estimating this parameter (coefficient of variation [CV]: 37.22% for females after Treatment C)). When a possible gender effect was assessed using an ANOVA model, the ratios of the geometric means of Cmax, AUClast, and AUCinf ranged from 93.89% to 102.05%.

| Parameter | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean | SD | CV% | n | Mean | SD | CV% |
| **Tmax (hr)** | **6** | **1.00 (0.75 – 4.00)** | | | **6** | **2.00 (1.00 – 2.00)** | | |
| Cmax (ng/mL) | 6 | 1.38 | 0.378 | 27.41 | 6 | 1.29 | 0.242 | 18.85 |
| AUClast (hr·ng/mL) | 6 | 11.95 | 3.952 | 33.06 | 6 | 10.84 | 1.958 | 18.06 |
| AUCinf (hr·ng/mL) | 6 | 13.03 | 4.094 | 31.41 | 6 | 13.02 | 3.075 | 23.62 |
| AUCextrap (%) | 6 | 8.73 | 2.50 | 28.66 | 6 | 15.73 | 8.08 | 51.33 |
| λz (hr-1) | 6 | 0.0521 | 0.0135 | 25.85 | 6 | 0.0322 | 0.0112 | 34.81 |
| T1/2 (hr) | 6 | 13.99 | 3.25 | 23.26 | 6 | 24.07 | 8.96 | 37.22 |

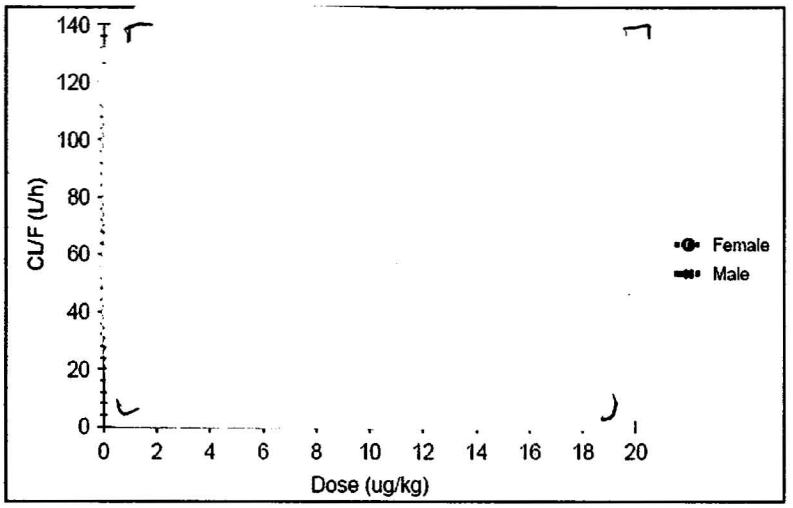
Statistical Analysis of Fentanyl Plasma Pharmacokinetic Parameters after 1 × 800 μg BEMA Fentanyl Citrate to Assess Gender Effect

| Dependent Variable | Geometric Mean[a] | | Ratio(%)[b] | Power [c] |
|---|---|---|---|---|
| | Female | Male | (Female/Male) | |
| ln(Cmax) | 1.2645 | 1.3386 | 94.46 | 0.4367 |
| ln(AUClast) | 10.6932 | 11.3889 | 93.89 | 0.3451 |
| ln(AUCinf) | 12.7380 | 12.4826 | 102.05 | 0.3408 |

a Geometric Mean for Females and Males based on Least Squares Mean of log-transformed parameter values
b Ratio(%) = Geometric Mean (Female)/Geometric Mean (Male)
c Due to small sample size, these comparisons were not sufficiently powered and should not be over interpreted.

In total, of the 54 healthy volunteers who participated in the five studies that used the final formulation there were 40 males and 14 females. There was no apparent relationship between the gender of the subject and the CL/F, expressed on a L/h basis.

**Relationship Between CL/F and Dose of BEMA Fentanyl, by Gender**




b(4)

2.3.1.6 Hepatic / Renal

Hepatic Impairment:

The effect of hepatic impairment on the pharmacokinetics of fentanyl has not been studied. However, once fentanyl reaches the general circulation, it is metabolized primarily by CYP3A4. It is recommended that fentanyl is titrated to clinical effect for all patients, and special care should be taken in patients with severe hepatic disease

Renal Impairment:

The effect of renal impairment on the pharmacokinetics of fentanyl has not been studied. It is recommended that fentanyl is titrated to clinical effect for all patients, and special care should be taken in patients with renal disease.

## 2.4 Extrinsic Factors

2.4.1 Drug-Drug interaction

No drug-drug interaction studies were conducted for Onsolis.

2.4.1.1 Is the drug a substrate of CYP enzymes?

Fentanyl is metabolized mainly via the CYP3A4. Potential interactions may occur when Onsolis is given concomitantly with agents that affect CYP3A4 activity. As with other

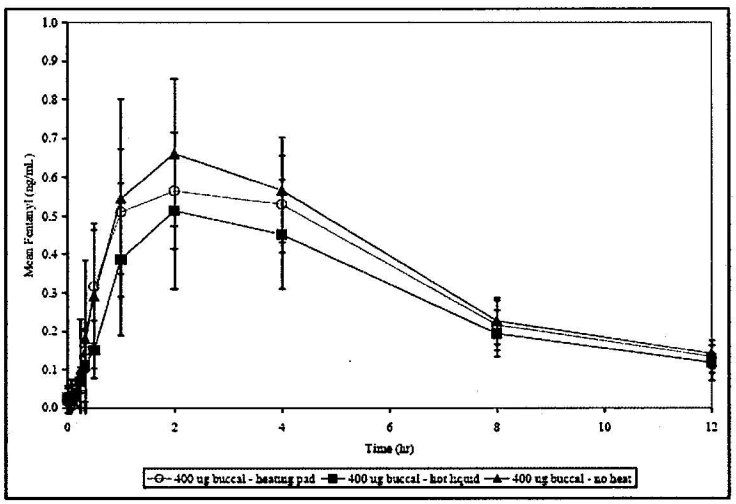
fentanyl products, the concomitant use of Onsolis with all CYP3A4 inhibitors is prohibited.

The concomitant use of Onsolis with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Onsolis. Patients receiving Onsolis with CYP3A4 inducers should be monitored for signs of decreased Onsolis activity and the dose of Onsolis should be titrated accordingly.

2.4.2 Are there any factors which may influence fentanyl release?

A study was performed to assess the effect of heat on the bioavailability of Onsolis. Onsolis 400 µg to the oral mucosa either without heat, with heat to the cheek area using a heating pad for 5 minutes prior to and 20 minutes after application, or with hot tea which was sipped and swished in the mouth for 3 minutes prior to application and, after waiting 5 minutes, sipped and swished hot tea for a further 3 minutes. Results of this study indicate that neither external application of heat nor hot tea alter signficantly the fentanyl absorption.

**Mean ± SD Fentanyl Concentration-Time Plots after Buccal and Transdermal Administration of BEMA Fentanyl**




**Effect of Heat on the Pharmacokinetic Parameters of Fentanyl After Buccal Administration of BEMA Fentanyl**

| | BEMA Fentanyl 400 µg (n=6) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Without Heat | | | With Heating Pad | | | With Hot Tea | | |
| **PK Parameter** | **Mean** | **SD** | **CV%** | **Mean** | **SD** | **CV%** | **Mean** | **SD** | **CV%** |
| Tmax (h) | **2.17** | 0.98 | 44.9 | **2.51** | 1.22 | 48.7 | **2.52** | 1.22 | 48.2 |
| Cmax (ng/mL) | **0.68** | 0.20 | 29.2 | **0.60** | 0.14 | 23.9 | **0.54** | 0.19 | 34.4 |
| AUClast (hr·ng/mL) | **4.43** | 0.99 | 22.3 | **4.10** | 0.89 | 21.8 | **3.51** | 1.0 | 28.4 |

## 2.5 General Biopharmaceutics

### 2.5.1 What is BEMA formulation?

Atrix Laboratories initially developed the drug product. This initial formulation was used in the pharmacokinetic Study FEN-104. In 2000, BioDelivery Sciences International Inc. (BDSI) licensed the technology from Atrix, further optimized the product formulation, and is the manufacturer of the to-be-marketed formulation.

Because fentanyl is a weak base, drug delivery may vary with pH. It is known that neutral drugs pass through biologic membranes more easily than ionized drugs. One can convert ionized molecule to the neutral form by adjusting the pH. The initial formulation (Study FEN-104) did not include any [redacted] b(4)

During the product development, the [redacted]

A mucoadhesive solution at pH [redacted] (designated as **Formulation 1** and was selected for Phase 3 clinical development and commercial product) resulted in a higher $C_{max}$ through the buccal mucosa than solutions at pH [redacted] in the pharmacokinetic study FEN-107. All three formulations delivered more fentanyl than the reference listed drug, Actiq®.

The final product design delivers fentanyl approximately 70% of the dose through the buccal mucosa and 30% of the dose through the GI tract (as determined in Study FEN-114).

### 2.5.2 Is TBM formulation used in Phase 3 studies?

The commercial formulation is the same as that used in the Phase 3 clinical trials (Formulation 1).

| Formulations used in Clinical Studies | | | |
|---|---|---|---|
| **Study** | **Title** | **Formulation** | **Lot(s)** |
| FEN-107 | A comparison of the pharmacokinetics of three different formulations of BEMA fentanyl with Actiq® | 1, 2, 3 | 34822, 34823, 34824 |
| FEN-109 | An evaluation of adherence and fentanyl absorption from BEMA™ discs under a range of conditions | 1 | 35149, 35152 |
| FEN-110 | An evaluation of the single-dose pharmacokinetics of BEMA™ fentanyl | 1 | 35117, 35133, 35134 |
| FEN-112 | An evaluation of the multiple-dose pharmacokinetics of BEMA in normal healthy volunteers | 1 | 35144 |
| FEN-113 | An evaluation of fentanyl absorption from the BEMA™ delivery system in the presence of mucositis | 1 | 35148 |
| FEN-114 | An evaluation of absolute bioavailability and transmucosal absorption of fentanyl from the BEMA™ delivery system | 1 | 35148, 35151 |
| FEN-201 | A double-blind, placebo controlled evaluation of the efficacy, safety and tolerability of BEMA™ fentanyl in the treatment of breakthrough pain in cancer subjects | 1 | 35117, 35120, 35142, 35143, 35133, 35144, 35135, 35145, 35134, 35146, 35152 |
| FEN-202 | An open-label, long-term treatment evaluation of the safety of BEMA™ fentanyl use for breakthrough pain in cancer subjects on chronic opioid therapy | 1 | 35117, 35120, 35142, 35143, 35133, 35134, 35135, 35144, 35145, 35146, 35148, 35149, 35150, 35151, 35152, 35315, 35316, 35317, 35318 |

**F: Formulation 1- pH 7.25; 2 – pH 6.0; 3 – pH 8.5**

2.5.3 What does dissolution data show?

There is no established dissolution method for this type of dosage form. Dissolution testing is performed using *USP* apparatus 1, although the drug product is neither a tablet nor a capsule. Dissolution is essentially completein 30 minutes. Since data was collected at 15 minutes and 30 minutes, it is likely that dissolution may be complete much before 30 minutes. Because the formulation is immediate release, an in vivo in vitro correlation has not been performed. The dissolution results for the lots used in the FEN-107 pH study, the pharmacokinetic studies, and similar strength lots from the clinical efficacy study FEN-201 are shown in the table below. No differences are apparent from inspection of the data.

| | Dissolution Apparatus Operating Conditions for STP 456 |
|---|---|
| Equipment | *USP Apparatus I (Rotating basket/shaft assemblies)* |
| Medium | 25-mM Phosphate buffered medium, pH 6.4, 60 mL, filtered, and degassed |
| Temperature | 37 ± 0.5 °C |
| Rotation Speed | 100 rpm |
| Sampling Time(s) | 5, 15, 30, 45, 60, and 75 min |
| Sampling Volume | Approximately 2.0 mL of medium from each vessel system |
| Medium Replacement | No replacement |
| Filters | [redacted] |

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Dissolution profiles for formulation development lots:

| Dissolution Profiles for Formulation Development Lots | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Type** | **Lot** | **Strength** | **Formulation** | **5** | **15** | **30** | **45** | **60** | **75** |
| 0436DA76 | Tox | 34789 | 273 | 1 | [redacted] | | | | | |
| 0436DA76 | Tox | 34787 | 273 | 2 | | | | | | |
| 0436DA76 | Tox | 34807 | 273 | 3 | | | | | | |
| FEN-107 | pH | 34822 | 800 | 1 | | | | | | |
| FEN-107 | pH | 34823 | 800 | 2 | | | | | | |
| FEN-107 | pH | 34824 | 800 | 3 | | | | | | |
| FEN-109 | PK | 35149 | 400 | 1 | | | | | | |
| FEN-109 | PK | 35152 | 1200 | 1 | | | | | | |
| FEN-110 | PK | 35117 | 200 | 1 | | | | | | |
| FEN-110 | PK | 35133 | 600 | 1 | | | | | | |
| FEN-110 | PK | 35134 | 1200 | 1 | | | | | | |
| FEN-112 | PK | 35144 | 600 | 1 | | | | | | |
| FEN-114 | PK | 35148 | 200 | 1 | | | | | | |
| FEN-114 | PK | 35151 | 800 | 1 | | | | | | |
| FEN-201 | Efficacy | 35148 | 200 | 1 | | | | | | |
| FEN-201 | Efficacy | 35142 | 200 | 1 | | | | | | |
| FEN-201 | Efficacy | 35117 | 200 | 1 | | | | | | |
| FEN-201 | Efficacy | 35145 | 800 | 1 | | | | | | |

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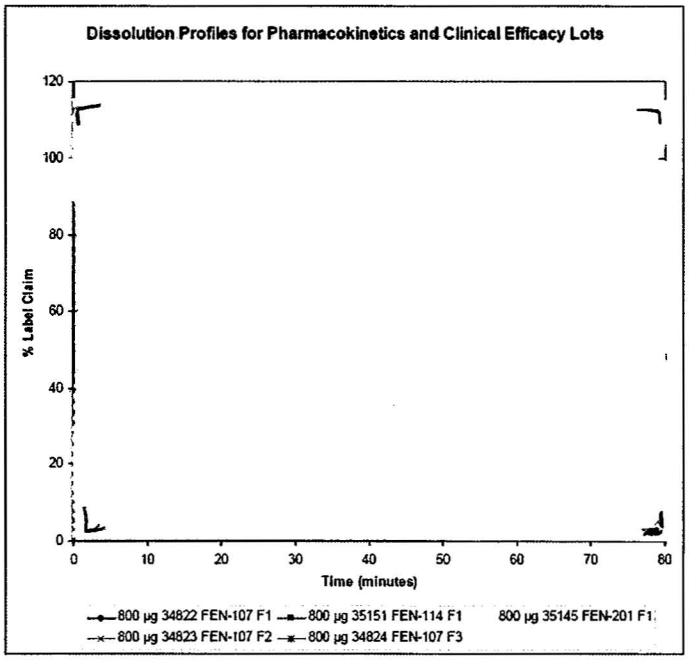
**F: Formulation 1- pH 7.25; 2 – pH 6.0; 3 – pH 8.5**

Dissolution Profiles of different pH Formulations (FEN-107) and 800 µg dose from efficacy study (FEN-201)

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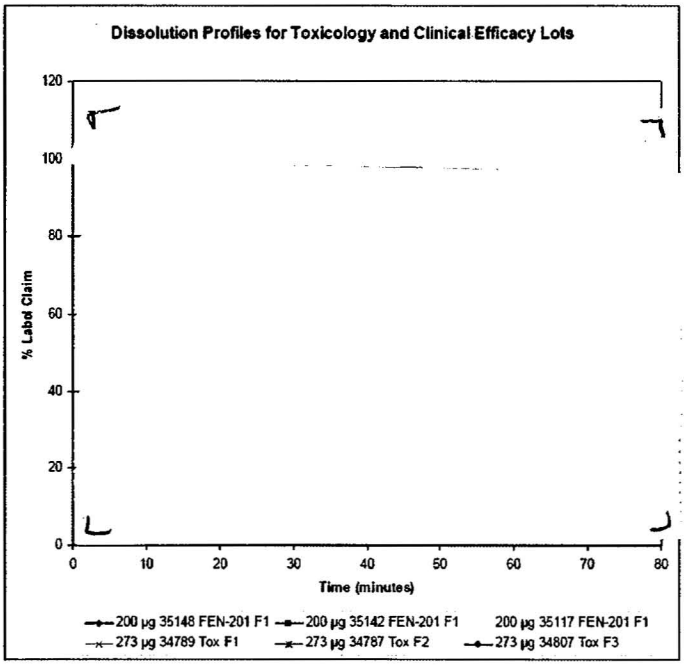
Dissolution Profiles of 200 µg dose from efficacy study (FEN-201) and Toxicology studies

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See ONDQA review by Xavier Ysern for final assessment of the adequacy of the dissolution method and dissolution specifications.

## 2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Plasma samples for all pharmacokinetic studies were analyzed by [redacted] b(4)

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Overall, the analytical assay methodology employed for all studies in this NDA was found to be acceptable.

## 3 Detailed Labeling Recommendations

Texts are deleted (~~crossed out~~) and new wording added in red fonts, as follows:

The following recommendations are proposed:

b(4)

22 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Partner Logo BDSI Logo

## 4.2 Individual study review - Available

## 4.3 Consult Review (including Pharmacometric Reviews) – Not applicable

## 4.4 Cover Sheet and OCPB Filing/Review Form

New Drug Application Filing and Review Form

| Office of Clinical Pharmacology<br>New Drug Application Filing and Review Form | | | |
|---|---|---|---|
| General Information About the Submission | | | |
| | Information | | Information |
| **NDA Number** | **22-266** | **Brand Name** | **Onsolis™** |
| OCP Division | II | **Generic Name** | **BEMA fentanyl** |
| Medical Division | HFD-170 | Drug Class | Anesthesia |
| OCPB Reviewer | David Lee | Indication(s) | Pain anesthesia |
| OCPB Team Leader | Suresh Doddapaneni | Dosage Form | Drug in adhesive |
| | | Dosing Regimen | Single dose |
| Date of Submission | //07 | Route of Administration | Buccal |
| Estimated Due Date of OCP Review | | Sponsor | |
| Medical Division Due Date | | Priority Classification | Standard |
| PDUFA Due Date | //08 | | |

| Clin. Pharm. and Biopharm. Information | | | | |
|---|---|---|---|---|
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| Single dose: | X | 6 | | |
| Multiple dose: | X | | | |

| | | | | |
|---|---|---|---|---|
| Dose proportionality | X | | | |
| Patients- | | | | |
| Single dose: | | 1 | | |
| Multiple dose: | | | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| **pediatrics:** | x | | | **"No incidence in ped. population"** |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD: | X | | | |
| Phase 1: | | | | |
| Phase 2/3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | x | | | Fentanyl i.v. |
| Relative bioavailability - | | | | ACTIQ |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total number of studies | | 7 | | |
| Filability and QBR comments | | | | |
| | **"X" if yes** | **Comments**<br><br>Related IND: | | |

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| | | |
|---|---|---|
| Application filable ? | X | Yes. As a 505(b)(2) application, the Applicant submitted relative BA, multiple dose and dose proportionality (looking at the maximum likely dosing scheme) information. |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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David Lee
7/17/2008 12:43:09 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/18/2008 06:09:02 AM
BIOPHARMACEUTICS