CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207932Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	207932
Applicant Name	Endo Pharmaceuticals, Inc.
Date of Submission	December 23, 2014
PDUFA Goal Date	October 23, 2015
Proprietary Name / Established (USAN) Name	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
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Pam Horn, MD
Statistical Review	James Travis, PhD, Freeda Cooner, PhD
Pharmacology Toxicology Review	Gary P Bond, PhD, Jay H Chang, PhD, R Daniel Mellon, PhD
CMC Review/OBP Review	Christopher Hough, PhD, Shujun Chen, PhD, Erika Pfeiler, PhD, Juandria Williams, PhD, Fang Wu, PhD, Don Henry ,Ciby Abraham, PhD, Paul Perdue
Clinical Pharmacology Review	David Lee, PhD, Yun Xu, PhD
CSS	Jovita Randall-Thompson, PhD, Alan Trachtenberg, MD, MPH, Michael Klein, PhD
CDTL Review	Josh Lloyd, MD
OSE/DMEPA	Millie Shah, PharmD, BCPS, Vicky Borders-Hemphill, PharmD,
OMP/DMPP OMP/OPDP	Koung Lee, RPh, MSHS, Morgan Walker, PharmD, MBA, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN
OSI	John Lee MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH
QT Interdisciplinary Review Team	Norman Stockbridge, MD, PhD

OND=Office of New Drugs
DMEPA=Division of Medication Errors Prevention
CDTL=Cross-Discipline Team Leader
DCDP=Division of Consumer Drug Promotion
DMPP=Division of Medical Policy Programs
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives

Signatory Authority Review Template

1. Introduction

Endo Pharmaceuticals, Inc. has submitted a 505(b)(2) 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). Belbuca was developed under IND 72,428, initially submitted by BioDelivery Sciences International on December 15, 2005, and the IND was transferred to Endo on January 6, 2012. The Applicant is referencing the Agency's prior findings of sfety and efficacy for 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). Subutex marketing has been discontinued; however, it was not discontinued or withdrawn for reasons of safety or efficacy (80 FR 8088).

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. In contrast to full mu agonists, buprenorphine is thought to exhibit a ceiling effect for central nervous system depression, respiratory depression and potentially analgesia. Buprenorphine is listed under Schedule III of the Controlled Substances Act. In addition to the referenced products, Buprenex, a parenteral formulation approved to manage pain, and Subutex, a sublingual formulation approved to treat opioid dependence, buprenorphine has also been approved as a transdermal patch formulation, Butrans, for the same indication proposed for Belbuca.

2. Background

Belbuca is a mucoadhesive buccal film that employs BDSI's BioErodable MucoAdhesive (BEMA) technology, consisting 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, avoiding poor oral bioavailability due to extensive first pass metabolism. During development, Belbuca was also referred to as BEMA buprenorphine. There is an oral transmucosal fentanyl product, Onsolis, that was approved with the BEMA platform. Onsolis is approved to manage breakthrough pain in cancer patients18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Because the reference products, Buprenex and Subutex are approved for different indications than Belbuca, the Applicant was required to provide evidence of efficacy and safety to support the proposed indication. The Applicant has submitted the results of two adequate and well-controlled efficacy studies, additional safety data from open-label safety studies, along

with a complete chemistry, manufacturing and controls, and pharmacokinetic program in support of this application.

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).

3. CMC/Biopharmaceutics

Review of the buprenorphine HCl drug substance under DMF (b) (4), and buprenorphine base under DMF (b) (4) concluded the DMFs are adequate to support the product. Buprenorphine HCl is the drug substance used for the product. The final drug product specifications are acceptable.

The drug product is formulated using the BioErodible MucoAdhesive (BEMA) technology platform that was used in the approved products Onsolis (NDA 022266, fentanyl buccal soluble film) and Bunavail (NDA 205637 buprenorphine and naloxone buccal film). Each individual buprenorphine HCl buccal film is packaged in a child-resistant, (b) (4) foil (b) (4) package, the same packaging material used for Bunavail. The film is light yellow to yellow on the mucoadhesive layer side and white to off-white on the backing layer side which is printed with black ink. The strength of a film is dependent on which of the area of the film and is based on two formulation strengths for the full range of film strengths. (b) (4) The film sizes range from 0.9 cm^2 to 2.4 cm^2. The formulation does not contain any novel excipients. The final specifications and acceptance criteria are acceptable.

The container closure system is a child-resistant, (b) (4)/foil, (b) (4) package 2.20 x 2.17 in. in size for all of the strengths and was found to be adequate to protect the product (b) (4) The manufacturing process and facilities are acceptable.

The dissolution method was found to be robust and to have adequate discriminatory capability. The dissolution acceptance criteria were found to be adequate.

The quality microbiology review found the microbial limits specification acceptable.

The request for a categorical exclusion from the environmental assessment requirements under 21CFR 25.40 was granted.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

During development, the Applicant was advised by the Division that based upon their reliance on the Agency's prior findings of safety and efficacy for Subutex, no nonclinical studies of buprenorphine were required. Because Belbuca and Subutex are based on different formulations, the only possible question was local toxicity. The Applicant was advised 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. The Applicant submitted a 28-day buccal toxicity study of BEMA buprenorphine in beagle dogs, which was originally submitted to support the safety of repeated applications of the film to the same buccal site for Bunavail. The only sign of local toxicity was a minimal to slight inflammatory cell infiltration of the oral mucosa and Dr. Bond concluded that the dog local tissue toxicity data support the proposed human dosing with Belbuca.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Seven clinical pharmacology studies along with a population pharmacokinetic analysis from two efficacy studies were submitted in support of this application. A scientific bridge to rely on the Agency's prior findings for Subutex was created in a relative bioavailability study (BUN-118) comparing a single 900 mcg dose of Belbuca and an 8 mg sublingual tablet of buprenorphine. As Subutex is no longer marketed, a sublingual tablet by Roxane Laboratories was used. The products are not bioequivalent and the exposure to buprenorphine was lower for both Cmax and AUC with Belbuca.

The absolute bioavailability was assessed in two studies. In Study BUP-115, a 500 mcg dose of Belbuca (b) (4) was compared to a 2 minute IV infusion of buprenorphine 150 mcg. The mean absolute bioavailability was 65%. In Study BUP-117, a single Belbuca dose of 75 mcg, 300 mcg, and 1200mcg (b) (4) was compared to a 2 minute IV infusion of buprenorphine 300 mcg. The mean absolute bioavailability ranged from 46 to 51% across the four tested doses.

The (b) (4) formulations were compared in a relative bioavailability study (BUP-117) using a single 300 mcg dose of each formulation. As noted by Dr. Lee:

The 90% CIs for buprenorphine AUC after 300mcg Belbuca from 2 formulations (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.

Dose linearity was demonstrated in a single-dose study (BUP-117) using the full range of strengths and a multiple-dose study (BUP-116) using 60 mcg to 240 mcg strengths. The results of these studies are provided in the following two tables from Dr. Lee's review.

Table 1. Buprenorphine Plasma Pharmacokinetic Parameters (mean±SD)

	BUP-121 60 ug	BUP-117 75 ug	BUP-117 300 ug	BUP-117 300 ug	BUP-115 500 ug	BUP-118 900 ug	BUP-120 900 ug	BUP-117 1200 ug (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

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
$AUC_{0-\tau}$ (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

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

Grade 3 mucositis resulted in an 80% higher Cmax and 60% higher AUC, supporting the need for dosage adjustment in these patients.

In a study evaluating the effect of temperature, Cmax was 26 to 31% lower and AUC was 23 to 27% following hot, cold or room temperature water. Administration following cola (low pH), Cmax and AUC decreased by 47 and 37%, respectively. There was no effect of a high pH liquid on the Cmax or AUC.

As noted by Dr. Lee:

> 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 ($p<0.001$).

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The reference product, Buprenex has an indication for pain, and as a parenteral product is suitable for acute pain. Subutex does not have an indication for analgesia. Therefore, the Applicant was required to provide evidence of efficacy to support the proposed indication. Three clinical trials were conducted to evaluate the efficacy of Belbuca. One trial did not demonstrate efficacy, but two clinical trials were successful.

As summarized by Dr. Travis, the development program for Belbuca was conducted under IND 72,428, initially submitted by BioDelivery Sciences International, Inc. (BDSI) in September 2005. The development program, including the protocol for BUP-301 to study the efficacy of Belbuca in treating moderate to severe chronic lower back pain (CLBP) in both opioid-naïve and opioid-experienced subjects, was discussed at the End of Phase 2 meeting in September 2010. Study BUP-301 failed to reach statistical significance on the primary efficacy endpoint. After ownership of IND 72,248 was transferred to Endo Pharmaceuticals in January, 2012, the protocols for Studies EN3409-307 (Study 307) and EN3409-308 (Study 308) were developed.

Study Design

The basic features of the protocols for Studies 307, 308, and 301are provided in the following table, modified from Dr. Horn's review.

Table 3 Summary of Double-Blind, Controlled Efficacy Study Designs

	307	308	301
Population	Opioid-experienced adults with well- or poorly controlled moderate to severe CLBP	Opioid-naïve adults with poorly controlled moderate to severe CLBP	Opioid-naïve and opioid-experienced adults with poorly controlled moderate to severe CLBP
Design	12-week, multicenter, enriched, double-blind, placebo-controlled, randomized withdrawal		

Prior Analgesic	• Around the clock, 30-160 mg oral morphine sulfate or equivalent (MSE) • Rescue up to 30 mg MSE • Stable at least 4 weeks • Taper up to 4 weeks to 30 mg MSE	• Non-opioid • Stable at least 4 weeks 8. Recue: up to 10 MSE opioid or additional as-needed non-opioid analgesic 9. No analgesic taper	10. Up to 60 mg MSE for at least 1 week or 11. Non-opioid analgesic
Open-label titration period	Up to 8 weeks		Up to 4 weeks
Initial Buprenorphine Dose	Based on prior opioid dose • 30-89 MSE:150 mcg q12h • 90-160 MSE: 300 mcg q12h	• Day 1: 75 mcg once • Day 2: 75 mcg q12h	• 60 mcg q 12 hr
Maximum Buprenorphine Dose	Titrate up to 900 mcg q12h	Titrate up to 450 mcg q12h	Titrated up to 240 mcg q12h
Rescue medication	Hydrocodone/acetaminophen 5/325 mg • 1 or 2 tablets • up to 2x per day for first 2 wks of DB period • up to 1x per day thereafter	Hydrocodone/acetaminophen 5/325 mg • 1 tablet • up to 2x per day for first 2 wks of DB period Acetaminophen 500 mg • 1 to2 tabs up to 1x per day thereafter	Acetaminophen Up to 2 g per day
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 (0-10 NRS)		
Proportion of Responder Analysis	Cochran-Mantel-Haenszel Chi-square test stratified by dose level to compare treatment groups at 30% and 50% pain reduction		Fisher's exact to compare treatments at each interval (0% to 100% in increments of 10%)

The inclusion criteria for chronic low back pain for Studies 307 and 308 was based on a clinical diagnosis of moderate-to-severe low back pain classified by the Quebec Task Force (QTF) Scale for low back pain: QTF Classes 1 to 2 non-neuropathic, Class 3, 4, 5, or 6 neuropathic, or class 9 symptomatic for more than 6 months after low back pain surgery, and pain for at least six months. These classes describe low back pain with and without radiation, including pain radiating below the knee; and pain due to any musculoskeletal etiology including disc herniation, but excluding confirmed spinal stenosis, metastases, visceral disease, compression fracture, spondylitis, or post-surgical pain of less than six months. Additional criteria included at least 18 years of age, not pregnant, and use of suitable birth control. Key exclusion criteria included a history of substance abuse or dependence within past 5 years per DSM-IV criteria, and a QTcF interval of 450 msec or more, hypokalemia, clinically unstable cardiac disease, a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications or Class III antiarrhythmic medications

For Study 307, during the taper phase, the prior opioid analgesic was 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 at least 5 on the 11-point NRS for three consecutive days. Once a patient met this criterion, rescue medication was allowed. Patients with poorly-controlled pain (i.e., 5 to 9 on an 11-point NRS over the last 7 days of screening) were allowed to start the taper with rescue medication. For Study 308, to enter open-label titration, subjects must have had a mean of average daily pain intensity scores from 5 to 9 on an 11-point NRS, and no daily pain intensity below 4, over the last 7 days of the Screening Phase.

For Study 307, during the titration phase, patients were switched to a dose of open-label Belbuca, 150 mcg twice daily for prior opioid of 30 to 89 MSE, 300 mcg twice daily for prior opioid of 90 to 160 MSE. For Studies 308 and 301, patients were started on a single dose of 75 mcg and then 75 mcg twice daily. All patients were then titrated to a stable dose of Belbuca (in 150 mcg increments every four to eight days) 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.

Results

Full details of the study results, including a review of the demographic characteristics and baseline scores can be found in the reviews by Drs. Travis, Horn, and Lloyd. As described in Dr. Travis' review, at the Pre-NDA meeting for this application, the Applicant explained their plans to exclude a site from the efficacy analysis for Studies EN3409-307 and EN3409-308 due to breaches in Good Clinical Practice (GCP). A site audit was conducted for Site 1008, finding several critical issues related to the integrity of the data. At the Agency's request, the Applicant conducted the primary efficacy analysis both including and excluding this site. At another site (1027), the primary investigator their medical license suspended resulting in closure of that site, but a site audit found no critical or major GCP nonconformities and the data from this site were included in the efficacy analysis.

The full details of subject disposition can be found in the reviews by Drs. Lloyd and Horn. Of the patients entering the open-label titration phase, 63% were successfully titrated in Study 307 and 64% completed the double-blind phase. In Study 308, 62% of patients were successfully titrated and 61% completed the double-blind phase. More patients randomized to placebo discontinued early in both studies, 43% in Study 307 and 28% in Study 308, predominantly due to lack of efficacy. The most common reason for early discontinuation in the active group was lack of efficacy in Study 307 and adverse event in Study 308.

The final titrated doses in Study 307 are presented in the following table which shows that the prior opioid dose did not predict the final titrated Belbuca dose. Also of note his that few patients on a prior opioid completed titration at the 150 mcg q12h dose.

Table 4 Study 307: Oral Opioid Dose at Study Entry in Oral Morphine Sulfate Equivalents, N=510

	Prior Oral Opioid Dose (MSE)				
	30 mg	31-60 mg	61-90 mg	91-120 mg	121-180* mg
Stabilized Belbuca Dose	N (%)	N (%)	N (%)	N (%)	N (%)
150 mcg q12h	8 (1.6%)	11 (2.2%)	1 (0.2%)	0	0
300 mcg q12h	26 (5.1%)	27 (5.3%)	5 (1.0%)	1 (0.2%)	0
450 mcg q12h	24 (4.7%)	40 (7.8%)	9 (1.8%)	1 (0.2%)	0
600 mcg q12h	20 (4.0%)	53 (10.4%)	9 (1.8%)	5 (1.0%)	1 (0.2%)
750 mcg q12h	21 (4.1%)	48 (9.4%)	10 (2.0%)	2 (0.4%)	2 (0.4%)
900 mcg q12h	29 (5.7%)	100 (19.6%)	32 (6.3%)	14 (2.7%)	11 (2.6%)

* There was one subject that had an oral MSE of 180 even though the entry criteria only allowed for up to 160 oral

In Study 308, the breakdown of the doses in subjects who were successfully titrated during the open-label titration was as follows:

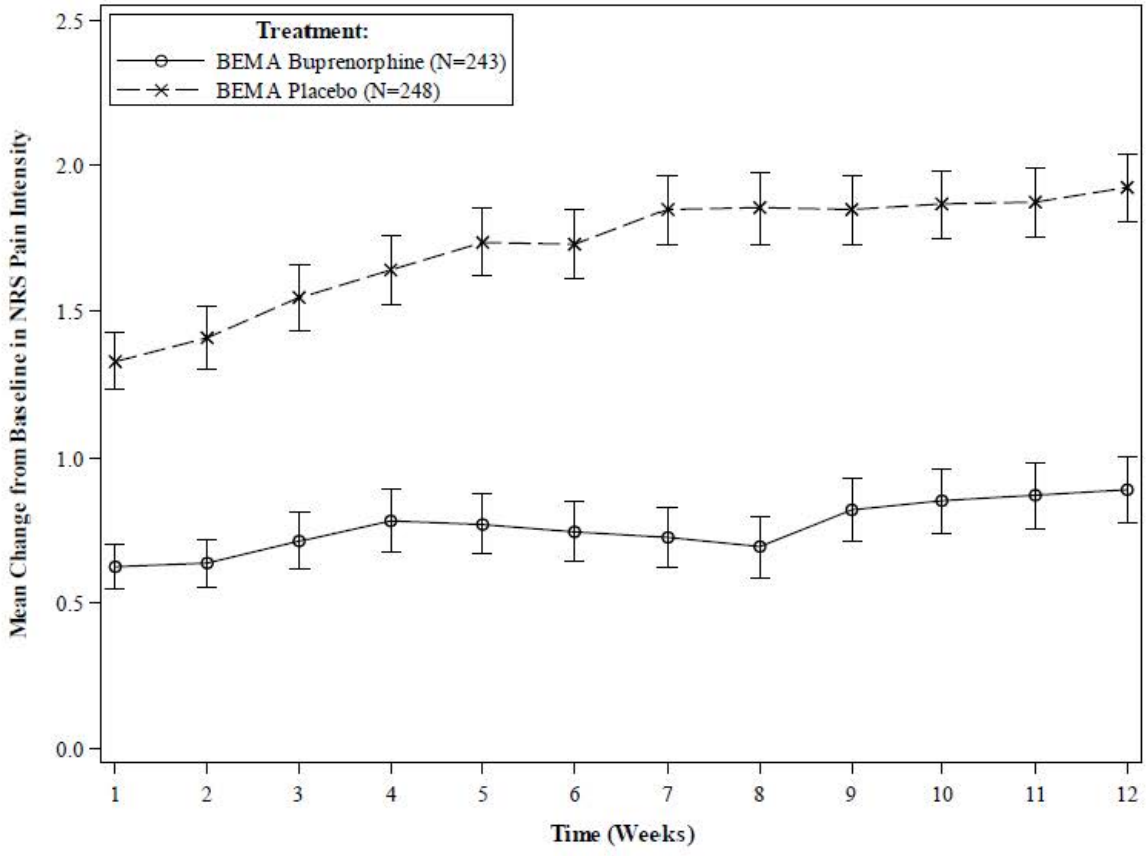
- 150 mcg q12h 113 (27%)
- 300 mcg q12h 123 (29%)
- 450 mcg q12h 184 (44%)

Dr. Travis confirmed a finding of efficacy for the prespecified primary efficacy analysis, change from Baseline to Week 12 in average pain intensity for Studies 307 and 308. Table 7 and Figure 3 from Dr. Travis' review describes the primary efficacy analysis and the change in pain intensity over the 12-week study period for Study 307.

Table 7 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	

Figure 3: Mean (±SE) of Weekly Change form Baseline Pain Intensity in Double Blind Treatment Phase (with Imputed Values) – Study EN3409-307 ITT Population



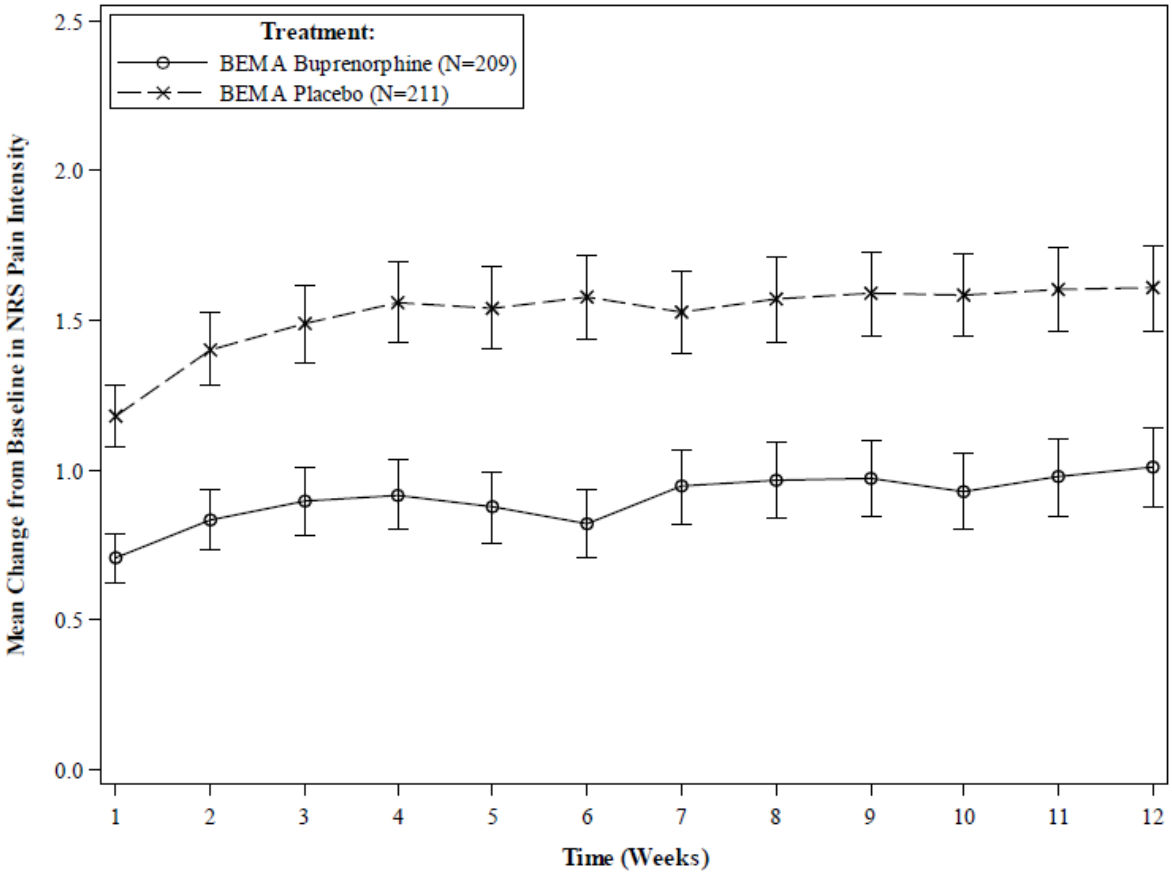
The findings were consistent for several secondary endpoints including use of rescue medication.

Table 17 and Figure 8 from Dr. Travis' review describes the primary efficacy analysis and the change in pain intensity over the 12-week study period for Study 308.

Table 17: 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 Buprenorphine n=209	BEMA Placebo 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	

Figure 8: Mean (±SE) of Weekly Change form Baseline Pain Intensity in Double Blind Treatment Phase (with Imputed Values) – Study EN3409-308 ITT Population



Figures 8 and 9 from Dr. Lloyd's review, reproduced below, represent continuous function curves of the percent reduction of pain by percentage of patients for Studies 307 and 308.

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

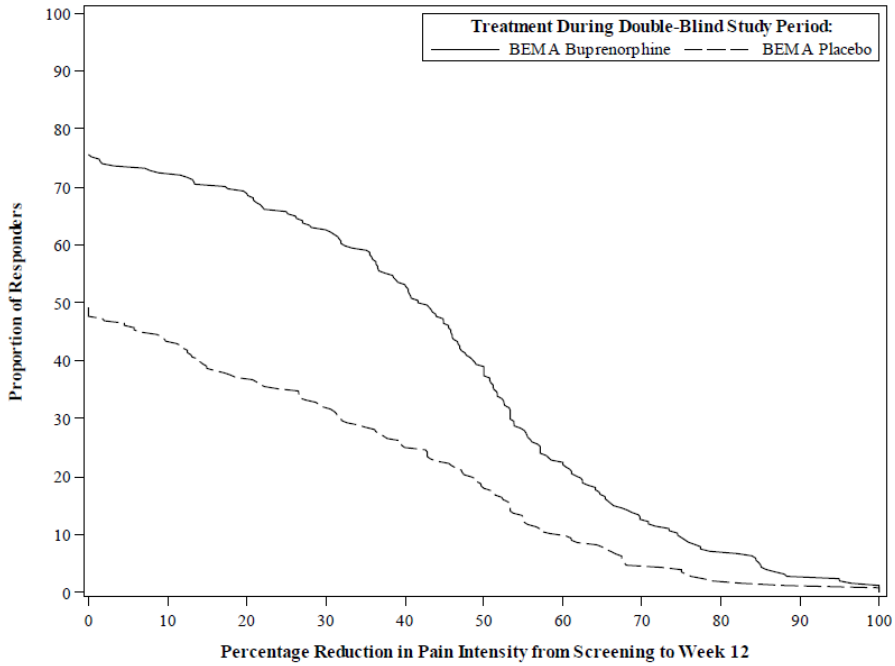
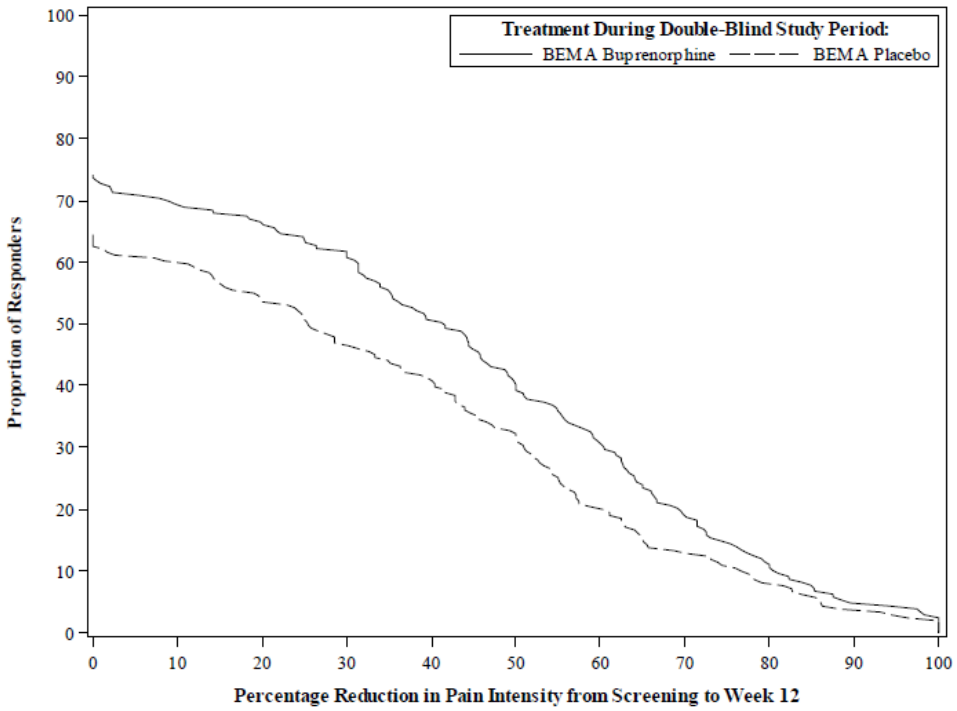


Figure 9. Proportion of Responders with Selected Percent Pain Reduction from Screening to Week 12 in Double-blind Treatment Phase – Study EN3409-308 ITT Population



The findings were consistent for several secondary endpoints including use of rescue medication for both studies.

As an additional analysis looking at whether patients on the highest prior opioid doses experienced efficacy, Table 5 shows the percent of patients experiencing either a 30% or 50% reduction in pain at the end of the 12 week double-blind period. The patients on the highest prior opioids, between 100 and 160 MSE at study entry, who were randomized to Belbuca, had the same rates of 30% and 50% reduction in pain as the whole study population.

Table 5 Rates of 30% and 50% Reduction in Pain Intensity, High Prior Opioid Group, Study 307

	30% Reduction in Pain	50% Reduction in Pain
Belbuca-treated Patients N=243	64%	39%
High Dose (100-160 mg oral MSE) Prior Opioid Subgroup N=16	63%	38%

There is clear evidence of efficacy for Belbuca when used to manage chronic low back pain from a variety of causes in patients who were previously treated with as much as 160 mg per day of morphine sulfate or its equivalent, as well as in patients who had previously been treated with nonopioid analgesics.

Dr. Travis explored subgroup analyses by sex and race. For Study 307, he noted that the estimated treatment effect was slightly larger for males than for females in Study 307 for all three analysis methods. However, for Study 308 the estimated treatment effect was considerably smaller for males than for females. The only racial subgroups with a sufficient number of subjects for an analysis was the White and Black/African American subgroups. The treatment effect was larger for the White subgroup than the Black/African American subgroup in both studies, and Dr. Travis notes this may be due to a larger placebo response in the Black/African American group, rather than worse pain scores in the active group.

Study 301 failed to demonstrate efficacy for Belbuca, but there were several important differences from Studies 307 and 308 that could account for the failure. In particular, patients were started on a lower dose and only able to titrate up to a maximum Belbuca dose of 240 mcg q12h. Only 4% of subjects in Study 307 titrated to the lowest dose, 150 mcg q12h, and an additional 11.6% titrated to 300 mcg q12h. In Study 308, 27% of subjects titrated to 150 mcg q12h, and 29% to 300 mcg q12h. This suggesting that the dosing range was too low in Study 301. Subjects also only had acetaminophen for rescue, in contrast to a hydrocodone/acetaminophen product for rescue during the early randomization phase when subjects randomized to placebo would have the most difficult time.

12. Safety

The safety database consists of 2,480 subjects exposed to buprenorphine in the 16 completed studies in the clinical development program, 2,127 from the Phase 3 program consisting of

Studies 301, 307 and 308, and two open-label, uncontrolled studies, 305 and 309. There were 504 subjects exposed for 6 months and 253 for one year.

There was one death reported, a 56 year old woman 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. The low buprenorphine exposure at this dose makes it unlikely Belbuca contributed to the cause of death.

The following paragraphs and tables describing the serious adverse events, adverse events leading to discontinuation, and common adverse events are verbatim from Dr. Lloyd's review:

> 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 3**. 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 3. 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 4** and **Table 5**.

Table 4. 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 5. 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 Evaluation

There have been reports of the possibility of QT prolongation associated with buprenorphine in the literature.[1] The Applicant was asked to conduct a thorough QT (TQT) study and to evaluate the effects of buprenorphine on cardiac repolarization in healthy subjects. TQT studies generally require administering supratherapeutic doses of the drug in question, which is difficult to operationalize with an opioid due to the CNS depressant effects. The Applicant conducted a thorough QT study, BUP-150, but for this study, subjects were naltrexone blocked to protect them from the CNS effects of buprenorphine. Study BUP-150 did not demonstrate any clinically significant delay in the QTc. However, while any effect of an opioid on the QT interval would not be expected to be mediated by the mu opioid receptor, (b) (4) Therefore, Study BUP-150 does not represent a complete analysis of the risk of buprenorphine for prolonging the QT interval. A repeat TQT study will be required as a postmarketing requirement. There were some increases in QT interval during the development program. The details of the QT findings are described in Dr. Lloyd's review, and reproduced in part here:

> Counting all subjects who were discontinued from studies for having a QT interval of 450 msec 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 during double-blind treatment. These discontinuations

1Moody DM. Metabolic and toxicological considerations of the opioid replacement therapy and analgesic drugs: methadone and buprenorphine, Expert Opinion on Drug Metabolism & Toxicology, 9:6, 675-697, 2013.

appeared to be largely based on study protocol rules rather than clinical concern on the part of the investigator and no subject exceeded 480 msec, 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.

As there were no clinically meaningfully prolonged QT intervals, the potential signal is not of sufficient magnitude to preclude approval of Belbuca, however, the findings are sufficient to warrant labeling Belbuca with appropriate warnings to alert prescribers to the risk, particularly in patients who have risk factors that may predispose them to QT prolongation. A repeat TQT study is necessary to provide quantitative information about the effect of Belbuca on QT interval and will support more specific labeling when available.

In Studies 307 and 308 there were several patients who were excluded from the study due to abnormal EKG and lab values but were classified as having been discontinued from the study due to protocol violations or other reasons. Dr. Horn determined that these subjects were to be reclassified as discontinued due to adverse events. Both studies were re-analyzed with these subjects reclassified appropriately.

Opioid Withdrawal

One of the challenges in converting a patient who is physically dependent from treatment with an opioid to buprenorphine, a partial agonist, is not precipitating an acute withdrawal syndrome. Subjects in Study 307 were tapered to no more than 30 mg per day MSE prior to initiating buprenorphine based on experience with starting physically-dependent patients on buprenorphine treatment for treatment of opioid dependence. Not many subjects discontinued in the open-label period of the controlled studies due to opioid withdrawal (11 subjects or 0.6%) and in Study 307, there was only 1 subject that discontinued due to opioid withdrawal in the open-label period in Study 308.

To evaluate whether patients could be transitioned directly to Belbuca without a taper of the prior opioid, the Applicant conducted Study EN3409-204, (Study 204). In this double-blind, active-controlled, two-period crossover study, subjects already receiving 80 mg to 220 mg oral MSE daily underwent two treatment periods characterized by 1) remaining on half of the prior opioid dose, or 2) being converted to Belbuca at the equivalent of half of their opioid dose. The conversion ratio for oral morphine sulfate to buprenorphine was 100:1. Subjects were divided into two groups based on opioid use. The Belbuca doses used were 300 mcg for subjects taking 80 to 160 mg at study entry and 450 mcg for 161 to 220 mg oral MSE. Physical dependence was confirmed using a naloxone challenge. The Clinical Opiate Withdrawal Scale (COWS) was used to assess withdrawal and the primary efficacy analysis

was a comparison of responders where a responder was either rescued with an opioid or had a COWS score of at least 13 (considered to be moderate withdrawal).

Thirty-one out of 33 subjects in the 80 to160 mg dose group and 5 of 6 in the 161 to 220 mg dose group completed the study. In spite of subjects being screened for a positive response to a naloxone challenge, there was only one subject that met the responder definition during treatment with buprenorphine and two subjects while on half of their prior opioid dose. The Applicant's analysis of the mean COWS was comparable for all subjects, regardless of prior dose or treatment period and ranged from 4.6 to 6.3. (b) (4) Belbuca will be labeled with the conversion method used during Study 307, to taper the prior opioid to no more than 30 mg of morphine sulfate or its equivalent prior to initiating Belbuca.

13. Advisory Committee Meeting

Belbuca represents the second buprenorphine product intended the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The data presented in support of the application were adequate to evaluate efficacy and safety and no novel issues arose that required discussion at an advisory committee meeting.

14. Pediatrics

As stated by Dr. Lloyd in his review:

> 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 what the information discussed at a scientific workshop held in December 2009 regarding pediatric trials.

15. Other Relevant Regulatory Issues

As stated by Dr. Lloyd in his review:

> *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.
>
> Two clinical sites high enrollment were selected for inspection. 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.

No irregularities were discovered upon review of the financial disclosure data.

There are no other unresolved relevant regulatory issues

16. Labeling

Labeling, including the carton and container, and proprietary name reviewers were obtained from DMEPA and all comments were conveyed to the Applicant and incorporated in labeling. The patient labeling team reviewed the medication guide and the instructions for use and found them acceptable once their recommended changes were implemented. The Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling

Additionally, the Controlled Substances Staff 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.

17. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

The Applicant has provided adequate evidence of efficacy for Belbuca that outweighs the adverse events found in the clinical studies, and that overall, when used as directed, outweighs the risks associated with an opioid, to support an approval for the proposed indication. Belbuca is dosed every 12 hours. The dosing interval of every 12 hours is based on the pharmacology of buprenorphine, not on characteristics of the formulation. Therefore, it cannot be manipulated for the purpose of extracting buprenorphine for faster delivery. Belbuca is not an abuse-deterrent formulation. While Schedule III products have a lower abuse liability than Schedule II opioids, buprenorphine is sought for, and abused by the oral transmucosal, nasal, and intravenous routes of abuse. This formulation of buprenorphine does not present any greater risk for abuse than other approved formulations indicated for pain.

Belbuca offers another option for managing patients with pain severe enough to require an around-the-clock clock, long-term opioid treatment and for which alternative treatment options are inadequate. It may be particularly useful for patients that do not require more than 160 mg of morphine sulfate or its equivalent, who have difficulty swallowing solid dosage forms. Belbuca, as with all opioid analgesics, and as stated in the labeling, should only be considered for patients for whom nonopioid analgesics, and immediate-release opioids used on an as needed basis are not able to adequately manage their pain. As with all patients with ongoing pain, attempts should be made to use a multidisciplinary approach to managing the patient's pain and minimize reliance on the long-term use of any analgesic medication to the extent possible. Once the decision has been made to use Belbuca, the patient and prescriber should plan specific goals for treatment, come to an agreement about expectations for compliance with prescribed medication, and have a plan for ongoing follow-up. Patients should be screened for the risk of addiction, and counseled on how to identify symptoms of possible addiction that may require the attention of the prescriber. Patients should also be counseled on the safe storage of Belbuca, and should be counseled on all of the important warnings and information for patients in the package insert and the ERLA Opioid REMS educational messages.

- Recommendation for Postmarketing Risk Management Activities

Belbuca will be included in the Extended-Release and Long-Acting Opioid Analgesic REMS, including all of the postmarketing requirements of that class.

- Recommendation for other Postmarketing Study Requirements

The following postmarketing study requirements have been agreed to by the Applicant.

2982-1 Conduct an open-label study to evaluate the pharmacokinetics and safety of BELBUCA in patients 7 through 16 years with pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which alternative treatment options are inadequate.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to:

- Assess the known serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics, of which BELBUCA (buprenorphine) is a member

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2065-1 Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.

These studies should address at a minimum the following specific aims:

a. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain. Stratify misuse and overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, addiction, overdose, and death.

b. Evaluate and quantify other risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of opioids for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify misuse and overdose by intentionality wherever possible.

2065-2 Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.

2065-3 Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

2065-4 Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.

Please note the following considerations regarding the postmarketing requirements detailed above. Given that misuse, abuse, addiction, overdose, and death are serious risks associated with the use of opioids as a class, FDA recommends that sponsors capture all opioid use among studied patient populations, rather than limit their efforts to specific products. However, specific product information should also be captured so as to better understand the role of specific product characteristics as risk factors for misuse, abuse, addiction, overdose, and death, as appropriate. Because many of the risk factors for misuse, abuse, addiction, overdose, and death cannot be captured using administrative databases alone, FDA is unlikely to find adequate protocols or strategies that evaluate administrative databases only as meeting the objectives outlined above.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to:

- Assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which BELBUCA is a member;
- Assess a signal of a serious risk of QT prolongation with BELBUCA treatment

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2065-5 Conduct a clinical trial 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. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.

2982-2 Conduct a multiple ascending dose clinical trial in adults to determine the maximum tolerated dose of BELBUCA without co-administration of naltrexone to inform the dosing for a thorough QT (tQT) trial of BELBUCA.

2982-3 Conduct a thorough QT trial in adults without naltrexone co-administration to assess the risk of QT prolongation with BELBUCA. This trial will provide information on the conduction effects of BELBUCA on the heart, specifically cardiac repolarization, at therapeutic and supratherapeutic dose regimens. The

tQT trial may be conducted as part of the required multiple ascending dose trial (PMR 2982-2).

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

/s/

SHARON H HERTZ
10/23/2015