO-02).

TreatmentA: 1×40 mg ALO-02 ER capsule administered with 240 mL of water under fasting conditions.

TreatmentB: 1×40 mg ALO-02 ER capsule administered with 240 mL of water under fed conditions (standard high fat breakfast).

TreatmentC: 1×40 mg ALO-02 with the ALO-02 pellets sprinkled on approximately 1 tablespoon of applesauce, and administered with 240 mL of water under fasting conditions.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy males or females between the ages of 18 and 55 years, inclusive, with a body mass index of 17.5 to 30.5 kg/m²; and a total body weight >50 kg (110 lbs). Subjects were not to have evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease, or any condition possibly affecting drug absorption (eg, gastrectomy).

Study Treatments: Oxycodone hydrochloride and naltrexone hydrochloride ER capsules (ALO-02/[PF-06412527]) were supplied by the sponsor as 40-mg capsules. The ALO-02 pellets that were sprinkled on approximately 1 tablespoon of applesauce in Treatment C were obtained by the clinical research unit (CRU) pharmacist from the 40-mg ALO-02 ER capsules. The ALO-02 pellets were prepared by the CRU pharmacy staff by breaking open individual 40-mg ALO-02 ER capsules and sprinkling pellets onto premeasured amounts (1 tablespoon) of applesauce to individual dosing spoons by 2 operators, one of whom was a qualified pharmacist. The lot number and dosage material number are provided in Table S1.

Table S1. Lot and Formulation Identification/Dosage Material Numbers

Study Drug	Lot Number	Dosage Material Number	Potency	Formulation
ALO-02 40-mg ER capsules in labeled 100-fill bottles	668B-1104-T109	D1100299	40 mg	Packaged bottles

ALO-02 = Oxycodone hydrochloride and naltrexone hydrochloride; ER = extended release.

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Subjects received study medication at approximately 0800 hours (± 2 hours). Subjects swallowed the study medication whole, and did not chew the medication (capsules or pellets) prior to swallowing. Specifics for each treatment are as follows:

TreatmentA: 1 \times 40-mg ALO-02 ER capsule administered with 240 mL of water under fasting conditions.

TreatmentB: 1 \times 40-mg ALO-02 ER capsule administered with 240 mL of water under fed conditions (standard high-fat breakfast). Study drug was swallowed whole, without chewing capsules, within 5 minutes after completion of the meal.

TreatmentC: 1 \times 40-mg ALO-02 with the ALO-02 pellets sprinkled on approximately 1 tablespoon of applesauce. The contents of the spoon were swallowed without mixing and without delay, and were followed immediately with 240 mL of water under fasting conditions.

Efficacy Evaluations: Not Applicable.

Pharmacokinetic and Pharmacogenomic Evaluations:

Pharmacokinetic: Blood samples for pharmacokinetic (PK) analyses of oxycodone were collected during each study period at 0, 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 24, 36, and 48 hours. Blood samples for analyses of naltrexone and 6- β -naltrexol were collected during each study period at 0, 1, 2, 4, 8, 12, 24, 48, and 120 hours. All samples were analyzed using a validated analytical method in compliance with sponsor standard operating procedures.

The PK parameters listed in [Table S2](#) for oxycodone, naltrexone, and 6- β -naltrexol (metabolite of naltrexone), which are the principal active ingredients of ALO-02 (PF-06412527) were calculated for each subject and treatment, as applicable, using noncompartmental analysis of concentration-time data. Samples below the lower limit of quantification were set to 0 for analysis. Actual sample collection times were used for the PK analysis.

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Table S2. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}^a	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where C_{last}^* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
C_{24}	Concentration at 24 hours postdose	Observed directly from data
$t_{1/2}^a$	Terminal elimination half-life	$\text{Log}_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.

PK parameters were calculated using an internally validated software system, eNCA (version 2.2.3).

AUC = area under the plasma concentration-time profile.

^a If data permit.

Pharmacogenomics: A 4-mL blood sample Prep D1 (dipotassium ethylenediamine tetraacetic acid whole blood collection optimized for deoxyribonucleic acid analysis) was collected at the Day 0 Period 1 visit and retained in the Pfizer BioBank for potential retrospective pharmacogenomic analyses related to drug response.

Safety Evaluations: Safety evaluations included adverse events (AEs), clinical laboratory evaluations (including hematology, chemistry, and urinalysis), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and pulse oximetry.

Statistical Methods:

Pharmacokinetics: The PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration in at least 1 treatment period. The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period.

Natural log transformed area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}), area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}), and maximum observed concentration (C_{max}) oxycodone were analyzed using a mixed-effect model with sequence, period, and treatment as fixed-effects and subject within sequence as a random-effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and

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90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. ALO-02 ER capsule under fasting conditions was the reference treatment. The 2 test treatments were ALO-02 ER capsule given with a high-fat breakfast and ALO-02 pellets sprinkled on applesauce. Relative bioavailability for oxycodone was estimated as the ratio of adjusted geometric means for the 2 test treatments and the reference for AUC_{inf} , AUC_{last} , and C_{max} .

The oxycodone PK parameters AUC_{inf} , C_{max} , AUC_{last} , concentration at 24 hours postdose (C_{24}), time for C_{max} (T_{max}), and terminal half-life ($t_{1/2}$) and 6- β -naltrexol AUC_{last} and C_{max} were summarized descriptively by treatment. Concentrations were listed and summarized descriptively by PK sampling time and treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time was used; for individual subject plots by time, the actual PK sampling time was used.

Safety: All subjects who received at least 1 dose of study medication were included in the safety analyses and listings. AEs were reported in accordance with the sponsor reporting standards. Laboratory data, vital signs, and ECG data were listed in accordance with the sponsor reporting standards. Pulse oximetry data was summarized categorically by treatment and also listed by period, day, and time.

RESULTS

Subject Disposition and Demography: A total of 24 healthy subjects (17 males and 7 females) were assigned to study treatment. All 24 subjects received treatment with ALO-02 40-mg ER capsules under fasting conditions, with ALO-02 40-mg ER capsules under fed conditions, and with ALO-02 40 mg pellets sprinkled over applesauce under fasting conditions, and completed the study. All subjects who were treated with ALO-02 were included in the PK analysis and were evaluated for safety parameters. Subject disposition is provided in Table S3.

Table S3. Subject Disposition

	ALO-02 ER Capsule 40 mg Fasting	ALO-02 ER Capsule 40 mg Fed	ALO-02 Pellets Sprinkled on Applesauce 40 mg Fasting
Number of subjects			
Assigned to study treatment = 24			
Treated	24	24	24
Completed	24	24	24
Discontinued	0	0	0

ALO-02 = Oxycodone hydrochloride and naltrexone hydrochloride; ER = extended-release.

Efficacy Results: Efficacy evaluations were not done.

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Pharmacokinetic Results:

Oxycodone: Relative oral bioavailability of oxycodone administered as ALO-02 capsules under fed conditions or ALO-02 pellets sprinkled on applesauce (test treatments) compared to the ALO-02 capsules administered under fasted conditions (reference treatment) based on the ratios of adjusted geometric means for AUC_{inf} , AUC_{last} , and C_{max} , were 99.2% and 101% for AUC_{inf} , 100% and 101% for AUC_{last} , and 107% and 97.5% for C_{max} , respectively. The 90% CIs for the ratios of test/reference for all 3 treatments were contained entirely within the bioequivalence limits of 80% to 125%. A statistical summary of treatment comparisons is provided in Table S4. The results indicate that ALO-02 could be taken with food or sprinkled over applesauce, as long as the pellets are not crushed or disrupted, to achieve a similar absorption and plasma PK profile for oxycodone to that of the intact ALO-02 capsules administered under fasted conditions.

Table S4. Statistical Summary of Treatment Comparison for Plasma Oxycodone PK Parameters Following ALO-02 Administration

Parameter (units)	Oxycodone Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio
	Test	Reference		
40 mg ALO-02 ER Capsules Fed (Test) versus 40 mg ALO-02 ER Capsules Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	514.3	518.5	99.18	(95.95, 102.52)
AUC_{last} (ng•hr/mL)	500.7	499.3	100.29	(97.17, 103.51)
C_{max} (ng/mL)	26.52	24.86	106.68	(98.42, 115.63)
40 mg ALO-02 Pellets Sprinkled on Applesauce (Test) versus 40 mg ALO-02 ER Capsules Fasted (Reference)				
AUC_{inf} (ng•hr/mL)	523.4	518.5	100.94	(97.65, 104.34)
AUC_{last} (ng•hr/mL)	503.3	499.3	100.81	(97.67, 104.04)
C_{max} (ng/mL)	24.23	24.86	97.45	(89.91, 105.63)

PK parameters are defined in Table S2.

ALO-02 = Oxycodone hydrochloride and naltrexone hydrochlorid; CI = confidence interval; ER = extended release; PK = pharmacokinetic(s)

^a The ratios (and 90% CIs) are expressed as percentages.

Naltrexone and 6-β-naltrexol Pharmacokinetics: Naltrexone plasma concentrations for all treatments were below the limit of quantitation (LOQ) (4.00 pg/mL); therefore, PK parameters were not calculated or presented. Overall, 6-β-naltrexol plasma concentrations and systemic plasma exposures were low for all ALO-02 treatments, with individual C_{max} ranging between 0 and 29.5 pg/mL. More than 50% of subjects in each ALO-02 treatment had plasma levels below the limit of detection (4.00 pg/mL).

Safety Results: There were no serious AEs (SAEs), deaths, dose reductions, temporary discontinuations, or permanent discontinuations due to AEs in this study. The most frequently reported AEs were nausea, vomiting, dizziness, somnolence, pruritus, constipation, and headache. Overall, the majority of AEs were considered mild in severity and were consistent with the known effects of opioid administration. In addition there were

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no clinically relevant treatment-related changes in clinical laboratory data, vital signs, 12-lead ECGs, or pulse oximetry.

Conclusion(s):

- There was no effect of administration of single, 40-mg dose of ALO-02 with a high-fat meal on the PK of oxycodone relative to ALO-02 capsules administered under fasted conditions. All of the 90% CIs for the ratios of test/reference for the oxycodone AUC_{inf} , AUC_{last} , and C_{max} were entirely contained within the bioequivalence limits of 80% to 125%. The $t_{1/2}$ and T_{max} values for oxycodone were similar regardless of treatment, with mean $t_{1/2}$ values ranging between 6.7 to 7.8 hours and median T_{max} values between 12 to 14 hours across treatments.
- There was no effect of administration of single, 40-mg dose of ALO-02 controlled-release pellets sprinkled on applesauce on the PK of oxycodone relative to ALO-02 capsules administered under fasted conditions. All of the 90% CIs for the ratios of test/reference for the oxycodone AUC_{inf} , AUC_{last} , and C_{max} were entirely contained within the bioequivalence limits of 80% to 125%. The $t_{1/2}$ and T_{max} values for oxycodone were similar regardless of treatment, with mean $t_{1/2}$ values ranging between 7.8 to 7.9 hours and median T_{max} values between 12 to 13.1 hours across treatments.
- Naltrexone plasma concentrations for all treatments were below the LOQ (4.00 pg/mL).
- Plasma concentrations of 6- β -naltrexol plasma concentrations were generally low (<30 pg/mL) for all treatments, with more than 50% of subjects in each treatment having plasma levels below the LOQ (<4.00 pg/mL).
- Administration of single oral doses of 40-mg ALO-02 given to healthy subjects in this study was considered safe and generally well-tolerated. There were no SAEs, deaths, dose reductions, temporary discontinuations, or permanent discontinuations due to AEs in this study. The majority of AEs were considered mild in severity and were consistent with the known effects of opioid administration.

CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Oxycodone Hydrochloride and Naltrexone Hydrochloride

Clinical Study Report Synopsis: Protocol [B4531004](#)

Protocol Title: An Open-Label, Single-Dose, Randomized, Three-Way Crossover Study to Estimate the Effects of Ethanol 20% and 40% on the Bioavailability a Controlled Release Formulation of Oxycodone 20 mg with Sequestered Naltrexone 2.4 mg in Healthy Volunteers

Investigators: Sanela Tarabar

Study Center: The study was conducted at 1 center at Pfizer Clinical Research Unit (PCRU), New Haven, CT, United States.

Publications Based on the Study: None

Study Initiation and Completion Dates: 20 September 2012 to 02 December 2012

Date of Report: 15 May 2013

Phase of Development: Phase 1

Study Objectives:

PrimaryObjective:

To estimate the effects of ethanol 20% and 40% on the bioavailability of oxycodone from a controlled-release formulation of oxycodone 20 mg containing 2.4 mg of sequestered naltrexone (ALO-02) in healthy volunteers.

SecondaryObjective:

To evaluate the safety and tolerability of a single dose of ALO-02, 20 mg administered with and without ethanol 20% and 40% under naltrexone block in healthy volunteers.

METHODS

Study Design: This was an open-label, single-dose, randomized, 3-period crossover study in healthy volunteers. Eighteen (18) subjects were to be enrolled and randomly assigned to 1 of 6 treatment sequences. Subjects received 1 of the 3 treatments as a single dose during each period.

Treatment A: 20 mg ALO-02 administered with 240 mL of chilled (refrigerated at temperature between 2° and 8°C) aqueous solution (water) under fasted conditions.

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Treatment B: 20 mg ALO-02 administered with 240 mL of a chilled (refrigerated at temperature between 2° and 8°C) aqueous solution of 20% ethanol under fasted conditions.

Treatment C: 20 mg ALO-02 administered with 240 mL of chilled (refrigerated at temperature between 2° and 8°C) aqueous solution of 40% ethanol under fasted conditions

Diagnosis and Main Criteria for Inclusion: Healthy male and/or female subjects aged between 21 and 55 years, with no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead electrocardiogram (ECG) or clinical laboratory tests.

Study Treatment: On the morning of Day 1 of each dosing period, investigator site personnel administered subjects 1 of the 3 single dose study treatments (Treatment A, B or C) with 240 mL of chilled (refrigerated at temperature between 2 to 8°C) water. Subjects swallowed the study medication whole, and not chewed the medication prior to swallowing. All subjects received 50 mg of naltrexone HCl at 12-hour and 1-hour before ALO-02 dosing and 24-hours after ALO-02 dosing orally with 120 mL of water. Study drug details are provided in Table S1.

Table S1. Lot and Dosage Material Identification (DMID) Numbers

Study Drug	Dosage Form	Lot Number	DMID Number
PF-06412527 (ALO-02) 20 mg capsule (b) (4)	Capsule	11-010707	D1100297

Abbreviation: ALO-02 20 mg=A controlled-release formulation of 20 mg oxycodone HCl with sequestered 2.4 mg naltrexone HCl, DMID=Dosage material identification.

Efficacy Evaluations: Not Applicable.

Pharmacokinetic Evaluations: Pharmacokinetic (PK) parameters for oxycodone included maximum plasma concentration [C_{max}], area under the plasma concentration-time profile from time 0 extrapolated to infinite time [AUC_{inf}], area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})[AUC_{last}], time for C_{max} [T_{max}], and terminal elimination half life ($t_{1/2}$).

During all study periods, blood samples (4 mL) to provide approximately 1.5 mL of plasma for PK analysis were collected into appropriately labeled tubes containing K₂EDTA serially for 48 hours after the administration of dose. Oxycodone samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (HPLC/MS/MS) method. All above PK parameters were determined using non-compartmental analysis of concentration-time data.

Safety Evaluations: Safety evaluations included adverse events (AEs), clinical laboratory tests (hematology, chemistry, urinalysis and others), physical examination, BP, pulse rate and 12-lead ECGs.

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Statistical Methods: Natural log transformed AUC_{inf} , AUC_{last} and C_{max} for oxycodone were analyzed using a mixed effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence interval (CI) were obtained from the model. The adjusted mean differences and 90% CI for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CI for the ratios. ALO-02 under fasting conditions was the reference treatment and the 2 test treatments were: ALO-02 given with 20% ethanol and 40% ethanol. Relative bioavailability for oxycodone was estimated as the ratio of adjusted geometric means for the 2 test treatments relative to the reference treatment for AUC_{inf} , AUC_{last} and C_{max} .

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S2. A total of 19 subjects were assigned to study treatment; 17 subjects received ALO-02 20 mg, 18 subjects received ALO-02 20 mg with 20% ethanol and 18 subjects received ALO-02 20 mg with 40% ethanol. One (1) subject was randomized and received 1 dose of oral naltrexone 1 but did not receive any further treatment. One (1) subject receiving ALO-02 20 mg with 20% ethanol discontinued from the study, due to no longer willing to participate in the study. Of the 19 subjects, the majority of subjects were male (18 subjects) and 1 female. Subjects ranged in age from 23 to 54 years with a mean (SD) age of 40.4 (9.0) years. A total of 9 subjects were black and 5 subjects white, and 5 subjects in the others category.

Table S2. Subject Disposition

Number of Subjects	ALO-02 20 mg	ALO-02 20 mg With 20% Ethanol	ALO-02 20 mg With 40% Ethanol
Assigned to study treatment ^a	19		
Treated	17	18	18
Completed	17	17	18
Discontinued	0	1	0
Related to study drug	0	1	0
No longer willing to participate in study	0	1	0

Discontinuations have been attributed to the last study treatment received.

Abbreviations: ALO-02 20 mg=A controlled-release formulation of 20 mg oxycodone HCl with sequestered 2.4 mg naltrexone HCl.

^a Subject 10011006 was randomized and received 1 dose of oral naltrexone but did not receive any further treatment.

Efficacy Results: No efficacy evaluations were carried out.

Pharmacokinetic Results: Following administration of single oral doses of ALO-02 20 mg capsules administered either with water or in combination with 20% or 40% ethanol, oxycodone individual C_{max} values were achieved within 6 to 14 hours post dose for all subjects and across all treatments with median T_{max} values of 12 hours post dose for the ALO-02 20 mg with water and ALO-02 20 mg with 20% ethanol treatments and 8 hours post

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dose for the ALO-02 20 mg with 40% ethanol treatment. Following attainment of C_{max} , oxycodone plasma concentrations declined in parallel with similar mean $t_{1/2}$ values of approximately 6 hours observed for all 3 treatments.

Overall, based on the results of the primary statistical analyses, oxycodone plasma exposure (based on geometric mean AUC_{inf} and C_{max} values) was similar between the ALO-02 20 mg administered with water and the ALO-02 20 mg with 20% ethanol treatment; however, following administration of ALO-02 20 mg with 40% ethanol, oxycodone exposure was higher with approximately a 13% and 37% increase in adjusted geometric mean AUC_{inf} and C_{max} values respectively, compared to the reference ALO-02 20 mg treatment administered with water (Table S3).

Based on the statistical analysis results of treatment comparison, test/reference ratios of adjusted geometric means for the ALO-02 20 mg with 20% ethanol test treatment relative to the ALO-02 20 mg with water (reference treatment) were 97%, 98%, and 101% for AUC_{inf} , AUC_{last} , and C_{max} , respectively, with all of the 90% CIs contained entirely within the 80%-125% interval.

Ratios of adjusted geometric means for the ALO-02 20 mg with 40% ethanol test treatment relative to the ALO-02 20 mg with water (reference treatment) were 113%, 115%, and 137% for AUC_{inf} , AUC_{last} , and C_{max} respectively, with the upper 90% CI limits outside the 80%-125% interval

Table S3. Statistical Summary of Treatment Comparisons for Oxycodone Pharmacokinetic Parameters (All Subjects with PK Data)

Parameter (units)	Comparisons	Oxycodone Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio
		Test	Reference		
AUC_{inf} (ng.hr/mL)	ALO-02 20 mg with 20% ethanol	187.8	194.1	96.79	(82.70, 113.27)
AUC_{last} (ng.hr/mL)	(test) versus ALO-02 20 mg	185.4	189.2	97.97	(84.17, 114.02)
C_{max} (ng/mL)	with the water (reference)	10.79	10.66	101.25	(87.34, 117.37)
AUC_{inf} (ng.hr/mL)	ALO-02 20 mg with 40% ethanol	219.9	194.1	113.30	(97.24, 132.02)
AUC_{last} (ng.hr/mL)	(test) versus ALO-02 20 mg	217.7	189.2	115.03	(99.22, 133.36)
C_{max} (ng/mL)	with the water (reference)	14.58	10.66	136.80	(118.45, 157.99)

Abbreviations: ALO-02 20 mg =A controlled-release formulation of 20 mg oxycodone HCl with sequestered 2.4 mg naltrexone HCl, AUC_{inf} =Area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} =Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), CI=confidence interval, C_{max} =Maximum plasma concentration.

^a The ratios (and 90% CIs) are expressed as percentages.

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Safety Results: The incidence of all causality (and treatment-related) treatment-emergent adverse events (TEAEs) following a naltrexone block is summarized in [Table S4](#). The most frequently occurred TEAEs were nausea (2 subjects, 8 subjects, 12 subjects and 1 subject in ALO-02 20 mg alone (ie, with water), ALO-02 20 mg with 20% ethanol, ALO-02 20 mg with 40% ethanol and naltrexone HCl 50 mg pre-treatment; respectively), vomiting (5 subjects and 6 subjects in ALO-02 20 mg with 20% ethanol and ALO-02 20 mg with 40% ethanol; respectively) and decreased appetite (3 subjects each in ALO-02 20 mg alone, ALO-02 20 mg with 20% ethanol, ALO-02 20 mg with 40% ethanol and 1 subject in naltrexone HCl 50 mg pre-treatment). All above reported AEs were considered related to study treatment by the investigator.

There were no deaths, SAEs, or permanent or temporary discontinuations due to AEs during the study. There were no significant findings reported in laboratory abnormalities and ECG data.

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Table S4. Incidence of Treatment-Emergent Adverse Events – All Causality (Treatment-Related)

Number of Subjects With AEs by SOC and MedDRA (v15.1) Preferred Term	ALO-02 20 mg (N=17)	ALO-02 20 mg With 20% Ethanol (N=18)	ALO-02 20 mg With 40% Ethanol (N=18)	Naltrexone HCL 50 mg Pre-Treatment
Ear and labyrinth disorders	0 (0)	0 (0)	1 (0)	0 (0)
Ear discomfort	0 (0)	0 (0)	1 (0)	0 (0)
Gastrointestinal disorders	5 (4)	10 (10)	13 (13)	1 (1)
Abdominal discomfort	1 (1)	0 (0)	1 (1)	0 (0)
Abdominal pain	0 (0)	1 (1)	1 (1)	0 (0)
Abdominal pain upper	1 (1)	1 (1)	2 (2)	0 (0)
Constipation	2 (1)	1 (1)	1 (1)	0 (0)
Diarrhoea	1 (1)	1 (1)	0 (0)	0 (0)
Flatulence	1 (1)	1 (1)	0 (0)	0 (0)
Nausea	2 (2)	8 (8)	12 (12)	1 (1)
Vomiting	0 (0)	5 (5)	6 (6)	0 (0)
General disorders and administration site conditions	0 (0)	2 (2)	4 (4)	0 (0)
Fatigue	0 (0)	1 (1)	3 (3)	0 (0)
Feeling hot	0 (0)	1 (1)	0 (0)	0 (0)
Sluggishness	0 (0)	0 (0)	1 (1)	0 (0)
Metabolism and nutrition disorders	3 (3)	3 (3)	3 (3)	1 (1)
Decreased appetite	3 (3)	3 (3)	3 (3)	1 (1)
Nervous system disorders	1 (1)	5 (5)	11 (11)	0 (0)
Balance disorder	0 (0)	0 (0)	1 (1)	0 (0)
Dizziness	0 (0)	1 (1)	1 (1)	0 (0)
Dysarthria	0 (0)	0 (0)	1 (1)	0 (0)
Headache	0 (0)	4 (4)	7 (7)	0 (0)
Somnolence	1 (1)	3 (3)	4 (4)	0 (0)
Psychiatric disorders	0 (0)	0 (0)	3 (0)	0 (0)
Depressed mood	0 (0)	0 (0)	1 (1)	0 (0)
Insomnia	0 (0)	0 (0)	1 (0)	0 (0)
Panic attack	0 (0)	0 (0)	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	0 (0)	1 (0)	0 (0)
Upper-airway cough syndrome	0 (0)	0 (0)	1 (0)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	1 (1)	0 (0)	0 (0)
Pruritus	0 (0)	1 (1)	0 (0)	0 (0)

Included all data collected since the first dose of study drug.

When a dictionary other than MedDRA was used, percentages of gender specific events were calculated using the corresponding gender.

MedDRA (v15.1) coding dictionary applied.

Abbreviations: AEs=Adverse events, ALO-02 20 mg=A controlled-release formulation of 20 mg oxycodone HCl with sequestered 2.4 mg naltrexone HCl, MedDRA=Medical Dictionary for Regulatory Activities, SOC=System organ class

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Conclusions:

- Administration of ALO-02 20 mg with 20% ethanol had no impact on the overall PK profile of oxycodone from the controlled release ALO-02 formulation. Ratios of adjusted geometric means for the test treatment (ALO-02 20 mg with 20% ethanol) relative to the reference (ALO-02 20 mg with the water) were 97%, 98%, and 101% for AUC_{inf} , AUC_{last} and C_{max} respectively with all of the 90% CIs contained entirely within the 80%-125% interval.
- Administration of ALO-02 20 mg with 40% ethanol resulted in an approximately 13% increase in AUC_{inf} and a 37% increase in geometric mean C_{max} values compared to the reference treatment. Ratios of adjusted geometric means for the test treatment (ALO-02 20 mg with 40% ethanol) relative to the reference (ALO-02 20 mg with the water) were 113%, 115%, and 137% for AUC_{inf} , AUC_{last} , and C_{max} respectively, with the upper 90% CI limits outside of the 80-125% interval.
- ALO-02 20 mg administered with ethanol 20% and 40% under naltrexone block was safe and generally tolerated except for AEs of nausea, vomiting and nervous systems affects (headache and somnolence) which are expected in this type of study. ALO-02 administered alone was safe and generally well tolerated.

CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc

Investigational Product: Oxycodone Hydrochloride and Naltrexone Hydrochloride (ALO-02)

Clinical Study Report Synopsis: [Protocol B4531006](#)

Protocol Title: An Open-Label, Single-Dose and Multiple-Dose, Randomized, Crossover Study to Evaluate Pharmacokinetics, Safety and Tolerability after Administration of ALO-02 40 mg Twice Daily Compared to ALO-02 80 mg Once Daily and to OxyContin 40 mg Twice Daily in Healthy Volunteers

Investigators: Sylvester S Pawlak

Study Center: This study was conducted at 1 center in the United States.

Publications Based on the Study: None.

Study Initiation and Completion Dates: 21 March 2012 to 17 May 2012

Date of Report: 03 January 2013

Phase of Development: Phase 1

Study Objectives: The primary objective of this study was to characterize the single- and multiple-dose pharmacokinetics (PK) of oxycodone following the administration of 40 mg doses of ALO-02 capsules twice a day (BID) in healthy volunteers.

The secondary objectives of this study were to: characterize the single- and multiple-dose PK of oxycodone following the administration of 80 mg doses of ALO-02 capsules once daily (QD) in healthy volunteers; to characterize the single- and multiple-dose PK of oxycodone following the administration of 40 mg doses of OxyContin tablets BID in healthy volunteers; to compare the single- and multiple-dose PK of equivalent daily doses of ALO-02 administered BID, ALO-02 administered QD, and OxyContin administered BID in healthy volunteers; and to assess the safety and tolerability of single and multiple doses of ALO-02 and OxyContin in healthy volunteers under a naltrexone block.

METHODS

Study Design: This was an open-label, single-dose and multiple-dose, randomized, 3-period crossover study in healthy volunteers. There were at least 5 days separating each treatment period. The study drug was ALO-02 capsules containing 40 mg and 80 mg of oxycodone hydrochloride (HCl) and 4.8 mg and 9.6 mg (12%) sequestered naltrexone HCl (referred to

as 40 mg and 80 mg ALO-02 capsules), respectively, and OxyContin 40 mg tablets. Eligible subjects were assigned to 1 of 6 treatment sequences to receive the following 3 treatments on Day 1-5 in each period.

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TreatmentA: 1×40 mg ALO-02 BID, administered approximately at 7 AM and 7 PM;

TreatmentB: 1×80 mg ALO-02 QD, administered approximately at 7 AM;

TreatmentC: 1×40 mg OxyContin BID, administered approximately at 7 AM and 7 PM.

All study drugs were administered as a single dose on the morning of Day 1. To minimize the risk of opioid related adverse events (AEs), oral doses of naltrexone HCl 50 mg were administered as background drug 30 minutes before the dosing of study drugs.

Diagnosis and Main Criteria for Inclusion: Subjects included healthy male and/or female of non-childbearing potential between the ages of 18 and 55 years, inclusive, who had a Body Mass Index (BMI) of 17.5 to 30.5 kg/m² and a total body weight >50 kg (110 lbs). Subjects were not to have evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease, or any condition possibly affecting drug absorption (eg, gastrectomy).

Study Treatment: ALO-02 was supplied by the sponsor as 40 mg and 80 mg capsules. OxyContin 40 mg tablets and naltrexone HCl 50 mg tablets were obtained commercially and sourced by the clinical research unit. ALO-02, naltrexone HCl and OxyContin were presented to the subjects in individual dosing containers. The lot number and dosage material number are provided in Table S1.

Table S1. Lot and Formulation identification/Dosage Material Numbers

Drug	Lot Number	Dosage Material Number	Formulation
PF-06412527 (ALO-02) 80mg (b) (4) capsule	11-010736	D1100301	Capsule
PF-06412527 (ALO-02) 40mg (b) (4) capsule	11-009555	D1100299	Capsule

Abbreviation: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride.

Efficacy Evaluations: Not Applicable.

Pharmacokinetic and Pharmacogenomic Evaluations:

Pharmacokinetic Evaluation: Blood samples were to be collected prior to dosing and at 1, 2, 4, 6, 8, 12, 14, 16, 24, 48, 72, 96, 96.5, 97, 98, 100, 102, 104, 108, (108.5, 109, 110, 112 for BID dosing only), 114, (116 for BID dosing only), 120, (132 for BID dosing only), 144 and 168 hours following dosing on Day 1, to provide plasma for PK analysis. Plasma samples were analyzed for ALO-02 concentrations using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (HPLC-MS/MS) method.

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Table S2 provides the PK parameters in this study, calculated for each subject for each treatment using noncompartmental analysis of concentration-time data.

Table S2. Pharmacokinetic Parameters Determined in the Study

Parameter	Definition	Method of Determination
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Day 1 (Single Dose, 0-24 hour Interval)		
AUC ₂₄	Area under the plasma concentration versus time curve from time zero to 24 hours (calculated for all treatments)	Linear/Log trapezoidal method.
AUC ₂₄ (dn)	Dose normalized AUC ₂₄	AUC ₂₄ /Dose
C _{max}	Maximum plasma concentration (observed over the entire 24 hours interval for all treatments)	Observed directly from data.
C _{max} (dn)	Dose normalized C _{max} over a 24 hours interval (all treatments)	C _{max} /Dose
T _{max}	Time for C _{max} (T _{max} over the entire 24 hours dosing interval for all treatments)	Observed directly from data as time of first occurrence
AUC _τ	Area under the concentration-time profile from time zero to time tau (τ), the dosing interval (0 to 24 hours for the QD treatment and from 0 to 12 hours for the BID treatments)	Linear/Log trapezoidal method
Day 5 (Multiple Dose)		
AUC ₂₄	Area under the concentration-time profile for the 24-hour period following the morning dose on Day 5	Linear/Log trapezoidal method. Same as AUC _τ for QD treatment; sum of 0-12 and 12-24 hour AUC _τ values for BID treatments.
AUC _τ	Area under the concentration-time profile from time zero to time tau (τ), the dosing interval (0 to 24 hours for the QD and from 0 to 12 hours and 12 to 24 hours for the BID treatments)	Linear/Log trapezoidal method
C _{max}	Maximum observed concentration during the specified interval ^{a, b}	Observed directly from data
C _{max} (dn)	Dose normalized C _{max} ^b	C _{max} /Dose
T _{max}	Times for C _{max} ^a	Observed directly from data as time of first occurrence
C _{min}	Lowest concentration observed during the specified interval ^a	Observed directly from data
C _{av}	Average concentration over the specified interval ^a	AUC ₂₄ /24 for the 24-hour interval for both QD and BID treatments; AUC _τ /12 for the morning and evening intervals for BID treatments only.
PTF	Peak-trough fluctuation ^a	(C _{max} - C _{min})/C _{av} - steady state parameters

Pharmacokinetic parameter values were calculated using eNCA version 2.2.3.

Abbreviations: dn = dose normalized, k_{el} = terminal phase rate constant, QD = once daily, BID = twice daily.

^a The specified intervals are from 0 to 24 hours following the morning dose for the QD treatment and from 0 to 12 hours (AM interval), and 12 to 24 hours (PM interval) for the BID treatments.

^b C_{max} and C_{max} (dn) over the 24 hours interval are also referred to as C_{max24} and C_{max24} (dn) in the source tables.

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Table S2. Pharmacokinetic Parameters Determined in the Study

Parameter	Definition	Method of Determination
Day 5 (Multiple Dose)		
R_{ac}	Accumulation ratios based on AUC_{τ} (AUC_{12}) for the BID treatments and AUC_{τ} (AUC_{24}) for the QD treatment	AUC_{τ} (Day 5)/ AUC_{τ} (Day 1)
$R_{ac,C_{max}}$	Accumulation ratios based on C_{max} over the entire 24 hours interval ($C_{max,24}$) for all treatments	C_{max} (Day 5)/ C_{max} (Day1)
$t_{1/2}$	Terminal half-life (calculated over the 24 hours interval for all treatments)	$\text{Log}_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.

Pharmacokinetic parameter values were calculated using eNCA version 2.2.3.

Pharmacogenomic Evaluation: Blood samples collected on Baseline visit (Day 0, Period 1) were to be retained for pharmacogenomic analysis related to drug response. Pharmacogenomic evaluation results are not included in the clinical study report.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (blood pressure [BP], pulse rate [PR] and respiratory rate [RR]), 12-lead electrocardiogram (ECG), pulse oximetry, AEs and safety laboratory tests.

Statistical Methods:

Pharmacokinetic Analyses: The PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration in at least 1 treatment period. The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period.

Natural log transformed oxycodone AUC_{24} was analyzed using a mixed effect model with sequence, period and treatment (ALO-02 40 mg BID, ALO-02 80 mg QD, and OxyContin 40 mg BID) as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. For the primary analysis, OxyContin 40 mg tablets BID was the Reference treatment and the Test treatment was ALO-02 40 mg capsules BID. For the secondary analyses, the reference treatments were ALO-02 40 mg capsules BID and OxyContin 40 mg tablets BID and the Test treatment was ALO-02 80 mg capsules QD.

As a secondary analysis, natural log transformed $C_{max,ss}$ oxycodone was analyzed with OxyContin 40 mg tablets BID as the Reference treatment and ALO-02 40 mg capsules BID

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as the Test treatment. Additionally, as a secondary analysis, natural log transformed oxycodone $AUC_{24}(\text{dn})$ and $C_{\text{max}}(\text{dn})$ was analyzed with reference treatments of ALO-02 40 mg capsules BID and OxyContin 40 mg tablets BID. The Test treatments were 80 mg ALO-02 capsules QD and 40 mg ALO-02 capsules BID. All secondary analyses used the same model as the primary analysis.

The oxycodone PK parameters AUC_{24} , $AUC_{24}(\text{dn})$, C_{max} , $C_{\text{max}}(\text{dn})$, AUC_{τ} , T_{max} , C_{min} , C_{av} , PTF, $t_{1/2}$, R_{ac} , $R_{\text{ac},C_{\text{max}}}$ were summarized descriptively by treatment. Concentrations were listed and summarized descriptively by PK sampling time and treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time was used; for individual subject plots by time, the actual PK sampling time was used.

Safety Analyses: Safety data, including AEs, vital signs (ECGs, BP, HR and RR), pulse oximetry value and safety laboratory data, are presented in tabular format and summarized descriptively according to the Sponsor's standards, when appropriate.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S3. A total of 13 subjects were assigned to study treatment with ALO-02; all subjects except for 1 completed the study.

All subjects were healthy males. The majority of subjects were white (7 out of 13 subjects). Subjects ranged in age from 25 to 55 years, with a mean BMI of 25.9 kg/m².

Table S3. Subject Disposition

Number of Subjects	ALO-02 40 mg BID	ALO-02 80 mg QD	OxyContin 40 mg BID	Naltrexone ^a
Assigned to study treatment	13			
Treated	13	12	12	13
Completed	12	12	12	13
Discontinued ^b	1	0	0	0
No longer willing to participate in study	1	0	0	0

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride, BID = twice a day, QD = once daily.

^a Naltrexone received prior to study medication (ALO-02/OxyContin) in each period was captured as treatment naltrexone.

^b Discontinuations were attributed to the last study treatment received.

Efficacy Results: There were no efficacy evaluations performed in this study.

Pharmacokinetic Results:

Oxycodone Pharmacokinetics-Single Dose (Day 1): Following administration of a single oral dose of ALO-02 (40 and 80 mg doses) compared to a single dose of OxyContin 40 mg,

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oxycodone from the ALO-02 treatments showed a prolonged median T_{max} of approximately 12 hours post dose compared to a median T_{max} of 4 hours post dose for the OxyContin 40 mg treatment.

Compared with the mean C_{max} of OxyContin 40 mg, oxycodone mean C_{max} for the ALO-02 40 mg and 80 mg treatments were approximately 27% and 23% lower, respectively, based on dose normalized values.

Overall, oxycodone plasma exposure obtained from the ALO-02 treatments was comparable to that observed from the OxyContin treatment based on mean AUC_{24} (40 mg ALO-02) and mean $AUC_{24}(dn)$ (80 mg ALO-02) and appeared to be dose proportional between the 40 mg and 80 mg ALO-02 doses for both AUC and C_{max} .

Statistical analysis of treatment comparison (Table S4) showed that the geometric mean ratios based on $AUC_{24}(dn)$ values for the test treatments (40 mg and 80 mg ALO-02) compared to the reference treatment (OxyContin 40 mg) were 92.63% and 98.18%, respectively, with all of the 90% CIs contained within the 80%-125% bioequivalence criteria while the geometric mean ratios based on $C_{max}(dn)$ values were 72.99% and 76.56%, respectively, with the 90% CIs at the lower bounds outside of the 80-125% limit.

Inter-subject variability for oxycodone exposure was similar between treatments with the percentage of coefficient of variation (%CV) values ranging between 21%-28% for $AUC_{24}(dn)$ and 27%-31% for $C_{max}(dn)$.

Noroxycodone and Oxymorphone Pharmacokinetics-Single Dose (Day 1): A similar trend in PK was observed for the oxycodone metabolites noroxycodone and oxymorphone following administration of the ALO-02 treatments and the OxyContin treatment.

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Table S4. Statistical Summary of Treatment Comparisons for Oxycodone on Day 1 and Day 5

Parameter (units)	Comparison (Test vs Reference)	Adjusted Geometric Means		Ratio (Test/Ref) of Adjusted Means ^a	90% CI for Ratio
		Test	Reference		
Day 1 (Single Dose, 0-24 hour Interval)					
AUC ₂₄ (dn) (ng•hr /mL/mg)	ALO-02 40 mg BID vs OxyContin 40 mg BID	10.10	10.90	92.63	(82.19, 104.41)
C _{max} (dn) (ng/mL/mg) ^b		0.7164	0.9815	72.99	(61.96, 85.98)
AUC ₂₄ (dn) (ng•hr /mL/mg)	ALO-02 80 mg QD vs ALO-02 40 mg BID	10.70	10.10	105.98	(94.42, 118.96)
C _{max} (dn) (ng/mL/mg) ^b		0.7514	0.7164	104.90	(89.52, 122.91)
AUC ₂₄ (dn) (ng•hr /mL/mg)	ALO-02 80 mg QD vs OxyContin 40 mg BID	10.70	10.90	98.18	(87.11, 110.65)
C _{max} (dn) (ng/mL/mg) ^b		0.7514	0.9815	76.56	(65.00, 90.19)
Day 5 (Multiple Dose)					
AUC ₂₄ (ng•hr/mL)	ALO-02 40 mg BID vs OxyContin 40 mg BID	1058	980.3	107.97	(101.89, 114.42)
C _{max} (ng/mL/mg) ^b		55.40	62.14	89.15	(82.17, 96.72)
AUC ₂₄ (ng•hr/mL)	ALO-02 80 mg QD vs ALO-02 40 mg BID	1126	1058	106.40	(100.41, 112.76)
C _{max} (ng/mL/mg) ^b		63.60	55.40	114.79	(105.81, 124.54)
C _{max} (dn) (ng/mL/mg) ^b		0.7948	1.386	57.35	(52.86, 62.21)
AUC ₂₄ (ng•hr /mL)		1126	980.3	114.89	(108.41, 121.75)
C _{max} (ng/mL/mg) ^b	ALO-02 80 mg QD vs OxyContin 40 mg BID	63.60	62.14	102.34	(94.33, 111.03)
C _{max} (dn) (ng/mL/mg) ^b		0.7948	1.554	51.13	(47.13, 55.47)

Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride, hr = hours, BID = twice a day, QD = once daily, CI=confidence interval, dn = dose normalized to 1 mg, vs = versus.

^a The ratios (and 90% CIs) were expressed as percentages.

^b C_{max} was assessed over the entire day (24 hours interval) for all treatments and was referred to as C_{max24} or C_{max24}(dn) in the source tables.

PK parameters defined in [Table S2](#).

Oxycodone Pharmacokinetics-MultipleDose(Day5): Following multiple oral doses of ALO-02 (40 mg BID and 80 mg QD) and OxyContin 40 mg BID, steady state for oxycodone was reached around Day 3 ([Figure S1](#)) for all treatments.

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Oxycodone PK parameters for the BID treatments for both the AM (0-12 hours) and PM (12-24 hours) dosing intervals were found to be approximately similar with the exception of PTF values which were slightly higher for the PM dosing intervals.

The steady-state oxycodone median plasma concentration time profiles over the 24 hours interval for the ALO-02 40 mg BID treatment appeared to be flat, with lower PTF values observed compared to the other treatments. Oxycodone individual C_{max} for the ALO-02 40 mg BID treatment were attained between 0 and 12 hours post each dose (AM and PM) with a median T_{max} of 1 hour for the first dosing interval (AM dose) and 8 hours for the second dosing interval (PM dose). The earlier T_{max} observed for the first dosing interval of the ALO-02 40 mg BID treatment was likely an artifact due to the flat concentration profile of this treatment.

Oxycodone individual C_{max} for the ALO-02 80 mg QD treatment were reached between 8-12 hours post dose (median T_{max} = 12 hours) in comparison to 2-8 hours post dose with a median T_{max} of 4 and 6 hours, respectively, for the AM and PM intervals for the OxyContin 40 mg BID treatment. $T_{1/2}$ of oxycodone was similar across all treatments and ranged between 6.6-8.1 hours.

C_{av} for oxycodone were similar across all treatments and higher C_{min} values were observed for the ALO-02 40 mg BID treatment group.

The overall oxycodone plasma exposures on Day 5 as measured by the mean AUC_{24} and C_{max24} were similar for all 3 treatments with similar mean AUC_{24} values and only slightly lower mean C_{max24} values (approximately 11%) observed for the ALO-02 treatments compared to the OxyContin treatment.

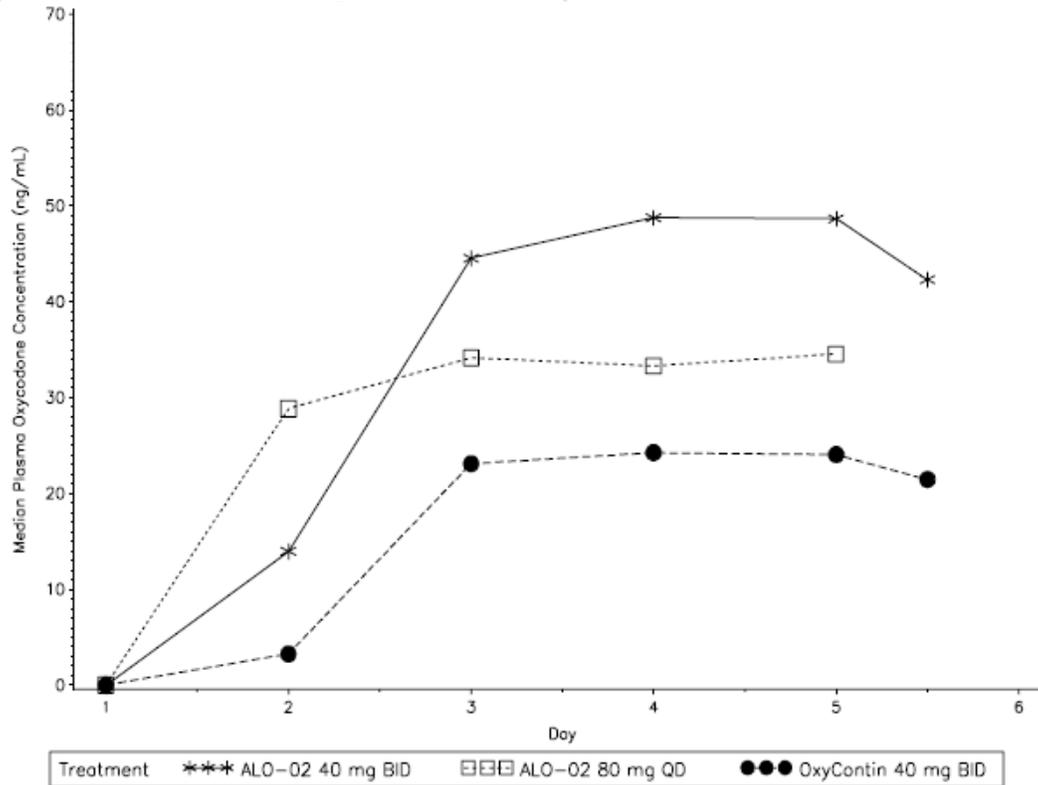
Statistical analysis of treatment comparison (Table S4) showed that the geometric mean AUC_{24} ratios of test/reference for the ALO-02 treatments (40 mg BID and 80 mg QD) compared to the OxyContin 40 mg BID treatment were 107.97% and 114.89%, respectively, while the geometric mean C_{max24} were 89.15% and 102.34%, respectively, with all of the 90% CIs for both AUC_{24} and C_{max24} contained within the 80%-125% bioequivalence limit. In comparison, based on the $C_{max}(dn)$ over the 24 hours interval, the exposure for the ALO-02 80 mg QD treatment was approximately 50% lower compared to the BID treatments which may be due in part to the higher accumulation observed following BID dosing compared to QD dosing.

Drug accumulation ratios (R_{ac}) for oxycodone on Day 5 were 1.3, 3.3, and 1.5 based on AUC_{τ} and 1.1, 1.9, and 1.6 based on C_{max24} ($R_{ac,C_{max}}$) for the ALO-02 80 mg QD, ALO-02 40 mg BID, and OxyContin 40 mg BID treatments, respectively. The apparent higher observed R_{ac} for ALO-02 40 mg BID was an over estimation as a result of the lower AUC_{τ} (AUC_{12}) value for ALO-02 on Day 1 due to prolonged T_{max} and a slow initial drug release.

Inter-subject variability on Day 5 was slightly higher for the ALO-02 40 mg BID treatment compared to the other treatments with %CV values ranging between 21-32% for AUC and 22-45% for C_{max} . Inter-subject variability based on % CV for AUC and C_{max} were 18-19% and 19-20% for the OxyContin 40 mg BID treatment, respectively, and 21% and 21-22% for the ALO-02 80 mg QD treatment, respectively.

CLINICAL STUDY REPORT SYNOPSIS

Figure S1. Median Plasma Oxycodone Trough Concentration-Time Profiles Following Single and Multiple Oral Doses of ALO-02 (40 mg BID and 80 mg QD) and OxyContin 40 mg BID



Abbreviations: ALO-02 = oxycodone hydrochloride and naltrexone hydrochloride, BID = twice a day, QD = once daily.

Day 1 12h's readings were not included in the figure since all study drugs were administered as a single dose on the morning of Day 1.

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0. The lower limit of quantification is 0.100 ng/mL.

Noroxycodone and Oxymorphone Pharmacokinetics-Multiple Dose (Day 5): A similar trend in PK was observed for the oxycodone metabolites noroxycodone and oxymorphone following administration of the ALO-02 treatments and the OxyContin treatment.

Safety Results: There were no deaths, serious AEs (SAEs), dose reduction, temporary or permanent discontinuations due to AEs reported in this study. The most frequently reported AE (all causality and treatment-related) was somnolence. All AEs reported during this study were mild in severity. One subject discontinued due to willingness to participate in the study.

There were no laboratory values of clinical concern. One subject had an abnormal blood urea nitrogen value and an abnormal mean platelet volume during treatment washout period.

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No subjects had vital signs data that were considered clinically significant. One subject had a maximum increase from baseline in supine systolic BP that exceeded 30 mm Hg during the treatment of ALO-02 40 mg BID. One subject had a supine systolic BP less than 90 mm Hg during the treatment of OxyContin 40 mg BID.

Conclusions:

Single-DosePK:

- Oxycodone plasma exposures based on mean $AUC_{24}(dn)$ values on Day 1 were similar for all treatments with all of the 90% CIs for test/reference contained within the bioequivalence limits (80%-125%). However, peak exposures based on mean $C_{max}(dn)$ values were approximately 27% and 23% lower for the ALO-02 40 and 80 mg treatments respectively compared to the OxyContin 40 mg treatment.
- The ALO-02 treatments showed a prolonged median T_{max} of approximately 12 hours or greater compared to that observed from the OxyContin treatment (approximately 4 hours).
- Exposure between the 40 mg and 80 mg doses of ALO-02 appeared dose proportional.
- A similar trend in PK was observed for the oxycodone metabolites noroxycodone and oxymorphone following administration of the ALO-02 treatments and the OxyContin treatment.

Multiple-DosePK:

- Oxycodone steady state was reached by Day 3, and the overall plasma exposures as measured by mean AUC_{24} and C_{max} values over the entire 24 hours interval were similar across all treatments with all of the 90% CIs of test/reference within the bioequivalence limit of 80%-125%.
- Peak to PTF for oxycodone were reduced by more than 50% for the ALO-02 40 mg BID treatment and plasma concentration profiles appeared flattened in comparison to the ALO-02 80 mg QD and OxyContin 40 mg BID treatments. PTF values were similar between the ALO-02 80 mg QD and OxyContin 40 mg BID treatments.
- Accumulation ratios based on AUC_{τ} and C_{max} were higher for the BID treatments compared to that observed for the ALO-02 80 mg QD treatment contributing to 50% higher $C_{max}(dn)$ values observed for the BID treatments compared to the QD treatment over a 24 hours dosing interval.
- A similar trend in PK was observed for the oxycodone metabolites noroxycodone and oxymorphone following administration of the ALO-02 treatments and the OxyContin treatment.

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Safety and Tolerability:

- The treatments of 40 mg ALO-02 BID, 80 mg ALO-02 QD and 40 mg OxyCotin BID were considered safe and well-tolerated in healthy subjects.
- No deaths, SAEs, severe AEs, dose reductions, or permanent discontinuations due to AEs occurred during the study. All the AEs reported were considered mild in severity and the most frequently reported AEs were consistent with the known effects of opioid administration.
- There were no laboratory values of clinical concern.

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/s/

SURESH B NARAHARISSETTI
09/14/2015

YUN XU
09/14/2015

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

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	<i>NDA-207621</i>	Brand Name	<i>Troxyca ER</i>
OCP Division (I, II, III, IV, V)	<i>II</i>	Generic Name	<i>oxycodone/naltrexone</i>
Medical Division	<i>DAAAP</i>	Drug Class	<i>Opioid</i>
OCP Reviewer	<i>Suresh B Naraharisetti</i>	Indication(s)	<i>Chronic Pain</i>
OCP Team Leader	<i>Yun Xu</i>	Dosage Form	<i>Extended- release Capsule</i>
Pharmacometrics Reviewer		Dosing Regimen	<i>BID</i>
Date of Submission	<i>December 19, 2015</i>	Route of Administration	<i>Oral</i>
Estimated Due Date of OCP Review		Sponsor	<i>Pfizer</i>
Medical Division Due Date		Priority Classification	<i>Standard 10-month clock</i>
PDUFA Due Date	<i>October 19, 2015</i>		

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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
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:				
multiple dose:	X	1		
Patients-				
single dose:				
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:				
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:				

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PD -				
	Phase 2:			
	Phase 3:			
PK/PD -				
	Phase 1 and/or 2, proof of concept:			
	Phase 3 clinical trial:			
Population Analyses -				
	Data rich:			
	Data sparse:	X	1	
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
	solution as reference:			
	alternate formulation as reference:	X	1	Roxicodone (NDA 21011) as reference in R BA study
Bioequivalence studies -				
	traditional design; single / multi dose:			
	replicate design; single / multi dose:			
Food-drug interaction studies		X	1	
Bio-waiver request based on BCS				
BCS class				
In vivo alcohol induced dose-dumping		X	1	
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Yes
Literature References				
Total Number of Studies			8	

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			
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, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					

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9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
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	
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 basic requirements for approvability of this product?	X			
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

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

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

BACKGROUND

Pfizer submitted a 505 (b) (2) NDA (207621) for Troxyca ER (oxycodone/naltrexone) capsules (b) (4)

As a 505(b) (2) NDA, Sponsor is relying on the Agency's findings on the safety and efficacy of Roxicodone (NDA 021011) for oxycodone and Revia (NDA 19932) for naltrexone. In support of this NDA, sponsor conducted the following Clinical Pharmacology/Clinical studies:

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Clinical Pharmacology Studies with final formulation:

Phase 1 B4531007: Relative BA to Oxycodone IR (Roxicodone)

- An open-label, single-dose, randomized, two-way crossover study to estimate the relative bioavailability of a ER formulation of oxycodone (40 mg) with sequestered naltrexone compared with IR oxycodone Tablets (20 mg) in healthy volunteers

Phase 1 B4531003: Food effect

- An open-label, single-dose, randomized, three-way crossover study in healthy volunteers to estimate the effects of food and of sprinkling ALO-02 pellets on applesauce on the bioavailability of oxycodone and naltrexone/6- β -naltrexol from an ER pellets-in-capsule formulation of oxycodone 40 mg with sequestered naltrexone 4.8 mg

Phase 1 B4531006: Single and Multiple dose PK

- An open-label, single-dose and multiple-dose, randomized, crossover study to evaluate pharmacokinetics, safety and tolerability after administration of ALO-02 40 mg twice daily compared to ALO-02 80 mg once daily and to oxycontin 40 mg twice daily in healthy volunteers.

Phase 1 B4531004: Alcohol Interaction

- An open-label, single-dose, randomized, three-way crossover study to estimate the effects of ethanol 20% and 40% on the bioavailability a ER formulation of oxycodone 20 mg with sequestered naltrexone 2.4 mg in healthy volunteers

Meta-analysis to identify influential covariates on oxycodone PK in healthy:

- Phase 1 studies included in the analysis B4531003, B4531004, B4531006, B4531007, B4531008

Abuse Potential Studies

- B4531008 (n=41): Oral relative abuse potential study
- B4531009 (n=32) Intranasal relative abuse potential study
- B4981002 (n=33) IV abuse potential study

Clinical Trials with final formulation:

Phase 3: Study B4531002: Primary Study

- A multicenter, 12-week, double-blind, placebo-controlled, randomized withdrawal study to determine the efficacy and safety of ALO-02 in subjects with moderate-to-severe CLBP is intended to form the primary basis of an efficacy claim in the NDA. (Study
 - Sparse PK sampling was done at end of end of double-blind weeks 4, 8 and 12 (or early termination). Measured oxycodone, noroxycodone, naltrexone and 6-beta-naltrexol levels.

Phase 3: Study B4531001: Supportive study:

- A multicenter, 12-month, open-label, single-arm, safety study of oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules in subjects with moderate to severe chronic noncancer pain (CNCP)
 - Sparse PK sampling was done at end of weeks 1 and 4, at the end of months 2, 3, 6, 9, and 12 or early termination. Measured oxycodone, noroxycodone, naltrexone and 6-beta-naltrexol levels.

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FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Suresh Babu Naraharisetti	February 04, 2015
Reviewing Clinical Pharmacologist	Date
Xu Yun	February 04, 2015
Team Leader/Supervisor	Date

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

/s/

SURESH B NARAHARISSETTI
02/05/2015

YUN XU
02/06/2015