analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

5.3 Exposure-Response Relationships

No specific exposure-response assessments were performed.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is 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.

6.1.1 Methods

Evidence for the efficacy of BEMA Fentanyl comes from a single study, FEN-201; a double-blind, placebo-controlled evaluation of the efficacy, safety, and tolerability of BEMA Fentanyl in the treatment of BTP in cancer subjects. The Division considered submission of a single adequate and well-controlled efficacy study in the context of previous Agency findings for fentanyl acceptable for this NDA submission.

Study FEN-202 (open-label safety study) provides support for the efficacy findings demonstrated in FEN-201.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint was the summed pain intensity difference 30 minutes after dosing (SPID 30). The SPID was calculated as a weighted sum of the pain intensity differences (PID) of all time points at or before the time point of interest. The original protocol specified that the primary endpoint was to have been the SPID 60; however this was changed in the amendment dated February 28, 2007. The Division stated that SPID 30 was an acceptable primary endpoint during a Type C meeting with the Applicant on September 15, 2006. The design and endpoints for the FEN-201 study are similar to previous pivotal studies of transmucosal fentanyl products, **including Actiq® and Fentora™.**

6.1.3 Study Design

Study FEN-201 was a double-blind, placebo-controlled, multiple-crossover, multicenter evaluation of the efficacy, safety and tolerability of BEMA Fentanyl in the treatment of BTP in cancer patients. Bias in this trial was minimized due to blinding, randomization, a prospective

statistical analysis plan, appropriate identification of endpoints, and the use of multiple study centers.

The study was comprised of a titration period of up to 14 days, and a double-blind period (up to 14 days) during which patients were treated for 9 episodes of BTP (6 with study drug and 3 with placebo). Although the duration of the controlled portion of the study was short, given what is known about the fentanyl moiety, it would be expected that the study drug would remain efficacious with chronic use with adjustments in dosage as needed.

The study population, cancer patients being treated for chronic pain with around-the-clock opioids and in addition experiencing one to four BTP episodes per day, is fully representative of the population intended for the use of the study drug. Therefore, findings of efficacy from this trial allow for generalization to the intended patient population.

6.1.4 Efficacy Findings

Study FEN-201
A Double-blind, Placebo Controlled Evaluation of the Efficacy, Safety and Tolerability of **BEMA™ Fentanyl in the Treatment of** Breakthrough Pain in Cancer Subjects
(Refer to appendix section 10.1 for a detailed review of this study)

Disposition of Subjects
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. One subject withdrew consent before taking any study drug. Forty-five percent of patients entering the titration period dropped out during titration.

Eighty-two subjects who completed the titration period entered the double-blind period and were **assigned to a randomized treatment order (BEMA™** Fentanyl or placebo). Of the 82 randomly assigned subjects, 81 received double-blind study drug according to the randomization scheme, and 80 subjects provided pain assessment within the 30-minute post-dose interval in the double-blind period (ITT population). Of the subjects who entered the double-blind period, 7.9% dropped out.

The following table summarizes the rates and reasons for dropout for both periods of the study. A total of 46.1% of the patients entering the study completed it.

Table 5

Summary of Subject Disposition: All Enrolled Subjects

	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

"Other" reasons for withdrawing from the titration period included starting chemotherapy (n=1); titration failure (n=1); background medication problems (n=2); study stopped as target enrollment was reached (n=2); breakthrough pain not at target site (n=1); SAE (n=1); drug accountability concerns (n=1), and other reasons (n=2). A full analysis of dropouts may be found in Section 7.

Demographics and Other Baseline Characteristics

Overall, there were no important differences between the titration population and the double-blind population related to demographics and baseline characteristics.

Table 6 below presents a summary of subject demographics for the titration and double-blind periods of study FEN-201.

Table 6: Summary of Subject Demographics

Characteristic	Titration N=151	Double-Blind (ITT) N=80
Age (yrs)		
Mean (SD)	57.1 (12.2)	56.8(12.9)
Min, Max	31,87	31, 82
Gender, n (%)		
Male	66 (43.7)	36 (45)

Female	85 (56.3)	44 (55.0)
Race, n (%)		
White	131(86.8)	72 (90)
Black	12 (7.9)	6 (7.5)
Asian	1 (0.7)	0
Other	7 (4.6)	2 (2.5)
Height(inches)		
Mean (SD)	66.4 (3.8)	66.6 (3.6)
Min, Max	57, 75	59, 74
Weight (pounds)		
Mean (SD)	160.9 (42)	164.2 (39)
Min, Max	80, 340	97, 277

In both populations, the most common cancer diagnoses were breast, lung, colorectal, and gastroesophageal (58% of titration and 56% of double-blind). The remaining cancer types were pancreatic, head and neck, prostate, ovarian, leukemia, cervical, myeloma, liver, melanoma, and bladder cancer.

The average duration since cancer diagnosis was 3.2 years in the titration group, and 3.7 years in the double-blind group. Approximately 55% of both populations received chemotherapy in the 6 months prior to receiving study drug, and 25% of the titration population and 19% of the double-blind population received radiation during that time period.

For approximately half of the subjects in both the titration and double-blind populations, the pain pathophysiology for both persistent pain and target breakthrough pain was somatic and/or visceral. The pain syndrome for persistent and target breakthrough pain was typically related to direct tumor involvement (84.8% and 86.1% subjects, respectively) or because of somatic/visceral lesions (83.4% and 84.8% subjects, respectively). Approximately one-third of the persistent pain and breakthrough pain was described as neuropathic in nature in both groups.

The following table shows the summary of pain therapy for both the titration population (safety) and the double-blind population (ITT).

Table 7

1 Summary of Pain Therapy: Safety and ITT Populations

	BEMA™ Fentanyl[a]	
	Safety (n = 151)	ITT (n = 80)
	Number of subjects (%)	
Stable opioid regimen for persistent pain		
Transdermal fentanyl	70 (46.4)	40 (50.0)
Oral long-acting morphine	36 (23.8)	14 (17.5)
Long-acting oxycodone	35 (23.2)	19 (23.8)
Methadone	12 (7.9)	10 (12.5)
Hydromorphone	3 (2.0)	1 (1.3)
Other	7 (4.6)	2 (2.5)
Target breakthrough pain medication(s)		
Hydrocodone	64 (42.4)	38 (47.5)
Short-acting oxycodone	40 (26.5)	19 (23.8)
Oral short-acting morphine	20 (13.2)	9 (11.3)
Hydromorphone	18 (11.9)	13 (16.3)
Propoxyphene	8 (5.3)	4 (5.0)
Tylenol/Aspirin with codeine	3 (2.0)	1 (1.3)
Fentanyl	3 (2.0)	1 (1.3)
Other	12 (7.9)	6 (7.5)

Note: Subjects may have been on more than one stable opioid or target breakthrough pain medication.
[a] BEMA™ Fentanyl included all dose levels: 200, 400, 600, 800, 1200 µg.

Source: FEN-210 Study Report, p. 57

Dosing Information

Subjects were titrated to a successful dose of **BEMA™ Fentanyl** to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, or 1200 µg). A summary of doses used by subjects in the double-blind period of the study is provided in the table below.

Table 8: Doses Used in Double Blind Study

BEMA strength (µg)	Double-blind phase N=81 n (%)
200	4 (4.9)
400	15 (18.5)
600	23 (28.3)
800	19 (23.4)
1200	20 (24.6)

Applicant's Analysis of Efficacy

The primary efficacy outcome variable was the sum of pain intensity differences at 30 minutes after dosing (SPID 30) for BEMA Fentanyl versus placebo during the double-blind period of the study. The analysis was conducted for all patients meeting the Intent-to-Treat definition (ITT); all subjects who entered the double-blind period, took at least one dose of study drug in the double-blind period, and had at least one pain assessment within the 30-minute post-dose period. The Per Protocol population, which was also used for the primary efficacy endpoint, was defined as all ITT subjects without major protocol violations that were considered to affect the efficacy analyses significantly.

The mean SPID30 for BEMA Fentanyl-treated episodes was statistically significantly greater (p=0.004) than the mean SPID30 for placebo-treated episodes. The SPID30 (LS mean ± SE) was 47.9 ± 3.87 for BEMA Fentanyl and 38.1 ± 4.30 for placebo. The difference in LS mean

SPIDs between BEMA Fentanyl and placebo was 9.74 (95% CI: 3.31, 16.18). The Applicant's table below illustrates this analysis.

Table 9

Sum of Pain Intensity Difference at 30 Minutes: ITT Population

SPID 30	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

Although several secondary endpoints were studied and analyzed, the Applicant did not apply multiplicity adjustments, and they are therefore considered only supportive and not suitable to support any additional claims. However, the results of the analyses of the secondary endpoints are supportive of the primary endpoint and the finding of efficacy BEMA Fentanyl compared to placebo. A more detailed discussion of the secondary endpoints may be found in Appendix 10.1.

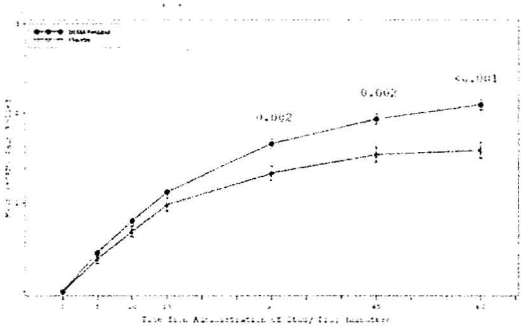
The effects of gender and age on the primary efficacy endpoint were not statistically significant. Responses to treatment with BEMA™ Fentanyl and placebo adjusted for gender and age were comparable with the overall population.

Reviewer's Comments Regarding Efficacy Findings

- The Applicant's statistical analysis was confirmed by Dr. Joan Buenconsejo of the Division of Biometrics II. Details of the statistical analyses may be found in Dr. Buenconsejo's review.
- Because of the Agency's extensive experience with oral transmucosal fentanyl products, one adequate and well-controlled Phase 3 trial is sufficient to support the efficacy of BEMA Fentanyl in an 505(b)(2) application.
- The efficacy findings for BEMA Fentanyl appear consistent with those for Fentora and Actiq. The primary endpoint used for the Actiq Phase 3 trial was pain relief, in contrast to Fentora and BEMA, which used SPID. Since pain relief data were collected as secondary endpoints for both Fentora and BEMA, that information can be used to compare the pain relief curves for each drug. Although comparison of inter-trial data is wrought with limitations, the figures below illustrate the similarity between the active

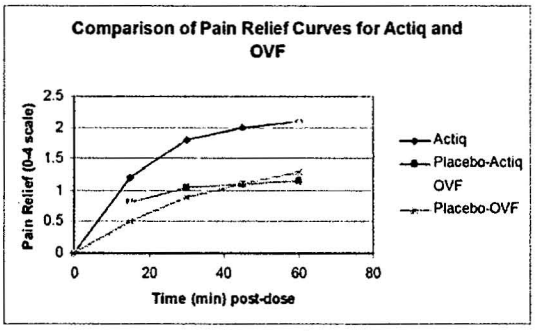
drug and placebo curves for each product, which implies similar behavior of the three transmucosal fentanyl drug products in terms of pain relief.

Fig 3: BEMA Fentanyl Pain Relief vs. Placebo and Fentora



Source: NDA 22-266 Study Report, p. 68

Fig. 4 Comparison of Pain Relief Curves for Actiq



Source: Shibuya, R: NDA 21-947 Clinical Review, 4/06

- Although the SPID values for BEMA Fentanyl differ significantly from placebo starting with SPID15, the onset of action cannot be accurately determined from this information. Pain relief was not assessed during the trial using the double stop-watch method (measuring time to "perceptible" pain relief and "meaningful" pain relief), so that the true onset of action of the drug was not measured during Study FEN-201, and no claims may be made regarding time to onset of pain relief.

6.1.5 Clinical Microbiology

This product is not an antimicrobial.

6.1.6 Efficacy Conclusions

Upon review, study FEN-201 supports a finding of efficacy for BEMA Fentanyl for the treatment of BTP in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Two Phase 3 studies (FEN-201 and FEN-202) were conducted in the intended opioid-tolerant cancer population with breakthrough pain and a single-dose pharmacokinetic study (FEN-113) was also done in cancer patients to assess the affect of mucositis on the absorption of fentanyl

from the BEMA delivery system. These 3 studies form the basis for the safety assessment of BEMA Fentanyl.

FEN-113 was an open-label, single-dose study in two groups of subjects with cancer, one with mucositis (Cohort 1) and a second group without mucositis (Cohort 2). Seven subjects with cancer and Grade 1 mucositis and seven age and gender matched controls without mucositis were recruited from two clinical sites. All subjects received a single 200-µg BEMA Fentanyl unit applied to the buccal mucosa by study personnel. In Cohort 1 subjects, the disc was applied to an area of mucosa that met the requirements for Grade 1 mucositis. In Cohort 2 subjects, the disc was applied to an area of the mucosa that was similar in location to that of the matched mucositis subjects. Vital signs, AEs, and mucosal irritation were assessed throughout the 4-hour study period and serial blood samples collected.

FEN-201 was a randomized, double-blind, placebo-controlled, multiple cross-over study comparing BEMA Fentanyl with placebo for the treatment of breakthrough pain in subjects with cancer receiving a stable opioid regimen for persistent pain. Eligible subjects were titrated to an effective dose (200 µg to 1200 µg) of BEMA Fentanyl in an open-label period. Subjects who identified an effective dose of BEMA Fentanyl entered the double-blind placebo controlled treatment period of the study. During this period, subjects received nine study drug doses to treat breakthrough pain episodes. Three discs contained placebo and six contained fentanyl at the dose found effective for that subject during the titration period. Subjects had three to four clinic visits over an approximate four-week span.

FEN-202 is an ongoing, open-label, multi-center study evaluating the safety of BEMA Fentanyl in adult subjects with cancer pain using a stable scheduled oral opioid regimen. Subjects are eligible to enter following successful completion of FEN-201, or directly if they met the same entry criteria as FEN-201. Subjects entering directly are titrated to an effective dose (200 µg to 2400 µg) in a similar manner to the one used in FEN-201. Once a dose has been identified, subjects will continue at that dose for an unlimited period, with dosage adjustments allowed as required to control breakthrough pain. Throughout the study, all subjects return to the clinic monthly for safety assessments, dosage adjustment, and dispensing of additional study medication.

The primary safety evaluations for all trials were AEs. Oral examinations for mucosal irritation were performed regularly in each of the studies. No laboratory safety data were collected.

For the purposes of the overall safety analysis, the results of the normal volunteer studies were considered not representative of the intended population and as such are not integrated with the safety information from cancer subjects.

Data presented below (Sections 7.1.1-7.2.9) represents that submitted in the original ISS (cut-off date August 28, 2007), unless otherwise stated. Additional data submitted in the 120-day safety update is presented in Section 7.2.9.

The following datasets were used for the safety review: *AF_AE.xpt, AF_CANC.xpt, AF_DISP.xpt, AF_DOSE.xpt, AF_EXP.xpt, AF_MED.xpt, AF_MOUTH.xpt, AF_PHYS.xpt, AF_VITAL.xpt, FORMATS.xpt, MPF.xpt.*

7.1.1 Deaths

Because of the nature of the patient population (cancer patients, often terminal), deaths during the clinical trials of BEMA Fentanyl were expected. A total of 54 deaths occurred during the development program. No deaths were attributed to the study drug by the Applicant. All information provided by the Applicant, which included CRFs, narratives, and data listings, were reviewed for each death. A summary of each death consisting of the pertinent facts may be found in Tables 57-59 in Appendix 10.2. Due to the study designs of FEN-201 (multiple cross-over) and FEN-202 (open-label), there is no placebo group with which to compare death rates.

Nine of the 54 patients who died received study drug on the day of their deaths. The relationship of the time of last dose to the time of death was not generally available for these patients. The remaining 45 patients had discontinued the study drug 1-51 days prior to their deaths.

For this review, the deaths were divided into three groups; those due to progression or recurrence of disease (tissue destruction due to tumor progression or metastases), those due to complications of the disease (e.g., sepsis, chemotherapy), and those not related to the underlying malignancy. In a number of instances, assigning the death to one of the above categories was not clear cut, however all information provided by the Applicant was utilized to adjudicate the cases.

Thirty-six deaths were determined to be due to progression or recurrence of disease, fourteen due to complications of the underlying disease, and four due to reasons unrelated to the underlying malignancy. Of these cases, three require further explanation, and are described below.

An additional 14 deaths were reported in the 120-day safety update. Details may be found in Section 7.2.9 of this review.

Individual Patient Death Summaries

Subject 006-2003 was a 66-year-old white female with lung cancer with metastases to liver and bone. Her past medical history included constipation, swallowing difficulty due to radiation, intermittent nausea related to medications, gastroesophageal reflux disease, difficulty with balance, discoid lupus erythematosus, hypothyroidism, myasthenia gravis, Raynaud's phenomenon, and shortness of breath with exertion, and anxiety. Background pain therapy included 25 µg/hr transdermal fentanyl patch for persistent pain. The subject received the first dose of study drug therapy in FEN-202 on 09 May 2006 and entered the maintenance phase of the study at a dose of 600 µg on 19 May 2006. The patient was treated for a total of 115 pain episodes with study drug, 109 of which were with the 800 mcg dose. The last dose taken before the event was 800 mcg on [redacted] b(6)