Table 49

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: FEN-201 Study Report, p.59

The Applicant also provided an analysis of the SPID 30 for the PP population. Consistent with the ITT population, the LS mean (SE) SPID 30 was statistically significantly greater for the BEMA Fentanyl than for placebo: 52.6 (4.03) versus 40.5 (4.54) (p=0.001).

Treatment-by-pooled site interaction (assessed using a type I error of 0.10) was also presented in. Neither site (p= 0.296) nor treatment-by-site interaction (p=0.156) was found to be statistically significant.

A summary of the analysis for the SPID 30 for the ITT population that ignored the pain assessments at 5 and 10 minutes (alternative calculation) showed that **the SPID 30 for BEMA™** Fentanyl-treated episodes was statistically significantly greater (p=0.005) than the LS mean SPID for placebo-treated episodes. The SPID 30 (LS mean ± SE) was **3.7 ± 0.30 for BEMA™** Fentanyl and 3.0 ± 0.34 for placebo.

A summary of the analysis for the SPID 30 using the mixed model as described for the primary **efficacy endpoint with an additional term "sequence" as a random effect, where sequence was a** categorical variable indicating which of the 15 randomization sequences was used for the subject (Section 9.7.1.11.2) for the ITT population showed there was no statistically significant sequence effect (p=0.264).

Secondary Efficacy Analysis
The following tables (50-53) summarize the descriptive statistics and p-values for the following secondary endpoints:

- Table 50: Mean SPID by time point
- Table 51: Mean PID by time point
- Table 52: Mean pain relief by time point
- Table 53: Mean total pain relief by time point

Table 50: Summary of Statistics for Mean SPID by Time Point (ITT population)

Secondary Endpoint	BEMA* (sem)	Placebo (sem)	p-value
SPID 5	5.7 (0.49)	5.0 (0.63)	0.179
SPID 10	0.8 (0.07)	0.7 (0.08)	0.458
SPID 15	12.7 (0.88)	10.6 (1.06)	**0.047**
SPID 45	92.9 (4.10)	73.4 (5.22)	**<0.001**
SPID 60	141.4 (5.86)	110.1 (7.70)	**<0.001**

*BEMA Fentanyl included at all dose levels

Table 51: Summary of Statistics for Mean PID[1] by Time Point (ITT population)

Secondary Endpoint	BEMA[2] (sem)	Placebo (sem)	p-value
Baseline Pain Intensity	6.9 (0.13)	6.9 (0.09)	-
PID 5	0.3 (0.04)	0.3 (0.06)	0.157
PID 10	0.8 (0.07)	0.7 (0.08)	0.458
PID 15	1.4 (0.09)	1.2 (0.10)	0.223
PID 30	2.5 (0.11)	1.9 (0.14)	**0.015**
PID 45	3.0 (0.13)	2.3 (0.17)	**0.001**
PID 60	3.3 (0.13)	2.4 (0.18)	**<0.001**

[1]Pain intensity difference was calculated as the baseline pain score minus the pain score at the specified time point. LOCF was used to impute missing data or data after rescue medication usage.
[2]BEMA Fentanyl included at all dose levels

Table 52: Summary of Statistics for Mean Pain Relief[1] by Time Point (ITT population)

Secondary Endpoint	BEMA[2] (sem)	Placebo (sem)	p-value
PR 5	0.4 (0.04)	0.4 (0.06)	0.193
PR 10	0.8 (0.05)	0.7 (0.06)	0.113
PR 15	1.1 (0.05)	1.0 (0.07)	0.192
PR 30	1.7 (0.05)	1.3 (0.08)	**0.002**
PR 45	1.9 (0.06)	1.5 (0.09)	**0.002**
PR 60	2.1 (0.06)	1.6 (0.09)	**<0.001**

[1] Pain Relief was measured using a 5-point categorical scale (0=no relief to 4=complete relief). LOCF was used to impute missing data or data after rescue medication usage.
[2]BEMA Fentanyl included at all dose levels

Table 53: Summary of Statistics for Mean Total Pain Relief[1] by Time Point (ITT population)

Secondary Endpoint	BEMA[2] (sem)	Placebo (sem)	p-value
TOTPAR 5	2.2 (0.21)	1.8 (0.28)	0.157
TOTPAR 10	6.1 (0.40)	5.2 (0.54)	0.278
TOTPAR 15	11.6 (0.62)	9.8 (0.82)	0.062
TOTPAR 30	36.1 (1.3)	29.5 (1.79)	**0.002**

TOTPAR 45	64.2 (2.05)	52.3 (2.93	**0.005**
TOTPAR 60	94.8 (2.84)	76.0 (4.16)	**0.001**

[1] 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. LOCF was used to impute missing data or data after rescue medication usage.
[2]BEMA Fentanyl included at all dose levels

Analyses of all of the above secondary endpoints support the primary efficacy finding for BEMA fentanyl. The mean SPID by time point showed positive results at 15, 45 and 60 minutes. The mean PID, PR, and TOTPAR all showed significant differences between placebo and study drug at 30, 45, and 60 minutes.

Overall satisfaction

Subjects evaluated their overall satisfaction with study drug 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 statistically **significantly higher for BEMA™ Fentanyl** than for placebo ($p<0.001$).

Overall, subjects rated 67.1% of the 359 episodes **of breakthrough pain treated with BEMA™** Fentanyl as good, very good, or excellent compared with 47.2% of 174 breakthrough pain episodes treated with placebo.

Responder analyses

Four types of responder analyses were performed:

- Percentage of episodes in which the pain intensity score was zero (pain-free episodes).
- Percentage of episodes in which the pain intensity score decreased by at least 50% from baseline
- Percentage of episodes in which the pain intensity score decreased by at least 33% from baseline
- Percentage of episodes in which pain relief was graded as complete (complete pain relief episodes).

The tables below illustrate the results of these analyses.

Table 54: Mean Percentage of Pain-Free Episodes: ITT population

Time post dose (min)	**BEMA[1] (sem)**	**Placebo (sem)**	**p-value**
5	1.0 (0.73)	1.4 (1.37)	1.0
10	1.0 (0.72)	1.4 (1.35)	1.0
15	2.3 (1.02)	2.0 (1.48)	0.563
30	5.3 (1.57)	4.4 (1.88)	0.498
45	10.5 (2.34)	6.4 (2.27)	0.077
60	14.2 (2.62)	9.6 (2.9)	**0.031**

[1]BEMA Fentanyl included all dose levels: 200, 400, 600, 800, 1200 pg.

Numerical improvements in the mean percentage of pain-free episodes were noted at 15 minutes after dosing and increased at each time point through 60 minutes, at which time they were statistically significantly **higher for BEMA™ Fentanyl** than for placebo.

Tables 55 and 56 summarize the percentage of episodes with meaningful (≥50% and ≥33%) decreases in pain scores at protocol-specified post dose time points for the ITT population by treatment. The mean percentage of episodes with at least a 50% reduction in pain scores was statistically significantly higher **for BEMA™ Fentanyl than for placebo at 30, 45, and 60 minutes** after dosing (p=0.002, p=0.008, and p=0.005, respectively). The mean percentage of episodes with at least a 33% reduction in pain scores was statistically **significantly higher for BEMA™** Fentanyl than for placebo at 30, 45, and 60 minutes after dosing (p=0.009, p=0.004, and p<0.001, respectively).

Table 55: Mean Percentage of Episodes with ≥50% Decreases in Pain Scores

Time (min)	**BEMA[1] (sem)**	**Placebo (sem)**	**p-value**
15	14.9 (2.81)	14.7 (3.35)	0.963
30	32.8 (3.78)	24.1 (3.87)	**0.002**
45	41.1 (4.11)	30.5 (4.10)	**0.008**
60	46.3 (4/17)	34.0 (4.30)	**0.005**

[1]BEMA Fentanyl included all dose levels: 200, 400, 600, 800, 1200 pg.

Table 56: Mean Percentage of Episodes with ≥ 33% Reduction in Pain Scores

Time (min)	**BEMA[1] (sem)**	**Placebo (sem)**	**p-value**
15	26.4 (3.55)	21.3 (3.66)	0.100
30	47.3 (4.05)	38.2 (4.45)	**0.009**
45	57.5 (3.93)	46.5 (4.50)	**0.004**
60	64.3 (3.72)	48.2 (4/51)	**<0.001**

[1]BEMA Fentanyl included all dose levels: 200, 400, 600, 800, 1200 pg.

The percentage of complete pain relief episodes per subject at protocol-specified post dose time points for the ITT population by treatment was also assessed by the Applicant. The mean percentage of complete pain relief episodes **was statistically significantly higher for BEMA™** Fentanyl than for placebo at 30 minutes (p=0.032) and 60 minutes after dosing (p=0.007). There were no statistically significant differences in the mean percentage of complete pain relief episodes at other time points.up yore hr\e
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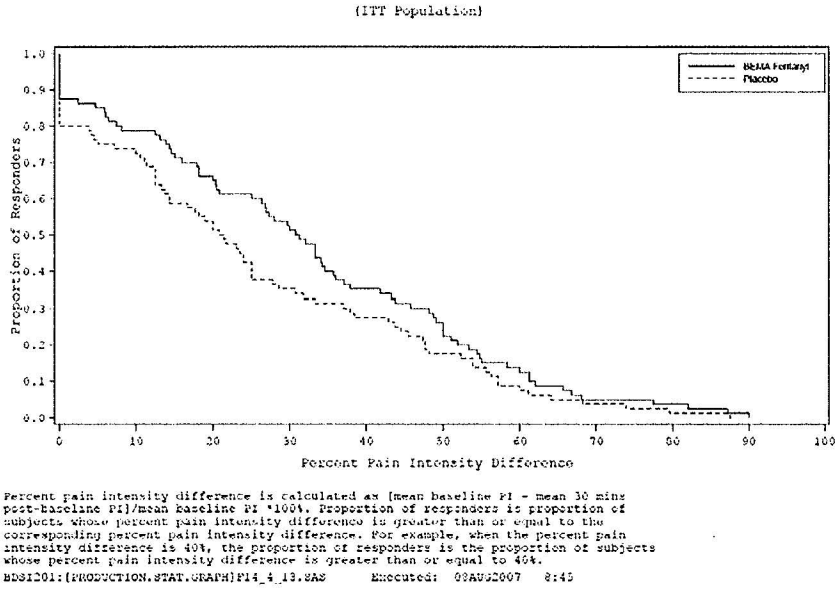
Cumulative responder analysis

The Applicant also presented an analysis of the cumulative proportion of responders as a function of the percent pain intensity difference as described by Farrar et al. The figure below is a plot of the cumulative proportion of responders as a function of the percent pain intensity **difference. It demonstrates that BEMA™ Fentanyl** has a higher number of responders at all response levels than placebo. The largest efficacy advantages over placebo occur when responder is defined as 20% to 50% PID improvement.

Figure 6: Summary of Cumulative Proportion of Responders at 30 Minutes Post-Dose by Treatment



Source: FEN-201 study report, p. 78

Use of rescue medication

An assessment was made of the percentage of episodes when rescue medication was used for the ITT population by treatment. Rescue medication was used in 30.0% of the breakthrough pain episodes treated with BEMA™ Fentanyl compared with 44.6% of the episodes treated with placebo (p=0.002).

The Applicant performed a subpopulation analysis of subjects with cancer breakthrough pain of neuropathic origin. The results showed that SPID values in subjects with breakthrough neuropathic pain were significantly higher for BEMA™ Fentanyl-treated episodes than for those treated with placebo beginning 15 minutes after study dose administration and continuing through 60 minutes. BEMA™ Fentanyl was as efficacious in this subgroup (SPID 30 = 47.7) as in the entire population (SPID 30 = 49.1).

Additional analyses

Rescue medication in relation to background opioid dose

Since the selection of a rescue medication dose for chronic pain patients is typically a percentage of the background medication dose, the Applicant chose to analyze the relationship of the background opioid dose to the "effective" BEMA Fentanyl dose. Studies with other transmucosal fentanyl products have not identified a relationship between the dose required for management of breakthrough pain and the dose of the around the clock opioid used to manage the background pain. An analysis of this relationship was performed for this study and there

does not appear to be a relationship between the background opioid dose and the dose of BEMA™ Fentanyl required for effective control of breakthrough pain.

Treatment by site interaction and site effect

This study was conducted at 30 centers in the United States. Sites with small numbers of subjects were pooled to have a sufficient number of subjects per treatment group within site for the primary efficacy analysis of SPID according to the prospectively defined algorithm. The treatment-by-pooled site interaction was investigated as an exploratory analysis in order to assess the nature of the interaction and to identify any outlier sites. Treatment-by-site interaction and site effect were not found to be statistically significant.

Gender and age

The effects of gender and age on the primary efficacy endpoint were not statistically significant Responses to treatment with BEMA™ Fentanyl and placebo adjusted for gender and age were comparable with the overall population.

Applicant's Efficacy Conclusions

1. BEMA™ Fentanyl, titrated to an effective dose in the range of 200 to 1200 µg, was shown to be effective in the treatment of cancer-related breakthrough pain in subjects receiving concomitant chronic opioid therapy. The SPID 30 for BEMA™ Fentanyl-treated episodes was statistically significantly greater than for placebo treated episodes.
2. The SPIDs for BEMA Fentanyl-treated episodes were statistically significantly greater than for placebo-treated episodes as early as 15 minutes after dosing and increased over time reaching a maximum difference at 60 minutes after dosing.
3. BEMA™ Fentanyl was statistically superior to placebo as measured by pain intensity differences and total pain relief at 30, 45, and 60 minutes.
4. BEMA™ Fentanyl was statistically superior to placebo at 30 minutes and beyond in responder analysis evaluating decreases in pain intensity of at least 50%, 33%, and complete pain relief.
5. At 60 minutes after dosing or at the time rescue medication was consumed, subjects rated their overall satisfaction with the study drug as good or better for 67.1% of their breakthrough pain episodes treated with BEMA™ Fentanyl compared with 47.2% of the breakthrough episodes treated with placebo. The mean score for overall satisfaction with the study drug was statistically significantly higher for BEMA™ Fentanyl than for placebo.
6. BEMA™ Fentanyl showed statistically significant improvements in the percentage of pain-free episodes at 60 minutes after dosing when compared with placebo. There were consistent numerical improvements in the percentage of pain-free episodes at 30 and 45 minutes when compared with placebo; however, these improvements did not reach statistical significance.
7. The percent of breakthrough pain episodes treated with rescue medication was significantly lower on BEMA™ Fentanyl than placebo.
8. BEMA™ Fentanyl was as efficacious in the subgroup of subjects with breakthrough neuropathic pain as in the entire population.
9. The analgesic effects of BEMA™ Fentanyl were not related to gender or age.