exposed for at least 90 days. The study design of FEN-201 (placebo-controlled, multiple-crossover) was based on that used for Actiq and Fentora, and appears satisfactory for this drug and indication. The open-label trial (FEN-202) provided adequate data regarding safety during long-term treatment.

The patient population, cancer patients receiving around-the-clock opioids for chronic pain, and experiencing up to four BTP episodes per day, represents the intended patient population for this product. The patients participating in the study were generally very ill and on multiple concomitant medications, mirroring what would be expected for targeted patient population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no special animal or *in vitro* testing carried out in this development program.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing performed in the BEMA Fentanyl development program appears adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This section is not applicable since this is a 505(b)(2) application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The adverse effects of the fentanyl moiety are well known and have been described in this review. Issues specific to this formulation include local toxicity of the BEMA Fentanyl disc, the effect of mucositis in the absorption of the study drug, the safety of the product in an outpatient setting given the pharmacokinetic profile of this product.

Regarding the typical opioid-related adverse events, the Applicant carried out an adequate evaluation of all adverse events elicited and/or spontaneously reported during the development program. The adverse events associated with the use of BEMA Fentanyl are those that would be expected for this class of drug in the target patient population.

The effect of mucositis on the safety of BEMA Fentanyl was adequately explored in Study FEN-113, and it appears that the presence of Grade 1 mucositis does not change the PK of the product, nor is it associated with additional safety concerns.

The third aspect of the safety of BEMA Fentanyl revolves around its safe use in the intended population in an outpatient setting. This is much more difficult to assess, especially in the setting of supervised clinical trials. During the development program, there were no reports of

unexpected adverse events or overdose. There were four reports in FEN-202 and five in FEN-201 of patients discontinuing participation without returning study drug. Although the data obtained from this relatively small clinical development program does not provide much insight into this issue, there do not appear to be any unexpected safety concerns beyond those of previously approved similar products (Actiq and Fentora).

7.2.8 Assessment of Quality and Completeness of Data

The original safety data in combination with additional information provided upon the Division's request during the review process was of adequate quality and completeness to allow conduct of the safety review. No data quality issues were discovered during the NDA review.

7.2.9 Additional Submissions, Including Safety Update

The Applicant submitted additional clinical information on January 24, 2008 at the Division's request. The submission included CRFs for all subjects in study FEN-201 who dropped out during the titration period. This information was requested because of the large drop-out rate during this phase of the study, and was incorporated in this safety review.

The 120-day safety update was submitted on February 28, 2008 (Amendment 0005). The cutoff date for the safety update was December 1, 2007. It reflects 95 days of new safety data, and contains data only from studies FEN-201 and FEN-202 (not FEN-113).

The Applicant's table below illustrates the subject disposition, comparing the original CTD submission with the updated submission. The safety update reflects an additional 12 subjects who were enrolled in FEN-202.

Table 41: Subject Disposition: Original ISS vs. 120-Day Safety Update

	FEN-201 Original CTD	FEN-202 Original CTD	FEN-202 120-day Safety Update	FEN-113	Total Original CTD	Total 120-day Safety Update [a]
Enrolled subjects	152	224	236	14	390	381 [b]
No dosing data	7	4	0 [b]	0	11	0 [b]
Subjects who took at least 1 dose of study medicine	145		236			381
FEN-202 subjects previously dosed in FEN-201 or FEN-113	N/A	78	81 [c,d]	N/A	78	81 [c]
ISS population	145	142	155	14	301	300

[a] Original CTD included FEN-113 subjects; 120-day Safety Update does not.
[b] Population for this 120-day Safety Update includes only subjects who took at least 1 dose of study medication.
[c] 81 subjects, consisting of 68 who completed FEN-201 and entered FEN-202 and 13 who discontinued FEN-201 and entered FEN-202, all of whom took at least 1 dose, see ISS update Table 1u.
[d] In the original CTD, subjects from FEN-113 who later participated in FEN-202 were subtracted from the FEN-202 totals. In this 120-day Safety Update, FEN-113 subjects are no longer subtracted from FEN-202 as their exposure in FEN-113 is no longer counted.
Source: FEN-201 CSR, FEN-202 CSR, Table 1u

Source: 120-Day Safety Update ISS, p. 13

Comparison between Original ISS and 120-Day Safety Update

The population demographics and baseline characteristics were not substantially different between the two submissions. The total exposure in terms of number of doses increased from ~60,000 doses of BEMA Fentanyl administered to cancer patients to ~75,000 doses. The proportion of doses administered at varying levels was similar to that seen in the original CTD.

Exposure

The original ISS included safety information for 301 cancer patients exposed to BEMA Fentanyl, with 112 treated for at least 60 days. The update provides safety information for a total of 300 opioid-tolerant cancer patients (from studies FEN-201 and 202 only, subjects in FEN-113 were not required to be opioid-tolerant) 122 of whom were treated for at least 60 days, and 98 of whom were treated for at least 90 days. This last group includes 45 treated for 180-364 days and 22 treated for at least 365 days.

The Applicant calculated the number of days a subject was treated from the day of the first dose of study drug to the day of the last dose. This does not account for interruptions in dosing during the treatment period. Of the 98 subjects who were treated for at least 90 days, five had gaps in treatment that reduced the treatment days to below 90.

Adverse Events

Short-term administration

The most commonly observed treatment-emergent adverse events are the same in both the original ISS and the 120-Day Safety Update. Those occurring in 5% or more of the population are nausea, vomiting, dizziness and somnolence. There was a slightly higher rate of nausea reported in the safety update, increasing from 9.6% to 12% for all doses. There was no evidence of a dose-related increase.

Long-term administration

The common treatment-emergent adverse events reported in the 120-day safety update were similar to those reported in the original ISS, and included nausea, vomiting, peripheral edema, dehydration, asthenia, and fatigue. .

A number of events which did not meet the ≥5% threshold in the original ISS did so in this 120-day safety update (thrombocytopenia, dry mouth, disease progression, bronchitis, upper respiratory tract infection, anorexia, arthralgia, pain in extremity, somnolence, depression, insomnia, cough and hypotension). Many of these AEs are attributable to the subjects' underlying condition and disease progression. Other adverse events that occurred at higher rates in the updated population include disease progression, back pain, and depression. These may reflect the longer duration of exposure of subjects with terminal illnesses.

Deaths

Eighteen additional deaths were reported between the original ISS submission and the 120-day safety update in the long-term population, bringing the total number of deaths (in the long-term population) to 58. None were deemed by the Applicant to be related to the administration of BEMA Fentanyl. Sixteen of the eighteen deaths were attributable to disease progression or

complications associated with the underlying disease. Two deaths were due to "other" reasons. One subject (018-2006) died of cardiac arrest, and the cause of the second subject's (082-2006) death was unknown. Neither death was likely related to the use of study drug. Narratives regarding these two deaths can be found in section 7.1.1.

This reviewer reviewed all new deaths reported in the safety update. All were related to either the patients' underlying disease or treatment/complications, with the exception of the two noted above. None appeared to be related to the study drug.

There were no additional deaths in the short-term population reported in the update.

Serious Adverse Events
Short-term treatment
No new SAEs were reported in the 120-day safety update.

Long-term treatment
In the original ISS, 79 subjects reported 128 SAEs. An additional 27 subjects experiences SAEs between the original CTD cut-off and the 120-day safety update, for a total of 106 subjects and 170 SAEs. The increase in the number of SAEs likely reflects the serious nature of the patients' cancer and its treatment. The overall picture of SAES presented in the update is similar to that in the original ISS.

The two SOCs most frequently affected by SAEs were Infections and Infestations (13.0%) and Neoplasms (16.4%). Individual preferred terms with the greatest frequency of SAEs were disease progression (n=22, 10.6%) and pneumonia (n=13, 6.3%). Two events occurred in four subjects each (dehydration and deep vein thrombosis), and two occurred in three subjects each (sepsis and pleural effusion). Serious adverse events occurring in two subjects were hip fracture, mental status change, hypoxia, hemoptysis, respiratory distress, respiratory failure and hematoma. All other SAEs occurred in only one subject.

SAEs which increased in frequency from the original CTD to this 120-day Safety Update include disease progression (4.7 v 10.6%) and pneumonia (4.7 v 6.3%), as well as the total frequency of Infections and Infestations (10.0 v 13.0%). The incidence of SAEs does not appear to be dose related.

One subject experienced urinary retention that was rated "possibly related" to study drug by the Applicant. This occurred in a setting of increased doses of background opiates.

Adverse events leading to discontinuation
Short-term treatment
An additional eight subjects prematurely discontinued study drug during short-term administration. Reasons for discontinuation were anemia, hypokalemia, nausea and vomiting, disease progression, pathological fracture, somnolence, sedation, and dizziness and confusional state. Theses reasons are similar to those reported in the original ISS.

Long-term treatment
An additional 17 subjects discontinued study drug prematurely during long-term administration. Disease progression (n=8) and neoplasms (n=6) accounted for the majority of withdrawals due to adverse events.

Adverse events of special interest
Adverse events involving the mouth
In the original CTD, in short-term administration there were four relevant AEs in three subjects **(1%). All were mild or "not assessable" in severity and none** resulted in study drug adjustment or discontinuation. In the 120-day Safety Update, in short-term administration, there were seven relevant events in six subjects. Newly reported events were gingival pain (moderate, in a patient with squamous cell carcinoma of the hard palate), esophageal hemorrhage and oral mucosal disorder (mild). The esophageal hemorrhage was severe in intensity and was classified as an SAE. This SAE was deemed related to the **patient's underlying tonsil/throat cancer.**

In the 120-day Safety Update, in long-term treatment, the incidence of oral AEs is relatively unchanged from the original CTD. In addition, a similar pattern in oral AEs was seen. Adverse events involving the mouth (excluding those clearly related to other causes) were seen 26 times (events) involving 6.7% of subjects (20/300). The majority of these events were mild; one was severe. No event led to discontinuation and the rate of ADRs (adverse events attributed by the Investigator to study drug) was 2.0% (six events in six subjects).

Hypoxia/Respiratory distress/Respiratory depression
One additional subject developed hypoxia while hospitalized for pneumonia and myocardial infarction. Other concurrent events included dyspnea, hypotension, hallucinations, confusional state, pulmonary edema and abdominal distension. It is unlikely that this was related to study drug.

No new events of respiratory distress or respiratory depression were reported in the safety update.

Discontinuations due to noncompliance with study drug or procedures
In the 120-day safety update, there were eight additional subjects who discontinued for noncompliance with study drug or procedures for reasons similar to those noted in the original ISS. One patient of interest was a 47 year old male with esophageal cancer and liver mets who was asked to return meds at the end of the study. **The patient stated 'I will not they work well and I need them', and he** left town. (052-2020).

In addition, a second patient did not discontinue the study for this reason but is noted here. The **subject's daughter used the subject's study drug. There were** no adverse effects to the daughter. The subject indicated understanding of need for greater security and continued in the study.

There were a total of 10 subjects who discontinued participation without returning study drug.

Other safety issues

There were no important differences between the original ISS and the safety update in terms of vital sign shifts. Concomitant medication use was also similar except for an increase in the use of antiepileptic drugs reported in the safety update.

Rapid vs. slow titration

Rapid titration included subjects who took only one dose per dose level during titration; slow titration included subjects who took more than one dose per dose level during titration; and single dose titration included subjects who only took doses of one level during titration (not included in comparison). The following table is a comparison of the adverse events in rapid vs. slow titration.

Table 42: Adverse Events Associated with Rapid vs. Slow Titration

	Original CTD Submission		120-day Safety Update	
	Rapid Titration (N=37)	Slow Titration (N=202)	Rapid Titration (N=36)	Slow Titration (n=218)
Adverse Events More Frequent with Rapid Titration, n (%)				
Vomiting	4 (10.8)	12 (5.9)	4 (11.1)	20 (9.2)
Dizziness	4 (10.8)	12 (5.9)	5 (13.9)	14 (6.4)
Headache	2 (5.4)	6 (3.0)	2 (5.6)	8 (3.7)
Sedation	2 (5.4)	1 (0.5)	2 (5.6)	1 (0.5)
Adverse Events More Frequent with Slow Titration, n (%)				
Diarrhea	0	6 (3.0)	0	6 (2.8)
Pain	0	5 (2.5)	0	5 (2.3)
Somnolence	0	14 (6.9)	0	13 (6)

Source: Bema Fentanyl, 120-day safety update

The frequent adverse events more frequent during rapid titration were vomiting, dizziness, headache, and sedation, and those more common during slow titration included diarrhea, pain, and somnolence. Those AEs more frequent during rapid titration also occurred in the slow titration group, but at a lower rate. Those AEs more frequent in the slow titration group did not occur in the rapidly titrated patients.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Important treatment-related adverse events typically reported by patients in this development program include nausea, vomiting, sedation, dizziness, somnolence and constipation. Mouth irritation occurred in less than 3% those exposed to the study drug. These events are reviewed in depth in Section 7.1.

The drug-related adverse events associated with the use of BEMA Fentanyl are those that would be expected.

The analysis of safety was limited by a lack of a clear comparator group, the fact that fentanyl was dosed in the context of around-the-clock opioids, and a study population with poor health and complex medical issues. Given these limitations, causality was determined by the Agency's

knowledge regarding the fentanyl moiety and similar drug products. Since this product is not first in its class, extrapolation from experience with other similar approved products is acceptable.

7.4 General Methodology

The safety data provided by the Applicant was reviewed in its entirety.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The safety data provided by the Applicant was reviewed in its entirety.

7.4.1.2 Combining data

Data from studies FEN-113, FEN-201, and FEN-202 were combined and analyzed by the exposure to study drug (i.e., short and long term treatment).

7.4.2 Explorations for Predictive Factors

Since BEMA Fentanyl was being dosed against a background of around-the-clock opioids (with similar adverse event profiles to the study drug), explorations for predictive factors were not conducted.

7.4.2.1 Explorations for dose dependency for adverse findings

This is not applicable to this application.

7.4.2.2 Explorations for time dependency for adverse findings

This is not applicable to this application.

7.4.2.3 Explorations for drug-demographic interactions

This is not applicable to this application.

7.4.2.4 Explorations for drug-disease interactions

This is not applicable to this application.

7.4.2.5 Explorations for drug-drug interactions

This is not applicable to this application.

7.4.3 Causality Determination

Since there was no actual "control group" in any of the studies and the patient population represented very complex medical issues, causality was determined by the Agency's knowledge regarding the fentanyl moiety and similar drug products. Since this product is not first in its class, extrapolation from experience with other similar approved products is acceptable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

During studies FEN 201 and FEN-202, subjects were given a box of 25 dose units for titration to an effective dose, defined as one producing satisfactory efficacy 60 minutes after application with minimal AEs. Each titration kit contained five dosage units of each of the five study doses. Starting at an initial dose of 200μg, subjects increased their dose on an episode by episode basis and then used the same dose for at least two BTP episodes to insure that is was the correct dose for their BTP. Subjects were contacted at least twice weekly by study personnel throughout the titration period and advised about dosage adjustments. Subjects who were unable to identify an effective dose were discontinued from the study by the end of the two-week titration period.

During the titration periods of FEN-201 and FEN-202, approximately 3% of subjects from each study could not find an effective dose of BEMA Fentanyl and withdrew. For the subjects that were able to find an effective dose, the distribution is shown in Table 43. The effective doses were comparable across the two studies.

Table 43: 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 NDA, Clinical Overview, p, 40.

Overall, the titration method used during the trials allowed the vast majority (97%) of subjects to find an effective dose of BEMA Fentanyl in a relatively safe manner. See Section 7.2.9 for an analysis of adverse events occurring during titration.

There were no additional or unexpected safety issues that arose during the titration periods of the clinical trials, and specifically, there were no reports of overdose. However, although the titration method was found safe and effective during the clinical trials, the ability to extrapolate these findings to "real life" is limited, due to the potential lack of supervision that occurs outside the setting of clinical trials.

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8.2 Drug-Drug Interactions

The pharmacokinetics of potential drug interactions were not assessed during the development program for BEMA Fentanyl, as this information is already known regarding the fentanyl moiety. Clinical drug interactions were assessed for drugs that have suspected potential for pharmacokinetic interaction (e.g., are known CYP3A4 inhibitors or inducers) and also for drugs in common use with a suspected potential for pharmacodynamic interaction (e.g., benzodiazepines and related agents).