

Study Schedule of Events

Table 45:

Schedule of Events

Study Period	Screening	Titration Period	Double-blind Period	Follow-Up
Study Days	-7 to 0	1 to 14	15 to 28	29
Study Visit	1	2 ^b	3	4
Medical history	X			
Physical examination	X			X
Vital signs (blood pressure, heart rate, and respiratory rate)	X			X
Urine pregnancy test ^a	X			X
Entry criteria	X			
Signed informed consent	X			
Dispensed open-label BEMA™ Fentanyl for dose titration		X ^c		
Subjects took open-label BEMA™ Fentanyl for target breakthrough pain episodes		X		
Subjects contacted twice weekly by investigator staff member		X		
Dispensed double-blind medication for crossover period (Days 5-14)			X ^d	
Subjects took double-blind medication for target breakthrough pain episodes			X	
Pain intensity recorded before taking a dose of medication and at 5, 10, 15, 30, 45, and 60 minutes after each study dose or until rescue		X	X	
Pain relief recorded at 5, 10, 15, 30, 45, and 60 minutes after each study dose or until rescue		X	X	
Global performance evaluation at time of rescue medication or 60 minutes after each study dose		X	X	
Evaluated mouth for irritation from study medication			X	X
Adverse event recording and evaluation		X	X	X
Concurrent medications recorded	X	X	X	X
Collected remaining study medication and electronic diary			X	X

^a Women of childbearing potential

^b Study Visit 2 may be combined with the screening visit.

^c First day of titration period only

^d First day of double-blind period only (Day 14)

Source: FEN-201 study report, p. 29

Study Conduct

Screening: Day -7 to 0

- H&P, VS, I/E criteria, evaluation of mouth for mucosal irritation, urine pregnancy test (if applicable)
- Stable dose of opioid defined as:

- A dose that has been taken by the subject for 3 consecutive days just prior to the screening visit
- Dose is yielding at least moderate pain relief
- Subject is generally experiencing 4 or less breakthrough pain episodes in each 24 hour period
- Current dose produces minimal opioid side effects
- Subject was to have been trained on BEMA application and dose titration

Titration period: Day 1-14

- Open-label BEMA fentanyl at escalating doses (200, 400, 600, 800, 1200 mcg)
- Subjects instructed to treat **only identified “target” BTP**
- Dose titration was to have started with 200 mcg
- Subjects were not to have taken another dose of study drug for 4 hours after their last dose
- Subjects were to have been allowed to take usual rescue medication 30 minutes after study drug administration if needed
- Subject were not to have increased their dose without authorization of investigator
- Successful dose was to have been defined as dose that produces satisfactory BTP relief for at least 2 episodes
- Subject was to have been contacted twice a week, with disposition as follows:
 - Increase dose if pain relief is inadequate
 - Reduce dose if there is excessive sedation or other adverse effect
 - Return to the clinic if at least 2 episodes were successfully treated at the same dose of study drug. Some subjects who experience breakthrough pain with variable intensity may benefit from successful pain relief being further defined by consistent dosing with a single dose of study drug in approximately 3 out of 4 episodes.
- Subjects unable to identify dose of BEMA that would adequately control BTP episodes were to have been discontinued from study.

Initiation of double-blind period: Day 14

- Randomization: 6 doses of BEMA and 3 of placebo in random sequence
- Review of diary card and pain assessments
- Evaluation of AEs, mouth for irritation

Double-blind period: Day 15-28

- Subjects were to have been allowed usual rescue medication 30 minutes after study drug, if needed
- Pain intensity (11-point numeric scale): was to have been recorded immediately before dose, and at 5, 10, 15, 30, 45, and 60 minutes after study drug administration
- Perceived pain relief (5-point categorical scale): was to have been recorded at 5, 10, 15, 30, 45, and 60 minutes
- Global evaluation (5-point categorical scale): was to have been recorded at time of rescue or at 60 minute time point

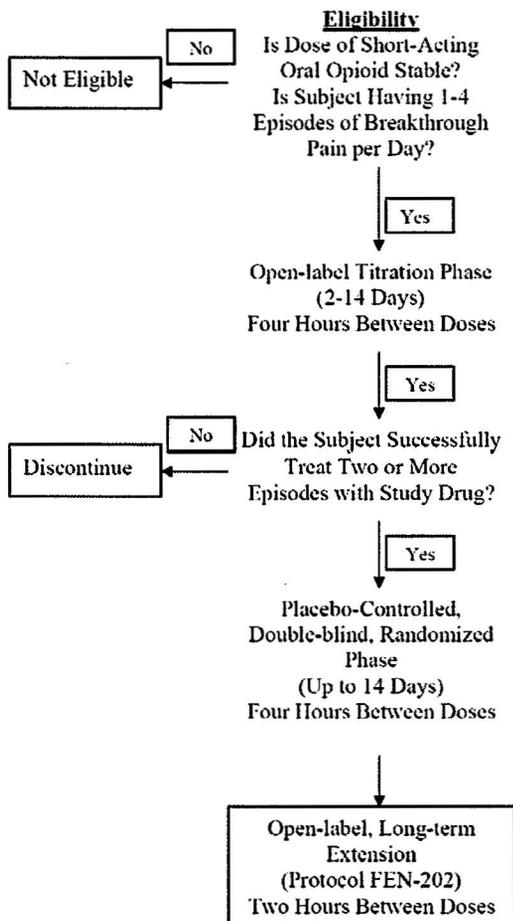
- Subjects were not to have taken another dose of study drug for 4 hours after last dose of study medication
- Rescue medication use was to have been recorded
- Subjects were to have been instructed to call PI if grade 3 or 4 mucositis develops

Follow-up: Day 28

- Retrieval of study medications and electronic diary card
- Review of pain assessments and global performance
- Evaluation of AEs
- VS
- Pregnancy test for females of childbearing potential
- Evaluation of mouth for mucosal irritation

Study Flow Chart

Figure 5



Removal of Subjects from Therapy or Assessment

- Subjects who were unable to identify a dose of BEMA™ Fentanyl that provided adequate control of their breakthrough pain episodes within two weeks of starting the dose titration period were withdrawn from the study.
- Additionally, the investigator could have withdrawn a subject from the study if a subject was not:
 - Regularly treating at least one episode of breakthrough pain each day
 - Completing the electronic diary at the time each breakthrough pain episode was treated with study medication
 - Placing the electronic diary into the cradle each night (see Appendix 16.1.3 for further details)
 - Able to apply the buccal disc properly
 - Following the sequence of study disc administration properly
 - Able to complete the study in the time allotted because of the development of Grade 3 or 4 mucositis while on study
- If a subject was discontinued because of an AE, the event was followed until it was resolved.
- Any subject was to have been able to withdraw consent at any time
- If a female subject became pregnant she was to have been withdrawn immediately

Concurrent therapy

- No new therapies which may have been expected to change the level of the subject's pain were to have been initiated during the study
- No new chemotherapy or radiation regimens were to have been initiated during the study
- Subjects administered inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) while receiving fentanyl were to have been carefully monitored and dosage adjustment made if warranted
- Subjects administered Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin were to have been carefully monitored and dosage adjustment made if warranted, since these drugs induce metabolism and as such may cause increased clearance of fentanyl.
- Concurrent medications were to have been coded using the WHO (World Health Organization) Dictionary.

Rescue Medication

Subjects were to have been allowed their usual rescue medication 30 minutes after study drug administration if adequate pain relief had not occurred. This was to have been permitted during the titration and double-blind periods of the study.

Outcome Measures

Efficacy

For each episode of target BTP treated with study medication, subjects were to have recorded on their electronic diary the date of the episode, time of study drug application, and pain intensity at that time. Response information was to have been recorded using the pain scales at 5, 10, 15, 30, 45, and 60 minutes after taking study drug.

- **Pain intensity:** Subjects were to have been asked “How bad is your pain”? Subjects were to have rated their pain intensity on an 11-point scale ranging from 0 = no pain to 10 = pain as bad as you can imagine
- **Pain relief:** Subjects were to have been asked “How much pain relief have you felt since taking the medication”? Subjects were to have rated their pain relief as: no relief; slight relief; moderate relief; lots of relief; and complete relief.
- **Global performance:** Subjects were to have been asked “What was your overall satisfaction with the medication”? Subjects were to have rated the global performance of the study drug as: poor; fair; good; very good; excellent
- **Rescue medication:** The time and use of rescue medication after study drug administration was to have been recorded for each BTP episode as yes or no

Primary Efficacy Endpoint

The primary outcome variable was to have been the sum of pain intensity differences (SPID) from 0 to 60 minutes post-dose for BEMA fentanyl (any dose) versus placebo during the double-blind portion of the study.

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 to have been the SPID 60 in the ITT population. The SPID was calculated as a weighted sum of the PID of all time points at or before the time point of interest.

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

Amendment#1 (February 28, 2007), changed the primary efficacy endpoint to the SPID at 30 minutes after application of study drug dose during the double-blind portion of the study. SPID was to have been calculated as a weighted sum of the pain intensity differences (PID) of all time points at or prior to the time point of interest. The primary analysis was to have been a comparison of the mean SPID values for episodes treated with BEMA fentanyl versus the episodes treated with placebo.

Secondary Efficacy Endpoints

- SPID at other time points
- Pain relief at each time point

- PID (pain intensity difference) at each time point
- TOTPAR (total pain relief) at each time point
- Global performance evaluation at time of rescue or 60 minutes after each dose

Amendment#1 (February 28, 2007) added use of rescue medication as secondary outcome variable

Safety

Safety was to have been evaluated by adverse event reporting, vital signs, and physical examination findings (including oral cavity).

Adverse events were to have been assessed from the start of study drug administration through the final follow-up visit.

Verbatim adverse events were to have been coded into standardized system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were to have been summarized by subject for each BEMA fentanyl dosage level and for placebo.

Statistical Analysis

Three datasets were to have been used for analysis: safety, intent-to-treat, and per-protocol. The definitions of these datasets follow:

- Safety Population: All subjects who received at least one dose of study medication and had at least one post-dose assessment
- Intent-to-Treat (ITT) Population: All subjects who entered the double-blind phase of the trial and who took at least one BEMA fentanyl and one placebo dose of study medication
- Per-protocol Population: All ITT subjects without major protocol violations that were considered to significantly affect the efficacy analyses.

Efficacy was to have been analyzed based on the ITT and Per-protocol populations. Missing data were to have been imputed on a subject-by-subject basis by carrying forward the last observed data value (LOCF). For subjects who took rescue medication, values at the time points after rescue medication administration were to have been imputed using last observation on or before rescue medication administration.

For calculations beyond 30 minutes, LOCF was to have been used to impute values for subjects who took rescue medication.

The primary endpoint of the mean sum of pain intensity differences (SPID) over the 60 minute post-study dose period for active and placebo was to have been analyzed using two-way analysis of variance with terms for treatment group, site, and treatment group by site.

“All ITT subjects without major protocol violations that were considered to significantly affect the efficacy analyses.”

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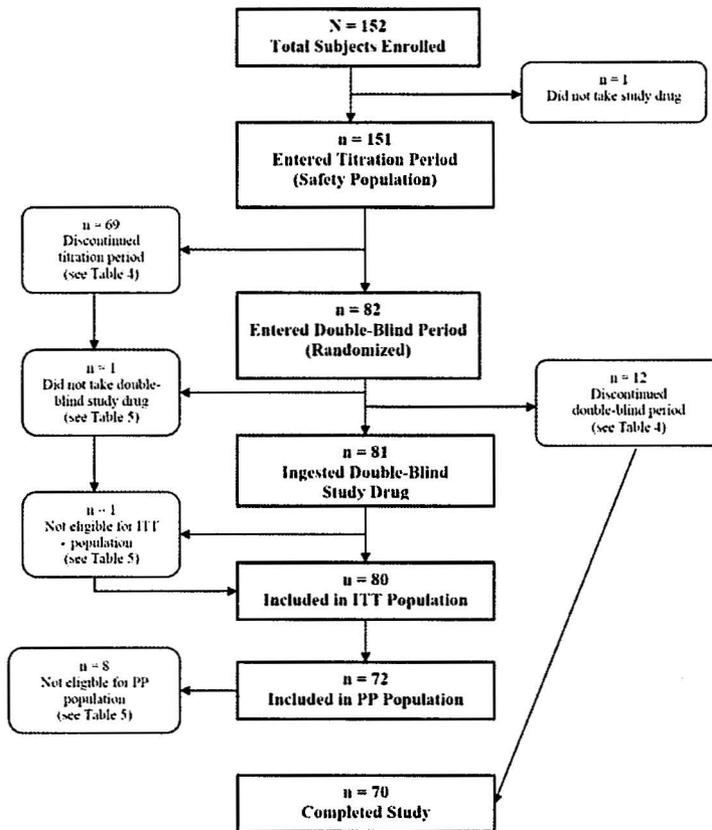
“All ITT subjects without major protocol violations that were considered to significantly affect the efficacy analyses. Major protocol violations that were considered to significantly affect the efficacy analyses include: treated pain that was not target breakthrough pain, study medication taken out of sequence, and the same dose of study medication reported being taken more than once.”

Results

Disposition of Subjects

The figure below illustrates patient disposition in study FEN-201.

Figure 6: Patient Disposition



Source: FEN-201 Study Report, p. 49

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.

A total of 69 subjects (45.4%) discontinued during the titration period including:

- 15 subjects because of difficulties or noncompliance with the electronic diary (8 – noncompliance; 6 – withdrew consent and had difficulties or were noncompliant with the electronic diary; 1 – other [failure to update the log pad])
- 14 subjects withdrew consent without explanation
- Five subjects for lack of efficacy
- Two subjects withdrew consent because of their cancer or its treatment
- Eleven subjects withdrew for a variety of other reasons such as 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), other reasons (n=2).

Table 46 below, from the Applicant’s study report, shows the reasons for discontinuation during the titration and double-blind portions of the study.

Table 46:

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

Source: FEN-201 Study Report, p. 48

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). Of the 82 randomly assigned subjects, 81 received double-blind study drug according to the randomization scheme,

and 80 subjects provided a pain assessment within the 30-minute post-dose interval in the double-blind period (ITT population).

Twelve subjects (7.9%) discontinued prematurely from the double-blind period of the study for the following reasons: four (4.9%) withdrew consent, three (3.7%) because of AEs, two (2.4%) for noncompliance with the electronic diary, two (2.4%) for not regularly treating one episode of pain per day, and one (1.2%) for lack of efficacy.

Of the 80 subjects in the ITT population, eight were excluded from the PP population. Subjects were excluded from the PP sample for two reasons: study drug taken out of sequence (five patients), and same dose of study drug being reported more than once (three patients).

There were a total of 13 subjects who discontinued from the study due to an AE: 10 subjects (6.6%) during the titration period and three (3.7%) during the double-blind period.

Protocol Deviations

Protocol deviations resulted in discontinuation of two subjects during the titration period. No subject discontinued during the double-blind period because of protocol deviations.

A major protocol violation that was considered to significantly affect the efficacy analysis was defined as 1) study drug was taken out of sequence, 2) same dose of study drug was reported more than once, or 3) treated pain that was not target breakthrough pain. Subjects in the ITT populations who met any of these criteria were excluded from the PP populations. Overall, eight subjects were identified with a significant protocol violation and were excluded from PP population including five subjects who took study drug out of sequence, and three subjects who reported taking the same dose of study drug more than once. These subjects were included in the ITT and the safety populations. There were no reports of subjects treating pain that was not the target breakthrough pain.

Demographics and Other Baseline Characteristics

Table 47 below presents a summary of subject demographics for the safety and ITT populations

Table 47:

6	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: FEN-201 Study Report, p. 53

Of the 151 subjects in the safety population, 85 (56.3%) were women and 66 (43.7%) were men. Subject age ranged from 31 to 87 years with a median age of 55 years. The majority of subjects (68.9%) were younger than 65 years old and 31.1% were 65 years and older. Subjects were white (86.8%), black (7.9%), or Asian (0.7%), and other (4.6%),

There were no important differences in the demographic characteristics between the safety and the ITT and PP populations.

In both the Safety and ITT populations, the most common cancer diagnoses were breast, lung, colorectal, and gastroesophageal (58% of Safety population and 56% of ITT). 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 Safety population, and 3.7 years in the ITT population. Approximately 55% of both populations received chemotherapy in the 6 months prior to receiving study drug, and 25% of the Safety population and 19% of the ITT population received radiation during that time period.

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 (84.8% and 86.1% subjects, respectively) or because of somatic/visceral lesions (83.4% and 84.8% subjects, respectively).

The most common stable opioid regimen was transdermal fentanyl for persistent pain taken by 46.4% of subjects and hydrocodone for target breakthrough pain taken by 42.4% of subjects. For nearly all subjects (149 of 151 [98.7%]) in the safety population, there were minimal opioid side effects from the current daily opioid dose. Table 48 below shows a summary of the pain therapy used by the study population.

Table 48:

	BEMA™ Fentanyl*	
	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.

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

Source: FEN-210 Study Report, p. 57

There were no important difference in demographics and other baseline characteristics between the safety and the ITT populations.

Treatment Compliance

Dosing compliance during the double-blind period showed a mean of 89.03% of doses taken as instructed. Three subjects were withdrawn from the study during the titration period because of noncompliance with study drug administration

Analysis of Efficacy

Primary Efficacy Endpoint: Sum of Pain Intensity Differences at 30 Minutes (SPID 30)

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

The SPID 30 for BEMA™ Fentanyl-treated episodes was statistically significantly greater (p=0.004) than the LS mean SPID for placebo-treated episodes. The SPID 30 (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.