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RESEARCH**

*APPLICATION NUMBER:*

**207932Orig1s000**

**MEDICAL REVIEW(S)**

Clinical Investigator Financial Disclosure  
Review Template

Application Number: 207932

Submission Date(s): 12/24/14

Applicant: Endo

Product: Belbuca

Reviewer: Pamela Horn, MD

Date of Review: 3/3/15

Covered Clinical Study (Name and/or Number): BUP-201, EN3409-204, BUP-301, EN3409-307, and EN3409-308

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>159 investigators and 631 sub-investigators</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p style="padding-left: 40px;">Significant payments of other sorts: <u>2</u></p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: <u>0</u></p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

**The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. The interests/arrangements do not raise questions about the integrity of the data because the investigators with the disclosed interests did not enroll any patients in the pivotal efficacy trials.**

**The disclosed financial interests/arrangements do not affect the approvability of the application.**

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<sup>1</sup> See <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm119145.htm>.

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/s/  
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PAMELA J HORN  
09/10/2015

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09/10/2015

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 207932  
Priority or Standard Standard

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Reviewer Name(s) Pamela Horn, MD  
Review Completion Date September 9, 2015

Established Name Buprenorphine HCl  
(Proposed) Trade Name Belbuca  
Therapeutic Class Opioid  
Applicant Endo Pharmaceuticals

Formulation(s) Buccal film  
Dosing Regimen Every 12 hours  
Indication(s) chronic pain  
Intended Population(s) Opioid-naïve and opioid-experienced patients with pain severe enough to require an around-the-clock opioid

Template Version: March 6, 2009

Appears this way on original

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

I recommend an Approval action for Belbuca buccal film (buprenorphine) 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 based on the review of clinical data and consideration of clinical issues.

The Applicant has submitted the results of two randomized, double-blind trials that demonstrated that the product was statistically significantly superior to placebo on an accepted primary efficacy endpoint for pain.

### **1.2 Risk Benefit Assessment**

The risk-benefit profile of the product is favorable for the proposed indication and the safety data collected in the clinical studies reveal no safety concern unique to this new formulation of buprenorphine.

The treatment effect of the product was shown to be superior to placebo in two adequate and well-controlled trials of pain patients. A third study that failed to show a statistically significant treatment effect had results that trended in a favorable direction for buprenorphine and had design flaws that may explain the lack of a statistically significant analysis result. Pain severe enough to require long-term opioid treatment can be serious and disabling. In this context, the risks of the product are outweighed by the benefits. Most patients in the clinical studies experienced adverse effects that did not lead to treatment discontinuation and they were largely effects known to occur with opioids, such as nausea and constipation. The most serious risks of respiratory depression, addiction, and overdose are known to occur with opioids and can be managed with appropriate dosing, monitoring, and prescriber and patient education, which can be addressed in the prescribing information and the recommended risk evaluation and mitigation strategy. Safety concerns with this product also include QT prolongation. The QT prolongation with the highest proposed strength to be marketed would be expected to be between 5 and 10 milliseconds, which is considered to be modest QT prolongation and warrants language in the dosing and administration section of the prescribing information advising prescribers not to exceed the 900 µg q12h recommended dose and a warning advising prescribers not to use the product in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA or III antiarrhythmic medications.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As a long-acting opioid, the class-wide risk evaluation and mitigation strategy for extended-release/ long-acting opioid analgesics, of which the other buprenorphine product with a pain indication is a part, is necessary and appropriate for this product to mitigate the risks of overdose, abuse, misuse, and addiction and to maintain a favorable risk-benefit profile for the product.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The applicant will have to fulfill the requirements of the Pediatric Research Equity Act. This product was brought to the Pediatric Review Committee (PeRC) on February 4, 2015. The agreed-upon pediatric study plan is to conduct studies evaluating pharmacokinetics and safety in a pediatric population age 7 to less than 17. (b) (4)

A waiver is recommended for the population from age 0 to less than 7 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.

Additionally, I recommend that the following class-wide postmarket requirement for ER/LA opioid products be required for Belbuca:  
Conduct one or more studies to provide quantitative estimates of the 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:

- I. Estimate the incidence of misuse, abuse, addiction, overdose, and death associated with use 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.
- II. 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.

## 2 Introduction and Regulatory Background

Buprenorphine is a partial agonist at the  $\mu$ -opioid receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence, a sublingual film formulation for opioid dependence and an extended-release transdermal film formulation for pain were approved in 2010, and a sublingual tablet formulation for opioid dependence was approved in 2013. In 2014, Bunavail, a buccal film, was approved for opioid dependence.

### 2.1 Product Information

Belbuca film employs the same BioErodible MucoAdhesive “BEMA” technology as Bunavail, the buccal film approved in 2014 for opioid dependence. Belbuca differs from Bunavail in that it contains only buprenorphine, rather than buprenorphine and naloxone, is being indicated for pain rather than addiction, and the proposed strengths are much lower than Bunavail. The proposed Belbuca strengths are 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg.

### 2.2 Tables of Currently Available Treatments for Proposed Indications

**Table 1 Available Pharmacologic Treatments for Chronic Pain**

Product Class	Route of Administration
NSAIDS	Oral
Acetaminophen	Oral
Opioids	Oral, Transdermal, Intramuscular, Subcutaneous, Intravenous, Sublingual, Patient Controlled Analgesia, Epidural, Intrathecal
Local Anesthetics (Regional and Local Analgesia)	Wound infiltration, nerve and plexus blocks, epidural, intrathecal

### 2.3 Availability of Proposed Active Ingredient in the United States

Approved Dosing Regimen for buprenorphine products for pain

Buprenorphine Hydrochloride Injection (Buprenex)

Adults: the usual dosage for persons 13 years of age and over is 0.3 mg buprenorphine (1 ml) given by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6-hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30

to 60 minutes after initial dosage. In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half.

Children: Buprenex has been used in children 2-12 years of age at doses between 2-6 micrograms/kg of body weight given every 4-6 hours. There is insufficient experience to recommend a dose in infants below the age of two years, single doses greater than 6 micrograms/kg of body weight, or the use of a repeat or second dose at 30-60 minutes (such as is used in adults). Since there is some evidence that not all children clear buprenorphine faster than adults, fixed interval or "round-the-clock" dosing should not be undertaken until the proper inter-dose interval has been established by clinical observation of the child.

Buprenorphine transdermal system (Butrans)

Opioid-Naïve Patients: Initiate treatment with Butrans 5mcg/h. The dose can be titrated to the next higher level after 72 hours. The maximum Butrans dose studied in analgesic trials was 20 mcg/h.

Conversion from Other Opioids to Butrans: For patients on less than 30 mg of oral morphine equivalent the recommended Butrans starting dose is 5 mcg/h. For subjects on 30-80 mg of oral morphine equivalent the recommended starting dose is 10 mcg/h. Butrans may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. The minimum titration interval is 3 days since steady state is obtained by the third day. The maximum Butrans dose studied in analgesic trials was 20 mcg/h.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Approved opioids, including buprenorphine, are all associated with potentially serious safety issues of respiratory depression, addiction and abuse.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The product was developed under IND 72428. The original Sponsor was BDSI, but was changed to Endo between the EOP2 meeting in 2010 and a Type A meeting in 2012. The Division provided the following key advice during the development program under IND 72428:

PIND meeting November 15, 2005:

- one adequate and well-controlled (AWC) study could be adequate to support a finding of efficacy, but studying (b) (4) will limit the indication (b) (4)

- the method of administration (b) (4) needs to be standardized

EOP2 meeting September 24, 2010:

- Using naltrexone in the tQT study will introduce a confounding factor and will result in a study that cannot be interpreted
- One positive AWC study should suffice to support efficacy for chronic pain indication

Type A meeting January 13, 2012:

Requested by BDSI, attended by Endo

- The single Phase 3 trial conducted in a combined population of opioid-naïve and opioid-experienced individuals failed to show a statistically significant treatment effect (BUP-301)

- (b) (4)

Type C Response in Writing May 24, 2012:

Feedback on two separate trials for opioid-experienced and opioid-naïve (BUP-307 and BUP-308)

- Primary endpoint of change from baseline to week 12 in the mean of average daily pain intensity scores due to CLBP using the 11-point NRS appears acceptable

- (b) (4) will not be permitted in labeling (b) (4)

- (b) (4)

- The proportion of responders will be eligible for inclusion in labeling. Subjects who discontinue early must be adjudicated as non-responders

- Rescue medication use and time to optimal dose of open-label study medication may be eligible for inclusion
- We encourage you to determine the lowest dose of opioid that would be necessary in order to begin treatment with this product without precipitating opioid withdrawal symptoms
- In general, an analysis of covariance is an acceptable statistical method for the proposed primary endpoint

Pre-NDA meeting July 15, 2014:

- Regarding QT interval prolongation: In the absence of a repeat tQT study without naltrexone blockade, we have safety information about the effect of buprenorphine on cardiac repolarization that can be applied to the risk-benefit assessment of your product. The results of a study submitted to FDA indicate that (b) (4)  
  
This safety information will be conveyed in product labeling. Therefore, while you are not required to repeat the thorough QT study with your product without naltrexone blockade, a repeat study is necessary if you wish to have data specific to your product that can be described in labeling to accompany the QT warnings.
- The Sponsor projected an exposure of at least 400 subjects for at least 24 weeks and at least 200 subjects for at least 48 weeks, which the Division said appeared to be acceptable to evaluate long-term safety

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

There were no issues with the quality of the submission that affected my ability to complete my review.

#### **3.2 Compliance with Good Clinical Practices**

The Applicant reported that the five Phase 3 clinical studies submitted in support of their NDA application were conducted in accordance with Good Clinical Practices (GCPs) with the following exceptions:

- Site 1008 (Studies 307, 308, 309), Principal Investigator Eduardo Almaguer, was terminated for apparent falsification of urine drug screen result. The pivotal efficacy analyses for studies 307 and 308 were conducted excluding data from site 1008.
- Site 1069 (Study 309), Principal Investigator Edward Tavel, was terminated for significant breach in Good Clinical Practice.

Additionally, site 1027 was terminated in study 307 in February 2014 because the principal investigator, Donald Taylor, had his license suspended for professional sexual misconduct. The Applicant reports that their audit revealed no critical or major GCP nonconformities. Because there was no evidence that GCPs had been compromised, the data was included in the pivotal efficacy analyses. The statistical reviewer conducted a sensitivity analysis excluding these data and found that the efficacy conclusions and statistical significance of the findings did not change. See 6.1.10 Additional Efficacy Issues/Analyses

Good Clinical Practice (GCP) inspection was conducted for site 1009 for study 307, clinical investigator James E. Wild, MD, and site 1040 for study 308, clinical investigator Bruce G. Rankin, DO.

The OSI reviewer, Dr. John Lee has concluded the data from both study sites appears to be reliable and the Applicant's monitoring of study conduct supports adequate adherence to GCP.

### **3.3 Financial Disclosures**

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. The interests/arrangements do not raise questions about the integrity of the data because the investigators with the disclosed interests did not enroll any patients in the pivotal efficacy trials.

The disclosed financial interests/arrangements do not affect the approvability of the application. See the Clinical Investigator Financial Disclosure Review Template for details.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.3 Preclinical Pharmacology/Toxicology**

Based on preliminary discussions, safety margins from a 28-day buccal dose study in dogs support local and systemic safety at the highest proposed dose of 900 µg bid. All excipients in the buccal film have been found to be acceptable for use previously in other approved chronically administered drug products.

### **4.4 Clinical Pharmacology**

Based on preliminary discussions, the clinical pharmacology team did not identify deficiencies in the application.

#### **4.4.1 Mechanism of Action**

Based on preliminary discussions, the clinical pharmacology team recommends that the prescribing information state that the clinical actions of buprenorphine (b) (4)

#### **4.4.2 Pharmacodynamics**

The pharmacodynamics section of labeling is similar to other approved buprenorphine products.

#### **4.4.3 Pharmacokinetics**

The clinical studies that the Applicant conducted demonstrated that steady-state plasma concentrations were achieved prior to the 6<sup>th</sup> dose and steady-state C<sub>max</sub> and AUC increased proportional to dose.

Systemic exposure was reduced by 23-27% by ingestion of liquids of all temperatures and should be avoided until the film has dissolved.

## **5 Sources of Clinical Data**

## 5.1 Tables of Studies/Clinical Trials

**Table 2 Efficacy and Safety Studies**

Study Identifier	Description	Efficacy review	Safety review
301	Efficacy in Chronic Pain	X	X
307		X	X
308		X	X
305	OL long-term safety		X
309			X
204	Tolerability of conversion from full agonist to buprenorphine		X

## 5.2 Review Strategy

All three Phase 3 pivotal trials are reviewed individually in section 5.3. Because the study designs are highly similar, study 307 is reviewed in detail and the differences between study 307 and studies 301 and 308 are summarized. The efficacy and safety reviews were completed by a single reviewer.

## 5.3 Discussion of Individual Studies/Clinical Trials

### Protocol EN3409-307

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

Protocol

### Objective/Rationale

The purpose of the clinical trial was to compare the analgesic efficacy of BEMA buprenorphine to placebo in patients with moderate-to-severe chronic low back pain

### Overall Design

The trial was to be a multicenter, double-blind, enriched enrollment, randomized withdrawal trial in opioid-experienced subjects with a 2-week screening phase, a 2-week analgesic taper phase, an 8-week open-label titration phase, a 12-week treatment phase, and a 3-week follow-up phase.

The analgesic taper phase was increased from 2 weeks to 4 weeks and the follow-up phase was shortened from 3 weeks to 2 weeks in Amendment 1 on 7/25/12.

## Population and Procedures

### *Inclusion/Exclusion Criteria*

Planned enrollment was approximately 475 subjects to provide a total of at least 284 subjects entering the double-blind treatment phase randomized 1:1 to each of two treatment arms

The planned enrollment was increased to 810 subjects to provide at least 500 subjects entering the double-blind treatment phase in Amendment 3 on 11/6/13

Key criteria that subjects were required to meet:

1. Clinical diagnosis of moderate-to-severe low back pain (CLBP) (Quebec Task Force 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) for at least 6 months as primary source of pain<sup>1</sup>
2. Treating their CLBP with a stable daily maintenance dose of around-the-clock (ATC) opioid analgesic medication equivalent to between 30 and 160 mg oral morphine sulfate equivalents (MSE) per day for at least 4 weeks; if subjects were taking as needed rescue in addition to the maintenance dose, the rescue could not exceed 30 oral MSE per day and the total of maintenance and rescue could not exceed 160 mg oral MSE per day
3. To enter the analgesic taper phase subjects were to be required to have demonstrated compliance with completing the interactive voice recognition/website system (IVR/WS) PI score during at least 11 of the last 14 days of the screening phase
4. To enter the open-label titration phase subjects were to be required to:
  - a. Have at least 3 consecutive average daily pain intensity scores of at least 5 on an 11-point NRS prior to addition of rescue during taper OR if they have a mean average PI score between 5 and less than 10 during the last 7 days of screening (skip taper)
  - b. Receiving no more than 30 mg MSE of prior opioid during last 3 days of taper phase
  - c. Taken no more than 4 tablets of hydrocodone/acetaminophen rescue per day during taper phase
  - d. Clinical opiate withdrawal scale (COWS) scores < 13 during taper phase
  - e. Demonstrated IVR/WS PI compliance of at least 11 of last 14 days during taper phase

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<sup>1</sup> Subjects with QTC Class 4-6 and 9 CLBP were added to the inclusion criteria in Amendment 2 on 4/19/13

5. To enter the double-blind treatment phase subjects were to be required to:
  - a. Receive optimal dose for at least last 14 days
  - b. Demonstrated at >80% medication adherence
  - c. IVR/WS PI compliance at least 11 of past 14 days
  - d. Taken no more than one dose of hydrocodone/acetaminophen (HC/APAP) per day in past 7 days
  - e. Achieved mean PI of 4 or less on last 3 consecutive days of titration and the mean PI is at least 2 points less than their mean score in first 3 days of taper prior to addition of rescue or last 7 days of screening if skipped taper

Key criteria that subjects were to be excluded for:

1. Cancer pain or chemotherapy within 6 months of screening
2. Any other chronic painful condition that investigator thought would interfere with assessment of CLBP or active diagnosis of fibromyalgia, reflex sympathetic dystrophy or causalgia (complex regional pain syndrome), acute spinal cord compression, cauda equina compression, acute nerve root compression, meningitis, discitis or back pain due to a secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm
3. Surgery to relieve pain in past 6 months or nerve/plexus block in past 28 days prior to screening
4. Intra-articular, intra-muscular, or spinally administered steroid within 3 months of screening
5. Spinal infusion pump use within 6 months of screening
6. Intend to alter physical therapy or transcutaneous electrical nerve stimulation during study
7. History of substance abuse or dependence within past 5 years per DSM-IV criteria
8. QTcF interval of 450 ms 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

Prohibited concomitant medications included:

- All non-opioid based analgesics including, but not limited to NSAIDs, cyclooxygenase-2 inhibitors, local anesthetics and acetaminophen  
Note: occasional non-opioid based analgesics such as ibuprofen (but preferably not acetaminophen) may be used on a short-term basis to treat minor ailments.
- All opioid based analgesics (including tramadol and tapentadol)
- MAOIs (e.g., isocarboxazid, moclobemide, phenelzine, tranylcypromine, selegiline, iproclazide, toloxatone)
- Corticosteroids other than topical steroids for dermatological conditions and inhalation steroids
- Chemotherapy

### *Procedures*

Subjects were to be required to report their average daily pain intensity score daily in the evening. After an initial screening visit, subjects were to report their daily pain intensity for two weeks during the screening phase. If they had reported their scores at least 11 of 14 days, they were to proceed to the taper phase. During the taper phase subjects were to continue to report their pain scores and had a clinic visit every 4 to 8 days while they tapered their medications by around 25% at each visit until they reached 30 mg oral MSE or less. Subjects were to then switch to open-label BEMA buprenorphine q12h. They were to have until week 6 to reach their stable BEMA buprenorphine dose before moving to the double-blind treatment phase at week 8.

At day 0 of the double-blind treatment period, subjects were to be randomized to BEMA buprenorphine at the same dose they had reached at the end of the open-label phase or to placebo. Hydrocodone/acetaminophen (HC/APAP) 5mg/325mg was to be used as rescue medication and to minimize the risk of opioid withdrawal in the placebo group. Subjects were permitted to use up to 2 doses of HC/APAP (1 or 2 tablets per dose depending on their dose level of BEMA buprenorphine; 1 tablet for 150 and 300 µg doses and 2 tablets for the higher doses) per day in the first two weeks of the double-blind treatment phase and were permitted up to one dose per day thereafter. Subjects were to be monitored with the Clinical Opiate Withdrawal Scale (COWS) assessment and were to be withdrawn from the study if they had moderate opioid withdrawal (COWS score of 13 or greater).

**Reviewer Comment: It is likely that the hydrocodone component of the rescue medication would have been blocked by the buprenorphine occupying the opioid receptors and the utility of rescue medication in the active treatment group would have been limited to the acetaminophen component, thereby likely rendering the rescue medication more efficacious in the placebo-treated subjects. This would not be expected to bias the efficacy results in favor of the BEMA buprenorphine group.**

The study assessments are summarized in the table below (section 4 Schedule of Events from study 307 protocol amendment 3 p. 17)





- <sup>A</sup> - If subjects withdraw prematurely during the Analgesic Taper Phase, the following assessments should be completed at Visit 26: abbreviated physical exam, vital signs, ECG, clinical lab assessment, suicidality assessment, review IXRS data and collect rescue medication.
- <sup>B</sup> - If subjects withdraw prematurely during the Open-label Titration Phase, the following assessments should be completed at Visit 26: abbreviated physical exam, vital signs, ECG, clinical lab assessment, pregnancy test (urine), suicidality assessment, AEs, con meds, review IXRS data, collect study medication and rescue medication.
- <sup>C</sup> - Medical History - if applicable, update at Visit 2 with any clinically-significant abnormal ECG and/or clinical laboratory results from Visit 1 (Screening).
- <sup>D</sup> - Physical Examination - full PE at Visit 1 (Screening) including at least general appearance, head [eyes, ears, nose, mouth, throat], skin, neurological, musculoskeletal, cardiovascular, respiratory, abdomen, and extremities; abbreviated symptom-directed PEs at rest of visits.
- <sup>E</sup> - Vital signs include temperature, body weight, pulse rate (beats per minute), blood pressure (systolic and diastolic blood pressure, mm Hg) and respiratory rate (respirations per minute) after at least 2 minutes at rest in a supine position. Height should only be recorded at Visit 1.
- <sup>F</sup> - Clinical Laboratory Assessments - During the Open-label Titration Phase, clinical labs should only be performed at Visits 9 and 13.
- <sup>G</sup> - Pituitary-Gonadal-Endocrine Assessments - Male subjects only.
- <sup>H</sup> - Drug of Abuse Screen - dipstick urine drug tests will screen for non-prescribed cannabis, cocaine, amphetamines, benzodiazepines and barbiturates.
- <sup>I</sup> - Pregnancy Test - All women will receive a serum pregnancy test at Visit 1 (sent to central laboratory), on site urine test at rest of the specified visits.
- <sup>J</sup> - Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) - should be performed at every visit.
- <sup>K</sup> - BEMA Buccal Film Training - site staff will train subjects how to apply the BEMA Buccal film using placebo films. If subjects are not able to successfully apply the films, they will not be eligible to participate or continue in the study.
- <sup>L</sup> - AEs and prior/concomitant medications will be collected in the source documents from the time of subject consent. For all subjects who enter the Analgesic Taper Phase, AEs and prior/concomitant medications must also be entered into the eCRF.
- <sup>M</sup> - During the Open-label Titration Phase, COWS and SOWS assessment should only be conducted at Visits 9, 10, and 11. If the subject returns to the clinic for an unscheduled visit between Visit 2 and Visit 9, COWS and SOWS assessments should be conducted at the Unscheduled visit.
- <sup>N</sup> - Prior analgesic medications - Subjects must stop all non-opioid analgesic medications and all PRN opioid analgesic medications at Visit 2; Subjects must stop all ongoing opioid analgesic medications at Visit 9.
- <sup>O</sup> - Open-label Study Medication - first dose of open-label study medication should be applied by the Subject at home, in the evening, just prior to contacting the IXRS.
- <sup>P</sup> - Analgesic rescue medication should not be dispensed to subjects with well controlled pain (defined as a mean of average daily pain intensity scores <5 on an 11-point NRS over the last 7 days of the Screening Phase) until they have reported daily average pain scores  $\geq 5$  on an 11-pt NRS for at least 3 consecutive days.
- <sup>Q</sup> - If a subject discontinues prematurely from the Double-blind Treatment Phase, all Visit 26 (EOT/ET) procedures should be conducted. Subjects should be converted to another analgesic regimen at the discretion of the PI, physician Sub-Investigator (Sub-I), or qualified designee. Site staff will follow up with the subject after 14 days via the Visit 27 telephone call to collect information regarding AEs, concomitant medications, and new analgesic medications.
- <sup>R</sup> - PK - Subjects will be scheduled to attend the clinic within a pre-agreed 3-hour time window at Visit 19 (Randomization/Baseline) and Visit 26 (EOT/ET). Time windows will be 0-3 hours, 3-6 hours, 6-9 hours, or 9-12 hours after their regular morning dosing time. Subjects should accurately record the time of their morning dose of study medication for these 2 visits. The Sponsor will provide a list to all sites of the time window when subjects should attend their clinic visit.
- <sup>S</sup> - Study medication and rescue medication will not be dispensed at Visit 26 (EOT/ET).
- <sup>T</sup> - At Visit 26 (EOT/ET), eligible subjects may enter the EN3409-309 Open-label Safety Study directly from this visit and their participation in the EN3409-307 study will be considered complete. If subjects are not eligible or chose not to continue into the EN3409-309 Open-label Safety Study at Visit 26, the subject will be converted to another analgesic regimen at the discretion of the PI, physician Sub-I, or qualified designee. Site staff will follow up with the subject after 14 days via the Visit 27 telephone call to collect information regarding AEs and concomitant medications.
- <sup>U</sup> - The screening period may be extended up to a maximum of 28 days with approval of the medical monitor.
- <sup>V</sup> - Additionally, subjects will complete a daily SOWS assessment (paper version) between Visits 19 and 20.
- <sup>W</sup> - Site staff may conduct additional study procedures if required.

## Evaluations/Endpoints

The primary efficacy variable was to be the change from Baseline to Week 12 of the Double-blind Treatment Phase in the mean of average daily pain intensity scores (using an 11-point NRS reported in the IXRS). Baseline weekly average pain intensity was to be the mean of available pain intensity in the last 7 days prior to randomization and the week 12 weekly average was to be the mean of the available pain intensity for the last 7 days prior to end of study treatment.

One of the secondary efficacy variables was to be the proportion of responders. A responder was a subject who achieved a specified percent pain reduction from the start of the open-label titration phase (Screening weekly average pain intensity prior to Open-label Titration Phase is to be the mean of available pain intensity for the last 7 calendar days prior to Open-label Titration Phase) to week 12 in the double-blind treatment phase.

The other secondary efficacy variables were to be as follows:

- Opioid rescue medication use
- Time to optimal dose of open-label study medication
- Time to treatment failure

- Patient reported outcome measures
  - Patient global impression of change
  - Roland Morris disability questionnaire
  - Medical outcomes score sleep subscale

## Statistical Plan

The primary efficacy analysis was to be an analysis of covariance (ANCOVA) with effects for treatment and covariate of baseline pain intensity score (prior to randomization) and screen pain intensity score (prior to Open-label titration phase). The least squared mean of the treatment difference and its standard deviation were to be estimated. The overall treatment difference, 95% two-sided confidence intervals and the p-value were then to be derived based on the subjects who were part of the interim analysis and the subjects who were randomized after the interim analysis using the Cui Hung-Wang's method.

The secondary analyses were to be proportion of responders, opioid rescue medication use, time to optimal dose of open-label study medication, time to treatment failure, and 3 PRO measures: Patient Global Impression of Change (PGIC), Roland Morris Disability Questionnaire (RMDQ), and Medical Outcomes Score Sleep Subscale (MOS).

The proportion of responders analysis was to be the cumulative proportion of subjects who achieve a range of percent pain reductions and did not discontinue from the study. A Cochran-Mantel-Haenszel Chi-square test stratified by dose level was to be used to compare treatment groups at 30% and 50% pain reduction.

## Results

Conducted 9/6/12 to 6/6/14

### Subject Disposition

Forty-three percent of potential subjects were reported as screen failures. Only one of 939 subjects who passed screening bypassed the taper phase. The subject was taking 30 mg of oral MSE per day and did not require taper. Eight hundred fifteen subjects completed the taper phase and entered the open-label titration phase and 124 subjects discontinued during the taper phase.

Of the 815 subjects enrolled in the open-label titration phase, 5 never received study medication, leaving a total of 810 subjects in the safety population. More than one third of subjects discontinued in the open-label titration phase (304/815 subjects, 37%). The reasons for discontinuation are summarized below:

**Table 4 Study 307 Subject Disposition in Open-Label Titration**

Reason for discontinuation	N (%)
Adverse Event	82 (10%)
Lack of Efficacy	64 (8%)
Protocol violation	43 (5%)
Opioid withdrawal	1 (0.1%)
Withdrew Consent	44 (5%)
Lost to follow-up	15 (2%)
Other	55 (7%)

Source: Reviewer-generated based on Table 7 of CSR and dataset DS

In the above table, I reclassified two subjects categorized by the Sponsor as subject decision, one to adverse event and one to lack of efficacy. In the “other” category, the majority of reasons for discontinuation were that the Sponsor closed randomization or entry criteria were not met. I did not reclassify any subjects in the “other” category into adverse event or lack of efficacy.

In the double-blind treatment phase there were 511 subjects randomized. More subjects discontinued in the placebo group than the BEMA group (43% placebo, 19% BEMA). Most of the difference in discontinuation between the treatment groups was captured by the lack of efficacy category (24% of the placebo subjects compared to 7% of BEMA), but there was also more opioid withdrawal in the placebo group as a reason for discontinuation. Reasons for discontinuation are summarized below:

**Table 5 Study 307 Subject Disposition in Double-blind Treatment**

Reason for discontinuation	BEMA n (%) N=254	Placebo n (%) N=257
Adverse Event	6 (2%)	14 (5%)
Lack of Efficacy	19 (7%)	61 (24%)
Protocol violation	3 (1%)	11 (4%)
Opioid withdrawal	1 (<1%)	9 (4%)
Withdrew Consent	11 (4%)	6 (2%)
Lost to follow-up	1 (<1%)	5 (2%)
Other	7 (3%)	4 (2%)

Source: Reviewer-generated based on Table 8 of CSR, dataset ADDS and dataset ADEG

Protocol violation was also a more frequent reason for discontinuation in the placebo group. Of 6 subjects who did not comply with the rules for rescue medication use, all were in the placebo group. This noncompliance with rescue medication rules is indicative of lack of efficacy and fits with the many lack of efficacy discontinuations in the placebo group. In the “other” category, 8 subjects were from site 1008, which was closed due to problems with the investigator, two were from site 1027, which was also

closed by the Sponsor. See section 3.2 Compliance with Good Clinical Practices for a description of the reason for site closure. Abnormal QT interval and investigator discretion accounted for the remaining two subjects in the category. Treatment-emergent abnormal QT interval was classified as a protocol violation for one subject in the BEMA group and as ‘other’ for one subject in the placebo group. These subjects were reclassified as Adverse Event in the above table.

#### Protocol Deviations

The most frequent protocol deviations concerned urine toxicology screens. Positive urine toxicology screen for drugs of abuse were observed in 636 subjects but only six of these were not expected or explainable based on a subject’s prior medications, allowed concomitant medication or allowed rescue medication. Urine toxicology screen for drugs of abuse was not done at baseline for 300 subjects. The protocol deviations section of the clinical study report also stated that safety laboratory tests were not done per protocol at baseline in 310 subjects and ECG was not done per protocol at baseline in 300 subjects. The Applicant clarified in a response to an information request that these data were missing from subjects who discontinued during the open-label titration phase and did not have a randomization visit. The allowable dose of HC/APAP of 4 tablets per day was exceeded in the analgesic taper phase and titration phase in 102 subjects.

#### Demographics

The table below illustrates demographic and baseline characteristics of the two treatment groups excluding site 1008.

**Table 6 Study 307 Demographic and Baseline Characteristics**

		BEMA (N=243)	Placebo (N=248)
Gender	n (%)		
	Female	130 (53%)	136 (55%)
	Male	113 (47%)	112 (45%)
Age	n (%)		
	18-64	211 (87%)	206 (83%)
	65-75	28 (12%)	39 (16%)
	>75	4 (2%)	3 (1%)
	Mean ± SD	52.5 ± 10.99	54.2 ± 11.30
	Range	27-78	23-79
Race	n (%)		
	White	193 (79%)	189 (76%)
	Black	49 (20%)	48 (19%)
	Other	1 (<1%)	11 (4%)

Mean NRS PI prior to OL titration	6.79	6.64
Mean NRS PI at baseline	2.91	2.84

N= number of subjects in the respective treatment group, n = number of subjects with respective characteristic, SD = standard deviation

Source: Applicant's Clinical Study Report, Table 10

The treatment groups were balanced on all characteristics.

The individual study results for study 307 are discussed in section 6. There was a statistically significant treatment effect favoring BEMA buprenorphine over placebo on the primary analysis and the  $\geq 30\%$  pain reduction and  $\geq 50\%$  pain reduction responder analyses.

### Studies 308 and 301

Studies 308 and 301 were similar in design to study 307. The key similarities and differences are summarized in the table below:

**Table 7 Comparison of Phase 3 Trial Designs**

	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 µg)	Buprenorphine (150/300/450 µg)	Buprenorphine (60/120/180/240 µg)
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	
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 secondary efficacy variables for study 308 were identical to the secondary efficacy variables for study 307. The protocol for Study 301 did not specify proportion of responders, rescue medication use, time to optimal dose of open-label study medication, time to treatment failure, or medical outcomes score sleep subscale as secondary efficacy variables. The secondary efficacy variables for study 301 were to be as follows:

- Patient's Global Impression of Change
- Roland-Morris Disability Rating Scale
- Treatment satisfaction questionnaire for medication
- Overall satisfaction with study drug (patient and investigator)

### Study 308 Results

Conducted 8/8/12 to 12/4/13

#### Subject disposition

Of the 752 subjects enrolled in the open-label titration phase 61% were randomized. Subjects most frequently dropped out during titration due to adverse events.

**Table 8 Study 308 Subject Disposition in Open-Label Titration**

Reason for discontinuation	N (%)
Adverse Event	109 (14%)
Lack of Efficacy	33 (4%)
Protocol violation	24 (3%)
Opioid withdrawal	0
Withdrew Consent	34 (5%)
Lost to follow-up	22 (3%)
Other	68 (9%)

Source: Table 4 308 CSR

In the double-blind treatment phase there were 462 subjects randomized. Subjects discontinued in a similar proportion in the placebo group and the BEMA group (25% placebo, 23% BEMA). A larger proportion of subjects in the placebo group discontinued due to lack of efficacy (10% of the placebo subjects compared to 3% of BEMA), and a larger proportion of subjects discontinued due to an adverse event in the BEMA group (8% of BEMA subjects compared to 3% of placebo subjects). Reasons for discontinuation are summarized below:

**Table 9 Study 308 Subject Disposition in Double-Blind Treatment**

Reason for discontinuation	BEMA n (%) N=230	Placebo n (%) N=232
Adverse Event	18 (8%)	8 (3%)
Lack of Efficacy	8 (3%)	23 (10%)
Protocol violation	7 (3%)	9 (4%)
Opioid withdrawal	3 (1%)	1 (<1%)
Withdrew Consent	12 (5%)	8 (3%)
Lost to follow-up	4 (2%)	9 (4%)
Other	2 (1%)	0

Source: Table 5 308 CSR, datasets ADDS, ADEG, ADLB

In the table above, I reclassified five subjects in the BEMA group from other to adverse event because 4 had treatment-emergent abnormal QT intervals and one had treatment-emergent abnormal ALT/AST. I also reclassified one subject in the placebo group with a treatment-emergent abnormal QT interval from protocol violation to adverse event.

#### Protocol Deviations

The most frequent protocol deviations were vital sign not done at screening (302 subjects), urine toxicology screen for drugs of abuse not done at baseline (288 subjects), safety laboratory tests not done per protocol at baseline (280 subjects), and positive urine toxicology screen for drugs of abuse for any urine drug screens occurring during the study (127 subjects). Similar to study 307, the labs that were not done per protocol were due to subject discontinuation and lack of a randomization visit.

#### Demographics

The table below illustrates demographic and baseline characteristics of the two treatment groups excluding site 1008.

**Table 10 Study 308 Demographic and Baseline Characteristics**

		BEMA (N=209)	Placebo (N=211)
Gender	n (%)		
	Female	107 (51%)	124 (59%)
	Male	102 (49%)	87 (41%)
Age	n (%)		
	18-64	180 (86%)	186 (88%)
	65-75	25 (12%)	24 (11%)
	>75	4 (2%)	1 (<1%)
	Mean ± SD	51.1 ± 12.90	48.7 ± 13.19
	Range	22-82	19-78
Race	n (%)		
	White	150 (72%)	137 (65%)
	Black	50 (24%)	56 (27%)
	Other	9 (4%)	18 (9%)
Mean NRS PI prior to OL titration		7.12	7.18
Mean NRS PI at baseline		2.82	2.79

Source: Applicant's Clinical Study Report, Table 7

The treatment groups were balanced on most characteristics. There was a larger proportion of female subjects in the placebo group. This is unlikely to have biased the pain efficacy outcomes in favor of the BEMA group.

The individual study results for study 308 are discussed in section 6. There was a statistically significant treatment effect favoring BEMA buprenorphine over placebo on the primary analysis and the ≥ 30% pain reduction but not the ≥ 50% pain reduction responder analyses.

### Study 301 Results

Conducted 11/17/10 to 7/26/11

Subject disposition

Of the 334 subjects enrolled in the open-label titration phase 70% were randomized. Subjects most frequently dropped out during titration due to adverse events.

**Table 11 Study 301 Subject Disposition in Open-Label Titration**

Reason for discontinuation	N (%)
Adverse Event	39 (12%)
Lack of Analgesic Effect	30 (9%)
Non-compliance	9 (3%)
Lost to follow-up	7 (2%)
Other	13 (4%)

Source: Table 14.1.1 301 CSR

In the double-blind treatment phase there were 235 subjects randomized. A higher proportion of subjects discontinued in the placebo group than the BEMA group (31% placebo, 24% BEMA). However, the reasons for discontinuations were similar in proportion between the treatment groups. There was a higher proportion of subjects in the placebo group that were lost to follow-up. Reasons for discontinuation are summarized below:

**Table 12 Study 301 Subject Disposition in Double-Blind Treatment**

Reason for discontinuation	BEMA n (%) N=117	Placebo n (%) N=118
Adverse Event	8 (7%)	6 (5%)
Lack of Analgesic Effect	5 (4%)	6 (5%)
Non-compliance	5 (4%)	4 (3%)
Opioid withdrawal	0	1 (1%)
Lost to follow-up	1 (2%)	7 (6%)
Other	9 (8%)	12 (10%)

Source: Table 14.1.2 301 CSR, dataset

Reasons for discontinuation classified as “other” were use of a prohibited medication in four placebo subjects and three BEMA subjects, withdrew consent in five placebo subjects and four BEMA subjects, and drug screen positive in two placebo subjects and one BEMA subject, one placebo subject was going to have shoulder surgery and one BEMA subject had too many missed doses (likely should be classified as non-compliance).

#### Protocol Deviations

The most common protocol deviation was drug compliance less than 70%, which occurred in 7% of BEMA subjects and 14% of placebo subjects. This could indicate that some subjects were aware that the placebo was not having an analgesic effect and that blinding was not optimal. Other protocol deviations were using other analgesics daily in 7% of BEMA subjects and 5% of placebo subjects, use of more than 2 g of APAP per

day in 2% of BEMA subjects and 1% of placebo subjects and less than 4 recorded pain scores during the last 7 days in 7% of BEMA subjects and 8% of placebo subjects.

### Demographics

The table below illustrates demographic and baseline characteristics of the two treatment groups.

**Table 13 Study 301 Demographic and Baseline Characteristics**

		BEMA (N=117)	Placebo (N=118)
Gender	n (%)		
	Female	62 (53%)	66 (56%)
	Male	55 (47%)	52 (44%)
Age	n (%)		
	18-64	100 (85%)	100 (85%)
	65-75	14 (12%)	17 (14%)
	>75	3 (3%)	1 (1%)
	Mean ± SD	51.2 ± 13.27	50.7 ± 13.32
	Range	21-89	20-77
Race	n (%)		
	White	95 (81%)	95 (80%)
	Black	21 (18%)	22 (19%)
	Asian	1 (1%)	1 (1%)
Mean NRS PI prior at baseline		3.23	3.26
Prior Opioid-Experienced		44 (38%)	36 (31%)

Source: Applicant's Clinical Study Report, Table 7

The treatment groups were balanced on most characteristics. There was a larger proportion of opioid-experienced subjects in the BEMA group and around a third of subjects were opioid-experienced in the ITT population overall.

The individual study results for study 301 are discussed in section 6. There was neither a statistically significant treatment effect favoring BEMA buprenorphine over placebo on the primary analysis nor the ≥ 30% pain reduction responder analysis, though numerically BEMA buprenorphine was favored over placebo. On the ≥ 50% pain reduction responder analysis placebo was favored numerically over BEMA buprenorphine.

## 6 Review of Efficacy

### **Efficacy Summary**

The Applicant has demonstrated efficacy in two trials compared to placebo (studies 307 and 308) and has shown a trend favoring their product in a third placebo-controlled trial that did not show a statistically significant difference between the treatment groups, likely due to a dose range that was too low and an open-label titration period that was too short to allow optimal dose titration and stabilization. The primary efficacy analysis, an analysis of covariance of the change from Baseline to Week 12 of the Double-blind Treatment Phase in the mean of average daily pain intensity scores (using an 11-point NRS), is not novel and the key secondary efficacy analyses (proportion of subjects that achieved 30% and 50% pain reduction) support the primary findings and are also not novel. The Sponsor has studied both an opioid-naïve and opioid-experienced population and has demonstrated efficacy in both populations. There are no direct comparisons with other analgesics for this product, but the treatment effect observed is generally within the range observed for other opioid analgesics.

### 6.1 Indication

The Applicant is seeking to label their product with the single indication (b) (4)

#### 6.1.1 Methods

Studies 301, 307, and 308 were all placebo-controlled, parallel group, randomized withdrawal studies. Because of the similar trial designs, the Applicant presented the efficacy data from all three trials separately and pooled together in the Integrated Summary of Efficacy. The analysis results from the individual trials were key for the purposes of regulatory decision making because there was no prespecified statistical analysis plan to pool data from the trials, the dose range and study populations differed between trials, and taken individually, the trials could show replicated evidence of efficacy. Study 301 included both opioid-naïve and opioid-experienced subjects (maximum 60 mg oral MSE per day) with a history of chronic low back of at least 3 months duration and poorly controlled pain. Study 307 included only opioid-experienced subjects on up to 160 mg oral MSE per day and could have any pain score at screening, and study 308 included only opioid-naïve subjects with poorly controlled pain. Subjects in studies 307 and 308 must have had chronic low back pain for at least 6 months.

#### 6.1.2 Demographics

Demographic characteristics were balanced in the pooled population between buprenorphine-treated and placebo subjects as shown in the table below.

**Table 14 Pooled Demographics and Baseline Characteristics for All Phase 3 Trials**

	Buprenorphine (N=600)	Placebo (N=606)
Mean Age	51.9	51.6
Age 65 or older	13.7%	15.0%
Females	53.7%	56.6%
Non-white	22.7%	26.4%
Mean NRS prior to titration	6.91	6.86
Mean NRS at baseline	2.97	2.92

Source: Table 10 ISE

**Table 15 Baseline Characteristics Individual Trials (site 1008 excluded)**

	301		307		308	
	Bup	Placebo	Bup	Placebo	Bup	Placebo
NRS prior to titration <sup>2</sup>	7.0		6.79	6.64	7.12	7.18
Median	7.0		6.86	6.71	7.29	7.17
Min, Max	5, 10		3.0, 10.0	2.7, 10.0	5.0, 10.0	5.0, 9.7
Mean NRS at baseline	3.23	3.26	2.91	2.84	2.82	2.79

Source: Table 9, ISE

The Sponsor employed the Screen Observation Carried Forward imputation strategy for subjects who discontinued due to an adverse event. For study 307, subjects may have had a mean NRS prior to titration of < 5, as shown in the table above, because patients with well-controlled pain on their current regimen were permitted into the study. For studies 301 and 308, the NRS score prior to titration that would be imputed would be more punitive, as it could only be between 5 and 10. For subjects who discontinued due to opioid withdrawal, the mean NRS at baseline was imputed. The mean baseline NRS scores were similar in all studies and treatment groups.

### 6.1.3 Subject Disposition

A larger proportion of subjects completed the open-label titration phase in study 301 (70%) compared to studies 307 (63%) and 308 (61%), though the proportions were fairly similar. The most common reason for discontinuation was an adverse event for all

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<sup>2</sup> For study 301, the NRS prior to observation was a single score. For studies 307 and 308, it was the mean PI on the last 7 days before taking study medication

studies and was the reason for discontinuation for between 10 and 15% of subjects in all studies.

During the double-blind treatment period, around 25% of subjects discontinued across the trials. The highest discontinuation percentage was in the opioid-experienced population that received placebo in study 307 where 43% of subjects discontinued. The placebo group had a larger proportion of discontinuations than the active treatment groups in all trials, but the biggest difference between treatment groups was also in study 307 as shown in the table below.

**Table 16 Disposition of Subjects in Treatment Period, All Phase 3 Trials**

	301		307		308	
	Bup	placebo	Bup	placebo	Bup	placebo
Randomized subjects	117	118	254	257	230	232
Completed treatment	76.1%	68.6%	81.1%	57.2%	76.5%	75%
Discontinued						
AE	6.8%	5.1%	2.4% <sup>3</sup>	5.4% <sup>4</sup>	7.8% <sup>7</sup>	3.4% <sup>5</sup>
LOE	4.3% <sup>6</sup>	5.1% <sup>6</sup>	7.5%	23.7%	3.5%	9.9%
Protocol violation	-	-	1.2% <sup>3</sup>	4.3%	3.0%	3.9% <sup>5</sup>
Opioid withdrawal	0	0.8%	0.4%	3.5%	1.3%	0.4%
Withdrew Consent	0	0.8%	4.3%	2.3%	5.2%	3.4%
Lost to follow-up	0.9%	5.9%	0.4%	1.9%	1.7%	3.9%
Other	7.7%	10.2%	2.8%	1.6% <sup>4</sup>	0.9% <sup>7</sup>	0
Non-compliance	4.3%	3.4%	-	-	-	-

Source: Tables 7 and 8 ISE

The Sponsor employed a multiple imputation strategy for missing data. Subjects categorized as discontinuing due to an adverse event had the least favorable imputed value, screen observation carried forward. In study 307, the mean NRS prior to titration (screen observation) could have been more favorable than in the other two studies, because subjects with a mean NRS < 5 were allowed in the study. However, this is

3 One subject with prolonged QTc interval reclassified from protocol violation to AE

4 One subject with prolonged QTc interval reclassified from other to AE

5 1 subject with prolonged QTc interval reclassified from protocol violation to AE

6 Reclassified from "other"

7 4 subjects with prolonged QTc interval and 1 subject with abnormal LFTs reclassified from "other" to "AE" in buprenorphine group

unlikely to bias the efficacy results in favor of BEMA buprenorphine, because more subjects discontinued due to adverse events in the placebo group in study 307 than in the BEMA buprenorphine group.

The strategy that would impute the most favorable values (baseline pain score) would be for subjects that discontinued due to opioid withdrawal. Overall, there was a higher percentage of subjects in the placebo group that were classified as discontinuing due to opioid withdrawal, so this imputation strategy also would not be expected to favor the buprenorphine group.

Subjects who withdrew due to lack of efficacy (LOE) were to have their last observation carried forward. The last observation would be expected to be a high pain score. This imputation strategy would be expected to impute more high pain scores in the placebo group than the buprenorphine group because there were a much larger proportion of subjects in the placebo group who dropped out due to lack of efficacy.

In study 301, there was no LOE category, but the Sponsor noted that a substantial proportion of the subjects in the “other” category had lack of analgesic effect reported as the reason for discontinuation. In table 6, I reclassified these subjects into the LOE category for comparison purposes. Because the reason for discontinuation due to lack of efficacy was not collected in the eCRF, the Sponsor defined subjects discontinuing for lack of efficacy in Study 301 for the purposes of imputing missing values as:

*Subjects discontinuing the trial prior to Week 12 and not having at least 4 of 7 NRS assessments directly prior to the Week 12 visit AND demonstrating no improvement (e.g., worsening by 2 units or more) on their last NRS assessments average compared to their baseline NRS score (e.g., the change in pain intensity from baseline to last available NRS assessment were calculated as the average of the daily pain scores from the subject’s last available 7 NRS assessments minus the average of the daily pain scores for the last 7 days prior to baseline).*

These two approaches to defining lack of efficacy only overlapped in 4 subjects. Two were in the placebo arm and two were in the buprenorphine arm. There were 7 other subjects with lack of analgesic effect reported as a reason for discontinuation; 4 in the placebo arm and 3 in the buprenorphine arm. There were 9 different subjects based on the imputation criteria in the efficacy analysis set; 6 in the placebo arm and 3 in the buprenorphine arm.

#### 6.1.4 Analysis of Primary Endpoint(s)

There were around twice as many subjects in the studies where the conclusion from the primary efficacy analysis rejected the null hypothesis (307 and 308) than in the study that failed to reject the null hypothesis (301). There were 235 randomized subjects in study 301 compared to 511 randomized subjects in study 307 and 462 randomized subjects in study 308. Even with the design features in study 301 that hindered the

identification of a treatment effect, including a smaller sample size than the other two studies, the difference in change from baseline pain score versus placebo was negative (favoring BEMA buprenorphine) in all studies, though it did not reach statistical significance for study 301.

**Table 17 Primary Efficacy Analysis Individual and Pooled Studies**

	301		307 (no site 1008)		308 (no site 1008)		Pooled (no site 1008)	
	Bup N=117	Placebo N=118	Bup N=243	Placebo N=248	Bup N=209	Placebo N=211	Bup N=569	Placebo N=577
Mean Baseline	3.23	3.26	2.91	2.84	2.82	2.79	2.95	2.92
Week 12 imputed <sup>8</sup>	3.57	3.72	3.8	4.75	3.76	4.39	3.79	4.47
Change from baseline imputed	0.33	0.46	0.88	1.92	0.94	1.59	0.84	1.55
Difference (95% CI) vs placebo	-0.14 (-0.646, 0.366)		-0.98 (-1.32, -0.64)		-0.67 (-1.07, -0.26)		-0.72	
P value	0.5870		<0.00001		0.0012		<0.001	

Source: Tables 12, 13, and 2.1.3 (p.181-2) ISE

In the pooled analysis, BEMA buprenorphine had a smaller change from baseline to week 12 mean pain score than placebo and the difference was statistically significant. In the above table, the pooled data excludes site 1008 from studies 307 and 308. With subjects from site 1008 included, the difference versus placebo from the pooled studies was -0.67 with a p-value of <0.0001.

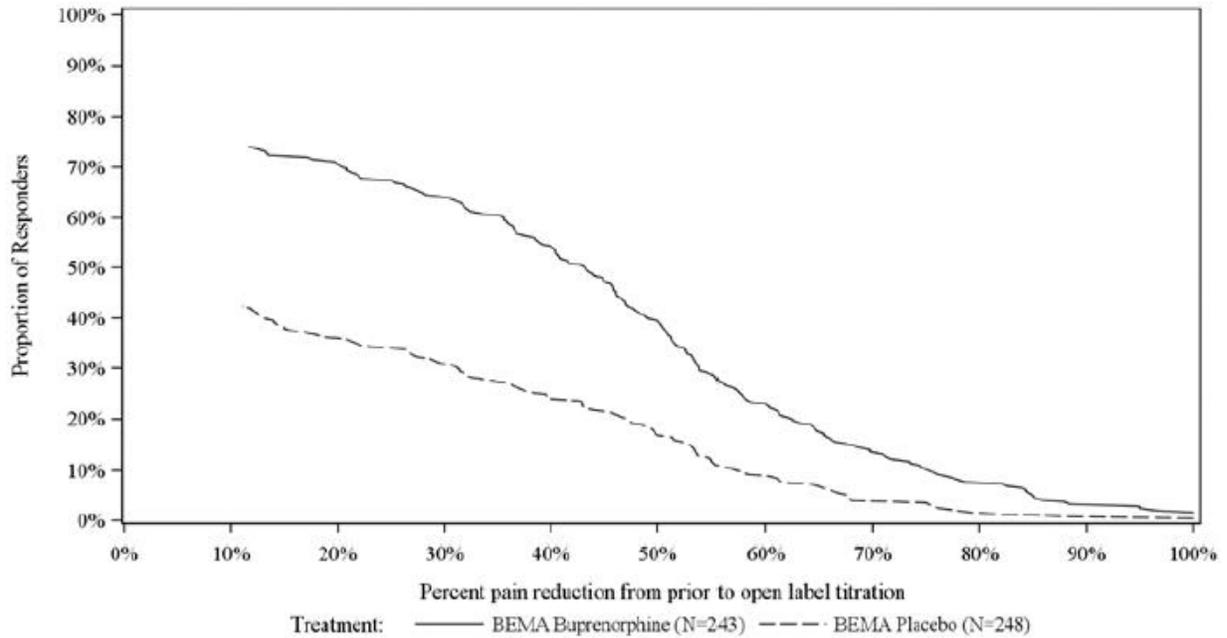
### 6.1.5 Analysis of Secondary Endpoints(s)



The following figure is figure 7 from the study 307 CSR:

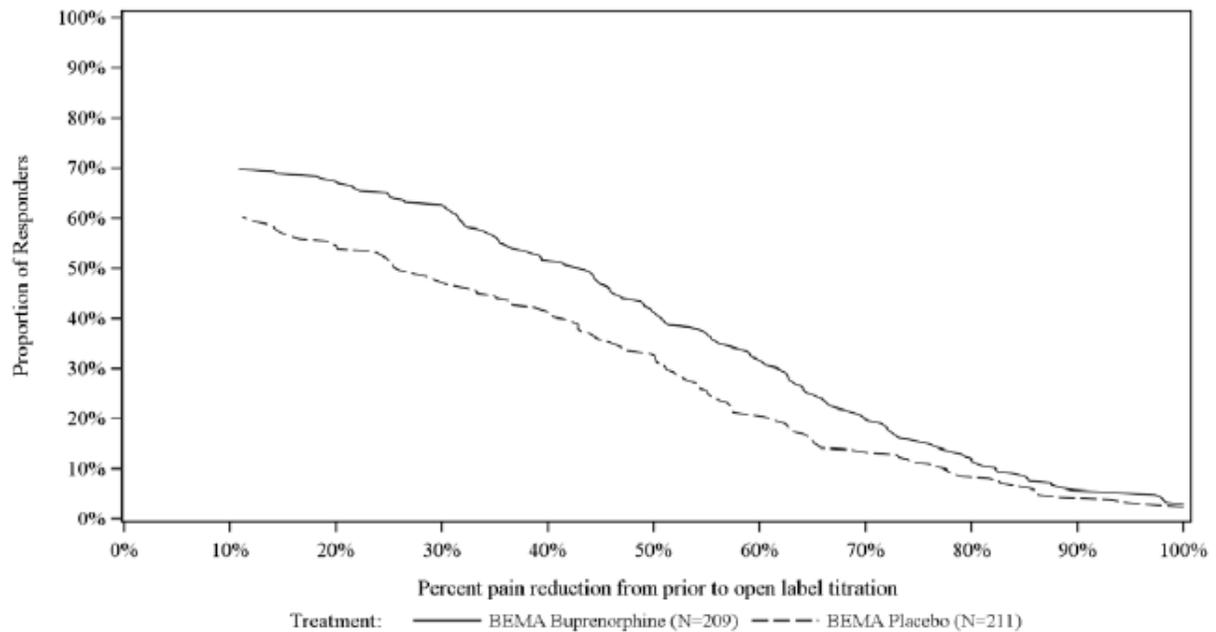
<sup>8</sup> LOCF for d/c due to LOE, SOCF for d/c due to AE, BOCF for d/c due to opioid withdrawal

**Figure 1 Study 307 Proportion of Responders ITT Population (Site 1008 Excluded)**



The following figure is figure 7 from the study 308 CSR:

**Figure 2 Study 308 Proportion of Responders ITT Population (Site 1008 Excluded)**



There is a more impressive separation between buprenorphine and placebo in the opioid-experienced population but both studies had a difference between buprenorphine

and placebo favoring the buprenorphine group in responders. The table below summarizes the comparisons at the 30% and 50% cutoffs for pain reduction.

**Table 18 Responders with  $\geq 30\%$  and  $\geq 50\%$  Pain Reduction by Individual Study (ITT Population, Site 1008 Excluded)**

Study Responders	Bup	placebo	P value
301			
N	117	118	
$\geq 30\%$ pain reduction	28 (24%)	27 (23%)	0.8785
$\geq 50\%$ pain reduction	13 (11%)	20 (17%)	0.2599
307			
N	243	248	
$\geq 30\%$ pain reduction	156 (64%)	76 (31%)	<0.0001
$\geq 50\%$ pain reduction	96 (40%)	42 (17%)	<0.0001
308			
N	209	211	
$\geq 30\%$ pain reduction	131 (63%)	99 (47%)	0.0012
$\geq 50\%$ pain reduction	86 (41%)	69 (33%)	0.0754

Source: Table 16, ISE

In study 301, the proportion of responders was lower than in the other two studies, especially in the buprenorphine groups. This may be due to the lower doses that subjects received in this study. The proportion of subjects who experienced a pain reduction at the 50% cutoff was actually higher in the placebo group than in the buprenorphine group in study 301. The proportion of subjects who met the 30% and 50% criteria were very similar in the buprenorphine groups for studies 307 and 308, but the proportion of responders in the placebo group was much lower in the placebo group for study 307 compared to study 308. This is likely a result of the different patient populations studied, with the opioid-experienced placebo-treated subjects in study 307 being more likely to have dropped out and also less likely to have had a pain reduction than the opioid-naïve placebo-treated subjects. The similarity between the 307 and 308 buprenorphine responders and the high percentages of responders indicates that there was a successful titration in the open-label period in both studies to provide clinically meaningful pain relief for subjects who stayed in the study.

The Sponsor included pooled analyses in the ISE. The 30% and 50% comparisons were both statistically significant favoring buprenorphine with a p-value of <0.0001 and the graphical representation of the pooled data was similar to figures 1 and 2 with separation between buprenorphine and placebo that was intermediate between studies 307 and 308.

### 6.1.6 Other Endpoints

#### Rescue Medication Use

In all three studies, data about rescue medication use was based on self-report in the electronic record.

The following table summarizes the mean number of tablets used by week in the Phase 3 trials.

**Table 19 Mean Rescue Medication Use in Phase 3 Trials**

	301		307		308	
	Bup N=117	Placebo N=118	Bup N=243	Placebo N=248	Bup N=209	Placebo N=211
Week 1	6.1	5.7	11.0	13.5	3.7	5.1
Week 2	6.5	7.2	10.1	13.8	4.1	5.2
Week 3			8.4	10.6	3.4	5.0
Week 4	6.5	7.1	7.7	10.0	3.3	4.7
Week 5			8.0	10.0	3.0	4.3
Week 6	6.8	7.3	7.7	9.4	3.0	4.7
Week 7			8.0	9.4	3.1	4.1
Week 8	6.2	6.9	7.7	9.4	2.9	4.0
Week 9			7.9	9.4	3.2	4.2
Week 10	5.8	6.9	7.8	9.7	2.7	4.0
Week 11			8.0	9.4	2.5	4.1
Week 12	6.8	6.4	6.7	8.1	2.3	3.6

Source: 301 study report table 14.2.11 and Statistical reviewer's analysis of data from studies 307 and 308

The number of tablets used was higher in the placebo groups than the parallel buprenorphine groups in all three studies at all weeks except in study 301 where subjects in the buprenorphine group used a higher mean number of tablets in weeks 1 and 12 than the subjects in the placebo group. For studies 307 and 308, where a statistically significant treatment effect was observed, this is consistent with buprenorphine being more efficacious than placebo. The mean number of tablets used was higher in study 307 than in studies 301 or 308. The rescue medication in study 307

was HC/APAP and was APAP in studies 301 and 308 (HC/APAP for first two weeks in 308) and study 307 had the most opioid-experienced population.

In study 301, 81% of subjects in the buprenorphine group and 79% of subjects in the placebo group used rescue medication. In study 307, use of rescue medication by week in the treatment period ranged from 83 to 89% in the buprenorphine group and from 88% to 93% in the placebo group, and in study 308, use of rescue medication by week in the treatment period ranged from 35 to 59% of subjects in the buprenorphine group and 48 to 67% of subjects in the placebo group. In studies 307 and 308 where there was a statistically significant treatment effect, a higher proportion of subjects used rescue medication in the placebo groups than in the buprenorphine groups overall, which is consistent with buprenorphine being more efficacious than placebo.

There was much more use of rescue medication in both treatment groups in study 307, where the population was opioid-experienced and the rescue medication was a combination of opioid and acetaminophen than in study 308 where the population was opioid-naïve and the rescue medication was acetaminophen alone.

The other secondary efficacy outcomes from the trials were generally supportive of the primary and key secondary analyses of efficacy. These outcomes were not part of the formal statistical analyses for the trials and do not add new information (b) (4)

The efficacy outcomes that measured function in studies 301, 307, and 308 are the Roland-Morris Disability Questionnaire (RMDQ), the Patient Global Impression of Change (PGIC). For the RMDQ, higher scores indicate worse function. For the PGIC, higher scores indicate more improvement in function.

**Table 20 RMDQ and PGIC scores**

		301		307		308	
		BEMA Bup N=117	Placebo N=118	BEMA bup N=241	Placebo N=238	BEMA bup N=206	Placebo N=201
RMDQ mean scores	Prior to OL titration	NR	NR	14.7	14.9	14.9	15.7
	Baseline	7.86	6.70	11.2	11.6	10.5	10.9
	End of Treatment (EOT)	7.67	7.56	11.6	13.0	11.0	11.9

PGIC mean scores	Baseline	5.38	5.32	5.4	5.3	5.3	5.2
	EOT	5.01	4.55	4.5	3.2	4.5	3.9

Source: CSR 307 and 308 table 14.2.10.1, 14.2.11.1, CSR 301 table 14.2.8 and 14.2.6

Of note, the mean RMDQ scores were much lower in study 301 compared to studies 307 and 308. There was a trend towards better function at end of treatment in the BEMA bup group as measured by these instruments in all studies.

Additionally, studies 307 and 308 measured sleep outcomes using the medical outcomes sleep subscale score, which has categories for sleep adequacy, somnolence, sleep disturbance, and sleep problems index. Higher scores indicate worse sleep outcomes. According to this instrument, sleep outcomes worsened during the study compared to prior to OL titration in both groups and there was no trend favoring BEMA buprenorphine.

**Table 21 Medical Outcomes Sleep Subscale Scores**

		307		308	
		BEMA bup N=241	Placebo N=238	BEMA bup N=206	Placebo N=201
Mean scores	Prior to OL titration	65.60	64.79	62.88	63.86
	Baseline	67.47	67.00	66.03	67.21
	EOT	67.23	65.78	65.92	67.31

Source: CSR 307 and 308 table 14.2.12.1

### 6.1.7 Subpopulations

In the buprenorphine-treated groups, similar proportions of subjects completed the treatment phase at the different dose groups (high (600 to 900 µg), middle (300 to 450 µg), and low (60-240 µg) 75-80% completion), and the opioid-experienced subjects completed the treatment phase in a similar proportion to the opioid-naïve subjects (77-80% completion). However in the placebo-treated groups, the high dose group had a lower treatment completion rate (57% compared to 68-70% in the low and middle groups) and the opioid-experienced group had a lower treatment completion rate than the opioid-naïve group (57% experienced compared to 75% naive). The major driver of these differences was a higher discontinuation due to lack of efficacy in the subjects

who received the highest doses (23%) and in opioid-experienced subjects (21%). These groups also had the highest incidence of discontinuation due to opioid withdrawal (5% of high dose placebo subjects and 3% of opioid-experienced subjects).

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only 10 out of 243 (4%) subjects in the buprenorphine arm were randomized to the 150 µg group in study 307 (opioid-experienced population) indicating that this dose is likely to be too low for most opioid-experienced individuals. A progressively higher proportion of subjects in the buprenorphine arm were randomized to the higher dose levels (12% to 300 µg, 14% to 450 µg, 15% to 600 µg, 17% to 750 µg and 38% to 900 µg).

In study 308, 26% of subjects in the buprenorphine arm were stabilized on and randomized to 150 µg q12h, 30% to 300 µg q12h and 44% to 450 µg q12h.

The lack of a statistically significant treatment effect in study 301, where the dose range was lower (60 to 240 µg q12h) than the dose range in studies 307 (150-900 µg q12h) and 308 (150-450 µg q12h), may be due in part to underdosing. Roughly one quarter of the subjects in the buprenorphine arm were stabilized on and randomized to the four dose levels, 60, 120, 180, and 240 µg q12h. However, the open-label period available for dose titration and stabilization was also shorter in study 301 than in studies 307 and 308, and subjects may have not reached their optimal dose in the allotted time, which was then observed as a non-statistically significant treatment effect in the double-blind period.

In a pooled analysis of the three studies, the treatment effect increased with increasing dose.

**Table 22 LS mean treatment difference (95% CI) between groups by dose subgroups using Mixed Model Repeated Measures method**

Low dose (60 to 240 µg)	Middle dose (300 to 450 µg)	High dose (600 to 900 µg)
-0.33 (-0.77 to 0.11)	-0.72 (-1.07 to -0.38)	-1.25 (-1.68 to -0.83)

Source: p. 77 ISE

A limitation of this pooled analysis is that the subjects are not randomized between dose groups and there may be confounding factors that have not been addressed in such an analysis. One factor is screening and baseline pain score, which was lowest in the low dose group and highest in the high dose group.

Additionally, the pooled studies had different dose ranges and study populations, making the pooled analysis difficult to interpret.

Dr. Travis also conducted the primary analysis for study 307 with subjects separated into a <750 µg and a 750 µg and greater dose group as shown below. This analysis also has the limitation of not being randomized between dose groups.

**Table 23 Study 307 Estimated Treatment Effect by Dose Group using Mixed Model Repeated Measures method**

< 750 µg	750 µg or greater
-1.13 (-1.62 to -0.64)	-1.17 (-1.67 to -0.67)

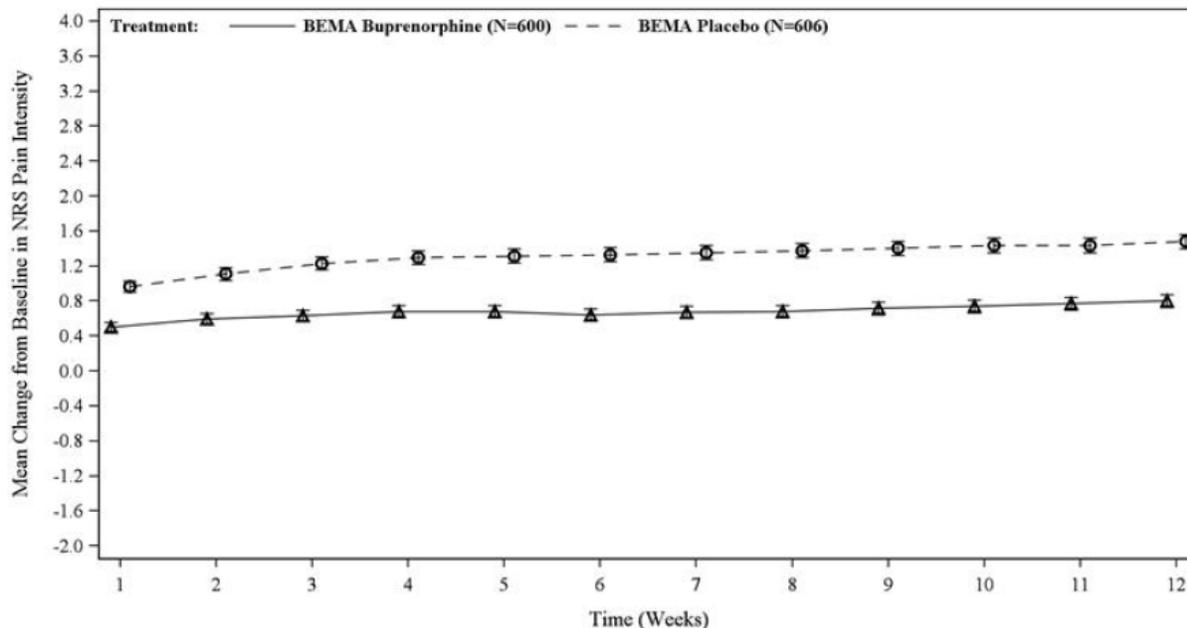
Source: generated by statistical reviewer, Dr. Travis

Recognizing that there are limitations to these analyses, the available information on titration to effect and treatment effect by dose group does not indicate that a ceiling effect was reached and does not raise concern for approving the highest proposed strengths.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Mean pain scores increased from double-blind baseline in both the buprenorphine and placebo groups at all subsequent weeks as shown in the figure below. The increase was less in the buprenorphine than the placebo groups. This indicates some tolerance and lack of persistence of efficacy for BEMA buprenorphine.

**Figure 3 Mean of Weekly Change from Baseline in NRS PI in Double-blind Treatment Phase in Pooled Phase 3 Studies (ITT with Imputed Values)**



Source: Figure 8 ISE

### 6.1.10 Additional Efficacy Issues/Analyses

Dr. Travis, statistical reviewer, conducted an additional sensitivity analysis to evaluate the effect of excluding the subjects enrolled at site 1027 in study 307 from the primary efficacy analysis. The analysis was done because site 1027 was closed by the Sponsor because the PI had his license suspended due to professional misconduct; the Sponsor concluded that there had been no major breach of Good Clinical Practice at the site and kept the data from the site in the analyses. The exclusion of these 11 subjects resulted in no change in the p value and a change in the difference and 95% CI vs Placebo from -0.95 (-1.29, -0.61) to -0.98 (-1.32, -0.64), indicating that the data from this site is not critical to the efficacy conclusions of the study.

## 7 Review of Safety

### Safety Summary

There were no new safety concerns for buprenorphine in a pain population identified in the development program safety database. From this pooled data, there were few serious adverse events, and the common adverse events are consistent with what is already known about buprenorphine and opioids in this treatment setting. While there are safety concerns with Belbuca, based on the available data, these concerns do not outweigh the benefits of the drug, as discussed above in Section 1.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant defined the following sets for the Phase 3 controlled studies (301, 307, and 308):

**Safety Set:** consists of all subjects who received at least 1 dose of buprenorphine HCl buccal film in any of the 3 controlled Phase 3 studies. This is the population used for the analysis of the safety data in the open-label titration phase or the 2 phases combined (open-label and double-blind) for the controlled studies.

**Double-blind (DB) Safety Set:** consists of all subjects in the Safety Set who received at least 1 dose of buprenorphine HCl buccal film or placebo in the double-blind treatment phase. This is the population used for the analysis of the safety data in the double-blind treatment phase that compares buprenorphine HCl buccal film and placebo for the 3 controlled clinical studies.

The Applicant defined the following sets for the Phase 3 uncontrolled studies (305 and 309):

**Safety Set:** consists of all subjects who received at least 1 dose of buprenorphine HCl buccal film in either of the 2 uncontrolled Phase 3 studies.

The applicant noted that the safety set that was used in analyses inadvertently excluded 14 subjects who discontinued during the open-label titration phase of study 305. Eight of the discontinuations were due to adverse events. These discontinuations were reviewed and are included in the discontinuations section 7.3.3 Dropouts and/or Discontinuations.

### 7.1.2 Categorization of Adverse Events

Adverse events were categorized using MedDRA. The pooled safety analyses used MedDRA version 12.0.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

BUP-301, BUP-305, EN3409-307, EN3409-308, and EN3409-309 were pooled, including a sub-analysis of Studies EN3409-301/307 and EN3409-301/308 based on prior opioid experience and by dose groups.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There were 2480 subjects exposed to buprenorphine in the 16 completed clinical studies in the development program. Of these, 2127 subjects were treated with buprenorphine (excluding the 14 subjects that were left out of the safety set analyses from study 305) in the Phase 3 development program (controlled studies 301, 307, 308, and uncontrolled studies 305, and 309).

There were at least 400 patients exposed for at least 6 months and 253 patients exposed for at least one year.

The overall exposure is adequate to assess the safety of the product in the pre-market setting.

### 7.2.2 Explorations for Dose Response

Safety analyses were conducted with subjects divided into high (600 to 900 µg), middle (300 to 450 µg), and low (60-240 µg) dose groups to assess the effect of dose on adverse events.

### 7.2.4 Routine Clinical Testing

The clinical laboratory tests conducted were adequate and included hematology, chemistry, and urinalysis in all Phase 3 studies. Twelve-lead ECG was also conducted. In the controlled studies, assessments were done at baseline and after 12 weeks.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Drugs of abuse screen was conducted at regular intervals in the controlled and uncontrolled studies because of the known potential for abuse of drugs like buprenorphine and the potential for subjects to be concealing abuse of other drugs.

Due to the potential for subjects to experience opioid withdrawal symptoms during transition periods in the studies, subjects underwent assessments with the Clinical Opiate Withdrawal Scale during transitions between full mu agonists and buprenorphine and between buprenorphine and placebo.

Suicidality assessments were done at baseline and at every subsequent visit to assess prospective suicidality risk.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There was one death in the development program in open-label safety study 305. The 56 year-old female subject was receiving 60 µg buprenorphine twice daily and died from a cardiac arrhythmia deemed to be caused by diabetic complications. She was found on her bathroom floor and no autopsy was done. She appeared to have poorly controlled diabetes as evidenced by random glucose values of 283 mg/dL at screening and 342 on study day 0.

#### 7.3.2 Nonfatal Serious Adverse Events

There were 88 nonfatal serious adverse events in 69 subjects. Three percent of subjects had a nonfatal serious adverse event in all Phase 3 studies. The serious adverse events that occurred in at least 2 subjects were: cellulitis, pneumonia, ileus, atrial fibrillation, coronary artery disease, cerebrovascular accident, syncope, transient ischemic attack, chest pain, non-cardiac chest pain, ankle fracture, cholecystitis, osteoarthritis, and dehydration.

#### SAEs in DB phase of controlled studies

There were 8 subjects with SAEs (8/600 or 1.3%) in the buprenorphine group and 5 subjects with SAEs (5/606 or 0.8%) in the placebo group in the double-blind period of studies 301, 307, and 308 combined.

In the buprenorphine group, the SAEs were evenly distributed over the three dose levels. There were 2 subjects in the low dose group (1.1%), 3 subjects in the middle dose group (1.3%) and 3 subjects in the high dose group (1.7%) that had SAEs. The SAEs in the placebo subjects were atrial flutter/ tachycardia, cellulitis/limb abscess, spider bite that caused cellulitis, ileus, and a transient ischemic attack. The ileus was diagnosed on day 20 of the double-blind period by abdominal x-ray due to a complaint of abdominal pain and resolved without surgery<sup>9</sup>. The SAEs in the buprenorphine group were cellulitis, pulmonary contusion due to a fall down stairs, cholecystitis, cerebrovascular accident, dysarthria likely associated with a psychiatric etiology,

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<sup>9</sup> There was an error in the patient narrative indicating that this patient was in the buprenorphine group. In a response to information request, the Applicant confirmed that the patient was in the placebo group.

bilateral knee osteoarthritis, atrial fibrillation, and small bowel obstruction. The fall leading to pulmonary contusion and small bowel obstruction may have been related to the study drug in my assessment. The 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.

### **SAEs in OL phase of controlled studies**

There were 19/1889 subjects (1.0%) that had SAEs in the open-label titration phase of controlled studies. Four subjects had pneumonia and all other SAEs occurred in only one subject. The other SAEs were acute respiratory failure and increased creatinine in one subject with pneumonia, myocardial infarction, right upper quadrant pain (which was likely due to a bowel obstruction in a patient with a history of small bowel obstruction), ileus (in subject with history of Crohn's disease and small bowel resection), bone graft due to non-healing of left femur, cellulitis, venous insufficiency (peripheral edema), chest pain, COPD exacerbation, non-cardiac chest pain, angina, exacerbation of chronic pancreatitis, dehydration and kidney infection, cerebrovascular accident, metastatic lung cancer, and osteomyelitis and gangrene in foot.

Two subjects that had small bowel obstruction or ileus had a history of GI surgeries or chronic GI disease or both. However, one subject who had a small bowel obstruction during the double-blind period on buprenorphine did not have a history of GI pathology. This subject had previously taken oxycodone prior to study entry, was stabilized on buprenorphine 450 µg bid, and had significant morbidity and sequelae associated with the bowel obstruction (underwent small bowel resection and had a subsequent wound infection).

### **SAEs in Uncontrolled Studies 305 and 309**

There were 48 SAEs in 39 subjects in the uncontrolled studies of long-term safety in patients (studies 305 and 309). The following table summarizes the body systems with three or more subjects with SAEs.

**Table 24 SAEs in Uncontrolled Phase 3 Studies**

Infections and Infestations	7 subjects: Bronchitis, diverticulitis, sepsis, aseptic meningitis, urosepsis, pneumonia, cellulitis
Neoplasms	5 subjects: Basal cell carcinoma, lymphoproliferative disorder, endometrial adenocarcinoma, pancreatic carcinoma, bladder cancer
General Disorders	4 subjects: Peripheral edema, non-

	cardiac chest pain (2 subjects), chest pain
Cardiac Disorders	4 subjects: Coronary artery disease, Atrial fibrillation, arrhythmia, unstable angina
Gastrointestinal Disorders	3 subjects: lower abdominal pain, ischaemic colitis, vomiting

Source: reviewer-generated from ISS ADAE dataset

Other SAEs that occurred in less than three subjects included: prolonged QT interval in one subject who had an ECG presumably as part of a medical evaluation for a transient ischemic attack, suicide attempt in one subject, and three lower extremity fractures.

Most SAEs observed in the long-term open-label safety studies are unlikely to be related to the study drug. For SAEs that could have been related to study drug, no novel safety signals arose.

### 7.3.3 Dropouts and/or Discontinuations

The following table summarizes the discontinuations due to adverse events in the double-blind phase where there was a placebo control.

**Table 25 Discontinuations due to Adverse Events in Double-Blind Period of Controlled Phase 3 Studies**

	bup low dose (60-240 µg) N=185	bup middle dose (300-450 µg) N=237	bup high dose (600-900 µg) N=178	bup all doses N=600	Placebo N=606
discontinuations due to a TEAE	10 (5.4%)	12 (5.1%)	3 (1.7%)	25 (4.2%)	32 (5.3%)

Source Table 61, ISS 120-day update

The adverse events that led to discontinuation in more than 1% of the buprenorphine group (all doses) were nausea and constipation and in the placebo group was drug withdrawal syndrome.

The interpretation of these findings is complicated by the study design, where all subjects were on buprenorphine prior to randomization and those that did not tolerate buprenorphine may have dropped out in the open-label phase and would not be captured in the controlled, double-blind phase. Additionally, the dropout in the placebo group is partly due to opioid withdrawal symptoms (10 subjects or one third of

discontinuations in the placebo group), which further limits the ability to interpret and compare the treatment groups in a way that informs the safety of buprenorphine.

The most frequent adverse events (those that occurred in 10 or more subjects) that led to discontinuations for buprenorphine-treated subjects in all Phase 3 controlled and uncontrolled studies are summarized in the following table.

**Table 26 Discontinuations due to Adverse Events during Buprenorphine treatment, 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 <sup>10</sup>	37 (1.7)
	Prolonged QT interval	10 (0.5)
Psychiatric Disorders	Anxiety	10 (0.5)

Source: Table 60, ISS 120-day update

With 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 3 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

These are expected adverse events that have been previously observed with buprenorphine. There is additional relevant safety information about prolonged QT interval and it is discussed further in section 7.3.5 Submission Specific Primary Safety Concerns

### 7.3.5 Submission Specific Primary Safety Concerns

#### QT interval prolongation

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<sup>10</sup> Includes the terms Alanine aminotransferase increased, liver function test abnormal, aspartate aminotransferase increased, gamma-glutamyltransferase increased, and hepatic enzyme increased

The QT-IRT reviewed the results of a tQT study (BUP-150) submitted to the application. Based on other information reviewed by FDA, the study design of BUP-150, which included administration of naltrexone concurrently with buprenorphine, has caused the study results to be uninterpretable. Naltrexone interferes with the effect of buprenorphine on cardiac repolarization. In the absence of data from a repeat study without naltrexone blockade, we must consider safety information about the effect of buprenorphine on cardiac repolarization that can be applied to the risk-benefit assessment of the product.

Therefore, the QT-IRT estimated the expected prolongation for the range of proposed doses of Belbuca based on the buprenorphine concentration-QTc relationship with data obtained from subjects who did not receive naltrexone.

The following table summarizes the predicted QTc Effects (excerpted from p. 2 of the June 17, 2015 QT-IRT consult response):

**Table 27 Predicted Belbuca QTc Effects**

At Interested Mean C <sub>max,ss</sub> (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

The upper bound of the 90% confidence interval for the highest proposed strength is less than 10 ms. The QT-IRT team characterizes the QTc prolongation as modest and proposed changes to the proposed labeling.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

In the double-blind period of the controlled studies the most common adverse events observed were nausea, vomiting, constipation, drug withdrawal syndrome and

headache, as shown in the table below. Nausea, vomiting, and constipation were more common in the buprenorphine group and are expected adverse reactions to opioids. Drug withdrawal syndrome was more common in the placebo group, which would be expected in a randomized withdrawal trial with a drug that is expected to have the potential for causing physical dependence.

**Table 28 TEAEs Occurring in at least 2% of Subjects in 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: reviewer-generated from ISS ADAE dataset

The open-label titration period at the beginning of the Phase 3 controlled studies gives information about what adverse events would be expected at the beginning of therapy with this product. Nausea and constipation were the most frequently reported adverse events during this period of the studies as shown in the table below. Dizziness and somnolence were more frequent in the early titration period than in the subsequent double-blind period. As shown in Table 26 Discontinuations due to Adverse Events during Buprenorphine treatment, All Phase 3 Studies, more of the discontinuations were due to nausea and vomiting, suggesting that dizziness and somnolence may have been less severe and time-limited.

**Table 29 TEAEs in the Open-Label Period of the Phase 3 Controlled Studies**

Adverse Event	Buprenorphine N=1889 n (%)
Number of subjects with at least 1 TEAE	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: ISS update Table 43

#### 7.4.2 Laboratory Findings

There were no patterns or trends in changes in laboratory values in the open-label or double-blind periods of the Phase 3 studies.

#### 7.4.3 Vital Signs

There were no patterns or trends in changes in vital signs in the open-label or double-blind periods of the Phase 3 studies.

#### 7.4.4 Electrocardiograms (ECGs)

There 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.

#### 7.4.5 Special Safety Studies/Clinical Trials

Study 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. It is discussed further in section 7.6.4

Overdose, Drug Abuse Potential, Withdrawal and Rebound. The proposed product labeling does not reference findings from Study 204.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

There was no observed relationship between dose and incidence of adverse events as shown in the table below.

The following table is compiled from the Applicant's summary in section 10 and table 70 of the ISS 120-day update:

**Table 30 Dose Dependence for Adverse Events**

Study Type and Phase	Adverse Event	Low dose group	Middle dose group	High dose group
Controlled, DB phase	Overall TE	56.2 %	40.1%	52.2%
	Gastrointestinal	21.6%	15.6%	20.2%
	D/c due to AE	5.4%	5.1%	1.7%
	SAEs	1.1%	1.3%	1.7%
Uncontrolled, long-term phase	Overall TE	66.4%	54.4%	52.6%
	Commonly associated with opioids <sup>11</sup>	21.2%	21.6%	17.8%
	Nausea	8.4%	9.3%	8.0%
	D/c due to AE	5.8%	0%	4.1%
	SAEs	7.1%	5.2%	3.3%

### 7.5.2 Time Dependency for Adverse Events

The most common adverse events occurred in a much larger proportion of subjects in the open-label period of the controlled studies than in the double-blind period, indicating that most adverse events occur early on in therapy. This is consistent with what has been observed in other development programs and with other opioids.

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<sup>11</sup> Common AEs associated with opioid use are: constipation, nausea, vomiting, somnolence, pruritus, dry mouth, headache, dizziness, sedation, and fatigue

### 7.5.3 Drug-Demographic Interactions

There were 290 subjects out of 1889 in the controlled Phase 3 trials that were aged 65 years and older.

The incidence of SAEs in this population was similar to the overall population. There were 6 SAEs in 3 subjects (1%) in the double-blind phase and 9 SAEs in 7 subjects (2%) in the open-label phase of the controlled studies in this population.

Like the general study population, the most frequent adverse events that led to discontinuation were nausea, vomiting, and dizziness.

The frequency of treatment-emergent adverse events in the open-label period was similar in this population to the general population, as shown below:

**Table 31 Frequent TEAEs During OL period of Controlled Phase 3 Studies in Geriatric Population**

Adverse Event	General Pop N=1889 n (%)	Geriatric Pop N=290 n (%)
Nausea	617 (33)	53 (18)
Constipation	200 (11)	22 (8)
Headache	153 (8)	10 (3)
Vomiting	132 (7)	13 (4)
Dizziness	120 (6)	15 (5)
Somnolence	114 (6)	9 (3)
Fatigue	81 (4)	14 (5)

Source: reviewer-generated and Table 43 ISS update

### 7.5.5 Drug-Drug Interactions

No new drug-drug interactions were studied or identified in the development program.

## 7.6 Additional Safety Evaluations

### 7.6.2 Human Reproduction and Pregnancy Data

The Division of Pediatrics and Maternal Health has reviewed the data for pregnancy and lactation and has completed a consult review with labeling recommendations. There were two pregnancies, one in study 305 (OL, safety) and one in study 309 (OL, safety).

Both subjects were discontinued from the studies. One subject was lost to follow-up and the other subject, who was exposed to Belbuca during the first trimester, delivered a full-term, healthy female.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

##### Study 204

Study 204 was designed to assess withdrawal in patients receiving 80 to 220 mg oral morphine sulfate equivalents (MSE) who were directly switched to buprenorphine at 50% of their oral MSE dose. The study population was enriched by enrolling subjects who had a positive naloxone challenge. The active control was to reduce their opioid to 50% of their stable dose and assess them for withdrawal (called ATC opioid treatment). The Clinical Opiate Withdrawal Scale was used to assess withdrawal and the primary efficacy analysis was a comparison of responders where a responder was either rescued or had a COWS score of at least 13 (considered to be moderate withdrawal).

Thirty-one out of 33 subjects in the 80-160 mg dose group and 5/6 in the 161-220 mg dose group completed the study. The Sponsor analyzed the data excluding four subjects. Two of these subjects met the responder definition, one in the ATC opioid period and one in the buprenorphine period.

There was only one subject that met the responder definition in the buprenorphine period and two subjects that met the responder definition in the ATC opioid period, making the planned analysis uninterpretable.

The total COWS score and change from baseline COWS score was summarized on the per protocol population, which excluded two responders. The mean COWS was 4.6 in the buprenorphine treatment period and 5.3 in the ATC opioid period for the 80-160 mg dose group and was 5.5 and 6.3 respectively in the 161-220 mg dose group.

Similarly, the mean change from baseline in COWS was essentially the same in all groups.

The Sponsor did not propose to report the results of this study in the product label and I concur with this approach because the small number of subjects who met the responder definition made the primary analysis uninterpretable and the study was largely uninformative and did not reveal any new safety concerns or concerns with the approach to switching that was used in the Phase 3 trials, which is the approach recommended in the proposed product label. The results indicate that subjects directly transitioned to buprenorphine from opioid doses higher than 30 mg oral morphine equivalents (which is the MSE dose that subjects were tapered to prior to beginning buprenorphine in study 307) do not have substantial withdrawal symptoms.

#### COWS assessments in Phase 3 controlled studies

Study BUP-301: the COWS was administered at baseline and on days 4, 7, and 14 of the open-label titration phase; and at baseline and on days 4, 7, 11, and 14 of the double-blind treatment phase.

Study EN3409-307: the COWS was administered at baseline and at each visit of the taper phase, and on the first visit of the open-label titration phase; and at baseline and days 7 and 14 of the double-blind treatment phase.

Study EN3409-308: the COWS was administered at baseline and days 7 and 14 of the double-blind treatment phase.

No subjects had a COWS of 13 or greater in the double-blind treatment phase.

## **7.7 Additional Submissions / Safety Issues**

### **Prospective suicidal ideation and behavior assessment**

Studies 301, 307, and 308 all included assessments for suicidal ideation and behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS). However, in study 301, the assessments were only done at baseline for the open-label titration and double blind-periods and at the end of the 12-week titration period, which is likely inadequate to detect a safety signal. In studies 307 and 308, the C-SSRS was to be administered at every study visit.

In study 307 there were no treatment-emergent C-SSRS assessments that were positive for suicidal ideation or behavior during the open-label titration phase. In the double-blind treatment phase there was one subject in the placebo group who had a positive C-SSRS assessment.

In study 308 there were was one treatment-emergent positive assessment in the open-label titration period and one treatment-emergent positive assessment in the double-blind period in the placebo group. There were two suicide attempts, one in the buprenorphine group and one in the placebo group (this is the same subject that had the positive assessment).

The results do not indicate that there is a safety signal for buprenorphine that requires further characterization.

## **8 Postmarket Experience**

Belbuca is not marketed in any other country. There is extensive postmarket experience with buprenorphine in the treatment of pain and opioid addiction. The proposed product labeling is consistent with the product labeling of other products for

pain and addiction in the sections that are informed by the collective postmarket experience for the buprenorphine molecule.

## 9 Appendices

### 9.2 Labeling Recommendations

The final labeling has not been established, but the following is a summary of the major recommended changes to the Applicant's proposed labeling:

-  (b) (4) QT prolongation (b) (4) is expected at the maximum steady-state concentration that results from the 900 µg bid dose, thus in section 2.2, the label has been modified to state that this dose should not be exceeded.
- In Section 6, Adverse Reactions, the most common adverse events should be reported as occurring in 5% or more of subjects to be more clinically informative

The trade name, Belbuca, was found to be acceptable from a promotional and medication error perspective.

### 9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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09/09/2015

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