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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: NDA 207-932

Supplement #: 0000

Drug Name: Belbuca (Buprenorphine Hydrogen Chloride (HCl) Buccal Film)

Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Applicant: Endo Pharmaceuticals, Inc.

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1 EXECUTIVE SUMMARY

Endo Pharmaceuticals, Inc. has submitted a New Drug Application (NDA) for Belbuca (Buprenorphine Hydrogen Chloride (HCl) Buccal Film) and is seeking an indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

This submission includes three multicenter, double-blind, placebo-controlled, enriched enrollment, randomized withdrawal studies conducted in subjects experiencing chronic lower back pain (CLBP). The first study, BUP-301, included both opioid naïve and opioid experienced patients and allowed the lowest dose of the three studies. Studies EN3409-307 and EN3409-308 were conducted concurrently and included only opioid experienced subjects and opioid naïve subjects respectively. The allowed dosage was also increased from BUP-301.

The primary efficacy endpoint for these studies was the change in mean pain intensity from Baseline (the week prior to randomization) to Week 12. The primary analysis was conducted on the Intent-to-Treat (ITT) population which included all randomized subjects who took at least one dose of study drug after randomization. For Studies EN3409-037 and EN3409-308 the applicant also analyzed the cumulative proportion of responders to treatment and the quantity of rescue medication used by subjects in the double-blind treatment phase. The applicant used a combination of single and multiple imputation techniques for the missing data in the analysis.

Study BUP-301 failed to demonstrate statistical significance ($p > 0.05$) for the primary endpoint. The two subsequent studies, EN3409-307 and EN3409-308, both showed statistical significance ($p < 0.05$) for the primary endpoint. This review will focus on studies EN3409-307 and -308.

There were issues with the conduct of studies EN3409-307 and EN3409-308 at two sites which were included in both studies. There were also several subjects in both studies whose reason for study discontinuation was considered to be misclassified by the clinical reviewer. The overall conclusion of the studies was unaffected by these issues.

The applicant conducted an analysis of the gender, racial, and age subgroups using only the subjects who completed the study. This reviewer reanalyzed the data for these subgroups using two additional methods. The estimated treatment effects are similar for both males and females for Study EN3409-307. For EN3409-308 however the estimated treatment effect for males is much smaller than for females. For both studies the estimated treatment effect for the Black/African American subgroup is much smaller than the White subgroup. Both these findings appear to be the result of lower pain scores in the placebo arm in these subgroups and not an increase in the pain scores for the Belbuca arm. This does not appear to be caused by differences in the rates of rescue medication usage between the treatment arms.

Overall, the results from two adequate and well-controlled Phase 3 studies show that Belbuca is superior to placebo for this indication as measured by change in mean pain intensity from baseline.

2 INTRODUCTION

2.1 Overview

Belbuca (Buprenorphine HCl Buccal Film) is an oral transmucosal form of the opioid analgesic Buprenorphine utilizing the BioErodible MucoAdhesive (BEMA) delivery technology and was developed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. Buprenorphine is contained in several products that have been approved for marketing in the United States. It was initially approved in 1981 in an injectable formulation, under trade name Buprenex, for the relief of moderate to severe pain. It has since been approved in a transdermal formulation under trade name Butrans for the management of moderate to severe pain. Buprenorphine is also approved for the treatment of opioid dependence as a sublingual tablet (Subutex) and in combination with naloxone in sublingual tablet (Suboxone, Zubsolv), sublingual film (Suboxone) and buccal film (Bunavail) formulations.

The development program for Belbuca was conducted under IND 72,428 which was initially submitted by BioDelivery Sciences International, Inc. (BDSI) in September 2005. The development program for the Phase 3 confirmatory trials was initially discussed at the End of Phase 2 meeting in September 2010. In the packet for the meeting BDSI submitted the protocol for one Phase 3 trial, BUP-301, which was designed to study the efficacy of Belbuca in treating moderate to severe chronic lower back pain (CLBP) in both opioid-naïve and opioid-experienced subjects. The applicant requested feedback on the study design at that time. The division provided feedback on several items including recommendations of a change in definition of the primary endpoint and a modification to the definition of the intended analysis population, feedback on the proposed sample size and a discussion of the intended missing data analysis strategy.

Study BUP-301 started enrollment in November 2010. The applicant submitted a revised protocol in February 2011 including a statistical analysis plan incorporated the modifications suggested by the agency. The agency provided additional feedback on the study design in June 2011. The feedback included requesting clarification on the interim analysis, a discussion of the missing data analysis strategy, a request for details of the intended sensitivity analyses, and a request for information on how the use of rescue medication will be included in the statistical analysis. The study was completed in July 2011 and included a total of 24 centers all within United States. The study failed to reach statistical significance on the primary efficacy endpoint.

The applicant then proposed [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED] This study was never initiated.

In January 2012 the ownership of IND 72,248 was transfer to Endo Pharmaceuticals. Following the transfer of ownership Endo met with the agency to discuss the clinical development of

Belbuca in January 2012. Following this meeting Endo requested another meeting in February 2012 to discuss two newly proposed studies which were later renamed to EN3409-307 and EN3409-308. These studies were to be conducted in subjects with CLBP, with study EN3409-307 enrolling only opioid experienced subjects and EN3409-308 enrolling only opioid naïve subjects. The maximum dose would also be increased from the 240 mcg twice daily (BID) allowed by Study BUP-301 to 900 mcg BID for EN3409-307 and 450 mcg BID for study EN3409-308.

The applicant requested feedback regarding the sample size re-estimation plan, the multiplicity adjustments for the secondary endpoints, and the overall statistical design of the study. Revised protocols and statistical analysis plans were submitted in July and August 2012 incorporating the agency's feedback.

The applicant submitted a 2nd revised version of the protocols in April and May 2013. Statistical feedback was given for this version of the protocols in June 2013 which included recommendations to revise the definition of the intended analysis population and to make every attempt to minimize missing data.

Study EN3409-307 was conducted from September 2012 until June 2014 and included a total of 66 sites within the United States. Study EN3409-308 was conducted from August 2012 until December 2013 and included a total of 60 sites within the United States. See Table 1 for a summary of the pivotal efficacy studies.

The Pre-NDA meeting for this submission was held in July 2014. In the meeting packet the applicant explained their plans to exclude a site from the efficacy analysis for Studies EN3409-307 and EN3409-308 due to breaches in Good Clinical Practice (GCP). The agency requested that the applicant include the results of the analyses with and without this site for the application.

This review will only discuss the results of the last two efficacy studies, EN3409-307 and EN3409-308. These two studies were designed to address the issues of the first study, BUP-301, which did not find a statistically significant difference between Belbuca and placebo on the primary efficacy endpoint. The results of Study BUP-301 are not discussed in this review.

All figures and tables are provided by the reviewer except where stated otherwise.

Table 1: List of all Pivotal Efficacy Studies

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
BUP-301	Phase 3	4 weeks open-label titration + 12 weeks double-blind	2 weeks	Planned: 102 per group Actual: 117 Belbuca 118 Placebo	Opioid-naïve and opioid-experienced subjects with moderate to severe CLBP
EN3409-307	Phase 3	4 weeks analgesic taper + up to 8 weeks open-label titration + 12 weeks double-blind	2 weeks	Planned: 142 per group Actual: 254 Belbuca 256 Placebo	Opioid-experienced subjects with moderate to severe CLBP
EN3409-308	Phase 3	Up to 8 weeks open-label titration + 12 weeks double-blind	2 weeks	Planned: 222 per group Actual: 229 Belbuca 232 Placebo	Opioid-naïve subjects with moderate to severe CLBP

2.2 Data Sources

All data was provided electronically by the Applicant as SAS transport files in the CDISC and ADaM data format and can be found at the following location in the CDER electronic document room (EDR):

<\\CDSESUB1\evsprod\NDA207932\0000\m5\datasets>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the submitted efficacy data was sufficient to reproduce the applicant's results for both the primary and key secondary endpoints.

The applicant reported that there were issues with the conduct of the study at two study sites used for Studies EN3409-307 and EN3409-308. The applicant reports that a site audit was conducted for Site 1008, during which several critical findings related to the integrity of the data were found. As a result the applicant conducted the primary efficacy analysis both including and excluding this site. The applicant also reported that the investigator for another site (1027) had their medical license suspended which caused the closure of that site. The applicant conducted a site audit and found no critical or major GCP nonconformities. As a result the applicant did not exclude this site from the efficacy analysis.

In addition, for Studies EN3409-307 and EN3409-308 there were several patients who were excluded from the study due to abnormal EKG and lab values but were classified as having been discontinued from the study due to protocol violations or other reasons. Dr. Horn determined that these subjects were to be reclassified as discontinued due to adverse events. Both studies were re-analyzed with these subjects reclassified appropriately.

3.2 Evaluation of Efficacy

The efficacy will be discussed separately for studies EN3409-307 and EN3409-308.

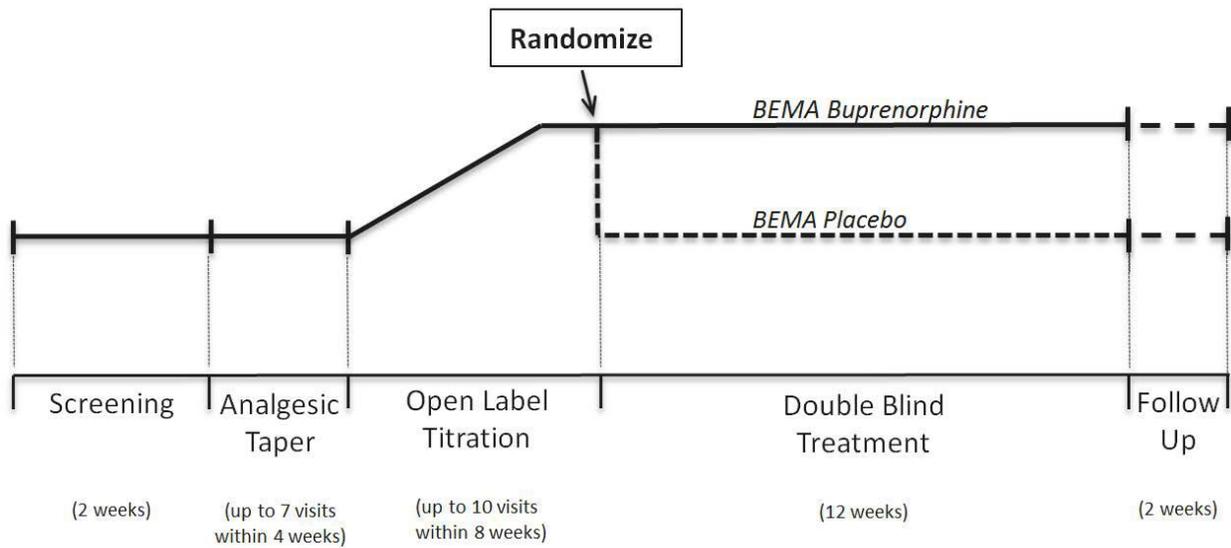
3.2.1 Study EN3409-307

3.2.1.1 Study Design and Endpoints

Study EN3409-307 was a Phase 3, multicenter, double-blind, placebo-controlled, enriched enrollment, randomized withdrawal study comparing BEMA Buprenorphine to BEMA Placebo in opioid experienced subjects with moderate to severe chronic lower back pain (CLBP) requiring opioid analgesia for an extended period of time.

The study consisted of several phases: a screening phase (2 weeks); an analgesic taper phase (up to 7 visits within 4 weeks); an open-label titration phase (up to 10 visits within 8 weeks [including at least 2 weeks at a stable "optimal" dose]); a double-blind, placebo-controlled, randomized withdrawal treatment phase (12 weeks) and a follow-up phase (2 weeks). See Figure 1 for a schematic of the study design.

Figure 1: Schematic of Study Design for EN3409-307



Source: Figure 1, Clinical Study Report

The subject's involvement in the trial began with an initial screening visit where the subject's eligibility for the study was determined. To be eligible for inclusion in the study, subjects must be male or female, at least 18 years of age at time of consent, have a clinical diagnosis of moderate to severe CLBP for at least 6 months as their primary source of chronic pain, and be treating their CLBP with a stable daily maintenance dose of around-the-clock (ATC) opioid analgesic medication equivalent to between 30 and 160 mg morphine sulfate equivalent (MSE) per day for at least 4 weeks.

During the screening visit the subjects were instructed in how to rate and record their pain. For this study pain was measured using an 11-point numerical rating scale (NRS), where a score of 0 represents "No pain" and a score of 10 represents "Pain as bad as you can imagine". Every day during the study the subjects rated their average daily pain intensity at approximately the same time each evening and recorded the score using an interactive voice/web response system (IXRS).

Following the screening visit, subjects were asked to record their pain once per day for the rest of the two-week screening phase. To be eligible to proceed to the analgesic taper phase of the study the subjects must have recorded their daily pain intensity score for at least 11 of the 14 days in the screening phase.

During the analgesic taper phase the subject's current opioid dosage was tapered down by 25% of their original dose every 4 to 8 days until a dose of 30 mg MSE or lower was reached. Once this dosage was reached the subjects were eligible to progress to the open-label titration phase if they had either poorly controlled pain during the screening phase (mean average daily pain intensity scores ≥ 5 and < 10 over the last 7 days of screening), or had daily average pain scores ≥ 5 for at least 3 consecutive days during the analgesic taper phase, prior to rescue medication.

Once the subjects entered the open-label titration phase they were switched from their prior opioid analgesic to either 150 mcg or 300 mcg of Belbuca depending on their original dose of opioid analgesic. The dosage can then be adjusted in increments of 150 mcg every 4 to 8 days until a stable optimal dose is reached. Once the subject reaches an optimal dose, it must be maintained for at least two weeks prior to entering the double-blind treatment phase. Note that the total length of the titration phase can be no longer than eight weeks. Consequently, an optimal dose must be reached by no later than the end of Week 6.

The subjects were then eligible to enter the double-blind treatment phase if they achieved a mean pain intensity score ≤ 4 over the last three days of the titration phase with no more than one dose of rescue medication per day during the last seven days of the titration phase and demonstrate continued compliance with the study medication and assessments. In addition, the mean pain intensity score must have been at least two points lower than either the score during the last three days of the analgesic taper phase or the average pain score over the last seven days of the screening phase. Upon entering the double-blind treatment phase the subjects were randomized to either continue with their current dose of study medication or the study medication will be discontinued and replaced with a BEMA placebo film.

The primary efficacy endpoint for this study was the change from Baseline to Week 12 of the double-blind treatment phase in the mean of the average daily pain intensity scores, where the baseline pain score is the mean of the last seven days prior to randomization. The applicant also specified several secondary efficacy endpoints as listed below:

- Proportion of Responders
- Opioid Rescue Medication Use
- Time to “optimal” dose of open-label study medication
- Time to treatment failure
- Patient Reported Outcome (PRO) Measures which include the following:
 - a. Patient Global Impression of Change (PGIC)
 - b. Roland Morris Disability Questionnaire (RMDQ)
 - c. Medical Outcomes Score (MOS) Sleep Subscale

The applicant specified several of these endpoints as key secondary endpoints that they intended to test using a sequential gatekeeping procedure. These endpoints are as follows in the order that they will be tested:

1. Proportion of Responders
 - a) Responder rate at 30% pain reduction
 - b) Responder rate at 50% pain reduction
2. Opioid Rescue Medication Use

3.2.1.2 Statistical Methodologies

Analysis of the primary efficacy endpoint: 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).

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

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

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

The analysis population for the primary efficacy endpoint was the Intent-to-Treat (ITT) population which was defined by the applicant as all randomized subjects who received at least 1 dose of double-blind study medication. The applicant also defined the per-protocol population for some sensitivity analyses. This population excluded any subjects who were determined to have any significant protocol deviations that were determined prior to database lock.

For this study the applicant conducted an interim analysis in order to re-estimate the sample size. The interim analysis was performed by an independent statistician after the first 120 of the 284 planned randomized subjects had completed or discontinued the study. It was found that the effect size was smaller than anticipated, and as a result, it was necessary to increase the sample size to maintain the desired power for the study. Since the sample size was increased it is necessary to adjust the final analysis in order to control the type I error and to obtain confidence intervals with the desired coverage level. The applicant used the methods described in (Cui, Hung, & Wang, 1999) to control the type I error and the methods described in (Lawrence & Hung, 2003) to adjust the confidence intervals.

The applicant also performed several sensitivity analyses for the primary efficacy endpoint using different imputation techniques and analysis models. The sensitivity analyses were as follows:

- Perform a Mixed Model with Repeated Measures (MMRM) analysis on the ITT population.
- Perform the primary analysis on the ITT population with all dropouts imputed using the LOCF method.

- Perform the primary analysis on the ITT population with all dropouts imputed using the BOCF method.
- Repeat the primary analysis on the Per-Protocol population.
- Perform an MMRM analysis on the Per-Protocol population.
- Perform an MMRM analysis on the ITT population with rescue medication use taken into account as described below.

For the final sensitivity analysis if a subject takes rescue medication on a specific day the pain score for that day will be replaced by the highest pain score recorded during the preceding 7 days. If the score on the day that rescue medication is taken exceeds any score during the preceding 7 days then it will not be replaced.

The MMRM analyses includes treatment group, week, and week-by-treatment group interaction as fixed factors, pain at baseline and screening as covariates, and week as repeated measures using an unstructured covariance matrix. Only observed data will be used for the MMRM analyses.

This reviewer also performed two additional sensitivity analyses as listed:

- Perform the primary analysis on the ITT population with all dropouts imputed using the SOCF method.
- Perform the primary analysis on the ITT population with rescue medication use taken into account as described above.

Analysis of the secondary efficacy endpoint: Proportion of Responders

The proportion of responders was defined as the cumulative proportion of subjects who achieved pre-specified percent pain reduction in the average pain score recorded in Week 12 of the study from the average pain score recorded in the seven days prior to the open-label titration phase. All subjects who did not complete the study were to be classified as non-responders. The applicant used a Cochran-Mantel-Haenszel Chi-Square test stratified by dose level to compare the proportion of responders for 30% and 50% pain reductions between the two treatment groups.

Analysis of the secondary efficacy endpoint: Opioid/Non-Opioid Rescue Medication Use

The rescue medication usage was summarized by the applicant in two ways. First, they computed the number and percentage of subjects in the study who used rescue medication each week. Second, they computed the average number of rescue medication tablets taken per week per subject who used rescue medication. This reviewer also computed the average number of rescue medication tablets taken per week per subject who were still in the trial.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The subject disposition in the open-label titration phase is shown in Table 2. A total of 1656 patients were screened for this study at a total of 66 sites. Approximately 31% (511) of the subjects who were screened for the study met all the inclusion criteria and were randomized into the double-blind treatment phase. There are, however, a number of the subjects who were randomized in the double-blind treatment phase that were excluded from the analysis population for this study by the applicant.

As discussed in Section 3.1 there was one clinical site, Site 1008, where the study was discontinued due to significant violations of GCP. There were a total of 19 subjects who had been enrolled into the study at this site in the double-blind treatment phase who were removed from the analysis population due to these violations by the investigator. The applicant analyzed the data both including and excluding these subjects and found no differences to the overall conclusion of the study. These subjects will be excluded from all analyses in this review.

In addition, one subject withdrew from the study after randomization but prior to receiving any doses of study medication and was excluded from the pre-specified ITT population by the applicant.

Table 2: Subject Disposition in Open-label Titration Phase (All Subjects) – Study EN3409-307

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

Source: Table 7 from applicant's study report

The subject disposition in the double-blind treatment phase is shown in Table 3. We see that for this study there is a large difference in the rate of study completion between the buprenorphine and placebo arms with considerably more subjects withdrawing from the placebo arm. The main

reason for withdrawal in both arms is lack of efficacy with 25% in the placebo arm and 8% in the buprenorphine arm.

In addition, as discussed in Section 3.1, there were two subjects who were originally classified as withdrawal due to protocol violation or other reasons that were reclassified as withdrawal due to adverse events for this study. Overall, the rate of adverse events for this study was higher in the placebo arm than the buprenorphine arm.

Table 3: Subject Disposition in Double-blind Treatment Phase – Study EN3409-307 ITT Population

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

The demographics and baseline characteristics for this study are shown in Table 4. The subjects were mostly female (54%) and white (78%). Approximately 20% of the subjects in the study were Black or African American. The demographics were roughly balanced between the two treatment arms.

There were no notable differences in the pain scores observed prior to the open-label titration phase or at baseline between the two treatment arms.

Table 4: Demographics and Baseline Characteristics in Double-blind Treatment Phase – Study EN3409-307 ITT Population

	BEMA Buprenorphine n=243	BEMA Placebo n=248	Overall n=491
Age			
Mean (SD)	52.5 (11.0)	54.2 (11.3)	53.3 (11.2)
(Min, Max)	(27, 78)	(23, 79)	(23, 79)
Age Group, n (%)			
18 to 64 years	211 (86.8)	206 (83.1)	417 (84.9)
65 to 75 years	28 (11.5)	39 (15.7)	67 (13.6)
>75 year	4 (1.6)	3 (1.2)	7 (1.4)
Gender, n (%)			
Female	130 (53.5)	136 (54.8)	266 (54.2)
Male	113 (46.5)	112 (45.2)	225 (45.8)
Race, n (%)			
White	193 (79.4)	189 (76.2)	382 (77.8)
Black Or African American	49 (20.2)	48 (19.4)	97 (19.8)
Asian	1 (0.4)	8 (3.2)	9 (1.8)
American Indian Or Alaska Native	0 (0.0)	1 (0.4)	1 (0.2)
Other	0 (0.0)	2 (0.8)	2 (0.4)
Pain Intensity Score Prior to Open-Label Titration			
Mean (SD)	6.79 (1.280)	6.64 (1.323)	6.71 (1.303)
(Min, Max)	(3.0, 10)	(2.7, 10)	(2.7, 10)
Pain Intensity Score at Baseline			
Mean (SD)	2.91 (0.985)	2.84 (1.051)	2.88 (1.019)
(Min, Max)	(0.0, 4.7)	(0.0, 6.5)	(0.0, 6.5)

The distribution of the subjects by titrated dose and treatment arm are shown in Table 5.

Table 5: Optimal Titrated Dose – Study EN3409-307 ITT Population

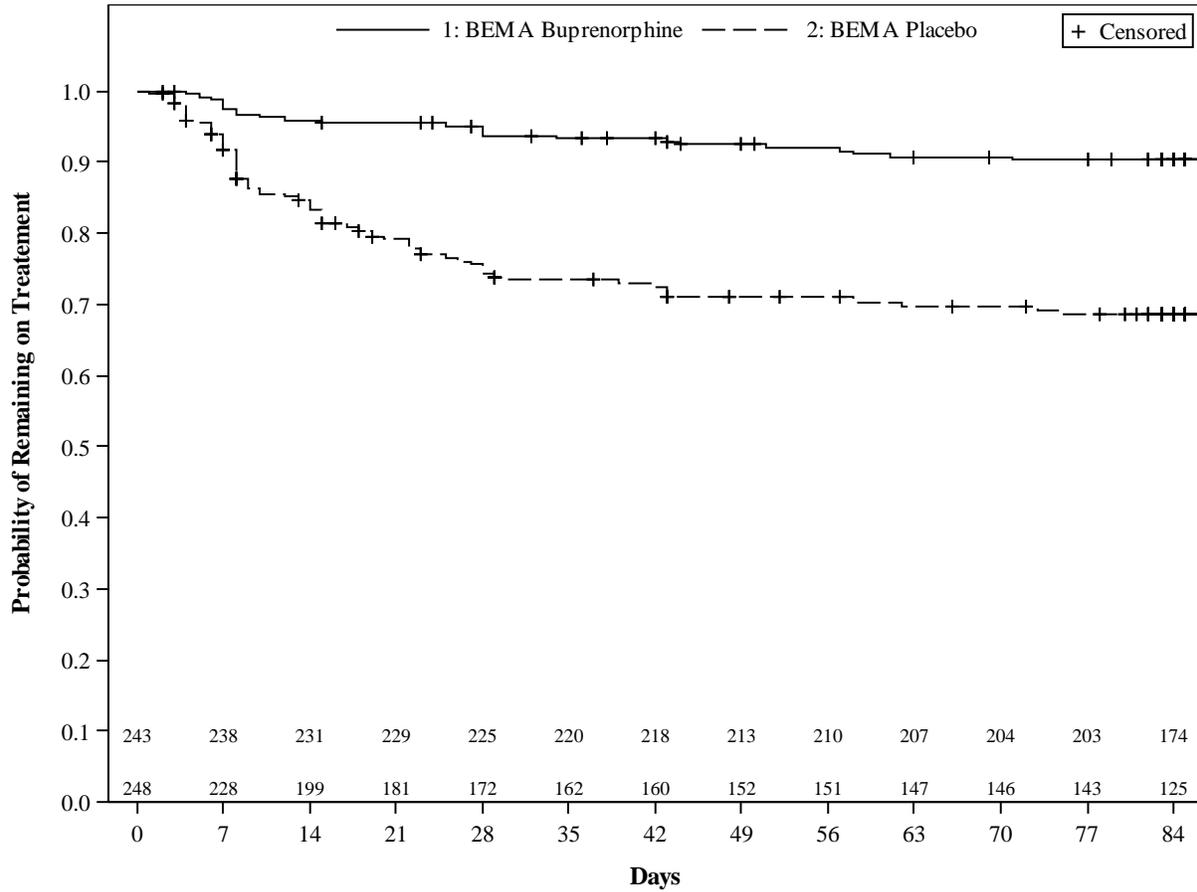
Titrated Dose	BEMA Buprenorphine n (%)	BEMA Placebo n (%)	Overall n (%)
150 mcg	10 (4.1)	10 (4.0)	20 (4.1)
300 mcg	30 (12.3)	28 (11.3)	58 (11.8)
450 mcg	33 (13.6)	36 (14.5)	69 (14.1)
600 mcg	36 (14.8)	40 (16.1)	76 (15.5)
750 mcg	41 (16.9)	41 (16.5)	82 (16.7)
900 mcg	93 (38.3)	93 (37.5)	186 (37.9)
Total	243	248	491

In order to compare the rate of drop-outs between the two treatment arms the applicant performed a Kaplan-Meier analysis of the time to treatment failure during the double-blind treatment phase. Treatment failures were defined as subjects who withdrew from the study due to either lack of efficacy, or adverse events. Subjects who complete the study or withdraw for any other reason were considered to be censored at the time of study completion/withdrawal. The resulting Kaplan-Meier curve of the time to failure is shown in Figure 2. Table 6 contains a summary of the number of failures/subjects censored. The applicant performed a log-rank test to compare the Kaplan-Meier curves for the time to treatment failure. The result is significant indicating that there is a significant difference in the survival function between the two treatment groups.

Table 6: Summary of Kaplan-Meier Analysis in Double-blind Treatment Phase – Study EN3409-307 ITT Population

Statistics	BEMA Buprenorphine n=243	BEMA Placebo n=248	Overall n=491
Number of subjects with treatment failure, n (%)	25 (10.3)	74 (29.8)	99 (20.2)
Number of subjects with censored, n (%)	218 (89.7)	174 (70.2)	392 (79.8)
P-value from log-rank test	<.0001		

Figure 2: Kaplan-Meier Curves for Proportion of Subjects Remaining on Treatment in Double-Blind Treatment Phase – Study EN3409-307 ITT Population



3.2.1.4 Results and Conclusions

The applicant’s analysis of the primary efficacy variable followed the procedure specified in the protocol and concluded that the treatment had a significant effect on the change from baseline to week 12 in average NRS pain intensity. This reviewer was able to confirm the applicant’s results both including and excluding Site 1008.

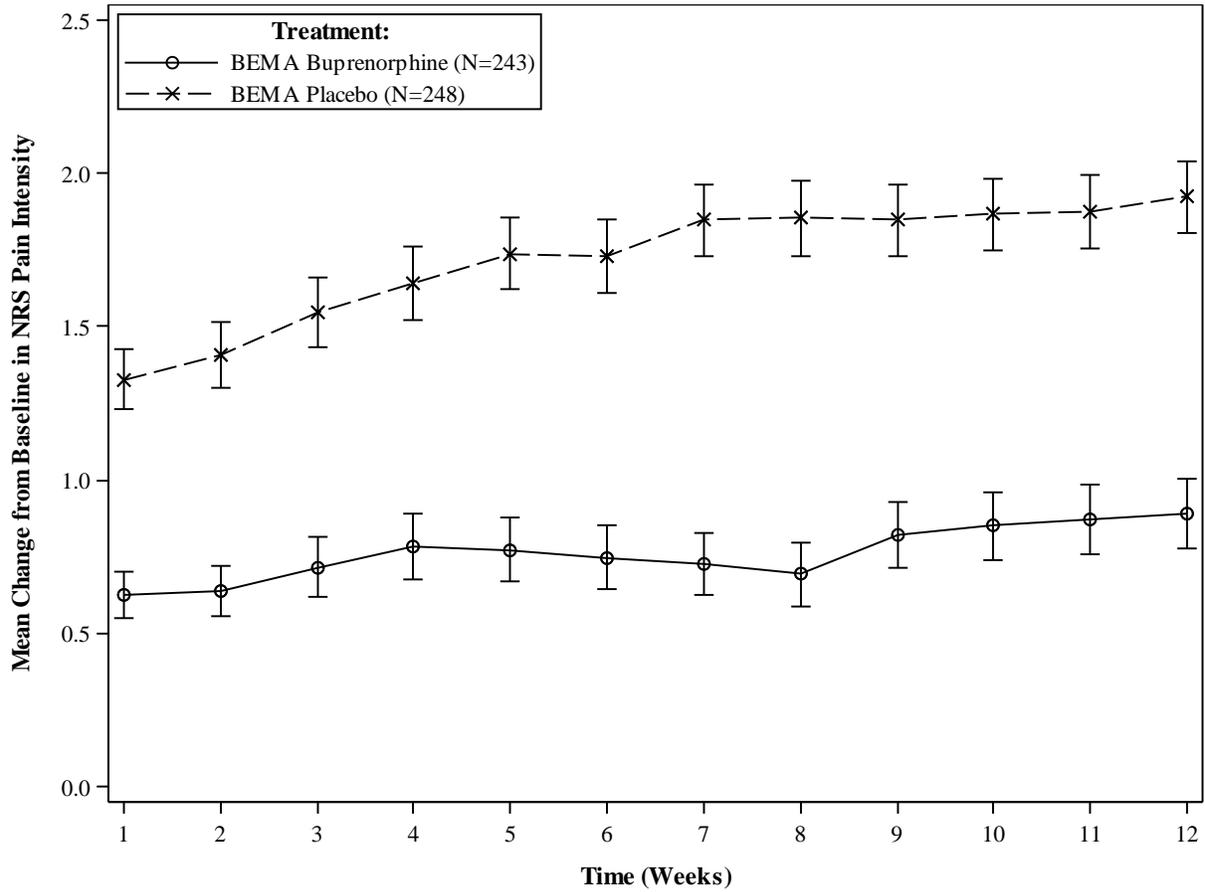
This reviewer re-analyzed the data with the subjects who were reclassified as adverse events (see Section 3.2.1.3) imputed as screen observation carried forward and confirmed the applicant’s conclusion that the change in pain intensity from baseline to the end of Week 12 is significantly better for the BEMA Buprenorphine group than the BEMA Placebo group. The results of this analysis are included in Table 7.

Table 7: Change from Baseline to Week 12 in Average Numeric Rating Scale Pain Intensity in Double-blind Treatment Phase – Study EN3409-307 ITT Population

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

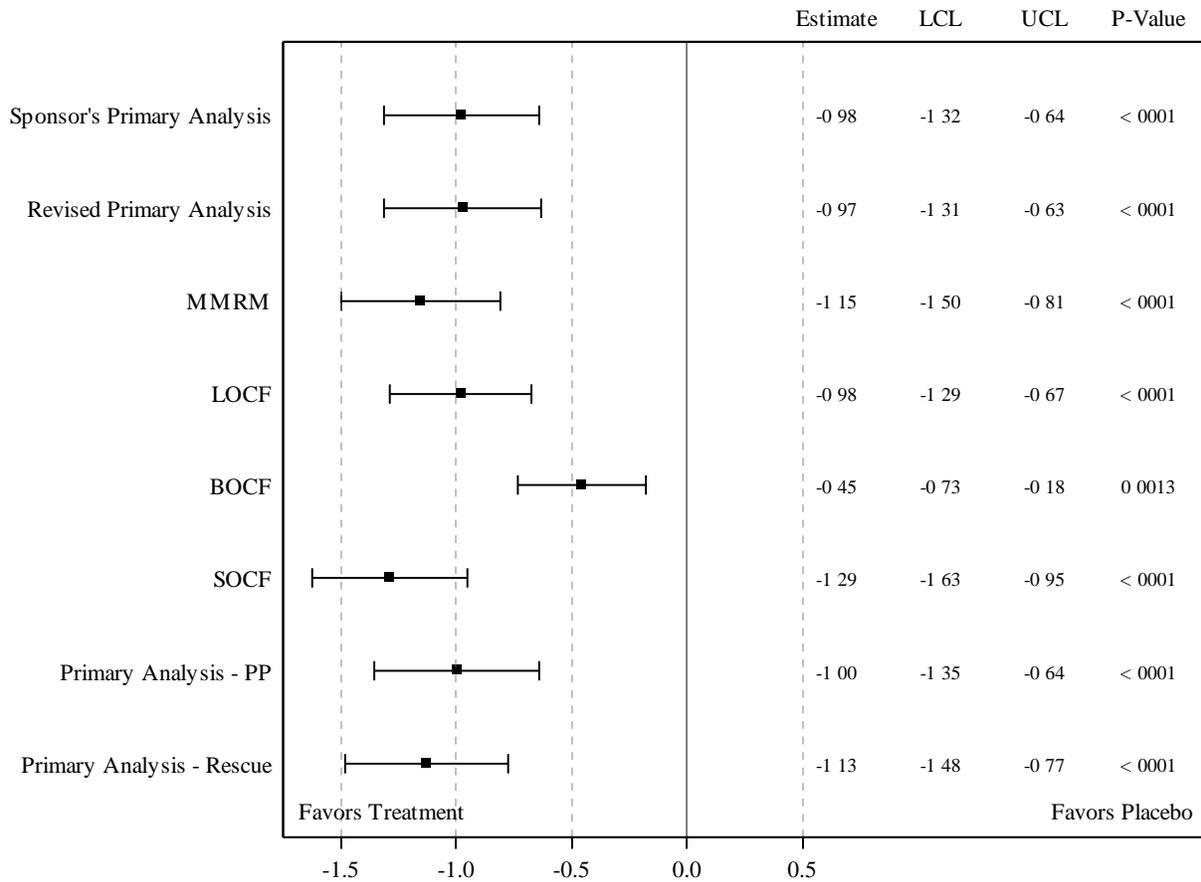
The mean (\pm SE) change in pain intensity from baseline for each week in the double-blind treatment phase of the study is displayed in Figure 3. The figure shows a clear separation between the two treatment groups for all twelve weeks of the study with the mean pain intensities for the BEMA Buprenorphine group consistently lower than the mean pain intensities for the BEMA Placebo group.

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



The results of the primary and a selection of the sensitivity analyses for this study are shown in Figure 4. The sensitivity analyses all support the conclusion of the primary analysis.

Figure 4: Primary, and Sensitivity Analyses of Change from Baseline to Week 12 in Numerical Rating Scale Pain Intensity in Double-Blind Treatment Phase – Study EN3409-307 ITT Population

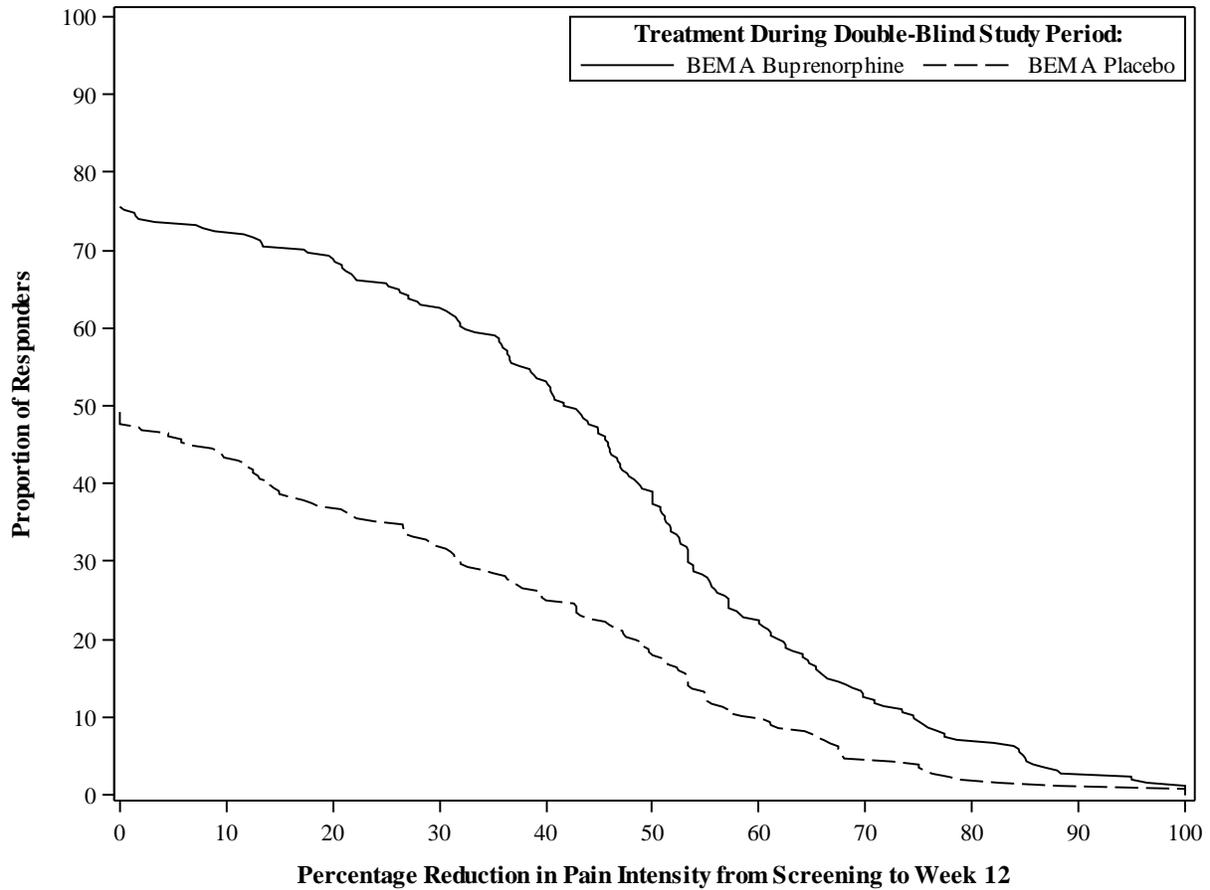


The plot of cumulative proportion of responders for this study is shown in Figure 5. The results of the Cochran-Mantel-Haenszel test for the 30% and 50% reduction in pain intensities are shown in Table 8. The difference in the responder rate between the treatment and placebo was found to be statistically significant in both cases. The applicant classified several subjects who discontinued from the study as responders in their analysis. These subjects were reclassified as non-responders for this analysis.

Table 8: Responders in Pain Reduction for Selected Percentages from Screening to Week 12 in Double-blind Treatment Phase – Study EN3049-307 ITT Population

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

Figure 5: Proportion of Responders with Selected Percent Pain Reduction from Screening to Week 12 in Double-blind Treatment Phase – Study EN3409-307 ITT Population



The number and percentage of subjects using rescue medication by week is shown in Table 9. The average number of patient reported rescue medication tablets used per week per subject enrolled in the trial is shown in Table 10 and the average number of patient reported rescue medication tablets used per week per subject who used rescue is shown in Table 11. The subjects in the buprenorphine treatment group used fewer rescue medication tablets and were less likely to use any rescue medication for all weeks in the study.

Table 9: Number (%) of Subjects with Rescue Medication Use by Week in Double-blind Treatment Phase – Study EN3409-307 ITT Population

Week	BEMA Buprenorphine (N=243)		BEMA Placebo (N=248)	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	242	215 (88.8%)	246	228 (92.7%)
Week 2	234	202 (86.3%)	204	185 (90.7%)
Week 3	229	197 (86.0%)	189	172 (91.0%)
Week 4	229	191 (83.4%)	179	164 (91.6%)
Week 5	222	186 (83.8%)	162	147 (90.7%)
Week 6	219	185 (84.5%)	161	146 (90.7%)
Week 7	213	178 (83.6%)	154	140 (90.9%)
Week 8	210	177 (84.3%)	152	137 (90.1%)
Week 9	207	173 (83.6%)	146	129 (88.4%)
Week 10	205	172 (83.9%)	145	130 (89.7%)
Week 11	203	172 (84.7%)	144	130 (90.3%)
Week 12	201	166 (82.6%)	141	128 (90.8%)

Table 10: Average Number of Patient Reported Rescue Medication Tablets per Subject Enrolled in the Study Double-blind Treatment Phase – Study EN3409-307 ITT Population

	BEMA Buprenorphine (N=243)		BEMA Placebo (N=248)	
	Number of Subjects Remaining in the Study	Average Number of Rescue Medication Tablets	Number of Subjects Remaining in the Study	Average Number of Rescue Medication Tablets
Week 1	242	11.0	246	13.5
Week 2	234	10.1	204	13.8
Week 3	229	8.4	189	10.6
Week 4	229	7.7	179	10.0
Week 5	222	8.0	162	10.0
Week 6	219	7.7	161	9.4
Week 7	213	8.0	154	9.4
Week 8	210	7.7	152	9.4
Week 9	207	7.9	146	9.4
Week 10	205	7.8	145	9.7
Week 11	203	8.0	144	9.4
Week 12	201	6.7	141	8.1

Table 11: Average Number of Patient Reported Rescue Medication Tablets per Subject Using Rescue in the Double-Blind Treatment Phase – Study EN3409-307 ITT Population

	BEMA Buprenorphine (N=243)		BEMA Placebo (N=248)	
	Number of Subjects Using Rescue Medication	Average Number of Rescue Medication Tablets	Number of Subjects Using Rescue Medication	Average Number of Rescue Medication Tablets
Week 1	215	12.3	228	14.6
Week 2	202	11.7	185	15.2
Week 3	197	9.7	172	11.7
Week 4	191	9.3	164	10.9
Week 5	186	9.6	147	11.0
Week 6	185	9.1	146	10.3
Week 7	178	9.6	140	10.4
Week 8	177	9.1	137	10.5
Week 9	173	9.5	129	10.6
Week 10	172	9.3	130	10.8
Week 11	172	9.5	130	10.4
Week 12	166	8.2	128	9.0

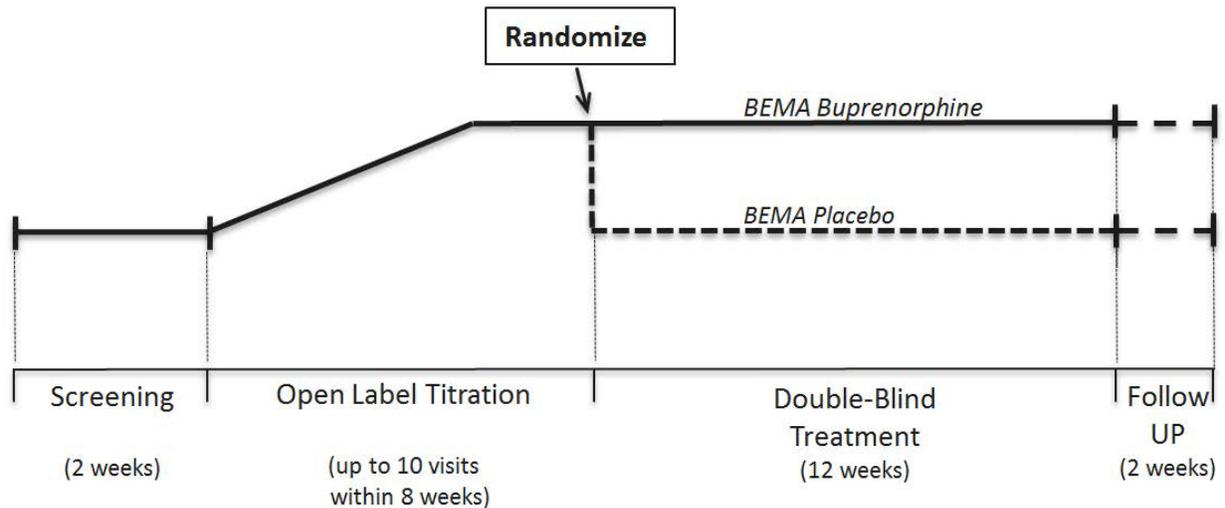
3.2.2 Study EN3409-308

3.2.2.1 Study Design and Endpoints

Study EN3409-308 was a Phase 3, multicenter, double-blind, placebo-controlled, enriched enrollment, randomized study comparing BEMA Buprenorphine to BEMA Placebo in opioid naïve subjects with moderate to severe chronic lower back pain (CLBP) and was conducted concurrently with EN3409-307. For this study the applicant defined opioid naïve subjects as subjects who are treating their CLBP with a stable daily maintenance dose of non-opioid analgesic medication for at least 4 weeks and a maximum of 10 mg MSE opioid analgesic medication per day.

The study design and endpoints were the same as described in Section 3.2.1.1 for Study EN3409-307 except for the following noted exception: Since this study only included subjects taking up to 10 mg MSE per day it was not necessary to include an analgesic taper phase and subjects progressed directly from the screening phase to the open-label titration phase. In addition, the inclusion criteria was modified so that to be eligible to enter the open-label titration phase of the study subjects must demonstrate a mean of average daily pain intensity scores ≥ 5 to < 10 on an 11-point NRS scale over the last 7 days of the screening phase, with no daily pain intensity scores ≤ 3 during the last 7 days. The schematic for this study is shown in Figure 6.

Figure 6: Schematic of Study Design for EN3409-308



Source: Figure 1, Clinical Study Report

3.2.2.2 Statistical Methodologies

This study used the same statistical methodology described in Section 3.2.1.2 for Study EN3409-307 with the exception of the analysis of the rescue medication. This data was reanalyzed using the same method as Study EN3409-307.

An interim analysis was performed by an independent statistician after the first 222 of the randomized subjects completed the study. The sample size was not modified as a result of the interim analysis and so the adjustment described by (Cui, Hung, & Wang, 1999) was not necessary for this study.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition for the screening and open-label titration phase is shown in Table 12. For this study a total of 1,633 subjects were screened for admission into the study at a total of 60 sites. Approximately 61% (462) of the subjects who were screened for the study met all inclusion criteria and were randomized into the double-blind treatment phase. There were, however, a number of subjects who were excluded from the analysis population by the applicant.

As discussed in Section 3.1, the study was discontinued at one site in the study due to significant violations of GCP. There were a total of 41 subjects enrolled at this site in this study. The applicant analyzed the data for this study both including and excluding these subjects and found no differences in the overall conclusion of the study. All analyses presented in this review will exclude these subjects.

In addition, one subject in this study withdrew prior to receiving any study medication after randomization and was not included in the ITT population by the applicant's definition.

Table 12: Subject Disposition in Open-label Titration Phase (All Subjects) – Study EN3409-308

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

Source: Table 4 from applicant’s study report

The demographic and baseline characteristics for this study are shown in Table 13. The subjects were mostly female (55%) and White (68%) and between 18 and 64 years of age (87%). There are some differences in the demographic characteristics between the two treatment groups. The BEMA Placebo group has a greater proportion of females than the BEMA Buprenorphine group (59% vs 51%). The breakdown of the racial subgroups is also dissimilar between the two treatment groups. The mean pain intensities prior to the open-label titration phase and at baseline were approximately the same for both treatment groups.

Table 13: Demographics and Baseline Characteristics in Double-blind Treatment Phase – Study EN3409-308 ITT Population

	BEMA Buprenorphine n=209	BEMA Placebo n=211	Overall n=420
Age (years)			
Mean (SD)	51.1 (12.9)	48.7 (13.2)	49.9 (13.1)
(Min, Max)	(22, 82)	(19, 78)	(19, 82)
Age Group, n (%)			
18 to 64 years	180 (86.1)	186 (88.2)	366 (87.1)
65 to 75 years	25 (12.0)	24 (11.4)	49 (11.7)
>75 year	4 (1.9)	1 (0.5)	5 (1.2)
Gender, n (%)			
Female	107 (51.2)	124 (58.8)	231 (55.0)
Male	102 (48.8)	87 (41.2)	189 (45.0)
Race, n (%)			
White	150 (71.8)	137 (64.9)	287 (68.3)
Black Or African American	50 (23.9)	56 (26.5)	106 (25.2)
Asian	8 (3.8)	14 (6.6)	22 (5.2)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	1 (0.5)	1 (0.2)
American Indian Or Alaska Native	0 (0.0)	3 (1.4)	3 (0.7)
Other	1 (0.5)	0 (0.0)	1 (0.2)
Pain Intensity Score Prior to Open-Label Titration			
Mean (SD)	7.12 (1.058)	7.18 (1.050)	7.15 (1.053)
(Min, Max)	(5.0, 10)	(5.0, 9.7)	(5.0, 10)
Pain Intensity Score at Baseline			
Mean (SD)	2.82 (1.014)	2.79 (1.122)	2.81 (1.068)
(Min, Max)	(0.0, 4.6)	(0.0, 6.1)	(0.0, 6.1)

The subject disposition in the double-blind treatment phase of the study is shown in Table 14. There were six subjects in this study who were reclassified from withdrawal due to protocol violation/other reasons to withdrawal due to adverse event as described in Section 3.1. All results presented in this review include this modification.

The percentage of subjects who completed the study is similar for both arms of the study, unlike Study EN3409-307. For the BEMA buprenorphine arm the most common reason for

discontinuation was stated as due to adverse events, whereas for the placebo arm most subjects discontinued due to lack of efficacy.

The distribution of the subjects by titrated dose and treatment arm are shown in Table 15.

Table 14: Subject Disposition in Double-blind Treatment Phase – Study EN3409-308 ITT Population

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

Table 15: Optimal Titrated Dose – Study EN3409-308 ITT Population

Titrated Dose	BEMA Buprenorphine n (%)	BEMA Placebo n (%)	Overall n (%)
150 mcg	55 (26.3)	58 (27.5)	113 (26.9)
300 mcg	63 (30.1)	60 (28.4)	123 (29.3)
450 mcg	91 (43.5)	93 (44.1)	184 (43.8)
Total	209	211	420

The rate of treatment failure for the two treatment groups was compared using a Kaplan-Meier analysis. The Kaplan-Meier curves are shown in Figure 7 and a summary of the number of treatment failures is shown in Table 16. Note that patients completing the study or discontinuing for reasons other than adverse events or lack of efficacy were considered to be censored for this analysis. For this study the rate of treatment failure was greater for the placebo population. However, the difference in the survival functions was not found to be statistical significantly different using the log-rank test (Table 16).

Figure 7: Kaplan-Meier Curves for Proportion of Subjects Remaining on Treatment in Double-Blind Treatment Phase – Study EN3409-308 ITT Population

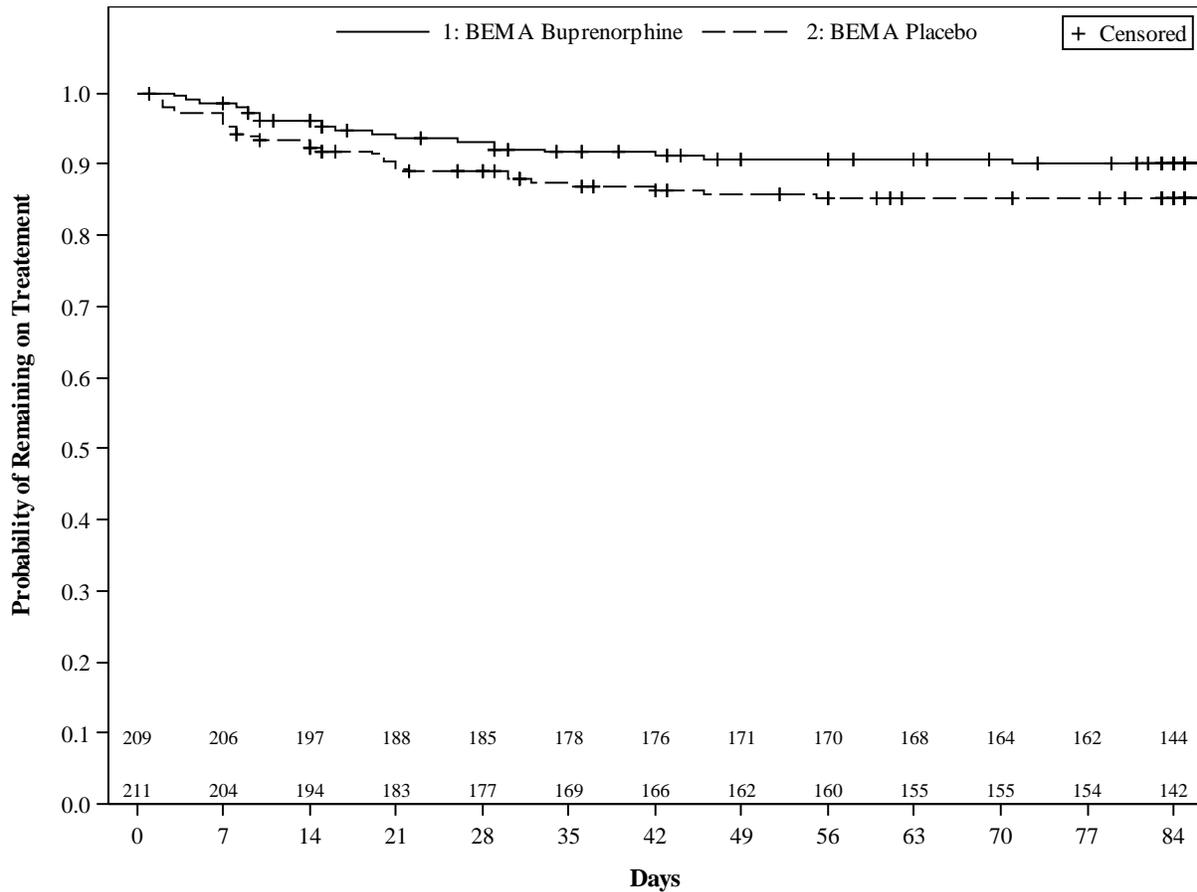


Table 16: Summary of Kaplan-Meier Analysis in Double-blind Treatment Phase – Study EN3409-308 ITT Population

Statistics	BEMA Buprenorphine n=209	BEMA Placebo n=211	Overall n=420
Number of subjects with treatment failure, n (%)	25 (12.0)	31 (14.7)	56 (13.3)
Number of subjects with censored, n (%)	184 (88.0)	180 (85.3)	364 (86.7)
P-value for log-rank test	0.3605		

3.2.2.4 Results and Conclusions

For this study the applicant again concluded that the pain intensities were statistically significantly lower in the BEMA Buprenorphine treatment arm than the BEMA Placebo arm

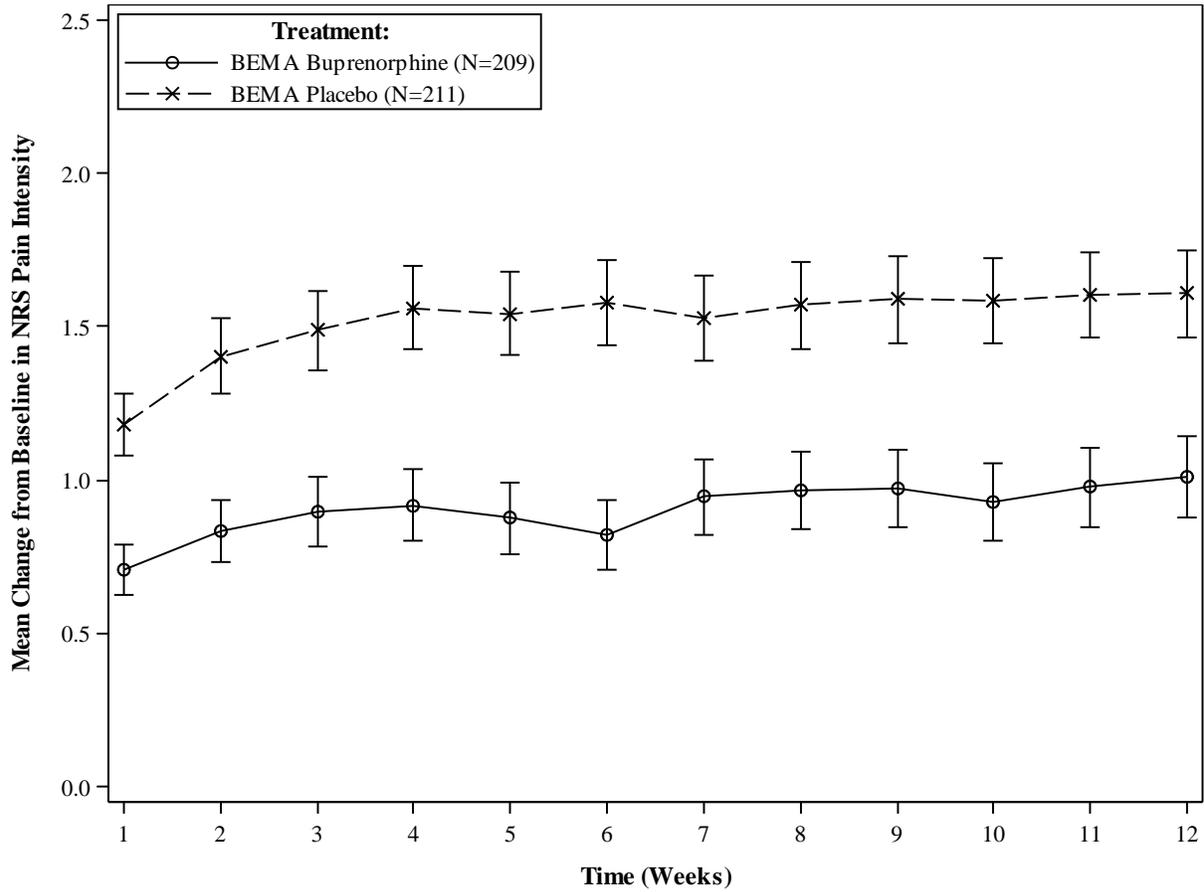
both including and excluding Site 1008. This reviewer was able to reproduce the applicant's results and reached the same conclusion even with the modifications summarized in Section 3.2.2.3. The result of the ANCOVA analysis with these modifications is shown in Table 17.

Table 17: Change from Baseline to Week 12 in Average Numeric Rating Scale Pain Intensity in Double-blind Treatment Phase – Study EN3409-308 ITT Population

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

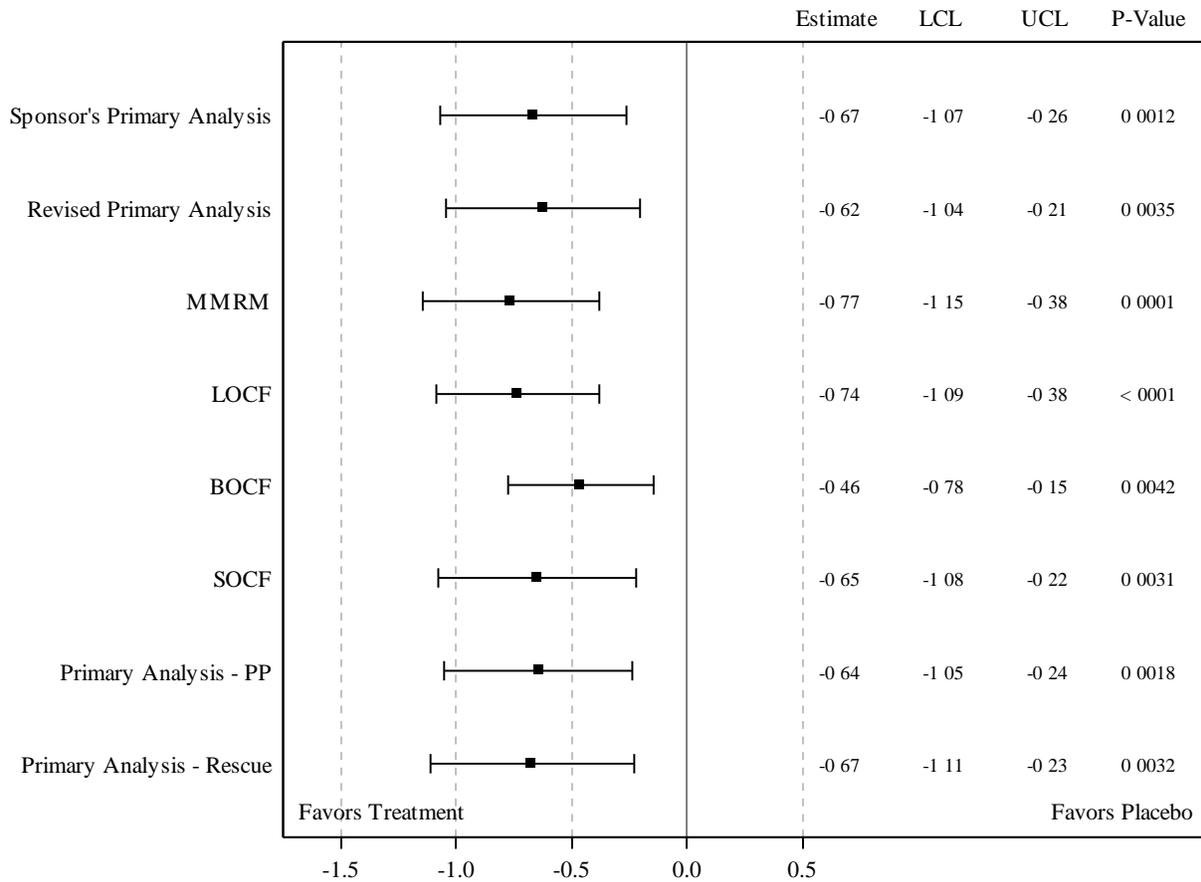
The mean change from Baseline pain intensity by week is shown in Figure 8. The pain scores are lower in the buprenorphine treatment group than the placebo group for all twelve weeks of the study.

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



The results of the primary and a selection of the sensitivity analysis are shown in Figure 9. All the sensitivity analyses support the conclusion of the primary analysis.

Figure 9: Primary, and Sensitivity Analyses of Change from Baseline to Week 12 in Numerical Rating Scale Pain Intensity in Double-Blind Treatment Phase – Study EN3409-308 ITT Population

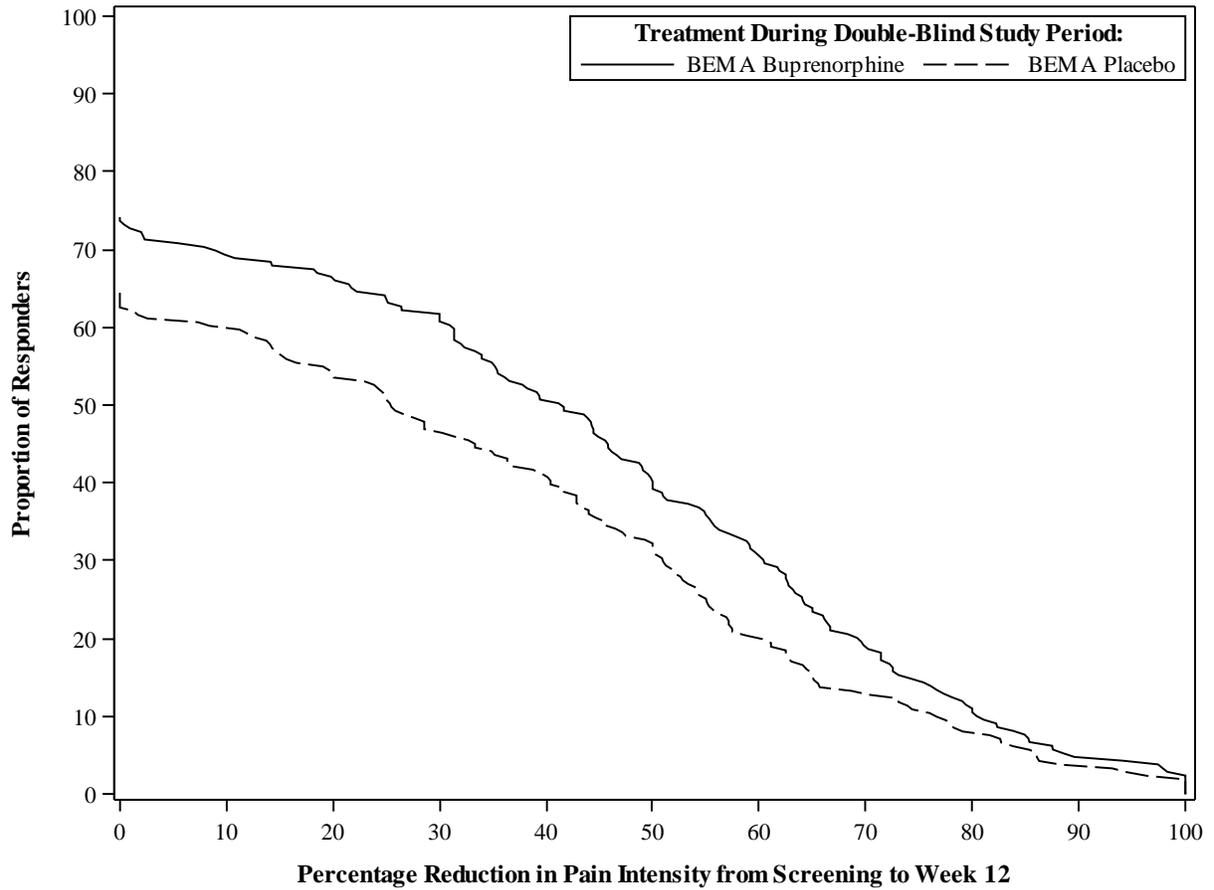


The plot of the cumulative proportion of responders is shown in Figure 10. We see that the response rate is greater for the BEMA Buprenorphine than the BEMA Placebo group. The results of the Cochran-Mantel-Haenszel for the 30% and 50% reductions in pain intensity are shown in Table 18. We see that the percentage of responders is statistically significant for the 30% reduction in pain but not for the 50% reduction in pain.

Table 18: Responders in Pain Reduction for Selected Percentages from Screening to Week 12 in Double-blind Treatment Phase – Study EN3049-308 ITT Population

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

Figure 10: Proportion of Responders with Selected Percent Pain Reduction from Screening to Week 12 in Double-blind Treatment Phase – Study EN3409-308 ITT Population



The number and percentage of subjects in the trial using rescue medication per week is shown in Table 19. The average number of patient reported rescue medication tablets taken per week per subject enrolled in the study that week is shown in Table 20 and the average number of rescue medication tablets per subject using rescue medication that week is shown in Table 21. The subjects in the buprenorphine treatment group used less rescue medication overall and were less likely to use rescue medication at all weeks.

Table 19: Number (%) of Subjects with Rescue Medication Use by Week in Double-blind Treatment Phase – Study EN3409-308 ITT Population

Week	BEMA Buprenorphine (N=209)		BEMA Placebo (N=211)	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	209	123 (58.9%)	210	140 (66.7%)
Week 2	201	112 (55.7%)	196	132 (67.3%)
Week 3	191	85 (44.5%)	186	107 (57.5%)
Week 4	187	81 (43.3%)	179	98 (54.7%)
Week 5	180	76 (42.2%)	172	92 (53.5%)
Week 6	178	74 (41.6%)	166	94 (56.6%)
Week 7	173	73 (42.2%)	163	85 (52.1%)
Week 8	169	64 (37.9%)	161	85 (52.8%)
Week 9	167	67 (40.1%)	158	82 (51.9%)
Week 10	165	60 (36.4%)	155	81 (52.3%)
Week 11	162	62 (38.3%)	154	72 (46.8%)
Week 12	160	56 (35.0%)	151	72 (47.7%)

Table 20: Average Number of Patient Reported Rescue Medication Tablets per Subject Enrolled in the Study Double-blind Treatment Phase – Study EN3409-308 ITT Population

	BEMA Buprenorphine (N=209)		BEMA Placebo (N=211)	
	Number of Subjects Remaining in the Study	Average Number of Rescue Medication Tablets	Number of Subjects Remaining in the Study	Average Number of Rescue Medication Tablets
Week 1	209	3.7	210	5.1
Week 2	201	4.1	196	5.2
Week 3	191	3.4	186	5.0
Week 4	187	3.3	179	4.7
Week 5	180	3.0	172	4.3
Week 6	178	3.0	166	4.7
Week 7	173	3.1	163	4.1
Week 8	169	2.9	161	4.0
Week 9	167	3.2	158	4.2
Week 10	165	2.7	155	4.0
Week 11	162	2.5	154	4.1
Week 12	160	2.3	151	3.6

Table 21: Average Number of Patient Reported Rescue Medication Tablets per Subject Using Rescue in the Double-Blind Treatment Phase – Study EN3409-308 ITT Population

	BEMA Buprenorphine (N=243)		BEMA Placebo (N=248)	
	Number of Subjects Using Rescue Medication	Average Number of Rescue Medication Tablets	Number of Subjects Using Rescue Medication	Average Number of Rescue Medication Tablets
Week 1	123	6.2	140	7.6
Week 2	112	7.3	132	7.7
Week 3	85	7.6	107	8.7
Week 4	81	7.7	98	8.7
Week 5	76	7.0	92	8.1
Week 6	74	7.2	94	8.3
Week 7	73	7.4	85	7.9
Week 8	64	7.6	85	7.6
Week 9	67	8.0	82	8.1
Week 10	60	7.6	81	7.7
Week 11	62	6.6	72	8.8
Week 12	56	6.5	72	7.6

3.3 Evaluation of Safety

The reader is referred to the Medical Review by Dr. Pamela Horn for an evaluation of the safety of Belbuca.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant conducted subgroup analyses by gender, race and age using an ANCOVA model using only the subjects with observed Week 12 pain scores and no imputation. This reviewer analyzed the subgroups using two additional models: the ANCOVA model used for the primary analysis and the MMRM model used as a sensitivity analysis for both studies.

4.1 Efficacy Analysis by Gender

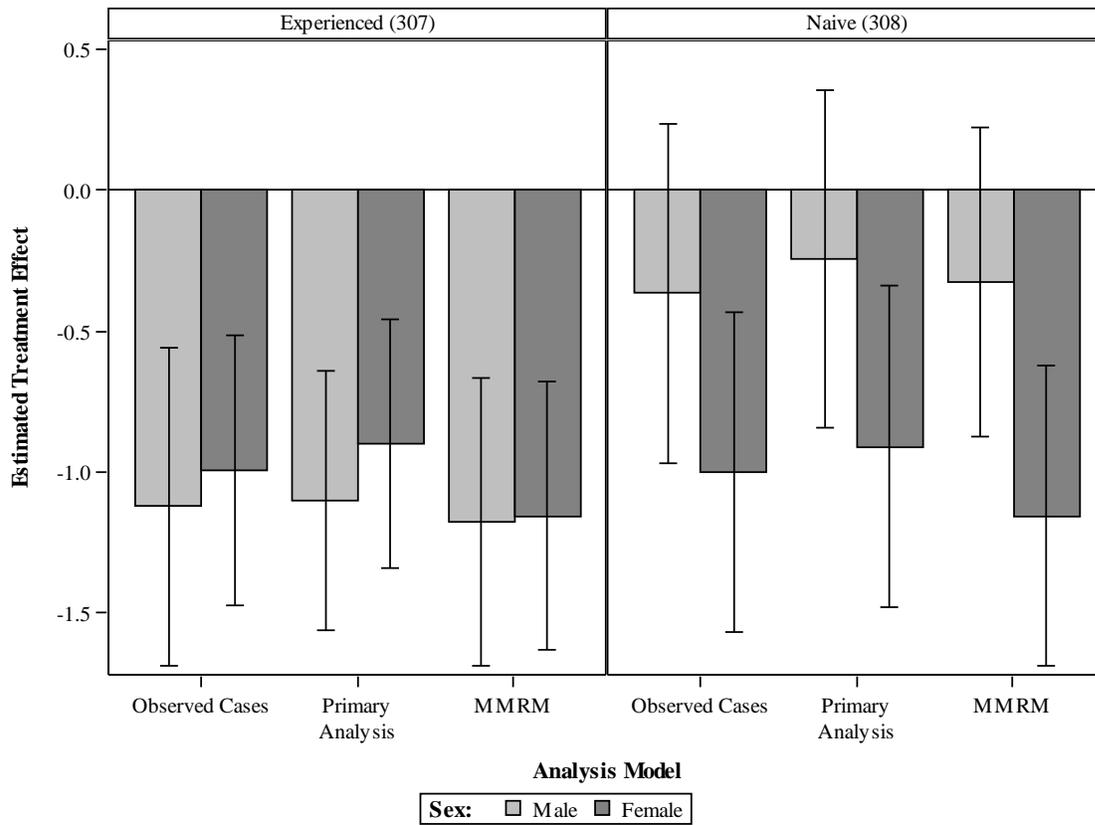
The subject disposition for gender subgroups for Studies EN3409-307 and EN3409-308 are shown in the appendix in Table A1 and Table A2 respectively.

Figure 11 and Table 22 contain a summary of the efficacy analysis by study, gender, and analysis method.

Table 22: Estimated Treatment Effect by Study, Gender and Analysis Method

Study	Sex	Analysis Model	Estimated Treatment Effect	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Experienced (307)	Male	Observed Cases	-1.12	0.285	-1.68	-0.56
Experienced (307)	Female	Observed Cases	-1.01	0.241	-1.48	-0.53
Experienced (307)	Male	Primary Analysis	-1.10	0.235	-1.56	-0.64
Experienced (307)	Female	Primary Analysis	-0.94	0.224	-1.38	-0.50
Experienced (307)	Male	MMRM	-1.17	0.259	-1.68	-0.66
Experienced (307)	Female	MMRM	-1.15	0.241	-1.63	-0.68
Naive (308)	Male	Observed Cases	-0.37	0.304	-0.97	0.24
Naive (308)	Female	Observed Cases	-1.00	0.288	-1.57	-0.43
Naive (308)	Male	Primary Analysis	-0.24	0.306	-0.84	0.36
Naive (308)	Female	Primary Analysis	-0.91	0.290	-1.48	-0.34
Naive (308)	Male	MMRM	-0.32	0.278	-0.87	0.22
Naive (308)	Female	MMRM	-1.15	0.270	-1.69	-0.62

Figure 11: Estimated Treatment Effect by Study, Gender and Analysis Method



4.2 Efficacy Analysis by Race

The subject disposition by racial subgroup for Studies EN3409-307 and EN3409-308 are shown in Table 23 and Table 24, respectively.

Table 23: Disposition by Race and Treatment Group – Study EN3409-307

	White n (%)		Black or African American n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	162 (83.9)	96 (50.8)	38 (77.6)	36 (75.0)
Adverse Event	3 (1.6)	11 (5.8)	3 (6.1)	2 (4.2)
Lack Of Efficacy	16 (8.3)	56 (29.6)	3 (6.1)	4 (8.3)
Protocol Violation	3 (1.6)	10 (5.3)	0 (0.0)	0 (0.0)
Withdrawal Due To Opioid Withdrawal	0 (0.0)	9 (4.8)	1 (2.0)	0 (0.0)
Withdrawal By Subject	8 (4.1)	3 (1.6)	3 (6.1)	3 (6.3)
Lost To Follow-Up	1 (0.5)	3 (1.6)	0 (0.0)	2 (4.2)
Other	0 (0.0)	1 (0.5)	1 (2.0)	1 (2.1)
Total	193	189	49	48

Table 24: Disposition by Race and Treatment Group – Study EN3409-308

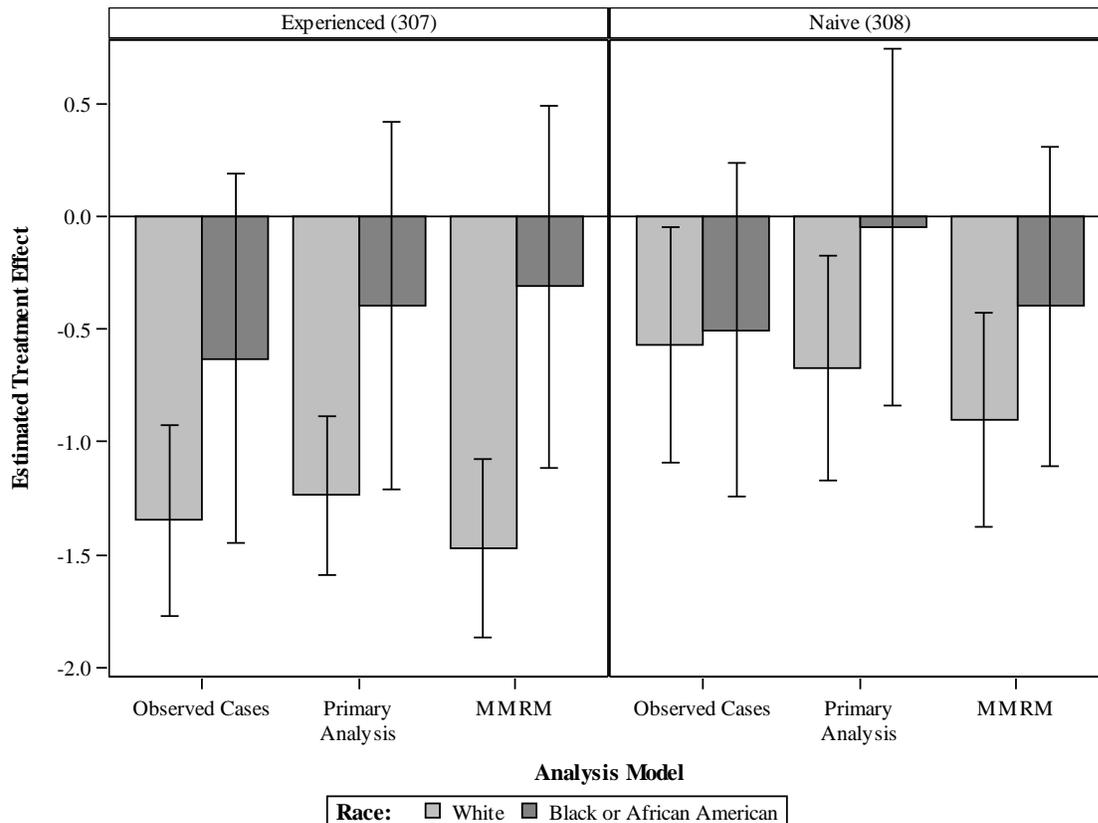
	White n (%)		Black or African American n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	113 (75.3)	90 (65.7)	37 (74.0)	48 (85.7)
Adverse Event	10 (6.7)	6 (4.4)	7 (14.0)	1 (1.8)
Lack Of Efficacy	6 (4.0)	22 (16.1)	2 (4.0)	1 (1.8)
Protocol Violation	5 (3.3)	5 (3.6)	1 (2.0)	4 (7.1)
Withdrawal Due To Opioid Withdrawal	2 (1.3)	1 (0.7)	1 (2.0)	0 (0.0)
Withdrawal By Subject	10 (6.7)	5 (3.6)	1 (2.0)	1 (1.8)
Lost To Follow-Up	4 (2.7)	8 (5.8)	0 (0.0)	1 (1.8)
Other	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Total	150	137	50	56

Figure 12 and Table 25 contain a summary of the efficacy analysis by study, gender, and analysis method.

Table 25: Estimated Treatment Effect by Study, Race and Analysis Method

Study	Race	Analysis Model	Estimated Treatment Effect	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Experienced (307)	White	Observed Cases	-1.34	0.215	-1.77	-0.92
Experienced (307)	Black/African American	Observed Cases	-0.63	0.410	-1.45	0.19
Experienced (307)	White	Primary Analysis	-1.23	0.179	-1.59	-0.88
Experienced (307)	Black/African American	Primary Analysis	-0.40	0.414	-1.21	0.42
Experienced (307)	White	MMRM	-1.47	0.201	-1.86	-1.07
Experienced (307)	Black/African American	MMRM	-0.31	0.404	-1.11	0.49
Naive (308)	White	Observed Cases	-0.57	0.263	-1.09	-0.05
Naive (308)	Black/African American	Observed Cases	-0.50	0.371	-1.24	0.23
Naive (308)	White	Primary Analysis	-0.67	0.255	-1.17	-0.17
Naive (308)	Black/African American	Primary Analysis	-0.05	0.402	-0.84	0.74
Naive (308)	White	MMRM	-0.90	0.241	-1.38	-0.43
Naive (308)	Black/African American	MMRM	-0.40	0.355	-1.10	0.31

Figure 12: Estimated Treatment Effect by Study, Race and Analysis Method



4.3 Efficacy Analysis by Age Group

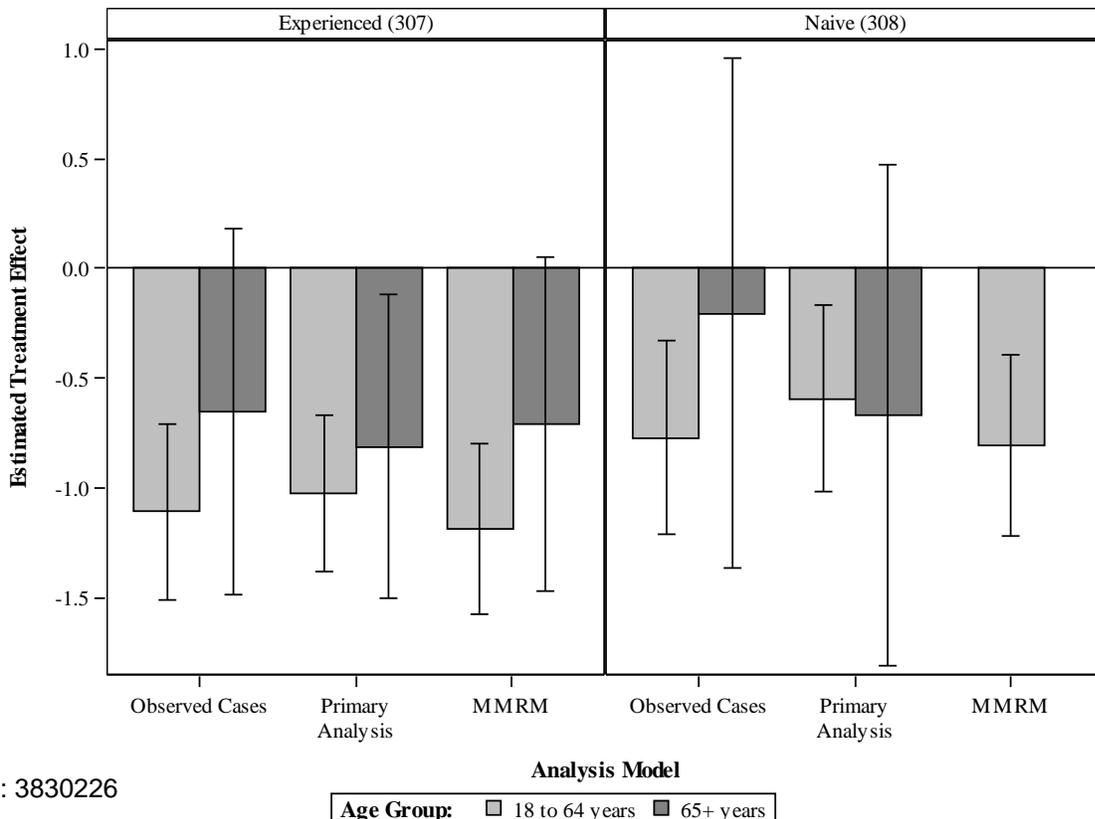
The subject disposition by age subgroup for Studies EN3409-307 and EN3409-308 are shown in the appendix in Table A3 and Table A4 respectively.

Figure 13 and Table 26 contain a summary of the efficacy analysis by study, gender, and analysis method.

Table 26: Estimated Treatment Effect by Study, Age Group and Analysis Method

Study	Age Group	Analysis Model	Estimated	Std. Error	95% CI	95% CI
			Treatment Effect		Lower Bound	Upper Bound
Experienced (307)	18 to 64 years	Observed Cases	-1.11	0.203	-1.51	-0.71
Experienced (307)	65+ years	Observed Cases	-0.65	0.415	-1.49	0.18
Experienced (307)	18 to 64 years	Primary Analysis	-1.02	0.182	-1.38	-0.67
Experienced (307)	65+ years	Primary Analysis	-0.81	0.353	-1.50	-0.12
Experienced (307)	18 to 64 years	MMRM	-1.19	0.197	-1.57	-0.80
Experienced (307)	65+ years	MMRM	-0.71	0.381	-1.47	0.05
Naive (308)	18 to 64 years	Observed Cases	-0.77	0.223	-1.21	-0.33
Naive (308)	65+ years	Observed Cases	-0.20	0.572	-1.37	0.96
Naive (308)	18 to 64 years	Primary Analysis	-0.59	0.216	-1.02	-0.17
Naive (308)	65+ years	Primary Analysis	-0.67	0.582	-1.81	0.47
Naive (308)	18 to 64 years	MMRM	-0.81	0.210	-1.22	-0.39

Figure 13: Estimated Treatment Effect by Study, Age Group and Analysis Method



4.4 Discussion of Findings

Both studies contained a similar proportion of females (54% Study 307, 55% Study 308). The disposition patterns shown in Table A1 **Error! Reference source not found.** and Table A2 are roughly the same for both genders in both studies. However, the efficacy results vary by study. For Study -307, estimated treatment effect was slightly larger for males than for females in Study 307 for all three analysis methods. However, for Study 308 the estimated treatment effect was considerably smaller for males (-0.24 – -0.37) than for females (-0.92 – -1.15).

For the racial subgroups analysis only the White and Black/African American subgroups contained enough subjects for inferential statistics and so this review will only discuss these two groups. See Table 4 and Table 13 for a summary of the racial demographics for Study 307 and 308 respectively.

The disposition patterns vary considerably for the racial subgroups in both studies. For Study 307 there is a large difference between the rates of study completion for the two treatment groups (84% buprenorphine, 51% placebo) for the White subgroup. However, for the Black/African American subgroup the rate of study completion is approximately the same (78% buprenorphine, 75% placebo). For Study 308, again, a larger rate of study completion can be observed in the buprenorphine group than the placebo group (75% vs 66%). For the Black/African American subgroup this is reversed and we see a larger rate of study completion in the placebo group than the buprenorphine group.

The estimated treatment effect is considerably larger for the White subgroup than the Black/African American subgroup for both studies for the primary analysis and MMRM analysis and for the observed case analysis for Study 307. For Study 308 the observed case analysis yields estimated treatment effects of approximately the same magnitude for both subgroups. The observed case analysis only considers the observed pain intensities of subjects who completed the study, whereas the primary analysis and the MMRM analysis include all subjects who were randomized.

The applicant separated the subjects into three different age groups, 18 to 64 years, 65 to 74 years and 75 years or greater. The last group included too few subjects to analyze (see Table 4 and Table 13) and so this reviewer merged the last two age groups for this analysis. The study completion rates and the estimated effect sizes were similar for both age groups in both studies.

The smaller effect size seen in the Black/African American patients in both studies and the male patients in Study 308 appears to be the result of a larger placebo response in these patients rather than an increase in the average pain score for the Belbuc patients (See Table A5 – Table A7). This is supported by the low rate of discontinuation due to lack of efficacy for Black/African American patients in both studies (Table 23 and Table 24).

Higher rescue usage in the placebo group is one possible cause for the higher rate of placebo response; however, this does not appear to be the case for these studies. For Study 308 the

proportion of subjects using rescue (Table A13 and Table A14) and average number of rescue medication tablets used per subject in the study (Table A15) are roughly similar for both the male and female patients in the study. The proportion of subjects using rescue (Table A16, Table A17, Table A19, and Table A20) and the average number of rescue medication tablets (Table A18 and Table A21) is also approximately the same for both White and Black/African American subjects for Studies 307 and 308.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no statistical issues with the primary efficacy analysis or with the responder analysis. However, there were statistical issues with the applicant's analysis of the rescue medication usage. For Study EN3409-308 the applicant's original analysis did not appear appropriate. The data were reanalyzed with the method used for Study EN3409-307. The applicant's Cochran-Mantel-Haenszel analyses did not appear appropriate as implemented.

5.2 Collective Evidence

The applicant conducted a total of three Phase 3 studies. The first study conducted, BUP-301, included both opioid naïve and opioid experienced subjects. Subsequently, the applicant conducted two studies, EN3409-307 and EN3409-308, where the population was divided based on prior opioid usage. The maximum allowed dosage was also increased from 240 mcg in BUP-301 to 900 mcg for Study EN3409-307 and 450 mcg for Study EN3409-308. Based on the differences in the population, study conduct, and observed subject disposition of these three studies, it does not appear appropriate to combine the efficacy results.

For the first study, BUP-301, the difference in pain intensity between the Belbuca and the placebo groups was not statistically significant. The subsequent studies, EN3409-307 and EN3409-308, both found that the average pain intensity in the Belbuca patients was statistically significantly lower than the placebo patients. The proportion of responders was also statistically significantly greater for both a 30% and 50% reduction in pain intensity for Study EN3409-307 and for a 30% reduction in pain intensity for Study EN3409-308. The proportion of subjects using rescue medication and average number of tablets per subject were both lower for the subjects in the Belbuca treatment group than the placebo group in Studies EN3409-307 and EN3409-308.

The applicant originally conducted subgroup analyses for the gender, racial, and age subgroups. The analyses were conducted by an analysis of covariance (ANCOVA) model using only the subjects who had observed data for Week 12. This reviewer analyzed the data using two additional models: an ANCOVA model with the imputation strategy used for the primary analysis and a Mixed Model with Repeated Measures (MMRM) that was used as a sensitivity analysis. This was important because the model originally used for the subgroup analyses does not take into account the observed pain scores for subjects who failed to complete the study. The findings of the subgroup analyses are summarized in Section 4.4. The analyses results for all the subgroup analyses should be interpreted with great caution because the study was not properly powered or designed to assess the subgroup effects.

5.3 Conclusions and Recommendations

Based upon the results of the Phase 3 studies, it can be concluded that Belbuca is superior to placebo in pain reduction.

5.4 Labeling Recommendations

The applicant submitted the following wording for the clinical study section of the labeling with the original submission.

14 CLINICAL STUDIES

(b) (4)



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

46



I have the following recommendations for Section 14 of the labelling for the applicant:

- Include a description of Study BUP-301 in the introduction to Section 14.
- Exclude the subjects who enrolled at Site 1008 from all of the statistics for the double-blind treatment phase.
- Removal all (b) (4) from the text.

- Remove all statistics for [REDACTED] (b) (4)
- Round all percentages to the nearest whole number.
- Round the mean NRS pain scores to 1 decimal place and the NRS pain standard deviations to 2 decimal places.
- Change the x-axis of the two figures to “Percent Improvement in Pain Intensity from Screening to Week 12”.
- Reclassify all subjects who did not complete the study as non-responders and update the percentages accordingly.
- Re-plot the graphs in Figures 1 and 2 with all subjects who did not complete the study reclassified as non-responders.
- Remove [REDACTED] (b) (4) from the text.

6 Bibliography

- Cui, L., Hung, H., & Wang, S. (1999). Modification of sample size group sequential clinical trials. *Biometrics*(55(3)), 853-857.
- Lawrence, J., & Hung, H. (2003). Estimation and confidence intervals after adjusting the maximum information. *Biometrical Journal*(45(2)), 143-152.
- Rubin, D. (1987). *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons.

7 APPENDICES

Table A1: Disposition by Gender and Treatment Group – Study EN3409-307

	Male n (%)		Female n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	92 (81.4)	67 (59.8)	109 (83.8)	74 (54.4)
Adverse Event	3 (2.7)	6 (5.4)	3 (2.3)	7 (5.1)
Lack Of Efficacy	8 (7.1)	29 (25.9)	11 (8.5)	32 (23.5)
Protocol Violation	2 (1.8)	6 (5.4)	1 (0.8)	5 (3.7)
Withdrawal Due To Opioid Withdrawal	1 (0.9)	2 (1.8)	0 (0.0)	7 (5.1)
Withdrawal By Subject	6 (5.3)	2 (1.8)	5 (3.8)	4 (2.9)
Lost To Follow-Up	1 (0.9)	0 (0.0)	0 (0.0)	5 (3.7)
Other	0 (0.0)	0 (0.0)	1 (0.8)	2 (1.5)
Total	113	112	130	136

Table A2: Disposition by Gender and Treatment Group – Study EN3409-308

	Male n (%)		Female n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	77 (75.5)	66 (75.9)	82 (76.6)	87 (70.2)
Adverse Event	9 (8.8)	2 (2.3)	8 (7.5)	6 (4.8)
Lack Of Efficacy	4 (3.9)	10 (11.5)	4 (3.7)	13 (10.5)
Protocol Violation	3 (2.9)	4 (4.6)	3 (2.8)	5 (4.0)
Withdrawal Due To Opioid Withdrawal	1 (1.0)	0 (0.0)	2 (1.9)	1 (0.8)
Withdrawal By Subject	5 (4.9)	2 (2.3)	6 (5.6)	6 (4.8)
Lost To Follow-Up	2 (2.0)	3 (3.4)	2 (1.9)	6 (4.8)
Other	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	102	87	107	124

Table A3: Disposition by Age Group and Treatment Group – Study EN3409-307

	Age Group (18 to 64 years) n (%)		Age Group (65+ years) n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	172 (81.5)	120 (58.3)	29 (90.6)	21 (50.0)
Adverse Event	6 (2.8)	9 (4.4)	0 (0.0)	4 (9.5)
Lack Of Efficacy	18 (8.5)	50 (24.3)	1 (3.1)	11 (26.2)
Protocol Violation	3 (1.4)	9 (4.4)	0 (0.0)	2 (4.8)
Withdrawal Due To Opioid Withdrawal	1 (0.5)	6 (2.9)	0 (0.0)	3 (7.1)
Withdrawal By Subject	9 (4.3)	5 (2.4)	2 (6.3)	1 (2.4)
Lost To Follow-Up	1 (0.5)	5 (2.4)	0 (0.0)	0 (0.0)
Other	1 (0.5)	2 (1.0)	0 (0.0)	0 (0.0)
Total	211	206	32	42

Table A4: Disposition by Age Group and Treatment Group – Study EN3409-308

	Age Group (18 to 64 years) n (%)		Age Group (65+ years) n (%)	
	BEMA Buprenorphine	BEMA Placebo	BEMA Buprenorphine	BEMA Placebo
Completed	138 (76.7)	137 (73.7)	21 (72.4)	16 (64.0)
Adverse Event	15 (8.3)	6 (3.2)	2 (6.9)	2 (8.0)
Lack Of Efficacy	6 (3.3)	18 (9.7)	2 (6.9)	5 (20.0)
Protocol Violation	5 (2.8)	7 (3.8)	1 (3.4)	2 (8.0)
Withdrawal Due To Opioid Withdrawal	2 (1.1)	1 (0.5)	1 (3.4)	0 (0.0)
Withdrawal By Subject	9 (5.0)	8 (4.3)	2 (6.9)	0 (0.0)
Lost To Follow-Up	4 (2.2)	9 (4.8)	0 (0.0)	0 (0.0)
Other	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Total	180	186	29	25

Figure A1: Change from Baseline by Study, Race and Treatment Group – Primary Analysis

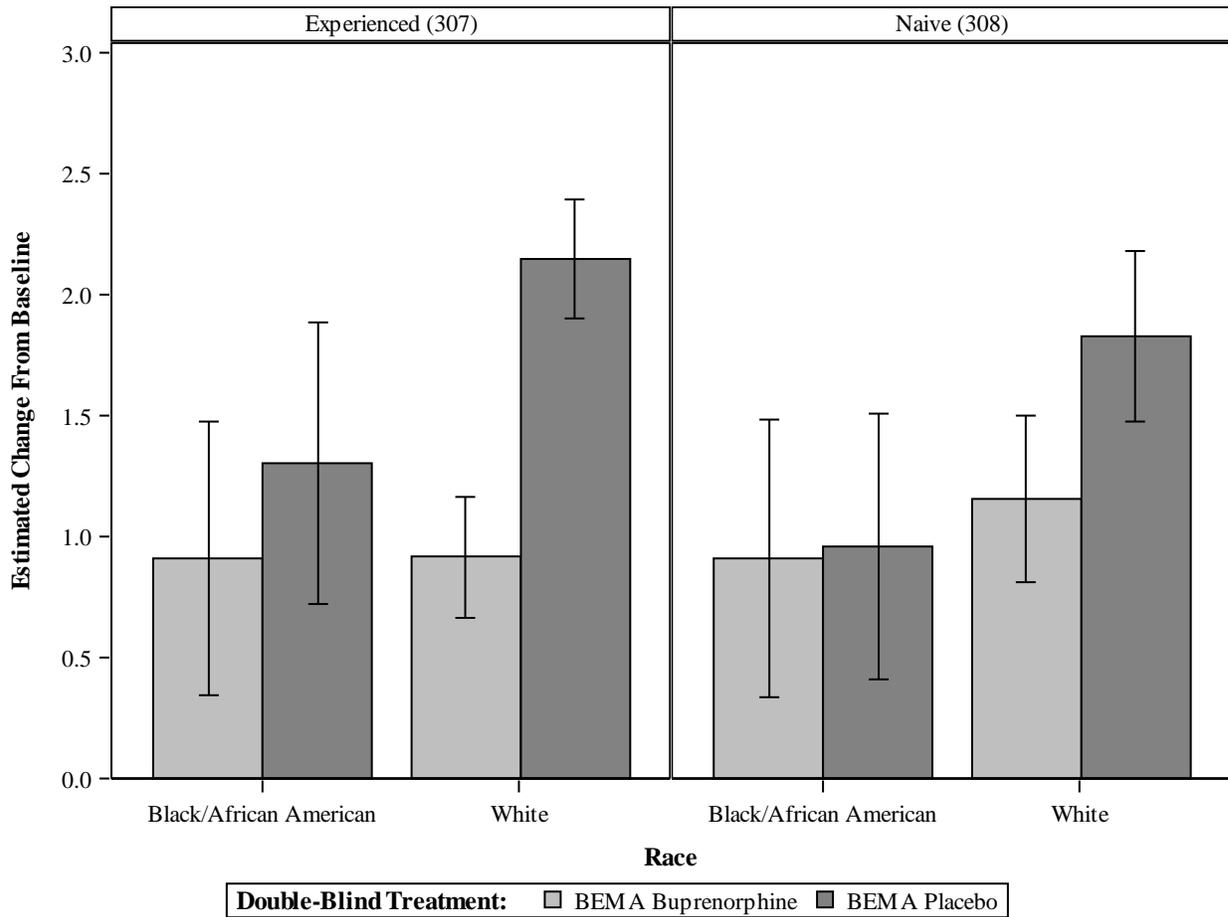


Table A5: Change from Baseline by Study, Race and Treatment Group – Primary Analysis

Study	Race	Treatment Group	Estimated Change From Baseline	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Experienced (307)	Black/African American	BEMA Buprenorphine	0.91	0.289	0.34	1.48
Experienced (307)	Black/African American	BEMA Placebo	1.30	0.297	0.72	1.89
Experienced (307)	White	BEMA Buprenorphine	0.92	0.127	0.67	1.16
Experienced (307)	White	BEMA Placebo	2.15	0.126	1.90	2.40
Naive (308)	Black/African American	BEMA Buprenorphine	0.91	0.291	0.34	1.48
Naive (308)	Black/African American	BEMA Placebo	0.96	0.279	0.41	1.51
Naive (308)	White	BEMA Buprenorphine	1.16	0.176	0.81	1.50
Naive (308)	White	BEMA Placebo	1.83	0.181	1.47	2.18

Figure A2: Change from Baseline by Study, Race and Treatment Group – Observed Cases

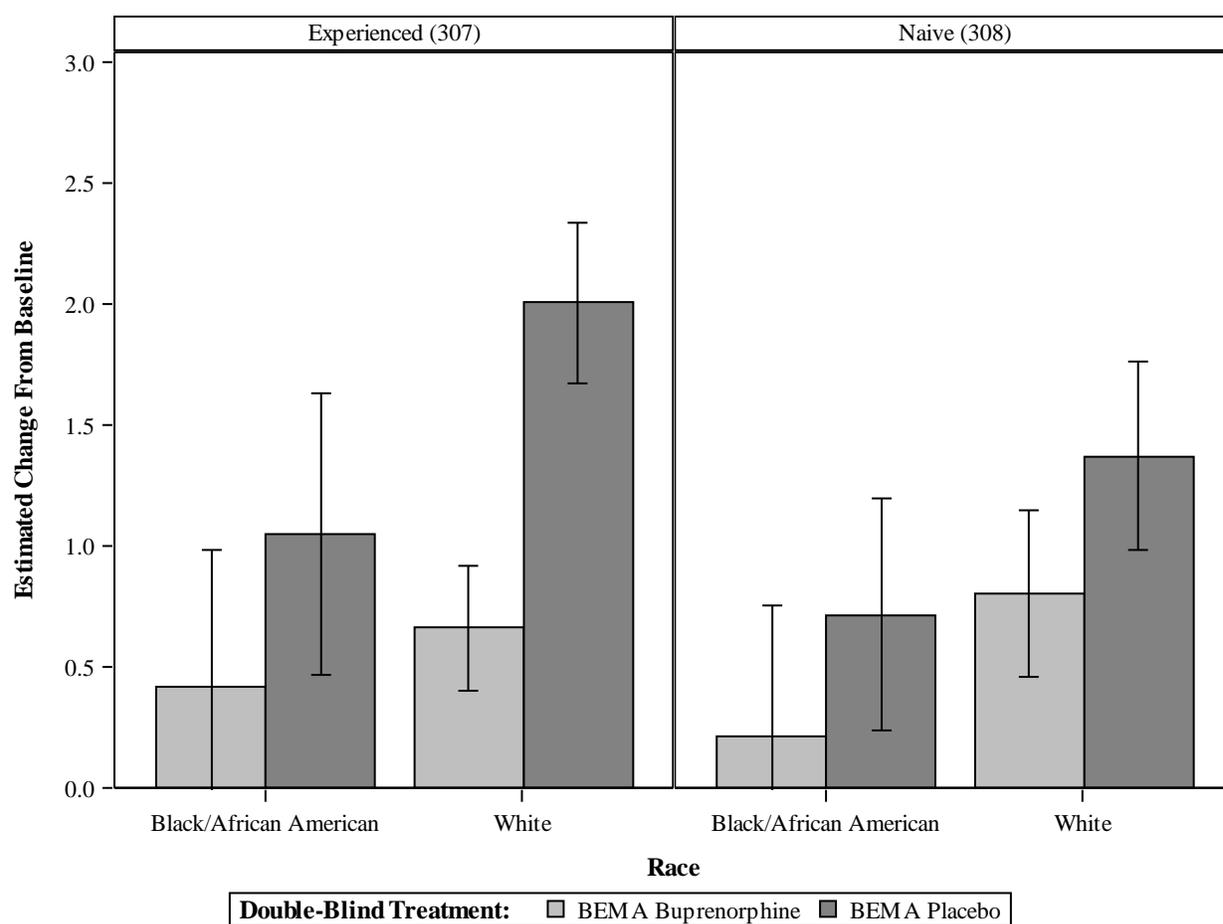


Table A6: Change from Baseline by Study, Race and Treatment Group – Observed Cases

Study	Race	Treatment Group	Estimated Change From Baseline	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Experienced (307)	Black/African American	BEMA Buprenorphine	0.42	0.281	-0.14	0.98
Experienced (307)	Black/African American	BEMA Placebo	1.05	0.292	0.47	1.63
Experienced (307)	White	BEMA Buprenorphine	0.66	0.131	0.40	0.92
Experienced (307)	White	BEMA Placebo	2.00	0.170	1.67	2.34
Naive (308)	Black/African American	BEMA Buprenorphine	0.21	0.274	-0.33	0.76
Naive (308)	Black/African American	BEMA Placebo	0.72	0.242	0.23	1.20
Naive (308)	White	BEMA Buprenorphine	0.80	0.173	0.46	1.14
Naive (308)	White	BEMA Placebo	1.37	0.196	0.98	1.76

Figure A3: Change from Baseline by Study, Race and Treatment Group – MMRM Analysis

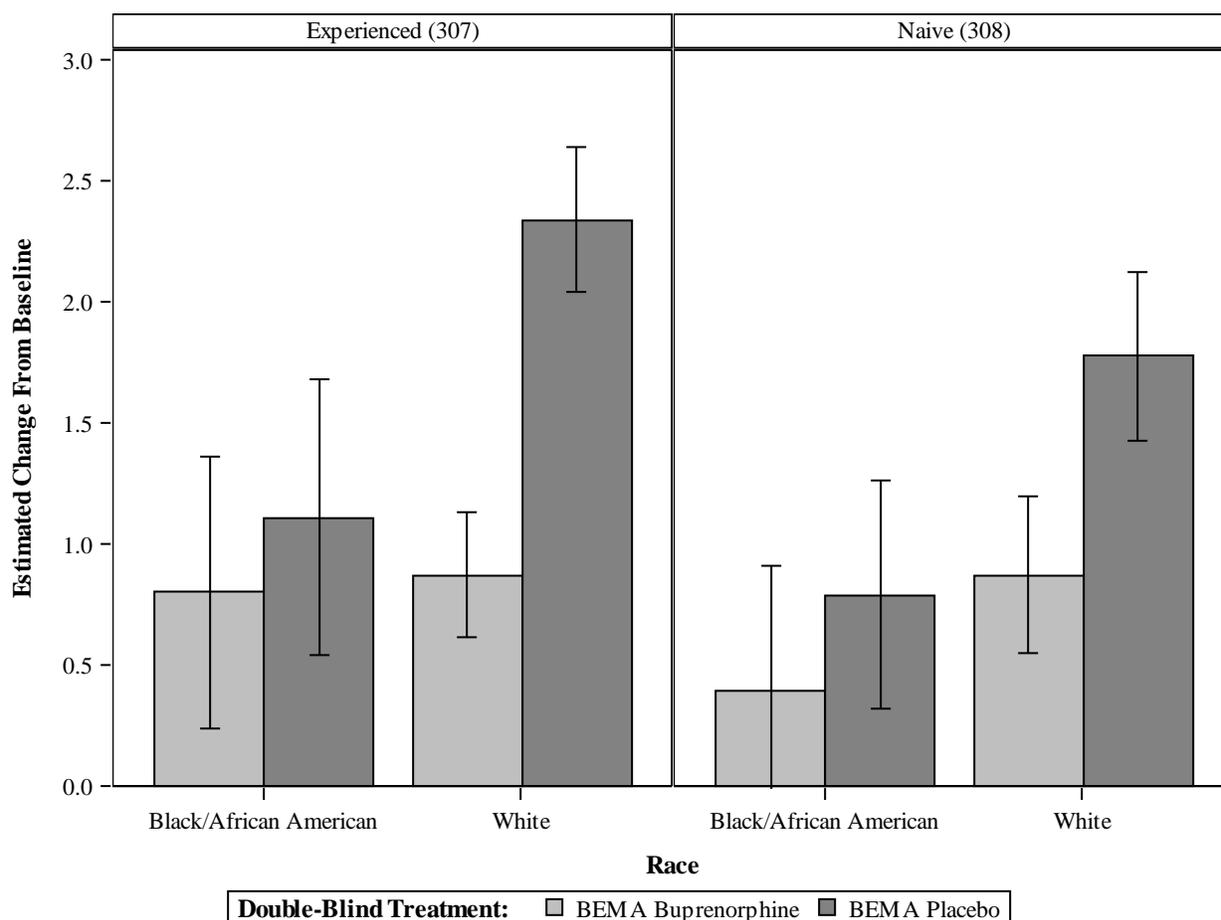


Table A7: Change from Baseline by Study, Race and Treatment Group – MMRM Analysis

Study	Race	Treatment Group	Estimated Change From Baseline	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Experienced (307)	Black/African American	BEMA Buprenorphine	0.80	0.283	0.24	1.36
Experienced (307)	Black/African American	BEMA Placebo	1.11	0.288	0.54	1.68
Experienced (307)	White	BEMA Buprenorphine	0.87	0.131	0.61	1.13
Experienced (307)	White	BEMA Placebo	2.34	0.152	2.04	2.64
Naive (308)	Black/African American	BEMA Buprenorphine	0.39	0.263	-0.13	0.91
Naive (308)	Black/African American	BEMA Placebo	0.79	0.238	0.32	1.26
Naive (308)	White	BEMA Buprenorphine	0.87	0.164	0.55	1.19
Naive (308)	White	BEMA Placebo	1.78	0.177	1.43	2.12

Figure A4: Responder Analysis by Sex and Study

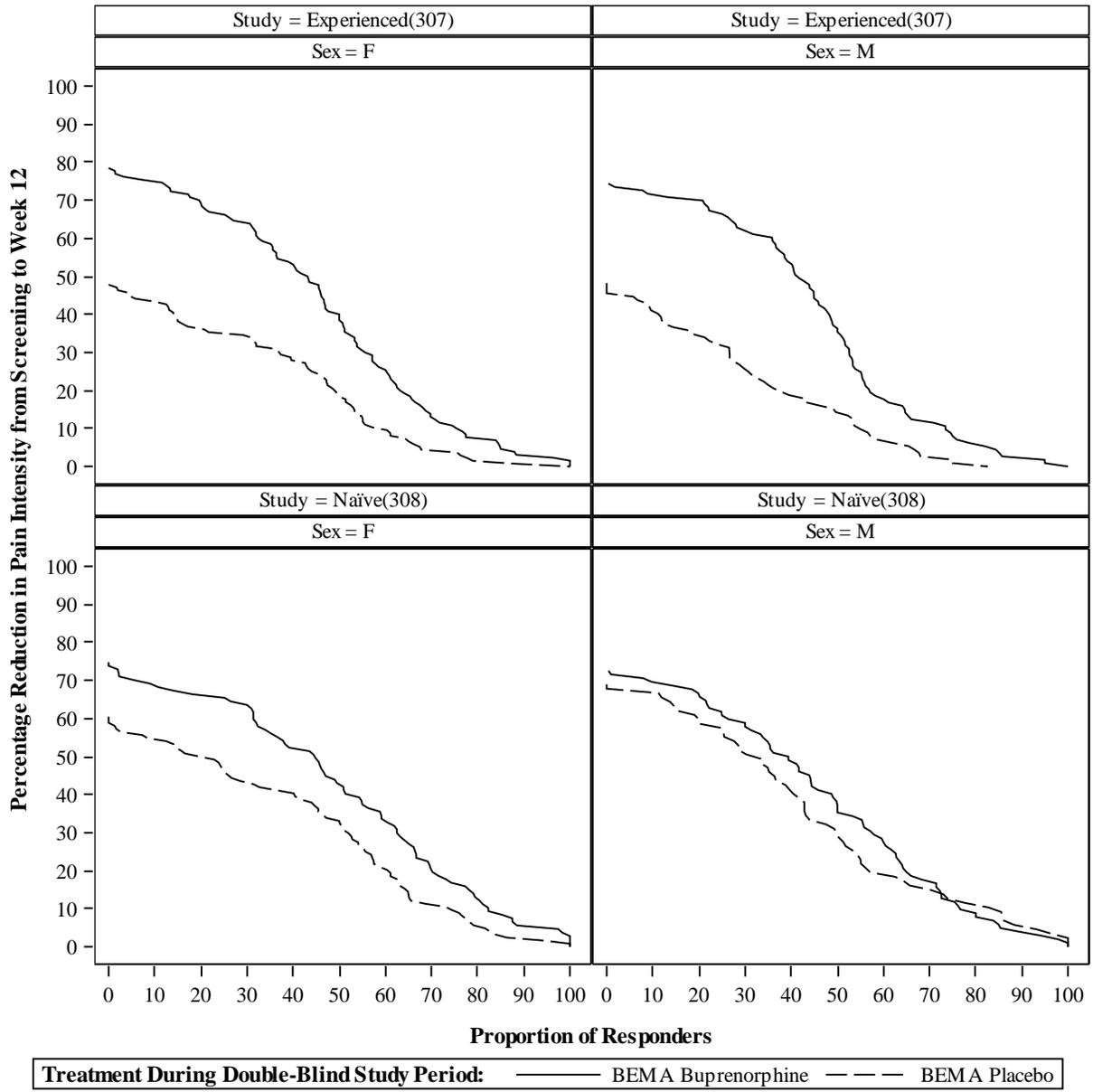


Table A8: Responders by Gender and Study

Responders, n(%)	Study	Gender	BEMA		P-value
			Buprenorphine	Placebo	
>=30% Pain Reduction	Experienced(307)	Female	84 (64.6)	47 (34.6)	<.0001
>=50% Pain Reduction	Experienced(307)	Female	53 (40.8)	26 (19.1)	0.0001
>=30% Pain Reduction	Experienced(307)	Male	71 (62.8)	29 (25.9)	<.0001
>=50% Pain Reduction	Experienced(307)	Male	42 (37.2)	16 (14.3)	<.0001
>=30% Pain Reduction	Naïve(308)	Female	69 (64.5)	54 (43.5)	0.0016
>=50% Pain Reduction	Naïve(308)	Female	46 (43.0)	42 (33.9)	0.1453
>=30% Pain Reduction	Naïve(308)	Male	61 (59.8)	45 (51.7)	0.2065
>=50% Pain Reduction	Naïve(308)	Male	39 (38.2)	27 (31.0)	0.2718

Figure A5: Responder Analysis by Race and Study

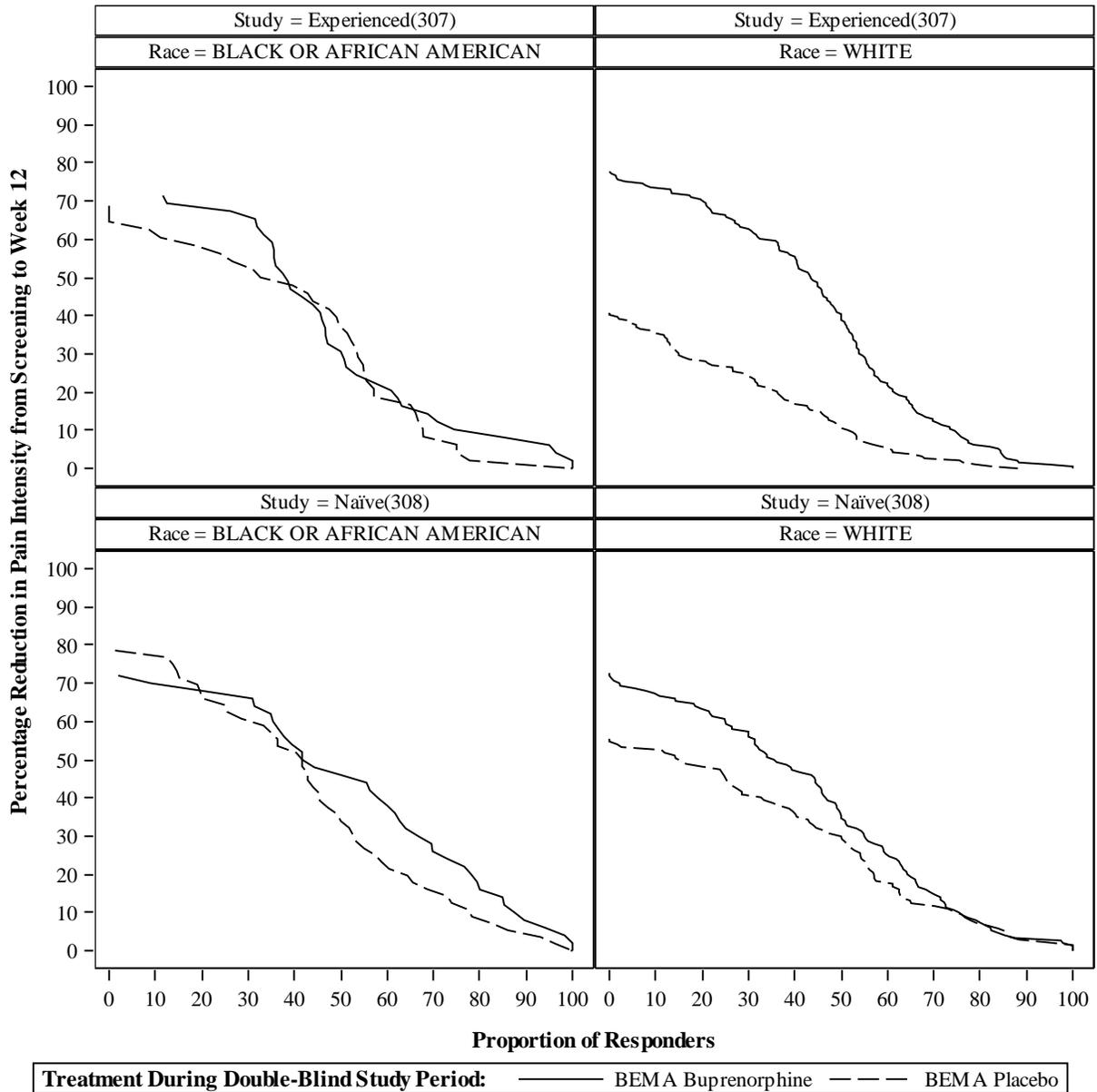


Table A9: Responders by Race and Study

Responders, n(%)	Study	Race	BEMA		P-value
			Buprenorphine	Placebo	
>=30% Pain Reduction	Experienced(307)	White	122 (63.2)	46 (24.3)	<.0001
>=50% Pain Reduction	Experienced(307)	White	79 (40.9)	21 (11.1)	<.0001
>=30% Pain Reduction	Experienced(307)	Black/African American	33 (67.3)	26 (54.2)	0.2046
>=50% Pain Reduction	Experienced(307)	Black/African American	16 (32.7)	18 (37.5)	0.6002
>=30% Pain Reduction	Naïve(308)	White	87 (58.0)	56 (40.9)	0.0041
>=50% Pain Reduction	Naïve(308)	White	54 (36.0)	42 (30.7)	0.3419
>=30% Pain Reduction	Naïve(308)	Black/African American	34 (68.0)	34 (60.7)	0.3707
>=50% Pain Reduction	Naïve(308)	Black/African American	24 (48.0)	20 (35.7)	0.1767

Table A10: Proportion of Subjects with Rescue Medication Usage for Females – Study EN3409-307

Week	Female			
	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	130	117 (90.0%)	135	125 (92.6%)
Week 2	127	113 (89.0%)	111	100 (90.1%)
Week 3	126	111 (88.1%)	103	95 (92.2%)
Week 4	126	107 (84.9%)	97	89 (91.8%)
Week 5	121	103 (85.1%)	87	80 (92.0%)
Week 6	120	106 (88.3%)	86	79 (91.9%)
Week 7	115	94 (81.7%)	82	73 (89.0%)
Week 8	114	98 (86.0%)	81	73 (90.1%)
Week 9	112	96 (85.7%)	77	66 (85.7%)
Week 10	111	93 (83.8%)	76	67 (88.2%)
Week 11	110	95 (86.4%)	76	67 (88.2%)
Week 12	109	93 (85.3%)	75	67 (89.3%)

Table A11: Proportion of Subjects with Rescue Medication Usage for Males – Study EN3409-307

Male				
Week	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	112	98 (87.5%)	111	103 (92.8%)
Week 2	107	89 (83.2%)	93	85 (91.4%)
Week 3	103	86 (83.5%)	86	77 (89.5%)
Week 4	103	84 (81.6%)	82	75 (91.5%)
Week 5	101	83 (82.2%)	75	67 (89.3%)
Week 6	99	79 (79.8%)	75	67 (89.3%)
Week 7	98	84 (85.7%)	72	67 (93.1%)
Week 8	96	79 (82.3%)	71	64 (90.1%)
Week 9	95	77 (81.1%)	69	63 (91.3%)
Week 10	94	79 (84.0%)	69	63 (91.3%)
Week 11	93	77 (82.8%)	68	63 (92.6%)
Week 12	92	73 (79.3%)	66	61 (92.4%)

Table A12: Average Number of Rescue Medication Tablets per Subject Enrolled by Sex – Study EN3409-307

	Female				Male			
	BEMA Buprenorphine		BEMA Placebo		BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets
Week 1	130	11.0	135	13.6	112	10.9	111	13.4
Week 2	127	10.1	111	13.3	107	10.1	93	14.3
Week 3	126	8.4	103	10.4	103	8.3	86	10.9
Week 4	126	7.7	97	9.9	103	7.8	82	10.1
Week 5	121	8.0	87	10.0	101	8.1	75	9.9
Week 6	120	8.0	86	9.7	99	7.5	75	9.0
Week 7	115	7.8	82	9.4	98	8.3	72	9.4
Week 8	114	7.8	81	9.4	96	7.6	71	9.5
Week 9	112	7.8	77	9.3	95	8.0	69	9.5
Week 10	111	7.5	76	9.6	94	8.1	69	9.8
Week 11	110	7.7	76	9.3	93	8.4	68	9.5
Week 12	109	6.6	75	7.9	92	6.8	66	8.5

Table A13: Proportion of Subjects with Rescue Medication Usage for Females – Study EN3409-308

Female				
Week	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	107	64 (59.8%)	124	85 (68.5%)
Week 2	103	58 (56.3%)	115	83 (72.2%)
Week 3	99	41 (41.4%)	109	66 (60.6%)
Week 4	95	43 (45.3%)	104	58 (55.8%)
Week 5	91	38 (41.8%)	100	55 (55.0%)
Week 6	90	38 (42.2%)	96	56 (58.3%)
Week 7	88	37 (42.0%)	93	55 (59.1%)
Week 8	85	33 (38.8%)	92	52 (56.5%)
Week 9	85	38 (44.7%)	91	50 (54.9%)
Week 10	83	29 (34.9%)	88	51 (58.0%)
Week 11	83	34 (41.0%)	88	40 (45.5%)
Week 12	82	31 (37.8%)	85	41 (48.2%)

Table A14: Proportion of Subjects with Rescue Medication Usage for Males – Study EN3409-308

Male				
Week	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	102	59 (57.8%)	86	55 (64.0%)
Week 2	98	54 (55.1%)	81	49 (60.5%)
Week 3	92	44 (47.8%)	77	41 (53.2%)
Week 4	92	38 (41.3%)	75	40 (53.3%)
Week 5	89	38 (42.7%)	72	37 (51.4%)
Week 6	88	36 (40.9%)	70	38 (54.3%)
Week 7	85	36 (42.4%)	70	30 (42.9%)
Week 8	84	31 (36.9%)	69	33 (47.8%)
Week 9	82	29 (35.4%)	67	32 (47.8%)
Week 10	82	31 (37.8%)	67	30 (44.8%)
Week 11	79	28 (35.4%)	66	32 (48.5%)
Week 12	78	25 (32.1%)	66	31 (47.0%)

Table A15: Average Number of Rescue Medication Tablets per Subject Enrolled by Sex – Study EN3409-308

	Female				Male			
	BEMA Buprenorphine		BEMA Placebo		BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets
Week 1	107	3.6	124	5.2	102	3.7	86	4.8
Week 2	103	3.7	115	5.5	98	4.4	81	4.8
Week 3	99	3.2	109	5.0	92	3.5	77	5.0
Week 4	95	3.1	104	4.9	92	3.5	75	4.5
Week 5	91	3.0	100	4.4	89	2.9	72	4.3
Week 6	90	2.7	96	4.7	88	3.3	70	4.7
Week 7	88	3.0	93	4.2	85	3.2	70	4.0
Week 8	85	2.6	92	4.1	84	3.2	69	4.0
Week 9	85	3.3	91	4.4	82	3.1	67	4.0
Week 10	83	2.4	88	4.2	82	3.1	67	3.9
Week 11	83	2.3	88	4.0	79	2.7	66	4.3
Week 12	82	2.1	85	3.5	78	2.5	66	3.8

Table A16: Proportion of Subjects with Rescue Medication Usage by White Patients – Study EN3409-307

White				
Week	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	192	169 (88.0%)	187	176 (94.1%)
Week 2	185	158 (85.4%)	147	134 (91.2%)
Week 3	182	152 (83.5%)	135	124 (91.9%)
Week 4	182	151 (83.0%)	126	116 (92.1%)
Week 5	177	147 (83.1%)	114	105 (92.1%)
Week 6	175	146 (83.4%)	113	103 (91.2%)
Week 7	170	142 (83.5%)	107	98 (91.6%)
Week 8	168	140 (83.3%)	106	98 (92.5%)
Week 9	166	141 (84.9%)	100	88 (88.0%)
Week 10	164	136 (82.9%)	99	90 (90.9%)
Week 11	163	138 (84.7%)	99	90 (90.9%)
Week 12	161	130 (80.7%)	96	89 (92.7%)

Table A17: Proportion of Subjects with Rescue Medication Usage for Black or African American Patients – Study EN3409-307

Black/African American				
Week	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	49	45 (91.8%)	48	42 (87.5%)
Week 2	48	43 (89.6%)	46	41 (89.1%)
Week 3	46	44 (95.7%)	44	39 (88.6%)
Week 4	46	39 (84.8%)	43	39 (90.7%)
Week 5	44	38 (86.4%)	38	33 (86.8%)
Week 6	43	38 (88.4%)	38	34 (89.5%)
Week 7	42	35 (83.3%)	38	34 (89.5%)
Week 8	41	36 (87.8%)	37	31 (83.8%)
Week 9	40	31 (77.5%)	37	33 (89.2%)
Week 10	40	35 (87.5%)	37	32 (86.5%)
Week 11	39	33 (84.6%)	36	32 (88.9%)
Week 12	39	35 (89.7%)	36	31 (86.1%)

Table A18: Average Number of Rescue Medication Tablets per Subject Enrolled by Race – Study EN3409-307

	White				Black/African American			
	BEMA Buprenorphine		BEMA Placebo		BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets
Week 1	192	11.1	187	14.0	49	10.5	48	12.5
Week 2	185	10.4	147	14.5	48	9.0	46	12.4
Week 3	182	8.3	135	11.3	46	8.9	44	9.6
Week 4	182	7.8	126	10.4	46	7.6	43	9.5
Week 5	177	8.1	114	10.2	44	7.7	38	10.0
Week 6	175	7.8	113	9.6	43	7.7	38	9.4
Week 7	170	8.2	107	9.6	42	7.6	38	9.7
Week 8	168	7.9	106	9.6	41	6.8	37	9.7
Week 9	166	8.1	100	9.3	40	7.1	37	10.3
Week 10	164	7.9	99	9.7	40	7.5	37	10.2
Week 11	163	8.1	99	9.4	39	7.7	36	10.4
Week 12	161	6.7	96	8.2	39	6.9	36	8.7

Table A19: Proportion of Subjects with Rescue Medication Usage for White Patients – Study EN3409-308

Week	White			
	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	150	91 (60.7%)	136	99 (72.8%)
Week 2	144	84 (58.3%)	123	88 (71.5%)
Week 3	138	64 (46.4%)	115	67 (58.3%)
Week 4	137	60 (43.8%)	110	60 (54.5%)
Week 5	130	58 (44.6%)	104	53 (51.0%)
Week 6	128	53 (41.4%)	98	55 (56.1%)
Week 7	125	53 (42.4%)	95	50 (52.6%)
Week 8	122	48 (39.3%)	94	50 (53.2%)
Week 9	120	49 (40.8%)	91	47 (51.6%)
Week 10	118	40 (33.9%)	90	45 (50.0%)
Week 11	116	42 (36.2%)	90	40 (44.4%)
Week 12	114	38 (33.3%)	89	39 (43.8%)

Table A20: Proportion of Subjects with Rescue Medication Usage for Black or African American Patients – Study EN3409-308

Week	Black/African American			
	BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication	Number of Subjects in Study	Number(%) of Subjects Using Rescue Medication
Week 1	50	31 (62.0%)	56	37 (66.1%)
Week 2	48	27 (56.3%)	56	36 (64.3%)
Week 3	44	19 (43.2%)	54	33 (61.1%)
Week 4	41	18 (43.9%)	52	31 (59.6%)
Week 5	41	17 (41.5%)	52	33 (63.5%)
Week 6	41	20 (48.8%)	52	33 (63.5%)
Week 7	39	19 (48.7%)	52	29 (55.8%)
Week 8	38	15 (39.5%)	51	29 (56.9%)
Week 9	38	17 (44.7%)	51	28 (54.9%)
Week 10	38	20 (52.6%)	50	31 (62.0%)
Week 11	37	17 (45.9%)	49	26 (53.1%)
Week 12	37	17 (45.9%)	47	28 (59.6%)

Table A21: Average Number of Rescue Medication Tablets per Subject Enrolled by Race – Study EN3409-308

	White				Black/African American			
	BEMA Buprenorphine		BEMA Placebo		BEMA Buprenorphine		BEMA Placebo	
	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets	Number of Subjects in Study	Number of Rescue Tablets
Week 1	150	3.8	136	5.7	50	3.8	56	4.8
Week 2	144	4.6	123	5.6	48	3.3	56	5.3
Week 3	138	3.7	115	5.1	44	2.9	54	5.4
Week 4	137	3.4	110	4.7	41	3.7	52	5.3
Week 5	130	3.2	104	4.3	41	2.8	52	4.8
Week 6	128	3.2	98	4.6	41	3.0	52	5.4
Week 7	125	3.3	95	4.2	39	3.1	52	4.3
Week 8	122	3.1	94	4.0	38	2.9	51	4.3
Week 9	120	3.4	91	4.1	38	3.4	51	4.5
Week 10	118	2.8	90	3.8	38	3.2	50	4.7
Week 11	116	2.5	90	4.2	37	2.9	49	4.2
Week 12	114	2.3	89	3.6	37	2.9	47	3.8

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/s/

JAMES E TRAVIS
10/07/2015

FREDA COONER
10/07/2015
I concur