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APPLICATION NUMBER:

207932Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 207932	Submission Date: 12/23/14
Submission Type; Code:	505(b)(2)
Brand/Code Name:	BELBUCA™
Generic Name:	Buprenorphine HCl buccal film
Clinical Pharmacology Primary Reviewer:	David Lee, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Anesthesia, Analgesia, and Addiction Product
Sponsor:	Endo Pharmaceuticals, Inc.
Relevant IND(s):	72428
Formulation; Strength(s):	Buccal film; 75, 150, 300, 450, 600, 750, 900 µg
Proposed Indication:	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (b) (4)
Proposed Dosage Regimen:	(b) (4)

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 207932, for Belbuca, submitted on 12/23/14. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable, pending agreement on the labeling language.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

Endo Pharmaceuticals Inc. has submitted a New Drug Application (NDA) for Belbuca, buprenorphine hydrochloride (HCl) buccal film, under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. (Note: the "BEMA® Buprenorphine" notation was also used throughout the drug development process, which was the designated identifier for this product prior to use of identifier Belbuca). The Applicant requested Priority Review Designation for this NDA, however, the application was considered a standard review. As a 505(b)(2) application, the Applicant is relying in part on the Agency's previous findings of safety and efficacy of 2 listed drugs, Buprenex (buprenorphine HCl, EQ 0.3 mg base/mL injection, NDA 18401) and Subutex (buprenorphine HCl, EQ 2mg and 8 mg base; sublingual tablets, *NDA 20732*) as references; Roxane's (buprenorphine HCl EQ 8 mg Base, ANDA 78633, sublingual tablet) buprenorphine sublingual tablet was also used to assess relative bioavailability, due to Subutex being withdrawn from the market in 2012 for reasons not related to safety and/or effectiveness.

Belbuca utilizes the same BioErodible MucoAdhesive (BEMA®) technology platform that was used by BDSI to develop the FDA-approved mucoadhesive film products, Onsolis® (fentanyl buccal soluble film) and Bunavail™(buprenorphine and naloxone buccal film).

The proposed indication is for the "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (b) (4) ." The proposed dosing regimen is every 12 hours.

The clinical program was conducted under IND 72,428. Two (2) formulations ((b) (4) were developed and used in Phase 3 clinical studies; (b) (4) The same formulations were used for manufacturing of registration and production scale batches and will be used for commercial product. The clinical program for the development of buprenorphine HCl buccal film includes 9 Phase 1 studies, 2 Phase 2 studies, and 5 Phase 3 studies.

Pharmacokinetic findings

The following studies provided buprenorphine exposure information (Table 1).

Table 1 Belbuca Pharmacokinetic studies

Study	SD	MD	Dose linearity	Ab BA	Rel BA: (Roxane 8 mg SL)	pH	Liquid temp.	Mucositis	QT
BUP-115	500 µg (b) (4)			X					
BUP-116		60 to 240 µg (b) (4)	X						
BUP-117	75 to 1200 µg (b) (4)		X	X					
BUP-118	900 µg (b) (4)				X	X			
EN3409-120	900 µg (b) (4)						X		
BUP-121	60 µg (b) (4)							X	
BUP-150	3000 µg (b) (4)								X
Pop PK	P3 studies: EN3409-307 and EN3409-308 (b) (4)								

Single-dose

The following are the single dose pharmacokinetic parameters from Belbuca administered in various different doses (Table 2).

Table 2 Buprenorphine Plasma Pharmacokinetic Parameters (mean±SD)

	BUP-121 60 µg	BUP-117 75 µg	BUP-117 300 µg	BUP-117 300 µg	BUP-115 500 µg	BUP-118 900 µg	BUP-120 900 µg	BUP-117 1200 µg (b) (4)
Cmax (ng/mL)	0.07± 0.02	0.17±0.30	0.37±0.10	0.47±0.47	0.55±0.12	1.32±0.41	1.36±0.42	1.43±0.45
AUCt (ng.h/mL)	0.23±0.09*	0.46±0.220	2.00±0.58	2.04±0.68	3.80±0.82	8.75±2.46	9.40±2.86	9.59±2.92
AUCinf (ng.h/mL)	-	0.63±0.24	2.23±0.63	2.26±0.69	4.40±1.11	9.53±2.74	10.1±3.03	10.46±3.32
T1/2 (h)	-	2.45±0.60	4.58±2.87	3.94±2.13	19.10±11.54	13.77±6.75	14.24±7.01	15.10±5.62
Tmax (h)	2.5	3.00	3.00	2.5	2	3.00	2	3.00

Note: 0-24h

After Belbuca 3000 µg single dose (QT study; (b) (4), which is not the TBM) the observed Cmax and AUC0-24 was 3.66 ng/mL and 25.3 ng.hr/mL, respectively.

Multiple-dose

Study BUP-116 was an open-label, dose-escalating, multiple-dose study in healthy subjects. Ten (10) healthy subjects were dosed in a sequential, dose escalating manner, that is, at 60, followed by 120, followed by 180, and, finally, at 240 µg (Table 3).

Table 3 Buprenorphine Plasma Pharmacokinetic Parameters after multiple doses

Parameter	BEMA Buprenorphine Dose (Study Day)			
	60 mcg (Day 3)	120 mcg (Day 6)	180 mcg (Day 9)	240 mcg (Day 12)
T_{max} (hours)	3.0 (2.0-4.0)	2.5 (2.0-4.0)	2.0 (0-3.0)	2.0 (2.0-3.0)
C_{max} (ng/mL)	0.0766±0.0195	0.156±0.0437	0.216±0.106	0.364±0.125
$AUC_{0-\tau}$ (h·ng/mL)	0.4903±0.1395	0.9658±0.2468	1.358±0.5951	2.343±0.7424
$T_{½}$ (hours)	NA	NA	NA	27.58±11.18

Dose linearity

Single-dose

Study BUP-117 indicated that buprenorphine Cmax and AUC increased linearly with an increase in dose from 75 to 1200 µg.

Multiple-dose

Study BUP-116 indicated that buprenorphine Cmax and AUC increased linearly with an increase in dose from 60 to 240 µg after 6 doses administered every 12 hours. The elimination half-life following the last dose was approximately 27.6 hours.

Relative Bioavailability

Study BUN-118 provided relative bioavailability information comparing single dose 900 µg Belbuca and 8 mg buprenorphine sublingual tablet, Roxane Laboratories. Buprenorphine mean Cmax value from Belbuca was 1.32 ng/mL compared to 6.73 ng/mL with sublingual tablet 8 mg. Buprenorphine mean AUC value from Belbuca was 9.53 ng.h/mL compared to 44.1 ng.h/mL with sublingual tablet 8 mg.

(b) (4) and (b) (4) formulation comparison

Study BUP-117 provided the buprenorphine exposure information from a single dose 300 µg Belbuca (b) (4) and (b) (4) formulations. The buprenorphine drug loading and surface area of the films are different for (b) (4) and (b) (4) formulations. Both formulations are designated as to-be-marketed formulations. The 90% CIs for buprenorphine AUC after 300 µg Belbuca from 2 formulations ((b) (4) and (b) (4) were within 0.80 to 1.25. The 90% CI for buprenorphine Cmax lower bound is slightly below of 0.8 (74.9%), perhaps due to a large % CV was observed for buprenorphine Cmax for (b) (4) formulation.

Absolute bioavailability

Study BUP-115 explored absolute bioavailability by comparing 500 µg single-dose Belbuca ((b) (4) a to-be-marketed formulation) and a 2-minute IV injection of 150 µg buprenorphine in 0.5 mL (Buprenex Injection). The mean absolute bioavailability (based on AUCinf) of buprenorphine from Belbuca was approximately 0.65 at dose level of 0.5 mg (Table 29).

Study BUP-117 explored absolute bioavailability by comparing 75, 300 and 1200 µg single-dose Belbuca ((b) (4) a to-be-marketed formulation) and a 2-minute IV injection of 300 µg buprenorphine (0.3 mg/1 mL; Buprenex Injection). The mean absolute bioavailability ranged from 0.46 to 0.51 across the 4 buccal doses

Grade 3 mucositis patients

In patients with Grade 3 mucositis (Study BUP-121) administered with 60 µg Belbuca, buprenorphine Cmax and AUC values were 80% higher and 60% greater compared to age and gender matched healthy subjects. Therefore, dose adjustment language will be added to the labeling regarding use in patients with mucositis.

Temperature effect

Study EN3409-120 explored the temperature effect on a single dose 900 µg Belbuca when hot, cold or room temperature water was co-administered.

Buprenorphine Cmax and AUC values were lower by 28% and 27%, respectively, following Belbuca administration with hot water compared with Belbuca administration without any liquids.

Buprenorphine Cmax and AUC values were lower by 31% and 23%, respectively, following Belbuca administration with cold water compared with Belbuca administration without any liquids.

Buprenorphine Cmax and AUC values were lower by 26% and 24%, respectively, following Belbuca administration with water at room temperature compared with Belbuca administration without any liquids.

pH effect

Buprenorphine Cmax and AUC decreased by 47 and 37%, respectively, when a single dose 900 µg Belbuca was co-administration with low pH liquid (room temperature decaffeinated cola). Co-administration with high pH liquid (room temperature sodium bicarbonate mixed with water) had no significant impact on buprenorphine exposure from Belbuca (Study BUP-118). The exposure to norbuprenorphine was comparable across the different treatments.

Due to the effect of temperature and pH, the consumption of liquids should be avoided until the buccal film has completely dissolved and such language will be added to the labeling.

QT effect

The Applicant reported moderate effect of 5.2 msec at 6 hours and 5.8 msec at 8 hours (the mean naltrexone-corrected, change from baseline QTcF (ΔΔQTcF) after Belbuca with naltrexone) post Belbuca administration.

The QT-Interdisciplinary Review Team's (IRT) review indicated that 'no significant QTc prolongation effect of BEMA Buprenorphine was detected in this TQT study" (IND 72428, dated 6/19/13). Additionally QT-IRT assessment based on the range of doses and QT prolongation, the review stated that "marginal clinically relevant QTc prolongation (comparable to that at (b) (4)) may occur for BEMA with doses of 600 µg q12h or above" (NDA 207932 dated 6/18/15). See QT-IRT reviews, respectively, for an in-depth discussion and assessment regarding QT prolongation.

Elderly and Sex

No dedicated pharmacokinetic studies were conducted in the development of Belbuca in order to address elderly or sex exposure differences. However the Applicant performed the population pharmacokinetics analysis to possibly identify and characterize patient factors which influence the variability in buprenorphine exposures. No variables such as age, body size or sex were found to be statistically significant factors ($p<0.001$).

Pediatric

The PK information from Belbuca has not been studied in pediatric patients. The Applicant requests a partial waiver from the requirement to submit assessment of Belbuca in pediatric subjects 0 to less than 7 years old due to the fact that 1) the necessary studies are impossible or highly impracticable and 2) the number of pediatric subjects meeting the indication in the age group are too small in number to make the studies feasible. In addition, pursuant to 21 CFR Part 314.55(c)(3)(i) and (ii) and 21 CFR 314.55(b)(1)(a) and 505B(a)(3)(A)(i) of the FD&C Act, the Applicant requests a deferral of submission of assessment in pediatric subjects aged 7 to 16 years old due to the fact that the product is ready for approval for use in adults and the pediatric study has not been initiated or completed. The Applicant plans to conduct pediatric studies to fulfill Pediatric Research Equity Act obligations.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

The Applicant's intention for developing Belbuca was to enable buccal absorption of buprenorphine delivered across the mucosa as the film dissolves in the mouth, bypassing the gastrointestinal absorption and first pass metabolism processes. Additionally it is thought that Belbuca will be

another useful dosage form to deliver *a single entity buprenorphine* to patients other than already approved single entity products as intravenous, sublingual or transdermal dosage forms.

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

The Applicant and its partner, BioDelivery Sciences International, Inc., (BDSI), have developed a buccal film dosage form of buprenorphine for oral application to buccal mucosa (inside of the cheek), a transmucosal form of buprenorphine. Belbuca uses BDSI BioErodible MucoAdhesive (BEMA®) delivery technology. This technology consists of flexible, water soluble polymeric film which adheres to the buccal mucosa and dissolves. Buprenorphine HCl is incorporated into the mucoadhesive layer of the film. At the end of the administration, there is no residual film to be removed from the mucosa. It is noted that Belbuca utilizes the same BioErodible MucoAdhesive (BEMA®) technology platform that was used by BDSI to develop the products such as Onsolis® (fentanyl buccal soluble film) and BUNAVAIL™ (buprenorphine and naloxone buccal film).

The Applicant developed several formulations (Table 4; % W/W). However, two (2) formulations ((b) (4) and (b) (4) Table 5) were further developed and used in clinical studies, including pharmacokinetic and Phase 3 clinical studies. Belbuca contains 75 µg, 150 µg, 300 µg, 450 µg, 600 µg, 750 µg, and 900 µg of buprenorphine per film. (b) (4) The same formulations were used for manufacturing of registration and production scale batches and will be used for commercial product.

The (b) (4) and (b) (4) formulations differ (b) (4)

It is noted that Study BUP-150, a QT study, utilized (b) (4) 2 x 1500 µg films). Although this study did not use the to-be-marketed formulations, (b) (4) and/or (b) (4) the exposure information obtained from 3000 µg single dose may be of usefulness in assessing the overall safety perspective. Therefore, a brief description of the study is provided in Section 2.2.4. The comparison of (b) (4) to either (b) (4) or (b) (4) appears to indicate that the difference is minimal in nature. (b) (4)

Table 4 Composition of Buprenorphine HCl Buccal Film Developmental Formulations (%w/w)

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(b) (4)

Sizes of the patches for strengths are displayed in Table 7.

Table 7 Formulation strengths and sizes

Formulation	Strength (µg)	Appearance	Size (cm^2)
(b) (4)	75	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E0' printed on the white to off-white side.	1.215
	150	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E1'printed on the white to off-white side.	2.431
	300	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E3' printed on the white to off-white side.	0.934
	450	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E4' printed on the white to off-white side.	1.400
	600	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E6' printed on the white to off-white side.	1.867
	750	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E7' printed on the white to off-white side.	2.334
	900	A rectangular unit with rounded corners, light yellow to yellow on one side and white to off-white on the other side. With black ink marking 'E9' printed on the white to off-white side.	2.801

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

Buprenorphine has partial agonist properties at mu opioid receptors and at ORL-1 (nociceptin) receptors and antagonist properties at kappa opioid receptors. The fundamental clinical actions are thought to result from high affinity binding to, and slow dissociation from, mu opioid receptors.

The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (b) (4)

2.1.4 What are the proposed dosage and route of administration?

The route of administration is via the buccal mucosa (oral cavity). The following are the proposed doing regimen:

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

The efficacy of Belbuca was assessed in 3 enriched enrollment, randomized withdrawal, placebo-controlled Phase 3 clinical studies (BUP-301, EN3409-307 and EN3409-308). Studies EN3409-307 and EN3409-308 are considered as pivotal studies. Study BUP-301 was conducted in both opioid-experienced and opioid-naïve subjects, which served as preliminary study to Studies EN3409-307 and EN3409-308. Study EN3409-307 was conducted in opioid-experienced subjects whereas Study EN3409-308 was conducted in opioid-naïve subjects. All studies employed subjects with chronic low back pain (CLBP). The reader is referred to medical officer's review for in depth discussion and assessment of the Phase 3 program.

Study EN3409-307 was a double-blind, placebo-controlled, enriched enrollment, randomized withdrawal study, evaluating the efficacy of buprenorphine HCl buccal film doses ranging from 150 to 900 µg in a population of subjects with CLBP, who were opioid experienced. Study EN3409-308 was a double-blind, placebo controlled, enriched enrollment, randomized withdrawal study, evaluating the efficacy of buprenorphine HCl buccal film doses ranging from 75 to 450 µg in a population of subjects with CLBP, who were opioid naive.

The following table (Table 8) presents the summary description of Phase 3 studies.

Table 8 Description of Completed Phase III Clinical Efficacy Studies

Protocol No.	Number of Study Centers Location(s) Study Start Date	Design and Control Type	Dose, Route and Regimen	Number of Subjects Planned and Randomized	Primary Study Objective	Treatment Duration	Gender Median Age (Range)	Diagnosis	Primary Efficacy Endpoint
BUP-301	24 centers United States 17-Nov-2010	Double-blind, placebo-controlled, multicenter, randomized	Open-label titration: buprenorphine (60/120/180/240 µg) Double-blind: buprenorphine (60/120/180/240 µg) placebo	Planned: 204 Randomized: 235	To determine the efficacy of twice daily dosing of buprenorphine HCl buccal film	4 weeks open-label titration + 12 weeks double-blind +2 weeks follow-up	183F/147M 51.0 (19-89) years	Opioid-naïve and opioid-experienced subjects with moderate to severe CLBP	Change from double-blind baseline to week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores
EN3409-307	66 centers United States 6-Sep-2012	Double-blind, placebo-controlled, multicenter, randomized	Open-label titration: buprenorphine (150/300/450/600/750/900 µg) Double-blind: buprenorphine (150/300/450/600/750/900 µg) Placebo	Planned: 500 Randomized: 511	To determine the analgesic efficacy of buprenorphine HCl buccal film Q12h	up to 4 weeks analgesic taper + up to 8 weeks open-label titration + 12 weeks double-blind + 2 weeks follow-up	266F/225M 53.3 (23-79) years	Opioid-experienced subjects with moderate to severe CLBP	Change from double-blind baseline to week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores
EN3409-308	60 centers United States 8-Aug-2012	Double-blind, placebo-controlled, multicenter, randomized	Open-label titration: buprenorphine (75/150/300/450 µg) Double-blind: buprenorphine (150/300/450 µg) placebo	Planned: 444 Randomized: 462	To determine the analgesic efficacy of buprenorphine Q12h	up to 8 weeks open-label titration + 12 weeks double-blind + 2 weeks follow-up	231F/189M 49.9 (19-82) years	Opioid-naïve subjects with moderate to severe CLBP	Change from double-blind baseline to week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores

CLBP=Chronic low back pain; F=Female; M=Male; Q12h=Every 12 hours

A full list of efficacy variables studied in the Phase 3 studies are presented in Table 9. The primary efficacy variable was the change from the double-blind baseline to week 12 in the mean of average daily pain intensity scores.

Table 9 Efficacy Variables in the Phase III Studies

	BUP-301	EN3409-307	EN3409-308
Primary Efficacy Variable			
Change from double-blind baseline to week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores	x	x	x
Secondary Efficacy Variables			
Proportion of responders	x	x	x
Rescue medication use	x	x	x
Time to optimal dose of open-label study medication		x	x
Time to treatment failure	x	x	x
Patient-reported outcome measures			
Patient Global Impression of Change questionnaire	x	x	x
Roland-Morris Disability Questionnaire	x	x	x
Medical Outcomes Score Sleep Subscale		x	x
Treatment Satisfaction Questionnaire for Medication	x		
Overall satisfaction with study drug by subject and investigator	x		

The Applicant stated that both pivotal efficacy studies met their primary and secondary efficacy endpoints. The Applicant presented the following information on their efficacy assessments (primary endpoint; also see Table 10 below).

Applicant's findings:

Study EN3409-307:
For the primary efficacy endpoint, the buprenorphine group showed a statistically significantly (P<0.00001) smaller mean change in numerical rating scale (NRS) pain intensity score from baseline to week 12 of the double-blind treatment phase compared with the placebo group, with a least squares mean treatment difference of -0.98 (2-sided 95% confidence interval [CI], -1.32 to -0.64) for the ITT population excluding subjects at site 1008. The results of the primary efficacy analysis were supported by consistent results for analyses for the PP population and the sensitivity analyses using the mixed-effects model repeated measures (MMRM), last observation carried forward (LOCF), and baseline observation carried forward (BOCF) methods. A treatment difference favoring the buprenorphine group compared with the placebo group was observed at each week in the double-blind treatment phase for the ITT population excluding subjects at site 1008 (week 1 -0.68; week 2 -0.80, week 3 -0.88, week 4 -0.97, week 5 -1.04, week 6 -1.05, week 7 -1.17, week 8 -1.25, week 9 -1.13, week 10 -1.12, week 11 -1.12, and week 12 -1.15). The weekly change from baseline in NRS pain intensity scores was smaller for subjects in each of the 6 buprenorphine dose strata than for subjects receiving matching placebo at each week during the double-blind treatment phase, except for the 150-µg level at week 1 and weeks 3 through 6. The least square mean difference (95% CI) compared to placebo in the change from baseline to week 12 was 0.25 (-1.51 to 2.01) for buprenorphine 150 µg, -0.46 (-1.40 to 0.48) for buprenorphine 300 µg, -0.64 (-1.53 to 0.25) for buprenorphine 450 µg, -2.02 (-3.00 to -1.04) for buprenorphine 600 µg, -0.74 (-1.79 to 0.31) for buprenorphine 750 µg, and -1.08 (-1.69 to -0.48) for buprenorphine 900 µg for the ITT population excluding subjects at site 1008.

Study EN3409-308:
The buprenorphine group showed a statistically significantly (P=0.0012) smaller mean change in NRS pain intensity score from baseline to week 12 of the double-blind treatment phase compared with the placebo group, with a mean treatment difference of -0.67 (95% CI, -1.07 to -0.26) for the ITT population excluding subjects at site 1008. The results of the primary efficacy analysis were supported by consistent results for the ITT population without site 1008 excluded, the PP population analysis, and the sensitivity analyses using the mixed-effects model repeated measures (MMRM), last observation carried forward (LOCF), and baseline observation carried forward (BOCF) methods. A treatment difference favoring the buprenorphine group compared with the placebo group was observed at each week in the double-blind treatment phase for the ITT population excluding subjects at site 1008. The weekly change from baseline in NRS pain intensity scores was smaller for subjects in each of the 3 buprenorphine dose strata than for subjects receiving matching placebo at each week during the double-blind treatment phase. The least squares mean difference (95% CI) compared to placebo in the change from baseline to week 12 was -0.24 (-1.04 to 0.57) for buprenorphine 150 µg, -1.04 (-1.73 to -0.35) for buprenorphine 300 µg, and -0.79 (-1.45 to -0.14) for buprenorphine 450 µg.

Table 10 Change from Double-Blind Baseline to Week 12 in Average Numerical Rating Scale Pain Intensity in Double-blind Treatment Phase of the Individual Phase 3 Studies (ITT Population, Subjects at Site 1008 Excluded)

	BUP-301		EN3409-307		EN3409-308	
Visit	Buprenorphine (N=117)	Placebo (N=118)	Buprenorphine (N=254)	Placebo (N=256)	Buprenorphine (N=229)	Placebo (N=232)
Prior to Open-label Titration[a]						
N	3.23 (1.194)	3.26 (1.217)	243	248	209	211
Mean (SD)	3.43	3.43	6.79 (1.280)	6.64 (1.323)	7.12 (1.058)	7.18 (1.050)
Median	0.0, 5.1	0.0, 5.1	6.86	6.71	7.29	7.17
Minimum, Maximum	3.23 (1.194)	3.26 (1.217)	3.0, 10.0	2.7, 10.0	5.0, 10.0	5.0, 9.7
Baseline[b]						
N	117	118	243	248	209	211
Mean (SD)	3.23 (1.194)	3.26 (1.217)	2.91 (0.985)	2.84 (1.051)	2.82 (1.014)	2.79 (1.122)
Median	3.43	3.43	3.00	3.00	3.00	3.00
Minimum, Maximum	0.0, 5.1	0.0, 5.1	0.0, 4.7	0.0, 6.5	0.0, 4.6	0.0, 6.1
Week 12 (Imputed)[c]						
N	117	118	243	248	209	211
Mean (SD)	3.57 (1.879)	3.72 (2.229)	3.80 (1.732)	4.75 (1.777)	3.76 (1.941)	4.39 (2.004)
Median	3.67	3.87	3.73	4.60	3.67	4.14
Minimum, Maximum	0.0, 8.6	0.0, 8.9	0.0, 9.6	0.0, 10.0	0.0, 8.6	0.0, 9.0
Change from Baseline (Imputed)						
N	117	118	243	248	209	211
Mean (SD)	0.33 (1.944)	0.46 (2.093)	0.88 (1.785)	1.92 (1.867)	0.94 (1.846)	1.59 (2.040)
Median	0.00	0.14	0.46	1.58	0.67	1.33
Minimum, Maximum	-3.7, 6.6	-4.7, 5.0	-3.0, 8.9	-2.3, 8.3	-3.2, 7.2	-3.9, 7.0
Difference (95% CI) vs Placebo	-0.14 (-0.646, 0.366)		-0.98 (-1.32, -0.64)		-0.67 (-1.07, -0.26)	
P value	0.5870[d]		<.00001[e]		0.0012[f]	

Data Source: BUP-301 CSR [Table 24 and Table 14.1.6.2], EN3409-307 CSR [Table 14.2.1.1], and EN3409-308 CSR [Table 14.2.1.1]

[a] Average of the subject diary NRS Pain Intensity measurements in the week prior to randomization for BUP-301, and the mean of pain intensity on the last 7 days before taking study medication prior to open-label titration phase.

[b] Baseline is defined as the mean of pain intensity on the last 7 days before taking study medication prior to the randomization date.

[c] Subjects with missing weekly subject diary data had their values imputed by multiple imputation methodology. Prior to multiple imputation, last observation carried forward (LOCF) was used to impute missing data for subjects prematurely discontinued due to lack of efficacy, screening observation carried forward (SOCF) was used for subjects prematurely discontinued due to adverse events, and baseline observation carried forward (BOCF) was used for subjects discontinued due to opiate withdrawal.

[d] *P* value is generated from *t* test for significance of treatment difference using PROC MIANALYZE by combining results from analysis of covariance (ANCOVA) model with change from baseline as the dependent variable, treatment as a factor and baseline value as a covariate from 5 imputed datasets.

[e] *P* value, treatment difference estimate, and 95% CI are calculated using Cui-Hung-Wang/Lawrence-Hung methods. After imputations, the ANCOVA model are performed with change from baseline as the dependent variable, treatment as a fixed effect and screen and baseline value as covariates from 10 imputed datasets.

[f] *P* value, treatment difference estimate, and 95% CI are calculated using PROC MIANALYZE by combining results from ANCOVA model, performed with change from baseline as the dependent variable, treatment as a fixed effect and screen and baseline value as covariates from 10 imputed datasets.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to II. F, Analytical Section; if no, describe the reasons)

Yes. See Analytical Section 2.6.

2.2.3 Exposure-response

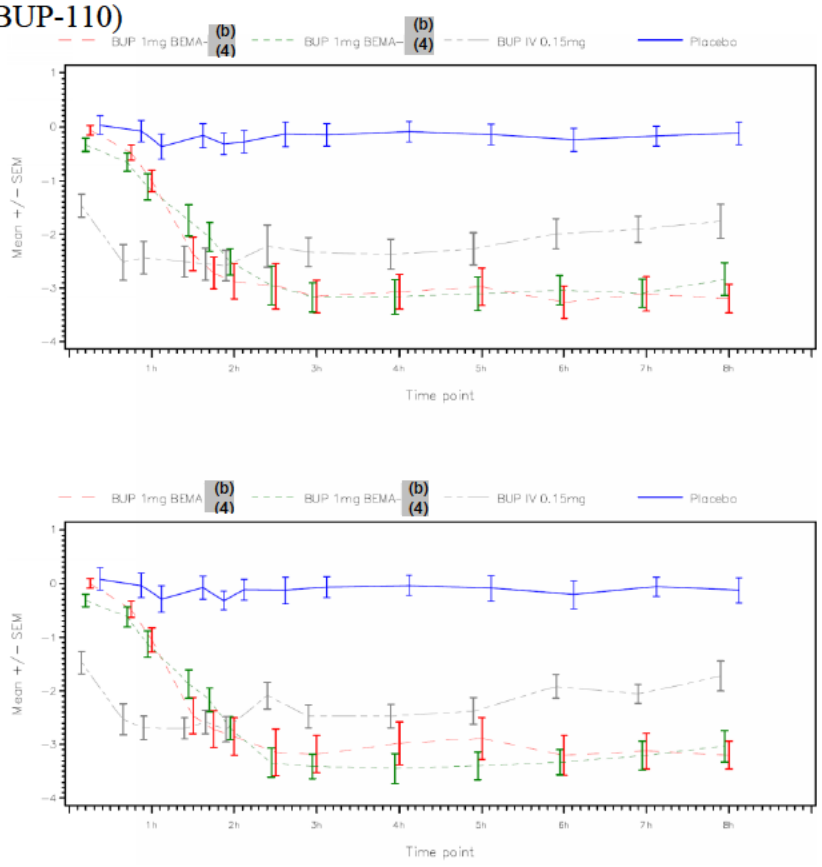
2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

No analgesic PK/PD characterizations (dose-response or concentration-response relationships) were conducted with the to-be-marketed formulations, (b) (4) and (b) (4) In Study BUP-10, however, Formulations (b) (4) and (b) (4) were examined in terms of overall PK (1000 µg single dose) and PD properties (e.g., pupillometry, thermal pain threshold, visual analog scale (VAS) nausea, and Tufts Addiction Research Center Inventory Morphine Benzedrine Group (ARCI-MBG) for euphoria). The study included 150 µg IV buprenorphine (single dose) and placebo treatments. Plasma samples were obtained at pre-dose, 0.25, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours post administration of buprenorphine.

Pupillometry:

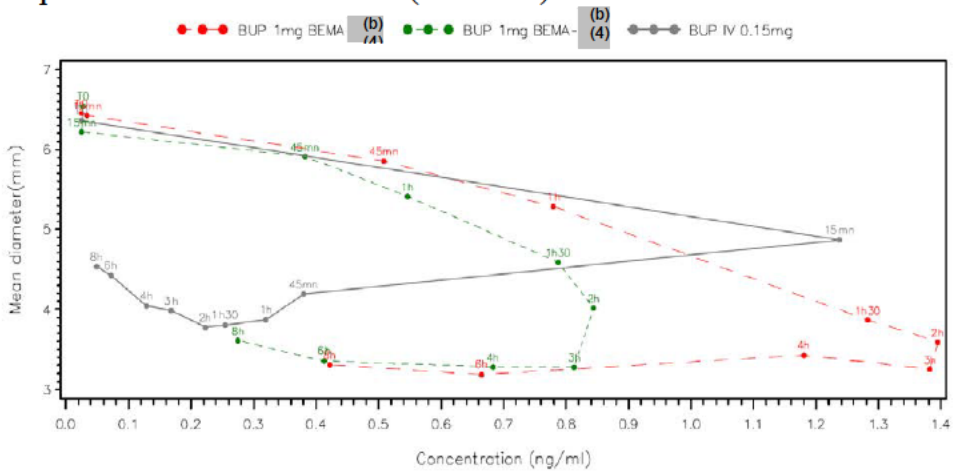
Pupil diameter was reduced (miosis) by all buprenorphine treatments (Figure 1). Pupil diameter decreased rapidly by 2.53 and 2.60 mm in the first 45 minutes after IV buprenorphine 150 μ g. The maximum mean decreases in pupil diameter were 2.53 and 2.67 mm observed at 0.75 and 2.0 hours, in the left and right eye, respectively, with very little reversal by 8 hours (1.90 and 1.80 mm median decrease).

Figure 1 Change in Pupil Size in Left Eye (Upper Figure) and Right Eye (Lower Figure) Expressed as Mean ± SEM (BUP-110)



Additionally, looking at the concentration-pupillometry relationship, pupil diameters were significantly decreased with increasing buprenorphine concentrations (Figure 2).

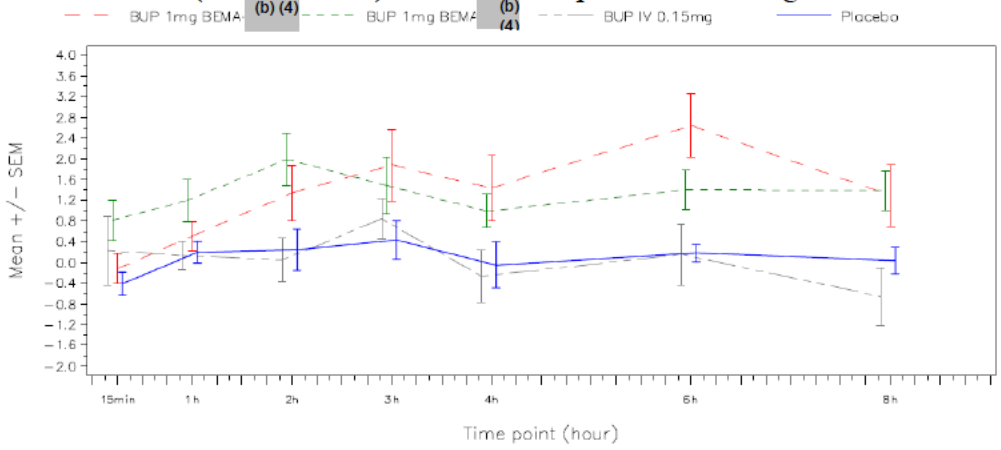
Figure 2 Pupillometry PK/PD Relationship: Hysteresis Curves of Mean Diameter (mm) Versus Mean Buprenorphine Plasma Concentration (BUP-110)



Thermal Pain Threshold:

Thermal pain threshold was increased by all buprenorphine treatments (Figure 3). Thermal pain threshold was significantly increased by (b) (4) starting 2 hours post dosing and by (b) (4) starting 1 hour post dosing.

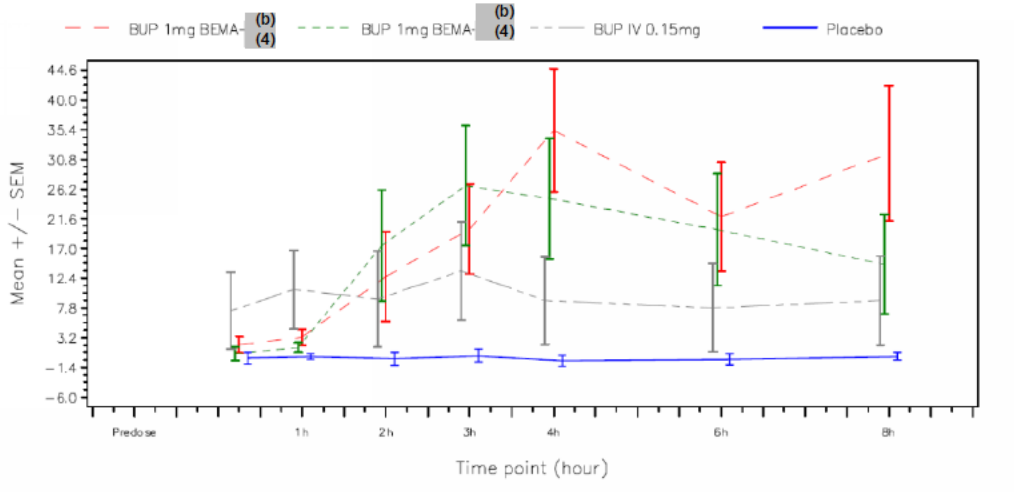
Figure 3 Pain Threshold (Mean ± SEM) Over Time Expressed as Change from Baseline



Visual Analog Scale (VAS) Nausea:

Nausea was increased by all buprenorphine treatments (Figure 4). Nausea was significantly increased by (b) (4) starting 3 hours post dosing and by (b) (4) starting 2 hours post dosing.

Figure 4 VAS Nausea Scores (Mean ± SEM) Over Time Expressed as Change from Baseline (BUP-110)



Addiction Research Center Inventory Morphine Benzedrine Group (ARCI-MBG) (Euphoria):
ARCI-MBG scores indicted that mood tended to be reduced after buprenorphine doses. Overall, only (b) (4) significantly depressed mood, compared to placebo. Neither IV buprenorphine 150 µg nor (b) (4) resulted in a significantly different effect than placebo. The comparison between buprenorphine HCl buccal film formulation (b) (4) versus placebo (P=0.0304) indicated that the mood score tended to be lower 4 and 6 hours post (b) (4) administration (Table 11).

Table 11 Summary of Statistically Significant Results on Tufts ARCI-MBG Scale (BUP-110)

Time (hours)	Main Time Effect (*P* Value)	Treatment Time Interaction (*P* Value)	Main Treatment Effect (*P* Value)	Contrasts Versus Placebo (*P* Value)		
				IV Buprenorphine 150 µg	***1000 µg Buprenorphine HCl Buccal Film*** (b) (4)	1000 µg Buprenorphine HCl Buccal Film (b) (4)
Overall	<0.001	NS	0.0360	NS	***0.0304***	NS
4.0				NS	***0.0489***	NS
6.0				NS	***0.0234***	NS
8.0				NS	***(0.0616)***	NS

2.2.3.2 Does this drug prolong the QT or QTc interval?

Study BUP-150 was a double-blind, placebo- and positive-controlled, randomized, 4-period crossover, single dose study to evaluate the effects of buprenorphine HCl buccal film on cardiac repolarization in healthy subjects. It is noted that (b) (4) not a to-be-marketed formulation, was used in this study. However, as briefly discussed in Section 2.1.2, Formulations, the differences between (b) (4) and (b) (4) (b) (4) seem to be minimal. Thus, a cursory review was conducted in order to obtain the buprenorphine exposure information from 3000 µg single dose, which can be used in

assessing the overall safety exposure information (e.g., comparison of 900 µg and 3000 µg exposures).

Subjects received each of the 4 treatments (following) in 1 of 4 sequences:

- Treatment A: Buprenorphine HCl buccal film 3000 µg formulation (b) (4) (2 × 1500 µg films) on day 1 with 4 doses of naltrexone 50 mg (over encapsulated), starting on the evening of day 0
- Treatment B: Placebo buccal film on day 1 with 4 doses of naltrexone 50 mg (over encapsulated), starting on the evening of day 0
- Treatment C: Placebo buccal film on day 1 with 4 doses of naltrexone placebo (over encapsulated), starting on the evening of day
- Treatment D: Moxifloxacin 400 mg (open label) on day 1 with 4 doses of naltrexone placebo (over encapsulated), starting on the evening of day 0

Oral naltrexone was co-administered to protect the subjects from potential opioid-induced AEs. Naltrexone was administered with placebo treatment group in order to control for naltrexone effects. Subjects were confined during each treatment periods. There was a washout period of at least 14 days between treatments. Continuous Holter 12-lead ECGs were recorded beginning on the afternoon of 2 days before dosing until 24 hours post dosing (the morning of the day after dosing). On the day of dosing, ECGs were collected at 45, 30, and 15 minutes before dosing and at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. Post drug/placebo heart rate-corrected QTc intervals were referenced to baseline pre-drug/placebo data. During each study period, blood samples were collected before dosing and at 1, 2, 3, 4, 6, 8, 12, and 24 hours post dosing. The reader is referred to IRT's review for in depth discussion and assessment of the findings from this study.

The following results were presented by the Applicant. Mean plasma concentrations of buprenorphine and norbuprenorphine versus time are presented in Figure 5 and Figure 6, respectively.

Figure 5 Mean (± SD) Plasma Concentrations of Buprenorphine Versus Time (PK Population)

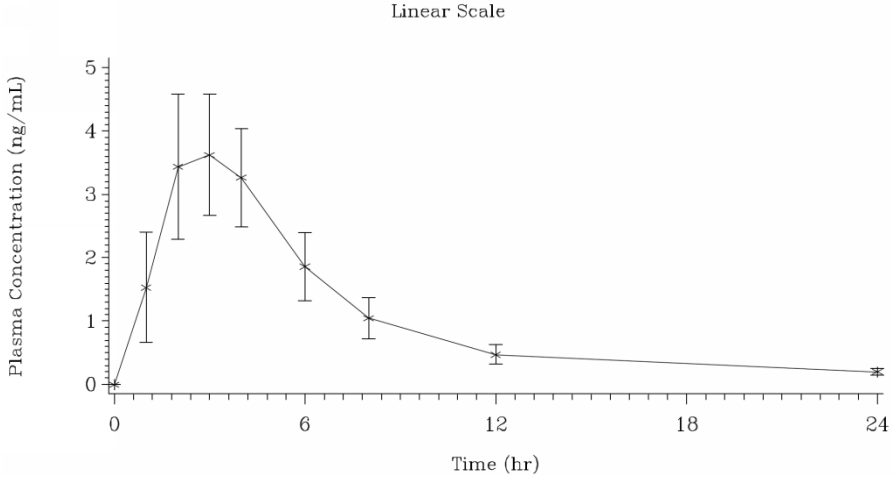
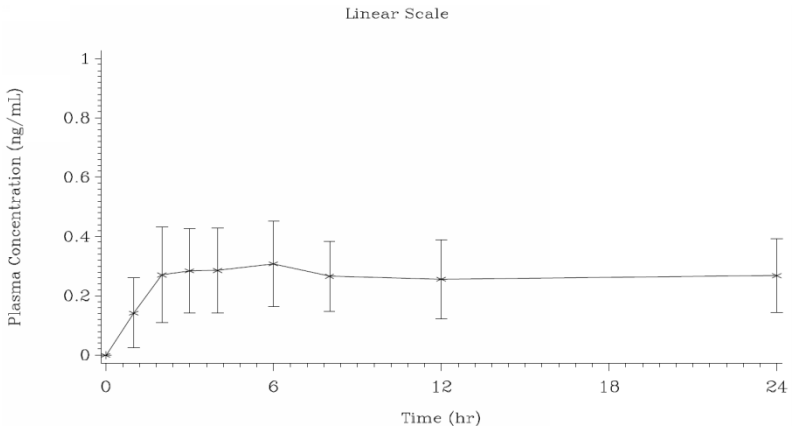


Figure 6 Mean (± SD) Plasma Concentrations of Norbuprenorphine Versus Time (PK Population)



Plasma PK parameters of buprenorphine and norbuprenorphine are summarized in Table 12 and Table 13, respectively.

Table 12 Mean (CV) Plasma Pharmacokinetic Parameters of Buprenorphine (PK Population)

Parameters (unit)[a]	**BEMA Buprenorphine With Naltrexone**[b] **(N = 54)**
$AUC_{0\text{-}24}$ (ng·hr/mL)[c]	25.3 (19)[d]
C_{max} (ng/mL)[c]	3.66 (26)
C_t (ng/mL)[c]	0.194 (22)
T_{max} (hr)[e]	3.17 (2.17, 4.18)

a Source Data: Table 14 2 2 1
b BEMA Buprenorphine with Naltrexone = BEMA Buprenorphine 3 mg with 4 doses of naltrexone 50 mg (Treatment A)
c Geometric mean was determined for $AUC_{0\text{-}24}$, C_{max}, and C_t
d N = 53; $AUC_{0\text{-}24}$ could not be estimated for Subject 129
e Median (minimum, maximum)

Table 13 Mean (CV) Plasma Pharmacokinetic Parameters of Norbuprenorphine (PK Population)

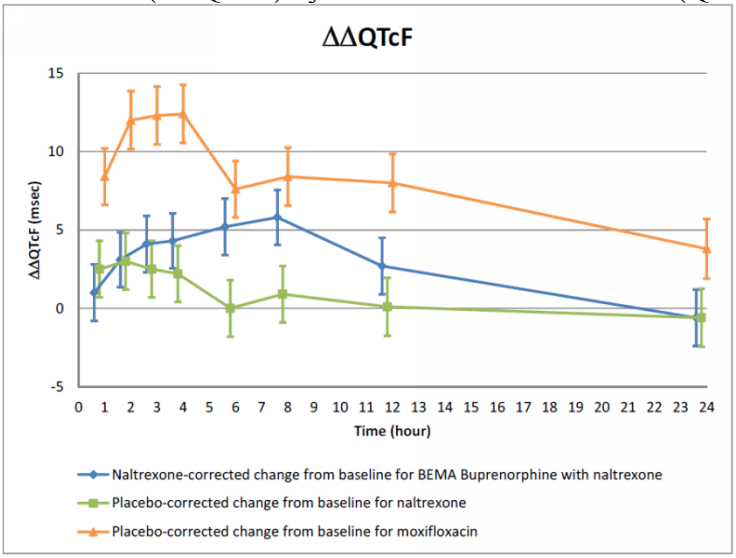
Parameters (unit)[a]	**BEMA Buprenorphine With Naltrexone**[b] **(N = 54)**
$AUC_{0\text{-}24}$ (ng·hr/mL)[c]	5.51 (46)
C_{max} (ng/mL)[c]	0.316 (47)
C_t (ng/mL)[c]	0.239 (46)
T_{max} (hr)[d]	6.17 (2.17, 24.25)

a Source Data: Table 14 2 2 2
b BEMA Buprenorphine with naltrexone = BEMA Buprenorphine 3 mg with 4 doses of naltrexone 50 mg (Treatment A)
c Geometric mean was determined for $AUC_{(0\text{-}24)}$, C_{max}, and C_t
d Median (minimum, maximum)

The mean naltrexone-corrected, change from baseline QTcF (ΔΔQTcF) after Belbuca with naltrexone reached 5.2 msec at 6 hours and 5.8 msec at 8 hours, with an upper bound of the 90% 2-sided CI of 7.0 msec and 7.5 msec, respectively (Figure 7 and Table 14). Naltrexone alone did not

have an effect on the placebo-corrected ΔQTcF (ΔΔQTcF). Moxifloxacin showed the largest mean ΔΔQTcF of 12.0 to 12.4 msec between 2 and 4 hours.

Figure 7 Placebo- or Naltrexone-Corrected, Change From Baseline QTc Using Fridericia's Correction (ΔΔQTcF) by Treatment and Time Point (QT/QTc Population)



BEMA Buprenorphine with naltrexone = BEMA Buprenorphine 3 mg with 4 doses of naltrexone 50 mg (Treatment A); Naltrexone = BEMA placebo with 4 doses of naltrexone 50 mg (Treatment B); Placebo = BEMA placebo with 4 doses of naltrexone placebo (Treatment C); Moxifloxacin = moxifloxacin 400 mg (open label) with 4 doses of naltrexone placebo (Treatment D). Note: ΔΔQTcF for BEMA Buprenorphine = ΔQTcF on Treatment A − ΔQTcF on Treatment B; ΔΔQTcF for naltrexone = ΔQTcF on Treatment B − ΔQTcF on Treatment C; ΔΔQTcF for moxifloxacin = ΔQTcF on Treatment D − ΔQTcF on Treatment C.

Table 14 Placebo- or Naltrexone-Corrected, Change From Baseline QTc Using Fridericia's Correction (ΔΔQTcF) by Treatment and Time Point (QT/QTc Population)

Time Point (hour)	Treatment[a]								
	BEMA Buprenorphine With Naltrexone[b]			Naltrexone[c]			Moxifloxacin[d]		
	Mean (msec)	SE	90% CI	Mean (msec)	SE	90% CI	Mean (msec)	SE	90% CI
1	1.0	1.1	−0.8, 2.8	2.5	1.1	0.7, 4.3	8.4	1.1	6.6, 10.2
2	3.1	1.1	1.4, 4.9	3.0	1.1	1.2, 4.8	12.0	1.1	10.1, 13.8
3	4.1	1.1	2.3, 5.9	2.5	1.1	0.7, 4.3	12.3	1.1	10.5, 14.2
4	4.3	1.1	2.6, 6.1	2.2	1.1	0.4, 4.0	12.4	1.1	10.5, 14.2
6	5.2	1.1	3.4, 7.0	0.0	1.1	−1.8, 1.8	7.6	1.1	5.8, 9.4
8	5.8	1.1	4.0, 7.5	0.9	1.1	−0.9, 2.7	8.4	1.1	6.6, 10.3
12	2.7	1.1	0.9, 4.5	0.1	1.1	−1.8, 1.9	8.0	1.1	6.1, 9.8
24	−0.6	1.1	−2.4, 1.2	−0.6	1.1	−2.4, 1.3	3.8	1.1	1.9, 5.7

a BEMA Buprenorphine with naltrexone = BEMA Buprenorphine 3 mg with 4 doses of naltrexone 50 mg (Treatment A); Naltrexone = BEMA placebo with 4 doses of naltrexone 50 mg (Treatment B); Placebo = BEMA placebo with 4 doses of naltrexone placebo (Treatment C); Moxifloxacin = moxifloxacin 400 mg (open label) with 4 doses of naltrexone placebo (Treatment D) b ΔΔQTcF for BEMA Buprenorphine = ΔQTcF on Treatment A − ΔQTcF on Treatment B c ΔΔQTcF for naltrexone = ΔQTcF on Treatment B − ΔQTcF on Treatment C d ΔΔQTcF for moxifloxacin = ΔQTcF on Treatment D − ΔQTcF on Treatment C Abbreviations: CI = confidence interval; SE = standard error

The QT-Interdisciplinary Review Team's (IRT) review indicated that 'no significant QTc prolongation effect of BEMA Buprenorphine was detected in this TQT study" (IND 72428, dated 6/19/13). The following excerpts are from the review:

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of BEMA Buprenorphine was detected in this TQT study. The largest upper bound of the 2-sided 90% CI's for the mean differences between BEMA Buprenorphine and placebo is below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI's for the ΔΔQTcF effect for moxifloxacin is greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 48 healthy subjects received Buprenorphine with naltrexone, Buprenorphine placebo with naltrexone, Buprenorphine placebo with naltrexone placebo, and a single oral dose of moxifloxacin 400 mg with naltrexone placebo. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BEMA Buprenorphine and Naltrexone and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Buprenorphine 3 mg	8	5.8	(3.6, 8.0)
Naltrexone 200 mg	2	2.9	(1.4, 4.4)
Moxifloxacin 400 mg *	2	12.4	(10.9, 13.9)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.3 ms.

The supratherapeutic dose (3 mg) produces mean C_{max} values of 2.4-fold higher than the mean Cmax for the therapeutic dose (1 mg). These concentrations are above those for the predicted worst case scenario (drug interaction with atanazavir) and show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of buprenorphine with atanazavir can elevate buprenorphine's mean Cmax as much as 1.6-fold higher than the Cmax of the 1 mg dose.

Additionally QT-IRT assessment based on the range of doses and QT prolongation, the review stated that "marginal clinically relevant QTc prolongation (comparable to that at 40 µg/h of Butrans) may occur for BEMA with doses of 600 µg q12h or above" (NDA 207932 dated 6/18/15). The following excerpts are from the review:

QT-IRT Comments for DAAAP

Please estimate the expected QT prolongation for the entire range of proposed doses (75 ug q12 h, 150 mcg q 12 h, 300 mcg q12h, 450 mcg q12h, 600 mcg q12h, 750 mcg q12h and 900 mcg q12h) based on the buprenorphine concentration-QTc relationship observed from the data available to the Agency on buprenorphine and include the QT prolongation from the 10 mcg/h, 20 mcg/h, 40 mcg/h, and 80 mcg/h doses of transdermal buprenorphine for comparison to aid us in our risk-benefit assessment and regulatory decision making. Please recommend language for labeling the QT effect.

QT-IRT's response: According to the exposure-response relationship between buprenorphine concentration (b) (4)

different QTc effects were predicted in the following table at various interested mean C_{max-ss} concentrations. Because of the uncertainty associated with provided mean C_{max} values, marginal clinically relevant QTc prolongation (comparable to that at (b) (4) may occur for BEMA with doses of 600 ug q12h or above.

Table 1: Predicted QTc Effect s at Various Clinically Relevant Concentrations.

At Interested Mean $Cmax_{ss}$ (ng/mL)	Predicted Placebo-Adjusted QTc Change from Baseline (ms)	
	Mean	90%CI upper bound
0.096 at 75 ug q12h of BEMA	0.6226	0.7352
0.196 at 150 ug q12h of BEMA	1.2711	1.5011
0.388 at 300 ug q12h of BEMA	2.5163	2.9715
0.533 at 450 ug q12h of BEMA	3.4567	4.082
0.723 at 600 ug q12h of BEMA	4.6889	5.5371
0.953 at 750 ug q12h of BEMA	6.1806	7.2985
1.121 at 900 ug q12h of BEMA	7.2701	8.5851
(b) (4)	(b) (4)	

2.2.4 What are the PK characteristics of the drug and its major metabolite?

The following buprenorphine general information is presented in the package inserts of listed references for this application, Buprenex and Subutex.

Distribution
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Metabolism
Buprenorphine undergoes both *N*-dealkylation, primarily by CYP3A4, to norbuprenorphine and glucuronidation by UGTisozymes (predominantly UGT1A1 and 2B7) to buprenorphine 3β-*O*-glucuronide. Norbuprenorphine, the major metabolite, can also undergo glucuronidation mainly via UGT1A3 prior to excretion. Norbuprenorphine has been found to bind to several opioid receptors *in vitro*; however, it has not been studied clinically for opioid-like activity.

2.2.4.1 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Single-dose:

Study BUP-115

Study BUP-115 was an open-label, single-dose, parallel-group study in healthy subjects. This study examined the exposure of 3 buprenorphine doses (200, 500, and 1500 µg) from 3 different

formulations of buprenorphine HCl buccal film [redacted] (b) (4) and [redacted] (b) (4) respectively). Additionally there was a 2-minute IV injection of 150 µg buprenorphine in 0.5 mL. Naltrexone was coadministered with the intermediate and high doses of BEMA Buprenorphine and with Buprenex. Blood samples were collected for determination of buprenorphine and norbuprenorphine plasma concentrations at pre-dose, 15, 30, 45, 60, 90, and 120 minutes, and 3, 4, 6, 8, 12, 16, 24, and 48 hours post dose. The buprenorphine information obtained from [redacted] (b) (4) and intravenous injection will be presented.

The mean buprenorphine and norbuprenorphine concentrations are plotted in Figure 8 and Figure 9, respectively.

Figure 8 Mean Buprenorphine Concentration-Time Data after Buprenorphine 0.2 mg BEMA Buccal Soluble Film (Treatment A), Buprenorphine 0.5 mg BEMA Buccal Soluble Film (Treatment B), Buprenorphine 1.5 mg BEMA Buccal Soluble Film (Treatment C), and Buprenex 0.15 mg Injection (Treatment D)

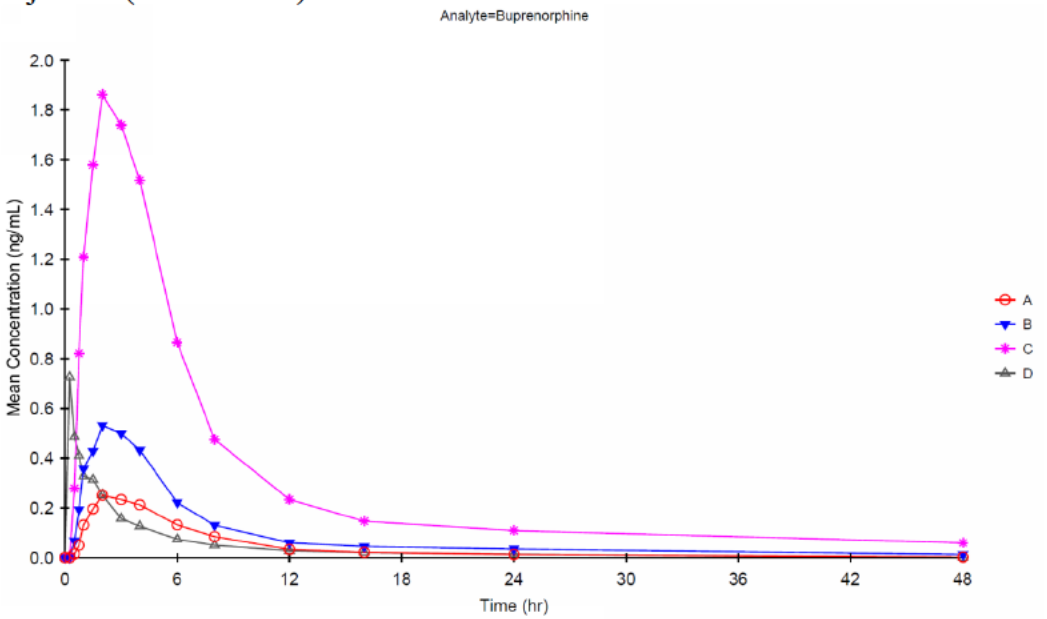
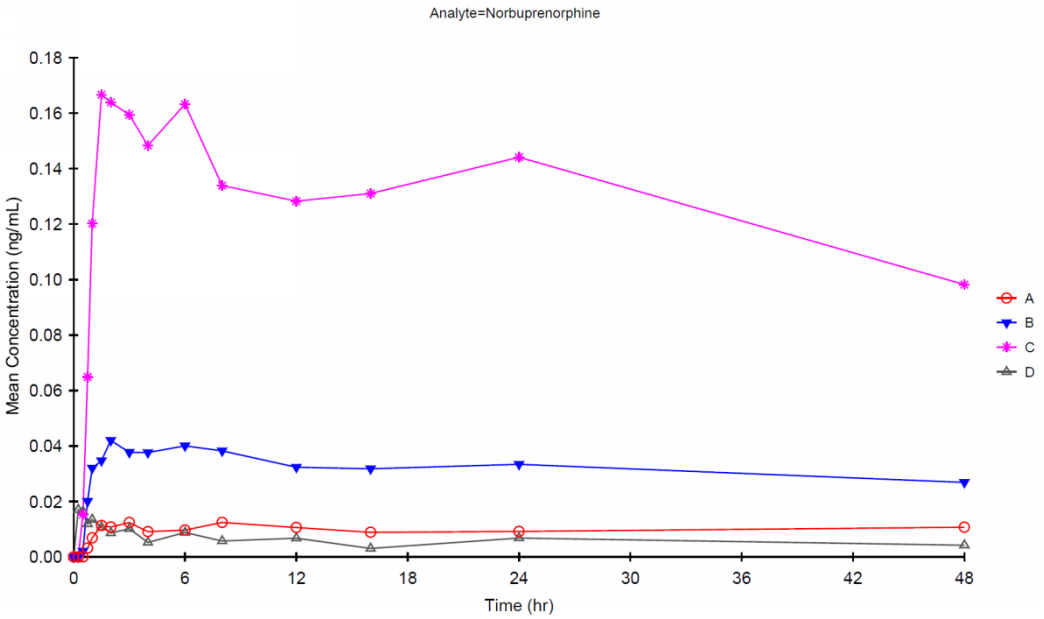


Figure 9 Mean Norbuprenorphine Concentration-Time Data after Buprenorphine 0.2 mg BEMA Buccal Soluble Film (Treatment A), Buprenorphine 0.5 mg BEMA Buccal Soluble Film (Treatment B), Buprenorphine 1.5 mg BEMA Buccal Soluble Film (Treatment C), and Buprenex 0.15 mg Injection (Treatment D)



Buprenorphine and norbuprenorphine pharmacokinetic parameters after each dose are provided in Table 15 and Table 16, respectively.

Table 15 Buprenorphine Pharmacokinetics after Single BEMA Buprenorphine Buccal and Intravenous Buprenorphine Doses Administered to Healthy Subjects-Arithmetic Mean±SD (%CV) (BUP-115)

Parameter	**BEMA Buprenorphine 500 µg ([redacted] (b) (4)) (N=8)**	**Buprenorphine IV 150 µg (N=8)**
T_{max} (h)[a]	2.00 (1.50-3.00)	0.25 (0.25-0.25)
C_{max} (ng/mL)	0.551±0.122 (22.10)	0.726±0.117 (16.07)
AUC_{0-t} (h*ng/mL)	3.802±0.8203 (21.58)	1.786±0.2859 (16.01)
AUC_{0-inf} (h*ng/mL)	4.399±1.114 (25.32)	2.026±0.2956 (14.59)
$t_{1/2}$ (h)	19.10±11.54 (60.45)	9.98±5.91 (59.26)

Data Source: 5.3.3.1, Study BUP-115 [Table 8, Table 14.2.2.1.1, Table 14.2.2.1.2, Table 14.2.2.1.3, and Table 14.2.2.1.4]
[a] Median (range).
Note: Full precision data used in pharmacokinetic analysis.

Table 16 Norbuprenorphine Pharmacokinetics after Single BEMA Buprenorphine Buccal and Intravenous Buprenorphine Doses Administered to Healthy Subjects-Arithmetic Mean±SD (%CV) (BUP-115)

Parameter	Treatment B: Buprenorphine 0.5 mg Buccal	Treatment D: Buprenex 0.15 mg Injection

	n	Mean	SD	CV%	n	Mean	SD	CV%
T_{max} (hr)	8	5.50	5.18	94.23	8	3.38	8.34	246.98
C_{max} (ng/mL)	8	0.0482	0.0183	37.84	8	0.0206	0.00868	42.17
AUC_{0-24}	8	0.8091	0.2524	31.20	8	0.1538	0.1494	97.09
AUC_{last}	8	1.411	0.5903	41.83	8	0.2371	0.2648	111.66
AUC_{inf}	8	7.135	7.925	111.07	5	1.230	1.150	93.53
$T_{1/2}$ (hr)	8	112.06	111.23	99.25	5	55.09	60.42	109.69

Note: Full precision data used in PK analysis

Study BUP-117

Study BUP-117 was an open-label, randomized, 5-sequence, 5-period design crossover study in healthy subjects. Subjects received single doses of BEMA Buprenorphine 75 µg, 300 µg (b) (4) BEMA Buprenorphine 300 µg, 1200 µg (b) (4) and intravenous buprenorphine 300 µg (Buprenex Injection) under fasted conditions. Table 17 compares (b) (4) and (b) (4) formulations used in this study. Each treatment period was separated by at least a 7-day washout period. Naltrexone (50 mg) was administered approximately 12 and 0.5 hours prior to administration of buprenorphine and again approximately 12 and 24 hours later in each treatment period. Blood samples were collected for determination of buprenorphine and norbuprenorphine plasma concentrations pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours post each dose.

Table 17 Comparison of (b) (4) and (b) (4) BEMA Formulations

(b) (4)

Plots of mean buprenorphine and norbuprenorphine concentrations versus time are provided in Figure 10 and Figure 11, respectively.

Figure 10 Mean Buprenorphine Concentration-Time Profiles after Administration of BEMA Buprenorphine Buccal Soluble Film 75 µg, Formulation (b) (4) (Treatment A); 300 µg, Formulation (b) (4) (Treatment B); 300 µg, Formulation (b) (4) (Treatment C); 1200 µg, Formulation (b) (4) (Treatment D); and Buprenorphine Injection 300 µg, (Treatment E) on Linear Scale

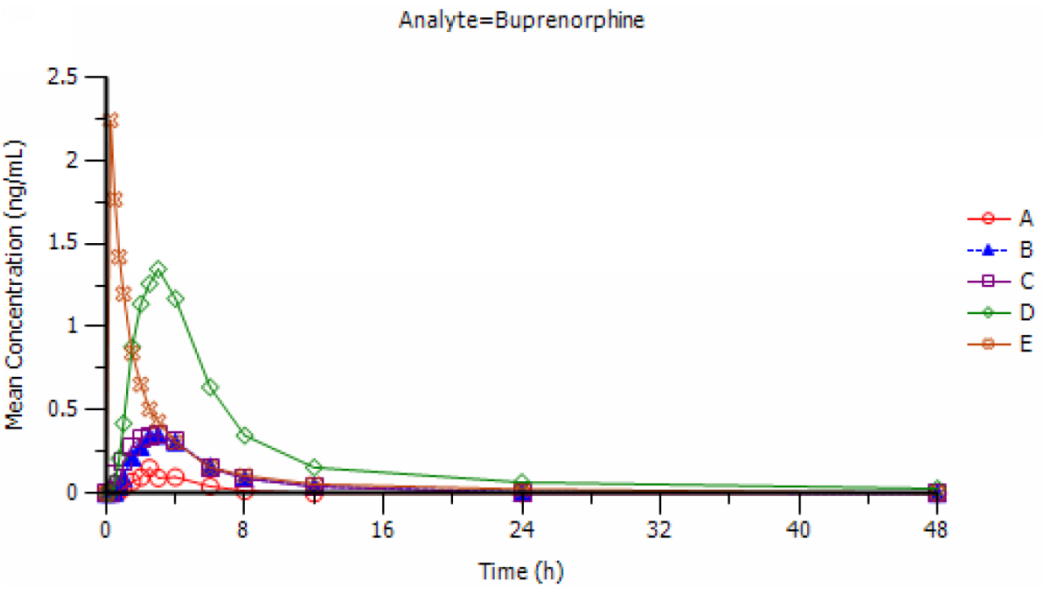
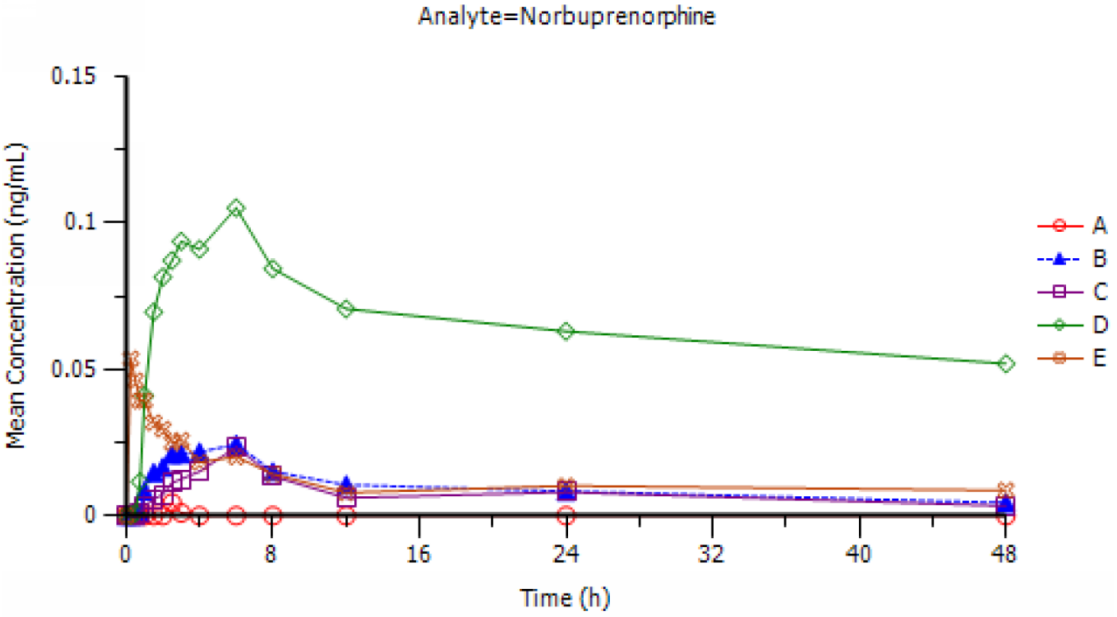


Figure 11 Mean Norbuprenorphine Concentration-Time Profiles After Administration of BEMA Buprenorphine Buccal Soluble Film 75 µg, Formulation [(b) (4)] (Treatment A); 300 µg, Formulation [(b) (4)] (Treatment B); 300 µg, Formulation [(b) (4)] (Treatment C); 1200 µg, Formulation [(b) (4)] (Treatment D); and Buprenorphine Injection 300 µg, (Treatment E) on Linear Scale



Buprenorphine and norbuprenorphine pharmacokinetic parameters after each study treatment are provided in Tables 18 and 19, and, Tables 20 and 21, respectively.

Table 18 Plasma Pharmacokinetics of Buprenorphine After Single Buccal Doses Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV)

Parameter	BEMA Buprenorphine ((b) (4) 75 µg N=23[a]	BEMA Buprenorphine ((b) (4) 300 µg N=21	BEMA Buprenorphine ((b) (4) 300 µg N=22	BEMA Buprenorphine ((b) (4) 1200 µg N=23
AUC_{last} (ng•h/mL)	0.455±0.2240 (49.2)	2.00±0.577 (28.9)	2.04±0.6754 (33.1)	9.59±2.924 (30.5)
AUC_{inf} (ng•h/mL)	0.632±0.2373 (37.5)	2.23±0.631 (28.3)	2.26±0.689 (30.5)	10.46±3.324 (31.8)
C_{max} (ng/mL)	0.172±0.303 (176)	0.367±0.0970 (26.5)	0.470±0.467 (99.4)	1.43±0.446 (31.2)
Tmax (h)[b]	3.00 (1.50-4.05)	3.00 (1.50-4.00)	2.50 (0.50-4.00)	3.00 (1.00-4.02)
C_{last} (ng/mL)	0.0495±0.0664 (134.3)	0.0377±0.00940 (24.9)	0.0405±0.0100 (24.8)	0.0398±0.0106 (26.5)
T_{last} (h)[b]	6.00 (4.00-8.00)	12.00 (12.00-24.00)	12.00 (8.00-24.00)	48.00 (24.00-48.00)
λ_z (1/h)	0.3000±0.0801 (26.7)	0.1925±0.0725 (37.7)	0.2029±0.0573 (28.3)	0.0559±0.0293 (52.4)
$t_{1/2}$ (h)	2.45±0.60 (24.4)	4.58±2.87 (62.7)	3.94±2.13 (54.1)	15.1±5.62 (37.3)
F[c]	0.486±0.1534 (31.6)	0.462±0.1788 (38.7)	0.461±0.1606 (34.9)	0.506±0.1637 (32.4)

a N=14 for AUC, λz, t½, F for BEMA Buprenorphine (b) 75 µg
b median (range)
c N=14 for BEMA Buprenorphine ((b) 75 µg, N= 21 for BEMA Buprenorphine ((b) 300 µg and ((b) 300 µg, and N=22 for BEMA Buprenorphine ((b) 1200 µg

Table 19 Plasma Pharmacokinetics of Buprenorphine After a Single 300 µg Intravenous Dose Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV)

Parameter	Buprenorphine 300 µg N=24
AUC_{last} (ng•h/mL)	4.79±1.169 (24.4)
AUC_{inf} (ng•h/mL)	5.20±1.251 (24.1)
C_{max} (ng/mL)	2.32±0.831 (35.8)
T_{max} (h)[a]	0.25 (0.25-0.50)
C_{last} (ng/mL)	0.0349±0.00616 (17.7)
T_{last} (h)[a]	24.00 (12.00-48.00)
λ_z (1/h)	0.1056±0.0590 (55.8)
$t_{1/2}$ (h)	8.62±5.15 (59.8)

a median (range)

Table 20 Plasma Pharmacokinetics of Norbuprenorphine After Single Buccal Doses of Buprenorphine Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV)

Parameter	BEMA Buprenorphine ((b) (4) 75 µg N=2[a]	BEMA Buprenorphine ((b) (4) 300 µg N=17	BEMA Buprenorphine ((b) (4) 300 µg N=18	BEMA Buprenorphine ((b) (4) 1200 µg N=23

C_{max} (ng/mL)	0.0617±0.0557 (90.4)	0.0379±0.0200 (52.8)	0.0324±0.0142 (43.9)	0.118±0.0635 (54.0)
T_{max} (h)[b]	2.75 (2.50-3.00)	4.00 (1.50-12.00)	6.00 (1.50-48.00)	6.00 (1.50-12.00)

a N=number of subjects in whom any concentrations above LLOQ were measured. A total of 23, 21, 22, 23 subjects were dosed with 75 µg, Formulation (b) (4) 300 µg Formulation (b) (4) 300 µg, Formulation (b) (4) and 1200 µg, Formulation (b) (4)
b median (range)

Table 21 Plasma Pharmacokinetics of Norbuprenorphine After a Single Intravenous Dose of Buprenorphine Administered to Fasted Healthy Subjects – Arithmetic Mean±SD (%CV)

Parameter	**Buprenorphine 300 µg N=23[a]**
C_{max} (ng/mL)	0.0603±0.0379 (62.8)
T_{max} (h)[b]	0.25 (0.25-3.00)

a N=number of subjects in whom any concentrations above LLOQ were measured. A total of 24 subjects were dosed with iv buprenorphine. No concentrations above LLOQ were measured for subject 1017
b median (range)

Comparison of 300 µg (b) (4) and (b) (4) formulations

See Section 2.5.2 for comparison.

Multiple-dose:

Study BUP-116 was an open-label, dose-escalating, multiple-dose study in healthy subjects. Ten (10) healthy subjects were dosed in a sequential, dose escalating manner, that is, at 60, followed by 120, followed by 180, and, finally, at 240 µg (Table 22; Dose escalation schedule). Each of the dose strength was administered every 12-hour for 6 doses. Film sizes were 0.97, 1.94, 2.92, and 3.89 cm^2 for doses of 60, 120, 180, and 240 µg Belbuca, respectively. Naltrexone (25 mg) was administered approximately 12- and 0.5-hours prior to, and 12-hours after the first dose of study drug, and, approximately 12 hours each subsequent morning dose.

Table 22 Dose Escalation Schedule for Study BUP-116

Study Period	**Study Days**	**BEMA Buprenorphine Dose (µg)[a]**
1	1 – 3	60
2	4 – 6	120

3	7 – 9	180
4	10 – 12	240

[a]Doses were administered every 12 hours

Blood samples were collected for determination of buprenorphine and norbuprenorphine plasma concentrations at the times listed in Table 23.

Table 23 Pharmacokinetic Sample Collection Times

Study Period	**Study Days**	**Pharmacokinetic Blood Sample Collection (Hours Post the First Dose in Study Period)**
1	1 – 3	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 60, 61, 62, 63, 64, 68
2	4 – 6	0, 24, 48, 60, 61, 62, 63, 64, 68
3	7 – 9	0, 24, 48, 60, 61, 62, 63, 64, 68
4	10 – 12	0, 24, 48, 60, 61, 62, 63, 64, 68, 72, 96, 120[a]

[a] The 96- and 120-hour pharmacokinetic (PK) sample collections were done during outpatient clinic visits on days 14 and 15, respectively.

Mean buprenorphine and norbuprenorphine plasma concentrations over time are shown in Figure 12 and Figure 13, respectively.

Figure 12 Mean Buprenorphine Concentration-Time Profiles after Administration of 60, 120, 180, and 240 µg BEMA Buprenorphine

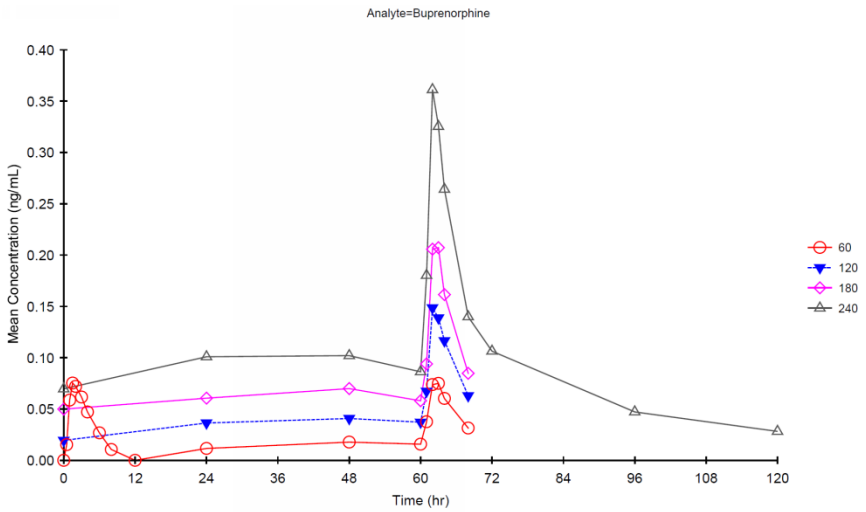
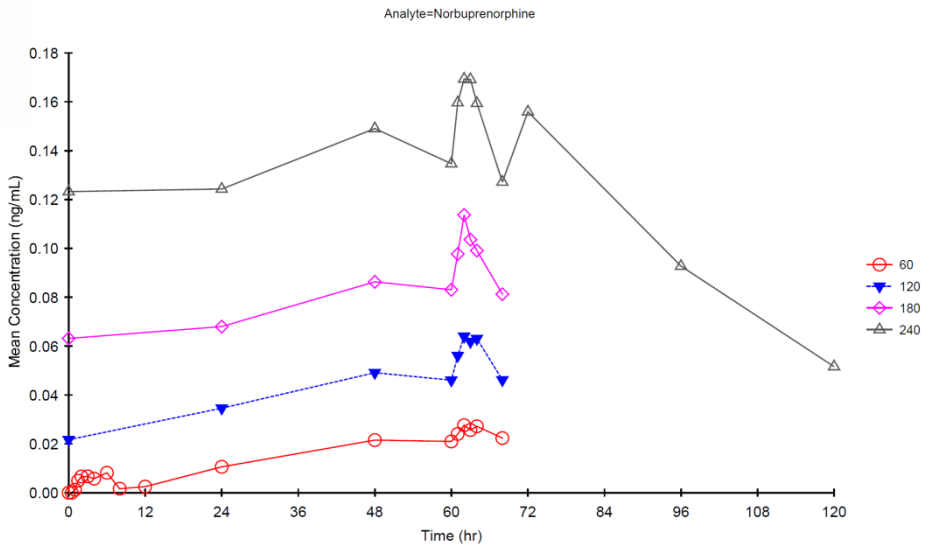


Figure 13 Mean Norbuprenorphine Concentration-Time Profiles after Administration of 60, 120, 180, and 240 µg BEMA Buprenorphine



Buprenorphine and norbuprenorphine pharmacokinetic parameters after each dose are provided in Table 24 and Table 25, respectively.

Table 24 Buprenorphine Plasma Pharmacokinetic Parameters

Parameter	**BEMA Buprenorphine Dose (Study Day)**				
	60 mcg (Day 1)	**60 mcg (Day 3)**	**120 mcg (Day 6)**	**180 mcg (Day 9)**	**240 mcg (Day 12)**
T_{max} (hours)	1.75 (1.0-3.0)	3.0 (2.0-4.0)	2.5 (2.0-4.0)	2.0 (0-3.0)	2.0 (2.0-3.0)
C_{max} (ng/mL)	0.0796±0.0180	0.0766±0.0195	0.156±0.0437	0.216±0.106	0.364±0.125
C_{avg} (ng/mL)	NA	0.0409±0.0116	0.0805±0.0206	0 113±0.0496	0.195±0.0619
C_{min} (ng/mL)	NA	0.0157±0.00899	0.0371±0.00855	0.0558±0.0210	0.0862±0.0278
$AUC_{0-\tau}$ (h·ng/mL)	NA	0.4903±0.1395	0.9658±0.2468	1 358±0.5951	2.343±0.7424
AUC_{last} (h·ng/mL)	0.3166±0.06967	0.4085±0.1017	0.7902±0.1981	1.111±0.5000	5.033±1.571
AUC_{inf} (h·ng/mL)	NA	NA	NA	NA	6.461±2.180
$T_{½}$ (hours)	NA	NA	NA	NA	27.58±11.18

Note: Data presented as mean ± SD, except Tmax which is presented as median (range).

Table 25 Norbuprenorphine Plasma Pharmacokinetic Parameters

Parameter	BEMA Buprenorphine Dose (Study Day)				
	60 mcg (Day 1)	60 mcg (Day 3)	120 mcg (Day 6)	180 mcg (Day 9)	240 mcg (Day 12)
T_{max} (hours)	3.0 (1.5-6.15)	2.0 (1.0-4.0)	3.0 (2.0-4.0)	2.0 (1.0-4.0)	2.0 (0-3.0)
C_{max} (ng/mL)	0.0141±0.00348	0.0328±0.0168	0.0671±0.0274	0.122±0.0564	0.179±0.0997
C_{avg} (ng/mL)	NA	0.0267±0.0127	0.0496±0.0212	0.0966±0.0443	0.149±0.0859
C_{min} (ng/mL)	NA	0.0201±0.0133	0.0420±0.0224	0.0694±0.0398	0.125±0.0794
$AUC_{0-\tau}$ (h·ng/mL)	NA	0.3203±0.1525	0.5955±0.2541	1.159±0.5321	1.784±1.031
AUC_{last} (h·ng/mL)	0.05834±0.05559	0.2228±0.1084	0.4521±0.2090	0.7673±0.4123	6.461±3.711
AUC_{inf} (h·ng/mL)	NA	NA	NA	NA	11.01±5.789
$T_{½}$ (hours)	NA	NA	NA	NA	73.08±129.57

Note: Data presented as mean ± SD, except Tmax which is presented as median (range).

Cmax values for buprenorphine and norbuprenorphine increased with an increase in dose; the same trend was noted for overall systemic exposure. The elimination half-life following the last dose was approximately 27.6 hours. Inspection of Figure xxx indicates that buprenorphine concentrations would be expected to have attained a steady state by approximately sixth dose.

2.2.4.2 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship

Single-dose

Study BUP-117

The dose linearity of buprenorphine pharmacokinetic parameters was examined across all buccal doses using both formulations ((b) (4) and (b) (4) Doses administered included 75 µg ((b) (4) 300 µg ((b) (4) 300 µg ((b) (4) and 1200 µg ((b) (4) When buprenorphine Cmax or AUCinf values are ploted against doses, the plots indicted that it is reasonable to predict that that both buprenorphine Cmax and AUCinf increased linearly with an increase in dose (Figure 14 and Figure 15, respectively)

Figure 14 Buprenorphine Cmax versus Dose after Administration of BEMA Buprenorphine Buccal Soluble Film 75 µg; (b) (4) (Treatment A), 300 µg; (b) (4) (Treatment B), 300 µg; (b) (4) (Treatment C), and 1200 µg; (b) (4) (Treatment D)

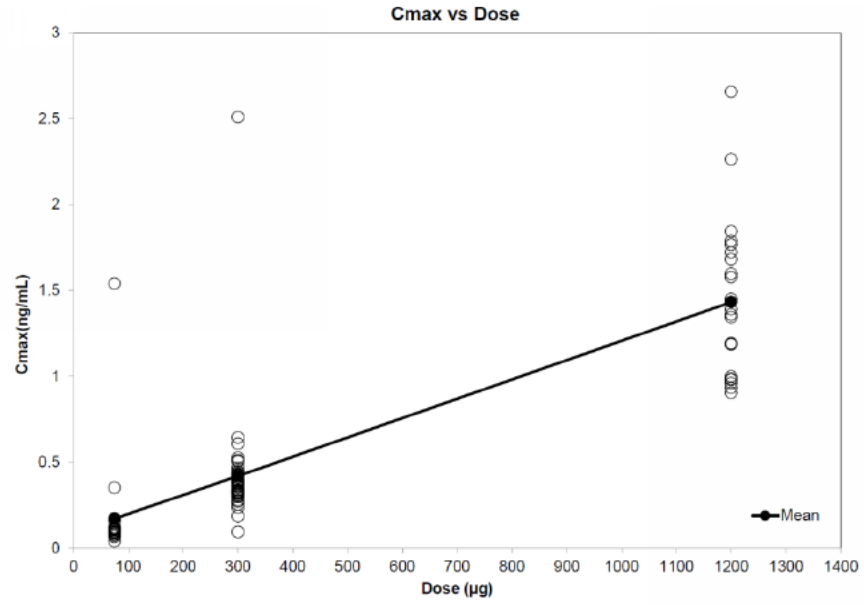
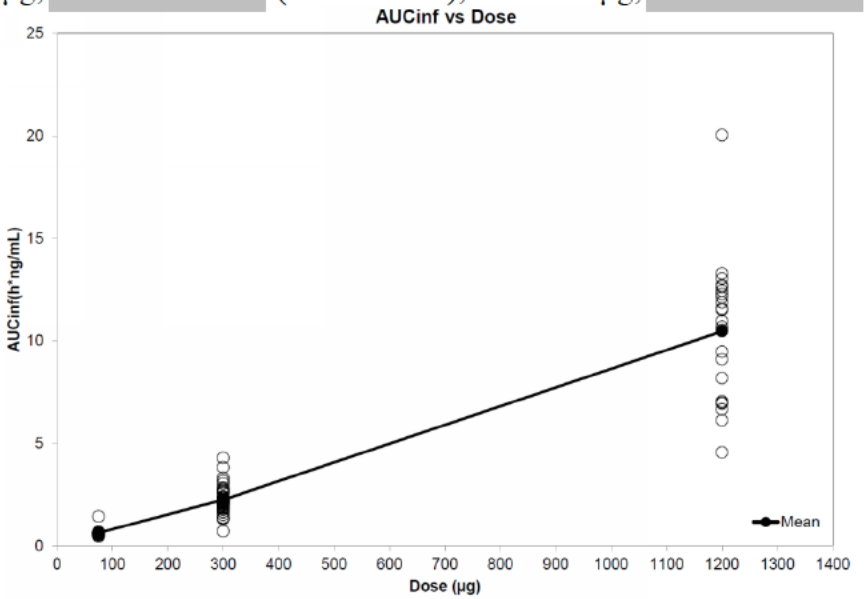


Figure 15 Buprenorphine AUCinf Versus Dose Administration of BEMA Buprenorphine Buccal Soluble Film 75 µg; [redacted] (b) (4) (Treatment A), 300 µg [redacted] (b) (4) (Treatment B), 300 µg; [redacted] (b) (4) (Treatment C), and 1200 µg; [redacted] (b) (4) (Treatment D)



Data Source: Figure 14.2.5.1.5

Multiple-dose (BUP-116)

The results indicated that both buprenorphine Cmax and AUC0-t increased linearly with an increase in dose after six doses administered every 12 hours (Table 26).

Table 26 Buprenorphine Plasma Cmax and AUC0-t after 6 doses administered every 12 hours

Parameter	BEMA Buprenorphine Dose (Study Day)			
	60 mcg (Day 3)	120 mcg (Day 6)	180 mcg (Day 9)	240 mcg (Day 12)
$C_{max,ss}$ (ng/mL)	0.0766±0.0195	0.156±0.0437	0.216±0.106	0.364±0.125
$AUC_{0-\tau}$ (h·ng/mL)	0.4903±0.1395	0.9658±0.2468	1.358±0.5951	2.343±0.7424

2.2.4.3 What is the bioavailability of Belbuca compared with other products?

Relative Bioavailability: Belbuca vs. buprenorphine sublingual tablet

Study BUN-118 provided relative bioavailability information comparing single dose 900 µg Belbuca and 8 mg buprenorphine sublingual tablet, Roxane Laboratories; see Section 2.4.1.1 for study description. Plots of mean buprenorphine and norbuprenorphine concentrations versus time are provided in Figure 16 and Figure 17, respectively.

Figure 16 Mean Plasma Concentrations of Buprenorphine Versus Time after BEMA Buprenorphine (900 µg) and Sublingual Buprenorphine (8 mg)(BUP-118)

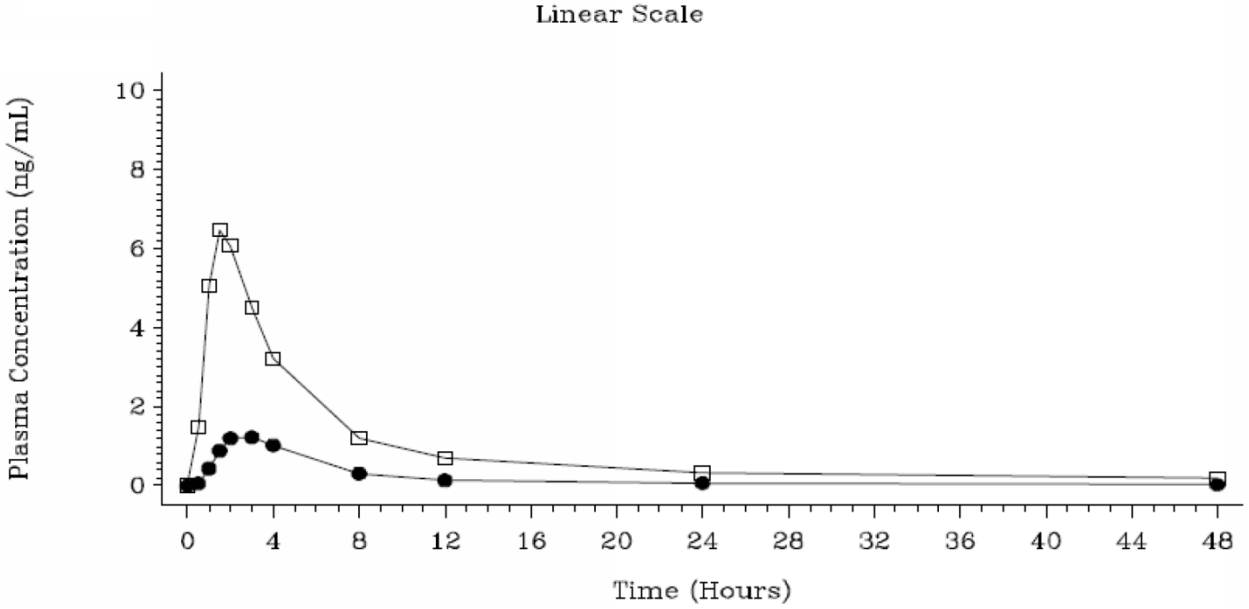
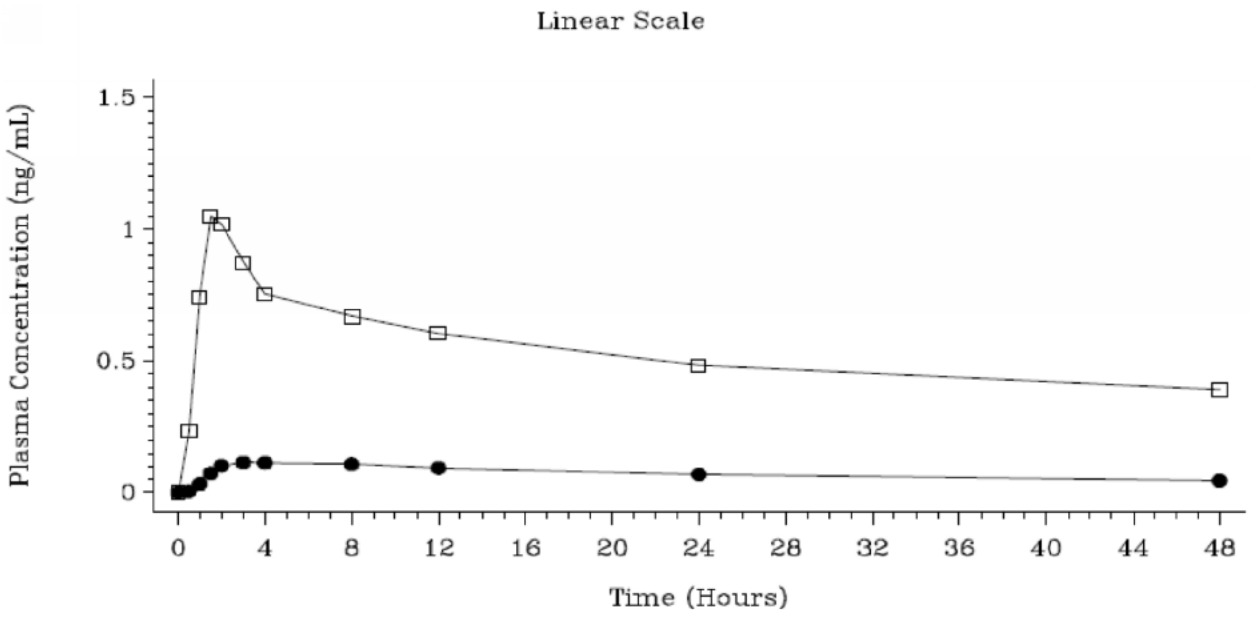


Figure 17 Mean Plasma Concentrations of Norbuprenorphine Versus Time after BEMA Buprenorphine (900 µg) and Sublingual Buprenorphine (8 mg)(BUP-118)



Buprenorphine and norbuprenorphine pharmacokinetics after BEMA Buprenorphine and sublingual buprenorphine, administered with no liquid (Treatments A and D, respectively) are provided in Table 27 and Table 28, respectively.

Table 27 Buprenorphine Pharmacokinetics after BEMA Buprenorphine (900 µg) and Sublingual Buprenorphine (8 mg) Administered to Fasted Healthy Subjects -Mean±SD (%CV) (BUP-118)

Parameters (unit)	BEMA Buprenorphine, 900 µg ([redacted] (b) (4) (N=29)[a]	Sublingual Buprenorphine, 8 mg (N=26)[b]
AUC_{0-t} (ng•h/mL)	8.75±2.46 (28.1)	41.9±13.2 (31.6)
AUC_{0-inf} (ng•h/mL)[c]	9.53±2.74 (28.8)	44.1±14.3 (32.4)
C_{max} (ng/mL)	1.32±0.409 (30.9)	6.73±2.65 (39.3)
T_{max} (h)[d]	3.00 (1.50-4.02)	1.50 (1.00-3.00)
$t_{½}$ (h)[e]	13.77±6.747 (49.0)	20.04±5.493 (27.4)
CL/F (L/h)[c,f]	104±37.6 (36.3)	206±84.4 (41.0)
V_z/F (L)[c,f]	1880±840 (44.6)	5610±2530 (45.1)
F[g]	1.98±0.792 (40.1)	-

Data Source: 5 3 1 2, Study BUP-118 [Table 14, Table 15, and Table 14 2 1 3]
a Treatment A=BEMA Buprenorphine 900 µg [redacted] (b) (4) without coadministered liquids
b Treatment D=Buprenorphine HCl sublingual tablet 8 mg without coadministered liquids
c N=21 for sublingual buprenorphine (Treatment D)
d Median (minimum, maximum) is presented for Tmax
e N=23 for sublingual buprenorphine (Treatment D)
f F represents absolute bioavailability
g F represents relative bioavailability of the 2 study treatments.

Buprenorphine mean Cmax value from Belbuca was 1.32 ng/mL compared to 6.73 ng/mL with sublingual tablet 8 mg. Buprenorphine mean AUC value from Belbuca was 9.53 ng.h/mL compared to 44.1 ng.h/mL with sublingual tablet 8 mg.

Table 28 Norbuprenorphine Pharmacokinetics after BEMA Buprenorphine (900 µg) and Sublingual Buprenorphine (8 mg) Administered to Fasted Healthy Subjects - Mean±SD (%CV) (BUP-118)

Parameters (unit)	BEMA Buprenorphine, 900 µg (b) (4) (N=29)[a]	Sublingual Buprenorphine, 8 mg (N=26)[b]
AUC_{0-t} (ng•h/mL)	3.46±1.44 (41.8)	25.4±12.3 (48.2)
C_{max} (ng/mL)	0.132±0.0691 (52.3)	1.21±0.652 (54.0)
T_{max} (h)[c]	4.00 (1.50-12.00)	1.50 (1.00-24.00)

Data Source: 5 3 1 2, Study BUP-118 [Table 16, Table 17, and Table 14 2 1 4]
a Treatment A=BEMA Buprenorphine 900 µg (b) (4) without coadministered liquids
b Treatment D=Buprenorphine HCl sublingual tablet 8 mg without coadministered liquids
c Median (minimum, maximum) is presented for Tmax

Norbuprenorphine mean Cmax value from Belbuca was 0.132 ng/mL compared to 1.21 ng/mL with sublingual tablet 8 mg. Buprenorphine mean AUC0-t value from Belbuca was 3.46 ng.h/mL compared to 25.4 ng.h/mL with sublingual tablet 8 mg.

Absolute bioavailability

Study BUP-115

Study BUP-115 (see above for further discussion on study design) explored absolute bioavailability by comparing 500 µg single-dose Belbuca ((b) (4) a to-be-marketed formulation) and a 2-minute IV injection of 150 µg buprenorphine in 0.5 mL. The mean absolute bioavailability (based on AUCinf) of buprenorphine from BEMA Buprenorphine soluble buccal film was 0.65 at dose level of 0.5 mg (Table 29).

Table 29 Mean Absolute Oral Bioavailability of Buprenorphine Comparing Buprenorphine 0.5 mg BEMA Buccal Soluble Film (Treatment B) to Buprenex 0.15 mg Injection (Treatment D)

Treatment	Mean AUClast Ratio (%)	Mean AUCinf Ratio (%)
B vs. D	63.86 (90% CI)	65.14 (90% CI)

Study SUP-117

Study BUP-117 (see above for further discussion on study design) explored absolute bioavailability by comparing 75, 300 and 1200 µg single-dose Belbuca ((b) (4) a to-be-marketed formulation) and a 2-minute IV injection of 300 µg buprenorphine (0.3 mg/1 mL). The mean absolute bioavailability ranged from 0.46 to 0.51 across the 4 buccal doses (Table 30).

Table 30 Mean Absolute Oral Bioavailability of Buprenorphine from Buprenorphine Buccal Soluble Film Compared to Buprenorphine 300 µg Intravenous Injection

Treatment	Absolute Bioavailability (F)					95% CI	
	Mean	SD	Min	Median	Max	Lower	Upper
75 µg [redacted] (b) (4)	0.4859	0.1534	0.2299	0.4757	0.8385	0.3973	0.5744
300 µg [redacted] (b) (4)	0.4615	0.1788	0.2557	0.4095	0.8603	0.3801	0.5429
300 µg [redacted] (b) (4)	0.4608	0.1606	0.1233	0.4339	0.8675	0.3877	0.5339
1200 µg ([redacted] (b) (4)	0.5057	0.1637	0.2634	0.4669	0.9704	0.4332	0.5783

Data Source: Table 14.2.4 and Listings 16.2.5.5.1.1 to 16.2.5.5.1.5
Absolute Bioavailability = [Dose (IV) * AUCinf (BEMA)] / [Dose (BEMA) * AUCinf (IV)] Based on 14, 21, 21, 22 pairs of data (buccal and IV) for 75 µg [redacted] (b) (4) 300 µg [redacted] (b) (4) 300 µg [redacted] (b) (4) 1200 µg [redacted] (b) (4) respectively

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

2.3.1.1 Elderly and sex differences

No dedicated pharmacokinetic studies were conducted in the development of Belbuca in order to address elderly or sex exposure differences. However the Applicant performed the population pharmacokinetics analysis to possibly identify and characterize patient factors which influence the variability in buprenorphine and norbuprenorphine exposures. In order to achieve the objectives, the Applicant utilized the following studies in the population pharmacokinetic analysis (Table 31).

Table 31 Studies Used for Analysis

Study	Sampling Scheme	Title

BUP-117	Rich	An Evaluation of the Bioavailability and Dose Linearity of BEMA® Buprenorphine in Healthy Subjects
EN3409-307	Sparse	A Phase 3, Double-blind, Placebo-Controlled, Multicenter, Randomized Withdrawal Study to Evaluate the Analgesic Efficacy, Safety, and Tolerability of BEMA® Buprenorphine in Opioid-Experienced Subjects with Moderate to Severe Chronic Low Back Pain Requiring Around-the-Clock Opioid Analgesia for an Extended Period of Time
EN3409-308	Sparse	A Phase 3, Double-blind, Placebo-Controlled, Multicenter, Randomized Withdrawal Study to Evaluate the Analgesic Efficacy, Safety, and Tolerability of BEMA® Buprenorphine in Opioid- Naive Subjects with Moderate to Severe Chronic Low Back Pain Requiring Around-the-Clock Opioid Analgesia for an Extended Period of Time

The plasma concentration-time data collected in these studies was analyzed using mixed effects modeling methods using NONMEM (v.7 or higher). The covariates tested were subject age at baseline, subject weight BSA, body mass index, height, formulation, formulation surface area, and dose level. Bootstrap methods with at least 2000 iterations were used in the final model. The final pharmacokinetic model for buprenorphine was a 2 compartment model with first order absorption with an absorption lag and a dose effect on CL and V2 and a study effect on absorption rate constant, KA. The final model, final model estimates (Table 32), and final parameter bootstrap parameters (Table 33) were reported to be: $KA = \theta_1 \bullet \theta_{10}^{BUP-117}$, $CL = \theta_2 \bullet \eta_1 \bullet \left(\frac{Dose}{600}\right)^{\theta_{11}}$, $V2 = \theta_3 \bullet (\eta_1 \bullet \theta_9) \bullet \left(\frac{Dose}{600}\right)^{\theta_{12}}$, $Q = \theta_4$, $V3 = \theta_5$, $F1 = \theta_6$, and $ALAG = \theta_8$.

Table 32 Final Model Parameter Estimates for Buprenorphine

Parameter (Units)		Population Mean (SE%)	%CV Inter-Individual Variance (shrinkage)
Absorption Rate Constant (KA)(1/h)	Θ_1	0.159 (18.7%)	-
Clearance (CL) (L/hr)	Θ_2	68.4 (5.9%)	66.8 (16.8%)
Central Volume (V2) (L)	Θ_3	347 (12.0%)	
Inter-compartmental Clearance (Q) (L/hr)	Θ_4	35.7 (7.6%)	-
Peripheral Volume (V3) (L)	Θ_5	1220 (22.5%)	-
Bioavailability (F1)	Θ_6	0.426 (4.1%)	-
Absorption Lag Time (ALAG) (hr)	Θ_8	0.446 (0.9%)	-
IIV Scale for V2	Θ_9	1.64 (10.1%)	-
BUP-117 Effect on KA	Θ_{10}	2.54 (18.4%)	-
Dose Effect on CL	Θ_{11}	0.138 (24.6%)	-
Dose Effect on V2	Θ_{12}	0.169 (19.1)	-
Residual Variability	Θ_7	44.7 %CV (1.2%)	-

KA- absorption rate, CL-clearance, V2 - central volume , Q - inter-compartmental clearance, V3 – peripheral volume, F1 – oral bioavailability, ALAG – absorption lag ADDS - residual variability, SE - standard error, CV- coefficient of variation
Source: base_2cmt_corrCLV_alag_KAstud_F1-form-SA_doseCLV.smr

Table 33 Bootstrap Parameter Estimates for Final Model

Parameter (Units)		Population Median (90% CI)	%CV Inter-Individual Variance
Absorption Rate Constant (KA)(1/h)	Θ_1	0.136 (0.035 – 0.269)	
Clearance (CL) (L/hr)	Θ_2	68.0 (61.7 – 74.9)	67.2 (61.5 – 72.7)
Central Volume (V2) (L)	Θ_3	328 (248 – 454)	
Inter-compartmental Clearance (Q) (L/hr)	Θ_4	35.3 (30.5 – 39.9)	
Peripheral Volume (V3) (L)	Θ_5	1175 (850 – 1595)	
Bioavailability (F1)	Θ_6	0.427 (0.397 – 0.460)	
Absorption Lag Time (ALAG) (hr)	Θ_8	0.452 (0.427 – 0.464)	
IIV Scale for V2	Θ_9	1.58 (0.85 – 2.21)	
BUP-117 Effect on KA	Θ_{10}	2.91 (1.47 – 11.0)	
Dose Effect on CL	Θ_{11}	0.136 (0.085 – 0.181)	
Dose Effect on V2	Θ_{12}	0.168 (0.107 – 0.228)	
Residual Variability	Θ_7	44.3 (41.9 – 47.2)	

Source: base_2cmt_allDoses_corrCLV_Fstudy_formF1_iivF1blk_formCorr3_saF1v7.smr

L/hr – liters per hour, CL – clearance, SE – standard error, CV – coefficient of variation, BSA – body surface area, V1 – central volume, V2 - peripheral volume 1, Q2 – inter-compartmental clearance 1, Q3 – inter-compartmental clearance 2, V3 - peripheral volume 2

Source: bootstrap_results_STID-1000.csv

The Applicant reported that CL and V increased with increasing dose, but, the effects are not critically significant and are not considered clinically relevant (for CL a less than 2-fold difference is shown over a 12-fold difference in dose 75-900 µg; a similar range is observed V2). No other demographic variables such as age, body size or sex were found to be statistically significant predictors ($p<0.001$) of the pharmacokinetic parameters for buprenorphine. The Applicant's finding appears to be reasonable since buprenorphine has not been reported to have differences in responses between elderly and younger patients.

2.3.1.2 Pediatric patients. What is the status of pediatric studies and/or any pediatric plan for study?

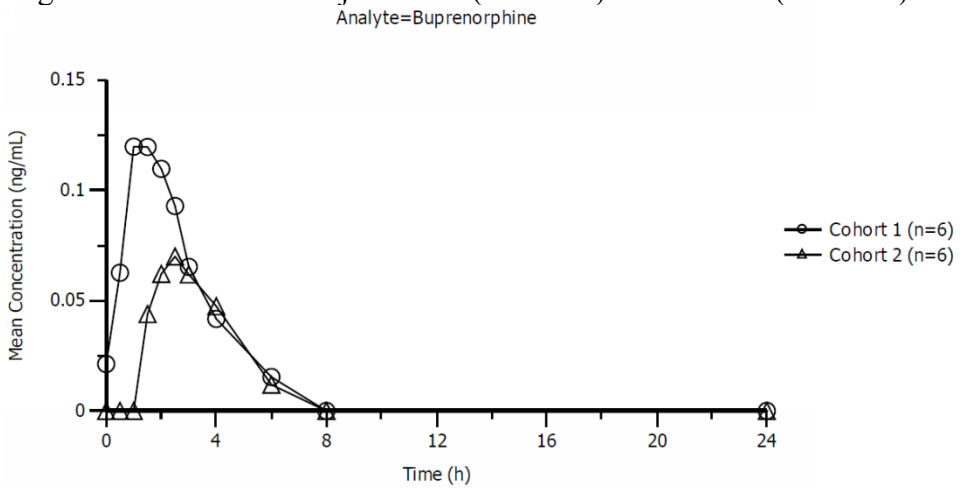
The PK information from Belbuca has not been studied in pediatric patients. The Applicant requests a partial waiver from the requirement to submit assessment of buprenorphine hydrochloride buccal film CIII in pediatric subjects 0 to 6 years old due to the fact that 1) the necessary studies are impossible or highly impracticable and 2) the number of pediatric subjects meeting the indication in the age group are too small in number to make the studies feasible. In addition, pursuant to 21 CFR Part 314.55(c)(3)(i) and (ii) and 21 CFR 314.55(b)(1)(a) and 505B(a)(3)(A)(i) of the FD&C Act, the Applicant requests a deferral of submission of assessment in pediatric subjects aged 7 to 16 years old due to the fact that the product is ready for approval for use in adults and the pediatric study has not been initiated or completed. The Applicant plans, as described in the iPSP, to conduct pediatric studies to fulfill Pediatric Research Equity Act obligations.

2.3.1.3 Buprenorphine exposure in Grade 3 mucositis patients

Study BUP-121 was an open-label, a 60 µg single dose Belbuca, administered in 2 cohorts: Cohort 1, six subjects with cancer and Grade 3 oral mucositis; Cohort 2: six healthy subjects without oral mucositis, age- and gender-matched to each subject in Cohort 1. In Cohort 1, the study drug dose was applied to an area of oral mucositis. In Cohort 2, the study drug dose was applied to a similar area of the oral mucosa as the matched subject in Cohort 1. Blood samples for buprenorphine and norbuprenorphine analysis were collected at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours post dose.

Mean plasma buprenorphine concentration-time profiles are provided in Figure 18. All concentrations for norbuprenorphine were below the lower limit of quantification.

Figure 18 Mean Plasma Buprenorphine Concentration-Time Profiles on Linear and Semi-Logarithmic Scales in Subjects with (Cohort 1) and without (Cohort 2) Oral Mucositis



The summary of buprenorphine for Cohorts 1 and 2 is provided in Table 34.

Table 34 Summary of Pharmacokinetic Parameters for Buprenorphine

	Cohort 1: Subjects With Oral Mucositis				**Cohort 2: Subjects Wthout Oral Mucositis**			
	n	**Mean (SD)**	**Min, Max**	**CV%**	**n**	**Mean (SD)**	**Min, Max**	**CV%**
T_{max} (hr)	6	1.52	0.50, 2.02	42.65	6	2.50	2.50, 3.00	7.69
C_{max} (ng/mL)	6	0.147 (0.0731)	0.0295, 0.227	49.62	6	0.0711 (0.0185)	0.0416, 0.0958	26.05
AUC_{0-24} (h/ng/mL)	6	0.4553 (0.2779)	0.04210, 0.8546	61.02	6	0.2299 (0.08977)	0.1058, 0.3764	39.05

Note: For T_{max} median values are presented.
Note: Full precision data used in pharmacokinetic analysis

The statistical analysis of buprenorphine PK parameters is provided in Table 35. Buprenorphine was absorbed more rapidly and had about 80% higher C_{max} and 60% greater AUC in subjects with mucositis compared to age and gender matched healthy subjects. The 90% confidence intervals (CI) were wide perhaps due to the small sample size: the 90% CI for geometric mean ration of C_{max} was 98.24-327.17; AUC_{0-24} 90% CI was 66.27-365.64.

Table 35 Statistical Analysis of Buprenorphine Pharmacokinetic Parameters

Dependent Variable	Geometric Mean		Geometric Mean Ratio (%)	90% CI for Geometric Mean Ratio	
	Cohort 1	Cohort 2	(Cohort 1/ Cohort 2)	Lower	Upper
C_{max}	0.1234	0.0688	179.28	98.24	327.17
AUC_{0-24}	0.3340	0.2146	155.67	66.27	365.64

Cohort 1=Subjects with oral mucositis; Cohort 2=Subjects without oral mucositis

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

2.4.1.1 Is there an effect of co-administered liquids of low and high pH levels on the relative bioavailability of Belbuca?

Study BUP-118 was an open-label, randomized, single-dose, single-center, crossover study in healthy subjects. Each buprenorphine dose was separated by at least 7 days. Subjects received a single dose of the following treatments under fasted conditions:

- Treatment A: BEMA Buprenorphine 900 µg (b) (4) without coadministered liquids;
- Treatment B: BEMA Buprenorphine 900 µg ((b) (4) with room temperature decaffeinated cola (low pH);
- Treatment C: BEMA Buprenorphine 900 µg (b) (4) with room temperature sodium bicarbonate mixed with water (high pH); and
- Treatment D: Buprenorphine HCl sublingual tablet 8 mg without coadministered liquids.

Subjects assigned to a treatment with a co-administered liquid began sipping the liquid 5 minutes after administration of Belbuca and finished the liquid within 15 minutes. Blood samples for PK analysis of buprenorphine and norbuprenorphine plasma concentrations were collected at pre-dosing, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post dosing.

Plots of mean buprenorphine and norbuprenorphine concentrations versus time are provided in Figure 19 and Figure 20, respectively.

Figure 19 Mean Plasma Concentrations of Buprenorphine Versus Time after BEMA Buprenorphine 900 µg Administered without Liquid and with Low or High pH Liquid (Treatments A, B, and C, Respectively) (BUP-118)

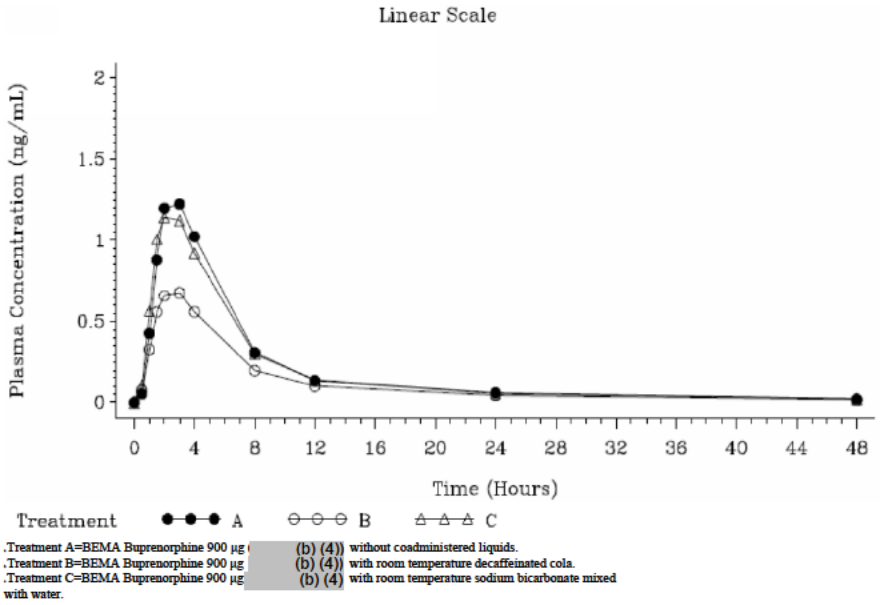
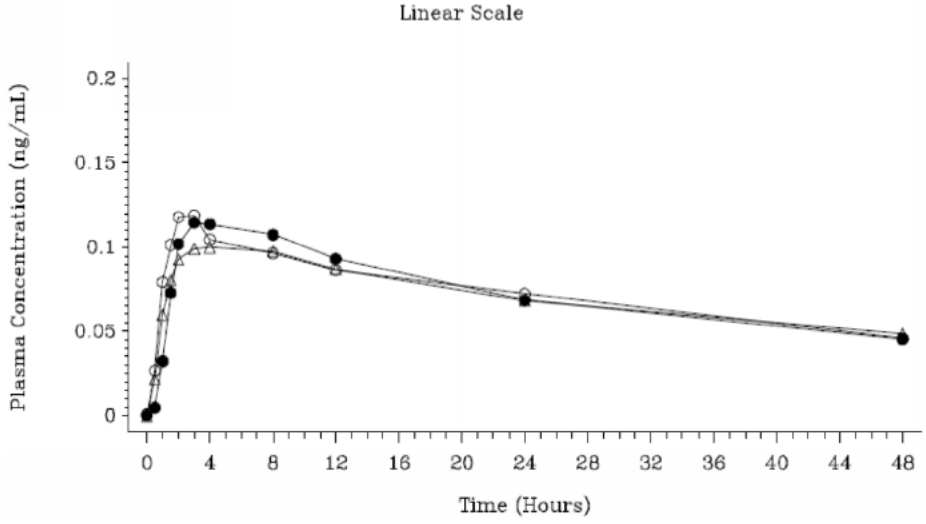


Figure 20 Mean Plasma Concentrations of Norbuprenorphine Versus Time after BEMA Buprenorphine 900 µg Administered without Liquid and with Low or High pH Liquid (Treatments A, B, and C, Respectively) (BUP-118)



The exposure to norbuprenorphine was comparable across the different treatments.

Plasma PK parameters of buprenorphine and norbuprenorphine are presented in Table 36 and Table 37, respectively.

Table 36 Buprenorphine Pharmacokinetics after BEMA Buprenorphine Administered without Liquid and with Low or High pH Liquid to Fasted Healthy Subjects - Mean±SD (%CV) (BUP-118)

Parameters (unit)	BEMA Buprenorphine, 900 µg ((b) (4)

	Treatment A[a]: Without Liquid (N=29)	Treatment B[b]: With Low pH Liquid (N=29)	Treatment C[c]: With High pH Liquid (N=28)
AUC_{0-t} (ng•h/mL)	8.75±2.46 (28.1)	5.34±2.15 (40.3)	8.45±2.48 (29.4)
AUC_{0-inf} (ng•h/mL)[d]	9.53±2.74 (28.8)	6.31± 2.22 (35.2)	9.05±2.74 (30.3)
C_{max} (ng/mL)	1.32±0.409 (30.9)	0.731±0.305 (41.8)	1.24±0.329 (26.6)
T_{max} (h)[e]	3.00 (1.50, 4.02)	3.00 (1.50, 4.00)	2.00 (1.00, 4.00)
$t_{½}$ (h)[f]	13.77±6.747 (49.0)	13.91±8.486 (61.0)	13.50±7.035 (52.1)
CL/F (L/h)[d]	104±37.6 (36.3)	159±54.1 (34.0)	113±55.8 (49.4)
V_z/F (L)[d]	1880±840 (44.6)	2890±1410 (48.9)	1830±742 (40.6)

[a] Treatment A=BEMA Buprenorphine 900 µg ((b) (4)) without coadministered liquids;
Treatment B=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature decaffeinated cola;
Treatment C=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature sodium bicarbonate mixed with water;
[b] N=27, N=26, and N=21 for Treatments B, C, and D, respectively
[c] N=27 and N=23 for Treatments C and D, respectively
[d] Median (minimum, maximum) is presented for T_{max}

Table 37 Norbuprenorphine Pharmacokinetics after BEMA Buprenorphine Administered without Liquid and with Low or High pH Liquid Administered to Fasted Healthy Subjects - Mean±SD (%CV) (BUP-118)

Parameters (unit)	BEMA Buprenorphine, 900 µg ((b) (4))		
	Treatment A[a]: Without Liquid (N=29)	Treatment B[b]: With Low pH Liquid (N=29)	Treatment C[c]: With High pH Liquid (N=28)
AUC_{0-t} (ng•h/mL)	3.46±1.44 (41.8)	3.47±1.56 (44.8)	3.38±1.27 (37.7)
C_{max} (ng/mL)	0.132±0.0691 (52.3)	0.132±0.0587 (44.4)	0.113±0.0451 (39.9)
T_{max} (h)[d]	4.00 (1.50, 12.00)	3.00 (1.00, 48.00)	4.00 (1.50, 12.00)

[a] Treatment A=BEMA Buprenorphine 900 µg ((b) (4)) without coadministered liquids;
Treatment B=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature decaffeinated cola;
Treatment C=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature sodium bicarbonate mixed with water;
[b] Median (minimum, maximum) is presented for T_{max}

Statistical analyses of plasma PK parameters of buprenorphine and norbuprenorphine are presented in Table 38 and Table 39, respectively.

Table 38 Statistical Analysis of Buprenorphine Plasma Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	Treatment Comparison[a]	N	Geometric LS Means	Ratio of Geometric LS Means (%)	90% CI of the Ratio

AUC_{0-t} (ng•h/mL)	B/A	29/29	4.8950/8.4468	57.952	53.017 - 63.345
	C/A	28/29	8.2234/8.4468	97.356	88.969 - 106.533
AUC_{0-inf} (ng•h/mL)	B/A	27/29	5.8025/9.1869	63.160	58.530 - 68.156
	C/A	26/29	8.8856/9.1869	96.721	89.510 - 104.512
C_{max} (ng/mL)	B/A	29/29	0.6687/1.2650	52.862	47.441 - 58.903
	C/A	28/29	1.2161/1.2650	96.136	86.165 - 107.260

[a] Treatment A=BEMA Buprenorphine 900 µg ((b) (4) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature decaffeinated cola (low pH); Treatment C=BEMA Buprenorphine 900 µg ((b) (4) with room temperature sodium bicarbonate mixed with water (high pH); Abbreviations: CI=confidence interval; LS=least squares

Table 39 Statistical Analysis of Norbuprenorphine Pharmacokinetic Parameters after BEMA Buprenorphine Administered with Low or High pH Liquid Compared to BEMA Buprenorphine Administered without Liquid (BUP-118)

Parameter	**Treatment Comparison[a]**	**N**	**Geometric LS Means**	**Ratio of Geometric LS Means (%)**	**90% CI of the Ratio**
AUC_{0-t} (ng•h/mL)	B/A	29/29	3.1304/3.0620	102.232	93.566 - 111.702
	C/A	28/29	3.1790/3.0620	103.820	94.914 - 113.563
C_{max} (ng/mL)	B/A	29/29	0.1183/0.1154	102.547	93.960 - 111.918
	C/A	28/29	0.1054/0.1154	91.404	83.659 - 99.866

[a] Treatment A=BEMA Buprenorphine 900 µg ((b) (4)) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature decaffeinated cola (low pH); Treatment C=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature sodium bicarbonate mixed with water (high pH); Abbreviations: CI=confidence interval; LS=least squares

Buprenorphine Cmax and AUC decreased by 47 and 37%, respectively, from Belbuca, when co-administration with low pH liquid. Coadministration with high pH liquid had no significant impact on buprenorphine exposure from Belbuca. The exposure to norbuprenorphine was comparable across the different treatments.

2.4.1.2 Is there an effect of co-administered liquids of various temperatures on the relative bioavailability of Belbuca?

Study BUP-120 was an open-label, randomized, single-dose, single-center, 4-sequence, 4-period crossover study in healthy subjects. Each buprenorphine dose was separated by a washout period of at least 7 days. Subjects received a single dose of the following treatments under fasted conditions:

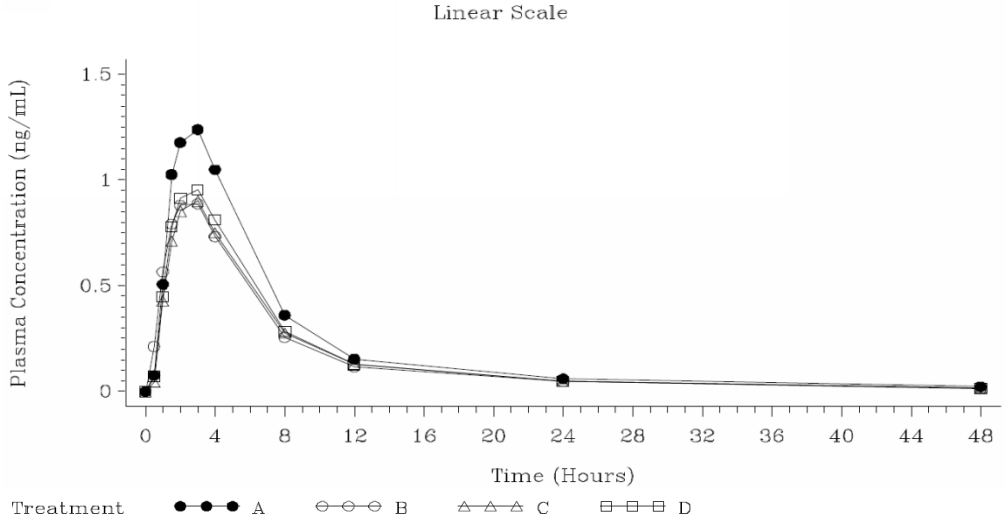
- Treatment A: BEMA Buprenorphine 900 µg ((b) (4)) without co-administered liquids;
- Treatment B: BEMA Buprenorphine 900 µg ((b) (4)) with hot water;
- Treatment C: BEMA Buprenorphine 900 µg ((b) (4)) with cold water; and
- Treatment D: BEMA Buprenorphine 900 µg ((b) (4)) with room temperature water.

Subjects assigned to a treatment with a co-administered liquid began sipping the liquid 5 minutes after administration of Belbuca and finished the liquid within 15 minutes. Blood samples for PK

analysis of buprenorphine and norbuprenorphine plasma concentrations were collected at pre-dosing, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, and 48 hours post dosing.

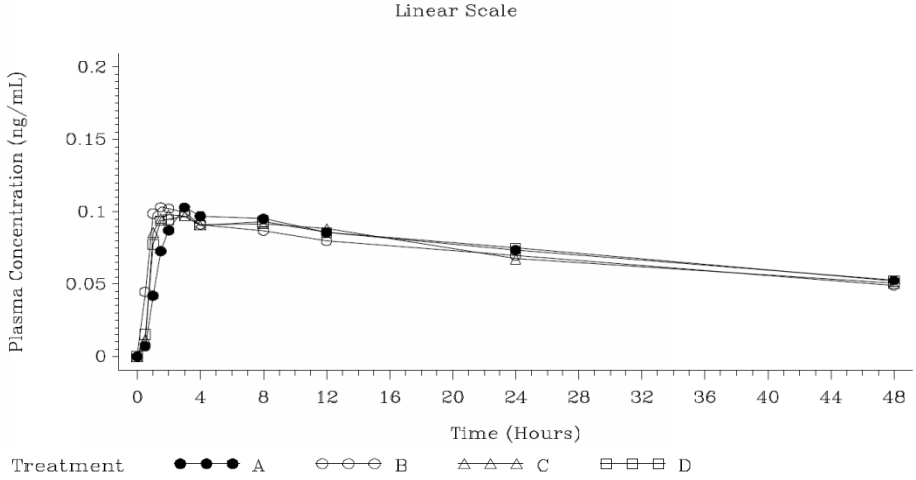
Mean plasma concentrations of buprenorphine and norbuprenorphine versus time are presented in Figures 21 and 22, respectively.

Figure 21 Mean Plasma Concentrations of Buprenorphine Versus Time (PK Population)



Source Data: Figure 14 2 1 1
Treatment A=BEMA Buprenorphine 900 µg (b) (4)) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg (b) (4)) with hot water; Treatment C=BEMA Buprenorphine 900 µg (b) (4)) with cold water; Treatment D=BEMA Buprenorphine 900 µg (b) (4)) with room temperature water

Figure 22 Mean Plasma Concentrations of Norbuprenorphine Versus Time



Source Data: Figure 14 2 1 2
Treatment A=BEMA Buprenorphine 900 µg (b) (4)) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg (b) (4)) with hot water;
Treatment C=BEMA Buprenorphine 900 µg ((b) (4)) with cold water; Treatment D=BEMA Buprenorphine 900 µg (b) (4)) with room temperature water

Plasma PK parameters of buprenorphine and norbuprenorphine are presented in Table 40 and Table 41, respectively.

Table 40 Buprenorphine Pharmacokinetics after BEMA Buprenorphine Administered without Liquid and with Hot, Cold, and Room Temperature Water to Fasted Healthy Subjects-Mean±SD (%CV) (EN3409-120)

Parameters (unit)	BEMA Buprenorphine, 900 µg ([redacted])[a]			
	Treatment A: Without Liquid (N=31)	Treatment B: With Hot Water (N=31)	Treatment C: With Cold Water (N=31)	Treatment D: With Room Temperature Water (N=31)
AUC_{0-t} (ng•h/mL)	9.40±2.86 (30.5)	6.88±2.62 (38.1)	6.93±2.49 (35.9)	7.37±2.93 (39.8)
AUC_{0-inf} (ng•h/mL)[b]	10.1±3.03 (29.8)	7.55±2.76 (36.6)	7.74±2.46 (31.7)	7.98±3.01 (37.7)
C_{max} (ng/mL)	1.36±0.422 (30.9)	1.01±0.393 (39.1)	0.974±0.359 (36.9)	1.03±0.400 (39.0)
T_{max} (h)[c]	2.00 (1.00-4.00)	2.00 (1.00-4.00)	2.00 (1.50-4.00)	2.00 (1.50-4.00)
$t_{½}$ (h)[d]	14.24±7.009 (49.2)	12.36±6.466 (52.3)	11.64±5.223 (44.9)	13.12±5.913 (45.1)
λ_z (/h)[d]	0.0640±0.3616 (56.5)	0.0727±0.03675 (50.6)	0.0724±0.03126 (43.2)	0.0691±0.04310 (62.4)

a Treatment A=BEMA Buprenorphine 900 µg ([redacted]) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg ([redacted]) with hot water; Treatment C=BEMA Buprenorphine 900 µg ([redacted]) with cold water; Treatment D=BEMA Buprenorphine 900 µg ([redacted]) with room temperature water b N=30, N=30, and N=28 for AUCinf of Treatments A, B, and C, respectively Linear regression lines could not be fitted through the terminal elimination phases of many profiles or the extrapolated AUCs were more than 20% of the AUC0-t c N=29 for t1/2 and λz of Treatment C Linear regression lines could not be fitted through the terminal elimination phases of some profiles d Median (minimum, maximum) is presented for Tmax

Table 41 Norbuprenorphine Pharmacokinetics after BEMA Buprenorphine Administered without Liquid and with Hot, Cold, or Room Temperature Water to Fasted Healthy Subjects - Mean±SD (%CV) (EN3409-120)

Parameters (unit)	BEMA Buprenorphine, 900 µg ([redacted])[a]			
	Treatment A: Without Liquid (N=31)	Treatment B: With Hot Water (N=31)	Treatment C: With Cold Water (N=31)	Treatment D: With Room Temperature Water (N=31)
AUC_{0-t} (ng•h/mL)	3.49±1.49 (42.7)	3.34±1.38 (41.3)	3.38±1.18 (34.9)	3.53±1.41 (40.1)
AUC_{0-inf}	–	4.24±1.32 (31.2)	4.21±0.397 (9.44)	–
C_{max} (ng/mL)	0.116±0.0513 (44.2)	0.126±0.0586 (46.7)	0.121±0.0492 (40.8)	0.119±0.0526 (44.2)
T_{max} (h)[c]	4.00 (1.00-24.00)	1.50 (0.50-24.00)	3.00 (1.00-48.00)	3.00 (1.00-24.00)
$t_{½}$ (h)[d]	31.90±7.782 (24.4)	30.99±8.763 (28.3)	26.50±5.873 (22.2)	32.35±5.998 (18.5)
λ_z (l/h)[d]	0.0231±0.00622 (27.0)	0.0243±0.00798 (32.8)	0.0274±0.00660 (24.1)	0.0221±0.00385 (17.4)

a Treatment A=BEMA Buprenorphine 900 µg ([redacted]) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg ([redacted]) with hot water; Treatment C=BEMA Buprenorphine 900 µg ([redacted]) with cold water; Treatment D=BEMA Buprenorphine 900 µg ([redacted]) with room temperature water b N=2 for Treatments B and C and N=0 for Treatments A and D AUCinf could not be calculated for many profiles because the linear regression lines could not be fitted through the terminal elimination phases or the extrapolated AUCs were more than 20% of the AUC0-t c N=10, N=11, N=9, and N=10 for Treatments A, B, C, and D, respectively Linear regression lines could not be fitted through the terminal elimination phases of many profiles d Median (minimum, maximum) is presented for Tmax

Statistical analyses of plasma PK parameters of buprenorphine and norbuprenorphine are presented in Table 42 and Table 43, respectively.

Table 42 Statistical Analysis of Buprenorphine Plasma Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	Treatment Comparison[a]	N	Geometric LS Means	Ratio of Geometric LS Means (%)	90% CI of the Ratio
AUC_{0-t} (ng•h/mL)	B/A	31/31	6.3979/8.9673	71.347	64.749 - 78.618
	C/A	31/31	6.4883/8.9673	72.355	65.664 - 79.729
	D/A	31/31	6.8215/8.9673	76.071	69.036 - 83.823
	B/C	31/31	6.3979/6.4883	98.606	89.487 - 108.655
	B/D	31/31	6.3979/6.8215	93.790	85.116 - 103.348
	C/D	31/31	6.4883/6.8215	95.116	86.319 - 104.808
AUC_{inf} (ng•h/mL)	B/A	30/30	7.0916/9.7307	72.879	67.012 - 79.260
	C/A	28/30	7.5080/9.7307	77.158	70.833 - 84.048
	D/A	31/30	7.4281/9.7307	76.337	70.269 - 82.930
	B/C	30/28	7.0916/7.5080	94.454	86.736 - 102.858
	B/D	30/31	7.0916/7.4281	95.470	87.873 - 103.723
	C/D	28/31	7.5080/7.4281	101.075	92.832 - 110.050
C_{max} (ng/mL)	B/A	31/31	0.9346/1.2994	71.925	64.643 - 80.026
	C/A	31/31	0.9025/1.2994	69.454	62.423 - 77.277
	D/A	31/31	0.9554/1.2994	73.530	66.087 - 81.813
	B/C	31/31	0.9346/0.9025	103.557	93.073 - 115.221
	B/D	31/31	0.9346/0.9554	97.816	87.914 - 108.834
	C/D	31/31	0.9025/0.9554	94.457	84.894 - 105.096

a Treatment A=BEMA Buprenorphine 900 µg ((b) (4) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg ((b) (4)) with hot water; Treatment C=BEMA Buprenorphine 900 µg ((b) (4)) with cold water; Treatment D=BEMA Buprenorphine 900 µg ((b) (4)) with room temperature water Abbreviations: CI=confidence interval; LS=least squares

Buprenorphine:

Plasma buprenorphine peak (Cmax) and total (AUC0-t and AUCinf) exposures were lower by 28%, 29%, and 27%, respectively, following BEMA Buprenorphine administration with hot water compared with BEMA Buprenorphine administration without any liquids.

Plasma buprenorphine peak (Cmax) and total (AUC0-t and AUCinf) exposures were lower by 31%, 28%, and 23%, respectively, following BEMA Buprenorphine administration with cold water compared with BEMA Buprenorphine administration without any liquids.

Plasma buprenorphine peak (Cmax) and total (AUC0-t and AUCinf) exposures were lower by 26%, 24%, and 24%, respectively, following BEMA Buprenorphine administration with water at room temperature compared with BEMA Buprenorphine administration without any liquids.

Plasma buprenorphine peak (Cmax) and total (AUC0-t and AUCinf) exposures were similar to each other following BEMA Buprenorphine administration with hot water, cold water, and water at room temperature.

Table 43: Statistical Analysis of Norbuprenorphine Plasma Pharmacokinetic Parameters (Pharmacokinetic Population)

Parameter	Treatment Comparison[a]	N	Geometric LS Means	Ratio of Geometric LS Means (%)	90% CI of the Ratio
AUC_{0-t} (ng•h/mL)	B/A	31/31	3.0979/3.2170	96.297	90.839 - 102.084
	C/A	31/31	3.2095/3.2170	99.767	94.111 - 105.762
	D/A	31/31	3.3041/3.2170	102.708	96.886 - 108.880
	B/C	31/31	3.0979/3.2095	96.522	91.051 - 102.323
	B/D	31/31	3.0979/3.3041	93.758	88.444 - 99.392
	C/D	31/31	3.2095/3.3041	97.136	91.630 - 102.973
C_{max} (ng/mL)	B/A	31/31	0.1133/0.1052	107.665	100.814 - 114.982
	C/A	31/31	0.1111/0.1052	105.580	98.862 - 112.755
	D/A	31/31	0.1081/0.1052	102.743	96.205 - 109.726
	B/C	31/31	0.1133/0.1111	101.975	95.486 - 108.905
	B/D	31/31	0.1133/0.1081	104.791	98.122 - 111.912
	C/D	31/31	0.1111/0.1081	102.761	96.222 - 109.745

a Treatment A=BEMA Buprenorphine 900 µg ((b) (4)) without coadministered liquids; Treatment B=BEMA Buprenorphine 900 µg (b) (4)) with hot water; Treatment C=BEMA Buprenorphine 900 µg (b) (4) with cold water; Treatment D=BEMA Buprenorphine 900 µg ((b) (4) with room temperature water Abbreviations: CI=confidence interval; LS=least squares

Norbuprenorphine:

Plasma norbuprenorphine peak (Cmax) and total (AUC0-t) exposures after BEMA Buprenorphine administration either with hot water or cold water or water at room temperature were similar compared with BEMA Buprenorphine administration without any liquids.

Plasma norbuprenorphine peak (Cmax) and total (AUC0-t) exposures following BEMA Buprenorphine administration with hot water were similar compared with BEMA Buprenorphine administration with either cold water or water at room temperature.

Plasma norbuprenorphine peak (Cmax) and total (AUC0-t) exposures following BEMA Buprenorphine administration with cold water were similar compared with BEMA Buprenorphine administration with water at room temperature.

2.5 General Biopharmaceutics

2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The pivotal pharmacokinetic studies were conducted with the TBM formulations, [redacted]

2.5.2 Are the [redacted] and [redacted] formulations providing similar buprenorphine concentrations?

Study BUP-117

Study BUP-117 provided the buprenorphine and norbuprenorphine exposure information from a single dose 300 µg Belbuca [redacted] and [redacted] formulations (see Section 2.2.4.1 for study description; See Table 44).

Table 44 Comparison of [redacted] and [redacted] BEMA Formulations

[redacted]

As previously presented above, [redacted] were different for [redacted] and [redacted] Both formulations are designated as to-be-marketed formulations. The Table 45 contains Cmax and AUC values of the two formulations.

Table 45 Mean (%CV) Buprenorphine Cmax and AUC values after single dose of 300 µg Belbuca

Parameter	**BEMA Buprenorphine ([redacted] 300 µg N=21**	**BEMA Buprenorphine ([redacted] 300 µg N=22**
AUC_{last} (ng•h/mL)	2.00±0.577 (28.9)	2.04±0.6754 (33.1)
AUC_{inf} (ng•h/mL)	2.23±0.631 (28.3)	2.26±0.689 (30.5)
C_{max} (ng/mL)	0.367±0.0970 (26.5)	0.470±0.467 (99.4)

A large % CV was observed for buprenorphine Cmax for [redacted] formulation. The 90% CIs for buprenorphine AUC after 300 µg BEMA Buprenorphine from 2 formulations ([redacted] and [redacted] were within 0.80 to 1.25 (Table 46). The 90% CI for buprenorphine Cmax lower bound is slightly below of 0.8, perhaps due to a large % CV was observed for buprenorphine Cmax for [redacted] formulation.

Table 46 ANOVA Results for Buprenorphine After Single Oral Doses of BEMA Buprenorphine 300 µg Administered to Fasted Healthy Subjects N=20

Parameter	Geometric Least Squares Means BEMA Buprenorphine 300 µg		Ratio of Means (%)	90% Confidence Interval (%)
	Formulation (b) (4)	Formulation (b) (4)		
AUC_{last} (ng•h/mL)	1.9239	1.8779	102.45	86.0-122.0
AUC_{inf} (ng•h/mL)	2.1724	2.1117	102.88	89.2-118.6
C_{max} (ng/mL)	0.3499	0.3738	93.61	74.9-117.1

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Blood samples were analyzed using a liquid chromatography-tandem mass spectrometry (LC-MS-MS) system equipped with a high performance liquid chromatography (HPLC) column. A typical set of standard calibration curve standards are presented below for buprenorphine and norbuprenorphine (Table 47 and Table 48, respectively).

Table 47 Calibration Standards for buprenorphine assay (BUP-118)

Concentration [ng/mL]	A 0.0250 ng/mL	B 0.0500 ng/mL	C 0.250 ng/mL	D 0.500 ng/mL	E 1.00 ng/mL	F 2.50 ng/mL	G 4.50 ng/mL	H 5.00 ng/mL
Batch 1	(b) (4)							
Batch 3								
Batch 4								
Batch 5								
Batch 6								
Batch 9								
Batch 10								
Batch 7								
Batch 8								
Batch 11								
Batch 12								
n	11	11	11	11	11	11	11	11
Overall Mean	0.0246	0.0517	0.252	0.500	1.00	2.49	4.44	4.95
S.D.	0.000526	0.00219	0.00644	0.00848	0.0188	0.0282	0.0845	0.0836
%CV	2.1	4.2	2.6	1.7	1.9	1.1	1.9	1.7
%Bias	-1.6	3.4	0.8	0.0	0.0	-0.4	-1.3	-1.0

Table 48 Calibration Standards for norbuprenorphine assay (BUP-118)

Concentration [ng/mL]	A 0.0200 ng/mL	B 0.0400 ng/mL	C 0.200 ng/mL	D 0.400 ng/mL	E 0.800 ng/mL	F 2.00 ng/mL	G 3.60 ng/mL	H 4.00 ng/mL
Batch 1								(b) (4)
Batch 3								
Batch 4								
Batch 5								
Batch 6								
Batch 9								
Batch 10								
Batch 7								
Batch 8								
Batch 11								
Batch 12								
Batch 16								
n	12	12	12	12	12	12	12	12
Overall Mean	0.0188	0.0394	0.206	0.412	0.816	2.04	3.57	3.96
S.D.	0.00163	0.00119	0.00733	0.0129	0.0207	0.0475	0.0403	0.0569
%CV	8.7	3.0	3.6	3.1	2.5	2.3	1.1	1.4
%Bias	-6.0	-1.5	3.0	3.0	2.0	2.0	-0.8	-1.0

A typical set of values for quality control samples for buprenorphine and norbuprenorphine are presented below (Table 49 and Table 50, respectively):

Table 49 Analytical Performance of Buprenorphine Quality Control Samples in Human K2-EDTA Plasma (Study BUP-118)

Run Date	Curve Number	QC Low 0.0750 ng/mL	QC Medium 0.500 ng/mL	QC High 4.00 ng/mL	QC Very High 25.0 ng/mL
12-Jun-2013	1				(b) (4)
13-Jun-2013	3				
13-Jun-2013	4				
14-Jun-2013	5				
14-Jun-2013	6				
14-Jun-2013	9				
14-Jun-2013	10				
15-Jun-2013	7				
15-Jun-2013	8				
15-Jun-2013	11				

		(b) (4)			
17-Jun-2013	12				
Mean		0.0714	0.489	3.90	25.1
S.D.		0.00287	0.0191	0.185	
%CV		4.0	3.9	4.7	
%Theoretical		95.2	97.8	97.5	100.4
%Bias		-4.8	-2.2	-2.5	0.4
n		40	40	40	2
Overall %CV		4.2			
# > 15%Bias					

Table 50 Analytical Performance of norbuprenorphine Quality Control Samples in Human K2-EDTA Plasma (Study BUP-118)

Run Date	Curve Number	QC Low 0.0600 ng/mL	QC Medium 0.400 ng/mL	QC High 3.20 ng/mL	QC Very High 20.0 ng/mL
12-Jun-2013	1		(b) (4)		
13-Jun-2013	3				
13-Jun-2013	4				
14-Jun-2013	5				
14-Jun-2013	6				
14-Jun-2013	9				
14-Jun-2013	10				
15-Jun-2013	7				
15-Jun-2013	8				
15-Jun-2013	11				

						(b) (4)
17-Jun-2013	12					
27-Jun-2013	16					
Mean		0.0560	0.393	3.06	20.6	
S.D.		0.00210	0.0162	0.0757		
%CV		3.8	4.1	2.5		
%Theoretical		93.3	98.3	95.6	103.0	
%Bias		-6.7	-1.8	-4.4	3.0	
n		42	42	42	2	
Overall %CV		3.5				

3 Detailed Labeling Recommendations

The following paragraphs are recommended for Belbuca.

2.4 Dosage Modifications in Patients with Severe Hepatic Impairment

In patients with severe hepatic impairment (i.e., Child-Pugh C), reduce the starting and titration incremental dose by half that of patients with normal liver function [see Warnings and Precautions (5.11), Use in Special Populations (8.6), Clinical Pharmacology (12.3)].

2.5 Dosage Modifications in Patients with Oral Mucositis

In patients with known or suspected mucositis, reduce the starting dosage and titration incremental dosage by half compared to patients without mucositis [see Warnings and Precautions (5.15), Clinical Pharmacology (12.3)].

12.3 Pharmacokinetics

Absorption

Systemic plasma levels of buprenorphine increased in a linear manner (Cmax and AUC) over the single dose range of 75 to 1200 mcg as shown in Table 7. The absolute bioavailability of BELBUCA ranged from 46 to 65%.

Table 7: Mean (± SD) BELBUCA Pharmacokinetic Parameters

	Table 7: Mean (± SD) BELBUCA Pharmacokinetic Parameters				
Regimen	Dosage (mcg)	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	AUC0-∞ (h·ng/mL)	T_{max}* (hr)
Single Dose	75	0.17±0.30	0.46±0.22	0.63±0.24	3.00 (1.50-4.00)
	300	0.47±0.47	2.00±0.68	2.3±0.68	32.50 (0.50-4.00)
	1200	1.43±0.45	9.6±2.9	10.5±3.32	3.00 (1.00-4.00)
[redacted]					(b) (4)
	* T_{max} values reported as median and range				

Following the multiple dose administration (60 to 240 mcg every 12 hours) of BELBUCA, apparent steady-state buprenorphine plasma concentrations was achieved prior to the 6th dose. Buprenorphine steady-state Cmax and AUC increased proportional to dose.

Systemic exposure to buprenorphine from BELBUCA film was reduced by 23-27% by the ingestion of liquids (cold, hot and room temperature water) during film administration; additionally coadministration with low pH liquid, such as decaffeinated cola, decreased buprenorphine exposure from BELBUCA by approximately 37%. The consumption of liquids should be avoided until the buccal film has completely dissolved [see Dosage and Administration (2.5)].

Distribution
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Elimination

Metabolism
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

Excretion
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4%

conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine was free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Based on multiple dose studies performed with BELBUCA, the mean plasma elimination half-life of buprenorphine was 27.6±11.2 hours.

Drug Interactions

CYP3A4 Inhibitors and Inducers: Buprenorphine (b) (4) by CYP3A4. The relatively low plasma concentrations of buprenorphine and its principal metabolite, norbuprenorphine, resulting from therapeutic doses of BELBUCA are not expected to raise significant drug-drug interaction concerns. (b) (4)

The interaction of buprenorphine with all CYP3A4 inducers has not been studied. [see Drug Interactions (7)].

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine has been found to be a moderate CYP2D6 inhibitor in in vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

Specific Populations

Hepatic Impairment

BELBUCA has not been evaluated in patients with severe hepatic impairment. The pharmacokinetics of buprenorphine following an IV infusion of 0.3 mg of buprenorphine were compared in 8 patients with mild hepatic impairment (Child-Pugh A), 4 patients with moderate impairment (Child-Pugh B) and 12 subjects with normal hepatic function. Buprenorphine and norbuprenorphine plasma levels did not increase in mild or moderately impaired patient cohorts.

In another pharmacokinetic study, the disposition of buprenorphine was determined after administering a 2.0/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function. In subjects with mild hepatic impairment, the changes in mean Cmax , AUC0-last, and half-life values of buprenorphine were not clinically significant. No dose adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean Cmax , AUC0-last, and half-life values of buprenorphine were increased. [see Warnings and Precautions (5.11) and Use in Specific Populations (8.6)].

Table x. Changes in Pharmacokinetic Parameters in Subjects With Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects
Moderate	C_{max}	8%
	$AUC_{0\text{-last}}$	64%
	Half-life	35%
Severe	C_{max}	72%
	$AUC_{0\text{-last}}$	181%
	Half-life	57%

Oral Mucositis
In an open-label pharmacokinetic study in 6 cancer patients with Grade 3 mucositis, buprenorphine was absorbed more rapidly from BELBUCA resulting in a higher Cmax (~79%) and AUC (~56%) compared to age- and gender-matched healthy control patients. [see Dosage and Administration (2.5), Warnings and Precautions (5.15)].

> Note: In the Dosage and Administration section the following may be suggested: In patients with known or suspected mucositis, reduce the starting dosage and titration incremental dosage by half compared to patients without mucositis.

Geriatric Patients
No notable differences in pharmacokinetics were observed from population PK analysis in subjects aged 65 compared to younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Patients
BELBUCA has not been studied in children and is not recommended for pediatric use.

Sex
No notable sex differences in pharmacokinetics were observed from population PK analysis.

Renal Impairment
No studies in patients with renal impairment have been performed with BELBUCA. In an independent study, the effect of impaired renal function on buprenorphine pharmacokinetics after IV bolus and after continuous IV infusion administration was evaluated; and no notable differences in

plasma buprenorphine concentrations were identified in patients with normal renal function compared to impaired or renal failure.

4 Appendices

4.1 Proposed Package Insert

(b) (4)

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.3 Consult Review (including Pharmacometric Reivews)

Not applicable.

4.4 Cover Sheet and OCPB Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	207932	**SDN**	
Applicant	Endo Pharmaceuticals, Inc.	**Submission Date**	12/23/14
Generic Name	Buprenorphine HCl buccal film	**Brand Name**	Belbuca
Drug Class	Analgesic		
Indication	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (b) (4) (b) (4)		
Dosage Regimen	Every 12 hours		
Dosage Form	Buccal film	**Route of Administration**	Buccal
OCP Division	DCP 2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	David Lee	Yun Xu	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	2/21/15	**74-Day Letter Date**	3/7/15
Review Due Date	9/11/15	**PDUFA Goal Date**	10/23/15

Application Fileability
Is the Clinical Pharmacology section of the application fileable? ☑Yes ☐ No If no list reason(s)
Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter? ☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability		2	Comparison against Buprenex i.v.
☑ Relative Bioavailability			Note: comparison against generic ROXANE sublingual 8 mg tablet (see below for further comments)
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	Linearity (75 to 1200 µg)
	☑ Multiple Dose	1	Tested 60, 120, 180 and 240 µg BID regimen
Patients	☑ Single Dose	1	Grade 3 mucositis with 60 µg
	☐ Multiple Dose		
☐ Mass Balance Study			
☑ Other (e.g. dose proportionality)		4	Formulations (comparison of Formulations (b) (4) and (b) (4) the TBM formulations); pH effect (high and

		low); temperature effect (hot, cold and room)
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		References Subutex
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☑ QT	1	Supratherapeutic dose 3000 µg with naltrexone block; consult to IRT team;
Pharmacometrics		
☑ Population Pharmacokinetics	2	From Phase 3 studies
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	12
Total Number of Studies to be Reviewed				8

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	Studies were conducted with TBM formulations
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	References Subutex
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	

4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505 b)(2) application?	☑Yes ☐No ☐N/A	Buprenex & Subutex as references; ROXANE's buprenorphine sublingual tablet was also used due to Subutex withdrawn from the market in 2012 for reasons not related to safety
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		

1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	No formal analysis was conducted; however, opioid PD effect using the pupillometry was explored
6. 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?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☑Yes ☐No ☐N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

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

/s/

DAVID J LEE
09/11/2015

YUN XU
09/11/2015