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RESEARCH**

APPLICATION NUMBER:

207932Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA	207932
Applicant	Endo Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) names	Belbuca buccal film / Buprenorphine hydrochloride
Dosage forms / Strength	Buccal film / 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
Recommended:	Approval

1. Introduction

Endo Pharmaceuticals, Inc. (“Applicant”) submitted this new drug application (NDA) for Belbuca (buprenorphine) buccal film 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 (i.e., chronic pain). The Applicant conducted the clinical development program under IND 72,428 and proposes to market Belbuca in 7 strengths, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg, to be applied to the buccal mucosa twice daily. The IND was submitted by BioDelivery Sciences International (BDSI) (also referred to as the “Applicant” throughout this review) on December 15, 2005, and the IND was transferred to Endo on January 6, 2012.

The Applicant submitted this NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act referencing the approved products Buprenex (buprenorphine hydrochloride injection; EQ 0.3 mg base/ml; NDA 18401; Indivior, Inc., approved 12/29/1981) and Subutex (buprenorphine hydrochloride sublingual tablets; EQ 2 mg and 8 mg base; NDA 20732; Indivior, Inc., approved 10/8/2002). Buprenex is indicated for the relief of moderate to severe pain, and Subutex is indicated for the treatment of opioid dependence. Subutex marketing has been discontinued; however, it was not discontinued or withdrawn for reasons of safety or efficacy (80 FR 8088).

The NDA submission consists of chemistry, manufacturing, and controls (CMC) information; nonclinical information; biopharmaceutics data; and clinical pharmacology and clinical data from seven pharmacokinetic (PK) studies; including a relative bioavailability (BA) study

(BUP-118) bridging to the agency's previous findings for Subutex,¹ an absolute BA study bridging to the agency's previous findings for Buprenex (BUP-117), a PK study in patients with oral mucositis (BUP 121), and a thorough QT (tQT) study (BUP-150); three Phase 3 randomized, double-blind clinical trials (BUP-301, BUP-307, BUP-308); and two Phase 3 open-label long-term safety studies (BUP-305, BUP-309).

The Applicant requested priority review for this NDA citing that Belbuca fulfills an unmet medical need and provides healthcare providers and patients with a new CIII option for the management of chronic pain. Despite the fact that most other opioids approved for a chronic pain indication are Schedule II, Butrans, a transdermal film product containing buprenorphine CIII is already available to treat chronic pain. The Applicant did not provide any data to support that Belbuca, if approved, would provide a significant improvement in the safety or effectiveness over this already available therapy. Therefore, the Applicant's request was denied and this NDA submission was reviewed on a standard review clock (i.e., 10-month).

I have concluded that this application should receive an Approval action and have discussed my reasons for this decision in Section 13 below. This review will cover the safety and efficacy of Belbuca for use in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, and it will specifically explore the safety of the product with respect to QT interval prolongation.

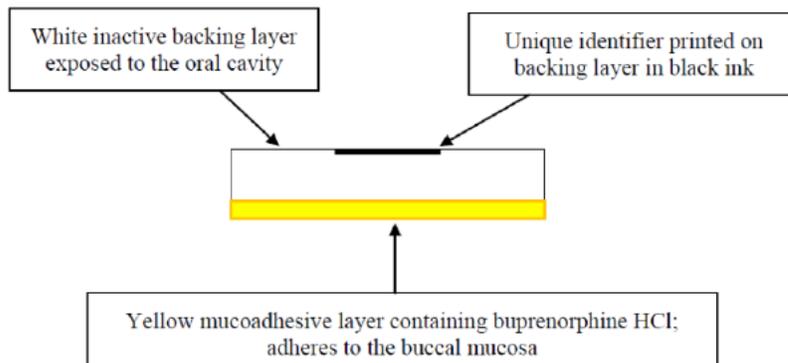
2. Background

Buprenorphine is a long-acting partial agonist at the mu-opioid and ORL-1(nociceptin) receptors and an antagonist at the kappa-opioid receptor with analgesic properties. The clinical actions are thought to result from high affinity binding to, and slow dissociation from, mu opioid receptors. Buprenorphine exhibits the typical properties of an opioid agonist, including life-threatening central nervous system (CNS) and respiratory system depression; however, it exhibits a ceiling effect to those properties. Buprenorphine is a Schedule III substance under the Controlled Substances Act (CIII) and is approved as an injection and an extended-release transdermal film for pain, in addition to several products for the treatment of opioid dependence.

Belbuca is a mucoadhesive buccal film that employs BDSI's BioErodable MucoAdhesive (BEMA) technology (Figure 1). BEMA technology consists of a flexible, water soluble polymeric film that adheres to the moist buccal mucosa and completely dissolves. The film is designed to enable buccal absorption of buprenorphine, therefore, avoiding gastrointestinal absorption and poor oral bioavailability due to the extensive first pass metabolism that is seen with buprenorphine. Belbuca was also referred to as BEMA buprenorphine throughout development, and, as such, the reviews conducted on this NDA use that nomenclature and Belbuca interchangeably.

¹ Conducted with Roxane's buprenorphine hydrochloride (EQ 8 mg base, ANDA 78633) sublingual tablet because Subutex is discontinued.

Figure 1. Schematic of Belbuca Viewed from the Side (not to scale)



Source: Applicant

The Division held Pre-IND, End-of-Phase 2, Type A, Type C, and Pre-NDA meetings with the Applicant during clinical development where agreement was reached that one positive adequate and well-controlled clinical trial would be sufficient to support a chronic pain indication as would a safety database that included at least 400 patients exposed at 24 weeks and at least 200 patients exposed at 48 weeks. The Division also agreed that a primary endpoint of change from baseline to week 12 in the mean of average daily pain intensity scores on an 11-point numeric rating scale (NRS) would be acceptable for a chronic low back pain (CLBP) population. The Applicant initially conducted one trial in CLBP in opioid-naïve and opioid-experienced patients that failed (see discussion in Section 7 of this review). In a subsequent Type A meeting the Applicant proposed (b) (4)

however, the Division cautioned that this proposal would only support an indication that (b) (4)

The Applicant ultimately decided to conduct two separate adequate and well-controlled clinical trials, one in an opioid-naïve CLBP population and one in an opioid-experienced CLBP population. The Applicant was also advised that conducting a tQT study under naltrexone blockade would render the results uninterpretable, both prior to conducting the study and after conducting the study under naltrexone blockade.

3. CMC/Device

The Quality Review Team consisted of Sukhamaya Bain, PhD (Drug Substance), Christopher Hough, PhD (Drug Product), Shujun Chen, PhD (Process), Erika Pfeiler, PhD (Microbiology), Juandria Williams, PhD (Facility), Fang Wu, PhD (Biopharmaceutics), and Don Henry (Project/Business Process Manager), and the team was led by Ciby Abraham PhD (Technical Lead) and Paul Perdue (ORA Lead). There are no unresolved CMC issues, and CMC recommends approval of this application with a 24-month expiry, based on the stability data provided, and the following storage statement: “Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).” The following is a summary of that review.

The drug substance for Belbuca is buprenorphine HCl, which is a white or off-white crystalline solid. The drug product utilizes BDSI’s BEMA technology, which has been used in

other FDA-approved drug products, including Onsolis (fentanyl buccal soluble film) and Bunavail (buprenorphine and naloxone buccal film). Each Belbuca buccal film is packaged in a child-resistant, (b) (4)/foil (b) (4) package, and this is the same packaging material used for Bunavail. Belbuca is a non-sterile single-dose, immediate-release oral drug product containing 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, or 900 mcg of buprenorphine per film. The film is light yellow to yellow on one side (i.e., the mucoadhesive layer) and white to off-white on the other side (i.e., the backing layer). The backing layer is printed with a unique identifier in black ink. Two formulations were developed for commercial production (i.e., (b) (4)

(b) (4)
Each strength has a different color container.

The drug substance specifications are satisfactory. Dr. Bain noted that these specifications meet USP requirements for buprenorphine HCl; however, the Applicant did not verify the USP method for impurities or one of the facilities' method for (b) (4). Dr. Bain noted that this information could be verified during inspection. Dr. Bain noted that the Pharmacology/Toxicology team expressed concern that the limits for the impurities were set above ICH Q3A(R2) thresholds. An information request was sent to the Applicant, and the Applicant tightened the Individual Specified Impurity limit to NMT (b) (4)%, as per ICH Q3A(R2).

From a drug product perspective, Dr. Hough notes that “[a]ll excipients are listed in the FDA inactive ingredients database, and none surpasses the composition by weight, calculated on the basis of daily dose of other drugs listed in the inactives database. None of the excipients are novel or animal derived and all are BSE/TSE free (certifications are provided). All excipients, with the exception of the black ink are compendial (NF or USP) and are controlled according to their respective monographs, and USP/NF analytical methods. The black ink used to print identifying information on the backing of the films is TekPrint[,]...which has been used before for other pharmaceutical products. The amount of ink in the drug product is negligible.” Dr. Hough further notes that “[t]he black ink complies with FD&C regulations for food and is present at relatively insignificant amounts in the drug product.” Regarding drug product specifications, Dr. Hough noted that “[t]he acceptance criteria for most degradants have been set higher than necessary. However, [pharmacology/toxicology] has evaluated these limits as adequate. A tightening of the limit for (b) (4) has been requested.”

Dr. Williams found all of the facilities to be acceptable, based on inspectional history and experience or inspectional history alone, and did not recommend preapproval inspection of any of the facilities. However, Dr. Williams recommends post-approval coverage during the next inspection for several of the facilities.

Dr. Pfeiler noted that “[t]he microbial limits specification for Belbuca is acceptable from a Product Quality Microbiology perspective.”

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by Gary Bond, PhD, with secondary concurrence by Jay Chang, PhD, and Dan Mellon, PhD. Dr. Bond notes that “[f]rom the nonclinical perspective, this NDA may be approved. Nonclinical data provide evidence for human safety for the expected systemic exposure to buprenorphine and potential local toxicity from BEMA buprenorphine film.” The following is a summary of that review.

Dr. Bond notes that the Applicant was informed that no chronic local toxicity study would be necessary if an adequate bridge was established between the to-be-marketed product and the reference product, Subutex, and local toxicity was adequately evaluated in clinical studies. In addition, the Applicant submitted a 28-day buccal toxicity study of BEMA buprenorphine in beagle dogs, which was originally submitted by BDSI to support the development of Bunavail, to support clinical safety in regard to potential local toxicity with repeated applications of the BEMA disc with buprenorphine. In this study, drug was administered to the same buccal site three times a day for 28 consecutive days. No additional buprenorphine-related effects were noted when compared to BEMA placebo except for what is already known about the pharmacological effect of buprenorphine in a nonclinical model. The only sign of local toxicity was a minimal to slight inflammatory cell infiltration of the oral mucosa, which was seen in both groups. The highest proposed strength of Belbuca has approximately 1.2 fold more buprenorphine per cm^2 than the BEMA buprenorphine disc used in the nonclinical study. Dr. Bond considered these differences of minimal importance for determining local toxicity. Furthermore, he identified no issues for determining potential systemic toxicity, as blood levels would be used to compare human and animal exposures. Although Dr. Bond noted several limitations for the local nonclinical toxicity of buprenorphine in BEMA buprenorphine to inform the assessment of potential local toxicity with Belbuca, Dr. Bond determined that “[t]he dog local tissue toxicity data support the proposed human dosing with Belbuca.”

Dr. Bond noted that “there are no nonclinical-based safety issues related to impurities, degradants, and excipients.”

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was conducted by David Lee, PhD, with secondary concurrence by Yun Xu, PhD. According to the clinical pharmacology team, this NDA is acceptable pending agreement between the Applicant and the Agency on the language in the package insert. A QT-interdisciplinary team (QT-IRT) consult was obtained, and the primary review was conducted by Jiang Liu with secondary concurrence by Norman Stockbridge, MD, PhD.

The biopharmaceutics review was conducted by Fang Wu, PhD, with secondary concurrence by John Duan, PhD. The proposed dissolution method and acceptance criterion are adequate, and an approval is recommended for this NDA from their perspective.

Clinical Pharmacology

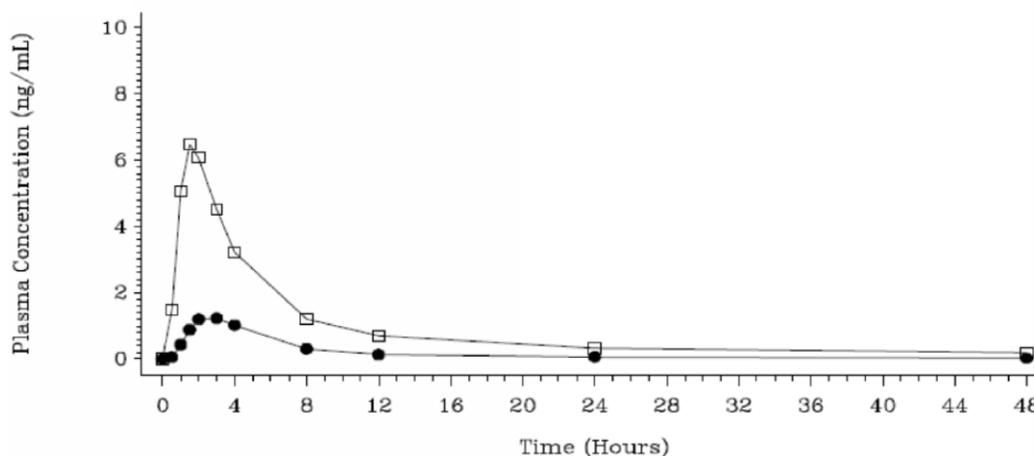
The Applicant submitted seven PK studies (i.e., BUP-115, BUP-116, BUP-117, BUP-118, EN3409-120, BUP-121, and BUP-150), including a PK study in patients with oral mucositis, to support the proposed product. All of the studies were conducted using the to-be-marketed formulation(s) with the exception of the tQT study (BUP-150). Additionally, the Applicant performed a population PK analysis based on data using the to-be-marketed formulations in the Phase 3 studies to characterize the effect, if any, of patient factors (e.g., age or sex) on buprenorphine exposure. The following is a summary of the clinical pharmacology and QT-IRT reviews.

Relative Bioavailability

Study BUP-118 evaluated the relative bioavailability between BEMA buprenorphine and buprenorphine sublingual tablets, and study BUP-117 evaluated the relative bioavailability between the two proposed to-be-marketed formulations.

BUP-118 was a randomized, open-label, single-dose, crossover study comparing 900 mcg of BEMA buprenorphine ((b) (4) administered with high and low pH liquids and without liquids compared to buprenorphine HCl 8 mg sublingual tablet conducted in healthy volunteers under fasted conditions. Dr. Lee notes that “[b]uprenorphine mean C_{max} 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.” The results from that study are presented in Figure 2 below.

Figure 2. Mean Plasma Concentrations of Buprenorphine Versus Time (linear scale) after BEMA Buprenorphine (900 mcg; filled-in circles) and Sublingual Buprenorphine (8 mg; open squares)



Source: Dr. Lee’s review, pg. 34

BUP-117 was a randomized, single-dose, 5-sequence, 5-period, crossover study in naltrexone-blocked healthy volunteers comparing the pharmacokinetics of the (b) (4) formulation of BEMA Buprenorphine 75 mcg and 300 mcg, the (b) (4) formulation of BEMA Buprenorphine 300 mcg and 1200 mcg, and intravenous buprenorphine 300 mcg (Buprenex Injection, given over two minutes) under fasted conditions. This study allows for a comparison of the two different to-be-marketed formulations. Refer to Table 1 below for a listing of the relevant PK parameters to compare the 300 mcg strength of the (b) (4) formulation to the 300 mcg strength of the (b) (4) formulation. Dr. Lee notes that “[t]he 90% [confidence intervals] (CIs) for buprenorphine

AUC after 300 [mcg] 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 0.8 (74.9%), perhaps due to a large %CV, [which] was observed for [the] buprenorphine Cmax for [the] (b) (4) formulation.” The 90% CI for buprenorphine Cmax upper bound is within 1.25.

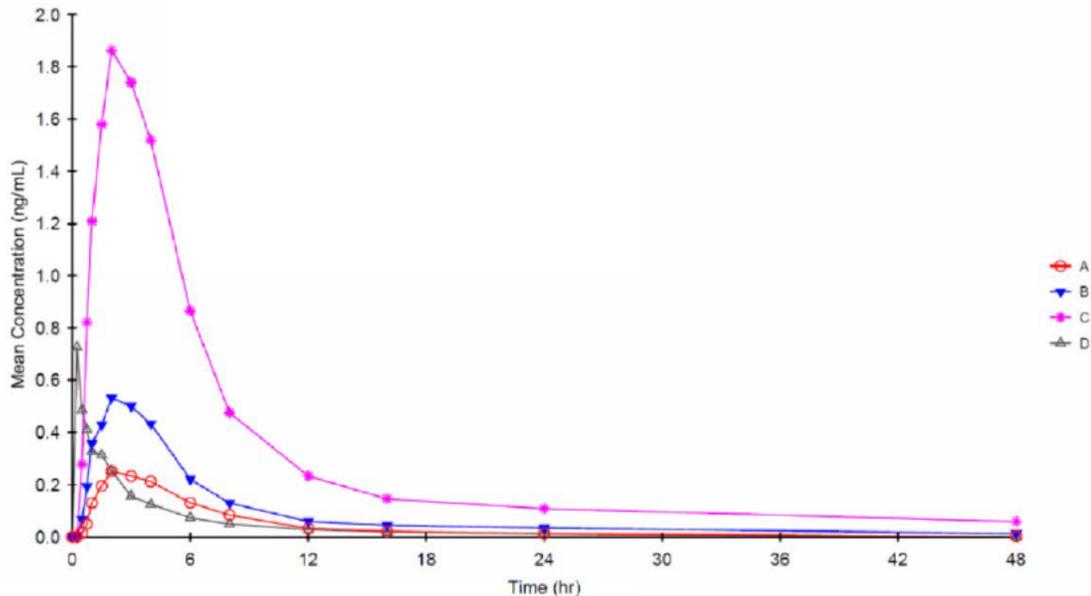
Absolute Bioavailability

Two studies evaluated the absolute bioavailability of buprenorphine, based on a comparison of Belbuca to Buprenex (IV buprenorphine).

BUP-115 was an open-label, single-dose, parallel-group study conducted in healthy volunteers to evaluate the PK of 200 mcg, 500 mcg, and 1500 mcg of 3 different formulations of BEMA buprenorphine ((b) (4)), respectively) compared to a 2-minute intravenous injection of Buprenex 0.15 mg under naltrexone blockade for the intermediate and high BEMA buprenorphine doses and Buprenex.

Mean Cmax values (Mean±SD (%CV)) were 0.551±0.122 ng/ml (22.10) and 0.726±0.117 ng/ml (16.07), median Tmax values (median (range)) were 2.00 h (1.50-3.00) and 0.25h (0.25-0.25), and mean AUC0-inf values (Mean±SD (%CV)) were 4.399±1.114 h*ng/ml (25.32) and 2.026±0.2956 h*ng/ml (14.59) for buprenorphine for BEMA buprenorphine 500 mcg and Buprenex, respectively. The mean buprenorphine concentrations are presented graphically below (Figure 3). Dr. Lee notes that “[t]he mean absolute bioavailability (based on AUCinf) of buprenorphine from Belbuca was approximately 0.65 at dose level of [500 mcg].”

Figure 3. Mean Buprenorphine Concentration–Time Data after BEMA Buprenorphine 200 mcg (Treatment A (b) (4)), BEMA Buprenorphine 500 mcg (Treatment B; (b) (4) BEMA Buprenorphine 1500 mcg (Treatment C (b) (4) and Buprenex 0.15 mg Injection (Treatment D)

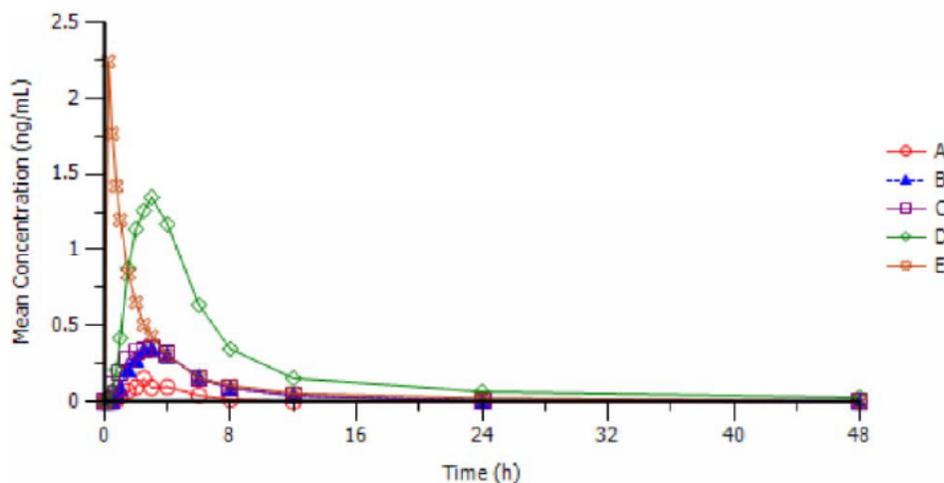


Source: Dr. Lee’s review, pg. 24

Study BUP-117 also explored the absolute bioavailability of buprenorphine; for a description of that study, refer to the “Relative Bioavailability” section above. The mean buprenorphine

concentrations are presented graphically below (Figure 4). Dr. Lee notes that “[t]he mean absolute bioavailability ranged from 0.46 to 0.51 across the 4 buccal doses.”

Figure 4. Mean Buprenorphine Concentration–Time Profiles (linear scale) after Administration of BEMA Buprenorphine Buccal Soluble Film 75 mcg, (b) (4) (Treatment A); 300 mcg, (b) (4) (b) (4) (Treatment B); 300 mcg, (b) (4) (b) (4) (Treatment C); 1200 mcg, (b) (4) (b) (4) (Treatment D); and Buprenorphine Injection 300 mcg, (Treatment E)



Source: Dr. Lee’s review, pg. 27

Single-dose PK

Single-dose PK of BEMA buprenorphine was studied in five clinical pharmacology studies (i.e., BUP-115, BUP-117, BUP-118, EN3409-120, and BUP-121) in addition to the tQT study. Table 1 lists the buprenorphine single-dose PK parameters with Belbuca at various doses of the to-be-marketed formulation. Note that study EN3409-120 is referred to as BUP-120 in the table.

Table 1. 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

Source: Dr. Lee’s review, pg. 4

Dr. Lee notes that “[a]fter Belbuca 3000 [mcg] single dose (QT study; (b) (4)), which is not the [to-be-marketed formulation]) the observed Cmax and AUC0-24 was 3.66 ng/mL and 25.3 ng.hr/mL, respectively (refer to discussion in “QT Assessment” below for the applicability of data using this formulation to the to-be-marketed formulation).

Multiple-dose PK

BUP-116 was an open-label, dose-escalating, multiple-dose study conducted in healthy volunteers under naltrexone blockade. Ten subjects were sequentially dosed starting at 60 mcg every 12 hours up to 240 mcg every 12 hours, where 6 doses were administered at each dose level before proceeding to the next dose level. The multiple-dose PK parameters are summarized in Table 2 below.

Table 2. 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-τ} (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

Source: Dr. Lee's review, pg. 5

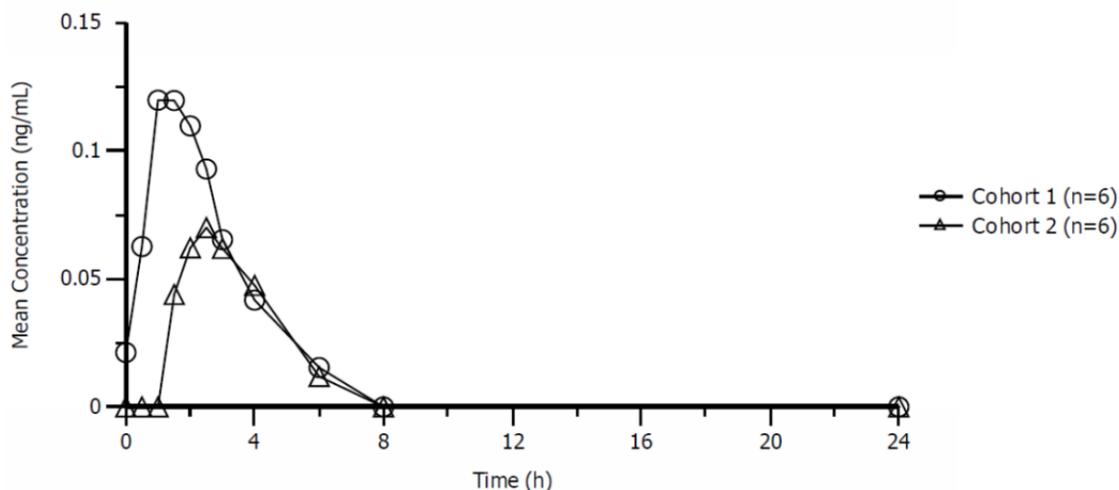
Dose Linearity

Single doses of BEMA buprenorphine in study BUP-117 demonstrated a linearly increased C_{max} and AUC for buprenorphine with an increasing dose from 75 mcg to 1200 mcg. Similarly, study BUP-116 demonstrated that buprenorphine C_{max} and AUC increased linearly with an increase in dose from 60 mcg to 240 mcg after 6 doses administered every 12 hours.

Grade 3 Mucositis

BUP-121 was an open-label study evaluating a single-dose of BEMA buprenorphine 60 mcg in 6 subjects with cancer and Grade 3 oral mucositis (cohort 1) and 6 healthy subjects without oral mucositis (cohort 2). In cohort 1, the buccal film was applied to an area of mucositis, and in cohort 2, the buccal film was applied to a similar area of the buccal mucosa as a matched subject in cohort 1. Dr. Lee notes that “[i]n patients with Grade 3 mucositis...buprenorphine C_{max} and AUC values were 80% higher and 60% greater compared to age and gender matched healthy subjects, [respectively]” (Figure 5). Therefore, the clinical pharmacology team recommended a dosage adjustment in patients with mucositis (i.e., in patients with known or suspected mucositis, reduce the starting dosage and titration incremental dosage by half compared to patients without mucositis).

Figure 5. Mean Plasma Buprenorphine Concentration-Time Profiles on Linear and Semi-Logarithmic Scales in Subjects with (Cohort 1) and without (Cohort 2) Oral Mucositis



Source: Dr. Lee's review, pg. 40

Effect of Temperature and pH

Study EN3409-120 and study BUP-118 evaluated the effect of temperature and pH, respectively, on the pharmacokinetics of buprenorphine with a single dose of Belbuca 900 mcg. C_{max} and AUC were lower with hot water, cold water, and room temperature water as compared to without liquid and lower with low pH liquid (i.e., room temperature decaffeinated cola). Coadministration of Belbuca with a high pH liquid had no significant effect on buprenorphine exposure. Due to the effect of temperature and pH on buprenorphine exposure, Dr. Lee recommends labeling the product to avoid consumption of liquids until the buccal film has completely dissolved.

Age and Sex

The Applicant performed a population pharmacokinetic analysis, based on data from the Phase 3 studies, to characterize any patient factors that may influence variability in buprenorphine exposures. This analysis did not identify any such variables (e.g., age, body size, sex).

QT Assessment

BUP-150 was a randomized, double-blind, single-dose, placebo- and positive-controlled, 4-period, crossover study to evaluate the effects of buprenorphine on cardiac repolarization in healthy subjects (tQT study). The study evaluated 3,000 mcg (b) (4) of BEMA buprenorphine HCl (not the to-be-marketed formulation) under naltrexone blockade. Dr. Lee notes that "Although this study did not use the to-be-marketed formulations, (b) (4) (b) (4) the exposure information obtained from [a] 3000 [mcg] single dose may be [useful for] assessing the overall safety... The comparison of (b) (4) to either (b) (4) or (b) (4) appears to indicate that the difference is minimal in nature." The study included the following treatment arms:

- BEMA buprenorphine 3000 mcg on Day 1 with 4 doses of naltrexone 50 mg starting on Day 0
- BEMA placebo on Day 1 with 4 doses of naltrexone 50 mg starting on Day 0

- BEMA placebo on Day 1 with 4 doses of naltrexone *placebo* starting on Day 0
- Moxifloxacin 400 mg on Day 1 with 4 doses of naltrexone placebo starting on Day 0

Naltrexone was included to protect the subjects from potential opioid toxicity, and it was also administered with placebo in a separate treatment group to control for naltrexone effects. However, the study design does not control for a mitigating effect that naltrexone may have on any buprenorphine-associated QT prolongation. The QT-IRT noted that QT prolongation has been observed with buprenorphine and that “[n]altrexone appears to blunt the QTc prolongation effect of buprenorphine. The mechanism underlying this finding is unknown.” The QT-IRT estimated the QT prolonging effect with Belbuca (Table 3), based on existing data available to the Agency that describe a buprenorphine concentration-QT prolongation relationship.

Table 3. Predicted QTc Effect s at Various Clinically Relevant Concentrations

At Interested Mean C _{max} (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)

Source: QT-IRT review, pg. 2

The QT-IRT further noted that “[b]ecause of the uncertainty associated with provided mean C_{max} values, marginal clinically relevant QTc prolongation...may occur for BEMA with doses of 600 [mcg] q12h or above.”

Refer to the Safety section below for additional discussion of the effects of Belbuca on the QT interval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The clinical efficacy portion of this NDA review was conducted by Pamela Horn, MD. The statistical review was conducted by James Travis, PhD, with secondary concurrence by Freda Cooner, PhD.

The Applicant submitted the results from three Phase 3, multicenter, double-blind, placebo-controlled, enriched enrollment, randomized withdrawal clinical trials in patients with chronic low back pain (CLBP) to support this NDA. BUP-301, which failed to demonstrate statistical significance for the primary endpoint, was conducted in opioid-naïve and opioid-experienced subjects. Subsequent studies were conducted in opioid-experienced and opioid-naïve populations separately (EN3409-307 and EN3409-308, respectively). Otherwise, the studies were similarly designed. Dr. Horn and Dr. Travis conducted a full review of these studies, as they are the pivotal trials intended to demonstrate efficacy in chronic pain for Belbuca. I will review the salient study design features of study EN3409-307, summarize how the other two studies differ in design, and describe the key efficacy results below.

Study EN3409-307

Title: 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

Primary objective: To compare the analgesic efficacy of BEMA buprenorphine to placebo in patients with moderate-to-severe chronic low back pain

Duration of treatment: 12 weeks

Population: Patients with CLBP for at least 6 months duration who were on a stable dose of around-the-clock opioid analgesic therapy equivalent to between 30 mg and 160 mg oral morphine sulfate equivalents (MSE) per day for at least 4 weeks.

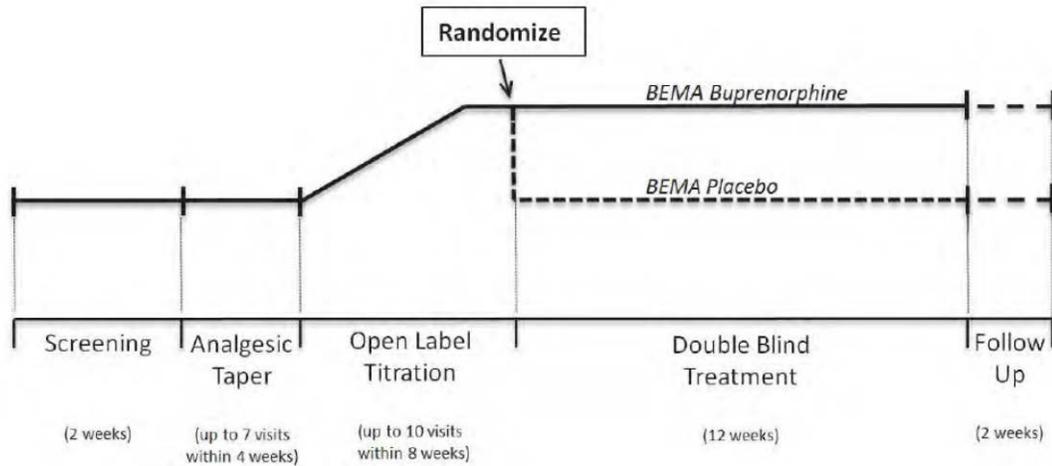
Treatment: Patients were randomized in a 1:1 fashion to one of the following treatment groups.

- Belbuca buccal film (150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, or 900 mcg) applied to the buccal mucosa every 12 hours
- Placebo buccal film

Rescue medication: Hydrocodone/acetaminophen tablets 5 mg / 325 mg

Design: This was a Phase 3, multicenter, double-blind, placebo-controlled, randomized-withdrawal, enriched enrollment study consisting of a 2-week screening phase, a 4-week analgesic taper phase, an 8-week open-label titration phase, a 12-week treatment phase, and a 2-week follow-up phase (Figure 6).

Figure 6. EN3409-307 Study Design Schematic.



Source: Applicant: EN3409-307 Protocol, pg. 33

In the taper phase, patients had their previous around-the-clock opioid dose tapered by 25% every 4 to 8 days until they reached a dose of 30 mg MSE or less. Patients with well-controlled pain (i.e., mean of the average daily pain intensity on an 11-point numeric rating scale [NRS] of 5 in the last 7 days of screening) were required to start the taper without rescue medication in order to confirm they had CLBP of sufficient severity to continue in the study, which was defined as their average daily pain intensity reaching ≥ 5 on the 11-point NRS for 3 consecutive days. Once a patient met this criterion, rescue medication was allowed. Patients with poorly-controlled pain (i.e., ≥ 5 to < 10 on an 11-point NRS over the last 7 days of screening) were allowed to start the taper with rescue medication.

In the titration phase, patients were switched to a dose of open-label Belbuca, based on their prior opioid dose (Table 4). Patients were then titrated to a stable dose of Belbuca (in 150 mcg increments every four to eight days) by the sixth week of the titration phase, as they were required to be on a stable dose for at least two weeks prior to entering the double-blind treatment phase. Patients who achieved a mean pain intensity score that was 4 or less on an 11-point NRS in the last 3 days of the titration phase and at least 2 points lower than their mean score prior to allowing rescue medication in the first 3 days of the taper phase or the last 7 days of the screening phase if the taper phase was started with rescue medication, were randomized to their stable dose of Belbuca or placebo at Day 0 of the double-blind treatment phase.

Table 4. Conversion from Prior Opioid Dose (in MSE) to Belbuca

Prior Daily Opioid MSE (Maintenance Dose + PRN Rescue Dose [mg])	BEMA Buprenorphine Starting Dose (μg Q12h)
30-89	150
90-160	300

Source: Applicant: EN3409-307 Protocol, pg. 40

Primary efficacy endpoint: Change from baseline to Week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores on an 11-point NRS. The baseline

score was the mean of the available pain intensity scores in the last 7 days prior to randomization and the Week 12 score was the mean of the available pain intensity for the last 7 days prior to end of study treatment.

Secondary efficacy endpoints: The Applicant included several secondary efficacy endpoints (refer to Dr. Horn's and Dr. Travis' reviews), including the following that were identified as key and intended to be tested in the order listed below using a sequential gatekeeping procedure.

- Proportion of responders
 - Responder rate at 30% pain reduction
 - Responder rate at 50% pain reduction
- Opioid rescue medication use

Statistical analysis plan: Dr. Travis notes in his review that:

For the primary analysis of the primary efficacy endpoint the applicant used an analysis of covariance (ANCOVA) model with change from baseline to Week 12 in average weekly NRS pain intensity as the dependent variable, treatment as a fixed effect, and screen and baseline pain intensity as covariates. The randomization was stratified by dose level, which is not included as a factor in the model for the final analysis.

The applicant used a mixture of single and multiple imputation strategies for the missing data depending on the reasons for discontinuation. The strategies used are described below:

- Missing values due to AEs/tolerability were imputed using the Screen Observation Carried Forward (SOCF) method. The weekly mean pain intensity score prior to the open-label titration phase was used for imputation.
- Missing values due to lack of efficacy were imputed using the Last Observation Carried Forward (LOCF) method. The latest weekly mean pain intensity score before discontinuation were used for imputation.
- Missing values due to opioid withdrawal were imputed using Baseline Observation Carried Forward (BOCF). The mean pain intensity scores prior to randomization were used for imputation.
- All other types of missing values were imputed using multiple imputation methods. A multiple imputation procedure as described by (Rubin, 1987) was applied to impute the missing values. A total of 10 multiple imputed data sets were created.

The analysis population for the primary efficacy endpoint was the Intent-to-Treat (ITT) population, which was defined by the applicant as all randomized subjects who received at least 1 dose of double-blind study medication.

Dr. Travis further notes that:

The proportion of responders was defined as the cumulative proportion of subjects who achieved pre-specified percent pain reduction in the average pain score recorded in Week 12 of the study from the average pain score recorded in the seven days prior to the open-label titration phase. All subjects who did not complete the study were to be classified as non-responders.

Studies EN3409-308 and BUP-301

Studies EN3409-308 and BUP-301 were very similar in design to study EN3409-307, and the key similarities and differences are noted in Table 5 below. EN3409-308 enrolled patients with CLBP who were opioid naïve, which was defined as being on a stable daily maintenance dose of non-opioid analgesic medication for at least 4 weeks and a maximum of 10 mg MSE “as needed” opioid analgesic medication per day.

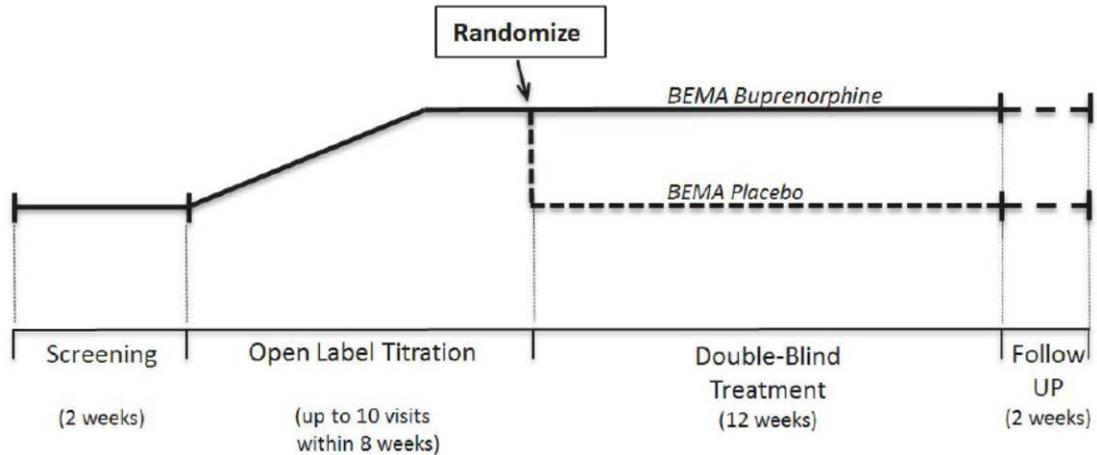
Table 5. Comparison of Studies EN3409-307, EN3409-308, and BUP-301.

	307	308	301
Population	Opioid-experienced subjects with well- or poorly controlled moderate to severe CLBP	Opioid-naïve subjects with poorly controlled moderate to severe CLBP	Opioid-naïve and opioid-experienced subjects with poorly controlled moderate to severe CLBP
Design	12-week, double-blind, placebo-controlled, multicenter, randomized withdrawal		
Open-label titration period	Up to 8 weeks		Up to 4 weeks
Dose (q12h)	Buprenorphine (150/300/450/600/750/900 mcg)	Buprenorphine (150/300/450 mcg)	Buprenorphine (60/120/180/240 mcg)
Rescue medication	1-2 5/325 mg HC/APAP up to 2x per day for first 2 wks of DB period, up to 1x per day thereafter	1 5/325 mg HC/APAP up to 2x per day for first 2 wks of DB period, 1-2 tabs 500 mg APAP up to 1x per day thereafter	2 g/day APAP
Primary efficacy endpoint	Change from double-blind baseline to week 12 of the double-blind treatment phase in the mean of average daily pain intensity scores		

Source: Dr. Horn’s review, pp. 25-6

In addition to the differences noted in Table 5, study EN3409-308 did not include an analgesic taper phase, as patients in this study were considered opioid naïve (Figure 7). All patients were initiated on a 75 mcg dose of Belbuca (once daily the first day and every 12 hours thereafter) and were then titrated to a stable dose in 150 mcg increments every 4 to 8 days. Patients were required to have been successfully titrated to a dose of at least 150 mcg every 12 hours to be continued into the double-blind treatment phase.

Figure 7. EN3409-308 Study Design Schematic.



Source: Applicant: EN3409-308 Protocol, pg. 30

Results

Study EN3409-307 subject disposition:

Dr. Horn reclassified a limited number of patients who discontinued from the open-label titration phase or double-blind treatment phase from the Applicant's administrative reason for discontinuation to discontinuations due to adverse events or lack of efficacy, and I concur with her assessments. The disposition described below represents that reclassification.

Additionally, patients from site 1008 are excluded (see Section 11 of this review for more detail regarding that site). One subject in this study withdrew prior to receiving any study medication after randomization and was not included in the ITT population by the Applicant's definition.

Of the 815 patients who enrolled in the open-label titration phase, 37% discontinued. Table 6 summarizes the reasons for discontinuation in the open-label titration phase for this study.

Table 6. Study EN3409-307, Subject Disposition, Open-label Titration Phase, All Subjects

	n (%)
Screened	1656 (100.0)
Screen Failures ^a	717 (43.3)
Entering Taper Phase ^a	938 (56.6)
Discontinued ^b	124 (13.2)
Enrolled in Open-label Titration Phase ^{c,d}	815 (100.0)
Not Exposed to Study Medication	5 (0.6)
Completed in Open-label Titration Phase	511 (62.7)
Discontinued ^{c,e}	304 (37.3)
Adverse Event	81 (9.9)
Lack of Efficacy	63 (7.7)
Protocol Violation	43 (5.3)
Withdrawal Due to Opioid Withdrawal	1 (0.1)
Withdrawal by Subject	46 (5.6)
Lost to Follow-up	15 (1.8)
Other	55 (6.7)

Source: Dr. Travis' review, pg. 15

Of the patients included in the ITT population, 17% discontinued in the Belbuca group and 43% discontinued in the placebo group from the double-blind treatment phase. Table 7 summarizes the reasons for discontinuation in the double-blind treatment phase for this study.

Table 7. Study EN3409-307, Subject Disposition, Double-blind Treatment Phase, ITT Population

	BEMA Buprenorphine n (%)	BEMA Placebo n (%)	Overall n (%)
Randomized	243 (100.0)	248 (100.0)	491 (100.0)
Completed	201 (82.7)	141 (56.9)	342 (69.7)
Discontinued	42 (17.3)	107 (43.1)	149 (30.3)
Adverse Event	6 (2.5)	13 (5.2)	19 (3.9)
Lack Of Efficacy	19 (7.8)	61 (24.6)	80 (16.3)
Protocol Violation	3 (1.2)	11 (4.4)	14 (2.9)
Withdrawal Due To Opioid Withdrawal	1 (0.4)	9 (3.6)	10 (2.0)
Withdrawal By Subject	11 (4.5)	6 (2.4)	17 (3.5)
Lost To Follow-Up	1 (0.4)	5 (2.0)	6 (1.2)
Other	1 (0.4)	2 (0.8)	3 (0.6)

Source: Dr. Travis' review, pg. 16

Study EN3409-308 subject disposition:

Dr. Horn reclassified a limited number of patients who discontinued from the double-blind treatment phase from the Applicant's administrative reason for discontinuation to discontinuations due to adverse events, and I concur with her assessments. The disposition

described below represents that reclassification. Additionally, patients from site 1008 are excluded (see Section 11 of this review for more detail regarding that site). One subject in this study withdrew prior to receiving any study medication after randomization and was not included in the ITT population by the Applicant's definition.

Of the 752 patients enrolled in the open-label titration phase, 39% discontinued. Table 8 summarizes the reasons for discontinuation in the open-label titration phase of this study.

Table 8. Study EN3409-308, Subject Disposition, Open-label Titration Phase, All Subjects

	n (%)
Screened	1633 (100.0)
Screen Failures ^a	881 (53.9)
Enrolled in Open-label Titration Phase ^b	752 (100.0)
Not Exposed to Study Medication	3 (0.4)
Completed in Open-label Titration Phase	462 (61.4)
Discontinued	290 (38.6)
Adverse Event	109 (14.5)
Lack of Efficacy	33 (4.4)
Protocol Violation	24 (3.2)
Withdrawal Due to Opioid Withdrawal	0
Withdrawal by Subject	34 (4.5)
Lost to Follow-up	22 (2.9)
Other	68 (9.0)

Dr. Travis' review, pg. 28

Of the patients included in the ITT population, 24% discontinued in the Belbuc group and 28% discontinued in the placebo group from the double-blind treatment phase. Table 9 summarizes the reasons for discontinuation in the double-blind treatment phase for this study.

Table 9. Study EN3409-308, Subject Disposition, Double-blind Treatment Phase, ITT Population

	BEMA Buprenorphine n (%)	BEMA Placebo n (%)	Overall n (%)
Randomized	209 (100.0)	211 (100.0)	420 (100.0)
Completed	159 (76.1)	153 (72.5)	312 (74.3)
Discontinued	50 (23.9)	58 (27.5)	108 (25.7)
Adverse Event	17 (8.1)	8 (3.8)	25 (6.0)
Lack Of Efficacy	8 (3.8)	23 (10.9)	31 (7.4)
Protocol Violation	6 (2.9)	9 (4.3)	15 (3.6)
Withdrawal Due To Opioid Withdrawal	3 (1.4)	1 (0.5)	4 (1.0)
Withdrawal By Subject	11 (5.3)	8 (3.8)	19 (4.5)
Lost To Follow-Up	4 (1.9)	9 (4.3)	13 (3.1)
Other	1 (0.5)	0 (0.0)	1 (0.2)

Dr. Travis' review, pg. 30

Study EN3409-307 efficacy results:

Dr. Travis confirmed the Applicant's efficacy analyses accounting for the subjects who were reclassified as adverse events (see "study EN3409-307 subject disposition" above).

He confirmed the primary efficacy analysis, which demonstrated that treatment with Belbuca was statistically significantly better than placebo on the primary endpoint, change from baseline to Week 12 in pain intensity on an 11-point NRS (Table 10).

Table 10. Change from Baseline to Week 12 in Average Numeric Rating Scale Pain Intensity in Double-blind Treatment Phase – Study EN3409-307 ITT Population

Visit	BEMA Buprenorphine n=243	BEMA Placebo n=248
Prior to Open-label Titration		
Mean (SD)	6.79 (1.280)	6.64 (1.323)
Median	6.86	6.71
Baseline		
Mean (SD)	2.91(0.985)	2.84(1.051)
Median	3.00	3.00
Week 12 (Imputed)		
Mean (SD)	3.80(1.737)	4.76(1.780)
Median	3.73	4.60
Change from Baseline (Imputed)		
Mean (SD)	0.89(1.789)	1.92(1.872)
Median	0.46	1.58
Difference (95% CI) vs Placebo	-0.97 (-1.31, -0.63)	
P value	<.0001	

Dr. Travis' review, pg. 20

Dr. Travis conducted a number of sensitivity analyses confirming these results. Refer to his review for more details.

Dr. Travis noted that:

The results of the Cochran-Mantel-Haenszel test for the 30% and 50% reduction in pain intensities are shown in [Table 11]. The difference in the responder rate between the treatment and placebo was found to be statistically significant in both cases.

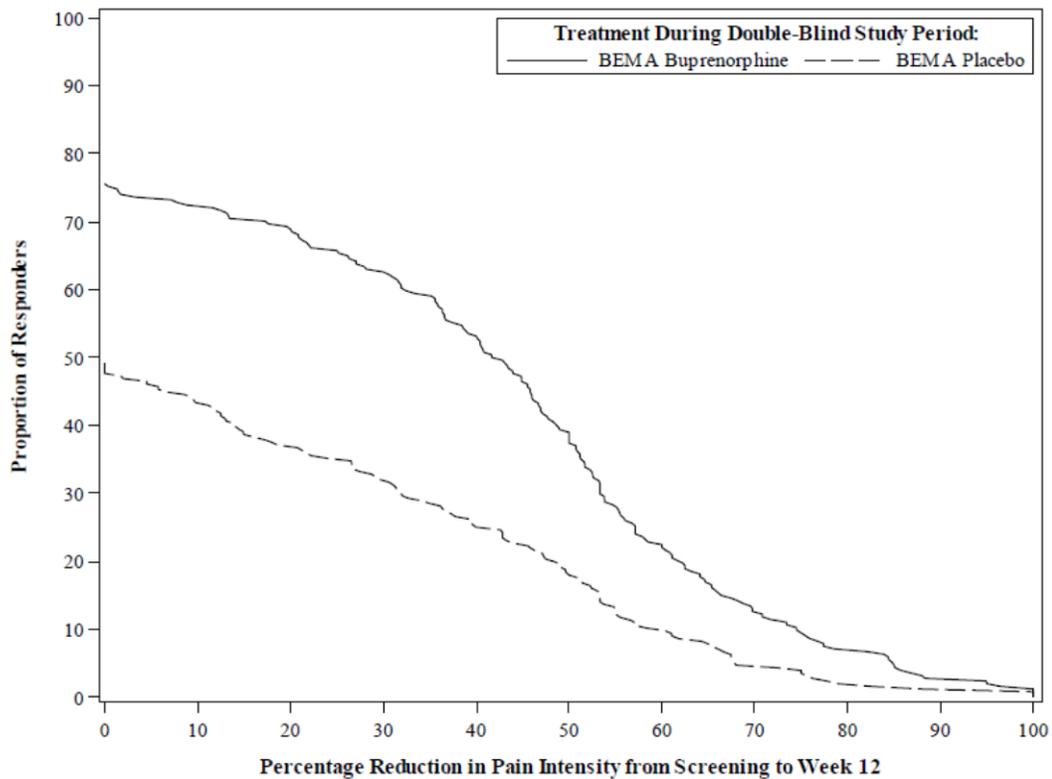
The cumulative responder analysis is presented in Figure 8 below.

Table 11. Responders in Pain Reduction for Selected Percentages from Screening to Week 12 in Double-blind Treatment Phase – Study EN3049-307 ITT Population

Responders, n (%)	BEMA		P-value
	Buprenorphine (N=243)	Placebo (N=248)	
≥30% Pain Reduction	155 (63.8)	76 (30.6)	<.0001
≥50% Pain Reduction	95 (39.1)	42 (16.9)	<.0001

Source: Dr. Travis’ review, pg. 22

Figure 8. Proportion of Responders with Selected Percent Pain Reduction from Screening to Week 12 in Double-blind Treatment Phase – Study EN3409-307 ITT Population



Source: Dr. Travis’ review, pg. 23

Study EN3409-308 efficacy results:

Dr. Travis confirmed the Applicant’s efficacy analyses accounting for the subjects who were reclassified as adverse events (see “study EN3409-308 subject disposition” above).

He confirmed the primary efficacy analysis, which demonstrated that treatment with Belbuca was statistically significantly better than placebo on the primary endpoint, change from baseline to Week 12 in pain intensity on an 11-point NRS (Table 12).

Table 12. Change from Baseline to Week 12 in Average Numeric Rating Scale Pain Intensity in Double-blind Treatment Phase – Study EN3409-308 ITT Population

Visit	BEMA	BEMA Placebo
	Buprenorphine n=209	n=211
Prior to Open-label Titration		
Mean (SD)	7.12 (1.058)	7.18 (1.050)
Median	7.29	7.17
Baseline		
Mean (SD)	2.82(1.014)	2.79(1.122)
Median	3.00	3.00
Week 12 (Imputed)		
Mean (SD)	3.83(2.000)	4.40(2.020)
Median	3.83	4.14
Change from Baseline (Imputed)		
Mean (SD)	1.01(1.887)	1.61(2.062)
Median	0.71	1.33
Difference (95% CI) vs Placebo	-0.62 (-1.04, -0.21)	
P value	0.0035	

Source: Dr. Travis' review, pg. 32

Dr. Travis conducted a number of sensitivity analyses confirming these results. Refer to his review for more details.

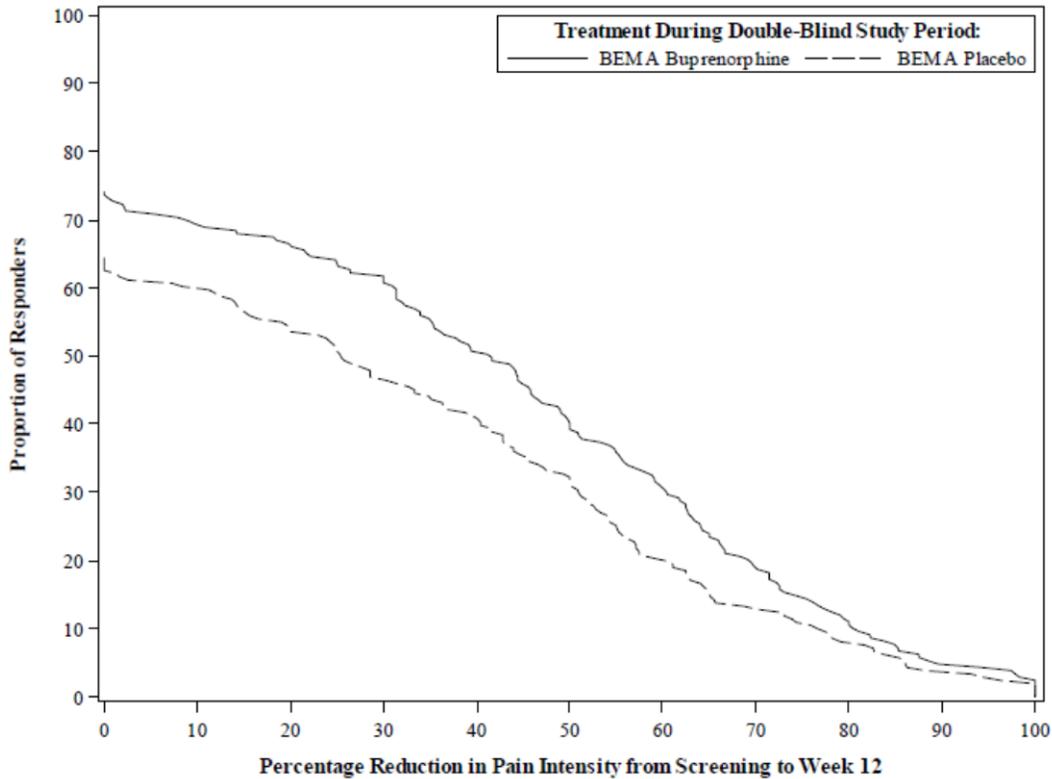
The results for the Cochran-Mantel-Haenszel for the 30% and 50% reductions in pain intensity are shown in Table 13. The difference in the responder rate between Belbuca and placebo was statistically significant for the 30% cutoff but not for the 50% cutoff. The cumulative responder analysis is presented in Figure 9 below.

Table 13. Responders in Pain Reduction for Selected Percentages from Screening to Week 12 in Double-blind Treatment Phase – Study EN3049-308 ITT Population

Responders, n (%)	BEMA	BEMA Placebo	P-value
	Buprenorphine (N=209)	(N=211)	
≥30% Pain Reduction	130 (62.2)	99 (46.9)	0.0017
≥50% Pain Reduction	85 (40.7)	69 (32.7)	0.0936

Source: Dr. Travis' review, pg. 34

Figure 9. Proportion of Responders with Selected Percent Pain Reduction from Screening to Week 12 in Double-blind Treatment Phase – Study EN3409-308 ITT Population



Source: Dr. Travis' review, pg. 35

BUP-301 results:

BUP-301 enrolled opioid experienced and opioid naïve patients; however, fewer overall patients were randomized into that study. Additionally, BUP-301 likely evaluated a dose range that was too low and included an open-label titration period that was too short to allow for optimal dose titration and stabilization. Despite these limitations in study design and although the results on the primary efficacy analysis did not reach statistical significance, the results did trend in the direction favoring a treatment effect for Belbuca. For a more complete discussion of the results from BUP-301, refer to Dr. Horn's review.

Efficacy Conclusions

Both Dr. Horn and Dr. Travis have concluded that the results from the Applicant's Phase 3 efficacy studies have demonstrated that Belbuca, at the proposed dose range, is superior to placebo in the proposed indication, and I concur with their assessment.

8. Safety

The safety portion of this NDA review was conducted by Pamela Horn, MD. No new or unexpected safety findings were identified for Belbuca beyond what is already known about buprenorphine and opioids in general in this treatment setting. Dr. Horn concluded that "[w]hile there are safety concerns with Belbuca, based on the available data, these concerns do

not outweigh the benefits of the drug,” and I concur with her assessment. The following is a summary of Dr. Horn’s review.

The safety evaluation of Belbuca in patients with chronic pain primarily consisted of data from the three Phase 3 efficacy and safety studies and two Phase 3 open-label, long-term safety studies (BUP-305 and EN3409-309), in addition to a Phase 2 study conducted to evaluate directly switching to Belbuca without a taper of the prior stable opioid dose (EN3409-204).

BUP-305 was an open-label, 52-week, long-term, extension study that enrolled patients from BUP-301 in addition to other patients with moderate to severe chronic pain, including osteoarthritis and neuropathic pain (evaluated 60 mcg, 120 mcg, 180 mcg, and 240 mcg Belbuca twice daily). EN3409-309 was a long-term, open-label, extension study with a 48-week treatment period that enrolled patients from EN3409-307 and EN3409-308 in addition to patients with at least a 3-month history of moderate to severe chronic noncancer-related pain, including CLBP with or without neuropathic involvement; osteoarthritis (OA) of the hip, knee and/or lumbosacral spine; and peripheral neuropathic pain (evaluated 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900mcg Belbuca twice daily).

Study EN3409-204 was a Phase 2, randomized, double-blind, active-controlled, two-period, crossover study to evaluate the tolerability of switching to Belbuca when opioid-dependent subjects with chronic pain are switched from their stable opioid dose to approximately 50% of their stable dose compared to an estimated 50% MSE dose of Belbuca after demonstrating precipitated opioid withdrawal following a naloxone challenge.

The integrated summary of safety (ISS) database consists of 2,480 subjects exposed to buprenorphine in the 16 completed studies in the clinical development program. Of these, 2,127 were treated with Belbuca in the Phase 3 program with 504 exposed at 6 months and 253 exposed for at least 1 year. The ISS database did not include 14 patients that were inadvertently left out of the safety analysis set for study BUP-305 by the Applicant. However, Dr. Horn accounted for these subjects in her safety review, and the inclusion of these subjects did not change the overall conclusions or trends. Dr. Horn concluded that “[t]he overall exposure is adequate to assess the safety of the product in the pre-market setting[.]” and I concur with her assessment. Safety assessments included the Clinical Opiate Withdrawal Scale (COWS) during transitions between full mu agonists and Belbuca and between Belbuca and placebo and the Columbia-Suicide Severity Rating Scale (C-SSRS) at baseline and at every subsequent visit to assess prospective suicidality risk.

One subject died in the clinical development program, and this occurred in open-label study BUP-305. The patient was a 56-year-old female with poorly controlled diabetes and hypercholesterolemia who died of a cardiac arrhythmia due to diabetic complications while on a 60 mcg twice daily dose of Belbuca. This case appears unrelated to study treatment, as the patient had significant cardiovascular risk and the dose is not in a range that we would expect significant prolongation of the QT interval.

There were 88 nonfatal serious adverse events (SAEs) in 69 patients in the clinical development program with 3% of patients in the Phase 3 studies experiencing SAEs. In the

double-blind phases of the Phase 3 studies, there were eight patients in the Belbuca group and five subjects in the placebo group who experienced SAEs. The SAEs in the Belbuca group included cellulitis, pulmonary contusion due to a fall down stairs, cholecystitis, cerebrovascular accident, dysarthria likely associated with a psychiatric etiology, bilateral knee osteoarthritis, atrial fibrillation, and small bowel obstruction. Dr. Horn concluded that “[t]he fall leading to pulmonary contusion and small bowel obstruction may have been related to the study drug.” The patient with small bowel obstruction did not have any underlying gastrointestinal pathology and ultimately underwent a small bowel resection. Two additional subjects in the open-label titration phase experienced small bowel obstruction and ileus SAEs, respectively; however, both patients had additional underlying risk factors. Dr. Horn notes that “[t]he proposed product labeling includes a contraindication for patients with paralytic ileus and a warning that it may impair mental and physical abilities in the context of driving and operating machinery.” Among the SAEs in the open-label, long-term safety studies, one patient experienced a prolonged QT interval that was identified on ECG during work-up for a transient ischemic attack; however, the QT value was not provided. The patient was also hypokalemic.

In the double-blind treatment phase of the controlled Phase 3 studies, 4% of Belbuca-treated patients and 5% of placebo-treated patients discontinued from the study due to adverse events. The adverse events that most frequently led to discontinuation (>1%) in the Belbuca group were nausea and constipation and in the placebo group was drug withdrawal syndrome. Comparing differences in discontinuation due to adverse events between treatments is limited by the fact that all patients initiated treatment with Belbuca during the open-label titration, and, therefore, at least some patients who did not tolerate Belbuca would likely have already discontinued and approximately one-third of the placebo subjects discontinued due to drug withdrawal syndrome, which was likely due to tapering off of Belbuca. The most frequent adverse events that led to discontinuation in all Phase 3 studies are summarized in Table 14. Dr. Horn noted that “[w]ith the addition of the subjects from study 305 that were left out of the safety set, there were an additional two subjects that discontinued due to nausea, an additional one subject that discontinued due to constipation, an additional three subjects that discontinued due to vomiting, an additional one subject that discontinued due to dizziness, and an additional one subject that discontinued due to dry throat.”

Table 14. Most Frequent Discontinuations due to Adverse Events During Belbuca Treatment (i.e., Occurring in ≥10 Patients), All Phase 3 Studies

System organ class	Adverse event	(N= 2127) N (%)
Gastrointestinal Disorders	Nausea	94 (4.4)
	Vomiting	35 (1.6)
	Constipation	17 (0.8)
Nervous System Disorders	Dizziness	29 (1.4)
	Headache	24 (1.1)
	Somnolence	23 (1.1)
General Disorders and Administration Site Conditions	Fatigue	16 (0.8)
	Drug withdrawal syndrome	15 (0.7)
Investigations	Liver function test abnormality	37 (1.7)
	Prolonged QT interval	10 (0.5)
Psychiatric Disorders	Anxiety	10 (0.5)

Source: Dr. Horn’s review, pg. 49

The most common adverse events reported in the controlled Phase 3 studies are summarized in Table 15 and Table 16.

Table 15. Most Frequent Adverse Events Reported (i.e., Occurring in at least 2% of Patients) in the Double-Blind Treatment Period of Controlled Studies

Adverse Event	Buprenorphine N=600		Placebo N=606	
	n	%	n	%
Nausea	53	9	46	8
Vomiting	29	5	11	2
Constipation	23	4	11	2
Headache	22	4	21	3
Sinusitis	13	2	9	1
Upper Respiratory Tract Infection	13	2	19	3
Urinary Tract Infection	13	2	9	1
Drug Withdrawal Syndrome	11	2	32	5
Back Pain	10	2	5	1
Diarrhea	10	2	19	3
Dizziness	10	2	4	1
Insomnia	10	2	12	2
Nasopharyngitis	9	2	15	2

Source: Dr. Horn’s review, pg. 51

Table 16. Most Frequent Adverse Events Reported with Belbuca in the Open-Label Period of the Phase 3 Controlled Studies

Adverse Event	Buprenorphine N=1889 n (%)
Number of subjects with at least 1 treatment emergent adverse event	1246 (66)
Nausea	617 (33)
Constipation	200 (11)
Headache	153 (8)
Vomiting	132 (7)
Dizziness	120 (6)
Somnolence	114 (6)
Fatigue	81 (4)
Dry Mouth	63 (3)
Diarrhea	58 (3)

Source: Dr. Horn’s review, pg. 52

QT interval prolongation

Studies EN3409-307, EN3409-308, and EN3409-309 included ECG monitoring, which allowed for an assessment of cardiac electrophysiology while on study drug. There was no evidence of clinically significant adverse events caused by QT prolongation in the development program, but, despite that Dr. Horn noted in her review that “[t]here were no patterns or trends in changes in ECG parameters, including QTc interval, in the open-label or double-blind periods of the Phase 3 studies,” there are data to suggest that Belbuca caused QT prolongation in subjects (Table 17 and Table 18). These data indicate that Belbuca may be causing QT prolongation. While there is no apparent relationship between the stabilized dose of Belbuca and QT prolongation, the study was not designed to provide a quantitative PK/PD evaluation of Belbuca and QT effects.

Table 17. Abnormal QTcF Interval Tabulations for Studies EN3409-307, EN3409-308, and EN3409-309

	Open-label Belbuca ² N=2065	Double-blind ³ Belbuca N= 483	Double-blind placebo N=488
ECG 450 msec +	32 (1.5%)	13 (3%)	6 (1%)
ECG change >10 msec from baseline	414 (20%)	290 (60%)	227 (47%)
ECG change >30 msec from baseline	75 (4%)	34 (7%)	32 (7%)
ECG change >60 from baseline	5 (0.2%)	0	0

Source: Generated by Dr. Horn based on ADEG ISS update dataset

Table 18. Abnormal QTcF Interval Tabulations by Dose Level During Double-blind Period of Studies EN3409-307 and EN3409-308

	Belbuca						Placebo N=488
	150 N=68	300 N=97	450 N=140	600 N=43	750 N=42	900 N=93	
ECG 450 msec +	0	2 (2%)	5 (4%)	1 (2%)	4 (10%)	1 (1%)	6 (1%)
ECG change >10 msec from baseline	39 (57%)	62 (64%)	82 (59%)	31 (72%)	25 (60%)	51 (55%)	227 (47%)
ECG change >30 msec from baseline	5 (7%)	10 (10%)	8 (6%)	2 (5%)	3 (7%)	6 (6%)	32 (7%)

Source: Generated by Dr. Horn based on ADEG ISS update dataset

Counting all subjects who were discontinued from studies for having a QT interval of 450 ms or greater, there were 18/1994 or 0.9% of subjects who were discontinued during open-label treatment with Belbuca in studies EN3409-307, EN3409-308, and EN3409-309, and 8/483 (1.7%) subjects in the Belbuca group and 5/488 (1.0%) in the placebo group discontinued

² All open-label periods of studies EN3409-307, EN3409-308, and EN3409-309

³ Studies EN3409-307 and EN3409-308

during double-blind treatment. These discontinuations appeared to be largely based on study protocol rules rather than clinical concern on the part of the investigator and no subject exceeded 480 ms, however, these data may suggest that Belbuca is causing an increase in the QT interval.

The data from the Phase 3 trials are sufficient to indicate that Belbuca, in the proposed dose range, may result in QT prolongation; however, these findings do not alter the risk benefit profile for the product, as no clinically relevant safety signals specific to QT prolongation arose in a very robust safety database. Although the studies submitted with this NDA support the safety of Belbuca, these data have identified a signal, and the Phase 3 studies cannot provide a definitive QT assessment due to the many factors that contribute to the variability in the QT interval that were not controlled in these Phase 3 trials. Therefore, I recommend requiring a postmarketing study to evaluate QT prolongation with Belbuca to provide additional information to confirm the safety of Belbuca, which may lead to additional labeling. In the meantime, I recommend including, in labeling, cautionary language for QT interval prolongation and recommending periodic ECG monitoring, along with a maximum dose (i.e., the maximum dose studied or 900 mcg every 12 hours). My recommendations and conclusions are solely based on the data submitted by the Applicant and not on data generated from other clinical development programs.

EN3409-204

Dr. Horn notes that “[s]tudy 204 was designed to determine if subjects with chronic pain receiving 80 mg to 220 mg oral morphine sulfate equivalents (MSE) can be safely transitioned on to buprenorphine at approximately 50% of their MSE dose without inducing opioid withdrawal or reversing analgesic effects.” Dr. Horn concluded that the results of this study were not interpretable due to the small numbers of subjects that met the responder definition. Although the study did not reveal any major concerns with directly switching patients to Belbuca, the study included relatively small numbers of subjects. It also did not provide any data to suggest that the approach that was used in the Phase 3 studies was not appropriate.

(b) (4)

I concur with her assessment. Refer to her review for more details regarding this study.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

10. Pediatrics

The Agency agreed with the Applicant’s pediatric study plan (PSP) on February 5, 2015, after discussing it at a meeting of the Pediatric Review Committee (PeRC) on February 4, 2015. The PSP consists of a waiver from birth to less than seven years of age because the necessary studies are impossible or highly impracticable and the number of pediatric subjects meeting the indication in the age group are too small in number to make the studies feasible. This is consistent with the Division’s approach for products used to treat chronic pain. The Applicant agreed to evaluate the PK and safety in patients 7 to less than 17 years of age

(b) (4)

The PSP was discussed at a meeting of the PeRC on October 7, 2015. PeRC recommended that the Division require the Applicant to additionally conduct pediatric studies in patients less than seven years of age. PeRC is generally recommending that studies in chronic pain be required down to two years of age but recommended that the lower age range for this product be based on the feasibility of younger patients being able to appropriately use the formulation. However, in the Division's experience, sponsors have had extreme difficulty enrolling patients down to even seven years. Therefore, the Division's policy is to require studies down to seven years of age in chronic pain, and this is consistent with the information discussed at a scientific workshop held in December 2009 regarding pediatric trials.

11. Other Relevant Regulatory Issues

Good Clinical Practice (GCP)

Site 1008 (EN3409-307, EN3409-308, EN3409-309) was terminated because of apparent falsification of urine drug screen results. This site was excluded from the efficacy analyses. Site 1027 in EN3409-307 was terminated due to professional misconduct; however, there was no evidence GCPs were compromised. This site was retained in the pivotal efficacy analysis; however, Dr. Horn noted in her review that Dr. Travis confirmed the efficacy results excluding this site.

John Lee, MD, completed the Clinical Inspection Summary for this NDA, with secondary concurrence by Janice Pohlman, MD, MPH, and Kassa Ayalew, MD, MPH.

According to Dr. Lee's review, the overall assessment of the inspectional findings was that:

No significant deficiencies were observed at either [clinical investigator] (CI) site: study conduct and data reporting appeared adequate and all audited data were verifiable among source records, CRFs, and NDA data listings. The data from the CI sites appear reliable as reported in the NDA, and more generally, the sponsor's monitoring of study conduct support adequate adherence to GCP overall for the two pivotal studies.

The following two study sites for the pivotal clinical trials were inspected due to high enrollment numbers (decision aided by use of the OSI site selection tool):

Name of Clinical Investigator / Site	Study / Number of Subjects	Date of Inspection	Final Classification
James E. Wild, M.D. Upstate Clinical Research Associates 8201 Main Street, Suite 1 Williamsville, New York Site 1009	Study 307 49 enrolled 30 randomized	May 12-20, 2015	NAI
Bruce G. Rankin, D.O. Avail Clinical Research, LLC 860 Peachwood Drive Deland, Florida Site 1040	Study 308 25 enrolled 12 randomized	May 4 - 8, 2015	VAI

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations (minor violations)

Financial Disclosures

The Applicant adequately disclosed financial interests/arrangements with clinical investigators, as recommended by the Agency. Two of the investigators had financial interests/arrangements for which the Applicant disclosed. However, these investigators did not enroll any patients into the pivotal efficacy trials.

505(b)(2) Committee

This application was presented at a meeting of the 505(b)(2) committee on October 14, 2015, and it was cleared for action from their perspective. (b) (4), (b) (5)



12. Labeling

The proprietary name, Belbuca, was found acceptable following review by the Division of Medication Error Prevention and Analysis (DMEPA). DMEPA also provided recommendations on the carton and container labeling as well as other aspects of labeling (i.e., prescribing information, instructions for use, medication guide). DMEPA found the carton and container labeling acceptable from their perspective, with their recommended revisions (refer to the DMEPA reviews for more details). The patient labeling team reviewed the medication guide and the instructions for use and found them acceptable with their recommended changes (refer to the Patient Labeling review for more details).

Additionally, the Controlled Substances Staff (CSS) and the Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling. CSS recommended that the language proposed for the product label on the risks of abuse and dependence should remain consistent with buprenorphine products indicated for pain. DPMH provided recommendations for the proposed labeling, based on their review.

Labeling is ongoing at the time of this writing, and specific recommendations have been made in the relevant sections of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The efficacy of Belbuca was demonstrated in two adequate and well-controlled clinical trials in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment. The two studies were conducted in opioid-naïve and opioid-experienced patients, respectively. A third study that was conducted in both opioid-naïve and opioid-experienced patients failed on its primary endpoint, at least in part, due to the limitations discussed in this review. However, the results of that study also trended in the direction favoring a treatment effect for Belbuca. The safety evaluation did not demonstrate any new signals for Belbuca beyond what is already known about buprenorphine and opioids, in general. Opioids are associated with the serious risks of life-threatening respiratory depression; addiction, abuse, and misuse; accidental exposure; death; and neonatal opioid withdrawal syndrome, along with other risks such as nausea, vomiting, constipation, and interactions with other drugs. These risks can be appropriately managed in labeling and with the class-wide extended-release/long-acting (ER/LA) opioid risk evaluation and mitigation strategy (REMS). Additionally, the clinical development program identified an important signal for Belbuca that is consistent with what is known about buprenorphine, that is, QT interval prolongation; however, the program did not demonstrate any clinically relevant adverse effects with regard to the QT interval in a very robust safety database. Therefore, it is appropriate to require a postmarketing study to evaluate the effects of Belbuca on the QT interval to provide additional information to confirm the safety of Belbuca, which may lead to additional labeling.

Belbuca is used to treat chronic pain that is severe enough to require around-the-clock opioid therapy, a serious and potentially disabling medical condition, and the risks of Belbuca are consistent with other ER/LA opioid analgesics, including buprenorphine. In this context, the benefits outweigh the risks of treatment with Belbuca for this patient population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Belbuca will be part of the class-wide Extended-Release/Long-Acting Opioid REMS.

- Recommendation for other Postmarketing Requirements and Commitments

I recommend requiring postmarketing studies to:

1. Assess the known serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics and to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain, consistent with what has been required for ER/LA opioid analgesics
 2. Evaluate the pharmacokinetic and safety of Belbuca in patients 7 to less than 17 years old with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, as required under the Pediatric Research Equity Act (PREA)
 3. Evaluate the QT prolonging effect of Belbuca to provide additional information to confirm the safety of Belbuca
- Recommended Comments to Applicant

None

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

/s/

JOSHUA M LLOYD
10/22/2015