Table 21: Summary of Application Site Reactions, Excluding Events Related to Causes Other than Study Drug (N=301 subjects)

Preferred Term	Events	Subjects	Severity [a, b]			Discontinuations [b]	Related or Possibly Related [a, b]
			Mild	Moderate	Severe		
Stomatitis	6	5 (1.6%)	5	0	0	0	2
Mouth Ulcer	2	2 (0.7%)	2	0	0	0	1
Hypoesthesia	2	2 (0.7%)	2	0	0	0	0
All Others [c]	6	5 (1.6%)	3	2	1	0	1
TOTAL	16	14 (4.6%)	12	2	1	0	4

a One AE of stomatitis did not have an assessment of severity or causality.
b Entries in these columns count AEs.
c "All Others" includes all Preferred Terms for which there was only one AE each. These were: Gingival Infection, Mucosal Inflammation, Aphthous Stomatitis, Odynophagia, Tooth abscess, and Toothache.

Respiratory Events of Special Interest

Hypoxia

There were three reports of hypoxia in two patients in the development program. Subject 063-2001 developed hypoxia following chemotherapy for colorectal carcinoma and was found to have alveolar consolidation, pleural effusion, and hypotension. The hypoxia continued despite oxygen supplementation. It is unlikely the study drug was related to this event. Subject 063-2008 had lung cancer, and developed hypoxia, shortness of breath, confusion, delusions and anxiety a week after starting study medications. The patient remained on study drug for two days during this event, however it was discontinued, and the adverse events were resolved the next day. It is possible that the study drug was related to this event of hypoxia. See patient narrative in Section 7.1.2.

Respiratory Distress/Apnea

There were two reports of respiratory distress. Subject 004-2005 developed it in the setting of left lung atelectasis and pulmonary embolism, and subject 028-2003 experienced respiratory distress and apneic episodes concurrently with asthma, which required several days of intubation and mechanical ventilation. Study drug was restarted following the hospitalization. As stated in the patient narratives in Section 7.1.2, both of these events of respiratory distress were determined to be unrelated to study drug.

Respiratory Depression

One subject experienced respiratory depression. This subject (011-2004) was using 100-µg transdermal fentanyl, 120 mg of oral long-acting morphine every six hours, and 2400 µg BEMA Fentanyl 4 times daily, and suffered a hip fracture requiring hospitalization. BEMA Fentanyl and Valium were discontinued on that day, other pain medications were adjusted, and the day following discontinuation of study drug the subject **had an episode of "narcotic respiratory depression". This resolved the same day. The** next day the subject was started on intravenous morphine by patient-controlled pump. The subject died of progression of cancer 10 days later. The complex sequence of events surrounding this AE suggests multiple etiologies in addition to any potential contribution from study drug, which had been discontinued the day before the AE.

Respiratory Failure
Subject 031-1002 was a 52-year-old white female with breast cancer and bone metastases. She was hospitalized with severe respiratory failure approximately seven weeks after her last dose of study drug. The patient expired the next day. Study drug was not related to this event, given the length of time since the last dose. See narrative in Section 7.1.1 for further details.

Aspiration
There was one report of aspiration in a patient (006-2003) with lung cancer with liver and bone metastases, and difficulty swallowing due to radiation treatment. She died at home due to aspiration of bloody sputum. She had on a stable dose of 800 mcg of study drug for several weeks prior to this event. It is unlikely that study drug was related. See narrative in Section 7.1.1.

There were no reported episodes of pneumonia associated with aspiration.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All spontaneously reported, elicited, and observed AEs were documented on the CRF. Data collection for AEs began after screening and continued until the cutoff date of August 28, 2007. Because AEs were not recorded before the first dosing, all AEs were considered treatment-emergent. This data does not include the 120-day safety update.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using MedDRA version 8.1. The appropriateness of the Applicant's coding was evaluated by comparing the preferred terms to the verbatim terms recorded by investigators. In the opinion of this reviewer, the coding was reasonably accurate.

7.1.5.3 Incidence of common adverse events

Adverse event data was collected starting with the first dose of study drug. The Applicant has chosen to present treatment-emergent adverse events according to short-term exposure (FEN-113 and titration periods of FEN-201 and FEN-202) and long-term exposure (FEN-201 double-blind period and FEN-202 open-label period) to study drug. This approach is similar to that used in the Actiq and Fentora labels, and is acceptable.

7.1.5.4 Common adverse event tables

In all tables, a subject was counted once if the subject reported multiple occurrences of the same adverse event at a given dose level.

Table 22 presents a summary of treatment-emergent AEs by dose that occurred in ≥ 5% of the subjects during short-term administration of study drug. Adverse events are attributed to the highest dose a subject took on the event onset date. This reviewer verified this data using the SAS dataset *AF_AE.xpt*. The most commonly observed AEs seen with BEMA Fentanyl are typical AEs associated with opioids and include nausea and vomiting in 9.6% and 6.6% of subjects, respectively. There was no evidence of dose-related increase in the frequency of these AEs. Dizziness and somnolence each occurred in 6.0% of subjects, and there did appear to be a dose-related increase in the frequency of these AEs.

Table 22: Adverse Events during Short-Term Administration at a Frequency of ≥ 5%

System Organ Class, Preferred Term, n (%)	BEMA Fentanyl Dose (µg)						Total (N=301)
	200 (N=297)	400 (N=235)	600 (N=186)	800 (N=122)	1200 (N=71)	>1200 (N=9)	
Number (%) of subjects with ≥1 adverse event	43 (14.5)	38 (16.2)	33 (17.7)	14 (11.5)	20 (28.2)	2 (22.2)	129 (42.9)
Gastrointestinal							
Nausea	9 (3.0)	11 (4.7)	4 (2.2)	3 (2.5)	3 (4.2)	0	29 (9.6)
Vomiting	6 (2.0)	8 (3.4)	5 (2.7)	1 (0.8)	0	0	20 (6.6)
Nervous System							
Dizziness	4 (1.3)	5 (2.1)	5 (2.7)	1 (0.8)	3 (4.2)	0	18 (6.0)
Somnolence	6 (2.0)	2 (0.9)	4 (2.2)	2 (1.6)	4 (5.6)	1 (11.1)	18 (6.0)

Source: BEMA NDA ISS, p.

The following table shows the percentage of treatment emergent adverse events occurring in ≥ 1% of patients. Constipation, a common opioid side-effect, occurred in 2% of the population.

Table 23: Adverse Events during Short-Term Administration at a Frequency of ≥ 1%

Adverse Event (PT)	#	%
Headache	10	3%
Anemia	8	3%
Constipation	7	2%
Diarrhea	6	2%
Pain	6	2%
Pneumonia	6	2%
Dehydration	5	2%
Anxiety	4	1%
Dry mouth	4	1%
Hypokalemia	4	1%
Confusional state	3	1%
Dysgeusia	3	1%
Dyspnea	3	1%
Fatigue	3	1%
Gastrointestinal hemorrhage	3	1%
Pyrexia	3	1%

Sedation	3	1%
Thrombocytopenia	3	1%

Table 24 presents a summary of treatment-emergent AEs that occurred during long-term treatment to BEMA Fentanyl in ≥ 5% of the 190 subjects. Subjects had selected an effective dose that was tolerated upon entry into these study periods.

Generally the reported AEs reflect the underlying cancers of the population studied or the cancer treatments administered to these subjects. The AEs reported at ≥ 5% in long-term treatment with BEMA Fentanyl that are typical of opiates (though cancer or other causes may have contributed in individual cases) were nausea (20.5%), vomiting (16.3%), asthenia (11.1%), fatigue (10.0%), confusional state (7.4%), constipation (6.8%), and dizziness (6.3%). Other commonly-reported AEs (≥ 10%) in long-term treatment were typical of a cancer population and included dehydration (11.6%). Anemia was seen in 9.5% of subjects. These AEs may be due to the underlying cancer, treatments such as chemotherapy, or the use of opioids, including BEMA Fentanyl for pain relief. A common opioid side effect, somnolence, occurred in <5% of subjects and is thus absent from Table 24.

The incidence of nausea and vomiting in the 1200 μg dose group was more than twice that at any lower dose and also higher than in the 24 subjects receiving any dose >1200 μg. In addition, diarrhea, dehydration, and pain were reported more frequently in this group. This may be a function of the increased duration of exposure in this group. The data in this table was verified by this reviewer.

Table 24: Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class, Preferred Term, n (%)	BEMA Fentanyl Dose (µg)						Total (N=190)
	200 (N=19)	400 (N=51)	600 (N=67)	800 (N=74)	1200 (N=66)	>1200 (N=24)	
Number of subjects with ≥1 treatment-emergent adverse event	11 (57.9)	33 (64.7)	42 (62.7)	52 (70.3)	44 (66.7)	17 (70.8)	148 (77.9)
Blood and lymphatic							
Anemia	0	3 (5.9)	4 (6.0)	11 (14.9)	1 (1.5)	0	18 (9.5)
Gastrointestinal							
Ascites	0	3 (5.9)	3 (4.5)	3 (4.1)	1 (1.5)	1 (4.2)	11 (5.8)
Constipation	1 (5.3)	1 (2.0)	4 (6.0)	2 (2.7)	3 (4.5)	2 (8.3)	13 (6.8)
Diarrhoea	1 (5.3)	2 (3.9)	3 (4.5)	5 (6.8)	7 (10.6)	0	18 (9.5)
Nausea	2 (10.5)	5 (9.8)	6 (9.0)	8 (10.8)	17 (25.8)	4 (16.7)	39 (20.5)
Vomiting	0	3 (5.9)	6 (9.0	7 (9.5)	15 (22.7)	3 (12.5)	31 (16.3)
General/Administration Site							
Asthenia	0	5 (9.8)	2 (3.0)	7 (9.5)	4 (6.1)	3 (12.5)	21 (11.1)
Fatigue	2 (10.5)	4 (7.8)	2 (3.0)	4 (5.4)	6 (9.1)	1 (4.2)	19 (10.0)
Oedema peripheral	1 (5.3)	6 (11.8)	5 (7.5)	5 (6.8)	5 (7.6)	2 (8.3)	24 (12.6)
Pain	1 (5.3)	3 (5.9)	4 (6.0)	5 (6.8)	6 (9.1)	0	18 (9.5)
Infections							
Pneumonia	0	1 (2.0)	2 (3.0)	6 (8.1)	5 (7.6)	1 (4.2)	15 (7.9)
Urinary tract infections	0	3 (5.9)	5 (7.5)	3 (4.1)	2 (3.0)	0	12 (6.3)
Metabolism/Nutrition							
Decreased appetite	0	4 (7.8)	3 (4.5)	4 (5.4)	1 (1.5)	2 (8.3)	14 (7.4)
Dehydration	1 (5.3)	3 (5.9)	5 (7.5)	5 (6.8)	8 (12.1)	1 (4.2)	22 (11.6)
Musculoskeletal							
Back pain	2 (10.5)	1 (2.0)	1 (1.5)	6 (8.1)	2 (3.0)	0	12 (6.3)
Nervous system							
Dizziness	1 (5.3)	3 (5.9)	2 (3.0)	2 (2.7)	2 (3.0)	2 (8.3)	12 (6.3)
Headache	2 (10.5)	1 (2.0)	2 (3.0)	6 (8.1)	2 (3.0)	0	12 (6.3)
Psychiatric							
Confusional state	0	0	4 (6.0)	2 (2.7)	5 (7.6)	3 (12.5)	14 (7.4)
Respiratory							
Dyspnoea	2 (10.5)	4 (7.8)	2 (3.0)	6 (8.1)	3 (4.5)	0	17 (8.9)

Table 63 in Appendix 10.4 shows the treatment emergent adverse events occurring in ≥ 1% of patients receiving long-term administration of study drug. Events possibly related to study drug or background opioids in this category include stomatitis (4%), mucosal inflammation (1%), sedation (1%), somnolence (4%), hypoxia (2%), and respiratory distress (1%).

7.1.5.5 Identifying common and drug-related adverse events

See section 7.1.5.4

7.1.5.6 Additional analyses and explorations

First Dose Safety

The Division requested that the Applicant obtain information regarding the safety profile of the first dose of BEMA Fentanyl. A summary of the safety profile following administration of the 200-µg dose in a clinical setting to 111 subjects from FEN-113 and FEN-202 is provided in the Applicant's table below (97 from FEN-202 and 14 from FEN-113). As specified in the protocol, each of these 111 subjects was observed closely by the investigator for approximately 1 to 4 hours after BEMA Fentanyl application. There were no occurrences of respiratory depression or nausea. The only reported AEs were mild somnolence in 2 subjects from the FEN-113 study. Both cases resolved within 2 hours. Of note, the subjects participating in FEN-113 were not required to be opioid-tolerant. The first dose of study drug does not appear to be associated with increased risk of adverse events.

Table 25: Summary of First Dose Safety-Studies FEN-113 and FEN-202

Subjects who took a single 200 µg dose of study drug administered in the clinic	111 [a]
Subjects with any of the following symptoms immediately after the first dose:	
Respiratory Depression	0
Drowsiness/somnolence	2 [b]
Nausea	0
Other	0

[a] 97 subjects from FEN-202 and 14 subjects from FEN-113
[b] Both subjects from FEN-113 and both with mucositis

Gender

A numerically greater percentage of female patients than male patients experienced AEs in the short-term administration population. The incidence of reported nausea and dizziness was more than twice as great in females as males, though the absolute number of subjects was small. Vomiting and somnolence were slightly more common in males. Less common adverse events in this group did not show an important gender difference.

Table 26: AEs during Short-Term Administration at a Frequency of ≥ 5% by Gender

System Organ Class, n (%)	BEMA Fentanyl	
	Males (N=140)	Females (N=161)
Number of subjects with ≥1 treatment-emergent adverse event	53 (37.9)	76 (47.2)
Gastrointestinal		
Nausea	8 (5.7)	21 (13.0)
Vomiting	10 (7.1)	10 (6.2)
Nervous System		
Dizziness	4 (2.9)	14 (8.7)
Somnolence	10 (7.1)	8 (5.0)

Source: BEMA Fentanyl ISS; p. 21

Table 27 presents a summary of the treatment-emergent AEs reported by ≥ 5% of subjects in the long-term treatment population by gender. A slightly greater percentage of women in the long-term treatment population experienced AEs than men. Amongst the common AEs presented in the table, the most notable difference was the higher rate of confusional state and dyspnea reported by women. Women also reported decreased appetite, constipation, and diarrhea more frequently while men reported more vomiting than women. It is not clear whether these differences are clinically meaningful. The rate of nausea was similar between the two groups.

A review of the less frequently reported AEs did not reveal significant patterns. Women did have more thrombocytopenia than men (6.7% vs. 2.4%, respectively), more infections (42.9% reported one or more AEs classified in the infections and infestations organ class vs. 32.9% for men), more respiratory problems, particularly cough (7.6% vs. 1.2%, respectively), and more skin problems, particularly rash and pruritus.

Table 27: AEs during Long-Term Administration at a Frequency of ≥ 5% by Gender

System Organ Class, Preferred Term, n (%)	BEMA Fentanyl	
	Male (N=85)	Female (N=105)
Number of subjects with ≥1 treatment-emergent adverse event	62 (72.9)	86 (81.9)
Blood and lymphatic		
Anemia	8 (9.4)	10 (9.5)
Gastrointestinal		
Ascites	5 (5.9)	6 (5.7)
Constipation	5 (5.9)	8 (7.6)
Diarrhoea	6 (7.1)	12 (11.4)
Nausea	17 (20.0)	22 (21.0)
Vomiting	17 (20.0)	14 (13.3)
General/Administration Site		
Asthenia	8 (9.4)	13 (12.4)
Fatigue	6 (7.1)	13 (12.4)
Oedema peripheral	9 (10.6)	15 (14.3)
Pain	8 (9.4)	10 (9.5)
Infections		
Pneumonia	7 (8.2)	8 (7.6)
Urinary tract infections	5 (5.9)	7 (6.7)
Metabolism/Nutrition		
Decreased appetite	4 (4.7)	10 (9.5)
Dehydration	10 (11.8)	12 (11.4)
Musculoskeletal		
Back pain	5 (5.9)	7 (6.7)
Nervous system		
Dizziness	6 (7.1)	6 (5.7)
Headaches	4 (4.7)	8 (7.6)
Psychiatric		
Confusional state	3 (3.5)	11 (10.5)
Respiratory		
Dyspnoea	4 (4.7)	13 (12.4)

Source: BEMA NDA ISS p. 22

Race

Conclusions regarding the effect of race on adverse events in the short-term population are limited due to the small proportion of non-whites enrolled in these trials. Eighty-four percent of the subjects in the short-term administration population were white, 9% black, 1% Asian, and the remaining 6% were "other".

Table 28: Adverse Events during Short-Term Administration at a Frequency of ≥5% by Race.

System Organ Class, n (%)	BEMA Fentanyl			
	White (N=254)	Black (N=27)	Asian (N=3)	Other (N=17)
Number of subjects with ≥1 treatment-emergent adverse event	111 (43.7)	9 (33.3)	1 (33.3)	8 (47.1)
Gastrointestinal				
Nausea	25 (9.8)	2 (7.4)	1 (33.3)	1 (5.9)
Vomiting	15 (5.9)	2 (7.4)	1 (33.3)	2 (11.8)
Nervous System				
Dizziness	17 (6.7)	1 (3.7)	0	0
Somnolence	15 (5.9)	3 (11.1)	0	0

Source: BEMA Fentanyl ISS; p. 23

Adverse events by race for the long-term administration group are shown below. Again, given that the majority of study subjects were white (86%), meaningful conclusions regarding the possible effects of race on adverse events are not possible.

Table 29: Adverse Events during Long-Term Administration at a Frequency of ≥5% by Race

System Organ Class, Preferred Term, n (%)	BEMA Fentanyl			
	White (N=164)	Black (N=18)	Asian (N=2)	Other (N=6)
Number of subjects with ≥1 treatment-emergent adverse event	131 (79.9)	12 (66.7)	2 (100)	3 (50.0)
Blood and lymphatic				
Anemia	17 (10.4)	1 (5.6)	0	0
Gastrointestinal				
Ascites	11 (6.7)	0	0	0
Constipation	11 (6.7)	2 (11.1)	0	0
Diarrhoea	16 (9.8)	2 (11.1)	0	0
Nausea	33 (20.1)	5 (27.8)	1 (50.0)	0
Vomiting	24 (14.6)	5 (27.8)	1 (50.0)	1 (16.7)
General/Administration Site				
Asthenia	19 (11.6)	1 (5.6)	0	1 (16.7)
Fatigue	15 (9.1)	2 (11.1)	1 (50.0)	1 (16.7)
Oedema peripheral	22 (13.4)	1 (5.6)	1 (50.0)	0
Pain	17 (10.4)	1 (5.6)	0	0
Infections				
Pneumonia	12 (7.3)	3 (16.7)	0	0
Urinary tract infections	10 (6.1)	1 (5.6)	0	1 (16.7)
Metabolism/Nutrition				
Decreased appetite	14 (8.5)	0	0	0
Dehydration	19 (11.6)	3 (16.7)	0	0
Musculoskeletal				
Back pain	11 (6.7)	1 (5.6)	0	0
Nervous system				
Dizziness	10 (6.1)	1 (5.6)	1 (50.0)	0
Headaches	10(6.1)	2 (11.1)	0	0
Psychiatric				
Confusional state	14 (8.5%)	0	0	0
Respiratory				
Dyspnoea	17 (10.4)	0	0	0

Source: Table 4.13

Age

In the short-term administration population, AEs were somewhat more frequent in subjects >65 years of age than those <65 years of age; 48.5% vs. 40% of patients, respectively, reported at least one AE. Amongst the four common AEs occurring in the short-term administration population, dizziness occurred about twice as often in the subjects >65 years of age (8.9%) as in those <65 years of age (4.5%). Otherwise AE rates were similar in the two age groups.

In the long-term treatment population, AEs were also somewhat more frequent in the subjects >65 years of age than in the subjects <65 years of age. There was an average of 6.7 AEs reported per elderly subject compared with 5.6 AEs reported per younger subject during the study. Some AEs that are typical of opiate use were more common in the elderly: constipation (10.2% vs. 5.3%), asthenia (18.6% vs. 7.6%), and confusional state (11.9% vs. 5.3%).

However, vomiting was more frequent in younger subjects (18.3% younger vs. 11.9%). AEs that are less typical of opiate use were also more common in the elderly: peripheral edema (18.6% vs. 9.9%), and decreased appetite (11.9% vs. 5.3%).

7.1.6 Less Common Adverse Events

In the review of the safety database, no unusual adverse events were noted.

7.1.7 Laboratory Findings

Due to the known clinical laboratory safety of fentanyl, no clinical laboratory safety data were collected in the clinical trial program.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In Study FEN-201, vital signs (sitting heart rate, systolic and diastolic blood pressure, and respiratory rate) were measured at screening and end of study.

In Study FEN-202, vital signs were measured at the Screening and Final visit within one week of last dose.

In Study FEN-113, vital signs were measured pre-dose, and at 30 minute intervals post-dose until four hours post dose of study drug.

In studies FEN-201 and 202, vital signs were not measured following individual doses of study medication.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See Section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

The Applicant's table below presents a summary of the shift of vital signs from screening to the final evaluation for the short-term administration population. Baseline vital are taken from the last assessment prior to the initial dose of study drug. The Final Evaluation Result is the last assessment recorded which for most of these subjects was at the end of long-term treatment. In study FEN-201, vital signs were not collected at the end of short-term administration (titration) unless the subject withdrew prematurely.

Assessments were made of the number and percent of subjects who had normal, high, or low values for each vital sign parameter at baseline and the number and percent of subjects who