

Reviewer comment: I agree with the investigator's determination that the events were unrelated to study drug. It is likely the abdominal pain, nausea and vomiting were due to gastroenteritis, given that the patient had a concurrent fever.

Subject 001-2008 was a 53 year-old female with cervical cancer who was hospitalized for moderate vomiting 7 days after initiating study medication. At the time of hospitalization, she had been in the Open-label Period for 4 days on 1600 µg of BEMA Fentanyl; last dose was on the day of hospital admission. She was treated with promethazine, metoclopramide and ondansetron. The event was considered resolved a week later. Study medication, which had interrupted for six days beginning on the day of admission, was restarted but discontinued permanently by the investigator after two days of treatment. The subject died eleven days later of disease progression. The investigator determined the event was unrelated to study drug.

Reviewer's comment: It is certainly possible that the study drug could have caused the patient's vomiting. However, she was extremely ill due to cervical cancer, and died soon after the event. It is not possible to definitively state that the study drug was unrelated to the vomiting. This reviewer concludes that the study drug was possibly related to the adverse event of vomiting.

Mucosal inflammation

Patient 023-1003 was a 49-year-old white female with head/neck cancer and a medical history of HIV. Pain therapy included 100 µg of transdermal fentanyl for persistent pain. The subject participated in Study 201 FEN-202. She received 11 days of study drug at 1200 mcg prior to the event of mucosal inflammation was on 08 May 2006.

On _____, the subject was hospitalized for dehydration and malnutrition and diagnosed with severe mucosal inflammation. Other concurrent events included gross mucositis with a herpetic eruption in the perioral area along with thrush, complications of pneumonitis, throat irritation, herpes zoster, mouth irritation, and pneumonitis. Study medication was interrupted for one month. The investigator judged the event of mucosal inflammation was unrelated to study drug.

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Reviewer's comment: This HIV positive subject had severe oral mucosal inflammation which led to dehydration, in the setting of a perioral herpetic eruption and thrush. Although it is possible that the study drug could be related to mucosal inflammation, in this situation, the patient's concurrent illnesses appear to have played a major role in the development of this SAE. This reviewer has determined that it is possible that the study drug contributed to the SAE; however it is more likely to have been caused by the herpetic eruption and thrush.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

A total of 190 patients withdrew from studies FEN-201 and FEN-202 prior to their completion. The table below shows a breakdown by study. There were no dropouts from study FEN-113.

Table 10: Dropouts by Study and Period for FEN-201 and FEN-202

Study	Period	# enrolled	#completed	# dropouts	% dropouts
FEN-201	Titration	151	82	69	46
	Double-blind	82	70	13	16
FEN-202	Titration ¹	146 ²	109	37	25
	Open-label	179 ³	95	84	46

¹Patients entering FEN-202 *de novo* underwent titration period similar to FEN-201

²150 subjects entered titration in FEN-202, however 4 were still in titration period at time of submission, so are not counted here

³Includes 70 patients enrolled from FEN-201

Dropouts from Titration Periods of FEN-201 and FEN-202

Of note, 46% (69/151) of patients dropped out of the titration phase of study FEN-201. Because almost half of the patients entering the titration phase of FEN-201 dropped out, the datasets, CRFs and available narratives were reviewed. The results are illustrated in Tables 11 and 12.

A total of 22 patients from 13 study sites were coded as “consent withdrawn”. There did not appear to be a predominant study site associated with this. Six of the 22 discontinuations were actually due to adverse events.

Table 11: Reasons for Discontinuation for Subjects Coded as “Consent Withdrawn”

Reason for Discontinuation	Number of Patients
Adverse event	6
No explanation	4
Noncompliant with study drug administration	4
Electronic diary issues	3
Subject did not use any doses of study med	3
Overwhelmed with cancer	1
Subject did not want to enter randomization period	1
Total	22

The reason for discontinuation for 11 subjects from 10 study sites was coded as “other”. Again, there did not appear to be an association with any particular study site. The readjudicated reasons for these subjects are shown below in Table 12.

Table 12: Reasons for Discontinuation for Subjects Coded as “Other”

Reason for Discontinuation	Number of Patients
Completed titration but didn't enter db phase/went on to 202	3
Protocol violation	2
Electronic diary issue	1

Required change in background pain medication	1
Titration failure	1
SAE (bone pain)	1
Study drug accountability (study drug missing)	1
Started new chemotherapy	1
Total	11

Table 13 illustrates the percentages of reasons for discontinuation during titration as adjudicated by the Applicant and this reviewer. The largest proportion of discontinuations during titration in FEN-201 (11.2% of the enrolled patients) was due to treatment-emergent adverse events. The relationship between the adverse events and use of study drug is discussed in Section 7.1.3.2, however most of the discontinuations due to adverse events in the short-term treatment population were due to opioid-related events such as nausea, vomiting, dizziness, and sedation. The next most common reason for discontinuation was noncompliance with the electronic diary, consisting of 7.9% of those enrolled in the titration phase of FEN-201.

The datasets, CRFs, and patient narratives provided by the Applicant for study FEN-202 were reviewed. This reviewer is in agreement with the Applicant's adjudication of dropouts for the titration period of FEN-202. The majority of discontinuations were due to withdrawal of consent (without other explanation), and adverse events, which comprised 4.1% of the treated patients.

Table 13: Reasons for Discontinuation from the Titration Periods of FEN-201 and FEN-202

Reason for Discontinuation	Titration Period FEN-201		Titration Period FEN-202
	Adjudicated by Applicant	Adjudicated by Reviewer	Adjudicated by Applicant/Reviewer
	# (%) N=151		# (%) N=146
Subject consent withdrawn	22 (14.5)	4 (2.6)	10 (6.8)
Other	11 (7.2)	5 (3.3)	5 (3.4)
Adverse event	10 (6.6)	17 (11.2)	6 (4.1)
Noncompliance with electronic diary	8 (5.3)	12 (7.9)	2 (1.4)
Lack of efficacy	5 (3.3)	5 (3.3)	5 (3.4)
Not regularly treating 1 episode per day	5 (3.3)	5 (3.3)	-
Noncompliance with study drug administration	3(2.0)	7 (4.6)	2 (1.4)
Did not use any doses of study medication	-	3 (2.0)	-
Death	3 (2.0)	3 (2.0)	4 (2.8)
Protocol deviation	2 (1.3)	4 (2.6)	2 (1.4)
Completed titration but didn't enter DB	1	4 (2.6)	-
Failed to return/lost to follow-up	-	-	1 (0.7)
TOTAL	69	69	37

To put the above findings into perspective, the rate of discontinuation during titration for study FEN-201 was compared to the results obtained for Actiq and Fentora. The design of the efficacy studies for all three drugs were very similar; open-label titration followed by a double-blind,

multi-crossover period where subjects received active drug and placebo in a randomized fashion for treatment of BTP episodes.

The table below shows the proportions of drop-outs during the titration periods for Actiq, Fentora and BEMA Fentanyl.

Table 14: Percentage of drop-outs during titration period for Actiq, Fentora, and BEMA Fentanyl

Drug	Number enrolled in titration period	Dropouts during titration	
		Number	Percent
Actiq	130	38	29.2
Fentora	123	46	37.3
BEMA Fentanyl FEN-201 ¹	151	69	45.6
BEMA Fentanyl FEN-202 ²	146	37	25

¹Doses in FEN-201: 200µg-1200µg

²Doses in FEN-202: 200µg-2400µg

The proportion of dropouts from the titration period for study FEN-201 was clearly higher than from either the Actiq or Fentora efficacy trials or from the titration period of FEN-202 (which had the lowest percentage of dropouts). There does not appear to be a reason inherent in the study drug that would result in a higher rate of dropouts during FEN-201. As noted above, the majority of dropouts were due to adverse events and noncompliance with both the electronic diaries and the administration of study drug. The differential proportion of dropouts due to adverse events may be a reflection of the higher bioavailability of BEMA Fentanyl compared to the other oral transmucosal fentanyl products on the market..

Dropouts from Double-Blind Period of FEN-201

Eighty-two patients entered the double-blind period of FEN-201, and 81 received study drug during this period. Table 15 below shows the disposition and reasons for dropout during this part of the trial as adjudicated by the Applicant, and readjudicated by this reviewer.

Upon review of the narratives and datasets provided by the Applicant, there were actually five patients coded as “consent withdrawn”, two of whom had concurrent SAEs of dehydration at the time of withdrawal from the study.

Table 15: Dropouts during the Double-Blind Period of FEN-201 as Adjudicated by the Applicant and Reviewer.

Reason for Discontinuation	Adjudicated by Applicant	Adjudicated by Reviewer
	# (%) N=81	
Subject consent withdrawn	4 (4.9)	2 (2.4)
Adverse event	3 (3.7)	5 (6.2)
Not regularly treating 1 episode per day	2 (2.4)	2 (2.4)
Noncompliance with electronic diary	2 (2.4)	2 (2.4)
Lack of efficacy	1 (1.2)	1 (1.2)
Changed background opioid dose		1 (1.2)
Total	12 (14.8)	13 (16)

Dropouts from Open-Label Period of FEN-202

Patients entered the open-label period either as roll-overs from FEN-201, or *de novo*. It is expected that there would be a significant number of drop-outs during this study due to adverse events and death, given the nature of the patient population and the length of the study (1 year). **The Applicant's table below shows the disposition of patients entering the open-label period.**

Table 16: Dropouts in the Open-label Period of FEN-202

Open-label Period	N (%)
Entering the Open-label Period	179 (79.9)
Discontinued during the Open-label Period	84 (37.5)
Enrolled in study ≥ 60 days	117 (52.2)
Enrolled in study ≥90 days	98 (43.8)
Discontinued from Open-label Period	84 (37.5)
Reason for discontinuation: Subject consent withdrawn	19 (10.6)
Lack of efficacy	6 (3.4)
Protocol deviation	0
Not regularly treating 1 episode of pain per day	3 (1.7)
Noncompliance with electronic/paper diary	2 (1.1)
Noncompliance with study drug administration	4 (2.2)
Adverse event	17 (9.5)
Pregnancy	0
Death	18 (10.1)
Failed to return / lost to follow-up	3 (1.7)
Other	13 (7.3)

a BEMA Fentanyl included all dose levels: 200, 400, 600, 800, 1200, 1600, 2400 µg.

Study drug discontinuation due to treatment-emergent adverse events is shown below by length of exposure (short-term vs. long-term) to study drug.

The most common adverse events leading to drop-out during short-term administration are shown in Table 17 below. Thirty-five subjects discontinued study drug due to adverse events. Fifty-six AEs were reported by these discontinued subjects – six of which were reported more than once (nausea, vomiting, disease progression, pneumonia, sedation, and dizziness). Of AEs potentially related to study drug and occurring in >1%, nausea (2.9) and vomiting (2.3%) were most frequently reported followed by dizziness (1.3%). Sedation occurred in 0.7% of patients. There was no evidence of a dose-related effect. There were no reports of application site reactions leading to study discontinuation in this group.

Table 17: Most Common Adverse Events Leading to Dropout during Short-Term Administration

Adverse Event	Number of patients (N=301)	%
Nausea	9	2.9
Vomiting, retching	8*	2.6
Dizziness	4	1.3
Sedation	2	0.7
Disease progression	2	0.7
Pneumonia	2	0.7

* One patient withdrew due to "retching" and was added to the 7 who withdrew due to vomiting

The most common adverse events leading to drop-out during long-term administration are shown in Table 18 below. Seventy-one AEs were reported by 54 subjects. The most common AEs were neoplasm, infections, and disease progression. AEs leading to discontinuation seen in more than one subject and typical of opiate use were: nausea (2.1%), dizziness (1.6%), agitation (1.1%), and hallucinations (1.1%). AEs leading to discontinuation that were not typical of opiate administration and were seen in more than one subject were: neoplasms (7.9%), infections (4.2%), disease progression (3.7%), deep vein thrombosis (1.6%), intestinal obstruction (1.1%), headache (1.1%), and acute renal failure (1.1%).

One subject (023-1003) discontinued due to oral pain, gingival bleeding, and stomatitis. This subject is discussed in Section 7.1.2.

There was no evidence of a dose-related effect for drop-outs experiencing opioid-related adverse events.

Table 18: Most Common Adverse Events Leading to Dropout during Long-Term Administration

Adverse Event	Times listed as leading to dropout (N=190)	%
Neoplasms	15	7.9
Infections	8	4.2
Disease progression	7	3.7
Nausea	4	2.1
Dizziness	3	1.6
DVT	3	1.6
Headache	2	1.1
Agitation	2	1.1
Hallucination	2	1.1
Acute renal failure	2	1.1
Intestinal obstruction	2	1.1

Dropouts Due to Noncompliance

In FEN-201 there were 22 of 151 subjects, and in FEN-202 there were 19 of 220 subjects who were discontinued for noncompliance with study drug or procedures. Details for subjects discontinued for noncompliance are shown in Table 19. Difficulties with either paper or electronic diary accounted for 46% of discontinuations due to noncompliance.

Table 19: Dropouts Due to Noncompliance

Reason	FEN-201	FEN-202	Total
Noncompliance with electronic diary	11	6	17
Not regularly treating one episode/day	7	3	10
Noncompliance with study medication administration	3	4	7
Noncompliance with paper diary	-	2	2
Drug accountability concern	1	-	1
Inappropriate use of opioid concomitant meds	-	1	1
Other	-	3	3
Total	22	19	41

7.1.3.2 Other significant adverse events

Significant opioid-related adverse events that led to dropout from the clinical trials include nausea, vomiting, dizziness, headache, and sedation. These events would be expected in this study population, either because of background opioid medications or the study drug.

There were no other significant adverse events (that have not been described elsewhere in this review) that occurred during this development program.

7.1.4 Other Search Strategies

Adverse Events Involving the Mouth

Oral symptoms related to the use of BEMA Fentanyl are of interest because of the product's route of administration. The possible relationship of study drug use to these events is complicated by the fact that mucositis is a common event in patients with cancer, either as a result of the underlying disease, treatment, or complications. It is estimated that up to 40% of cancer patients overall and 80% of patients being treated for head and neck cancer experience mucositis.

The Applicant performed the following analysis. Relevant AEs for inclusion in this analysis were identified by search of AE listings for high-level, preferred and verbatim terms including "Oral," "ging*," "mouth," "stoma*," "tooth," "dental*" and "mucos*" (where * represents any following text) and additionally by manual search of AE listings. "Dry mouth," "candidiasis," "tongue disorder," and "vocal cord paralysis" were included but are totaled separately as they are likely less related to study drug application.

In short-term administration (FEN-113, and titration periods of FEN-201 and 202) there were four relevant AEs in three subjects (1%). They included oral hypoesthesia, mouth ulceration, mucosal inflammation, and stomatitis. There were also four reports of dry mouth in three patients, and two reports of oral candidiasis in two patients. All were mild or "not assessable" in severity and none resulted in study drug adjustment or discontinuation.

Stomatitis was the most common oral AE (not counting dry mouth and candidiasis) in long-term treatment (FEN-201 double-blind phase and FEN-202 open-label), occurring seven times in six subjects (3.2% of the population). One subject (023-1003) experienced stomatitis that was classified as an SAE and resulted in study drug discontinuation (see narrative in section 7.1.2). However, this event occurred concurrently with pneumonia and herpes zoster infection which resulted in the patient's hospitalization and discontinuation of study drug. The other AE seen in 1% or more of subjects was mucosal inflammation (2 AEs in 2 subjects, 1.1%). One of these was actually "colon ileitis", therefore mucosal inflammation involving the mouth occurred in less than 1% of the long-term population. The Applicant's Table 20 shows incidence of oral symptoms in the long-term population.

Table 20: Treatment-Emergent Oral Symptoms by Dose in Long-Term Population

Preferred Term ^a	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)	
Aphthous stomatitis	0/0	0/0	0/0	0/0	1/1 (1.5%)	0/0	1/1 (0.5%)
Gingival bleeding	0/0	0/0	0/0	1/1 (1.4%)	0/0	0/0	1/1 (0.5%)
Gingival infection	0/0	0/0	0/0	1/1 (1.4%)	0/0	0/0	1/1 (0.5%)
Hypoesthesia oral	0/0	1/1 (2.0%)	0/0	0/0	0/0	0/0	1/1 (0.5%)
Mouth ulceration	1/1 (5.3%)	0/0	0/0	0/0	0/0	0/0	1/1 (0.5%)
Mucosal inflammation	0/0	1/1 (2.0%)	0/0	0/0	1/1 (1.5%)	0/0	2/2 (1.1%)
Mucous membrane disorder	0/0	1/1 (2.0%)	0/0	0/0	0/0	0/0	1/1 (0.5%)
Odynophagia	0/0	0/0	0/0	0/0	0/0	1/1 (4.2%)	1/1 (0.5%)
Oral pain	0/0	0/0	0/0	1/1 (1.4%)	0/0	0/0	1/1 (0.5%)
Stomatitis	0/0	0/0	1/1 (1.5%)	2/2 (2.7%)	3/3 (4.5%)	1/1 (4.2%)	7/6 (3.2%)
Tooth abscess	0/0	0/0	0/0	0/0	1/1 (1.5%)	0/0	1/1 (0.5%)
Toothache	0/0	0/0	0/0	0/0	1/1 (1.5%)	0/0	1/1 (0.5%)
TOTAL	1/1 (5.3%)	3/3 (5.9%)	1/1 (1.5%)	5/3 (4.1%)	7/6 (9.1%)	2/2 (8.3%)	19/15 (7.9%)
Dry mouth	0/0	2/2 (3.9%)	2/2 (3.0%)	1/1 (1.4%)	2/2 (3.0%)	0/0	7/7 (3.7%)
Oral candidiasis	0/0	1/1 (2.0%)	1/1 (1.5%)	1/1 (1.4%)	0/0	0/0	3/3 (1.6%)
Tongue disorder	0/0	0/0	0/0	0/0	1/1 (1.5%)	0/0	1/1 (0.5%)
Vocal cord paralysis	0/0	0/0	0/0	0/0	2/2 (3.0%)	0/0	2/2 (1.1%)
TOTAL	0/0	3/3 (5.9%)	3/3 (4.5%)	2/2 (2.7%)	5/4 (6.1%)	0/0	13/12 (6.3%)

^a Entries in this table show number of AEs, number of subjects, and percent of subjects.

Upon review of the oral symptoms, 16 events in 14 patients were felt to be relevant to BEMA Fentanyl (long and short-term exposures combined). The AEs that were excluded were done so only when there was a clear reason to attribute the AE to a cause other than study drug. The following AEs were excluded: vocal cord paralysis (2), oral candidiasis (5), and dry mouth (12).

The Applicant's table below shows the application site reactions related or possibly related to study drug. This reviewer, following review of CRFs, datasets, and narratives, is in agreement with the Applicant's determination. Less than 5% of the safety population had application site reactions possibly related to study drug.