The interpretation of the data is limited by the fact that the concomitant medications themselves may be the causal agent for an adverse event of interest. In addition, the condition leading to treatment with the concomitant medication may lead to an increase in a particular AE (e.g., subjects taking sedative-hypnotic agents may be more likely to report an AE of insomnia).

CYP3A4 Inhibitors and Inducers

Among 25 subjects (8.3% of 301 subjects) taking CYP3A4 inducers, constipation, nausea and vomiting were more common compared to subjects not taking these medications. CYP3A4 inducers considered in this analysis were: barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, and troglitazone. (See Table 64 in Appendix 10.5)

CYP3A4 inhibitors were used by 13% of subjects (40 of 301 subjects). All AEs for which differences exceeded 5% between subjects taking and subjects not taking CYP3A4 inhibitors were greater in the group of subjects taking inhibitors. The inhibitors considered were: indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, erythromycin, fluconazole, grapefruit juice, verapamil, diltiazem, and cimetidine. (See Table 65 in Appendix 10.5)

Potentially opiate-related AEs occurring more frequently in subjects taking inhibitors included nausea, vomiting, and mental status changes. However, nausea and vomiting are increased both in the group of subjects taking inhibitors and in the group taking inducers.

Sedative-Hypnotic and Anxiolytics Agents

Sedative-hypnotic agents (benzodiazepines and related drugs) were used by 28.6% of subjects. These subjects were more likely to report insomnia as an AE compared to subjects not using sedative-hypnotic agents. Neither sedation nor typical-opioid related AEs were increased in this group. (See Table 66 in Appendix 10.5)

Anxiolytic agents (including alprazolam, clonazepam, clorazepate-dipotassium, diazepam, and lorazepam) were used by 40.8% of subjects (123 out of 301 subjects). Among subjects taking these agents, the most notable difference in AE rates compared to the remaining population was confusional state. Confusional state was present in 11.4% of subjects taking anxiolytics and 1.7% of those not taking these agents (Table 39). Several other AEs were seen at increased rate in this group including constipation, nausea, pain and dyspnea. (See Table 67 in Appendix 10.5)

8.3 Special Populations

Special populations were not specifically studied in the development program for BEMA Fentanyl. The patient population in the clinical trials represented a wide range of adult patients with malignancies.

During the long-term treatment, 31% of patients were $\geq$ 65, and the doses used by this group were similar to those used by non-elderly. Data provided in the 120-day safety update did not

alter this conclusion. Overall, no important difference in AE rates was seen between elderly and non-elderly population (76.3% v 81.4%). During short-term administration, dizziness was more common in elderly subjects (8.9%) compared to those <65 years of age (4.5%); other AEs showed a similar distribution. In long-term treatment, 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%). Because BEMA Fentanyl is to be titrated to effect and tolerability, no specific dosage adjustments are required for the elderly patient population, although doses should be titrated cautiously.

The information in the product label related to special populations should reflect knowledge regarding the use of the fentanyl moiety in these populations, as is stated in the Actiq label.

8.4 Pediatrics

The Applicant has requested a partial waiver for pediatric studies for [redacted] and less based on the following factors: b(4)

- The lowest dosage strength available for BEMA Fentanyl is a bioerodable mucoadhesive system containing 50 mcg of fentanyl. This oral transmucosal dose of fentanyl is expected to be too high to safely administer to this population;
- The population of opioid-tolerant children younger than [redacted] with breakthrough cancer pain is too small to justify the development of a dosage strength specific to this population; b(4)
- The approved labeling for the reference listed drug Actiq® (fentanyl citrate) oral transmucosal lozenge states that the safety and efficacy in pediatric patients below the age of 16 years have not been established;
- The approved labeling for Duragesic® (fentanyl transdermal system) states that the safety of Duragesic has not been established in children less than 2 years of age. Duragesic should be administered to children only if they are opioid-tolerant and 2 years of age or older; and
- The approved labeling for Sublimaze® (fentanyl citrate) Injection states that the safety and efficacy of Sublimaze in children under 2 years of age have not been established.

The Applicant has also asked for a deferral of the Pediatric Assessment required under PREA because the NDA was ready for submission. The Applicant submitted a Pediatric Development Plan to the Division on March 10, 2006.

The Division issued a Written Request on June 28, 2007 for pediatric studies in children aged 3 to 17 years old. The type of study(ies) requested was a randomized, placebo-controlled, double-blind, fixed-dose trial to assess the efficacy, safety and pharmacokinetics of BEMA Fentanyl in the pediatric population (ages 3-16) for the indication of management of breakthrough cancer pain [redacted] who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain. Reports of studies must be submitted to the Agency on or before July 10, 2011. b(4)

A meeting is scheduled with PERC (Pediatric Research Committee) on July 30, 2008 to review the Applicant's requests.

8.5 Advisory Committee Meeting

There is no advisory committee meeting planned for this application.

8.6 Literature Review

Literature is referenced throughout the review as needed.

8.7 Postmarketing Risk Management Plan

The Applicant submitted a Risk Minimization Action Plan (RiskMAP) for BEMA Fentanyl. The RiskMAP includes the following features:

- A program for disseminating important risk and safety information about BEMA Fentanyl to key stakeholders;
- Active and passive surveillance systems to identify, capture, analyze, and report on safety signals associated with intended and unintended use of BEMA Fentanyl; and
- A plan for continually evaluating and reporting on the effectiveness of the RiskMAP and for making appropriate modifications to improve the RiskMAP.

The plan identifies three goals as follows:

4. BEMA Fentanyl should be used only in opioid tolerant patients, and these patients should not experience severe AEs related to its administration;
5. BEMA Fentanyl should not be misused, abused, or diverted; and
6. Accidental ingestion of BEMA Fentanyl should be prevented

The RiskMAP objectives are as follows:

HCPs, patients, and caregivers will be informed about the potential for BEMA Fentanyl diversion and abuse and the importance of safe storage, handling, and use. RiskMAP tools have been designed to effect behavioral changes in these key stakeholders to achieve RiskMAP objectives, as follows:

• **HCPs will understand the approved** indication of BEMA Fentanyl;

• **HCPs will understand the proper population (i.e.,** opioid tolerant) for use of BEMA Fentanyl;

• **HCPs, patients, and caregivers will know the major** risks associated with BEMA Fentanyl (i.e., respiratory depression, particularly in opioid non-tolerant individuals, and the risk of death in children who accidentally ingest BEMA Fentanyl)

• **HCPs, patients, and caregivers will understand** the proper application and dosing of BEMA Fentanyl;

• **HCPs, patients and caregivers will know the** potential for diversion and abuse; and

• **HCPs, patients, and caregivers will understand proper** storage, handling, and disposal of BEMA Fentanyl.

The strategies identified in the RiskMAP include:

- Identification of specific key stakeholders (HCPs, patients, and caregivers) to ensure appropriate, tailored risk and safety messages are developed for each specific stakeholder and disseminated at different points along the patient care continuum;

- Development of the educational component, which includes:
  - Design and testing of RiskMAP tools
  - Integration of RiskMAP messages and tools into launch materials to ensure that they will become an integral part of the commercialization process, and
  - Incorporation of redundant educational messages across multiple RiskMAP components to disseminate risk and safety information across all relevant stakeholders and ensure minimization of any gaps in the communication of this information.

- Evaluation of the effectiveness of RiskMAP components and outcomes through feedback mechanisms and monitoring of appropriate databases.

In addition, BEMA Fentanyl will be designated Schedule II under the federal CSA. The product will be subject to strict regulatory controls along its entire distribution pathway to ensure that access to the product is restricted in accordance with regulatory requirements.

The Division of Risk Management (DRISK) in The Office of Safety and Epidemiology (OSE), DDMAC, and DMETS have been consulted to review the Applicant's proposed RiskMAP, and interactions between the Applicant and the Agency are ongoing at this time.

8.8 Other Relevant Materials

The following groups were consulted on relevant aspects of this NDA application:

- Division of Medication Errors and Technical Support: proposed proprietary trade name
- Division of Drug Marketing, Advertising, and Communications (DDMAC):Proposed product labeling
- Controlled Substances Staff (CSS) and Division of Risk Management (DRISK): Risk Minimization Action Plan

DMETS has completed their evaluation of the proposed tradename, and found *Onsolis* to be acceptable. [redacted] b(4)

The remainder of the consults are pending at this writing.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
I am in agreement with the Applicant that Study FEN-201 supports a finding of efficacy for BEMA Fentanyl for the treatment of breakthrough pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The primary endpoint, the mean SPID30 for BEMA Fentanyl-treated episodes was statistically significantly greater (p=0.004) than the mean SPID30 for placebo-treated episodes. In addition, the analyses of all of the secondary endpoints supported the primary findings. Refer to Section 6 for a detailed discussion of the efficacy.

Safety
No new or unexpected safety concerns regarding the use of oral transmucosal fentanyl became evident during the review of this NDA. The size of the safety database and the duration of exposure met the requirements imposed by the Division.

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.

Safety issues identified during the review that must be addressed prior to approval include:
1. Safety during titration
2. Development of the RiskMAP
3. Labeling regarding safe conversion between the previously approved oral transmucosal fentanyl products and BEMA Fentanyl.

9.2 Recommendation on Regulatory Action

Pending satisfactory completion of the product label and REMS I recommend that BEMA Fentanyl be approved for the management of breakthrough pain in opioid-tolerant cancer patients.

9.3 Recommendation on Postmarketing Actions

The REMS should be designed to allow for vigilant monitoring of abuse, misuse and diversion of BEMA Fentanyl. Since there will be three oral transmucosal fentanyl products on the market indicated for the management of breakthrough pain in opioid-tolerant cancer patients, none of

which are bioequivalent to the other two, there must be close monitoring of medication errors related to prescribing, improper substitutions by pharmacists, and errors in use of the product by the patients.

The REMS must be reassessed at regular intervals so that updates can be made based on post-marketing experience.

9.3.1 Risk Management Activity

The Applicant has submitted a Risk Management Plan. Formal negotiations regarding the plan are in process at the time of this writing.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Important issues regarding the product label will be placed in an addendum to this review.
At this time the following points can be made:

1. The tradename *Onsolis* has been deemed acceptable by DMETS and the Division.
2. A Medication Guide has been proposed by the Applicant, and will be reviewed by DRISK and the Division.

9.5 Comments to Applicant

Comments may be issued to the Applicant pending complete review of the label and RiskMAP.

10 APPENDICES

10.1 Review of Individual Study Reports

NDA 22-266 is supported by a single adequate and well-controlled clinical trial, protocol FEN-201.

Title
A Double-blind, Placebo-Controlled Evaluation of the Efficacy, Safety and Tolerability of **BEMA™ Fentanyl in the Treatment of** Breakthrough Pain in Cancer Subjects

Objectives

1. To compare the efficacy of BioErodible **MucoAdhesive (BEMA™) Fentanyl with** placebo in the treatment of breakthrough pain in cancer patients

2. **To determine the range of BEMA™ Fentanyl** doses required to control breakthrough pain in subjects with cancer related pain receiving chronic opioid therapy

3. To evaluate the safety and tolerability **profile of BEMA™ Fentanyl** in subjects with cancer-related pain receiving chronic opioid therapy.

Study Design
Randomized, placebo-controlled, double-blind, multiple-crossover efficacy and safety trial

Duration
The study was to have consisted of a screening period of up to one week before enrollment, a titration period of up to two weeks, a double-blind period of up to two weeks, and a one-day follow-up. The total duration of participation in this study was to have been approximately five weeks.

Sample Size
According to the original protocol, 150 subjects with cancer-related pain and frequent episodes of acute breakthrough pain superimposed on their chronic pain were to have been enrolled into the titration portion of the study in order that approximately 100 subjects be enrolled in the double-blind portion of the study.

Amendment#1 (February 28, 2007), changed the planned enrollment to 77 subjects entering the double-blind portion of the study as a result of recalculation of the power requirements.

Inclusion Criteria

1. Male or non-pregnant, non-lactating female ≥ 18 years old
2. Pain associated with cancer or cancer treatment

3. A stable current regimen of oral opioids equivalent to 60-1000 mg/day of oral morphine or 50-300 mcg/hr of transdermal fentanyl
4. Regularly experience 1-4 breakthrough pain episodes per day that require additional opioids for pain control
5. At least partial relief of BTP by use of opioid therapy
6. Subject is able to self-administer study medication correctly
7. Subject willing and able to complete electronic diary card with each pain episode
8. Signed consent obtained at screening prior to any procedures being performed

Exclusion Criteria

1. Psychiatric/cognitive or neurological impairment that would limit the subject's ability to understand or complete the diary
2. Cardiopulmonary disease that, in the opinion of the investigator, would significantly increase the risk of respiratory depression
3. Recent history or current evidence of alcohol or other drug substance (licit or illicit) abuse
4. Rapidly escalating pain that the investigator believes may require an increase in the dosage of background pain medication during the study
5. Moderate (Grade 3) to severe (Grade 4) mucositis (subjects with less than moderate mucositis are permitted and must be instructed to not apply the BEMA disc at a site of inflammation)
6. Strontium 89 therapy within the previous 6 months
7. Any other therapy prior to the study that the investigator considers could alter pain or the response to pain medication. Use of an investigational drug within 4 weeks preceding this study
8. History of hypersensitivity or intolerance to fentanyl
9. Regularly more than 4 episodes of BTP per day
10. ECOG performance status of 4 or 5
11. Pregnant, trying to become pregnant, or not on adequate contraceptive measures

Treatments

Titration period: All subjects were to have received open-label BEMA fentanyl, in escalating doses from 200-1200 mcg/dose

Double-blind period: Subjects were to have received nine doses of study drug; six doses were to have been active, and three matching placebo. Patients were to have used doses in the order specified at randomization. Placebo doses were to have been randomly distributed over the double-blind period with one placebo dose included among every three doses, and at least one active dose between two placebo doses.

Study Schedule of Events

Table 45:

Schedule of Events

Study Period	Screening	Titration Period	Double-blind Period	Follow-Up
Study Days	**-7 to 0**	**1 to 14**	**15 to 28**	**29**
Study Visit	**1**	**2[b]**	**3**	**4**
Medical history	X			
Physical examination	X			X
Vital signs (blood pressure, heart rate, and respiratory rate)	X			X
Urine pregnancy test[a]	X			X
Entry criteria	X			
Signed informed consent	X			
Dispensed open-label BEMA™ Fentanyl for dose titration		X[c]		
Subjects took open-label BEMA™ Fentanyl for target breakthrough pain episodes		X		
Subjects contacted twice weekly by investigator staff member		X		
Dispensed double-blind medication for crossover period (Days 5-14)			X[d]	
Subjects took double-blind medication for target breakthrough pain episodes			X	
Pain intensity recorded before taking a dose of medication and at 5, 10, 15, 30, 45, and 60 minutes after each study dose or until rescue		X	X	
Pain relief recorded at 5, 10, 15, 30, 45, and 60 minutes after each study dose or until rescue		X	X	
Global performance evaluation at time of rescue medication or 60 minutes after each study dose		X	X	
Evaluated mouth for irritation from study medication			X	X
Adverse event recording and evaluation		X	X	X
Concurrent medications recorded	X	X	X	X
Collected remaining study medication and electronic diary			X	X

[a] Women of childbearing potential
[b] Study Visit 2 may be combined with the screening visit.
[c] First day of titration period only
[d] First day of double-blind period only (Day 14)

Source: FEN-201 study report, p. 29

Study Conduct

Screening: Day -7 to 0

- H&P, VS, I/E criteria, evaluation of mouth for mucosal irritation, urine pregnancy test (if applicable)
- Stable dose of opioid defined as: