# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-266**

# STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

# Statistical Review and Evaluation

## CLINICAL STUDIES

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| NDA: | 22-266 |
| Name of drug: | BEMA Fentanyl (fentanyl bioerodible microadhesive b(4) |
| Indication: | management of breakthrough cancer pain who are tolerant to opioid therapy |
| Applicant: | BioDelivery Sciences International |
| Dates: | Letter 10-31-2007 ; PDUFA 08-29-2008 |
| Review priority: | S |
| Biometrics division: | Division of Biometrics II |
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| Keywords: | NDA review, clinical studies |

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# 1 EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

The Applicant, BioDelivery Sciences International, seeks to market BEMA Fentanyl (fentanyl bioerodible mucoadhesive [redacted] for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. BEMA Fentanyl is a bioerodible mucoadhesive system which delivers fentanyl across the buccal mucosa and is available in five dose strengths: 200, 400, 600, 800, and 1200 μg fentanyl free base per unit.

b(4)

After careful review of the Applicant's data and study report, there is evidence that BEMA Fentanyl, titrated to an effective dose in the range of 200 to 1200 μg, is effective in the treatment of cancer-related breakthrough pain in subjects receiving concomitant chronic opioid therapy based on the pre-specified primary efficacy endpoint, sum of pain intensity difference at 30 minutes (SPID30).

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The efficacy of BEMA Fentanyl in treating episodes of breakthrough cancer pain has been established in a single Phase 3 study (Study FEN-201). This study is a double-blind, multiple period, placebo-controlled, crossover study. Subjects underwent open-label titration to a tolerable, effective dose and then were randomized. There were 152 subjects recruited, and 80 subjects provided efficacy data in the double-blind period.

The development plan for BEMA Fentanyl was previously discussed during several meetings with the US Food and Drug Administration's (FDA's) Division of Anesthesia, Analgesia and Rheumatology Products from 13 December 2000 through 28 June 2007. Key statistical advice received from the Agency was that the primary endpoint (SPID30) for the pivotal studies and the last observation carried forward (LOCF) convention were acceptable. The Division also requested that information be provided in the study report on the randomization schedule(s) used in FEN-201. In the 28 June 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 in Study FEN-201.

The main focus of this statistical review is on the placebo-controlled crossover study (Study FEN-201). The Applicant included the result from this study in their proposed product label.

## 1.3 STATISTICAL ISSUES AND FINDINGS

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. These discrepancies were found not to affect the overall conclusion.

The following are the key findings of the study:

- The primary efficacy endpoint (i.e. 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.

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

# 2 INTRODUCTION

## 2.1 OVERVIEW

The Applicant, BioDelivery Sciences International Inc. (BDSI), seeks to market BEMA Fentanyl (fentanyl bioerodible mucoadhesive _____ for the management of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. b(4)

BEMA Fentanyl is a bioerodible mucoadhesive system which delivers fentanyl across the buccal mucosa and is available in five dosage strengths: 200, 400, 600, 800, and 1200 µg fentanyl free base per unit. According to the Applicant,

> BEMA Fentanyl is an alternative product to Actiq that does not require the subject to paint the inside of the mouth with the dosage form continuously. The BDSI product is a small disc that is placed against the mucosal membrane inside the mouth. The mucoadhesive polymers in the disc readily adhere to the mucosal membrane (within five seconds) when moistened. The components of the disc are bioerodible, so the entire dosage form dissolves within 30 minutes of application.

The development plan for BEMA Fentanyl was previously discussed during several meetings with **the US Food and Drug Administration's Division of Anesthesia, Analgesia and Rheumatology** Products from 13 December 2000 through 28 June 2007. The key milestones in the clinical **development program are highlighted in Dr. Fields' review.** Statistical issues were discussed during several meetings and key issues are summarized below:

1. September 15, 2006 Meeting

   a. The primary endpoint (SPID30) for the pivotal studies, using the last observation carried forward (LOCF) convention was acceptable. The Division also recommended that in the calculation of SPID30, the Applicant use a weighted average to account for the frequency and timing of the PID measurements across the 30 minute interval.

   b. The Division also requested that detailed information be provided in the statistical analysis plan on the randomization procedure to be used (i.e. randomization procedure of patients to treatment sequences in the double-blind phase).

   c. The size of the safety database (at least 300 patients) was acceptable.

2. 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 in Study FEN-201. All subjects who drop out of the study should be considered non-responders.

The main focus of this statistical review is on the placebo-controlled crossover study (Study FEN-201). Key characteristics of the study are summarized in Section 3.1.1.

### 2.2 DATA SOURCES

This statistical review is based on data submitted in study FEN-201.

The electronic submission of this NDA can be found at:
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## 3 STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

The clinical program of BEMA Fentanyl comprised a single, placebo-controlled, cross-over study (conducted from 24 February 2006 to 14 March 2007) and one long-term safety study (FEN-202).

#### 3.1.1 STUDY DESIGN AND ANALYSIS PLAN

Study FEN-201 was a randomized, double-blind, placebo-controlled, multiple crossover, multicenter study. The purpose of this study was to evaluate **the efficacy of BEMA™ Fentanyl at any dose** (ranging from 200 μg to 1200 μg) in the management of breakthrough pain in cancer subjects on background opioid therapy. The objectives were to:

1. **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.
2. **To determine the range of BEMA™ Fentanyl doses required to control breakthrough** pain in subjects with cancer-related pain receiving chronic opioid therapy.
3. To evaluate the safety and tolerability profile **of BEMA™ Fentanyl in subjects with** cancer-related pain receiving chronic opioid therapy.

The study design is summarized as follow:

> **Eligible subjects self-administered open-label BEMA™ Fentanyl over a period of up to two** weeks. Before entering the titration period, eligible subjects were trained on the application **of the BEMA™ Fentanyl disc and received instructions** on self-administration of the study drug during dose titration and use of the electronic diary. Starting at an initial dose of 200 μg, subjects continued the treatments at doses titrated upward until they identified a dose that produced satisfactory pain relief of breakthrough pain for at least two episodes. Breakthrough pain was defined as a transitory period of moderate to severe pain that occurred at a specific site on a background of persistent pain controlled by the opioid regimen. Subjects were contacted at least twice weekly by study personnel throughout this period and advised about dosage adjustments and to return to the study site for

discontinuation from or entry into the double-blind period of the study. Subjects who were **unable to identify a dose of BEMA™ Fentanyl** that adequately controlled their breakthrough pain episodes were discontinued from the study by the end of the two-week period.

**Those subjects who identified a dose of BEMA™** Fentanyl that produced satisfactory relief of breakthrough pain episodes entered the double-blind placebo-controlled period of the trial. At least 100 subjects were projected to enter this period of the study during which they self-administered three placebo doses and **six BEMA™ Fentanyl doses in a random** sequence. The placebo doses were randomly distributed over the double-blind period with one placebo dose being included among every three doses, but with at least one active dose between two placebo doses. No consecutive placebo doses were allowed. There were 21 treatment sequences that met the criteria. Fifteen sequences were randomly selected and three sequences were randomly assigned to each of the five dose levels.

Subjects were trained on the use of study drug in a sequential manner and received instructions on self-administration of the study drug during the randomization period dose. Subjects were allowed to use their standard breakthrough pain medication 30 minutes after the study dose application for pain episodes that did not respond adequately. Subjects were not to take another dose of study medication for four hours after their last study dose. The subsequent dose of study medication was for the emergence of a new target breakthrough pain episode and not for a previous episode that was treated and not resolved.

Immediately before a self-administration of study dose, and at 5, 10, 15, 30, 45, and 60 minutes after this self-administration, subjects recorded pain intensity (using an 11-point numeric scale [from 0 = no pain to 10 = worst pain]). At 5, 10, 15, 30, 45, and 60 minutes after self-administration of study dose, subjects recorded perceived pain relief (using a five-point categorical scale [from 0 = no relief to 4 = complete relief]). Pain intensity and pain relief were not assessed once the subject had taken rescue medication. Subjects completed a global evaluation of study medication performance (subject overall satisfaction with the study drug) either at the time rescue medication was consumed or at the 60-minute time point using a five-point categorical scale (from 0 = poor to 4 = excellent).

An electronic diary was used to record pain intensity, pain relief, subject overall satisfaction with the study drug, date and time of study medication administration, and whether any **changes in the subject's medical condition** had occurred. Additional medications used to treat an episode of breakthrough pain were also recorded in the electronic diary.

## Efficacy Endpoints

As mentioned, pain intensity (PI) (using an 11-point [0 = no pain to 10 = worst pain] numeric scale) was recorded immediately before dosing and at 5, 10, 15, 30, 45, and 60 minutes after dosing. Pain intensity difference was defined as the baseline pain score minus the pain score of each time point. The primary endpoint was the SPID30.

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. See Appendix 1.

The SPID was calculated as a weighted sum of the PID of all time points at or before the time point of interest.

$$\text{SPID} = \sum_{i=1}^{n} [(\text{time of the } i^{th} \text{ PI measurement} - \text{time of the } (i-1)^{th} \text{ PI measurement}) \times (\text{the } i^{th} \text{ PID score})].$$

The weight of the ith PID score was the time interval between ith and (i-1)th PI measurements, disregarding if the (i-1)th PI measurement was missing or not. That is, if the first one or few postbaseline measurements were missing, the contribution to the SPID from those time points will be zero.

Several secondary endpoints were explored in the study that includes:

1. The PID at the 5-, 10-, 15-, 30-, 45-, and 60-minute time points after dosing for BEMA Fentanyl and placebo.

2. Pain relief (PR) using a 5-point categorical scale (0 = no relief to 4 = complete relief) at the 5-, 10-, 15-, 30-, 45-, and 60- minute time points after dosing for BEMA Fentanyl and placebo.

3. Total pain relief (TOTPAR) over the 5-, 10-, 15-, 30-, 45-, and 60-minute time points after dosing for BEMA Fentanyl and placebo. The TOTPAR was calculated as a weighted sum of the pain relief of all time points at or before the time point of interest using the following equation:

$$\text{TOTPAR} = \sum_{i=1}^{n} [(\text{time of the } i^{th} \text{ PR measurement} - \text{time of the } (i-1)^{th} \text{ PR measurement}) \times (\text{the } i^{th} \text{ PR score})]$$

4. 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).

5. The percentage of pain-free episodes (defined as an episode with a pain intensity of 0 at a postdose time point) per subject at the 5-, 10-, 15-, 30-, 45-, and 60-minute time points after dosing for BEMA Fentanyl and placebo. An episode was included in the percentage calculation only if the time points were on or after when the first non-missing post-baseline pain intensity was reported.

6. The percentage of episodes with meaningful decreases in pain (defined separately as a 50% or 33% reduction in pain score) at the 15-, 30-, 45-, and 60-minute time points **after dosing for BEMA™ Fentanyl and placebo**. An episode was included in the percentage calculation only if the time points were on or after when the first non-missing post baseline pain intensity was reported.

7. The percentage of complete pain relief episodes (defined as an episode with a pain relief value of 4) at the 5-, 10-, 15-, 30-, 45-, and 60-minute time points after dosing for BEMA Fentanyl and placebo. An episode was included in the percentage calculation only if the time points were on or after when the first non-missing post-baseline pain relief was reported.

8. The percentage of episodes when rescue medication was taken for BEMA Fentanyl and placebo. The percentage of episodes when rescue medication was taken for BEMA Fentanyl was calculated as the number of **BEMA™ Fentanyl-treated episodes in which** rescue medication was taken divided by the number of BEMA Fentanyl-treated episodes. The percentage of episodes when rescue medication was taken for placebo was calculated similarly.

## Efficacy Analysis

The following is a summary of the statistical methods used in the analysis of the primary and secondary efficacy variables.

All efficacy analyses were conducted using the ITT population and the primary efficacy endpoint was also analyzed using the PP population. Analysis in the PP population was considered secondary. The ITT population is defined as all subjects who entered the double-blind period of the trial and who took at least one dose of study medication and had at least one pain assessment within the 30-minute postdose period. The PP population is defined as all ITT subjects without major protocol violations that were considered to affect the efficacy analyses significantly. Major protocol violations that were considered to affect the efficacy analyses significantly included: treated pain that was not target breakthrough pain, study medication taken out of sequence, and the same dose of study medication reported being taken more than once.

The SPID30 was also analyzed using the mixed model **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.

The SPID30 was also analyzed by gender and age (less than 65 and 65 or greater) subgroups, using the same model described previously. Separate analyses explored the treatment-by-pooled site interaction in the event there was a significant treatment-by-pooled site interaction (assessed using a type I error of 0.10). Further exploratory analyses were performed with descriptive statistics and interaction plots to determine the nature of the **interaction (eg, whether it was a "qualitative" interaction) and to identify any outlier sites.**

All secondary endpoints were analyzed by comparing the within subject means using the one-sample Wilcoxon signed rank test.

**Statistical Decision Rule (Multiple Comparisons)**

Although the 30-minute SPID endpoint is the only primary endpoint, the Applicant is considering using the results from earlier time points for promotional materials. Therefore they used a closed, sequential approach, stepping backwards through the time points to control the overall type I error rate. Thus if the SPID at an individual time point is significant, the next shortest interval will be tested moving progressively from 30 to 15 to 10 to 5 minutes.

**Sample size**

The design and endpoints for this study are similar to previous pivotal studies of transmucosal fentanyl products, including Actiq (Farrar, 1998) and Fentora (Portenoy, 2006). The assumptions used to calculate the sample size was based on the results from the Actiq study (original power calculation, N=100) and the Fentora study (amended power calculation, N=77). The sample size of 77 was determined to provide at least 90% power to detect treatment group difference of 1.2 units in SPID30 between fentanyl and placebo with a standard deviation of no larger than 3.2.

**Handling of Missing Data**

Missing data were imputed on an episode-by-episode basis by carrying forward the last observed data value (last observation carried forward [LOCF]). For subjects who took rescue medication, values at the time points after rescue medications administration were imputed using the last observation on or before rescue medications administration.

**Pooling of Low-Enrolling Sites**

Low-enrolling sites were pooled for analysis. According to the Applicant, the goal of pooling low-enrolling sites was to have a sufficient number of subjects per treatment group within site for the primary efficacy analysis of SPID.

The pooling rule was as follows:

> Low-enrolling sites were defined as those that had fewer than eight subjects with valid data for SPID during the double-blind treatment period. Within these low-enrolling sites, pooling was done from the largest to the smallest with respect to the total number of subjects with valid data for SPID during the double-blind treatment period, and then by site number within those having the same number of subjects. Low-enrolling sites were pooled until the pooled site had at least eight subjects with data for valid SPID during the double-blind treatment period. Any leftover sites that did not have a sufficient number of subjects to form another pooled site were pooled with the last pooled site.

**Changes in Study Protocol and Analysis Plan**

The following is a listing of changes made in the study as well as analysis plan. The protocol and the analysis plan were amended before database lock and unblinding of the data.

1. The sample size for study FEN-201 was changed from at least 100 subjects to approximately 77 subjects.

2. The primary efficacy endpoint was changed from the SPID from 0 to 60 minutes after dosing during the double-blind portion of the study to the SPID30 minutes during the double-blind portion of the study.

3. The analysis method for the primary efficacy endpoint of SPID was changed from a two-way analysis of variance with terms for treatment to a mixed model of repeated measures with fixed effects for treatment, pooled site, and a random effect for subjects.

4. The secondary outcomes were changed from SPID at all other time points other than 60 minutes, pain relief at each time point, the PID at each time point, total pain relief calculated at each time point, global performance evaluation at the time of rescue or 60 minutes after each dose to SPID at time points other than 30 minutes, PID at all time points, pain relief at all time points, total pain relief across all time points, global performance evaluations, and rescue medication usage.

5. The analysis method for the secondary efficacy endpoints was changed from a two-way analysis of variance for continuous endpoints and Cochran Mantel Haenszel General Association Test stratified by site for categorical endpoints, to the one-sample Wilcoxon signed rank test.

6. The study population definitions for the safety, ITT, and PP populations were clarified.

7. Additional analyses were performed for the Cumulative Proportion of Responders, **Subpopulation Analysis – Neuropathic Pain, and Background Opioid Dose Relationship to BEMA™ Fentanyl Dose.**