

remained in the same category or shifted to one of the other two categories at the final visit. Final evaluation results were not necessarily obtained when subjects had recently taken a dose of study medication.

Vital sign data was available on only 63 subjects in the short-term administration population.

Shifts of subjects from normal systolic blood pressure (BP; 100 to 140 mmHg) to low systolic pressure were infrequent (2 of 51 subjects; 4%) and were similar to the rate of subject shifts from normal to elevated systolic pressure (6%). Similarly, the frequency of shifts from normal diastolic BP (60 to 90 mmHg) to low diastolic pressure was similar to the frequency of shifts from normal to high diastolic pressures; 4 of 61 (7%) subjects with normal baseline diastolic pressures shifted to low pressures at the final evaluation and 6 of 61 (10%) subjects with normal baseline diastolic pressures shifted to high pressures. Subjects with low baseline systolic or diastolic pressures did not shift to high pressures and subjects with high baseline systolic or diastolic pressures did not shift to low pressures.

Seven of 56 subjects (12.5%) with normal baseline heart rates (55 to 100 beats per minute) had elevated heart rates at the Final Visit. Shifts from normal to low heart rates did not occur. Subjects with low baseline heart rates did not shift to having high heart rates and subjects with low baseline heart rates did not shift to having high heart rates.

These findings in the short-term administration population do not raise special concerns about adverse effects of study drug on vital signs.

Table 30: Shift of Vital Signs-Short Term Administration.

Parameter	Short-term Administration (N=301)				
	Baseline Result	Final Evaluation			Total
		Low	Normal	High	
Systolic Blood Pressure (mmHG)	Low	0	3 (4.8)	0	3 (4.8)
	Normal	2 (3.2)	46 (73.0)	4 (6.3)	52 (82.5)
	High	0	4 (6.3)	4 (6.3)	8 (12.7)
	Total	2 (3.2)	53 (84.1)	8 (12.7)	63 (100.0)
Diastolic Blood Pressure (mmHG)	Low	0	1 (1.6)	0	1 (1.6)
	Normal	4 (6.3)	52 (82.5)	5 (7.9)	61 (96.8)
	High	0	0	1 (1.6)	1 (1.6)
	Total	4 (6.3)	53 (84.1)	6 (9.5)	63 (100.0)
Pulse Rate (beats per minute)	Low	0	0	0	0
	Normal	1 (1.6)	48 (76.2)	7 (11.1)	56 (88.9)
	High	0	5 (7.9)	2 (3.2)	7 (11.1)
	Total	1 (1.6)	53 (84.1)	9 (14.3)	63 (100.0)
Respirations (breaths per minute)	Low	0	0	0	0
	Normal	0	54 (90.0)	3 (5.0)	57 (95.0)
	High	0	3 (5.0)	0	3 (5.0)
	Total	0	57 (95.0)	3 (5.0)	60 (100.0)

Source: BEMA NDA ISS, p. 55

In Study FEN-113, vital sign assessments were performed prior to dosing, and repeatedly after the single applied dose. Note that these subjects were not required to be opiate-tolerant, and received a single dose of 200 µg of BEMA Fentanyl. Two subjects with and 6 subjects without mucositis experienced a post-baseline decrease in either systolic or diastolic BP of ≥ 15 mmHg at any post-treatment assessment. Three of the non-mucositis patients had decreases ≥ 30 mmHg. These values were in the high-normal range and none of the 8 subjects was symptomatic. The subject (Subject 4002) with the largest decrease had BP of 175/84 mmHg at baseline versus 138 to 154 mmHg (systolic) and 66 to 75 mmHg (diastolic) post-treatment; suggesting an elevated baseline reading. No subject experienced a change in respiratory rate of >2 breaths per minute. The decreases in blood pressure experienced by these patients are likely due to the fact that they were not opioid-tolerant.

The Applicant's table below shows a summary of the shift of vital signs from screening to the final visit for the long-term treatment population. Baseline vital signs (sitting heart rate, systolic and diastolic BP) are taken from the last assessment prior to the initial dose of study drug. For subjects enrolling into FEN-202 from FEN-201, the Baseline Result is the last assessment prior to the initial dose of study drug in FEN-201. The Final Evaluation Result is the last assessment recorded. Final evaluation results were not necessarily obtained when subjects had recently taken a dose of study medication.

Vital sign data were available on 104 subjects in the long-term treatment population.

The frequency of shifts from normal systolic BP (60 to 90 mmHg) to low systolic pressure was similar to the frequency of shifts from normal to high systolic pressures; 9 of 87 subjects (10%) with normal baseline systolic pressures, shifted to low systolic pressures at the final evaluation and 10 of these 87 subjects 11.5% (10%) shifted to high systolic pressures.

Similarly, the frequency of shifts from normal diastolic to low diastolic pressure was low and similar to the frequency of shifts from normal to high systolic pressures; 5 of 89 subjects (6%) with normal baseline diastolic pressures, shifted to low diastolic pressures at the final evaluation and 4 of these 89 subjects (4%) shifted to high diastolic pressures.

Fourteen of 96 (15%) subjects with normal baseline heart rates (55 to 100 beats per minute) had elevated heart rates at the final visit. Shifts from normal to low heart rates did not occur.

These findings in the long-term treatment population do not raise special concerns about adverse effects of study drug on vital signs. The findings are consistent with a combination of expected variability and deteriorating physical status of subjects with serious cancers.

Table 31: Shift of Vital Signs-Long-Term Treatment

Parameter	Long-term Treatment (N=190)				
	Baseline Result	Final Evaluation			Total
		Low	Normal	High	
Systolic Blood Pressure (mmHG)	Low	0	5 (4.9)	0	5 (4.9)
	Normal	9 (8.7)	68 (66.0)	10 (9.7)	87 (84.5)
	High	0	6 (5.8)	5 (4.9)	11 (10.7)
	Total	9 (8.7)	79 (76.7)	15 (14.6)	103 (100.0)
Diastolic Blood Pressure (mmHG)	Low	1 (1.0)	8 (7.8)	0	9 (8.7)
	Normal	5 (4.9)	80 (77.7)	4 (3.9)	89 (86.4)
	High	0	4 (3.9)	1 (1.0)	5 (4.9)
	Total	6 (5.8)	92 (89.3)	5 (4.9)	103 (100.0)
Pulse Rate (beats per minute)	Low	0	0	1 (1.0)	1 (1.0)
	Normal	0	82 (78.8)	14 (13.5)	96 (92.3)
	High	0	3 (2.9)	4 (3.8)	7 (6.7)
	Total	0	85 (81.7)	19 (18.3)	104 (100.0)
Respirations (breaths per minute)	Low	0	0	0	0
	Normal	0	90 (88.2)	4 (3.9)	94 (92.2)
	High	0	5 (4.9)	3 (2.9)	8 (7.8)
	Total	0	95 (93.1)	7 (6.9)	102 (100.0)

Source: BEMA NDA ISS, p. 57

This reviewer reassessed the above data, using source tables and dataset *AF_Vital.xpt*, and agrees with the Applicant's findings regarding the effect of study drug on vital signs.

7.1.8.4 Additional analyses and explorations

There were no additional analyses carried out on vital sign data.

7.1.9 Electrocardiograms (ECGs)

ECGs were not performed during the development program for BEMA Fentanyl

7.1.10 Immunogenicity

This category is not applicable to this study drug.

7.1.11 Human Carcinogenicity

For this limited indication in patients with advanced malignancy, an assessment of carcinogenicity was not required.

7.1.12 Special Safety Studies

FEN-113 was a Phase 1 pharmacokinetic study done to evaluate the fentanyl absorption from the BEMA delivery system in the presence of Grade 1 mucositis. Secondary objectives included 1)

the evaluation of the local irritation associated with the application of the BEMA disc to oral mucosa that was classified as having Grade 1 mucositis; 2) evaluation of the percentage of disc present at specific time points through the first hour after dosing; and 3) the assessment of the tolerability of a 200µg dose of BEMA Fentanyl.

The study was an open-label, single-dose study in two groups of cancer subjects. Cohort 1 subjects had Grade 1 mucositis, and Cohort 2 subjects were age- and gender-matched controls without mucositis. A total of 14 subjects were enrolled, seven in each cohort. Eligible subjects received a single 200 µg dose of BEMA Fentanyl, which was applied to the buccal mucosa by study personnel. The disc was applied to the area of the mucosa that met the requirements for Grade 1 mucositis (Cohort 1) or to a location of the mucosa similar to the site used for the matched subject with mucositis (Cohort 2).

The Applicant utilized the NCI mucositis grading system as shown in Table 32.

Table 32: NCI Mucositis Grading System

NCI MUCOSITIS GRADING SYSTEM				
0	1	2	3	4
No changes	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers, but can eat or swallow	Painful erythema, edema, or ulcers requiring IV hydration	Severe ulcerations or requires parenteral or enteral nutritional support or prophylactic intubation

Safety Results

Fourteen subjects participated in this study and each received a single 200 µg dose of BEMA Fentanyl.

The only adverse event was mild somnolence that occurred in two subjects in Cohort 1 (mucositis) and no subjects in Cohort 2 (no mucositis). No treatment was administered and both events resolved within two hours of reporting. There was no evidence of respiratory depression following dosing. There were no deaths or SAEs in this study.

The Applicant also assessed application site irritation by serial evaluation of the application site. All 7 subjects with mucositis had associated pain at baseline, five mild, 1 moderate, and 1 severe mucositis pain. None of the subjects without mucositis had baseline oral pain. Of the six subjects with mild or moderate pain at baseline, five became pain free within one hour, and one pain free within two hours. The one subject with severe pain at baseline became pain free at one hour, and then mild pain returned through four hours. Since pain decreased after study drug application, it appears there was no additional application site pain caused by the study drug in the mucositis patients.

Please refer to the Biopharmaceutics review for a complete review of the pharmacokinetic findings; however the study did show that application of BEMA Fentanyl to an area of Grade 1 mucositis does not expose a cancer patient to a risk of increased fentanyl plasma concentrations compared to cancer patients without mucositis.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No studies were performed to assess the abuse potential of fentanyl in the BEMA delivery system.

Normal volunteers that participated in the pharmacokinetic studies received concurrent naltrexone to block the effects of fentanyl. No withdrawal symptoms were observed.

Subjects eligible for the Phase 3 clinical trials were required to be on a stable dose of a background opioid equal in analgesic activity to 60 to 1000 mg of oral morphine daily. No withdrawal or rebound from BEMA Fentanyl was expected or reported in these studies.

7.1.14 Human Reproduction and Pregnancy Data

There is no data on human reproduction and pregnancy for this study drug.

7.1.15 Assessment of Effect on Growth

There was no assessment for the effect of this drug on growth.

7.1.16 Overdose Experience

There were no reports of overdose in the BEMA Fentanyl development program.

7.1.17 Postmarketing Experience

There is no postmarketing experience for this study drug as it is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

This submission consisted of six Phase 1 PK studies in healthy volunteers, one Phase 1 PK study in cancer patients with mucositis (FEN-113), one adequate and well controlled Phase 3 efficacy study (FEN-201), and one long-term, open-label trial (FEN-202).

The following safety datasets were submitted by the Applicant with the original NDA submission: *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*, and *MPF.xpt*. Data from studies FEN-201, FEN-202, and FEN-113 were included in these datasets.

The studies included in the ISS are summarized below:

Table 33: Overview of Studies Included in ISS

Study	Doses Used (µg)	Study Design	Short-term Administration Analyses	Long-term Treatment Analyses
FEN-113	200	Two center, open-label, single-dose	All	None
FEN-201	200 – 1200	Multi-center, double-blind, randomized, placebo-controlled, multiple cross-over	Titration period	Double-blind
FEN-202	200 – 2400	Multi-center, open-label	Titration period	Open-label long-term treatment

Source: BEMA Fentanyl ISS, p. 12

7.2.1.1 Study type and design/patient enumeration

A total of 449 subjects were enrolled in the BEMA Fentanyl development program. Sixty-six of these were non-cancer subjects that received single or multiple doses of study drug. All studies were carried out in the United States. Table 34 summarizes the studies and enrollment for Phases 1-3.

Table 34: All Subjects Exposed to BEMA Fentanyl

Protocol	Study Category	Duration of Exposure	Dose (µg)	Number of Subjects
FEN-104	Pharmacokinetic in normal subjects	Single dose	200	12
FEN-107	Pharmacokinetic in normal subjects	Single dose	800	12
FEN-109	Clinical pharmacology in normal subjects	Single dose	400 Buccal, 1200 Transdermal	6
FEN-110	Pharmacokinetic in normal subjects	Single dose	200, 600, 1200	12
FEN-112	Pharmacokinetic in normal subjects	Single and multiple dose	600	12
FEN-114	Pharmacokinetic in normal subjects	Single dose	800	12
FEN-113	Pharmacokinetic in cancer subjects	Single dose – short-term	200	14
FEN-201	Efficacy in cancer subjects with breakthrough pain	Up to 4 weeks – short-term and long-term	200 – 1200	145
FEN-202	Long-term safety in cancer subjects with breakthrough pain	Unlimited – short-term and long-term	200 – 2400	224
Total				449

Source: BEMA Fentanyl ISS, p. 9

A total of 390 cancer patients were enrolled in the three studies that comprise the safety database. Seventy-eight patients enrolled in FEN-202 had previously received study drug in

either FEN-113 or FEN-201. Dosing administration data were not available for eleven subjects. The safety population for the ISS analysis consists of 301 cancer patients.

Table 35: ISS Population

	FEN-201	FEN-202	FEN-113	Total
Enrolled subjects	152	224	14	390
No dosing data	7	4	0	11
Subjects previously dosed in FEN-201 or FEN-113	Not applicable	78	Not applicable	78
ISS population	145	142	14	301

Source: FEN-201 CSR; FEN-202 CSR; FEN-113 CSR

Source: BEMA Fentanyl ISS, p. 13

A total of 301 cancer subjects received at least one dose of BEMA Fentanyl. These are included in the short-term administration analyses. A total of 190 subjects entered the long-term treatment period.

7.2.1.2 Demographics

Table 36 is a summary of the demographics of the study population for all studies. For Phase 1 studies, the average age ranged from 26-32 years, the gender ratio was predominantly male, and the subjects were racially diverse.

Table 36: Demographic and Background Characteristics of Study Subjects

Study	Age mean (range)	Gender (M/F)	Race ^a	Weight kg mean (range)	Primary Diagnosis	Concomitant therapy	Smoking Status	Ethanol Use
FEN-104 ^b	19 - 39	12/0	7 B 4 C 1 A	61 - 92	Normal	None	No	No
FEN-107	32 (21 - 44)	9/3	5 H 4 C 3 B	70 (52 - 86)	Normal	Naltrexone	No	No
FEN-109	27 (19 - 33)	5/1	3 C 2 H 1 A	72 (69 - 72)	Normal	Naltrexone	No	No
FEN-110	27 (23 - 31)	11/1	5 C 4 O 3 H	75 (64 - 84)	Normal	Naltrexone	No	No
FEN-112	26 (19 - 34)	9/3	7 C 3 B 2 H	70 (53 - 87)	Normal	Naltrexone	No	No
FEN-114	27 (19 - 37)	6/6	6 B 4 C 2 H	71 (63 - 84)	Normal	Naltrexone	No	No
FEN-113	61 (45 - 77)	10/4	10 C 4 H	92 (55 - 145)	Cancer	Not Required	NC ^c	NC ^c
FEN-201	57 (31 - 87) 104 <65 47 ≥65	66/85	131 C 12 B 7 O 1 A	69 (36 - 155)	Cancer	>60 mg oral morphine/day	NC ^c	NC ^c
FEN-202	58.2 150 <65 70 ≥65	103/117	187 C 22 B 2 A 9 O	73.9 (44 - 127)	Cancer	>60 mg oral morphine/day	NC ^c	NC ^c

a Race: A = Asian; B = African American; C = Caucasian; H = Hispanic; O = Other
 b Early formulation
 c Not collected

The demographics for the short and long-term populations included in the ISS are summarized below. The mean age is similar for both groups (57-58 years), and approximately one-third are over 65 years of age. The gender make-up and weights are also similar for both groups. Slightly less than half of the cancer patients are male. As shown in Table 37, the majority of patients comprising the ISS are Caucasian.

Table 37: ISS Population Demographics

	Exposure Population	
	Short-term (N=301)	Long-term (N=190)
Age		
Mean	58.4	57.7
Range	29 - 87	29 - 86
<65	200 (66.4)	131 (68.9)
≥65	101 (33.6)	59 (31.1)
Gender		
Males	140 (46.5%)	85 (44.7%)
Females	161 (53.5%)	105 (55.3%)
Weight – Males (pounds)		
Mean	174.0	173.6
Range	113 - 300	113 - 277
Weight – Females (pounds)		
Mean	155.6	153.2
Range	80 - 340	97 - 263

Source: BEMA Fentanyl ISS, p. 14

Table 38 summarizes the baseline characteristics of the safety population. In both the short and long-term exposure groups, the most common cancers were lung, breast, and colon/rectal. More than half of both groups were using transdermal fentanyl as their background opioid. Two short-acting opioids, oxycodone and hydrocodone, were used by approximately 30% of subjects in both groups.

Table 38: Baseline Characteristics

	Exposure Duration	
	Short-term (N=288)	Long-term (N=190)
Cancer diagnosis reported by >10% of subjects – n (%)		
Lung	48 (16.7)	28 (14.7)
Breast	57 (19.8)	35 (18.4)
Colon/rectal	30 (10.4)	21 (11.1)
Stable opioid regimen used by >10% of subjects – n (%)		
Long-acting morphine	69 (24.0)	47 (24.7)
Transdermal fentanyl	145 (50.3)	100 (52.6)
Long-acting oxycodone	63 (21.9)	40 (21.1)
Breakthrough pain medications used by >10% of subjects – n (%)		
Short-acting morphine	45 (15.6)	32 (16.8)
Short-acting oxycodone	90 (31.3)	56 (29.5)
Hydromorphone	41 (14.2)	33 (17.4)
Hydrocodone	95 (33.0)	64 (33.7)

Source: BEMA Fentanyl ISS, p. 15

7.2.1.3 Extent of exposure (dose/duration)

The following table summarizes the exposure data by dose, duration, and number of doses. Over 60,000 doses of study drug were administered to cancer patients during the development program. Fifty-six percent were at doses of 800µg or 1200µg. Less than 5% of the doses used were 200 µg, while almost 11% were over 1200 µg. Notably, the number of doses used at the 1200 µg dose level was over 25% greater than at the 800 µg dose level, while the number of subjects treated at 1200 µg was 30% less than at 800 µg, indicating a longer duration of exposure per subject at the 1200 µg dose level.

There appears to be a direct relationship between the mean number of doses used per day and the dose of BEMA Fentanyl, with subjects using a mean of 2 doses per day in the 200 to 400 µg dose range, 3 doses per day in the 600 to 1200 µg dose range, and 4 doses a day above 1200 µg.

Table 39: Exposure Data by Dose and Duration for ISS Population

	BEMA Fentanyl Dose (µg)						Total
	200	400	600	800	1200	>1200	
Number of subjects	297	239	199	150	100	24	301
Number (%) of doses	2616 (4.3)	7871 (13.1)	9094 (15.1)	15161 (25.2)	18990 (31.6)	6366 (10.6)	60098
Number of subject days in study	1449	3229	3486	5684	5954	1796	21211
Mean number of doses/ subject day	2	2	3	3	3	4	3
Total exposure							
Mean days							82.2
≥60 days							112
≥90 days							91

Source: BEMA Fentanyl ISS, p. 17

At the time of NDA submission, 112 patients had been treated with BEMA Fentanyl for ≥ 60 days, and 91 for ≥ 90 days. The Division had specified that there should be ≥100 patients receiving drug for ≥ 90 days. The Applicant stated that, as Study FEN-202 is ongoing, the 120 day safety update will contain data on the additional patients. Please refer to Section 7.2.9 for updated exposure data.

Exposure to the 1200µg dose in terms of number of patients is 30% smaller than the 800µg dose, however the mean number of doses per subject day is the same, and the total number of doses is 25% greater in the 1200µg dose group.

Table 40 below is a comparison of the effective doses found across studies. Similar percentages of subjects found doses in the range of 200µg to 1200 µg to be effective in the titration portions of FEN-201 and FEN-202 studies. FEN-202 subjects were allowed to titrate beyond 1200µg, but

the initially effective dose did not exceed 1200µg for 95% of the subjects. Only 9% of the 172 subjects treated in the open-label period of FEN-202 used a dose >1200µg. In both studies, ≤ 8% of patients found 200µg to be an effective dose.

Table 40: Comparison of Effective Doses Across Studies

Dose (µg)	FEN-201 N (%) Dose Distribution in Double-blind Period	FEN-202 N (%) Initial Effective Dose	FEN-202 N (%) Effective Dose at Interim Cutoff
200	4 (5%)	14 (8%)	13 (8%)
400	15 (18%)	35 (20%)	29 (17%)
600	23 (28%)	40 (23%)	29 (17%)
800	19 (23%)	43 (25%)	41 (24%)
1200	20 (25%)	30 (17%)	43 (25%)
1600	NA	6 (3.5%)	11 (6%)
2400	NA	4 (2%)	3 (3%)
Total	81 (100%)	172 (100%)	172 (100%)

Source: BEMA Fentanyl ISS, p. 16

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There are no secondary sources of clinical data for this application.

7.2.2.2 Postmarketing experience

There is no post-marketing experience for this product as it is not approved in any country.

7.2.2.3 Literature

The Applicant submitted 13 literature references pertaining to breakthrough pain, analysis of endpoints, pharmacokinetics of fentanyl, and the analysis of efficacy data in similarly designed studies.

The literature provided appears adequate to assist in the evaluation of previous experience with fentanyl in the treatment of cancer breakthrough pain.

7.2.3 Adequacy of Overall Clinical Experience

The Division recommended that the safety population be comprised of 300 to 500 patients, with at least 100 receiving study drug for greater than 90 days. The number of subjects exposed to BEMA Fentanyl during the development program was adequate to determine its safety from a pre-marketing standpoint, given that so much is known about the fentanyl moiety and its safety profile. The safety database, including the 120-day safety update, consisted of 300 opioid-tolerant cancer patients, 122 of which were exposed for at least 60 days, and 98 who were