

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

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

CLINICAL PHARMACOLOGY REVIEW

NDA: 204242	Submission Date(s): September 5, 2012, December 27, 2012 and May 10, 2013
Proposed Brand Name	Zubsolv™
Generic Name	Buprenorphine and naloxone sublingual tablet
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Orexo AB
Relevant IND(s)	IND 110,637
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Sublingual tablet (buprenorphine/naloxone): 5.7/1.4 mg and 1.4/0.36 mg
Indication	For the maintenance treatment of opioid dependence

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA submissions dated September 5, 2012, December 27, 2012, and May 10, 2013 and finds them acceptable from clinical pharmacology perspective.

Optional Intra-Division Level OCP briefing was held on June 4, 2013.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Key clinical pharmacology findings:

1. Zubsolv™ 5.7/1.4 mg sublingual tablet exhibited equivalent systemic exposure (C_{max}, AUC_t, and AUC_{inf}) to buprenorphine in comparison to the listed drug, Suboxone 8/2 mg sublingual tablet.
2. Zubsolv™ 5.7/1.4 mg sublingual tablet had equivalent naloxone C_{max}, 12% lower naloxone AUC_t, and 16% lower naloxone AUC_{inf} values in comparison to Suboxone 8/2 mg sublingual tablet.
3. The median dissolve time of Zubsolv™ 5.7/1.4 mg was 5 minutes while the median dissolve time of Suboxone 8/2 mg sublingual tablet was 12.5 minutes.
4. Dose-proportionality was not demonstrated for buprenorphine C_{max} and AUC values over the range of 1.4 mg to 11.4 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 1.4 to 11.4 mg.
5. Dose-proportionality was demonstrated for naloxone AUC_t and AUC_{inf} over the range of 0.36 mg and 2.8 mg. C_{max} values increased in a slightly less than dose proportional fashion.

Zubsolv™ (also known as OX219) sublingual tablets (buprenorphine and naloxone combination) is presented in a 4:1 ratio of free bases which has been used in the approved sublingual tablet and sublingual film formulations under the trade name of Suboxone. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal when administered parenterally in individuals physically dependent on full

opioid agonists. When taken sublingually as intended, naloxone will have no or insignificant effect due to its low plasma levels.

Orexo AB submitted a 505(b)(2) NDA 204242 for Zubsolv™ sublingual tablet 5.7/1.4 mg and 1.4/0.36 mg for the maintenance treatment of opioid dependence. Orexo's primary objective for development of OX219 is to provide a more convenient, rapidly disintegrating tablet for sublingual administration, which will provide similar overall safety and efficacy as Suboxone sublingual tablets. Sponsor proposed to rely on the Agency's previous finding of the safety and efficacy of the listed drug, Suboxone sublingual tablets 8/2 mg and 2/0.5 mg (NDA 20-733) from Reckitt Benckiser.

The clinical and clinical pharmacology database for this NDA consists of 4 Phase 1 studies (OX219-001, OX219-002, OX219-003, and OX219-004). The earlier formulations OX219-1 and OX219-3 were used in Studies 001 and 002, respectively, to determine the final formulation and strengths. The to-be-marketed formulation (OX219-4) was used in pivotal Studies 003 and 004. Comparative bioavailability of the higher strength of the to-be-marketed formulation (5.7/1.4 mg) and the listed drug Suboxone sublingual tablet (8/2 mg) was studied in Study OX219-003. Dose proportionality of OX219-4 formulation was evaluated in Study OX219-004. As agreed in Pre-IND and Pre-NDA meetings, sponsor needs to demonstrate that 5.7/1.4 mg will have equivalent buprenorphine exposure to Suboxone 8/2 mg tablet. It was also agreed that lower naloxone exposure in OX219 as compared to Suboxone 8/2 mg tablet is acceptable. It was agreed that lower norbuprenorphine exposure would not lead to requirement for efficacy study because has not been studied clinically for opioid-like activity. This review will focus on the two pivotal studies (Study OX219-003 and Study OX219-004).

Sponsor requested biowaiver for the lower strength of the to-be-marketed formulation (1.4/0.36 mg) and the biowaiver was granted by ONDQA/Biopharm reviewer, Dr. Akm Khairuzzaman (see Biopharm review dated March 5, 2013).

Relative Bioavailability of OX219 5.7/1.4 mg Sublingual Tablet in Comparison to Listed Drug Suboxone 8/2 mg Sublingual Tablet

OX219 5.7/1.4 mg sublingual tablet exhibited equivalent systemic exposure (C_{max}, AUC_t, and AUC_{inf}) to buprenorphine in comparison to the listed drug, Suboxone 8/2 mg sublingual tablet, because the 90% CI of OX219:Suboxone geometric mean ratios for buprenorphine C_{max}, AUC_t, and AUC_{inf} fell within the bioequivalent limits of 80 to 125%. The point estimate (90% CI) of the geometric mean ratio (OX219:Suboxone) for buprenorphine C_{max}, AUC_t, and AUC_{inf} values are 98% (91 – 106%), 88% (83 – 94%), and 86% (80 – 92%) respectively. Median t_{max} was the same for both formulations (1.75 hr).

OX219 5.7/1.4 mg had equivalent free naloxone C_{max} as the 90% CI of OX219:Suboxone geometric mean ratio for free naloxone C_{max} fell within the bioequivalence limit of 80 to 125%. Median t_{max} was the same for both formulations (0.83 hr). OX219 did not exhibit equivalent AUC_t and AUC_{inf} values to naloxone in comparison to Suboxone 8/2 mg because the lower 90% CI limit below 80%. The point estimates (90% CI) of the geometric mean ratios (OX219:Suboxone) for naloxone C_{max}, AUC_t and AUC_{inf} values are 92% (82 – 104%), 84% (77 – 93%), and 88% (79 – 97%), respectively. Slightly lower naloxone exposure in comparison to Suboxone, when they are used sublingually, is acceptable because naloxone levels in these products are not expected to play a role when they are given sublingually due to its low exposure. The total naloxone exposure of OX219 is also lower than Suboxone.

Dissolve Time:

The median dissolve time of OX219 5.7/1.4 mg was 5 minutes while the median dissolve time of Suboxone 8/2 mg sublingual tablet was 12.5 minutes. The dissolve time ranges of (b) (4) for OX219 are similar to the dissolve time range of (b) (4) for Suboxone. The corresponding t_{max} values of buprenorphine and naloxone for OX219 and Suboxone sublingual tablets are similar.

Dose Proportionality:

Based on the power model, definitive dose proportionality of buprenorphine PK parameters was not demonstrated over the dose range of 1.4 to 11.4 mg because the

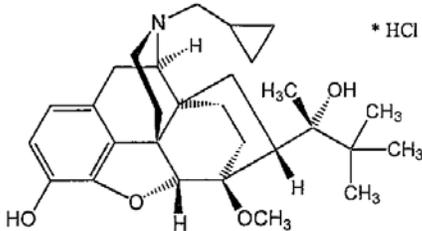
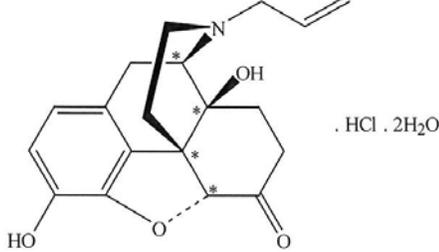
90% CIs for Beta1 (the slope of the power model) were not entirely contained in the acceptance range of (0.8927, 1.1073). The Cmax, AUCt, and AUCinf values increased slightly less than proportional with dose over the dose range of 1.4 to 11.4 mg. Dose proportionality of unconjugated naloxone was demonstrated for AUCt and AUCinf over the dose range of 0.36 to 2.8 mg because the 90% CIs for Beta1 were entirely contained in the acceptance range of (0.8927, 1.1073). The Cmax values increased slightly less than proportional with doses over the same dose range.

2 Question Based Review

2.1 General Attributes of the Drug

1. What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?

Table 1 Physical-Chemical Properties of Buprenorphine Hydrochloride and Naloxone Hydrochloride

Drug Name	Buprenorphine Hydrochloride	Naloxone Hydrochloride
Chemical Name	(2S)-2-[17-Cyclopropylmethyl-4,5a-epoxy-3-hydroxy-6-methoxy-6a,14-ethano-14a-morphinan-7a-yl]-3,3-dimethylbutan-2-ol hydrochloride	17-Allyl-4,5a-epoxy-3,14-dihydroxymorphinan-6 hydrochloride
Structure	 <p style="text-align: center;">$C_{29}H_{41}NO_4 \cdot HCl$</p>	 <p style="text-align: center;">$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$</p>
Molecular Weight	504.10	399.87

Appearance	white to off-white crystalline powder	White to off-white powder
Solubility	Sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane	Freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether

Three formulations of OX219, designated as OX219-1, OX219-3, and OX219-4, were developed and used in 4 PK studies. OX219-4 is the final commercial product (FCP), which were used in Studies OX219-003 and OX219-004. The ratio of Buprenorphine/Naloxone in all OX219 formulations is 4:1, which is the same as the listed drug, Suboxone sublingual tablet. The components and compositions of all the formulations are listed in **Table 2**.

Table 2 Components and Composition of and the FCP and Two Earlier Formulations of OX219

Formulation	OX219-1	OX219-3	OX219-3	FCP OX219-4	FCP OX219-4
Strength (mg) buprenorphine/naloxone	(b) (4)			1.4/0.36	5.7/1.4
Clinical study	OX219-001	OX219-002	OX219-002	OX219-004	OX219-003 and OX219-004
Components	Amount per tablet (mg)				
Buprenorphine HCl	(b) (4)				
Naloxone HCl	(b) (4)				
Mannitol	(b) (4)				
Citric acid	(b) (4)				
Sodium citrate	(b) (4)				
Microcrystalline cellulose	(b) (4)				
Croscarmellose sodium	(b) (4)				
Sucralose	(b) (4)				
Menthol	(b) (4)				
Silicon dioxide	(b) (4)				
Sodium stearyl fumarate	(b) (4)				
Tablet weight	(b) (4)				

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

OX219 sublingual tablet contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal

signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

OX219 sublingual tablet is indicated for the maintenance treatment of opioid dependence.

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

Administer OX219 sublingual tablet sublingually as a single daily dose. The recommended daily dose for maintenance is 11.4/2.8 mg.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of buprenorphine and naloxone for the listed drug, Suboxone sublingual tablet?

Plasma levels of buprenorphine increased with sublingual doses (in the range of 4 to 16 mg) but not in a directly dose-proportional manner. Naloxone did not affect the pharmacokinetics of buprenorphine. There was a trend toward an increase in naloxone concentrations with increase in dose. At the three naloxone doses of 1, 2, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects.

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Elimination half-life of

buprenorphine ranges from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours.

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

Buprenorphine and its major metabolite norbuprenorphine are measured in all PK studies. For naloxone, free naloxone and total naloxone (free naloxone plus naloxone-3 β -glucuronide) are measured in all PK studies.

3. Do the exposures of buprenorphine and naloxone following the administration of OX219 sublingual tablets increase in a dose proportional manner?

Based on the power model, definitive dose proportionality of buprenorphine PK parameters was not demonstrated over the dose range of 1.4 to 11.4 mg because the 90% CIs for Beta1 were not entirely contained in the acceptance range of (0.8927, 1.1073). The C_{max}, AUC_t, and AUC_{inf} values increased slightly less than proportional with dose over the dose range of 1.4 to 11.4 mg. Dose proportionality of unconjugated naloxone was demonstrated for AUC_t and AUC_{inf} over the dose range of 0.36 to 2.8 mg because the 90% CIs for Beta1 were entirely contained in the acceptance range of (0.8927, 1.1073). The C_{max} values increased slightly less than proportional with doses over the same dose range.

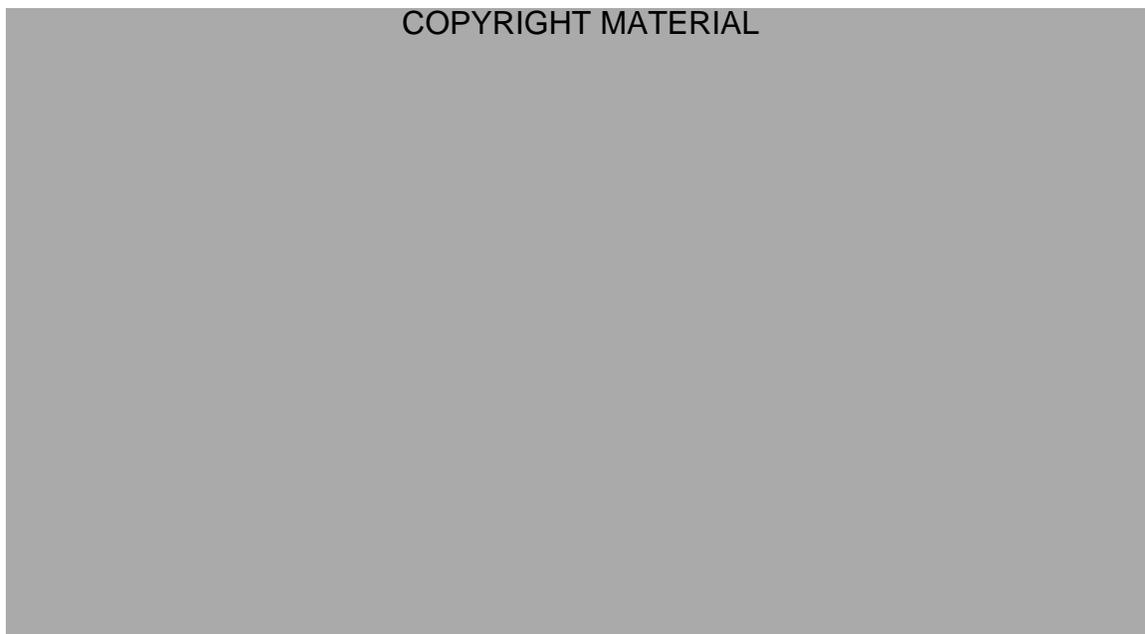
The dose proportionality of buprenorphine and naloxone pharmacokinetics following single dose administration of the lower strength of OX219 (1 x 1.4/0.36 mg), the upper strength of OX219 (1 x 5.7/1.4 mg), the dose of 8.5/2.12 mg (2 x 1.4/0.36 plus 1 x 5.7/1.4 mg), and the dose of 11.4/2.8 mg (2 x 5.7/1.4 mg) was assessed in 48 healthy subjects under naltrexone block in Study OX219-004. Study OX219-004 was a single-dose, fasting, open-label, randomized, four-period crossover study. Four single-dose treatments were administered with a 14-day washout period between doses. Dose proportionality was primarily examined using the power model, i.e., $P = \text{Beta}_0 \times \text{Dose}^{\text{Beta}_1}$. Log-transformation was used to transform the power model to the following equation:

$$\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$$

where $\ln(P)$ represents the natural log-transformed PK parameter such as C_{\max} , AUC_t , and AUC_{inf} , $\ln(\text{Beta}0)$ is the y-intercept, $\text{Beta}1$ is the slope, $\ln(\text{Dose})$ is the natural log-transformed dose, and Epsilon is the error term. The power model was fit to individual subject data using the linear mixed effects analysis with subject as a random effect. A 90% confidence interval of $\text{Beta}1$ was calculated from the model. Sponsor used equivalence limits of 0.75 to 1.3333 for evaluation of dose proportionality and an acceptance interval of (0.8617, 1.1383) based on a dose ratio of 8 between highest and lowest dose was determined according to Smith et al¹. According to Smith et al., dose proportionality would be declared when the 90% confidence interval for $\text{Beta}1$ lies entirely within the critical region $(1 + \ln(\Theta_L)/\ln(r), 1 + \ln(\Theta_H)/\ln(r))$, where Θ_L and Θ_H are the lower and upper limit of equivalence limits and r is the dose ratio. This criterion is equivalent to having the ratio of dose-normalized geometric mean values contained completely within the equivalence interval (Θ_L, Θ_H) . Using the typical bioequivalence limit of (0.80, 1.25), the critical region would be (0.8927, 1.1073). In other words, if the 90% CI of $\text{Beta}1$ falls within the acceptance range of (0.8927, 1.1073), dose proportionality can be claimed.

Mean plasma concentration-time profiles of buprenorphine are shown in **Figure 1**. Buprenorphine PK parameters are summarized in **Table 3**. Buprenorphine displayed a rapid absorption with the median time to peak concentrations varied between 1.13 hr and 1.50 hr for the four doses. Mean terminal half-life values ranged from 22.6 to 27.5 hrs.

Figure 1 Mean Buprenorphine Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



1. Smith BP et al., Confidence Interval Criteria for Assessment of Dose Proportionality. *Pharmaceutical Research* 17:1278-83 (2000)

Table 3 Mean \pm SD (%CV) PK parameter of Buprenorphine (Study OX219-004)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	Treatment A: OX219 1.4/0.36 mg (N=41) ²	Treatment B: OX219 5.7/1.4 mg (N=42)	Treatment C: OX219 8.5/2.12 mg (N=42)	Treatment D: OX219 11.4/2.8 mg (N=42) ³
AUC _{0-t} (ng·hr/mL)	5.62 \pm 2.58 (45.9)	21.21 \pm 7.21 (34.0)	29.12 \pm 8.63 (29.6)	36.28 \pm 12.55 (34.6)
AUC _{0-inf} (ng·hr/mL)	7.01 \pm 2.70 (38.5)	23.51 \pm 7.79 (33.2)	32.27 \pm 9.55 (29.6)	41.51 \pm 14.28 (34.4)
C _{max} (ng/mL)	0.807 \pm 0.377 (46.7)	2.66 \pm 1.15 (43.1)	3.68 \pm 1.37 (37.3)	4.58 \pm 2.05 (44.9)
Median t _{max} (hr) ¹	1.50 (0.50-4.00)	1.38 (0.50-3.00)	1.13 (0.50-3.00)	1.27 (0.50-4.00)
Kel (1/hr)	0.0504 \pm 0.0360 (71.4)	0.0297 \pm 0.0105 (35.3)	0.0305 \pm 0.0093 (30.5)	0.0278 \pm 0.0079 (28.4)
t _{1/2} (hr)	22.6 \pm 17.0 (75.2)	26.1 \pm 8.9 (34.0)	24.8 \pm 7.5 (30.4)	27.5 \pm 10.2 (37.1)

¹ t_{max} expressed as the median (range)

² n=39 for AUC_{0-inf}, Kel and t_{1/2}

³ n=41 for AUC_{0-inf}, Kel and t_{1/2}

Based on the power model, definitive dose proportionality of buprenorphine PK parameters was not demonstrated over the dose range of 1.4 to 11.4 mg because the

90% CIs for Beta1 were not entirely contained in the range of (0.8927, 1.1073) (**Table 4**). The C_{max}, AUC_t, and AUC_{inf} values increased slightly less than proportional with dose over the dose range of 1.4 to 11.4 mg.

Table 4 Assessment of Dose Proportionality of Buprenorphine using a Mixed Effects Statistical Model Based on a Power Function (Study OX219-004)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
Dose Range 1.4 to 11.4 mg Buprenorphine					
ln(AUC _t)	ln(dose)	0.9486	0.8908	1.0063	13.9366
ln(AUC _{inf})	ln(dose)	0.8617	0.8257	0.8978	5.2094
ln(C _{max})	ln(dose)	0.8556	0.7951	0.9161	4.0723

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

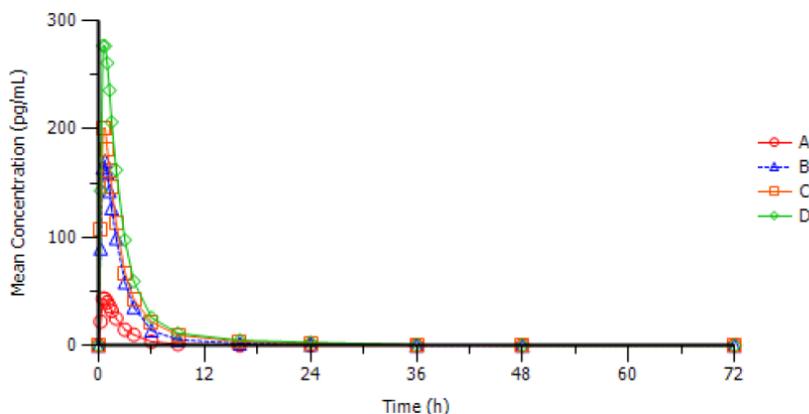
and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

Mean plasma concentration-time profiles of unconjugated naloxone are shown in **Figure 2**. Naloxone PK parameters are summarized in **Table 5**. naloxone displayed a rapid absorption with the median T_{max} values of 0.75 hr for all doses. Mean terminal half-life values ranged from 2.19 to 7.4 hrs for the four dose levels.

Figure 2 Mean Unconjugated naloxone Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



Treatment A=OX219-4 1.4/0.36 mg buprenorphine/naloxone sublingual tablets (n=41); Treatment B=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment C=OX219-4 8.5/2.12 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment D=OX219-4 11.4/2.8 mg buprenorphine/naloxone sublingual tablets (n=42).

Table 5 Mean \pm SD (%CV) PK Parameter of Unconjugated Naloxone (Study OX219-004)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	<u>Treatment A:</u> OX219 1.4/0.36 mg (N=41) ²	<u>Treatment B:</u> OX219 5.7/1.4 mg (N=42) ³	<u>Treatment C:</u> OX219 8.5/2.12 mg (N=42)	<u>Treatment D:</u> OX219 11.4/2.8 mg (N=42)
AUC _{0-t} (pg·hr/mL)	119.6 \pm 60.55 (50.6)	495.8 \pm 220.9 (44.6)	633.2 \pm 307.3 (48.5)	873.1 \pm 489.5 (56.1)
AUC _{0-inf} (pg·hr/mL)	125.4 \pm 61.45 (49.0)	491.2 \pm 197.9 (40.3)	650.1 \pm 310.3 (47.7)	890.9 \pm 493.8 (55.4)
C _{max} (pg/mL)	49.5 \pm 27.6 (55.8)	190 \pm 113 (59.2)	232 \pm 127 (54.7)	315 \pm 183 (58.1)
Median t _{max} (hr) ¹	0.75 (0.25-4.00)	0.75 (0.25-1.25)	0.75 (0.25-1.50)	0.75 (0.25-1.50)
Kel (1/hr)	0.4360 \pm 0.1546 (35.5)	0.2217 \pm 0.1306 (58.9)	0.1455 \pm 0.0784 (53.9)	0.1379 \pm 0.0836 (60.6)
t _{1/2} (hr)	2.19 \pm 2.71 (123.5)	4.40 \pm 2.89 (65.7)	6.68 \pm 4.39 (65.7)	7.40 \pm 4.96 (67.1)

¹ t_{max} expressed as the median (range)

² n=40 for AUC_{0-inf}, Kel and t_{1/2}

³ n=41 for AUC_{0-inf}, Kel and t_{1/2}

Based on the power model, dose proportionality of unconjugated naloxone was demonstrated for AUC_t and AUC_{inf} over the dose range of 0.36 to 2.8 mg because the 90% CIs for Beta1 were entirely contained in the range of (0.8927, 1.1073) (Table 6). The C_{max} values increased slightly less than proportional with doses over the same dose range.

Table 6 Assessment of Dose Proportionality of Unconjugated Naloxone using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Dose Range 0.36 to 2.8 mg Naloxone</u>					
ln(AUC _t)	ln(dose)	0.9822	0.9202	1.0441	36.7645
ln(AUC _{inf})	ln(dose)	0.9618	0.9051	1.0186	20.7370
ln(C _{max})	ln(dose)	0.8999	0.8306	0.9693	5.4626

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

2.3 Intrinsic Factors

1. *What is the pediatric plan?*

Sponsor requested full waiver for three pediatric age groups, 0 - 5 weeks, 5 weeks – 12 years, and 12 - 16 years. The PREA waiver was granted due to safety reasons in a pediatric population. Please find medical officer's review for details about the assessment of the waiver request.

2.4 General Biopharmaceutics

1. *What are the relative bioavailabilities of buprenorphine and naloxone following the administration of OX219 sublingual tablet in comparison to the listed drug, Suboxone sublingual tablet?*

OX219 5.7/1.4 mg exhibited equivalent systemic exposure to buprenorphine but lower exposure to naloxone in comparison to the listed drug Suboxone 8/2 mg tablet. The relative bioavailabilities of buprenorphine and naloxone following the administration of OX219 tablet administered as 1 x 5.7/1.4 mg dose in comparison to the listed drug, Suboxone tablet administered as 1 x 8/2 mg dose were evaluated in a single dose, open-label, randomized, fasting, 2-period cross-over study (Study OX219-003) in healthy subjects under naltrexone block. The interval between doses was 14 days.

The buprenorphine plasma concentration-time profiles for OX219 tablets and Suboxone tablets are shown in **Figure 3**. Median t_{max} was the same for both formulations (1.75 h). The statistical analysis results for the assessment of relative bioavailability are presented in the **Table 7**. OX219 5.7/1.4 mg exhibited equivalent C_{max} , AUC_t , and AUC_{inf} to Suboxone tablet 8/2 mg as the 90% CIs of OX219:Suboxone geometric mean ratios for buprenorphine C_{max} , AUC_t , and AUC_{inf} fell within the bioequivalence limits of 80 to 125%.

Figure 3 Mean buprenorphine plasma concentration (ng/mL) time profiles (OX219-003) (N = 49)

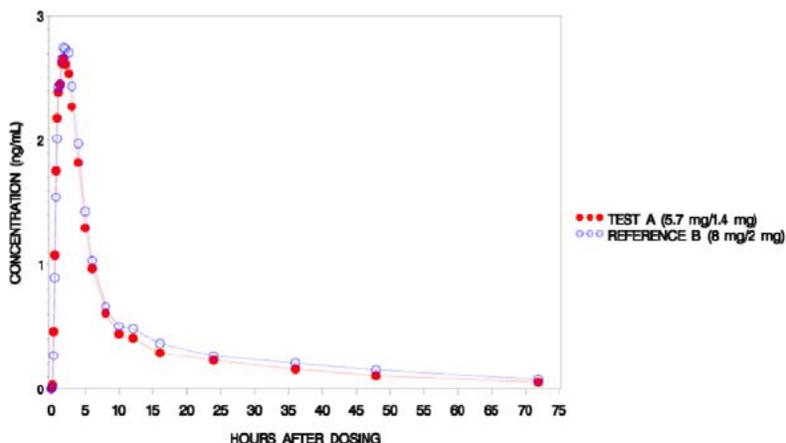


Table 7 Mean \pm SD (%CV) PK parameter of buprenorphine following single oral administration of 1 x 5.7/1.4 mg OX219 tablet and 1 x 8/2 mg Suboxone tablet in healthy adult subjects (OX219-003)

Parameter	OX219 5.7/1.4 mg (1 x 5.7/1.4mg) (N = 49) ^b	Suboxone Tablet 8/2 mg (1 x 8/2 mg) (N = 49) ^c
AUClast (ng.hr/ml)	23.7 \pm 8.10 (34.2)	27.0 \pm 8.91 (33.0)
AUCinf (ng.hr/mL)	26.1 \pm 9.66 (37.1)	29.9 \pm 10.6 (35.5)
Cmax (ng/mL)	3.02 \pm 1.14 (37.6)	3.10 \pm 1.16 (37.7)
T1/2 (hr)	25.9 \pm 9.78 (37.7)	25.2 \pm 9.26 (36.7)
Tmax (hr) ^a	1.75 (0.67, 4.00)	1.75 (0.67, 3.00)
Kel (1/hr)	0.029 \pm 0.008 (28.0)	0.031 \pm 0.013 (40.9)
Geometric Mean Ratio of PK Parameter (OX219 tablet/Suboxone Tablet) % (90% CI)		
AUClast	87.9 (82.7 – 93.5)	
AUCinf	85.7 (80.2 – 91.5)	
Cmax	98.0 (90.7 – 105.9)	

^a tmax reported as median (min, max)

^b n = 48 for AUCinf, Kel, and t1/2 for OX219 5.7/1.4 mg

^c n = 45 for AUCinf, Kel, and t1/2 for Suboxone 8/2 mg

The naloxone plasma concentration-time profiles for OX219 5.7/1.4 mg tablets and Suboxone 8/2 mg tablets are shown in **Figure 4**. Median t_{max} was the same for both formulations (0.83 h). OX219 exhibited equivalent rate of absorption as the 90% CIs of OX219:Suboxone geometric mean ratio for unconjugated naloxone C_{max} fell within the bioequivalence limits of 80 to 125%. 90% CIs of OX219:Suboxone geometric mean ratios for naloxone AUC_t and AUC_{inf} did not fall within the bioequivalence limits of 80 to 125% with the lower CI limit below 80% (AUC_t 76.6% and AUC_{inf} 78.9%). As the upper CI limit of the 90% CIs were lower than 125%, the extent of naloxone absorption was not higher from OX219 than for Suboxone.

Figure 4 Mean naloxone plasma concentration (pg/mL) time profiles (Study OX219-003) (N = 53)

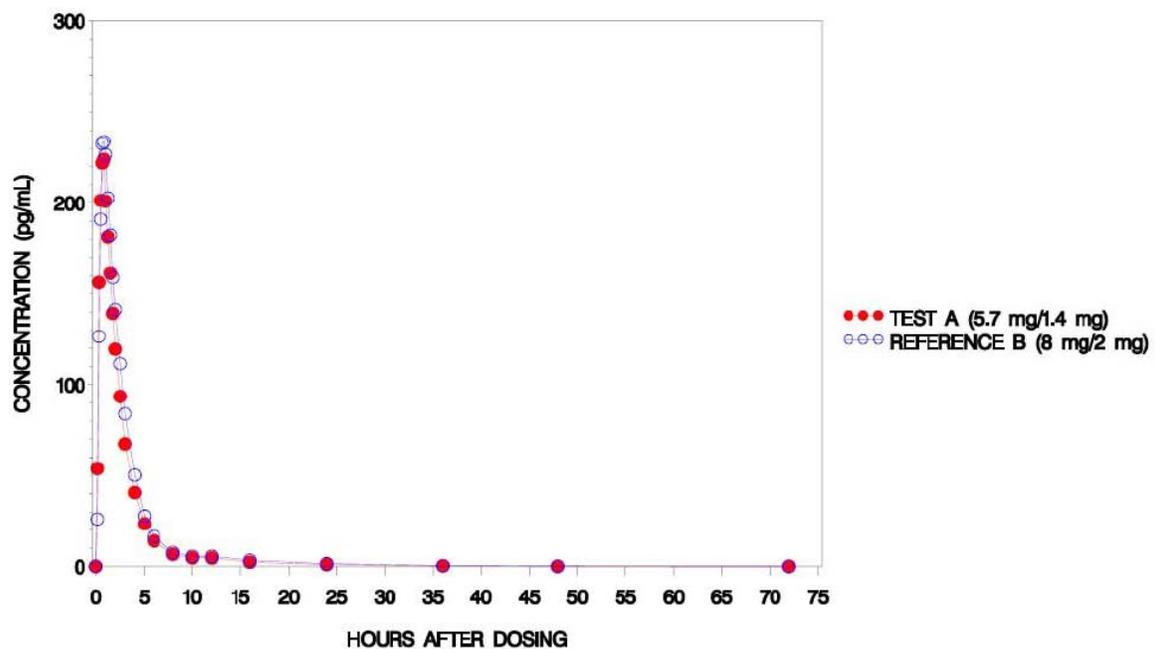


Table 8 Mean \pm SD (%CV) PK parameter of naloxone following single oral administration of OX219 5.7/1.4 mg tablet (1 x 5.7/1.4 mg) and Suboxone 8/2 mg tablet (1 x 8/2 mg) in healthy adult subjects (OX219-003)

Parameter	OX219 5.7/1.4 mg (1 x 5.7/1.4 mg) (N = 53) ^b	Suboxone Tablet 8/2 mg (1 x 8/2 mg) (N = 53) ^c
AUClast (pg.hr/ml)	593 \pm 378 (63.7)	674 \pm 306 (45.4)
AUCinf (pg.hr/mL)	637 \pm 391 (61.5)	723 \pm 309 (42.8)
Cmax (pg/mL)	262 \pm 209 (79.9)	273 \pm 171 (62.7)
T1/2 (hr)	7.20 \pm 6.08 (84.4)	8.76 \pm 6.10 (69.6)
Tmax (hr) ^a	0.83 (0.33, 1.50)	0.83 (0.33, 2.50)
Kel (1/hr)	0.148 \pm 0.107 (72.3)	0.111 \pm 0.065 (58.6)
Geometric Mean Ratio of PK Parameter (OX219/Suboxone) % (90% CI)		
AUClast	84.5 (76.6 – 93.2)	
AUCinf	87.5 (78.9 – 97.1)	
Cmax	92.5 (81.8 – 104.5)	

^a tmax reported as median (min, max)

^b n=44 for AUCinf, Kel, and t1/2 for OX219 5.7/1.4 mg

^c n=46 for AUCinf, Kel, and t1/2 for Suboxone 8/2 mg

OX219 5.7/1.4 mg tablets exhibited lower norbuprenorphine and total naloxone exposure in comparison to Suboxone 8/2 mg tablet (**Tables 9 and 10**).

Table 9 Summary of PK Parameters of Norbuprenorphine (Study OX219-003)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=49) ²	Suboxone 8/2 mg (N=49) ³
AUC _{0-t} (ng·hr/mL)	24.1 \pm 12.0 (49.7)	33.1 \pm 15.1 (45.5)
AUC _{0-inf} (ng·hr/mL)	32.4 \pm 17.8 (54.8)	44.6 \pm 23.3 (52.3)
AUC _{0-t} /AUC _{0-inf} ratio	0.781 \pm 0.096 (12.2)	0.738 \pm 0.144 (19.6)
C _{max} (ng/mL)	0.920 \pm 0.503 (54.7)	1.14 \pm 0.555 (48.6)
Median t _{max} (hr) ¹	1.00 (0.50-72.00)	1.50 (0.67-48.00)
Kel (1/hr)	0.024 \pm 0.008 (34.4)	0.022 \pm 0.010 (45.7)
t _{1/2} (hr)	32.2 \pm 10.2 (31.8)	40.5 \pm 29.8 (73.5)

¹t_{max} expressed as the median (range)

²N=39 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³N=36 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for Suboxone 8/2 mg

Table 10 Summary of PK Parameters of total naloxone (Study OX219-003)

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³
AUC _{0-t} (ng·hr/mL)	31.1 \pm 11.1 (35.5)	44.9 \pm 15.1 (33.6)
AUC _{0-inf} (ng·hr/mL)	32.2 \pm 11.7 (36.4)	46.3 \pm 15.4 (33.3)
AUC _{0-t} /AUC _{0-inf} ratio	0.972 \pm 0.013 (1.38)	0.975 \pm 0.018 (1.79)
C _{max} (ng/mL)	14.9 \pm 6.92 (46.6)	21.4 \pm 9.11 (42.6)
Median t _{max} (hr) ¹	0.67 (0.33-5.02)	0.67 (0.33-2.50)
Kel (1/hr)	0.119 \pm 0.037 (30.9)	0.111 \pm 0.036 (32.2)
t _{1/2} (hr)	6.41 \pm 1.99 (31.1)	6.94 \pm 2.35 (33.8)

¹t_{max} expressed as the median (range)

²N=47 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³N=49 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for Suboxone 8/2 mg

OSI inspected the clinical and analytical sites of this pivotal study OX219-003 and concluded that the data from study OX219-003 are acceptable for further review. OSI reviewer noted that for subject #6, calcium carbonate was taken one day after Period 1 dosing and two weeks before period 2 dosing. This reviewer is of the opinion that the one time dose of calcium carbonate taken one day after Period 1 dosing does not affect

the PK of buprenorphine and naloxone because OX219 tablet is for sublingual absorption and the absorption is complete before 24 hours after dosing.

2. *What are the dissolve times for OX219 sublingual tablets in comparison to Suboxone sublingual tablet?*

Data obtained from Study OX219-004 showed that in vivo dissolve time was highly variable between subjects but similar between different doses (1.4/0.36 mg to 11.4/2.8 mg), using up to 3 tablets administered simultaneously, with a median in vivo dissolve time of 4.3 to 5.9 minutes for OX219.

Table 11 Descriptive Statistics of In Vivo Dissolve Time (Study OX219-004)

	<i>In vivo</i> dissolve time [min]			
	1.4/0.36 mg ¹	5.7/1.4 mg ²	8.5/2.12 mg ³	11.4/2.8 mg ⁴
N	45	46	45	44
Mean	6.1	6.4	8.1	6.4
SD	4.74	5.39	9.89	3.97
Median	4.3	5.4	5.9	5.0
(b) (4)				

¹ One low strength tablet

² One high strength tablet

³ One high strength and two low strength tablets

⁴ Two high strength tablets

The dissolve time for OX219 5.7/1.4 mg had a median time of 5 minutes in contrast to 12.5 minutes for Suboxone 8/2 mg tablet.

Table 12 Descriptive Statistics of Dissolve Time (minutes) for OX219 5.7/1.4 mg Tablets (Treatment A) and Suboxone 8/2 mg tablet (Treatment B) (Study OX219-003)

Treatment	N	Mean (SD)	Min.	Median	Max
A	53	7.17 (7.14)	(b) (4)	5.00	(b) (4)
B	60	15.87 (9.41)		12.50	

Test Product A: OX219-4 Sublingual Tablet, Buprenorphine 5.7 mg/Naloxone 1.4 mg; Sponsor: Orexo AB;

Reference Product B: Suboxone[®] (buprenorphine and naloxone) Sublingual Tablet 8 mg/2 mg.

3. Does the pH and temperature affect the bioavailability of OX219?

The OX219 formulation contains (b) (4) and the measured pH of a suspension/solution of one OX219 tablet in 5 mL purified water (pH 7.0) or 5 mL artificial saliva (pH 7.0) was 5.4 and 5.5, respectively. (b) (4)

(b) (4) The sublingual pH decrease is expected to be temporary in clinical use of buprenorphine as the buffering capacity of the saliva would bring the pH back to about 7. Sponsor stated that their data suggested the effect of acidic and basic beverages on oral pH was transitory and the pH returned to baseline levels within approximately 10 minutes.

Sponsor has no information about the effects of temperature or pH on transmucosal bioavailability of buprenorphine specific to OX219. Literature search was conducted and no publication was found regarding oral temperature and buprenorphine absorption. Four articles (Compton et al., Drug Alcohol Depend 2006 Mar 15;82(1):25-31; Harris et al., Clin Pharmacokinet 2004;43(5):329-40; Mendelson et al., J Clin Pharmacol 1997 Jan;37(1):31-7; and Nath et al., J Clin Pharmacol 1999 Jun;39(6):619-23) were found with regards to oral pH on buprenorphine absorption or tablet dissolution. Sponsor concluded that the literature review did not provide conclusive information on the effect of temperature or pH on oral transmucosal absorption of buprenorphine. Although they consider it unlikely that pH and/or temperature would have significant effect on the transmucosal bioavailability of buprenorphine from the OX219 formulation, due to the limited amount of information available, sponsor proposed the addition of a general recommendation to section 2.2 of the OX219/Zubsolv™ label, advising patients not to eat or drink anything until the tablet is completely dissolved. This approach seems reasonable.

2.5 Analytical Section

1. Do the bioanalytical methods adequately validated for determining plasma concentrations of buprenorphine, norbuprenorphine, naloxone and total naloxone?

Validated LC-MS/MS methods were used for the determination of buprenorphine, unconjugated naloxone, norbuprenorphine, and total naloxone (including both unconjugated naloxone and naloxone conjugates) in human plasma in Studies OX219-003 and OX219-004. The assay precision and accuracy of the analytical methods are summarized in the following tables.

Table 13 Buprenorphine Assay Precision and Accuracy in Studies OX219-003 and OX219-004

Study No.	QC Low 0.0750 ng/mL	QC Medium 0.750 ng/mL	QC New 1.88 ng/mL ¹	QC High 7.50 ng/mL
Precision (%CV)				
OX219-003	4.4	2.8	3.1	2.4
OX219-004	3.7	2.8	-	2.5
Accuracy (%Bias)				
OX219-003	-7.9	-5.3	-3.7	-7.1
OX219-004	-7.9	-6.0	-	-8.1

Table 14 Norbuprenorphine Assay Precision and Accuracy in Studies OX219-003 and OX219-004

Study No.	QC Low 0.0600 ng/mL	QC Medium 0.600 ng/mL	QC New ¹ 1.50 ng/mL	QC High 6.00 ng/mL
Precision (%CV)				
OX219-003	7.7	3.4	3.1	2.7
OX219-004	5.2	2.8	-	2.8
Accuracy (%Bias)				
OX219-003	-8.2	-4.0	-2.0	-7.0
OX219-004	-7.0	-3.5	-	-7.3

Table 15 Unconjugated Naloxone Assay Precision and Accuracy in Studies OX219-003 and OX219-004

Study No.	QC Low 3.00 pg/mL	QC Medium 50.0 pg/mL	QC High 200 pg/mL
Precision (%CV)			
OX219-003	5.2	5.0	6.1
OX219-004	6.1	4.5	4.6
Accuracy (%Bias)			
OX219-003	3.0	2.6	-0.5
OX219-004	3.7	3.6	0.0

Table 16 Total Naloxone Assay Precision and Accuracy in Studies OX219-003 and OX219-004

Study No.	Hydrolysis QC Low 0.150 ng/mL	QC Low 0.150 ng/mL	QC Medium 2.50 ng/mL	QC New ¹ 10.0 ng/mL	Hydrolysis QC High 40.0 ng/mL	QC High 40.0 ng/mL
Precision (%CV)						
OX219-003	6.9	6.5	3.8	4.2	5.1	3.9
OX219-004	7.2	6.2	4.1	6.6	4.6	5.0
Accuracy (%Bias)						
OX219-003	-0.7	-1.3	-2.8	-0.9	-4.5	-5.0
OX219-004	-4.0	-6.0	0.0	-0.2	-10.0	-7.3

3 Labeling Recommendations

(~~RED Strikeout~~ text should be removed from labeling; Blue double underlined text should be added to labeling)

The following labeling comments are preliminary and as of today (6/4/2013) labeling negotiation with sponsor is still ongoing.

Section 12.2 Pharmacodynamics

ZUBSOLV has been shown to have (b) (4) different bioavailability compared to another buprenorphine/naloxone-containing sublingual products. One ZUBSOLV 5.7 mg/1.4 mg tablet provides equivalent buprenorphine exposure and 12% lower naloxone exposure to one SUBOXONE 8 mg/2 mg tablet. The pharmacodynamic information of other currently marketed buprenorphine/naloxone-containing sublingual products is not directly comparable on a mg basis to ZUBSOLV. (see section 2.6).

Subjective Effects:

... In opioid-experienced subjects who were not physically dependent, acute sublingual doses of (b) (4) Suboxone tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone.

...

Effect of Naloxone

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and (b) (4) Suboxone tablets were similar at equivalent dose levels of buprenorphine....

Section 12.3 Pharmacokinetics

Absorption

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of ZUBSOLV sublingual tablet. There was wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased (b) (4) -with the increase in dose (in the range of 1.4 to 11.4 mg), although the increase was not directly dose-proportional. Naloxone did not affect the pharmacokinetics of buprenorphine.

ZUBSOLV has been shown to have different bioavailability compared to another buprenorphine/naloxone-containing sublingual product. One ZUBSOLV 5.7 mg/1.4 mg tablet provides equivalent buprenorphine exposure and 12% lower naloxone exposure to one SUBOXONE 8 mg/2 mg tablet.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	204242		Proposed Brand Name	OX219
OCP Division (I, II, III, IV, V)	II		Generic Name	Buprenorphine and naloxone sublingual tablet
Medical Division	DAAAP		Drug Class	opioid
OCP Reviewer	Wei Qiu, Ph.D.		Indication(s)	For the maintenance treatment of opioid dependence
OCP Team Leader	Yun Xu, Ph.D.		Dosage Form, Strength	Sublingual tablet: 5.7/1.4 mg and 1.4/0.36 mg
Pharmacometrics Reviewer			Dosing Regimen	11.4/2.8 mg once daily
Date of Submission	9/5/12		Route of Administration	sublingual
Primary Review Goal Date (GRMP)	5/5/13		Sponsor	Orexo AB
PDUFA Due Date	7/6/13		Priority Classification	Standard
			Relevant INDs	IND 110637
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	4		Studies 001, 002, 003, and 004
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study 004
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		Studies 001, 002 and 003
Bioequivalence studies -				
traditional design, single / multi dose:				
replicate design, single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

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?			√	To be marketed formulation was used in PK studies 003 and 004.
2	Has the applicant provided metabolism and drug-drug interaction information?	√			Reviewed literature. No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with the list drug, Suboxone (buprenorphine and naloxone) sublingual tablet (NDA 20-733)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable,	√			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	does it have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	√			
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)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
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?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
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?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

In the initial submission, sponsor included a PK dataset with PK parameters in Study 003. However, sponsor failed to submit the PK raw data (concentrations at each time point for calculation of PK parameters) and dataset with PK parameters for the BE analysis. In addition, no PK dataset was submitted for Study 004. The following comments were conveyed to the sponsor on October 29, 2012:

1. For Study OX219-003, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your bioequivalence analysis, as well as the SAS code.
2. For Study OX219-004, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your dose proportionality analysis, as well as the SAS code.

Sponsor replied that they do have the data and anticipated being able to respond to this request by late last week (November 2, 2012). At the internal filing meeting on November 2, 2012, per discussion with Dr. Bob Rappaport, if sponsor failed to submit the requested datasets by November 5, 2012 (60 days after their initial submission), this NDA should be refused to file. Around 3 PM on November 5, 2012, Sponsor submitted the requested datasets. After a quick look at the submitted datasets, we think we can conduct analysis on these datasets and this NDA can be filed.

This NDA is fileable from clinical pharmacology perspective.

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.

There are no comments for sponsor at this time.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Background:

On 5 September 2011, Orexo AB submitted a 505(b)(2) NDA 204242 for OX219 (buprenorphine and naloxone) sublingual tablets for the maintenance treatment of opioid dependence.

This NDA relies on the Agency's previous findings of safety and effectiveness for Suboxone sublingual tablet (NDA 20-733) and literature. The to-be-marketed formulation was used in

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

relative bioavailability study (Study 003) and dose proportionality study (Study 004). Sponsor requested biowaiver for the lower strength based on dissolution data. This biowaiver request is deferred to ONDQA/Biopharm team.

The overall clinical and clinical pharmacology program consisted the 4 single dose Phase 1 (Studies 001, 002, 003 and 004). Earlier formulations were used in Studies 001 and 002 to select the final commercial formulation. The final formulation was used in pivotal relative bioavailability study (Study 003) and dose proportionality study (Study 004). Since the final formulation was used in Studies 003 and 004, this review will focus on these two studies.

Sponsor's summary on relative bioavailability of OX219 in comparison to the list drug, Suboxone, and dose proportionality:

- OX219 5.7/1.4 mg exhibited equivalent C_{max} and AUC values of buprenorphine in comparison to Suboxone 8/2 mg
- OX219 5.7/1.4 mg exhibited lower exposure to naloxone, norbuprenorphine, and total naloxone in comparison to Suboxone 8/2 mg
- OX219 5.7/1.4 mg had shorter dissolve time in comparison to Suboxone 8/2 mg
- Dose proportionality was demonstrated for buprenorphine AUC_t, naloxone AUC_t and AUC_{inf}, norbuprenorphine AUC_t and AUC_{inf}, over the range of 1.4/0.36 mg and 11.4/2.8 mg.

4.2 Individual Study Summary

Study OX219-003

In this 2 period crossover study, 53 subjects received a single dose of formulation OX219-4 (5.7/1.4 mg BUP/NLX), and a single dose of Suboxone® (8/2 mg BUP/NLX). Fifty-three subjects had data for total and unconjugated naloxone. Forty-nine subjects had data for BUP and NBUP. Four subjects were excluded from the BUP and NBUP analysis, as these subjects experienced emesis within 2 x the median t_{max} of an analyte.

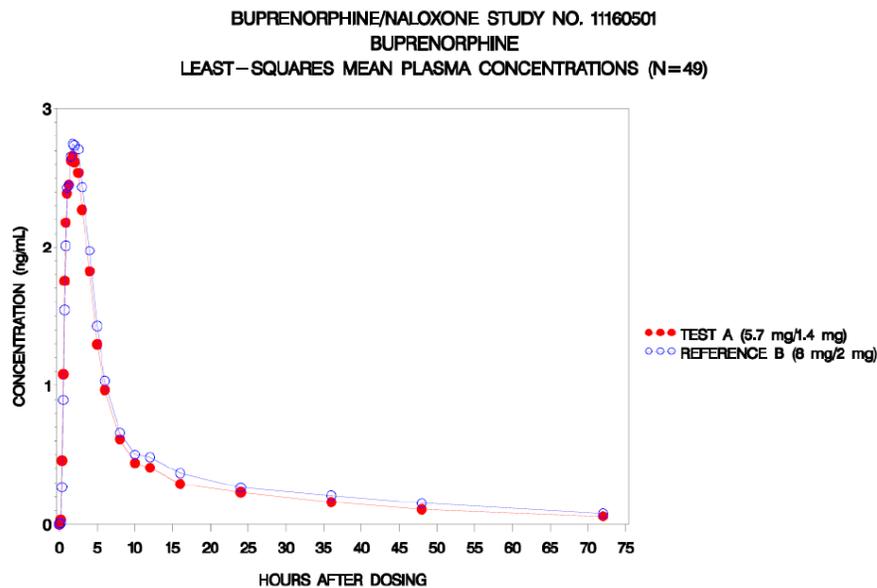
Pharmacokinetic Analysis

The primary comparison between treatments was based on BUP and unconjugated NLX data. Data for NBUP and total NLX are presented as supportive data. The BUP pharmacokinetic parameters are summarized in Table 4 and the NLX pharmacokinetic parameters are summarized in Table 6. The BUP concentration data are presented in Figure 2. The NLX concentration data are presented in Figure 3. NBUP pharmacokinetic parameters are summarized in Table 8 and concentration data are presented in Figure 4. Total NLX pharmacokinetic parameters are summarized in Table 10 and concentration data are presented in Figure 5.

Buprenorphine

The 90% confidence intervals (CIs) of OX219:Suboxone® geometric mean ratios (GMRs) for BUP AUC_{0-t} , AUC_{0-inf} and C_{max} fell within the standard bioequivalence limits of 80.00 to 125.00% (Table 5). Median t_{max} was the same for both formulations (1.75h) (Table 4). Equivalent rate and extent of BUP absorption was concluded between OX219 5.7/1.4 mg sublingual tablet and Suboxone® 8/2 mg sublingual tablets, under fasted conditions.

Figure 2: Mean Concentration versus Time Plot (Linear): Buprenorphine (Study OX219-003)



Test A=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=49); Reference B=Suboxone® 8/2 mg buprenorphine/naloxone sublingual tablets (n=49).

Table 4: Summary of Pharmacokinetic Parameters Untransformed Data: Buprenorphine

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=49) ²	Suboxone 8/2 mg (N=49) ³
AUC _{0-t} (ng·hr/mL)	23.7 \pm 8.10 (34.2)	27.0 \pm 8.91 (33.0)
AUC _{0-inf} (ng·hr/mL)	26.1 \pm 9.66 (37.1)	29.9 \pm 10.6 (35.5)
AUC _{0-t} /AUC _{0-inf} ratio	0.914 \pm 0.050 (5.47)	0.902 \pm 0.058 (6.46)
C _{max} (ng/mL)	3.02 \pm 1.14 (37.6)	3.10 \pm 1.16 (37.3)
Median t _{max} (hr) ¹	1.75 (0.67-4.00)	1.75 (0.67-3.00)
Kel (1/hr)	0.029 \pm 0.008 (28.0)	0.031 \pm 0.013 (40.9)
t _{1/2} (hr)	25.9 \pm 9.78 (37.7)	25.2 \pm 9.26 (36.7)

¹ t_{max} expressed as the median (range)

² N=48 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³ N=45 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for Suboxone 8/2 mg

Table 5: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Buprenorphine

Parameter	OX219 5.7/1.4 mg (N=49) ²	Suboxone 8/2 mg (N=49) ³	Ratio	CI ¹	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	22.4	25.5	0.8793	0.8268 – 0.9352	18.1
AUC _{0-inf} (ng·hr/mL)	24.6	28.7	0.8569	0.8024 – 0.9150	18.5
C _{max} (ng/mL)	2.80	2.86	0.9805	0.9074 – 1.0594	22.9

¹ Equivalent if confidence intervals are within 0.8000-1.2500 (80.00 to 125.00%) limits.

² N=48 for AUC_{0-inf} for OX219 5.7/1.4 mg

³ N=45 for AUC_{0-inf} for Suboxone 8/2 mg

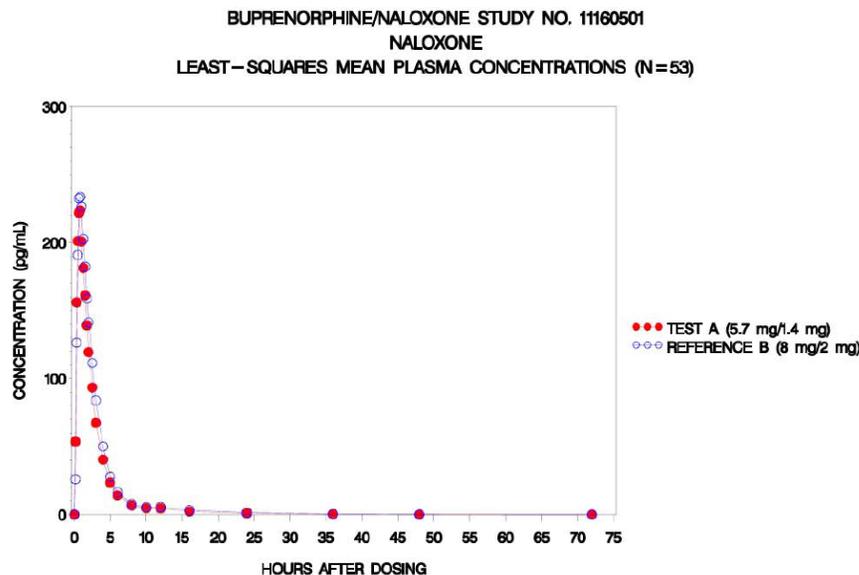
Unconjugated Naloxone

Mean pharmacokinetics demonstrated a slightly lower rate (C_{max} 4% lower) and lower extent (AUC_{0-t} 9% lower, AUC_{0-inf} 12% lower) of unconjugated NLX absorption comparing OX219 to Suboxone® (Table 6).

The 90% confidence intervals of OX219:Suboxone® geometric mean ratio for unconjugated NLX C_{max} fell within the standard bioequivalence limits of 80.00 to 125.00% (Table 7). Median t_{max} was the same for both formulations (0.83 h) (Table 6). Equivalent rate of NLX absorption is concluded between OX219 5.7/1.4 mg sublingual tablet and Suboxone® 8/2 mg sublingual tablets under fasted conditions.

The 90% confidence intervals of OX219:Suboxone® geometric mean ratios for NLX AUC_{0-t} and AUC_{0-inf} did not fall within the standard bioequivalence limits of 80.00 to 125.00% with the lower CI limit below 80.00% (AUC_{0-t} 76.61%, and AUC_{0-inf} 78.86%) (Table 7). Equivalent extent of NLX absorption could not be concluded between OX219 5.7/1.4 mg sublingual tablet and Suboxone® 8/2 mg sublingual tablets under fasted conditions. As the upper CI limit of the 90% CIs were lower than 125.00%, it could be concluded that the extent of NLX absorption was not higher from OX219 than from Suboxone®.

Figure 3: Mean Concentration versus Time Plot (Linear): Unconjugated Naloxone (Study OX219-003)



Test A=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=53); Reference B=Suboxone® 8/2 mg buprenorphine/naloxone sublingual tablets (n=53).

Table 6: Summary of Pharmacokinetic Parameters Untransformed Data: Unconjugated Naloxone

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³
AUC _{0-t} (pg·hr/mL)	593 \pm 378 (63.7)	674 \pm 306 (45.4)
AUC _{0-inf} (pg·hr/mL)	637 \pm 391 (61.5)	723 \pm 309 (42.8)
AUC _{0-t} /AUC _{0-inf} ratio	0.962 \pm 0.061 (6.31)	0.966 \pm 0.030 (3.07)
C _{max} (pg/mL)	262 \pm 209 (79.9)	273 \pm 171 (62.7)
Median t _{max} (hr) ¹	0.83 (0.33–1.50)	0.83 (0.33–2.50)
Kel (1/hr)	0.148 \pm 0.107 (72.3)	0.111 \pm 0.065 (58.6)
t _{1/2} (hr)	7.20 \pm 6.08 (84.4)	8.76 \pm 6.10 (69.6)

¹ t_{max} expressed as the median (range)

² N=44 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³ N=46 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and T_{1/2} for Suboxone 8/2 mg

Table 7: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Unconjugated Naloxone

Parameter	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³	Ratio	CI ¹	Intra-Subject %CV
AUC _{0-t} (pg·hr/mL)	511	605	0.8449	0.7661 – 0.9319	30.5
AUC _{0-inf} (pg·hr/mL)	560	640	0.8752	0.7886 – 0.9713	28.0
C _{max} (pg/mL)	211	228	0.9248	0.8183 – 1.0453	38.6

¹ Equivalent if confidence intervals are below the 1.2500 (125.00%) limit.

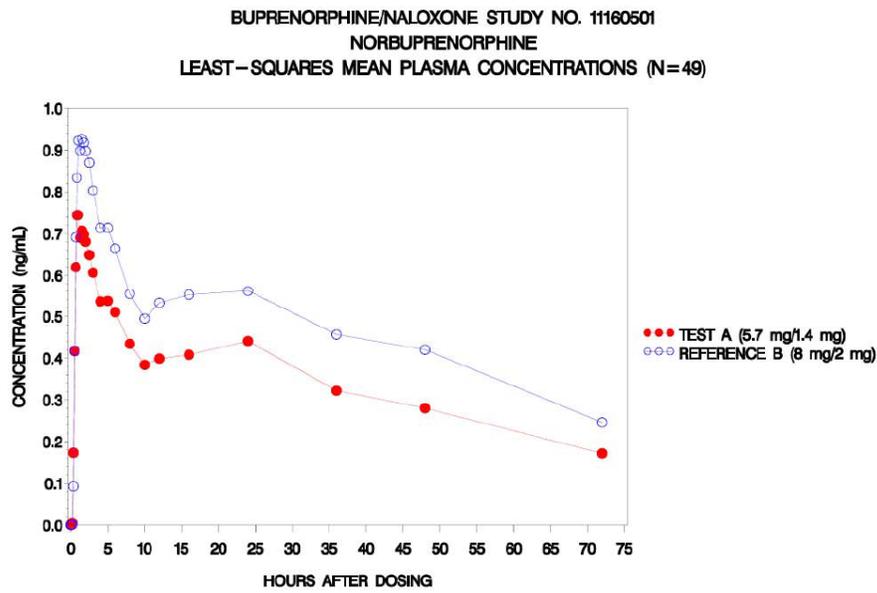
² N=44 for AUC_{0-inf} for OX219 5.7/1.4 mg

³ N=46 for AUC_{0-inf} for Suboxone 8/2 mg

Analysis of Secondary Objectives – Norbuprenorphine and Total Naloxone

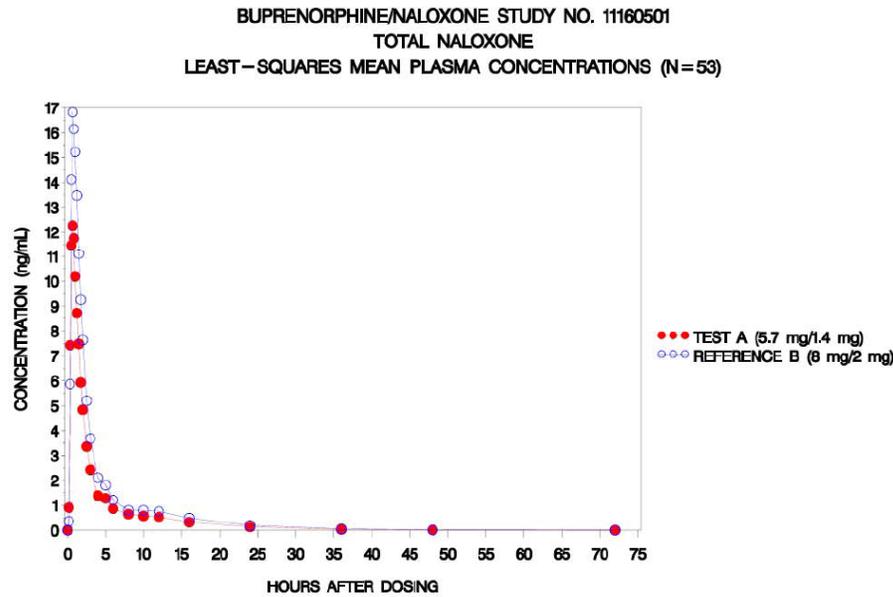
The 90% confidence intervals of OX219:Suboxone geometric mean ratio for the secondary analytes NBUP and total naloxone AUC_{0-t}, AUC_{0-inf} and C_{max} did not fall within the standard bioequivalence limits of 80.00 to 125.00% with the lower CI limit and point estimates below 80.00% (Table 9 and Table 11). A lower metabolite extent of exposure could be concluded for OX219 5.7/1.4 mg sublingual tablet compared to Suboxone® 8/2 mg sublingual tablets under fasted conditions (Table 8 and Table 10).

Figure 4: Mean Concentration versus Time Plot (Linear): Norbuprenorphine (Study OX219-003)



Test A=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=49); Reference B=Suboxone® 8/2 mg buprenorphine/naloxone sublingual tablets (n=49).

Figure 5: Mean Concentration versus Time Plot (Linear): Total Naloxone (Study OX219-003)



Test A=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=53); Reference B=Suboxone® 8/2 mg buprenorphine/naloxone sublingual tablets (n=53).

Table 8: Summary of Pharmacokinetic Parameters Untransformed Data: Norbuprenorphine

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=49) ²	Suboxone 8/2 mg (N=49) ³
AUC _{0-t} (ng·hr/mL)	24.1 \pm 12.0 (49.7)	33.1 \pm 15.1 (45.5)
AUC _{0-inf} (ng·hr/mL)	32.4 \pm 17.8 (54.8)	44.6 \pm 23.3 (52.3)
AUC _{0-t} /AUC _{0-inf} ratio	0.781 \pm 0.096 (12.2)	0.738 \pm 0.144 (19.6)
C _{max} (ng/mL)	0.920 \pm 0.503 (54.7)	1.14 \pm 0.555 (48.6)
Median t _{max} (hr) ¹	1.00 (0.50-72.00)	1.50 (0.67-48.00)
Kel (1/hr)	0.024 \pm 0.008 (34.4)	0.022 \pm 0.010 (45.7)
t _{1/2} (hr)	32.2 \pm 10.2 (31.8)	40.5 \pm 29.8 (73.5)

¹ t_{max} expressed as the median (range)

² N=39 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³ N=36 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for Suboxone 8/2 mg

Table 9: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Norbuprenorphine

Parameter	OX219 5.7/1.4 mg (N=49) ²	Suboxone 8/2 mg (N=49) ³	Ratio	CI	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	22.0	29.8	0.7391	0.6867 – 0.7954	21.7
AUC _{0-inf} (ng·hr/mL)	28.4	40.8	0.6958	0.6250 – 0.7745	24.6
C _{max} (ng/mL)	0.80	1.01	0.7919	0.7234 – 0.8670	26.9

¹ N=39 for AUC_{0-inf} for OX219 5.7/1.4 mg

² N=36 for AUC_{0-inf} for Suboxone 8/2 mg

Table 10: Summary of Pharmacokinetic Parameters Untransformed Data: Total Naloxone

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)	
	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³
AUC _{0-t} (ng·hr/mL)	31.1 \pm 11.1 (35.5)	44.9 \pm 15.1 (33.6)
AUC _{0-inf} (ng·hr/mL)	32.2 \pm 11.7 (36.4)	46.3 \pm 15.4 (33.3)
AUC _{0-t} /AUC _{0-inf} ratio	0.972 \pm 0.013 (1.38)	0.975 \pm 0.018 (1.79)
C _{max} (ng/mL)	14.9 \pm 6.92 (46.6)	21.4 \pm 9.11 (42.6)
Median t _{max} (hr) ¹	0.67 (0.33-5.02)	0.67 (0.33-2.50)
Kel (1/hr)	0.119 \pm 0.037 (30.9)	0.111 \pm 0.036 (32.2)
t _{1/2} (hr)	6.41 \pm 1.99 (31.1)	6.94 \pm 2.35 (33.8)

¹t_{max} expressed as the median (range)

²N=47 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for OX219 5.7/1.4 mg

³N=49 for AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf} ratio, Kel, and t_{1/2} for Suboxone 8/2 mg

Table 11: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Total Naloxone

Parameter	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³	Ratio	CI	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	29.5	42.6	0.6926	0.6663 – 0.7200	11.9
AUC _{0-inf} (ng·hr/mL)	30.2	44.1	0.6849	0.6552 – 0.7159	12.3
C _{max} (ng/mL)	13.7	19.9	0.6884	0.6397 – 0.7408	22.6

¹N=47 for AUC_{0-inf} for OX219 5.7/1.4 mg

²N=49 for AUC_{0-inf} for Suboxone 8/2 mg

Analysis of Secondary Objectives – *In Vivo* Dissolve Times

In Study OX219-003, tablet dissolve time was reported, and confirmed by study personnel, when the subject felt the tablet was dissolved. The dissolve time for OX219 5.7/1.4 mg exhibited a median time of 5.00 minutes in contrast to 12.5 minutes for Suboxone® 8/2 mg (Table 12). OX219 5.7/1.4 mg dissolved faster than Suboxone® 8/2 mg with a median difference in dissolve time of 8 minutes (Hodges-Lehmann Estimate, 95% CI of 5 to 10 minutes faster) (Table 13).

Table 12: Descriptive Statistics of Dissolve Time (minutes) by Treatment: Safety Population

Treatment	N	Mean (SD)	Min.	Median	Max
A	53	7.17 (7.14)	(b) (4)	5.00	(b) (4)
B	60	15.87 (9.41)		12.50	

Test Product A: OX219-4 Sublingual Tablet, Buprenorphine 5.7 mg/Naloxone 1.4 mg; Sponsor: Orexo AB;

Reference Product B: Suboxone® (buprenorphine and naloxone) Sublingual Tablet 8 mg/2 mg.

Table 13: Difference of Medians and 95% Confidence Intervals of Dissolve Time (minutes): Safety Population

	Test Median	Reference Median	Hodges-Lehmann Estimate	Lower CI	Upper CI
Treatment A vs. B	5	12.5	8	5	10

Test Product A: OX219-4 Sublingual Tablet, Buprenorphine 5.7 mg/Naloxone 1.4 mg; Sponsor: Orexo AB;

Reference Product B: Suboxone® (buprenorphine and naloxone) Sublingual Tablet 8 mg/2 mg.

Study OX219-004

In this 4 period crossover study, subjects received a single dose of formulation OX219-4 (1.4/0.36 mg BUP/NLX; n=41), a single dose of formulation OX219-4 (5.7/1.4 mg BUP/NLX; n=42), a single dose of formulation OX219-4 (8.5/2.12 mg BUP/NLX; n=42), or a single dose of formulation OX219-4 (11.4/2.8 mg BUP/NLX; n=42).

Pharmacokinetic Analysis

Pharmacokinetic parameters were determined using non-compartmental analysis of individual plasma concentration vs time profiles for BUP, NLX (unconjugated), NBUP and total NLX (including conjugates). The primary objective of dose proportionality was determined on parameters the AUC_t , AUC_{inf} and C_{max} for BUP, using a power model. The BUP pharmacokinetic parameters are summarized in [Table 14](#) and the NLX pharmacokinetic parameters are summarized in [Table 16](#). The BUP concentration data are presented in [Figure 6](#). The NLX concentration data are presented in [Figure 10](#). NBUP pharmacokinetic parameters are summarized in [Table 18](#) and concentration data are presented in [Figure 11](#). Total NLX pharmacokinetic parameters are summarized in [Table 20](#) and concentration data are presented in [Figure 12](#).

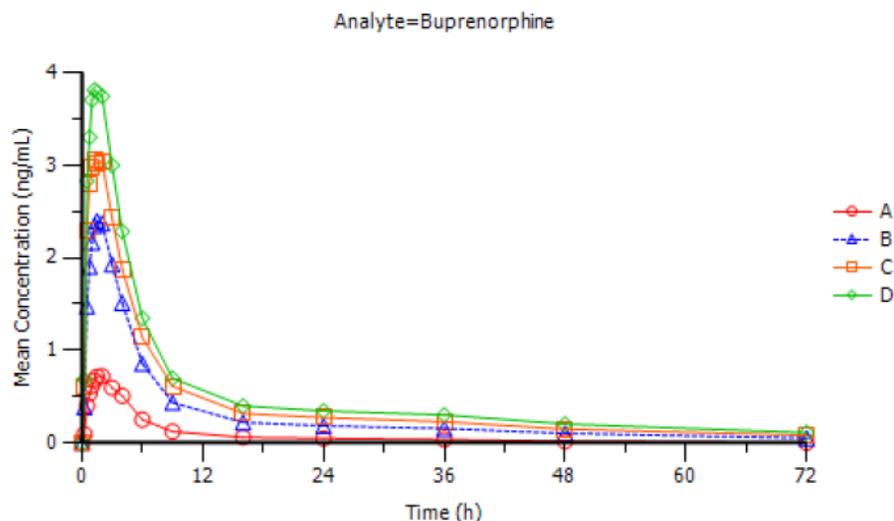
Buprenorphine

BUP displayed a rapid absorption with quantifiable concentrations in most subjects at the first sample time point (0.25 h) also for the lowest dose. Plasma concentrations increased with increasing doses in a linear fashion. The median time to peak concentration varied between 1.13 h and 1.50 h for the different doses, with a total range between 0.50 h and 4.00 h. BUP PK parameters AUC and C_{max} increased with dose in a linear fashion ([Table 14](#)).

Dose proportionality of buprenorphine was confirmed for AUC_t over the entire 8-fold dose range (1.4 to 11.4 mg). AUC_{inf} increased linearly but slightly less than proportionally with dose over the 8-fold dose range. Dose proportionality was confirmed for both AUC_t and AUC_{inf} over > a 4-fold dose range supporting dose proportional extent of absorption between the two tablet strengths (1.4 and 5.7 mg buprenorphine). C_{max} increased linearly but slightly less than proportionally with dose over the 8-fold dose range ([Table 15](#)).

For this summary, AUC_t , AUC_{inf} and C_{max} versus dose are shown in [Figure 7](#), [Figure 8](#) and [Figure 9](#). The figures used regression of the mean PK parameters versus the dose (data from [Table 14](#)). These figures also demonstrated the linearity of the PK parameters over the dosage range studied.

Figure 6: Mean Buprenorphine Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



Treatment A=OX219-4 1.4/0.36 mg buprenorphine/naloxone sublingual tablets (n=41); Treatment B=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment C=OX219-4 8.5/2.12 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment D=OX219-4 11.4/2.8 mg buprenorphine/naloxone sublingual tablets (n=42).

Table 14: Pharmacokinetic Parameters of Buprenorphine

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	Treatment A: OX219 1.4/0.36 mg (N=41) ²	Treatment B: OX219 5.7/1.4 mg (N=42)	Treatment C: OX219 8.5/2.12 mg (N=42)	Treatment D: OX219 11.4/2.8 mg (N=42) ³
AUC _{0-t} (ng·hr/mL)	5.62 \pm 2.58 (45.9)	21.21 \pm 7.21 (34.0)	29.12 \pm 8.63 (29.6)	36.28 \pm 12.55 (34.6)
AUC _{0-inf} (ng·hr/mL)	7.01 \pm 2.70 (38.5)	23.51 \pm 7.79 (33.2)	32.27 \pm 9.55 (29.6)	41.51 \pm 14.28 (34.4)
C _{max} (ng/mL)	0.807 \pm 0.377 (46.7)	2.66 \pm 1.15 (43.1)	3.68 \pm 1.37 (37.3)	4.58 \pm 2.05 (44.9)
Median t _{max} (hr) ¹	1.50 (0.50-4.00)	1.38 (0.50-3.00)	1.13 (0.50-3.00)	1.27 (0.50-4.00)
Kel (1/hr)	0.0504 \pm 0.0360 (71.4)	0.0297 \pm 0.0105 (35.3)	0.0305 \pm 0.0093 (30.5)	0.0278 \pm 0.0079 (28.4)
t _{1/2} (hr)	22.6 \pm 17.0 (75.2)	26.1 \pm 8.9 (34.0)	24.8 \pm 7.5 (30.4)	27.5 \pm 10.2 (37.1)

¹ t_{max} expressed as the median (range)

² n=39 for AUC_{0-inf}, Kel and t_{1/2}

³ n=41 for AUC_{0-inf}, Kel and t_{1/2}

Figure 7: Buprenorphine AUC_{0-t} after Sublingual Administration of OX219 (1.4 mg/0.36 mg through 11.4 mg/2.8 mg)

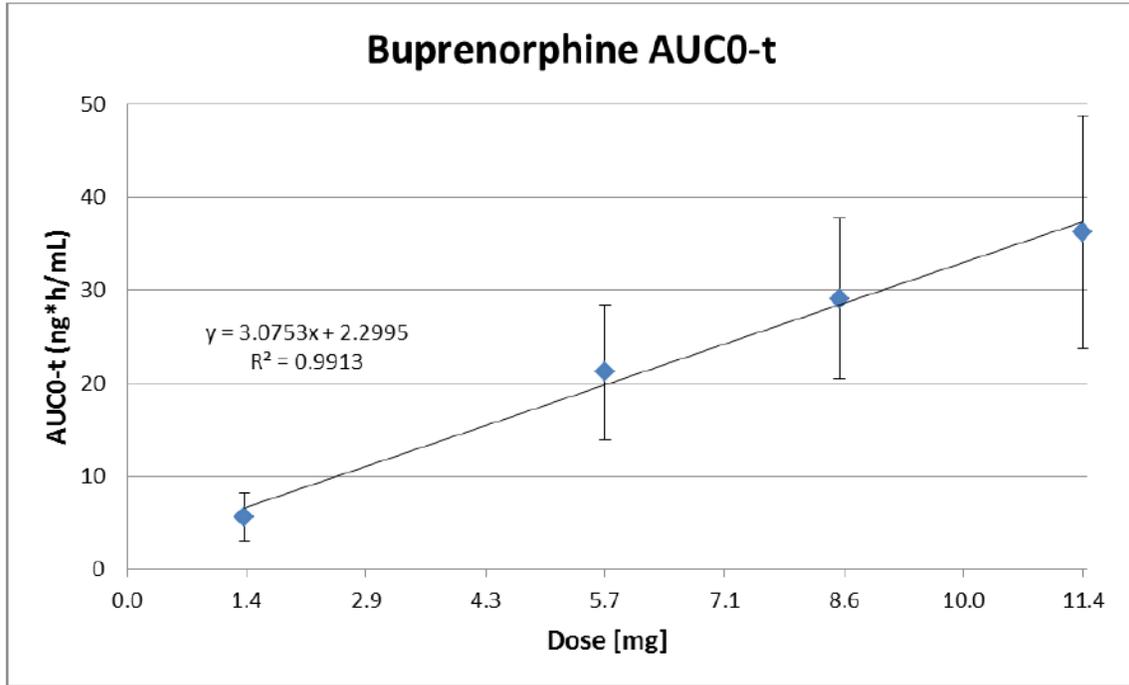


Figure 8: Buprenorphine AUC_{inf} after Sublingual Administration of OX219 (1.4 mg/0.36 mg through 11.4 mg/2.8 mg)

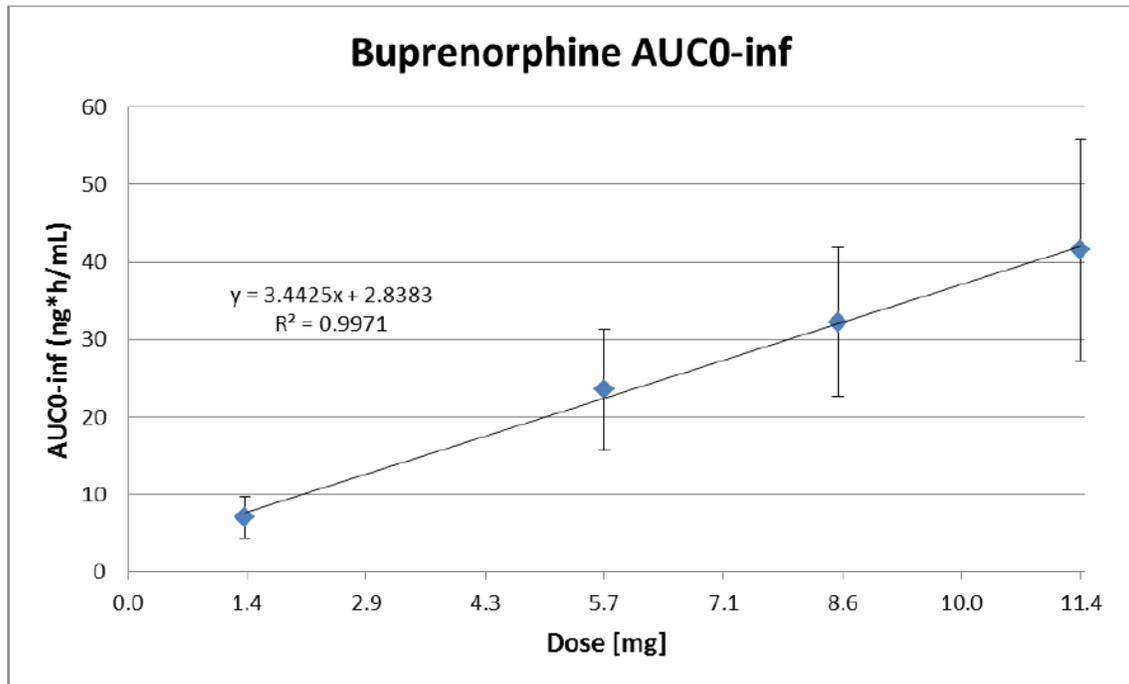


Figure 9: Buprenorphine C_{max} after Sublingual Administration of OX219 (1.4 mg/0.36 mg through 11.4 mg/2.8 mg)

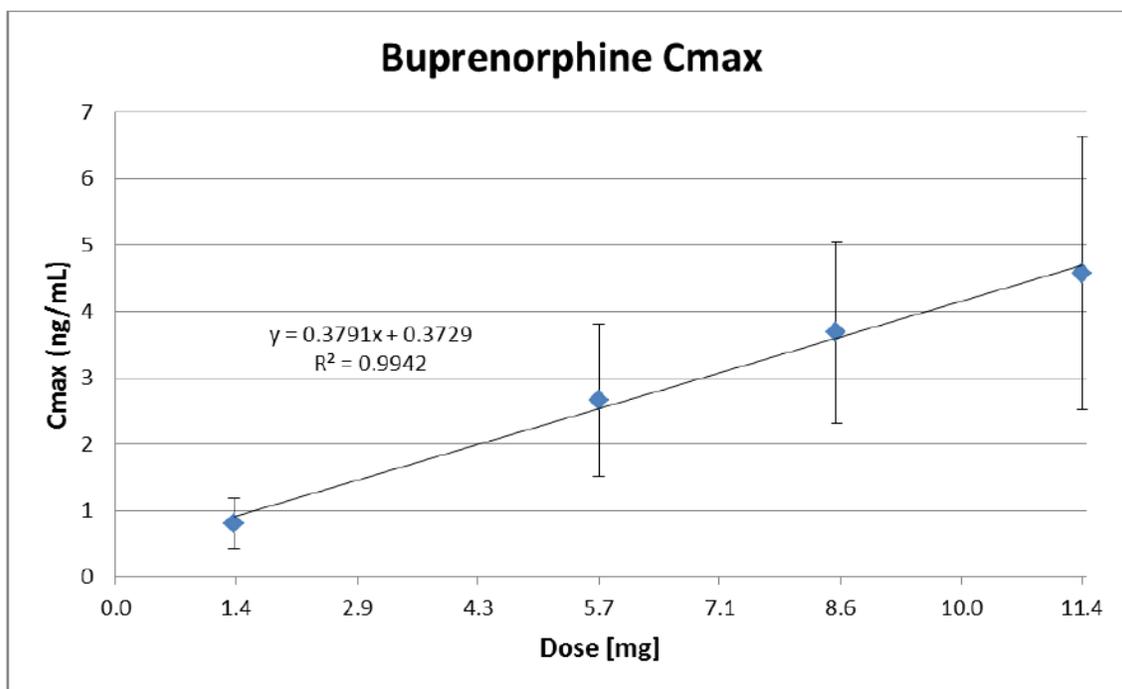


Table 15: Assessment of Dose Proportionality of Buprenorphine using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Dose Range 1.4 to 11.4 mg Buprenorphine</u>					
ln(AUC _t)	ln(dose)	0.9486	0.8908	1.0063	13.9366
ln(AUC _{inf})	ln(dose)	0.8617	0.8257	0.8978	5.2094
ln(C _{max})	ln(dose)	0.8556	0.7951	0.9161	4.0723

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

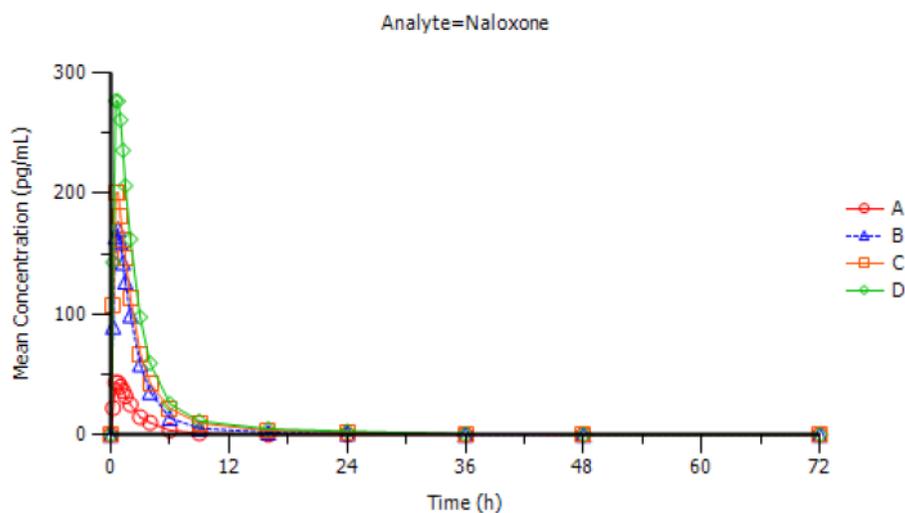
^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

Analysis of Secondary Objectives – Naloxone, Unconjugated

NLX displayed a rapid absorption with quantifiable concentrations in all but one sample at the first sample time point (0.25 h). Plasma concentrations increased with increasing doses. The median time to peak concentration was 0.75 h with a total range between 0.25 h and 4.00 h (Table 16). Mean NLX PK parameters AUC and C_{max} increased with dose.

Dose proportionality was confirmed for naloxone AUC_t and AUC_{inf} over the entire 8-fold dose range (0.36 to 2.8 mg) supporting proportional increase in extent of absorption with increased dose. Naloxone C_{max} increased linearly but slightly less than proportionally with dose over the entire 8-fold dose range (0.36 to 2.8 mg). Dose proportionality for naloxone C_{max} was confirmed over the 4-fold dose range 0.36 to 1.4 mg, supporting dose proportional rate of absorption between the two tablet strengths (Table 17).

Figure 10: Mean Unconjugated Naloxone Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



Treatment A=OX219-4 1.4/0.36 mg buprenorphine/naloxone sublingual tablets (n=41); Treatment B=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment C=OX219-4 8.5/2.12 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment D=OX219-4 11.4/2.8 mg buprenorphine/naloxone sublingual tablets (n=42).

Table 16: Pharmacokinetic Parameters of Unconjugated Naloxone

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	<u>Treatment A:</u> OX219 1.4/0.36 mg (N=41) ²	<u>Treatment B:</u> OX219 5.7/1.4 mg (N=42) ³	<u>Treatment C:</u> OX219 8.5/2.12 mg (N=42)	<u>Treatment D:</u> OX219 11.4/2.8 mg (N=42)
AUC _{0-t} (pg·hr/mL)	119.6 \pm 60.55 (50.6)	495.8 \pm 220.9 (44.6)	633.2 \pm 307.3 (48.5)	873.1 \pm 489.5 (56.1)
AUC _{0-inf} (pg·hr/mL)	125.4 \pm 61.45 (49.0)	491.2 \pm 197.9 (40.3)	650.1 \pm 310.3 (47.7)	890.9 \pm 493.8 (55.4)
C _{max} (pg/mL)	49.5 \pm 27.6 (55.8)	190 \pm 113 (59.2)	232 \pm 127 (54.7)	315 \pm 183 (58.1)
Median t _{max} (hr) ¹	0.75 (0.25-4.00)	0.75 (0.25-1.25)	0.75 (0.25-1.50)	0.75 (0.25-1.50)
Kel (1/hr)	0.4360 \pm 0.1546 (35.5)	0.2217 \pm 0.1306 (58.9)	0.1455 \pm 0.0784 (53.9)	0.1379 \pm 0.0836 (60.6)
t _{1/2} (hr)	2.19 \pm 2.71 (123.5)	4.40 \pm 2.89 (65.7)	6.68 \pm 4.39 (65.7)	7.40 \pm 4.96 (67.1)

¹ t_{max} expressed as the median (range)

² n=40 for AUC_{0-inf}, Kel and t_{1/2}

³ n=41 for AUC_{0-inf}, Kel and t_{1/2}

Table 17: Assessment of Dose Proportionality of Unconjugated Naloxone using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
Dose Range 0.36 to 2.8 mg Naloxone					
ln(AUC _t)	ln(dose)	0.9822	0.9202	1.0441	36.7645
ln(AUC _{inf})	ln(dose)	0.9618	0.9051	1.0186	20.7370
ln(C _{max})	ln(dose)	0.8999	0.8306	0.9693	5.4626

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

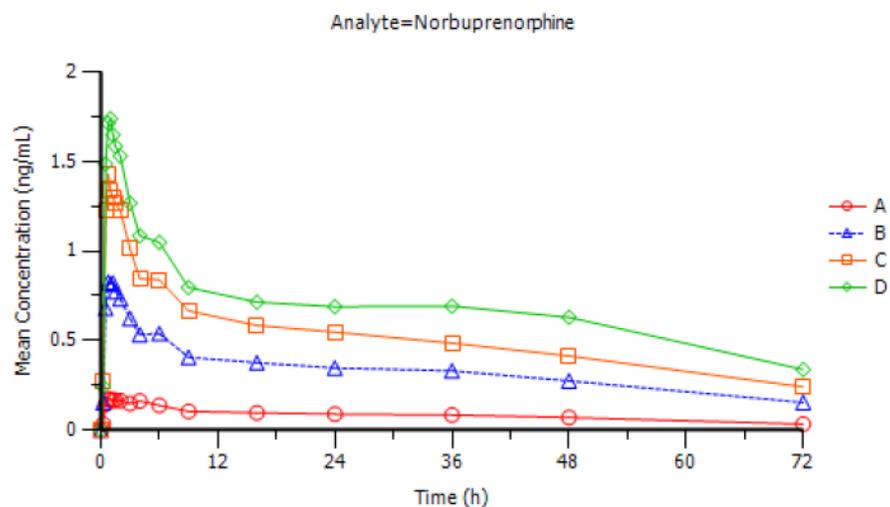
^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

Analysis of Secondary Objectives – Norbuprenorphine

NBUP increased and reached maximum plasma concentration in a median time of 1.00-1.13 h (over the different doses) (Table 18). Plasma concentration vs. time profiles of this metabolite was more variable than for BUP, with secondary and/or late peaks in some subjects (range of t_{max} was 0.25 h to 36.00 h). NBUP PK parameters AUC and C_{max} increased with dose in a linear fashion.

Dose proportionality was confirmed for norbuprenorphine AUC_t , AUC_{inf} and C_{max} over the entire 8-fold buprenorphine dose range (1.4 to 11.4 mg) (Table 19).

Figure 11: Mean Norbuprenorphine Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



Treatment A=OX219-4 1.4/0.36 mg buprenorphine/naloxone sublingual tablets (n=40); Treatment B=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment C=OX219-4 8.5/2.12 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment D=OX219-4 11.4/2.8 mg buprenorphine/naloxone sublingual tablets (n=42).

Table 18: Pharmacokinetic Parameters of Norbuprenorphine

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	Treatment A: OX219 1.4/0.36 mg (N=40) ²	Treatment B: OX219 5.7/1.4 mg (N=42)	Treatment C: OX219 8.5/2.12 mg (N=42)	Treatment D: OX219 11.4/2.8 mg (N=42) ³
AUC _{0-t} (ng·hr/mL)	5.88 \pm 2.51 (42.6)	23.69 \pm 9.95 (42.0)	36.52 \pm 16.92 (46.3)	48.87 \pm 18.93 (38.7)
AUC _{0-inf} (ng·hr/mL)	8.60 \pm 4.14 (48.1)	34.47 \pm 22.29 (64.7)	50.56 \pm 24.79 (49.0)	70.43 \pm 37.93 (53.9)
C _{max} (ng/mL)	0.238 \pm 0.185 (77.6)	1.01 \pm 0.47 (46.7)	1.71 \pm 0.88 (51.3)	2.10 \pm 1.14 (54.2)
Median t _{max} (hr) ¹	1.13 (0.25-36.0)	1.00 (0.50-24.0)	1.00 (0.50-6.00)	1.00 (0.50-36.00)
Kel (1/hr)	0.0225 \pm 0.0116 (51.7)	0.0233 \pm 0.0105 (45.0)	0.0221 \pm 0.0086 (38.7)	0.0218 \pm 0.0094 (43.1)
t _{1/2} (hr)	44.3 \pm 41.3 (93.2)	38.4 \pm 26.1 (67.9)	37.9 \pm 21.4 (56.5)	38.9 \pm 21.4 (54.9)

¹ t_{max} expressed as the median (range)

² n=38 for AUC_{0-inf}, Kel and t_{1/2}

³ n=40 for AUC_{0-inf}, Kel and t_{1/2}

Table 19: Assessment of Dose Proportionality of Norbuprenorphine using a Mixed Effects Statistical Model Based on a Power Function

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Dose Range 1.4 to 11.4 mg Buprenorphine</u>					
ln(AUC _t)	ln(dose)	1.0298	0.9995	1.0600	120.7467
ln(AUC _{inf})	ln(dose)	1.0097	0.9626	1.0567	159.7804
ln(C _{max})	ln(dose)	1.0856	1.0399	1.1312	8.9611

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

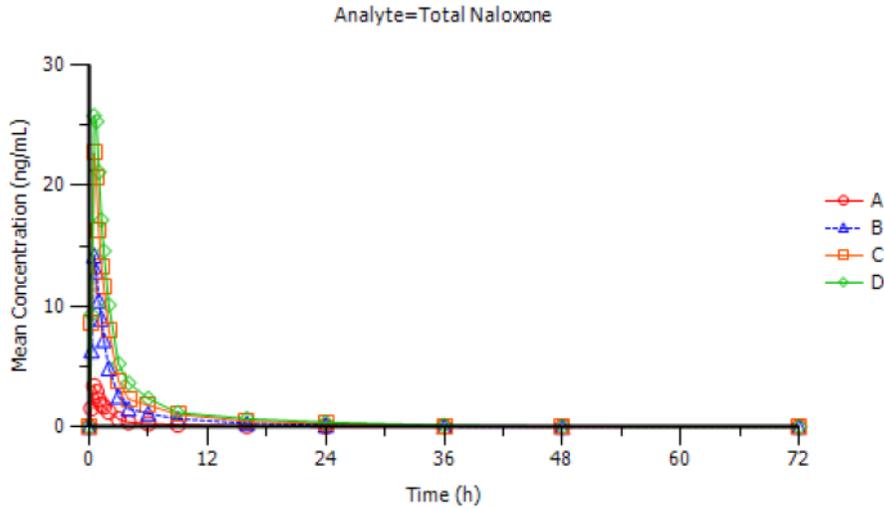
^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

Analysis of Secondary Objectives – Naloxone, Total

Total NLX displayed a rapid absorption with quantifiable concentrations in most subjects at the first sample time point (0.25 h). Plasma concentrations increased with increasing doses in a linear fashion (Table 20). The median time to peak concentration varied between 0.50 h and 0.52 h for the different doses, with a total range between 0.25 h and 4.00 h.

Dose proportionality was confirmed for total naloxone (free naloxone and naloxone glucuronide conjugates) AUC_{inf} and C_{max} over the entire 8-fold naloxone dose range (0.36 to 2.8 mg). Total naloxone AUC_t increased linearly and slightly more than proportionally with dose over the entire 8-fold naloxone dose range. Excluding the lowest dose, dose proportionality for AUC_t was confirmed over the upper dose interval (1.4 to 2.8 mg) (Table 21).

Figure 12: Mean Total Naloxone Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)



Treatment A=OX219-4 1.4/0.36 mg buprenorphine/naloxone sublingual tablets (n=40); Treatment B=OX219-4 5.7/1.4 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment C=OX219-4 8.5/2.12 mg buprenorphine/naloxone sublingual tablets (n=42); Treatment D=OX219-4 11.4/2.8 mg buprenorphine/naloxone sublingual tablets (n=42).

Table 20: Pharmacokinetic Parameters of Total Naloxone

Pharmacokinetic Parameter	Arithmetic mean \pm SD (%CV)			
	<u>Treatment A:</u> OX219 1.4/0.36 mg (N=41)	<u>Treatment B:</u> OX219 5.7/1.4 mg (N=42)	<u>Treatment C:</u> OX219 8.5/2.12 mg (N=42)	<u>Treatment D:</u> OX219 11.4/2.8 mg (N=42)
AUC _{0-t} (ng·hr/mL)	7.79 \pm 2.34 (30.0)	34.02 \pm 7.50 (22.1)	54.31 \pm 12.48 (23.0)	70.54 \pm 14.64 (20.8)
AUC _{0-inf} (ng·hr/mL)	8.33 \pm 2.45 (29.4)	35.39 \pm 7.59 (21.4)	55.58 \pm 12.56 (22.6)	71.69 \pm 14.47 (20.2)
C _{max} (ng/mL)	4.01 \pm 1.56 (38.8)	16.6 \pm 5.30 (32.0)	25.6 \pm 7.78 (30.5)	31.6 \pm 10.4 (32.9)
Median t _{max} (hr) ¹	0.50 (0.25-3.00)	0.50 (0.25-3.00)	0.50 (0.50-2.00)	0.52 (0.25-4.00)
Kel (1/hr)	0.1852 \pm 0.1081 (58.4)	0.1032 \pm 0.0417 (40.4)	0.1049 \pm 0.0311 (29.7)	0.0970 \pm 0.0314 (32.3)
t _{1/2} (hr)	4.90 \pm 2.50 (50.9)	7.97 \pm 3.73 (46.8)	7.14 \pm 1.94 (27.1)	7.86 \pm 2.39 (30.4)

Table 21: Assessment of Dose Proportionality of Total Naloxone using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Dose Range 0.36 to 2.8 mg Naloxone</u>					
ln(AUC _t)	ln(dose)	1.1176	1.0531	1.1822	4.8489
ln(AUC _{inf})	ln(dose)	1.0814	1.0279	1.1348	8.4456
ln(C _{max})	ln(dose)	1.0452	0.9765	1.1139	12.4987

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

where P is the pharmacokinetic parameter tested,

ln(Beta0) is the y-intercept, Beta1 is the slope,

and Epsilon is an error term (Subject was used as the random effects term in the analysis)

^a90% confidence intervals (lower and upper)

^bHigh/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

Analysis of Secondary Objectives – *In Vivo* Dissolve Times

In Study OX219-004, *in vivo* dissolve time was assessed by the subjects for each dosing as the time from placement of the tablet/tablets under the tongue until the last tablet had completely dissolved. When multiple tablets were needed for a dose, all tablets were administered simultaneously. Up to three tablets were administered for a single dose. The 8.5/2.12 mg dose used 3 tablets. Dissolve time was highly variable between subjects but similar between different doses with a median *in vivo* dissolve time of 4.3 to 5.9 minutes (Table 22).

Table 22: Descriptive Statistics of *In Vivo* Dissolve Time

	<i>In vivo</i> dissolve time [min]			
	1.4/0.36 mg ¹	5.7/1.4 mg ²	8.5/2.12 mg ³	11.4/2.8 mg ⁴
N	45	46	45	44
Mean	6.1	6.4	8.1	6.4
SD	4.74	5.39	9.89	3.97
Median	4.3	5.1	5.9	5.0 (b) (4)

¹ One low strength tablet

² One high strength tablet

³ One high strength and two low strength tablets

⁴ Two high strength tablets

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/s/

WEI QIU
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06/05/2013

BIOPHARMACEUTICS INITIAL ASSESSMENT and FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 204-242	Reviewer: Akm Khairuzzaman, Ph.D.	
Submission Date:	09/05/2012		
Division:	Division of Anesthesia and Analgesia Products	Team Leader: Angelica Dorantes, PhD	
Sponsor:	DJA Global Pharmaceuticals, Inc.		
Trade Name:	ZUBSOLV™	Date Assigned:	09/06/2012
Established Name:	Buprenorphine and Naloxone Sublingual Tablets	Date of Review:	02/20/2013
Indication:	Maintenance of treatment of opioid dependence	Type of Submission: Original NDA 505(b)2	
Formulation/strengths	Tablets, 5.7/1.4mg and 1.4/0.36mg buprenorphine/naloxone		
Route of Administration	Sublingual		

EXECUTIVE SUMMARY:

Submission: This NDA was submitted under the Section 505(b)(2) of the Food, Drug and Cosmetic Act. The NDA was submitted as a rolling submission using the electronic common technical (eCTD) format. The drug product is a sublingual tablet containing buprenorphine and naloxone in a 4:1 ratio in the dosage strengths 1.4 mg/0.36 mg and 5.7 mg/1.4 mg (buprenorphine/naloxone).

Background: Buprenorphine is a partial μ -opioid receptor agonist and Naloxone, a full μ -opioid receptor antagonist. Buprenorphine hydrochloride is sparingly soluble in water on the other hand, naloxone is soluble in water. The drug product is formulated using common pharmaceutical grade excipients used in sublingual tablets such as mannitol, citric acid, sodium citrate (b) (4), microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide and sodium sterayl fumerate. (b) (4)

The two strengths are dose similar. The total weight of the dosage form remains (b) (4) of the total weight of the strength used in the pivotal BA/BE study (i.e. the higher strength). The same inactive ingredients are used in both strengths and the changes in the inactive ingredients are within the limits defined by SUPAC-IR guidance (Level II). Therefore, the biowaver for the lower strength can be granted.

Review: The Biopharmaceutics review is being focused on the evaluation and acceptability of: 1) the data supporting the approval of using the disintegration test in lieu of the dissolution test, and 2) the data supporting the biowaiver request for the lower 1.4/0.36mg buprenorphine/ naloxone strength.

The drug product was developed utilizing some elements of the Quality by Design (QbD) concept. The Applicant identified disintegration time as one of the biopharmaceutics related Critical Quality Attribute (CQA), because the Quality Target Product Profile (QTTP) is linked to its rapid disintegration in the sublingual environment, once administered. Therefore, following

the ICH Q6A (decision tree # 7, dissolution > 80% within 15 minutes at pH 1.2, 4.0 and 6.8), the Applicant established the use of the disintegration test in lieu of a dissolution test for day to day commercial batch release (instead of dissolution) and stability testing.

Based on the comparative data provided between the dissolution and disintegration, this reviewer is convinced that the disintegration test (with limit of (b) (4) seconds) can be used as quality test instead of dissolution and therefore the Applicant's disintegration proposal is acceptable. The drug product stability data did not show any trend in disintegration time during the course of the stability studies.

However, the applicant should keep their developed dissolution method, because it will be needed to support the approval of any future post-approval changes that require documentation for dissolution profile comparison and similarity f2 testing.

RECOMMENDATION

NDA201424 for ZUBSOLV™ (buprenorphine and naloxone) Sublingual Tablets is recommended for **APPROVAL** from the Biopharmaceutics perspective.

Akm Khairuzzaman, Ph.D.
Interdisciplinaire Scientist, ONDQA

Date

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader, ONDQA

Date

cc: NDA 204242/DAARTS, RLostritto

BIOPHARMACEUTICS ASSESSMENT – REVIEWER NOTES

SUBMISSION:

This NDA was submitted under the Section 505(b)(2) of the Food, Drug and Cosmetic Act. The NDA was submitted as a rolling submission using the electronic common technical (eCTD) format. The drug product is a sublingual tablet containing buprenorphine and naloxone in a 4:1 ratio in the dosage strengths 1.4 mg/0.36 mg and 5.7 mg/1.4 mg (buprenorphine/naloxone).

Buprenorphine is a partial μ -opioid receptor agonist and Naloxone, a full μ -opioid receptor antagonist. Buprenorphine and naloxone products in a 4:1 ratio are approved in the United States (US) as Suboxone® sublingual tablet (NDA 20733) and Suboxone® sublingual film (NDA 22410). This NDA was submitted Section 505(b)(2) of the Food, Drug and Cosmetic Act whereby the approved product, Suboxone® sublingual tablet was used as a reference listed drug (RLD) during the course of development.

1. The Reviewer’s analyses on the formulation development:

Evaluation: Acceptable.

Principles of quality by design (QbD) were used to design the final formulation. Two different designs of experiment (DoE) studies were performed to evaluate the robustness of the composition and the manufacturing process. The design space of the composition was (b) (4). A low strength tablet, containing (b) (4) compared to the high strength, was developed to be (b) (4). The following different formulation compositions were used for various clinical studies. It is to be noted that all the formulation compositions were qualitatively similar, (b) (4).

Tab. 1. Formulation composition of clinical and commercial drug product

	OX219-1	OX219-3	OX219-3	OX219-4 (FCP)	OX219-4 (FCP)
Strength (mg/mg) buprenorphine/naloxone	(b) (4)			1.4/0.36	5.7/1.4
Clinical study	OX219-001	OX219-002	OX219-002	OX219-004	OX219-003 OX219-004
Components	Amount per tablet (mg)				
Buprenorphine HCl, micronized	(b) (4)				
Naloxone HCl dihydrate, (b) (4)	(b) (4)				
Mannitol	(b) (4)				
Citric acid, anhydrous	(b) (4)				
Sodium citrate, (b) (4)	(b) (4)				
Microcrystalline cellulose	(b) (4)				
Croscarmellose sodium (b) (4)	(b) (4)				
Sucralose	(b) (4)				
Menthol	(b) (4)				
Silicon dioxide, (b) (4)	(b) (4)				
Sodium stearyl fumarate	(b) (4)				
Tablet weight	(b) (4)				

OX219-4 was the final commercial formulation composition. The finished product has two different geometries to distinguish the two strengths as follow:

Figure 1: Tablet Shape and Debossing



2. The Reviewer's analyses on the manufacturing process development using dissolution and disintegration test:

Evaluation: Acceptable.

The drug product is manufactured utilizing a simple

(b) (4)

(b) (4)

(b) (4)

The resulting tablet breaking force, average of 10 tablets as shown above, varied from (b) (4) N to (b) (4) N and the (b) (4) for the 6th (last) tablet varied from (b) (4) seconds to (b) (4) seconds. The (b) (4) for all batches which was well below the acceptance criteria of (b) (4) minutes for the DoE. However, after the commercial scale DoE (tablet (b) (4) the specification limit for (b) (4). The following table summarizes the experimental design of the commercial scale DoE:



(b) (4)

Multiple linear regressions were used for fitting the model to data. The model quality was statistically evaluated by using goodness of fit, R2. Model regression significance was tested by ANOVA. A significant model was defined as having a positive predictive ability after refinement, with a regression model with $p < 0.05$ according to ANOVA.

Comparative dissolution data (USP Apparatus 1, 50 rpm, 500 ml of pH 6.8 buffered medium at 37°C) from another study (effect of ) were also provided by the applicant as follows:



(b) (4)

Reviewer's comment: *There is no effect on dissolution as a function of different  (b) (4). Applicant has conducted sufficient design of experiments at small scale as well as commercial scale using the both quality test and it is reasonable to use the disintegration test instead of dissolution test which is further discussed under question number 4 in this review.*

3. The Reviewer’s analyses on the manufacturing site change

Evaluation: Acceptable.

The commercial scale manufacturing process with the design space established at Orexo was transferred to the US CMO AAIPharma in a 1:1 transfer. The PQ (process qualification) batches, one of each strength, were manufactured following the same manufacturing process and equipment intended for regular commercial production. The CMC details of the site transfer are subject to review by the ONDQA-CMC Reviewer. From biopharmaceutics point of view, the respective CQA, disintegration was found to be within the specification (see table below) from these two PQ batches (higher and lower strength) when operated using different [REDACTED].

Tab. 3. In-process Results for PQ Batches Using [REDACTED] at Target Speed

Batch No. (strength)	[REDACTED]
B120245 (1.4 mg/0.36 mg)	[REDACTED]
B120246 (5.7 mg/1.4 mg)	[REDACTED]

When compared the disintegration data with that of the original site batch (Orexo), trend in slight increase was observed in the batches manufacture at the new site (see table below).

Tab. 4. Comparison of Batches Manufactured at Orexo and AAIPharma, Low Tablet Strength (1.4 mg/0.36 mg)

Test	Acceptance criteria	F11-K045 Orexo (pivotal clinical)	B120245 AAIPharma (PQ)
Physical			(b) (4)
Disintegration (s)			[REDACTED]
- Beginning			[REDACTED]
- Middle			[REDACTED]
- End			[REDACTED]

4. The Reviewer’s analyses on disintegration method as an alternative to dissolution test:

Evaluation: Acceptable.

The desired product characteristics, *i.e.* quality target product profile (QTPP) of the OX219 drug product are a sublingual tablet with a small tablet size, rapid disintegration and an acceptable taste. The applicant has thus identified disintegration time as one of the critical quality attribute (CQA). However, during the course of development a validated well developed dissolution method was also used as a development quality control test in addition to the test for disintegration.

The dissolution method developed is as follows:

Apparatus: USP 1 (basket)
 Stirring speed: 50 rpm
 Medium: 500 ml of pH 6.8 buffered medium (KH₂PO₄, 0.05)
 Sampling times: 2, 5, 10, and 15 minutes.

During the course of drug product development, it was found that dissolution medium did not change the dissolution characteristics significantly as follows:

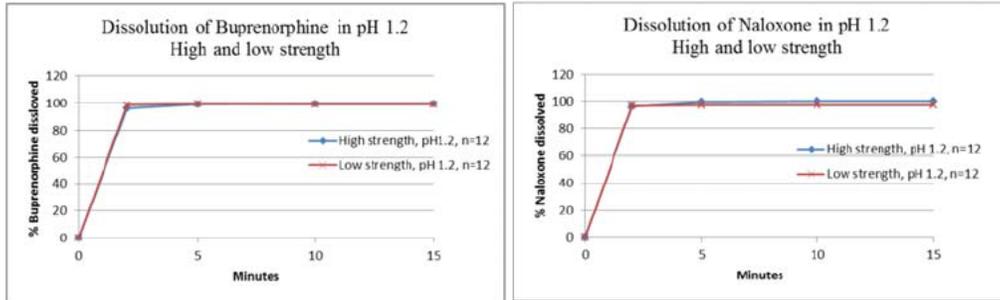


Fig.4. Dissolution of Naloxone in pH 14.2 for Batch Nos.: F11-K043 and F11-K045



Fig.6. Dissolution of Naloxone in pH 4.5 for Batch Nos.: F11-K043 and F11-K045

Tab.1. Disintegration Data

	Low strength 1.4/0.36 Batch No. F11-K045	High strength 5.7/1.4 Batch No. F11-K043
Disintegration (6 tablets without discs)		

(b) (4)

Despite of the having no differences in dissolution characteristics, interestingly differences in disintegration time as a function of different strength was observed as shown in the above table.

Is disintegration capable of distinguishing manufacturing process?

Reviewer's Assessment: Yes.

The most critical unit operation for the drug product manufacture is tablet (b) (4). Any (b) (4) is expected to impact the tablet (b) (4). Therefore, the Applicant has provided additional (from clinical as well as stability batches) to show the impact of breaking force (b) (4) on disintegration / dissolution as follows:

Tab. 5. Disintegration and Dissolution for OX219-4 (FCP) used in Clinical and Primary Stability Studies

Batch No.	Strength (mg/mg)	Tablet breaking force (N)	Disintegration (s)	Dissolution, buprenorphine at 15 minutes (%)	Dissolution, naloxone at 15 minutes (%)
F11-K045B	1.4/0.36	(b) (4)	(b) (4)	(b) (4)	(b) (4)
F11-K046B	1.4/0.36				
F11-M049A	1.4/0.36				
F11-K043A	5.7/1.4				
F11-L047A	5.7/1.4				
F11-M050A	5.7/1.4				

Interestingly, there are no differences in dissolution characteristics, but some differences observed in disintegration time. These batches however did not show any significant differences in dissolution. Additional DOE studies (see table 2 and figure 3) showed that the tablet (b) (4) does not have any impact on dissolution (fig 3) where more than (b) (4) % drug was release in (b) (4) from tablets (b) (4) with a very wide range of tablet (b) (4), but shows some degree of difference in disintegration (see table 2).

(b) (4)

Reviewer's Note: No differences were observed in dissolution between the lower and the higher strength product from pH study. The drug product is very rapidly dissolving; more than (b) (4) % dissolution was achieved in less than (b) (4) for both buprenorphine and naloxone in all different pH media at a fairly low speed, 50 RPM. It is to be noted that, this product is designed (b) (4)

helps to obtain a very rapid dissolution once the tablet is disintegrated. Additionally, no differences were observed in dissolution as a function of manufacturing variability (e.g. tablet (b) (4)). But differences were observed in disintegration time. Therefore, the reviewer considers that the disintegration is the rate limiting step and the critical quality attribute (CQA) for this product.

The Applicant's approach is supported by ICH Q6A guideline (Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical

Substances), where it is stated that for rapidly dissolving drugs (dissolution > (b) (4) % within (b) (4)) disintegration may be substituted for dissolution. However, the applicant should use their developed dissolution method to support any future post approval changes.

5. The Reviewer’s analyses on the data supporting the biowaiver request for the lower strength:

Evaluation: Acceptable.

Based on the information provided under the formulation composition (see Table 1 in this review) the low strength meets (b) (4)

Tab. 6. Compositions of Strengths of the Final Commercial Product (FCP) – SUPAC IR Comparisons

Strength mg (buprenorphine/naloxone)		1.4/0.36		5.7/1.4		Difference (%)	SUPAC-IR Level II (% w/w)
Component	Function	Each tablet contains (mg)	% of total weight	Each tablet contains (mg)	% of total weight		
Buprenorphine HCl	Active ingredient						(b) (4)
Naloxone HCl dihydrate	Active ingredient						(b) (4)
Mannitol							(b) (4)
Citric acid, (b) (4)							(b) (4)
Sodium citrate, (D) (4)							(b) (4)
Microcrystalline cellulose							(b) (4)
Croscarmellose sodium							(b) (4)
Sucralose							(b) (4)
Menthol							(b) (4)
Silicon dioxide, (b) (4)							(b) (4)
Sodium stearyl fumarate							(b) (4)
Total							(b) (4)

Therefore, this information in addition to the dissolution profile data (fig. 3 through 6) support the approval of a biowaiver request for the lower strength.

6. Reviewer’s evaluation on the proposed acceptance criterion for disintegration:

Evaluation: Acceptable.

The proposed acceptance criterion of disintegration time as ≤ (b) (4) seconds (for both strengths) appears to be reasonable based on the batch analysis data, stability data and from the following study:

Tab. 7. Disintegration and Dissolution for OX219-4 (FCP) used in Clinical and Primary Stability Studies

Batch No.	Strength (mg/mg)	Tablet breaking force (N)	Disintegration (s)	Dissolution, buprenorphine at 15 minutes (%)	Dissolution, naloxone at 15 minutes (%)
F11-K045B	1.4/0.36				(b) (4)
F11-K046B	1.4/0.36				
F11-M049A	1.4/0.36				
F11-K043A	5.7/1.4				
F11-L047A	5.7/1.4				
F11-M050A	5.7/1.4				

The highest disintegration time observed was (b) (4) sec (from Batch MA111003:1A) at initial stability time point under the (b) (4) RH storage condition.

7. Reviewer’s evaluation on disintegration stability during product shelf life :

Evaluation: Acceptable.

All stability data at all time points showed disintegration time within the (b) (4) seconds limit and there was no trend observed in the disintegration time during the stability shelf period. The highest disintegration time observed was (b) (4) sec (from Batch MA111003:1A) at initial stability time point under the (b) (4) RH storage condition.

8. Does the selected acceptance criterion time of (b) (4) seconds for the disintegration rejects batches outside of the specification ranges for (b) (4) ?

The Applicant has in process tablet hardness test during the (b) (4) operation. The range was developed based on the DOE response such as disintegration and dissolution. The range established from the DOE was (b) (4) with a target of (b) (4). DOE data shows that the DT test will reject batches tablets with (b) (4) above (b) (4).

Evaluation: Acceptable.

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/s/

AKM KHAIRUZZAMAN

03/05/2013

Recommended for approval from biopharmaceutics point of view

ANGELICA DORANTES

03/05/2013

BIOPHARMACEUTICS INITIAL ASSESSMENT and FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 204-242	Reviewer: Akm Khairuzzaman, Ph.D.	
Submission Date:	09/05/2012		
Division:	Division of Anesthesia and Analgesia Products	Team Leader: Angelica Dorantes, PhD	
Sponsor:	DJA Global Pharmaceuticals, Inc.		
Trade Name:	ZUBSOLV™	Date Assigned:	09/06/2012
Established Name:	Buprenorphine and Naloxone Sublingual Tablet	Date of Review:	11/19/2012
Indication:	Maintainance of treatment of opioid dependence	Type of Submission: Original NDA 505(b)2	
Formulation/strengths	Tablets, 5.7/1.4mg and 1.4/0.36mg buprenorphine/naloxone		
Route of Administration	sublingual		

SUBMISSION:

This NDA was submitted under the Section 505(b)(2) of the Food, Drug and Cosmetic Act. The NDA was submitted as a rolling submission using the electronic common technical (eCTD) format. The drug product is a sublingual tablet containing buprenorphine and naloxone in a 4:1 ratio in the dosage strengths 1.4 mg/0.36 mg and 5.7 mg/1.4 mg (buprenorphine/naloxone).

Buprenorphine is a partial μ -opioid receptor agonist and Naloxone, a full μ -opioid receptor antagonist. Buprenorphine and naloxone products in a 4:1 ratio are approved in the United States (US) as Suboxone® sublingual tablet (NDA 20733) and Suboxone® sublingual film (NDA 22410). As agreed with FDA during the February 3, 2011 pre-IND meeting, the Suboxone® sublingual tablet is the reference listed drug (RLD) product for this NDA.

Buprenorphine hydrochloride is sparingly soluble in water on the other hand, naloxone is soluble in water. The drug product is formulated using common pharmaceutical grade excipients used in sublingual tablets such as mannitol, citric acid, sodium citrate (b) (4), microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide and sodium sterayl fumerate. The two strengths are dose similar. The total weight of the dosage form remains within (b) (4) of the total weight of the strength used in the pivotal BA/BE study (i.e. the higher strength). The same inactive ingredients are used in both strengths and the changes in the inactive ingredients are within the limits defined by SUPAC-IR guidance (Level II). This information is subject to further review. The Applicant claims that the disintegration test is more discriminating than the dissolution test. Therefore, as per the ICH Q6A, where it is stated that for rapidly dissolving drugs (dissolution > 80% within 15 minutes at pH 1.2, 4.0 and 6.8), the Applicant is not performing the dissolution test for drug product's release, instead a disintegration test has been implemented. All the data supporting the proposed strategy of using disintegration in lieu of dissolution is subject to review.

BIOPHARMACEUTIC INFORMATION: In support of approval, this NDA includes the following Biopharmaceutics data for review and evaluation:

- Tablet disintegration data including all clinical batches
- Rational why dissolution can be replaced with disintegration test
- Limited dissolution method development.
- Dissolution data in three different pH media for the lower and higher strength products
- Tablet disintegration data for registration batches at release and on stability
- A biowaver for the lower strength

COMMENTS & RECOMMENDATION: Fileable from biopharmaceutics perspective.

74 DAY LETTER COMMENTS:

(i) Provided information/data showing a relationship between dissolution and disintegration. Note that regardless of the agency's future decision on your strategy of disintegration test in lieu of dissolution for your product, future SUPAC changes under post-approval supplements should be supported with dissolution profile and f2 data.

(ii) Provide solubility data of the drug Buprenorphine hydrochloride as per the ICH Q6A, Decision tree # 7.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader, ONDQA

A. ONDQA-BIOPHARMACEUTICS Initial overview of the NDA application for filing				
	Parameter			Comment
1.	Is the QTPP (Quality Target Product Profile) defined for drug release? (3.2.P.2)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not a QbD Application
2.	Has the risk assessment been performed to evaluate the criticality of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
3.	Is there any manufacturing parameter evaluated using in vitro release as an end point?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
4.	Is there any design space proposed using in vitro release as an end point?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	
5.	Is the control strategy related to in vitro dissolution/drug release? (3.2.P.2/3.2.P.5)	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	A disintegration test is proposed based on ICH Q6, Decision Tree # 7
6.	Solubility (3.2.S.1)	High <input type="checkbox"/>	Low <input type="checkbox"/>	No detailed solubility data has been provided
7.	Permeability (2.7.1)	High <input type="checkbox"/>	Low <input type="checkbox"/>	None reported
8.	BCS Class	I <input type="checkbox"/> II <input type="checkbox"/>	III <input type="checkbox"/> IV <input type="checkbox"/>	None reported
9.	Is the study report included for the development of the in vitro release method? (3.2.P.2/3.2.P.5)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	Limited report is included. After review necessary comments may be communicated to the applicant.
10.	In the study report, are the individual data, the mean, the standard deviation and the plots provided?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
11.	Has the discriminating ability been shown for the in vitro release methodology using formulation variants? (3.2.P.2/3.2.P.5)	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	A disintegration test is proposed based on ICH Q6, Decision Tree # 7
12.	Is the justification provided for the acceptance criteria of the in vitro release? (3.2.P.2/3.2.P.5)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	A disintegration test is proposed based on ICH Q6, Decision Tree # 7
13.	Are the proposed acceptance criteria adequate? (3.2.P.5)	Yes <input type="checkbox"/>	No <input type="checkbox"/>	A disintegration test is proposed based on ICH Q6, Decision Tree # 7
14.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
15.	Are all the to-be-marked strengths used in the pivotal clinical trials?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	
16.	Have any biowaivers been requested? (1.12/2.7.1)	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	For the lower strength, there is a biowaver request in the application
17.	Is there any IVIVC information submitted? (5.3.1)	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>	
18.	If the IVIVC information presented, are the study report and data provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not applicable

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
19.	IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	➤ The NDA is fileable from the Biopharmaceutics Perspective
20.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not applicable.
21.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Not applicable.
22.	Are there any potential review issues identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	None at this stage
23.	Are there any comments to be included in the 74-Day letter?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	The reviewer comments listed in page 2 should be conveyed to the Applicant in the 74-Day letter.

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

/s/

AKM KHAIRUZZAMAN

11/19/2012

Fileable from biopharmaceutics point of view

ANGELICA DORANTES

11/19/2012

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	204242	Proposed Brand Name	OX219	
OCP Division (I, II, III, IV, V)	II	Generic Name	Buprenorphine and naloxone sublingual tablet	
Medical Division	DAAAP	Drug Class	opioid	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	For the maintenance treatment of opioid dependence	
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Sublingual tablet: 5.7/1.4 mg and 1.4/0.36 mg	
Pharmacometrics Reviewer		Dosing Regimen	11.4/2.8 mg once daily	
Date of Submission	9/5/12	Route of Administration	sublingual	
Primary Review Goal Date (GRMP)	5/5/13	Sponsor	Orexo AB	
		Priority Classification	Standard	
PDUFA Due Date	7/6/13	Relevant INDs	IND 110637	
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	4		Studies 001, 002, 003, and 004
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study 004
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		Studies 001, 002 and 003
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

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?			√	To be marketed formulation was used in PK studies 003 and 004.
2	Has the applicant provided metabolism and drug-drug interaction information?	√			Reviewed literature. No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with the list drug, Suboxone (buprenorphine and naloxone) sublingual tablet (NDA 20-733)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable,	√			

Clinical Pharmacology Filing Form/Checklist for NDA 204242

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	does it have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	√			
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)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
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?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
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?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

In the initial submission, sponsor included a PK dataset with PK parameters in Study 003. However, sponsor failed to submit the PK raw data (concentrations at each time point for calculation of PK parameters) and dataset with PK parameters for the BE analysis. In addition, no PK dataset was submitted for Study 004. The following comments were conveyed to the sponsor on October 29, 2012:

1. For Study OX219-003, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your bioequivalence analysis, as well as the SAS code.
2. For Study OX219-004, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your dose proportionality analysis, as well as the SAS code.

Sponsor replied that they do have the data and anticipated being able to respond to this request by late last week (November 2, 2012). At the internal filing meeting on November 2, 2012, per discussion with Dr. Bob Rappaport, if sponsor failed to submit the requested datasets by November 5, 2012 (60 days after their initial submission), this NDA should be refused to file. Around 3 PM on November 5, 2012, Sponsor submitted the requested datasets. After a quick look at the submitted datasets, we think we can conduct analysis on these datasets and this NDA can be filed.

This NDA is fileable from clinical pharmacology perspective.

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.

There are no comments for sponsor at this time.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Background:

On 5 September 2011, Orexo AB submitted a 505(b)(2) NDA 204242 for OX219 (buprenorphine and naloxone) sublingual tablets for the maintenance treatment of opioid dependence.

This NDA relies on the Agency's previous findings of safety and effectiveness for Suboxone sublingual tablet (NDA 20-733) and literature. The to-be-marketed formulation was used in

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

relative bioavailability study (Study 003) and dose proportionality study (Study 004). Sponsor requested biowaiver for the lower strength based on dissolution data. This biowaiver request is deferred to ONDQA/Biopharm team.

The overall clinical and clinical pharmacology program consisted the 4 single dose Phase 1 (Studies 001, 002, 003 and 004). Earlier formulations were used in Studies 001 and 002 to select the final commercial formulation. The final formulation was used in pivotal relative bioavailability study (Study 003) and dose proportionality study (Study 004). Since the final formulation was used in Studies 003 and 004, this review will focus on these two studies.

Sponsor's summary on relative bioavailability of OX219 in comparison to the list drug, Suboxone, and dose proportionality:

- OX219 5.7/1.4 mg exhibited equivalent C_{max} and AUC values of buprenorphine in comparison to Suboxone 8/2 mg
- OX219 5.7/1.4 mg exhibited lower exposure to naloxone, norbuprenorphine, and total naloxone in comparison to Suboxone 8/2 mg
- OX219 5.7/1.4 mg had shorter dissolve time in comparison to Suboxone 8/2 mg
- Dose proportionality was demonstrated for buprenorphine AUC_t, naloxone AUC_t and AUC_{inf}, norbuprenorphine AUC_t and AUC_{inf}, over the range of 1.4/0.36 mg and 11.4/2.8 mg.

Please find the filing slides for more details.



NDA 204-242 OX219 (Buprenorphine and Naloxone Sublingual Tablets)

Sponsor: Orexo AB

CP Filing Meeting
November 2, 2012

1



Drug Product

- Sublingual buprenorphine and naloxone (BUP/NLX) combination in a 4:1 ratio of free bases which has been approved as sublingual tablet and sublingual film formulations under the trade name Suboxone
 - Proposed indication: for the maintenance treatment of opioid dependence.
 - Proposed strengths: 5.7/1.4 mg and 1.4/0.36 mg to match the List Drug Suboxone
 - 505(b)(2) NDA
 - Listed Drug: Suboxone sublingual tablet 8/2 mg and 2/0.5 mg (NDA 20-733)

2

Previous Agreements

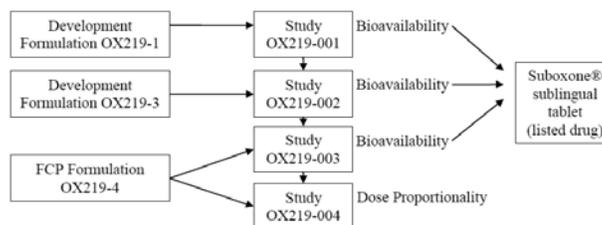
- Conduct a BE study with higher strength (5.7/1.4 mg) vs. Suboxone 8/2 mg
- Request biowaiver for the lower strength (1.4/0.36 mg)
- Dose proportionality study from 1.4/0.36 mg to 11.4/2.8 mg
- Lower norbuprenorphine (NorBUP) exposure will not lead to requirement for efficacy study
- Lower NLX exposure will be acceptable since its main purpose is for abuse deterrence
- Provide information on the time it takes for the product to completely dissolve when administered in humans.
- Since you are only developing your product for maintenance treatment of opioid dependence, address what should be used for induction (labeling language).
- Provide data demonstrating that your product releases sufficient NLX under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids.

3

Clin Pharm/Clin Development Program

- Four (4) Single Dose Clin Pharm Studies

Figure 2.5 - 1: Pharmacokinetic (PK) Studies to Bridge OX219 Formulations to Suboxone®



- 2 pilot studies using earlier formulations to determine the final formulation and strengths:
 - OX219-001: Formulation OX219-1 (1 x 6/1.5 mg) vs. Suboxone® 1 x 8/2 mg → confirmed higher BUP and NLX bioavailability of OX219-1
 - OX219-002: Formulation OX219-3 (1 x 4.5/1.125 mg and 1 x 5.5/1.373 mg) vs. Suboxone® 1 x 8/2 mg → led to selection of the doses of the Final Commercial Product, formulation OX219-4 with 2 strengths (5.7/1.4 mg and 1.4/0.36 mg)
- 1 pivotal relative BA study OX219-003: FCP 1 x 5.7/1.4 mg vs. Suboxone 1 x 8/2 mg
- 1 dose proportionality study OX219-004: FCP 1 x 1.4/0.36 mg, 1 x 5.7/1.4 mg, 8 5/2.12 mg (1 x 5.7/1.4 + 2 x 1.4/0.36 mg), 11.4/2.8 mg (2 x 5.7/1.4 mg)
- Biowaiver request (defer to Biopharm team)
- No Phase 3 studies

4

Comparative BA Study (Study OX219-003)

- OL, fasting, R, 2-period CV comparative BA study, healthy (n=53), PK, tolerability, safety
 - OX219 sublingual tablet (1 x 5.7/1.4 mg)
 - Suboxone® sublingual tablet (1 x 8/2 mg)

5

Study OX219-003 Result – BUP

Equivalent AUCs and Cmax w/ Similar Tmax

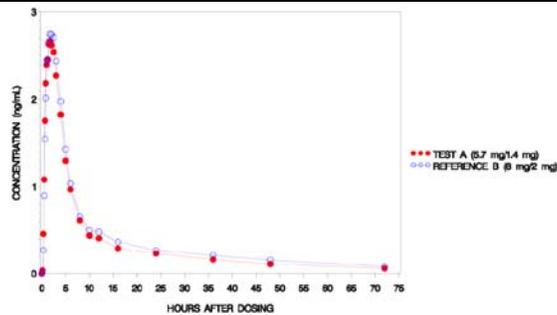


Table 5: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Buprenorphine

Parameter	OX219 5.7/1.4 mg (N=49) ¹	Suboxone 8/2 mg (N=49) ¹	Ratio	CI ¹	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	22.4	25.5	0.8793	0.8268 – 0.9352	18.1
AUC _{0-inf} (ng·hr/mL)	24.6	28.7	0.8569	0.8024 – 0.9150	18.5
C _{max} (ng/mL)	2.80	2.86	0.9805	0.9074 – 1.0594	22.9

6

Study OX219-003 Result – NLX

Lower AUCs and Equivalent Cmax w/ Similar Tmax

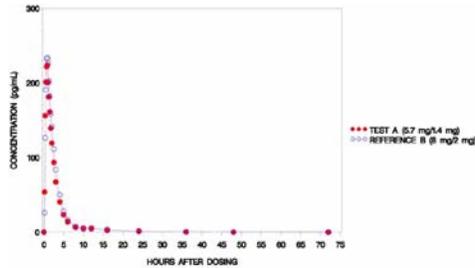


Table 7: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Unconjugated Naloxone

Parameter	OX219 5.7/1.4 mg (N=53) ¹	Suboxone 8/2 mg (N=53) ³	Ratio	CI ¹	Intra-Subject %CV
AUC _{0-t} (pg·hr/mL)	511	605	0.8449	0.7661 – 0.9319	30.5
AUC _{0-inf} (pg·hr/mL)	560	640	0.8752	0.7886 – 0.9713	28.0
C _{max} (pg/mL)	211	228	0.9248	0.8183 – 1.0453	38.6

7

Study OX219-003 Result – NorBUP

Lower AUCs and Cmax

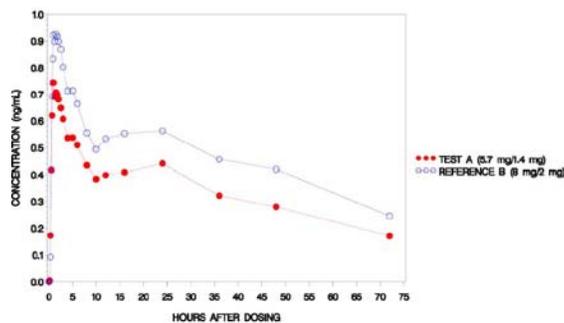


Table 9: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Norbuprenorphine

Parameter	OX219 5.7/1.4 mg (N=49) ¹	Suboxone 8/2 mg (N=49) ³	Ratio	CI	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	22.0	29.8	0.7391	0.6867 – 0.7954	21.7
AUC _{0-inf} (ng·hr/mL)	28.4	40.8	0.6958	0.6250 – 0.7745	24.6
C _{max} (ng/mL)	0.80	1.01	0.7919	0.7234 – 0.8670	26.9

8

Study OX219-003 Result – Total NLX Lower AUCs and Cmax

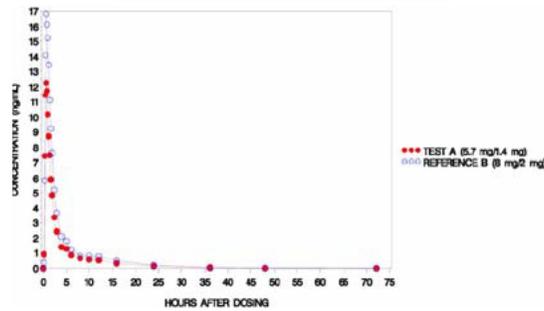


Table 11: Geometric Means, Ratio of Means, and 90% Confidence Intervals Based on ANOVA of Natural Log-Transformed Data: Total Naloxone

Parameter	OX219 5.7/1.4 mg (N=53) ²	Suboxone 8/2 mg (N=53) ³	Ratio	CI	Intra-Subject %CV
AUC _{0-t} (ng·hr/mL)	29.5	42.6	0.6926	0.6663 – 0.7200	11.9
AUC _{0-inf} (ng·hr/mL)	30.2	44.1	0.6849	0.6552 – 0.7159	12.3
C _{max} (ng/mL)	13.7	19.9	0.6884	0.6397 – 0.7408	22.6

3

Study OX219-003 Result – Dissolve Time for OX219 and Suboxone

**Table 14.2.9 Descriptive Statistics of Dissolve Time (minutes) by Treatment:
Safety Population**

Treatment	N	Mean (SD)	Min.	Median	Max
A	53	7.17 (7.14)	(b) (4)	5.00	(b) (4)
B	60	15.87 (9.41)		12.50	

Test Product A: OX219-4 Sublingual Tablet, Buprenorphine 5.7 mg/Naloxone 1.4 mg; Sponsor: Orexo AB
 Reference Product B: Suboxone® (buprenorphine and naloxone) Sublingual Tablet
 CIII, 8 mg/2 mg; Mfg. by: Reckitt Benckiser Healthcare (UK) Ltd.; Dist.
 by: Reckitt Benckiser Pharm. Inc.

10

Dose Proportionality Study (Study OX219-004)

- Title: OL, fasting, R, 4-period cross-over, comparative BA study, healthy (n=49), dose proportionality, tolerability, safety
- Treatment Doses:
 - OX219 1.4/0.36 mg (1x OX219 1.4/0.36 mg)
 - OX219 5.7/1.4 mg (1x OX219 5.7/1.4 mg)
 - OX219 8.5/2.12 mg (1x OX219 5.7/1.4 mg + 2x OX219 1.4/0.36 mg)
 - OX219 11.4/2.8 mg (2x OX219 5.7/1.4 mg)
- Power model to evaluate dose proportionality
 - $P = \text{Beta}0 \cdot \text{Dose}^{\text{Beta}1} \cdot \text{Exp}(\epsilon)$
 - $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \epsilon$
 - P: PK parameter
 - $\ln(\text{Beta}0)$: y-intercept
 - Beta1, the slope, measures the proportionality between Dose and P.
 - IF Beta1 = 1, dose proportionality can be declared.

11

Study OX219-004 Result – BUP PK Proportional Increase in AUC_t

Figure 6: Mean Buprenorphine Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)

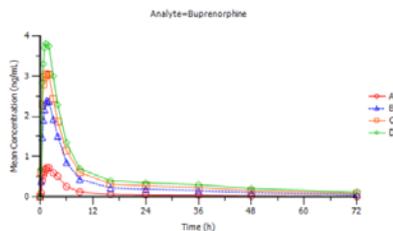


Table 15: Assessment of Dose Proportionality of Buprenorphine using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
Dose Range 1.4 to 11.4 mg Buprenorphine					
$\ln(\text{AUC}_t)$	$\ln(\text{dose})$	0.9486	0.8908	1.0063	13.9366
$\ln(\text{AUC}_{\text{inf}})$	$\ln(\text{dose})$	0.8617	0.8257	0.8978	5.2094
$\ln(\text{C}_{\text{max}})$	$\ln(\text{dose})$	0.8556	0.7951	0.9161	4.0723

Power Model: $\ln(P) = \ln(\text{Beta}0) + \text{Beta}1 \cdot \ln(\text{Dose}) + \text{Epsilon}$

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Study OX219-004 Result – NLX PK Proportional Increase in AUCt and AUCinf

Figure 10: Mean Unconjugated Naloxone Concentration-Time Profiles after Administration of OX219 1.4/0.36 mg (Treatment A), OX219 5.7/1.4 mg (Treatment B), OX219 8.5/2.12 mg (Treatment C), and OX219 11.4/2.8 mg (Treatment D) (Study OX219-004)

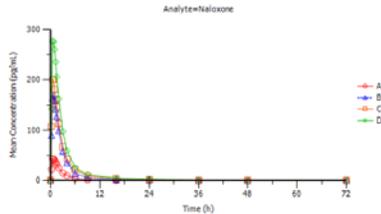


Table 17: Assessment of Dose Proportionality of Unconjugated Naloxone using a Mixed Effects Statistical Model Based on a Power Function (primary analysis)

Dependent Variable	Model Variable	Estimate (Beta)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Dose Range 0.36 to 2.8 mg Naloxone</u>					
ln(AUC _t)	ln(dose)	0.9822	0.9202	1.0441	36.7645
ln(AUC _{inf})	ln(dose)	0.9618	0.9051	1.0186	20.7370
ln(C _{max})	ln(dose)	0.8999	0.8306	0.9693	5.4626
Power Model: ln(P) = ln(Beta0) + Beta1*ln(Dose) + Epsilon					

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Study OX219-004 Result – NorBUP and Total NLX PK Proportional Increase in NorBUP AUCt and AUCinf

Dependent Variable	Model Variable	Estimate (Beta1)	Lower CL ^a	Upper CL ^a	Rho ^b
<u>Norbuprenorphine</u>					
ln(AUC _t)	ln(dose)	1.0298	0.9995	1.0600	120.7467
ln(AUC _{inf})	ln(dose)	1.0097	0.9626	1.0567	159.7804
ln(C _{max})	ln(dose)	1.0856	1.0399	1.1312	8.9611
<u>Total naloxone</u>					
ln(AUC _t)	ln(dose)	1.1176	1.0531	1.1822	4.8489
ln(AUC _{inf})	ln(dose)	1.0814	1.0279	1.1348	8.4456
ln(C _{max})	ln(dose)	1.0452	0.9765	1.1139	12.4987

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Summary

- Relative BA: OX219 vs. Suboxone
 - BUP: equivalent exposure
 - NLX: lower AUCs and equivalent Cmax
 - NorBUP and total NLX: lower AUCs and Cmax
- Dose proportionality:
 - OX219:
 - BUP: proportional in AUC; slightly less than dose proportional for AUCinf and Cmax
 - NLX: proportional increase in AUCs, slightly less than dose proportional for Cmax
 - Proposed labeling: Both Cmax and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 1.4 to 11.4 mg), although the increase was not directly dose-proportional. There was no description of NLX PK.
 - Suboxone®: Both Cmax and AUC of BUP increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional. Within each subject (for most of the subjects), across the doses there was a trend toward an increase in naloxone concentrations with increase in dose.

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Recommendation

- Filable from Clin Pharm perspective
- Inspection on the pivotal relative BA Study OX219-003 was requested (10/9): OSI review requested by April 1, 2013.
- Comments to Sponsor:
 - 1. For Study OX219-003, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your bioequivalence analysis, as well as the SAS codes.
 - 2. For Study OX219-004, provide the dataset with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your dose proportionality analysis, as well as the SAS codes.

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Backup Slides

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Approval of Suboxone film

- 2/0.5 mg and 8/2 mg film was approved based on these three BE studies
 - BE study at 2/0.5 mg between film and tablet (BE)
 - BE study at 8/2 mg between film and tablet (not BE)
 - BE study at 12/3 mg (8+2+2) between film and tablet (BE)

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/s/

WEI QIU
11/06/2012

YUN XU
11/06/2012