

Buccal drug absorption is dependent upon dissolution of the product in saliva, the mucosal surface area over which the dissolved product is in contact, and the time of that contact.

The surface area for buccal absorption is 25 cm² per side of the mouth and saliva, with a pH of approximately 7, is produced at a rate of 0.04 mL/minute per side (non-stimulated). These factors present challenges for buccal delivery of fentanyl which has a pKa of 8.4, and is most soluble at pH 6 or below.

The BEMA technology has two distinct features. First, there is a direct relationship between dose and surface area of the dose unit, because a single formulation is used. Second, dose units have mucoadhesive qualities when moistened. Theoretically, the combined ability to control the surface area for absorption and the residence time enables fentanyl to be delivered in a predictable manner.

The formulation addresses the issue of fentanyl solubility in the manufacturing process.

b(4)

2.2 General Clinical Pharmacology

2.2.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes.

2.2.2 Exposure-response

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety and efficacy?

No Exposure-response relationship was assessed in this program.

2.2.2.2 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section)

Single dose

The following PK parameters were obtained from the P1 studies. The parameters from across studies were similar.

| Treatments | n | Cmax Mean (SD) ng/mL | AUC 0-inf Mean (SD) h·ng/mL | Tmax Median (Range) h |
|---|----|----------------------------|-----------------------------------|-----------------------------|
| Reference: Fentanyl 200 µg IV | 12 | 1.46 (0.66) | 4.62 (1.5) | 0.17 (0.08–0.37) |
| Reference: Fentanyl 800 µg PO | 12 | 0.69 (0.21) | 6.39 (2.28) | 3.0 (1.0–4.0) |
| Reference: Actiq 800 µg | 12 | 1.03 (0.25) | 10.3 (3.8) | 2 (0.5–4) |
| BF 200 µg | 11 | 0.38 (0.08) | 3.46 (0.72) | 2 (1–4) |
| BF 200 µg (patients with mucositis) | 7 | 0.47 (0.32) | 1.14 (0.71) ^a | 1 (0.45–3.92) |
| BF 200 µg (patients without mucositis) | 7 | 0.69 (0.54) | 1.29 (0.87) ^a | 1 (0.5–1.5) |
| BF 400 µg Without Heat | 6 | 0.68 (0.2) | 4.43 (0.99) | 2.0 (1–4) |
| BF 400 µg Heating Pad | 6 | 0.6 (0.14) | 4.1 (0.89) | 2.0 (1–4) |
| BF 400 µg Hot Tea | 6 | 0.54 (0.19) | 3.51 (1.0) | 2.0 (1–4) |
| BF 600 µg | 12 | 1.16 (0.19) | 11.72 (5.3) | 2 (1–4) |
| BF 600 µg | 12 | 1.08 (0.25) | 9.1 (3.8) | 1.0 (0.75–4) |
| BF 600 µg | 12 | 1.01 (0.23) | 9.6 (3.6) | 2.0 (2–4) |
| BF 800 µg – pH 6 | 12 | 1.4 (0.49) | 13.7 (4.5) | 2 (0.75–4) |
| BF 800 µg – pH 7.25^b | 12 | 1.67 (0.75) | 14.46 (5.4) | 1 (0.75–4) |
| BF 800 µg – pH 8.5 | 12 | 1.39 (0.41) | 13.11 (4.8) | 2 (0.5–4) |
| BF 800 µg | 12 | 1.33 (0.31) | 13.03 (3.45) | 1.5 (0.75–4.0) |
| BF 800 µg (4 x 200 µg units) | 12 | 1.33 (0.43) | 13.09 (3.62) | 2.5 (1.0–4.0) |
| BF 1200 µg | 12 | 2.19 (0.54) | 20.4 (4.5) | 3 (2–4) |

a AUC is from 0-4 h interval

b Final pH

Multiple dose

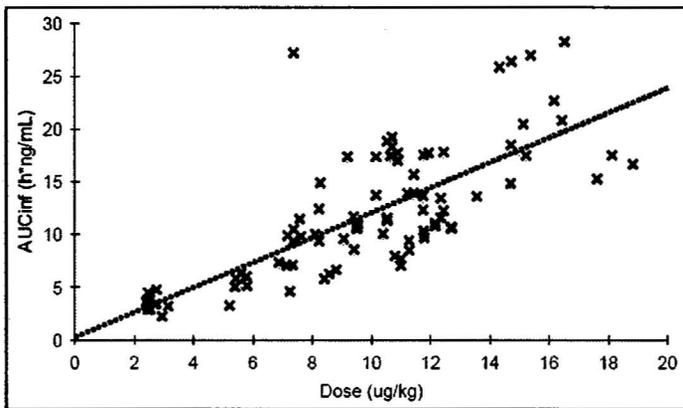
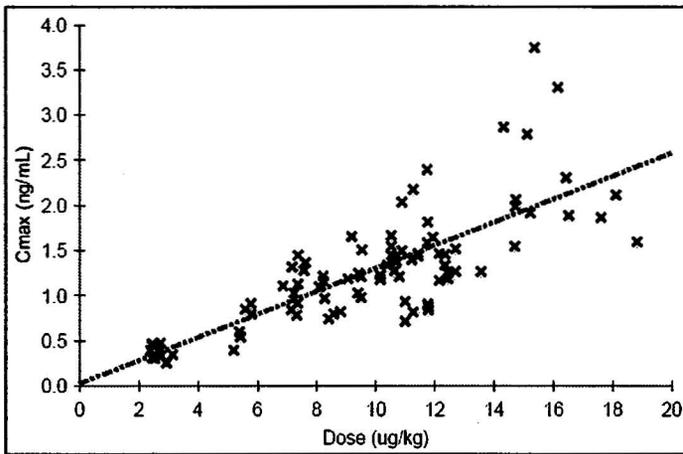
The Applicant conducted a ‘multiple’ dose study with Onsolis (FEN-112). However, Onsolis was not administered in a ‘true’ multiple dose format. In this study one 600 µg Onsolis dosage unit was administered every hour for 3 consecutive times. Previously, the known fentanyl t_{1/2} from Onsolis was ~ 10 hours. Thus, in this study it turned out that the subjects received one 1800 µg dose.

The results indicated that both fentanyl C_{max} and AUC values from the 1800 µg dose showed ‘linear’ kinetics compared to 600 µg dose.

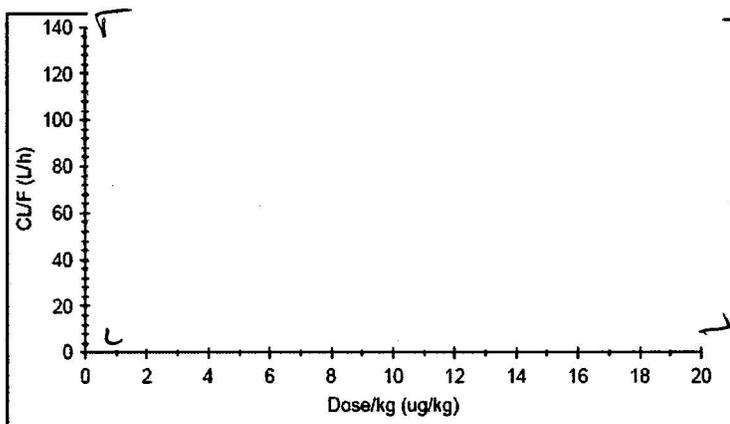
| Parameter | Period 1 Study Day 1 BEMA 600 µg Single Dose N=12 | | | Period 3 Study Day 7 BEMA 600 µg x 3 Hourly Doses Total 1800 µg N=12 | | |
|---------------------------------|--|--------------|--------------|---|--------------|--------------|
| | Mean | SD | CV% | Mean | SD | CV% |
| Tmax (hr) (median value) | 1.03 (0.75 – 4.0) | | | 3.50 (3.25 – 3.75) | | |
| Cmax (ng/mL) | 1.08 | 0.252 | 23.36 | 3.31 | 0.807 | 24.36 |
| AUCinf (hr·ng/mL) | 9.143 | 3.754 | 41.06 | 30.31 | 10.42 | 34.36 |
| T1/2 (hr) | 9.84 | 5.02 | 50.95 | 15.60 | 5.95 | 38.15 |

2.2.2.3 What information is available to assess linearity?

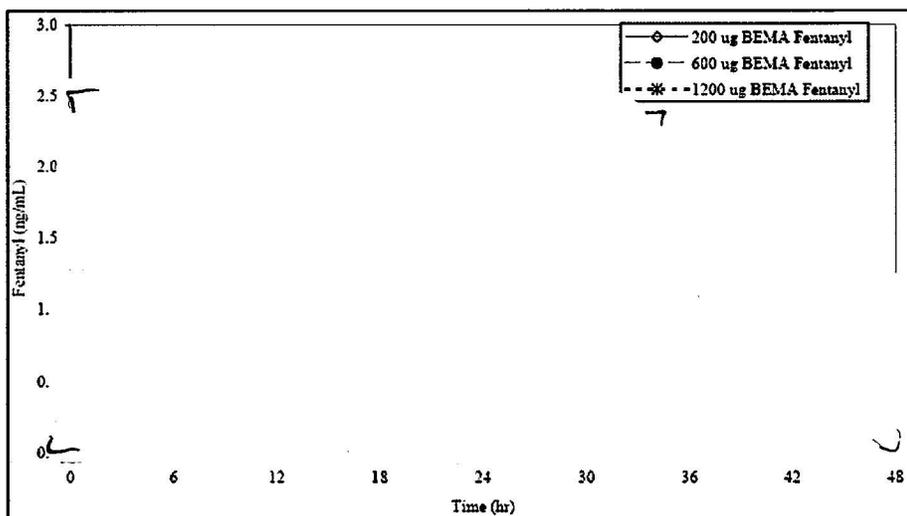
The fentanyl Cmax and AUC values were dose-linear from 200 to 1200 µg (study FEN-110).



Similarly, a plot of CL/F versus Onsolis dose on a $\mu\text{g}/\text{kg}$ basis suggested that CL/F does not change with dose.



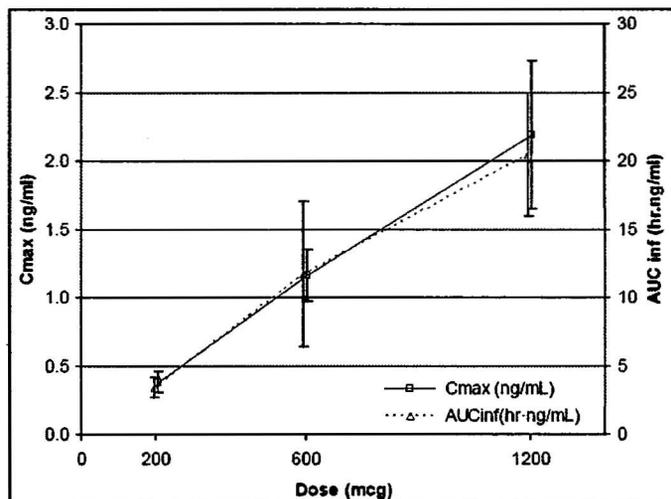
b(4)



b(4)

| Pharmacokinetic Parameter (Mean \pm SD) | BEMA 200 μg | BEMA 600 μg | BEMA 1200 μg |
|---|------------------------|------------------------|-------------------------|
| Cmax (ng/mL) | 0.38 \pm 0.07 | 1.16 \pm 0.19 | 2.19 \pm 0.54 |
| AUCinf (hr-ng/mL) | 3.46 \pm 0.72 | 11.72 \pm 5.29 | 20.43 \pm 4.52 |
| Tmax (hr) (Median (range)) | 2.00 (1.00 – 4.00) | 2.00 (1.00 – 4.00) | 3.00 (0.75 – 4.00) |
| T1/2 (hr) | 8.15 \pm 1.8 | 14.49 \pm 8.40 | 13.60 \pm 4.81 |

Dose linearity plot of Cmax and AUC at 200, 600 and 1200 µg:



2.2.2.4 What is the absolute bioavailability?

The absolute bioavailability of fentanyl from the BEMA formulation was approx. ~71% (Study FEN-114). The absolute bioavailability of fentanyl administered as an oral solution was approx. 35%.

| Parameter | Treatment A: 200 µg IV Fentanyl Citrate | | | | Treatment B: 800 µg Oral Fentanyl Citrate | | | |
|-------------------|---|--------------------|-------|-------|---|--------------------|-------|-------|
| | n | Mean | SD | CV% | n | Mean | SD | CV% |
| Tmax (hr) a | 12 | 0.17 (0.08 – 0.37) | | | 12 | 3.00 (1.00 – 4.00) | | |
| Cmax (ng/mL) | 12 | 1.46 | 0.656 | 44.97 | 12 | 0.694 | 0.210 | 30.21 |
| AUCinf (hr.ng/mL) | 12 | 4.620 | 1.513 | 32.76 | 12 | 6.385 | 2.275 | 35.63 |
| T1/2 (hr) | 12 | 18.03 | 10.08 | 55.91 | 12 | 13.26 | 5.68 | 42.80 |

| Parameter | Treatment C: 1 × 800 µg BEMA Fentanyl | | | | Treatment D: 4 × 200 µg BEMA Fentanyl | | | |
|-------------------|---------------------------------------|--------------------|-------|-------|---------------------------------------|--------------------|-------|-------|
| | N | Mean | SD | CV% | n | Mean | SD | CV% |
| Tmax (hr) a | 12 | 1.50 (0.75 – 4.00) | | | 12 | 2.50 (1.00 – 4.00) | | |
| Cmax (ng/mL) | 12 | 1.33 | 0.307 | 23.01 | 12 | 1.33 | 0.429 | 32.30 |
| AUCinf (hr.ng/mL) | 12 | 13.03 | 3.452 | 26.50 | 12 | 13.09 | 3.616 | 27.62 |
| T1/2 (hr) | 12 | 19.03 | 8.31 | 43.67 | 12 | 18.29 | 4.14 | 22.61 |

Last time point: 48 hours

Comparison of AUCinf values following buccal and oral administration indicated that 51% of the administered BEMA Fentanyl dose is absorbed via the buccal mucosa.

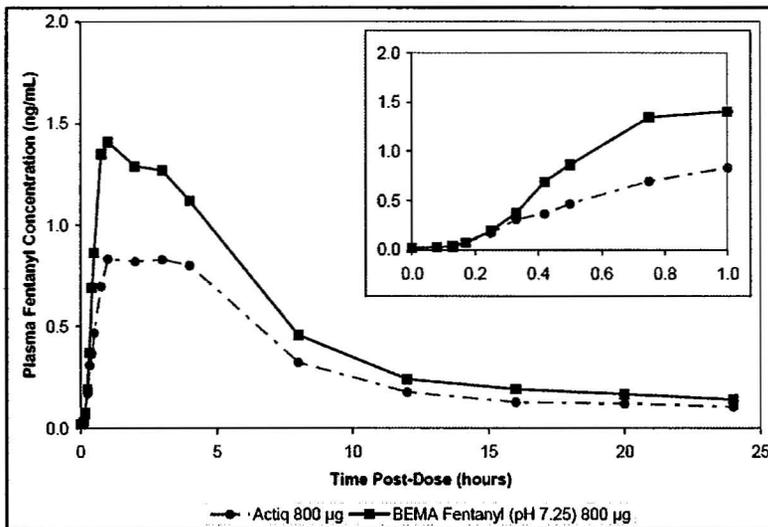
For the presently marketed ACTIQ formulation, the reported absolute bioavailability is approx. 47%.

Since fentanyl exposure is greater from Onsolis, Onsolis should not be substituted for Actiq on a μg for μg basis.

2.2.2.5 What is the relative bioavailability?

Compared to ACTIQ, Onsolis provided 62 and 40 % higher fentanyl C_{max} and AUC, respectively. As stated above, Onsolis should not be substituted for ACTIQ on a μg for μg basis.

Mean Fentanyl Plasma Concentration Versus Time Profiles Following Single Doses of BEMA Fentanyl and Actiq in Healthy Subjects



Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Receiving Single Doses of BEMA Fentanyl (pH 7.25) or Actiq:

| Pharmacokinetic Parameter | BEMA Fentanyl pH 7.25 (800 µg) | Actiq (800 µg) |
|-------------------------------|--------------------------------|----------------|
| C _{max} (ng/mL) | 1.67 ± 0.75 | 1.03 ± 0.25 |
| AUC _{inf} (hr·ng/mL) | 14.46 ± 5.4 | 10.30 ± 3.8 |

BEMA relative bioavailability compare with Actiq:

| Pharmacokinetic Parameter | BEMA 800 µg/ Actiq (800 µg) |
|-------------------------------|-----------------------------|
| C _{max} (ng/mL) | 62.1% greater |
| AUC _{inf} (hr·ng/mL) | 40.4% greater |

2.2.2.6 Does BEMA show dosage form equivalence?

Yes. One 800 µg Cmax and AUC values are similar to 2 x 400 µg values.

FEN-114

| Parameter | Treatment C: 1 × 800 µg BEMA Fentanyl | | | | Treatment D: 4 × 200 µg BEMA Fentanyl | | | |
|--------------------|---------------------------------------|--------------------|--------|-------|---------------------------------------|--------------------|--------|-------|
| | N | Mean | SD | CV% | n | Mean | SD | CV% |
| Tmax (hr) a | 12 | 1.50 (0.75 – 4.00) | | | 12 | 2.50 (1.00 – 4.00) | | |
| Cmax (ng/mL) | 12 | 1.33 | 0.307 | 23.01 | 12 | 1.33 | 0.429 | 32.30 |
| AUClast (hr·ng/mL) | 12 | 11.40 | 3.029 | 26.57 | 12 | 11.70 | 3.201 | 27.37 |
| AUCinf (hr·ng/mL) | 12 | 13.03 | 3.452 | 26.50 | 12 | 13.09 | 3.616 | 27.62 |
| Az (hr-1) | 12 | 0.0422 | 0.0157 | 37.32 | 12 | 0.0400 | 0.0107 | 26.71 |
| T1/2 (hr) | 12 | 19.03 | 8.31 | 43.67 | 12 | 18.29 | 4.14 | 22.61 |

Last time point: 48 hours

2.2.2.7 What other clinical pharmacology information is available?

The following fentanyl information is available from the literature.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by CYP3A4. Norfentanyl was not found to be pharmacologically active in animal studies. Avoidance of first-pass metabolism by the liver accounts for the increased bioavailability of BEMA Fentanyl compared to oral formulations of fentanyl.

Elimination

Fentanyl is eliminated (> 90%) by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted as a parent drug in the urine, and only about 1% is excreted as a parent drug in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl following intravenous administration is reported to be approximately 42 L/h, indicating that it is a high extraction drug with significant first-pass metabolism, and providing rationale for buccal administration. Similarly, the systemic clearance of fentanyl following intravenous fentanyl citrate administration averaged 47.4 L/h (0.67 L/h/kg). This systemic clearance of 47.4 L/h, or ~0.8 L/min, is slightly greater than 50% of hepatic blood flow of 1.5 L/h.

In Study FEN-107, the apparent clearance (CL/F) following 800 µg Onsolis administration averaged 61.8 L/h (0.88 L/h/kg). The total plasma clearance of fentanyl following ACTIQ administration was 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg).

2.3 Intrinsic Factors

2.3.1 Based upon what is known what dosage adjustment is recommended for each of these subgroups?

2.3.1.1 Age

The majority of the subjects who participated in the BEMA Fentanyl Phase 1 studies were healthy volunteers (18 to 45 years). The effect of age on CL/F was assessed by plotting the CL/F in L/hr/kg versus age in years. It is difficult to conclude that there is a correlation between age and CL/F.



2.3.1.2 Elderly

No pharmacokinetic studies were performed in elderly population.

There were 47 and 25 elderly subjects (≥ 65 years old) in the FEN-201 efficacy study for safety and ITT assessments, respectively. There were no overall differences in effectiveness or safety was observed between elderly subjects and younger subjects.

Of the 300 opioid tolerant cancer patients with breakthrough cancer pain in Onsolis clinical studies, 97 (32.3%) were 65 years of age and older. The Applicant reported that there was no difference in the median titrated dose in patients aged 65 years and older compared to those < 65 years. No clinically meaningful difference was noted in the safety profile of the group 65 years of age and older as compared to younger patients.

However, elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, one should be cautious when administering Onsolis to elderly patients.

2.3.1.3 Mucositis patients

The effect of mucositis on bioavailability of Onsolis was assessed in Grade 1 mucositis patients (FEN-113). No major differences were detected between Grade 1 mucositis patients compared to that of the healthy subjects.

Fentanyl Plasma Pharmacokinetics in Cancer Patients with and without Grade 1 Mucositis

| Parameter | Grade 1 mucositis; N=7 Mean | Controls; N=7 Mean |
|-------------------------------|--|-------------------------------|
| C _{max} (ng/mL) | 0.47 (range: 0.19 – 1.13) | 0.69 (range: 0.13 – 1.55) |
| AUC ₀₋₄ (hr·ng/mL) | 1.14 | 1.29 |

2.3.1.4 Pediatrics

The Applicant requests a partial waiver for the _____ pediatric age group, in accordance with 21 CFR 314.55(c)(3). The Applicant provided the following factors for their justification:

b(4)

- The lowest dosage strength available for BEMA Fentanyl is 50 mcg of fentanyl, and is expected to be too high to safely administer to this population;
- The population of opioid-tolerant children _____ with breakthrough cancer pain is too small to justify the development of a dosage strength specific to this population;
- 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 under 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.

b(4)

On 6/28/07, the Agency responded with a formal Written Request for pediatric studies in children aged 3 to 17 years old.

The Applicant also requests, in accordance with 21CFR314.55(b)(1), a deferral of the requirement in 21CFR314.55(a) until _____, based on the fact that the pivotal efficacy and safety studies for BEMA Fentanyl in the adult population (18 years of age and older) have already been completed and are ready for submission in this NDA and that a Pediatric Development Plan with a Proposed Pediatric Study Request was submitted to the FDA on 3/10/06 (Serial No. 028 to IND 62,864).

b(4)

The Applicant believes that the clinical data submitted in this Original NDA demonstrates that BEMA Fentanyl is safe and effective in adult patients (18 years of age and older) when used in accordance with approved labeling and that adequate data exists to proceed to clinical studies in pediatric patients. Additionally, the Applicant believes this justification meets the requirements for a deferral of the Pediatric Assessment required under the Pediatric Research Equity Act (PREA).

2.3.1.4.1 What is the proposed pediatric study request and amendments for this drug?

As part of the process of fulfilling this required assessment, a Pediatric Development Plan with a Proposed Pediatric Study Request was submitted to the Agency on 3/10/06 (Serial No. 028 to IND 62,864). In this submission, the Applicant proposed a pediatric development plan of two (2) pediatric clinical studies of BEMA Fentanyl in pediatric patients aged 3 to 17 years old. This development program was designed to provide an assessment of the pharmacokinetics, safety, and efficacy of BEMA Fentanyl in this population. As stated above, the Applicant requested a partial waiver of the requirement for pediatric studies with BEMA Fentanyl for the _____ pediatric age group.

b(4)

The Agency responded with a formal Written Request for pediatric studies which granted the Applicant's request for a waiver of the _____ pediatric age group and set a 7/10/11 date for submission of the study report(s).

b(4)

The Applicant stated that they are currently evaluating the Written Request and developing a response. They noted that there are significant differences between the initial pediatric development plan submitted by the Applicant and the Written Request received from the Agency, however, they are committed to conducting the pediatric study with due diligence and at the earliest possible time, once agreement is reached with the Agency on the appropriate study design and endpoints.

2.3.1.5 Gender

When stratified by gender, the PK parameters of fentanyl after the administration of 1 × 800 µg BEMA Fentanyl, particularly the exposure parameters C_{max}, AUC_{last}, and AUC_{inf}, were similar for male and female subjects.

Although the mean half-life (T_{1/2}) was somewhat longer for female subjects, the difference in the mean values across gender may be attributed to the longer T_{1/2} value for 2 female subjects (Subjects 11 and 12, the small sample size, and the variability in