### 3.1.4 EFFICACY CONCLUSION

The Applicant was able to demonstrate that BEMA Fentanyl, titrated to an effective dose in the range of 200 to 1200 μg, was effective in the treatment of cancer-related breakthrough pain in subjects receiving concomitant chronic opioid therapy based on a pre-specified primary efficacy endpoint (i.e. SPID30).

The primary efficacy endpoint of this study was the SPID30 during the double-blind period. The SPID30 for BEMA Fentanyl-treated episodes was statistically significantly greater than for placebo treated episodes. 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 numerical difference at 60 minutes after dosing.

Several secondary endpoints were explored and showed numerically consistent findings in support of the result of the primary efficacy analysis.

## 3.2 EVALUATION OF SAFETY

Dr. Ellen Fields reviewed the safety of BEMA Fentanyl in detail. The reader is referred to Dr. **Fields' review for information regarding the adverse event profile.**

# 4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

## 4.1 SEX, RACE AND AGE

Subgroup analyses were conducted with respect to gender, race (caucasian and others), and age (<65 and ≥65 years) for the primary efficacy endpoint SPID30 in the ITT population. A descriptive summary of the primary endpoint by each subgroup is presented (Table 10). A mixed model analysis adjusting for the interaction term was conducted to explore the relationship between the subgroups and treatment.

Both the gender and age subgroups were of sufficient size to allow meaningful analyses. Of the 80 subjects in the ITT population, 55% were women and 45% were men, 69% were younger than 65 years old, and 31% were at least 65 years old. There were no remarkable effects of gender or age according to the primary endpoint analysis. Because of the small numbers of non-caucasians, any **claims of parity in terms of patient's race are** essentially unsupported. Nonetheless, there was no evidence of an effect of race to the primary endpoint analysis.

Table 10: Sum of Pain Intensity Difference by Subgroup: ITT Population

| SPID30 | Placebo | BEMA Fentanyl | Subgroup*Treatment p-value |
|---|---|---|---|
| | | All | |
| # of episodes | 197 | 394 | |
| Mean (SD) | 39.0 (41.4) | 49.1 (47.6) | |
| Range | -30, 170 | -75, 240 | 9.7 |
| LS Mean (SE)* | 38.1 (4.3) | 47.9 (3.9) | (3.3, 16.2) |
| | | By Gender | |
| Male | | | |
| # of episodes | 89 | 178 | |
| Mean (SD) | 39.6 (41.8) | 48.2 (47.6) | |
| Range | -30, 170 | -75, 240 | |
| Female | | | |
| # of episodes | 108 | 216 | |
| Mean (SD) | 38.5 (41.2) | 49.9 (47.6) | |
| Range | -30, 160 | -50, 205 | 0.798 |
| | | By Age | |
| Age < 65 | | | |
| # of episodes | 134 | 273 | |
| Mean (SD) | 35.3 (38.3) | 48.8 (46.4) | |
| Range | -30, 170 | -75, 240 | |
| Age ≥ 65 | | | |
| # of episodes | 63 | 121 | |
| Mean (SD) | 46.7 (46.6) | 49.9 (50.3) | |
| Range | -30, 165 | -75, 190 | 0.124 |
| | | By Race Group | |
| Caucasian | | | |
| # of episodes | 181 | 363 | |
| Mean (SD) | 38.6 (41.1) | 49.2 (48.1) | |
| Range | -30, 170 | -75, 240 | |
| Others | | | |
| # of episodes | 16 | 31 | |
| Mean (SD) | 43.4 (45.5) | 48.1 (41.8) | |
| Range | -30, 150 | 0, 135 | 0.600 |

* Compound Symmetry covariance structure

# 5 SUMMARY AND CONCLUSIONS

## 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

I did not identify any statistical issues in the NDA submission that could not be resolved by recoding and re-analyzing the data. For example, I identified various discrepancies between the raw and derived datasets. Reasons for most of these discrepancies were found not to affect the overall conclusion.

The primary objective of this study was to compare **the efficacy of BEMA™ Fentanyl (at any dose)** with placebo in the treatment of breakthrough pain in subjects with cancer-related pain receiving chronic opioid therapy. The primary efficacy endpoint of this study was the SPID30 during the double-blind period using LOCF imputation for missing data.

The SPID30 for BEMA Fentanyl-treated episodes was statistically significantly greater than for placebo treated episodes. 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.

Although several secondary endpoints were analyzed and studied, the Applicant did not apply multiplicity adjustment and therefore these are considered exploratory. Nonetheless, the results from these secondary endpoint analyses had shown numerically consistent finding in support of the result of the primary efficacy analysis.

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

**I conclude that the Applicant was able to demonstrate the efficacy of BEMA™ Fentanyl (at any** dose) with placebo in the treatment of breakthrough pain in subjects with cancer-related pain receiving chronic opioid therapy.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

# 7 APPENDIX

## Appendix 1: Primary endpoint analysis

The primary endpoint SPID30 was analyzed using a mixed model of repeated measures with fixed effects for treatment, pooled site, and a random effect for subjects.

Let $Y_{ijkl}$ be the SPID over the 30-minute postdose period of the $i$th episode assigned to the $k$th treatment for the $j$th subject at pooled site $l$, where $i = 1, 2,..., 9$, $j = 1, 2,...,N$, $k = 1, 2$, and $l = 1, 2,..., L$. The SPID was analyzed using the mixed model of repeated measures:

$$Y_{ijkl} = \mu + \tau_k + \gamma_l + \nu_j + \varepsilon_{jkl}$$

where,

$\mu$ was the overall mean,

$\tau_k$ was the effect of the treatment $k$,

$\gamma_l$ was the effect of the pooled site $l$,

$\nu_j$ was the random effect associated with the jth subject

$\varepsilon_{jkl}$ was the random error of episodes assigned to the $k$th treatment of the $j$th subject at the pooled site $l$.

The random effect $\nu_j$ was independently and identically distributed as N(0, $\sigma_\nu^2$) and the error term

$\varepsilon_{jkl}$ was independently and identically distributed as N(0, $\sigma_\varepsilon^2$). This model described a uniform covariance structure. Hypothesis testing for the comparison of the BEMA™ Fentanyl to placebo was based on the model described previously.

Appendix 2: Randomization Scheme (Original and Actual)

| Original Sequence | N | Actual | N | Complete or Not (Reason) | Complete | Incomplete |
|---|---|---|---|---|---|---|
| AAPAAPAPA | 7 | A | 1 | Not regularly treating 1 ep/d | 5 | 2 |
| | | AAPAA | 1 | Adverse event | | |
| | | AAPAAPAPA | 5 | Complete | | |
| AAPAPAAAP | 9 | A | 1 | **Skipped – Problematic** | 6 | 3 |
| | | AAPAAAP | 2 | Skipped | | |
| | | AAPAPAAAP | 6 | Complete | | |
| AAPAPAAPA | 6 | AAPAPAAPA | 6 | Complete | 6 | 0 |
| AAPAPAPAA | 11 | AAAPPAPAA | 1 | Switched | 7 | 4 |
| | | AAPAPA | 1 | Skipped - Problematic | | |
| | | AAPAPAPA | 1 | Adverse Event | | |
| | | AAPAPAPA | 1 | Non-compliance wt. elec. diary | | |
| | | AAPAPAPAA | 7 | Complete | | |
| APAAAPAAP | 6 | A | 1 | Subject consent withdrawn | 3 | 3 |
| | | APA | 1 | Subject consent withdrawn | | |
| | | APAAAPAA | 1 | Non compliance wt elec. diary | | |
| | | APAAAPAAP | 3 | Complete | | |
| APAAPAAAP | 5 | APAA | 1 | Adverse Event | 4 | 1 |
| | | APAAPAAAP | 4 | Complete | | |
| APAAPAPAA | 1 | APAAPAPAA | 1 | Complete | 1 | 0 |
| APAPAAAAP | 1 | APPAAAP | 1 | Skipped/Switched | 0 | 1 |
| APAPAAPAA | 8 | APAPAAPAA | 8 | Complete | 8 | 0 |
| PAAAAPAAP | 7 | PAA | 1 | Subject consent withdrawn | 5 | 2 |
| | | PAAAAP | 1 | **Skipped – Problem** | | |
| | | PAAAAPAAP | 5 | Complete | | |
| PAAAAPAPA | 2 | PAAAAPA | 1 | Skipped - Problem | 1 | 1 |
| | | PAAAAPAPA | 1 | Complete | | |
| PAAAPAAPA | 4 | AAAPAAPA | 1 | Skipped | 2 | 2 |
| | | P | 1 | Subject consent withdrawn | | |
| | | PAAAPAAPA | 2 | Complete | | |
| PAAAPAPAA | 4 | PA | 1 | Not regularly treating 1 ep/d | 3 | 1 |
| | | PAAAPAPAA | 3 | Complete | | |
| PAAPAAAPA | 6 | PAAPAAAPA | 6 | Complete | 6 | 0 |
| PAAPAAPAA | 4 | PAAPAAPA | 1 | **Skipped – Problem** | 3 | 1 |
| | | PAAPAAPAA | 3 | Complete | | |
| | | | | | | |
| Total | | | | | 60 (74%) | 21 (26%) |

## Appendix 3: Subjects excluded from Per-Protocol Population

Listing 16.2.3
Subjects Excluded from Per-Protocol Population
(All Enrolled Subjects)

| Site/Subject | Study Drug Taken out of Sequence | Same Dose of Study Drug being Reported More Than Once | Treated Pain That was not Target Breakthrough Pain |
|---|---|---|---|
| 006/1011 | Yes | | |
| 018/1007 | | Yes | |
| 018/1010 | Yes | | |
| 018/1011 | | Yes | |
| 018/1012 | Yes | | |
| 023/1003 | Yes | | |
| 051/1002 | Yes | | |
| 057/1004 | | Yes | |

Source: Clinical Study Report Data Listing 16.2.3

Appendix 4: Summary of Subject Demographics: Safety and ITT Populations

| | BEMA™ Fentanyl[a] | |
|---|---|---|
| | Safety (n = 151) | ITT (n = 80) |
| **Age (years)** | | |
| n | 151 | 80 |
| Mean (SD) | 57.1 (12.20) | 56.8 (12.95) |
| Median | 55.0 | 56.5 |
| Minimum, Maximum | 31, 87 | 31, 82 |
| **Age group (years)** | | |
| <65 | 104 (68.9) | 55 (68.8) |
| ≥65 | 47 (31.1) | 25 (31.3) |
| **Gender, n (%)** | | |
| Male | 66 (43.7) | 36 (45.0) |
| Female | 85 (56.3) | 44 (55.0) |
| **Race, n (%)** | | |
| White | 131 (86.8) | 72 (90.0) |
| Black | 12 (7.9) | 6 (7.5) |
| Asian | 1 (0.7) | 0 |
| Other[c] | 7 (4.6) | 2 (2.5) |
| **Weight (pounds)** | | |
| n | 151 | 80 |
| Mean (SD) | 160.89 (42.01) | 164.2 (39.15) |
| Median | 154.0 | 160.0 |
| Minimum, Maximum | 80, 340 | 97, 277 |
| **Height (inches)** | | |
| n | 149 | 78 |
| Mean (SD) | 66.4 (3.86) | 66.6 (3.65) |
| Median | 66.0 | 67.0 |
| Minimum, Maximum | 57, 75 | 59, 74 |
| **Female reproductive status[b], n (%)** | | |
| Postmenopausal | 43 (50.6) | 23 (52.3) |
| Sterile | 38 (44.7) | 17 (38.6) |
| Premenarchal | 0 | 0 |
| Potentially able to bear children | 3 (3.5) | 3 (6.8) |

[a] BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.
[b] Denominators of percentages were the numbers of female subjects.
[c] Other: Hispanic
Source: Tables 14.2.1.1 and 14.2.1.2

Source: Study Report, page 54

Appendix 5: Summary of Cancer Diagnosis: Safety and ITT Populations

| | BEMA™ Fentanyl[a] | |
|---|---|---|
| | Safety (n = 151) | ITT (n = 80) |
| **Cancer diagnosis, n (%)** | | |
| Breast | 35 (23.2) | 19 (23.8) |
| Lung | 26 (17.2) | 10 (12.5) |
| Colon/Rectal | 16 (10.6) | 10 (12.5) |
| Gastroesophageal | 11 (7.3) | 6 (7.5) |
| Pancreatic | 9 (6.0) | 5 (6.3) |
| Head/Neck | 7 (4.6) | 3 (3.8) |
| Prostate | 5 (3.3) | 2 (2.5) |
| Ovarian | 5 (3.3) | 4 (5.0) |
| Leukemia | 4 (2.6) | 1 (1.3) |
| Other[b] | 33 (21.9) | 20 (25.0) |
| **Duration since diagnosis (years)** | | |
| n | 117 | 65 |
| Mean (SD) | 3.24 (4.464) | 3.66 (5.187) |
| Median | 1.61 | 2.17 |
| Minimum, Maximum | 0.0, 30.3 | 0.0, 30.3 |
| **Cancer treatment in the last 6 months, n (%)** | | |
| Chemotherapy | 84 (55.6) | 43 (53.8) |
| Radiation | 38 (25.2) | 15 (18.8) |

[a] BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.

[b] Other includes cervical cancer, myeloma, liver cancer, melanoma, bladder cancer, and other cancers occurring in one subject only.

Source: Tables 14.2.2.1 and 14.2.2.2

Source: Clinical Study Report, page 56

Appendix 6: Summary of Target Pain: Safety and ITT Populations

| | BEMA™ Fentanyl[a] | |
|---|---|---|
| | Safety (n = 151) | ITT (n = 80) |
| | Number of subjects (%) | |
| **Pain pathophysiology – persistent pain** | | |
| Somatic | 85 (56.3) | 47 (58.8) |
| Visceral | 79 (52.3) | 40 (50.0) |
| Neuropathic | 53 (35.1) | 24 (30.0) |
| Unknown | 6 (4.0) | 4 (5.0) |
| **Pain syndrome for persistent pain** | | |
| Related to direct tumor involvement | 128 (84.8) | 65 (81.3) |
| Due to somatic/visceral lesion | 126 (83.4) | 65 (81.3) |
| Neoplastic damage to bone and joints | 63 (41.7) | 33 (41.3) |
| Neoplastic damage to viscera | 72 (47.7) | 40 (50.0) |
| Neoplastic damage to soft tissues and miscellaneous syndromes | 64 (42.4) | 37 (46.3) |
| Related to therapy | 42 (27.8) | 25 (31.3) |
| Due to nervous tissue lesions | 21 (13.9) | 7 (8.8) |
| Unknown | 10 (6.6) | 6 (7.5) |
| Other | 15 (9.9) | 8 (10.0) |
| **Pain pathophysiology – target breakthrough pain** | | |
| Somatic | 87 (57.6) | 48 (60.0) |
| Visceral | 76 (50.3) | 39 (48.8) |
| Neuropathic | 49 (32.5) | 23 (28.8) |
| Unknown | 6 (4.0) | 5 (6.3) |
| **Pain syndrome for target breakthrough pain** | | |
| Related to direct tumor involvement | 130 (86.1) | 66 (82.5) |
| Due to somatic/visceral lesion | 128 (84.8) | 66 (82.5) |
| Neoplastic damage to viscera | 70 (46.4) | 41 (51.3) |
| Neoplastic damage to soft tissues miscellaneous syndromes | 67 (44.4) | 41 (51.3) |
| Neoplastic damage to bone and joints | 64 (42.4) | 32 (40.0) |
| Related to therapy | 41 (27.2) | 27 (33.8) |
| Due to nervous tissue lesions | 21 (13.9) | 9 (11.3) |
| Unknown | 13 (8.6) | 10 (12.5) |
| Other | 13 (8.6) | 7 (8.8) |

Note: Subjects may have had more than one pain pathology and pain syndrome category.

[a] BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.

Source: Tables 14.2.2.1 and 14.2.2.2

Source: Clinical Study Report, page 57

Appendix 7: Number of Doses of Study Drug: Safety Population

| Number of Doses | Placebo | BEMA™ Fentanyl | Total |
|---|---|---|---|
| **Titration period** | | | |
| n | - | 141 | 141 |
| Mean number of doses (SD) | - | 9.3 (4.81) | 9.3 (4.81) |
| Median | - | 9.0 | 9.0 |
| Minimum, Maximum[a] | - | 1, 25 | 1, 25 |
| **Double-blind period** | | | |
| n[b] | 78 | 80 | 81 |
| Mean number of doses (SD) | 2.8 (0.59) | 5.5 (1.34) | 8.0 (2.20) |
| Median | 3.0 | 6.0 | 9.0 |
| Minimum, Maximum[a] | 1, 3 | 1, 7 | 1, 10 |
| **Entire study** | | | |
| n | 78 | 141 | 141 |
| Mean number of doses (SD) | 2.8 (0.59) | 12.4 (6.19) | 14.0 (7.22) |
| Median | 3.0 | 14.0 | 15.0 |
| Minimum, Maximum[a] | 1, 3 | 1, 26 | 1, 29 |

[a] The maximum number of doses in the double-blind period was 10 for some subjects because they reported taking the same dose twice.

[b] In the double-blind period, the number of subjects is the number who took placebo, BEMA™ Fentanyl, or either at any point.

Source: Table 14.3.2

Source: Clinical Study Report, page 87

Appendix 8: Summary of Days of Study Drug Exposure During the Study: Safety Population

| | Total Days[a] |
|---|---|
| **Titration period** | |
| n | 141 |
| Mean (SD) | 6.6 (4.05) |
| Median | 6.0 |
| Minimum, Maximum | 1, 23 |
| **Double-blind period** | |
| n | 81 |
| Mean (SD) | 5.9 (3.17) |
| Median | 5.0 |
| Minimum, Maximum | 1, 14 |
| **Entire study** | |
| n | 141 |
| Mean (SD) | 10.1 (6.33) |
| Median | 9.0 |
| Minimum, Maximum | 1, 27 |

[a] Total days include all days from the first dose date to the last dose date, regardless of whether BEMA™ Fentanyl or placebo was taken on those days.

Source: Table 14.3.3

Source: Clinical Study Report, page 88

Appendix 9: Summary of Drug Compliance During Double-blind Treatment Period by Dose Level and Treatment: Safety Population

| Compliance (%) | Placebo | BEMA™ Fentanyl[a] | Total |
|---|---|---|---|
| n | 78 | 80 | 81 |
| Mean (SD) | 91.88 (19.508) | 90.42 (21.992) | 89.03 (24.184) |
| Minimum, Maximum | 33.3, 100.0 | 16.7, 100.0 | 11.1, 100.0 |

Note: Percent compliance of BEMA™ Fentanyl was calculated for each subject as (total number of BEMA™ Fentanyl discs used/6)*100. Percent compliance of placebo was calculated for each subject as (total number of placebo discs used/3)*100. Overall percent compliance was calculated for each subject as (total number of discs used/9)*100. If a subject reported taking the same disc more than once, that disc was counted only once in the compliance calculation.

* BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.

Source: Table 14.3.4

Source: Clinical Study Report, page 59

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