

On _____, the subject died at home secondary to aspiration of bloody sputum. An autopsy was not performed and the death certificate was not available. Concurrent events at the time of death included somnolence, which the subject had reported since 25 May 2006. The relationship of the time of the last dose of study drug and time of death was not presented by the Applicant.

b(6)

Concomitant medications in addition to background opioid at the time of the event were lorazepam, moxifloxacin hydrochloride, docusate sodium, salbutamol/ipratropium, folic acid, lidocaine, macrogol, multivitamins, polysaccharide-iron complex, senna, levothyroxine sodium, ascorbic acid, salbutamol sulfate, prochlorperazine, megestrol acetate, and guaifenesin. The investigator judged that the event of aspiration was unrelated to the study drug therapy.

Reviewer comment: The study subject had been receiving the 25µg/h transdermal fentanyl patch since prior to entry into the study, and had been taking study drug to treat BTP for 52 days (115 doses). Although fentanyl can cause respiratory depression and somnolence, and subsequent aspiration, this patient was reported to have been on a stable dose of study drug and background pain medication. It appears unlikely then that this patient's death was due to the study drug, and was instead caused by the patients underlying disease and dysphagia secondary to radiation. I am in agreement with the Applicant regarding the causality of the patient's death.

Subject 031-1002 was a 52-year-old white female with breast cancer with bone metastases, and a medical history of anxiety, degenerative joint disease, depression, fibromyalgia, hypercholesterolemia, nodular goiter, osteoporosis, peptic ulcer disease, and right pelvic lipoma removal-resulting in right sciatic nerve injury with foot drop. Background pain therapy included 100 µg/hr transdermal fentanyl patch for persistent pain. The subject previously participated in FEN-201, last dose on 14 March 2006. The subject received the first dose of study drug therapy in FEN-202 on 03 April 2006 and began the maintenance phase in the study at a dose of 400 µg on 03 April 2006. The last dose before the event was or _____

b(6)

On _____, the subject was hospitalized with severe respiratory failure. At that time she was taking 400 mcg of study drug for BTP episodes. The patient had not been feeling well according to the hospital admit note. She was found unresponsive by family members who called 911. She was transported to the hospital where she expired the next day. The investigator judged that the event was unlikely to be related to study medication. There were no concurrent adverse events associated with this death.

b(6)

Concomitant medications at the onset of the event included pamidronate disodium, capecitabine, zoledronic acid, bupropion, calcium, celecoxib, furosemide, gabapentin, multivitamins, nicotinic acid, potassium acetate, and sertraline. The investigator judged that the event of respiratory failure was unlikely to be related to study drug therapy.

Reviewer comment: The patient had received a total of 62 doses of 400 mcg of study drug over a 52 day period, and had been on a stable dose of 100 mcg/hr transdermal fentanyl patch for the duration of the study. It is unlikely that continued use of these drugs as directed would have led to the patient's respiratory failure and death. Although the reason for the patient's death was

not provided by the Applicant, it does not appear to have been associated with the use of study drug.

Subject 082-2002 was a 53-year old white female with breast cancer with widely spread bone metastases, and a medical history of deep vein thrombosis and muscle spasm. Background pain therapy included 75 µg/hr transdermal fentanyl patch and 15 mg of extended-release oral morphine for persistent pain. The subject received the first dose of study drug therapy in FEN-202 on 08 March 2007. The last dose before the event was on _____

b(6)

After 4 days in the titration phase, on _____, the patient experienced a cardiac arrest and died. She had taken one 800 mcg dose of study medication at an unknown time that day. The husband witnessed the event. Both were sitting at home watching a DVD. The husband stated that this was the best day she had had in a long time, laughing at the movie, etc. She abruptly slumped forward in her chair and would not respond. He called 911 immediately and initiated CPR prior to the arrival of the medics. She did not recover. There were no other adverse events reported for this patient. The investigator judged that the event was unrelated to study medication.

b(6)

Concomitant medications at the onset of the event included acetylsalicylic acid, fentanyl, hydrocodone/paracetamol, morphine sulfate, enoxaparin, and metaxalone. The investigator judged that the event of cardiac arrest was unrelated to the study drug therapy.

Reviewer comment: This patient's death was unexpected based on the information provided by the Applicant. She had taken a total of 7 doses of study drug, titrating from an initial dose of 200 mcg on March 8 to 800 mcg for the final two doses, one taken on the day of death _____ and one the preceding day. She was concurrently on a stable background opioid treatment consisting of transdermal fentanyl patch (75mcg/hr) and 15 mg ER morphine once a day. Fentanyl, like other opioids, is known to produce respiratory depression, the severity of which is dependent on the dose of fentanyl, the patient's tolerance to opioid effects and the presence of underlying illness. Although bradycardia has been associated with the use of fentanyl, cardiac arrest (in the absence of preceding respiratory arrest) is not generally associated with its use. In the setting of a relatively stable opioid regimen in an opioid tolerant patient, it is unlikely that the study drug was associated with patient's cardiac arrest and subsequent death.

b(6)

The following two deaths were submitted with the 120-Day Safety Update

Subject 082-2006 was a 29-year-old female with Hodgkin's lymphoma and cervical cancer. She had a history of bone marrow transplant, bone metastases, chronic graft-versus-host disease, and immunodeficiency. Her background pain therapy included long-acting oxycodone 40mg BID and hydrocodone 2 mg (? frequency). The subject received the first dose of study drug therapy in FEN-202 on 25 June 2007 and entered the maintenance phase of the study at a dose of 800 µg on 26 June 2007. During FEN-202, the subject's dose of study medication was between 800 and 1200 mcg, and was lowered to 800mcg 14 days prior to the cardiac arrest. The last dose before the event of cardiac arrest (800mcg) was given on _____ which was also the last dose taken in the study. On _____ the subject died from cardiac arrest. No other

b(6)

information was available about this event at the time of this report. The investigator judged that the fatal event of cardiac arrest was unlikely related to study drug therapy.

Reviewer comment: There is inadequate data available to determine the cause of this subject's cardiac arrest. As stated in the reviewer comments related to Subject 082-2002 above, cardiac arrest is not generally associated with the use of fentanyl. In the setting of a relatively stable opioid regimen in an opioid-tolerant patient, it is unlikely that the study drug was associated with patient's cardiac arrest and subsequent death.

Subject 018-2001 was a 71-year-old white male with colon/rectal cancer and a medical history of heartburn, mild hypertension, and prostate cancer. Background pain therapy included 30mg of long-acting morphine for persistent pain. The subject received the first dose of study drug therapy in FEN-202 on 27 June 2006 and titrated to a dose of 800 µg on 01 July 2006. The last dose of study drug was on _____ On 10 July 2006, the subject withdrew consent from further participation in the study. No adverse events were reported during the study. Or _____, the subject died. There is no additional information available at the time of this report. Concomitant medications included acetylsalicylic acid, calcium, bicalutamide, ibuprofen, leuporelin acetate, magnesium, lansoprazole, vitamins, and zinc.

b(6)

Reviewer comment: There is inadequate data available to determine the cause of this subject's death. However, since the last dose of study medication was 18 days prior to the subject's death, it is highly unlikely that the death was related to the study drug.

7.1.2 Other Serious Adverse Events

The Applicant presented SAEs by short-term administration (titration periods of FEN-201 and 202, and FEN-113) and long-term administration (open-label phase of FEN-202 and double-blind period of FEN-201). There were 29 SAEs in 25 of the 301 patients receiving short-term administration of BEMA fentanyl, and 128 SAEs in 79 patients receiving long-term treatment. Some of the SAEs in the above accounting included those leading to death, which have been discussed in the previous section.

This reviewer assessed all SAEs that did not result in death by reviewing the CRFs, narratives, and datasets provided by the Applicant. There were a total of 108 SAEs occurring in 74 patients that did not result in death during the BEMA fentanyl development program. There were no SAEs during study FEN-113.

Due to the large number of SAEs (which is an expected finding given the patient population), this review does not contain a narrative summary for each patient who experienced an SAE. Instead, a tabular summary of all SAEs may be found in Tables 60-62 in Appendix 10.3. The majority of adverse events were due to the patients underlying malignancies, progression, and complications of underlying malignancy. Twenty were due to other reasons.

As adjudicated by this reviewer, none of the SAEs were definitely due to the administration of study drug. Two cases of hypoxia (063-2001 and 063-2008), a case of mucosal inflammation (023-1003), and a case of vomiting (001-2008) were determined to be possibly related to study drug, however the clinical status of the patients made it more likely that that the events were unrelated.

In summary, none of the SAEs could definitely be attributed to the use of BEMA Fentanyl. While some could reasonably be attributed to study drug, the events were found to be consistent with the patients' malignancies, treatments, concomitant medications, or other events surrounding the SAEs. Brief patient summaries and reviewer comments are provided below for ten selected patients where further explanation clarifies the adjudication.

Additional SAEs were reported in the 120-day safety update. Details may be found in section 7.2.9 of this review.

Individual Serious Adverse Event Summaries:

Hypoxia

Patient 063-2001 was a 44 year-old female with colon/rectal cancer who had been taking study medication for 7 months with an overall stable dosing pattern, when, following administration of chemotherapy, she complained of being cold and became weak and cyanotic. Adverse events of shortness of breath had been recorded for the month prior to this event. Her oxygen saturations dropped to less than 70% despite supplemental oxygen. She was taken to the hospital and was found to have a marked increase in D-dimer levels. A computed tomography angiogram found patchy alveolar consolidation in both lobes and was negative for pulmonary embolus. The subject was unable to be successfully weaned off oxygen and was admitted and treated with antibiotics, bronchodilators, low molecular weight heparin, and corticosteroids. Ultrasound was negative for deep vein thrombosis. Concurrent adverse events of hypoxia, hypotension and pleural effusion were recorded. The subject improved and was discharged home after two days. The investigator reported that the event was not related to study medication. The subject had taken study medication on the day of the event at 16:15 hours and at 20:30 hours, continued using 2 to 4 doses per day throughout the event for pain episodes while in the hospital and remained on study drug after discharge.

Reviewer comment: Although the study drug is known to cause respiratory depression, it is unlikely it did so in this case, since the event resolved despite the continued use of study drug during and after the event.

Patient 063-2008 was a 67 year-old female with lung cancer, in the Open-label Period of the study and taking 1200 µg of BEMA Fentanyl for approximately 3 days, who was hospitalized with severe hypoxia, confusion, and delusions that resolved three days later. The subject remained on study drug and over the next two days, she developed moderate shortness of breath which was deemed "not related" to study drug, as well as moderate right arm pain, mild confusion, moderate delusions, mild anxiety, and mild increased weakness which were all noted as "possibly related" to study drug. At that point she discontinued study drug due to AE. Eighteen days later she died due to progression of her lung carcinoma.

Reviewer comment: It is possible that this SAE of hypoxia was related to the use of study drug. The patient had terminal lung cancer, which is frequently associated with hypoxia. The event described here was possibly due to a combination of the patient's underlying malignancy and the use of study drug, but unlikely to be due to study drug alone.

Respiratory Distress

Patient 004-2005 was a 67 year-old female with uterine cancer who had been on study medication for about two months when she was hospitalized for severe respiratory distress accompanied by neutropenic sepsis, urinary tract infection, pancytopenia, diarrhea, and vomiting. A computed tomography scan revealed atelectasis in the left base. She was treated with antibiotics and supplemental oxygen, improved and was discharged from the hospital. Study medication was not changed. Two weeks after this event the subject was hospitalized with pulmonary embolism, hypotension and deep vein thrombosis from which she recovered and was discharged eight days after admission. She continued on study medication but was discontinued two weeks later for inability to maintain diary entries. The adverse events listed above (including the respiratory events) were all judged by the investigator to be not related to study medication except for vomiting, which was described as unlikely related.

Reviewer comment: I concur with the investigator's findings.

Patient 028-2003, a 51 year-old female with multiple myeloma, asthma, pulmonary sarcoidosis, and sleep apnea, developed two episodes of respiratory distress due to an exacerbation of her asthma. Both episodes required endotracheal intubation and mechanical ventilation and were treated with corticosteroids, bronchodilators, antibiotics, and supportive care. During the first hospitalization she also developed episodes of sleep apnea. Her study medication had been interrupted for 10 days prior to her first hospitalization.

Reviewer comment: This patient had underlying pulmonary illnesses (asthma, sarcoidosis), which could reasonably have contributed to the SAE of respiratory distress. Additionally, the patient had not received study drug for 10 days prior to the first hospitalization. I concur with the investigator that use of the study drug was not related to this SAE.

Loss of Consciousness, mental status changes

Patient 028-2009 was a 51 year-old female with breast cancer and partial seizures. She was taking methadone 50 mg/day for persistent pain, and had been on a stable dose of 600mcg of study drug for approximately 7 weeks. She had received no study drug for 6 days prior to the event of loss of consciousness. The subject had been reducing her seizure medication and was found unconscious with an abrasion on her cheek. She was hospitalized for further examination but was discharged 2 days later. She continued on study medication the next day. About five months later she was hospitalized for mild mental status changes which resolved the next day. She remained on study medication. The investigator considered these events unrelated to study medication.

Reviewer comment: I concur with the investigator's determination that the events of LOC and mental status change were not related to use of the study drug.

Patient 004-1010, a 47 year-old female with metastatic adenocarcinoma of the liver, had been on study medication for a year. The study coordinator noticed inconsistencies within the diary,

called the subject, and noted that she appeared confused. The family was contacted and found the subject wearing nine transdermal fentanyl patches (100 µg/hour each) with a total dose of 900 µg/hour rather than the 300 µg/hour prescribed. The study coordinator told the family to remove six of the transdermal patches and the coordinator drove to the subject's home and retrieved all study medication. The subject apparently improved but was hospitalized a week later for a second episode of confusion. At that time she was taking phenergan, Vicodin, metoclopramide hydrochloride, diphenhydramine, and eszopiclone. The investigator judged that the mental status changes that led to this hospitalization were not related to study drug.

Reviewer comment: I agree with the investigator's determination. Although the study drug has the potential to cause mental status changes, it is likely that in this case the event was due to the large dose of fentanyl resulting from the use of nine 100 mcg patches rather than the prescribed dose of three patches.

Patient 006-1003 was a 51-year-old white female with ovarian cancer and a medical history significant for Type 2 diabetes mellitus, diabetic neuropathy, hypercholesterolemia, hypertension, and left-sided weakness (residual stroke). Current pain therapy included 30 mg of long-acting oxycodone 3 times a day for persistent pain. There were multiple inaccuracies in the recorded dosing data of study drug during the titration phase of study FEN-201 (1 dose of 200 µg, 10 doses of 600 µg, 11 doses of 800 µg, and no 1200 µg doses recorded) and the subject was withdrawn for noncompliance with study drug administration without entering the double-blind portion of the study. One day after the last dose of study drug, the subject was hospitalized for moderate confusional state with concurrent events of convulsions, delusion, suicidal depression, and hallucinations. Work-up was negative other than a CT scan of the head revealed small vessel ischemia with no metastatic disease. The subject was transferred to a psychiatric unit, but no specific treatment was given for the confusional state. The event of confusional state resolved after 4 days. Concomitant medications at the onset of the event were acetylsalicylic acid, warfarin sodium, lisinopril, lovastatin, omeprazole, docusate sodium, alprazolam, and tizanidine hydrochloride. The investigator judged that the event of confusional state was unlikely related to the study drug therapy.

Reviewer comment: Depending upon how much study drug the patient was self-administering, the event of confusion (associated with convulsions, delusion, suicidal depression, hallucination) could have, at least partially, been a result of acute withdrawal, since the patient had poor compliance with the study drug, and it was taken back by the investigator the day prior to the event. It does not appear however, that the event was directly caused by study drug.

Nausea, vomiting

Patient 047-2003 was a 48 year-old male with non-small cell lung cancer and anal cancer who was hospitalized 40 days after starting study medication for abdominal pain, nausea, and vomiting with fever (101°F). He responded to supportive therapy including intravenous fluids, ondansetron for nausea and vomiting, morphine for pain, and paracetamol for fever. He was discharged two days later and study medication was restarted after 12 days. Pain medication included morphine sulfate extended release 60mg BID for persistent pain, and 600 mcg of study drug for BTP. He had been on a stable dose of study drug for approximately one month prior to the adverse event of nausea and vomiting. The investigator judged the event unrelated to study drug.