3.1.2 PATIENT CHARACTERISTICS AND DISPOSITIONS

Patient Disposition

A total of 152 subjects were screened and enrolled for participation in the study at 30 sites. Of the 152 enrolled subjects, 151 entered the titration period and received study drug and comprise the evaluable safety population. One subject withdrew consent before taking any titration study drug. A total of 69 subjects (45.4%) discontinued during the titration period (Table 1). All 82 subjects who completed the titration period entered the double-blind period and were assigned to a randomized treatment order (BEMA™ Fentanyl or placebo).

Table 1: Subject Disposition

	BEMA™ Fentanyl[a] (n = 152)
	Number of subjects (%)
TITRATION PERIOD	
Enrolled	152 (100)
Entering the titration period (in safety population[b])	151 (99.3)
Dosing of study drug was recorded	141 (92.8)
Discontinued during the titration period	69 (45.4)
Reason for discontinuation	
Subject consent withdrawn	22 (14.5)
Other[c]	11 (7.2)
Adverse event	10 (6.6)
Noncompliance with electronic diary	8 (5.3)
Lack of efficacy	5 (3.3)
Not regularly treating one episode of pain per day	5 (3.3)
Noncompliance with study drug administration	3 (2.0)
Death	3 (2.0)
Protocol deviation	2 (1.3)
DOUBLE-BLIND PERIOD	
Entering the double-blind period (randomized)	82 (53.9)
Taking double-blind study drug	81 (53.3)
Discontinued during the double-blind period	12 (7.9)
Completed the study	70 (46.1)
Reason for discontinuation	
Subject consent withdrawn	4 (4.9)
Adverse event	3 (3.7)
Not regularly treating one episode of pain per day	2 (2.4)
Noncompliance with electronic diary	2 (2.4)
Lack of efficacy	1 (1.2)

[a] BEMA™ Fentanyl includes all dose levels: 200, 400, 600, 800, 1200 µg.
[b] All subjects who received at least one dose of drug.
[c] See Data Listing 16.2.1 for a listing of "other" reasons.
Source: Table 14.1.1

Source: Clinical Study Report page 49

Of the 82 randomly assigned subjects, 81 received double-blind study drug according to the randomization scheme. Appendix 2 summarized the original randomization sequence and the actual sequence received. Eleven of the 81 treated subjects discontinued from the study. Three of these subjects discontinued due to AE. Meanwhile, there were 10 subjects who either skipped or switched treatments. Five subjects were listed as having drugs taken out of sequence by the Applicant (Appendix 3). However, I found five more subjects which were neither reported to be discontinued

nor were classified as having drugs taken out of sequence. These five subjects did not complete the 9-episode scheme.

According to the Applicant, 80 subjects provided pain assessment within the 30-minute post-dose interval in the double-blind period (ITT population). However, re-analyses of the data showed that there were 2 subjects (18/1003 and 35/1002) who did not have post-baseline pain data such that SPID30 were missing for both subjects. Both these subjects were classified as having completed the 9-episode treatment. In my analyses, I also found that there were a total of 652 recorded episodes (fentanyl 437, placebo 215), but only 591 episodes have pain scores. Sixty one episodes (in 22 subjects, including those two subjects with no SPID30 pain scores) have missing pain scores. Except for those two subjects, all subjects had pain score(s) in at least one active and at least one placebo treatment.

Of the 80 subjects in the ITT population, eight were excluded from the PP population for two reasons: study drug taken out of sequence (5 subjects or 3%), and same dose of study drug being reported more than once (3 subjects or 2%), see Appendix 3.

Patient characteristics

A summary of subject demographics for the safety and ITT populations is presented in *Appendix 4*.

> Of the 151 subjects in the safety population, 85 (56%) were women. Subject age ranged from 31 to 87 years with a median age of 55 years. The majority of subjects were younger than 65 years old (69%) and were white (88%).

Baseline characteristics for cancer diagnoses and target pain are summarized in Appendix 5 and Appendix 6, respectively.

> Breast cancer, lung cancer, colorectal cancer, and gastroesophageal cancer were the most common cancer types in the safety population. A large percentage of subjects had individual **cancers grouped under the category of "Other" including cervical cancer, myeloma, liver** cancer, melanoma, and bladder cancer.
>
> Overall, subjects had suffered from the current primary cancer a mean period of 3 years. More than half of the subjects (56%) had received chemotherapy and a quarter had received radiation therapy in the last six months before study entry.
>
> For approximately half of the subjects in the safety population, the pain pathophysiology for both persistent pain and target breakthrough pain was somatic and/or visceral. For most subjects in the safety population, the pain syndrome for persistent and target breakthrough pain was typically related to direct tumor involvement (85% and 86% subjects, respectively) or because of somatic/visceral lesions (83% and 85% subjects, respectively).
>
> The most common stable opioid regimen was transdermal fentanyl for persistent pain taken by 46% of subjects and hydrocodone for target breakthrough pain taken by 42% of subjects. For nearly all subjects (99%) in the safety population, there were minimal opioid side effects from the current daily opioid dose.
>
> There were no important difference in demographics and other baseline characteristics between the safety and the ITT populations.

Exposure to Study Medication

The number of doses taken and the duration of exposure to study drug during the titration period, the double-blind treatment period, and the entire study for the safety population are summarized in Appendix 7 and Appendix 8.

> **Subjects took a mean of 12.4 doses of BEMA™** Fentanyl over the entire study period with a mean of 9.3 doses during the titration period and a mean of 5.5 during the double-blind period. The mean number of placebo doses taken during the study was 2.8. The mean **duration of exposure to the study drug (BEMA™** Fentanyl and placebo) was 6.6 days in the titration period, 5.9 days in the double-blind period, and 10.1 days in the entire study period. The minimum period of exposure was one day and the maximum was 27 days.

Furthermore, according to the Applicant,

> Of the 141 subjects who were treated and had records of study drug dosing in the titration period, 137 started dosing at the 200-µg level. One subject (023/1007) started at the 600-µg level and 3 subjects did not enter 200-µg dosing data because of log pad issues.
>
> The number of subjects who titrated to the 400-, 600-, 800, and 1200-µg level were 120, 97, 63, and 38 subjects, respectively. Of the 81 subjects taking double-blind study drug, 4, 15, 23, 19, and 20 subjects took 200 µg, 400 µg, 600 µg, 800 µg, or 1200 µg of study drug, respectively.

3.1.3 SUMMARY OF RESULTS FROM STUDY FEN-201

The result of the primary analysis is summarized in Table 2.

The SPID30 for BEMA Fentanyl-treated episodes was statistically significantly greater (p=0.004) than placebo-treated episodes. The difference in SPID30 between BEMA Fentanyl and placebo was 9.7 (95% CI: 3.3, 16.2).

Table 2: Sum of Pain Intensity Difference at 30 Minutes: ITT Population

SPID 30[a]	Placebo (n = 77)	BEMA™ Fentanyl[b] (n = 79)
Number of episodes	197	394
Mean (SEM)	39.0 (2.95)	49.1 (2.40)
SD	41.38	47.55
Median	25.0	37.5
Minimum, Maximum	-30, 170	-75, 240
LS Mean[c] (SEM)	38.1 (4.3)	47.9 (3.87)
Difference (95% Confidence interval)[d]	9.74 (3.31, 16.18)	
P value[e]	0.004	

[a] SPID was calculated as a weighted sum of the pain intensity difference of all time points at or before the time point of interest. LOCF was used to impute missing data or data after rescue medication usage.
[b] BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.
[c] LS means are from a mixed model. LS means are estimates of means that would be expected for a balanced design.
[d] 95% Confidence interval for difference between BEMA™ Fentanyl and placebo based on LS means.
[e] P value for testing null hypothesis of no difference between BEMA™ Fentanyl and placebo based on a mixed model of repeated measures including main effects for treatment, (pooled) site, and treatment-by-site interaction and subject as a random effect.
Source: Table 14.4.1.1

Source: Clinical Study Report, page 60

Consistent with the ITT population, there was also a difference in SPID30 between BEMA Fentanyl and placebo when PP population is used. The difference in SPIDs 30 between BEMA Fentanyl and placebo was 12.1 (95% CI: 5.0, 19.2).

Table 3: Sum of Pain Intensity Difference at 30 Minutes: PP Population

SPID over 30 min[2]	Placebo (N=69)	BEMA Fentanyl[1] (N=71)
n (Number of Episodes)	177	353
Mean (SEM)	41.3 (3.10)	52.0 (2.48)
SD	41.28	46.63
Median	30.0	40.0
Min, Max	-30, 170	-75, 240
LS Mean[3] (SEM)	40.5 (4.54)	52.6 (4.03)
Difference between BEMA Fentanyl and Placebo		12.12
95% Confidence Interval[4]		(5.02, 19.22)
P-value for Treatment Effect[5]		0.001
P-value for Site Effect[5]		0.296
P-value for Treatment by Site Interaction[5]		0.156

[1] BEMA Fentanyl includes all dose levels: 200, 400, 600, 800, 1200 mcg.
[2] SPID is calculated as a weighted sum of the pain intensity differences (PID) of all time points at or prior to the time point of interest. Last observation carried forward (LOCF) is used to impute missing data or data after rescue medication usage.
[3] Least-squares means are LS Means from a mixed model. LS Means are estimates of means that would be expected for a balanced design.
[4] 95% Confidence Interval for difference between BEMA Fentanyl and placebo based on LS Means.
[5] P-value for testing H0: No difference between BEMA Fentanyl and placebo based on a mixed model of repeated measures including main effects for treatment, (pooled) site, and treatment by site interaction and subject as a random effect.
Source Data: Listing 16.2.6

Source: Clinical Study Report, page 210

The Applicant also conducted additional sensitivity analyses to assess the robustness of the primary efficacy analyses. These include the inclusion of 'sequence' as a random effect in the mixed model, as well as re-analysis of the SPID30 that ignored the pain assessments at 5 and 10 minutes (alternative calculation). There was no statistically significance sequence effect, and that the alternative calculation of SPID30 did not alter the result/conclusion on the primary analysis.

The following are exploratory analyses I conducted to assess the robustness of the primary efficacy result.

In the crossover trial, each study participant provided multiple assessments of pain, and the assessments are correlated. Statistically, the correlation results in a need to specify a covariance structure. The Applicant did not specify the type of covariance structure used in the mixed model (or random effects model). After further exploration and re-analyses of the data, it is apparent that they used 'compound symmetry' as the covariance structure in the mixed model. This structure implies that the correlation between measurements is approximately equal. In general, the structure is acceptable for this type of study design (i.e. cross-over). Nonetheless, I re-analyzed the data by assigning the less restrictive 'unstructured' covariance matrix to the mixed model. The result (Table 4) was no different from the result using 'compound symmetry' (Table 2).

In the Applicant's analysis of the primary endpoint (SPID30), any subjects who had no post-baseline scores (i.e. no SPID30 score) in an episode were not included in the analysis. I re-analyzed the data by assigning these subjects with zero change from baseline (i.e. PID=0). Using the same mixed model with compound symmetry, the SPID30 for BEMA Fentanyl-treated episodes was still superior to placebo-treated episodes (Table 4).

As mentioned in the Patient Disposition section (Section 3.1.2), there were 11 subjects who discontinued from the study and 10 subjects who appeared to have switched or skipped treatment assignments. The SPID30 data for these 21 subjects were recorded based on the available pain intensity data. Therefore, subjects who dropped out of the study after an episode (e.g. episode 2) would have missing data on the episode(s) following discontinuation while retaining their pain scores on the episodes before they dropped out of the study. In this type of design, this is generally acceptable, because we do not run the risk of giving a good score to subjects who dropped out of the study (like adverse events), since these episodes are independent of each other. Besides, there were only three subjects who dropped out due to AE. For those subjects who switched or skipped treatments, re-analysis of the data excluding these subjects did not alter the conclusion. There is still evidence that SPID30 for BEMA Fentanyl-treated episodes was superior to placebo-treated episodes (Table 4).

Table 4: Sum of Pain Intensity Difference at 30 Minutes (Reviewer's): ITT Population

SPID30	Placebo	BEMA Fentanyl	Difference (95% CI)	p-value
Using Unstructured Covariance				
N	77	79		
# of episodes	197	394		
Mean (SD)	39.0 (41.4)	49.1 (47.5)		
Range	-30, 170	-75, 240	8.4	
LS Mean (SE)	38.1 (4.0)	46.6.0 (3.6)	(2.8, 14.1)	0.004
PID=0 for missing data				
N	78	80		
# of episodes	215	437		
Mean (SD)	35.7 (41.1)	44.3 (47.5)		
Range	-30, 170	-75, 240	9.1	
LS Mean (SE)*	34.9 (4.2)	44.0 (3.8)	(3.1, 15.1)	0.004
Exclude subjects who Skipped/Switched Treatments				
N	67	69		
# of episodes	176	351		
Mean (SD)	38.2 (39.4)	49.5 (45.3)		
Range	-30, 165	-75, 205	11.8	
LS Mean (SE)*	36.4 (4.4)	48.3 (4.0)	(5.0, 18.7)	0.001

* Compound Symmetry covariance structure

The Applicant also explored SPID at different time points (i.e. 5-, 10-, 15-, 45- and 60-minute post-dose intervals) for the ITT population. The result from my re-analysis of the data is summarized in Table 5. Note that the number of episodes increases over time because of the missing data imputation (LOCF) within episode. For example: at 5 minutes, only 537 out of 652 episodes have pain scores reported; meanwhile at 10 minutes, there were 524 episodes with reported pain scores, but because of missing data imputation (i.e. LOCF), 563 episodes had recorded pain scores, and so on.

Based on the multiplicity adjustment rule provided by the Applicant (i.e. a closed, sequential approach, stepping backwards through the time points to control the overall type I error rate), only the next shortest interval will be tested moving progressively from 30 to 15 to 10 to 5 minutes. Results after 30 minutes will be considered exploratory. SPID values for BEMA Fentanyl were greater than placebo for all post-dose time points. The between-treatment differences also reached statistical significance by 15 minutes (p=0.047).

Table 5: Sum of Pain Intensity Difference by Time Point: ITT Population

	Placebo	BEMA Fentanyl	Difference (95% CI)	p-value
		5 minutes		
# of episodes	176	361		
Mean (SD)	1.5 (3.8)	1.6 (3.9)		
Range	-10, 50	-15, 80	0.3	
LS Mean (SE)*	1.5 (0.4)	1.8 (0.3)	(-0.4, 0.9)	0.440
		10 minutes		
# of episodes	184	379		
Mean (SD)	5.0 (8.5)	5.7 (9.6)		
Range	-10, 50	-15, 80	0.9	
LS Mean (SE)*	4.9 (0.9)	5.9 (0.8)	(-0.4, 2.3)	0.179
		15 minutes†		
# of episodes	194	382		
Mean (SD)	10.6 (14.7)	12.7 (17.3)		
Range	-15, 75	-30, 120	2.3	
LS Mean (SE)*	10.4 (1.6)	12.7 (17.3)	(0.04, 4.6)	0.047
		45 minutes†		
# of episodes	198	404		
Mean (SD)	73.4 (73.4)	92.9 (82.3)		
Range	-60, 305	-150, 360	19.7	
LS Mean (SE)*	70.8 (7.4)	90.5 (6.6)	(8.5, 30.9)	<0.001
		60 minutes†		
# of episodes	198	408		
Mean (SD)	110.1 (108.3)	141.4 (118.4)		
Range	-90, 440	-225, 480	32.0	
LS Mean (SE)*	106.0 (10.6)	138.0 (9.4)	(15.8, 48.1)	<0.001

* Compound Symmetry covariance structure
†Source: Clinical Study Report, page 62

The Applicant also conducted several secondary endpoint analyses including the pain intensity differences by time point and treatment, pain relief by timepoint and by treatment, and overall satisfaction with the study drug. One-sample Wilcoxon signed rank test was used by the Applicant to compare the within subject mean for episodes treated with BEMA Fentanyl to the within subject mean for episodes treated with placebo. Because these are secondary endpoints and no multiplicity adjustments were provided, only descriptive statistics are reported in this review. The results summarized in Table 6 and Table 7 suggest that mean PID values (using LOCF for missing data) as well as mean pain relief values (using LOCF for missing data) for BEMA Fentanyl were slightly greater than placebo at 10 minutes after dosing and all time points thereafter.

Table 6: Pain Intensity Difference by Time Point: ITT Population

	Placebo	BEMA Fentanyl	Mean Difference (SD) †
	At Baseline		
# of episodes	212	431	
Mean (SD)	6.9 (0.1)	6.9 (0.1)	
	5 minutes		
# of episodes	176	361	N=71 pairs
Mean (SD)	0.3 (0.1)	0.3 (0.0)	0.0 (0.6)
	10 minutes		
# of episodes	184	379	N=73 pairs
Mean (SD)	0.7 (.01)	0.8 (0.1)	0.1 (0.7)
	15 minutes		
# of episodes	194	382	N=74 pairs
Mean (SD)	1.2 (0.1)	1.4 (0.1)	0.1 (1.0)
	30 minutes		
# of episodes	197	394	N=75 pairs
Mean (SD)	1.9 (0.1)	2.5 (0.1)	0.5 (1.5)
	45 minutes		
# of episodes	198	404	N=75 pairs
Mean (SD)	2.3 (0.2)	3.0 (0.1)	0.6 (1.8)
	60 minutes		
# of episodes	198	408	N=75 pairs
Mean (SD)	2.4 (0.2)	3.3 (0.1)	0.8 (2.0)

Source: Clinical Study Report, page 63
†Reviewer's using paired difference

Table 7: Pain Relief by Time Point: ITT Population

	Placebo	BEMA Fentanyl	Mean Difference (SD) †
	5 minutes		
# of episodes	176	361	N=71 pairs
Mean (SD)	0.4 (0.1)	0.4 (0.0)	0.0 (0.5)
	10 minutes		
# of episodes	184	379	N=73 pairs
Mean (SD)	0.7 (.01)	0.8 (0.1)	0.1 (0.5)
	15 minutes		
# of episodes	194	382	N=74 pairs
Mean (SD)	1.0 (0.1)	1.1 (0.1)	0.1 (0.6)
	30 minutes		
# of episodes	197	394	N=75 pairs
Mean (SD)	1.3 (0.1)	1.7 (0.1)	0.3 (0.7)
	45 minutes		
# of episodes	198	404	N=75 pairs
Mean (SD)	1.5 (0.1)	1.9 (0.1)	0.3 (1.0)
	60 minutes		
# of episodes	198	409	N=75 pairs
Mean (SD)	1.6 (0.1)	2.1 (0.1)	0.5 (1.0)

Source: Clinical Study Report, page 66
†Reviewer's using Paired Difference

Total pain relief was calculated as the weighted sum of the pain relief of all time points at or before the time point of interest. Table 8 summarizes the total pain relief over protocol specified post-dose time points using LOCF for the ITT population by treatment. Total pain relief scores for BEMA Fentanyl were higher than placebo at all timepoints, particularly after 30 minutes of dosing.

Table 8: Total Pain Relief by Time Point: ITT Population

	Placebo	BEMA Fentanyl	Mean Difference (SD) †
	5 minutes		
# of episodes	176	361	N=71 pairs
Mean (SD)	1.8 (0.3)	2.2 (0.2)	0.0 (2.6)
	10 minutes		
# of episodes	184	379	N=73 pairs
Mean (SD)	5.2 (0.5)	6.1 (0.4)	0.3 (4.0)
	15 minutes		
# of episodes	194	382	N=74 pairs
Mean (SD)	9.8 (0.8)	11.6 (0.6)	1.2 (6.5)
	30 minutes		
# of episodes	197	394	N=75 pairs
Mean (SD)	29.5 (1.8)	36.1 (1.3)	5.7 (16.6)
	45 minutes		
# of episodes	198	404	N=75 pairs
Mean (SD)	52.3 (2.9)	64.2 (2.1)	9.7 (29.4)
	60 minutes		
# of episodes	198	409	N=75 pairs
Mean (SD)	76.0 (4.2)	94.8 (2.8)	16.2 (43.9)

Source: Clinical Study Report, page 69
†Reviewer's using Paired Difference

Subjects evaluated their overall satisfaction of the study medication performance (global performance evaluation) at the time rescue medication was consumed or at the 60-minute time point using a 5-point categorical scale (0=poor to 4=excellent). The mean score for overall satisfaction with the study drug was higher for BEMA Fentanyl than for placebo (Table 9). Overall, subjects rated 67% of the 359 episodes of breakthrough pain treated with BEMA Fentanyl as good, very good, or excellent compared with only 47% of 174 breakthrough pain episodes treated with placebo.

Table 9: Subject Overall Satisfaction with the Study Drug: ITT Population

	Placebo	BEMA Fentanyl	Mean Difference (SD) †
	Mean Evaluation Score		
# of episodes	174	359	N=72 pairs
Mean (SD)	1.5 (0.1)	2.0 (0.1)	0.5 (1.0)
	Number of Episodes		
Evaluation			
Poor	50 (29%)	52 (15%)	
Fair	42 (24%)	66 (18%)	
Good	40 (23%)	103 (29%)	
Very Good	29 (17%)	96 (27%)	
Excellent	13 (8%)	42 (12%)	

Source: Clinical Study Report, page 70
†Reviewer's using Paired Difference

The Applicant conducted several secondary analyses including four types of responder analyses, cumulative proportion of responders (i.e. continuous responder analyses), as well as rescue medication usage. The results suggest numerical improvements in pain intensity scores and pain relief scores as well as pain-free episodes at protocol-specified post-dose time points for the ITT population by treatment while these improvements are in favor of episodes treated with BEMA Fentanyl.

The percentage of episodes when rescue medication was used for the ITT population was also explored. Rescue medication was used in 30% of the breakthrough pain episodes treated with BEMA Fentanyl compared with 45% of the episodes treated with placebo.

In the June 28, 2007 pre-NDA meeting, the Division requested that a cumulative responder analysis be performed to evaluate the number of subjects achieving a reduction in pain across multiple cutoffs. All subjects who drop out of the study should be considered non-responders. The Applicant conducted the said analysis using the same approach presented in a recent publication by Farrar et al[1]. A plot of the cumulative proportion of responders as a function of the percent pain intensity difference by treatment, as well a summary of the number needed to treat across the range of possible percent pain intensity differences were provided.

Although it is informative to plot continuous responder curves by treatment, caution should be exercised when interpreting the two curves. It is informative to look at the curves individually and to assess the proportion of response across different cutoffs individually. However, unlike parallel group study design, the proportion of response may be correlated between the two treatments such that comparison between the two curves may not be meaningful or informative.

[1] Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. J Pain Symptom Manage. 2006;31:369-77.