

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206099Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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PRODUCT (Generic Name):	Sumatriptan Succinate
NDA:	206099
SUBMISSION DATES	1/27/2014, 4/30/2014
PRODUCT (Brand Name):	Onzetra
DOSAGE FORM:	Nasal Powder (filled in a capsule)
DOSAGE STRENGTHS:	11 mg per nose piece
INDICATION:	For the acute treatment of migraine with or without aura in adults.
NDA TYPE:	505 (b)(2)
SPONSOR:	Avanir Pharmaceuticals
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Angela Men, M.D, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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### TABLE OF CONTENTS

<b>I. EXECUTIVE SUMMARY.....</b>	<b>3</b>
<b>A. RECOMMENDATION.....</b>	<b>3</b>
<b>B. PHASE IV COMMITMENTS.....</b>	<b>3</b>
<b>C. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS .....</b>	<b>4</b>
<b>II. QUESTION BASED REVIEW.....</b>	<b>6</b>
<b>A. GENERAL ATTRIBUTES.....</b>	<b>6</b>
<b>B. GENERAL CLINICAL PHARMACOLOGY.....</b>	<b>7</b>
<b>C. INTRINSIC FACTORS .....</b>	<b>8</b>
<b>D. EXTRINSIC FACTORS .....</b>	<b>8</b>
<b>E. GENERAL BIOPHARMACEUTICS .....</b>	<b>9</b>

**F. ANALYTICAL.....12**

**III.LABELING RECOMMENDATIONS..... 14**

**IV.APPENDIX..... 22**

**A INDIVIDUAL STUDY REVIEW .....22**

**B OCP FILING MEMO.....33**

## I. EXECUTIVE SUMMARY

The sponsor is seeking approval of Onzetra, a drug-device product used for nasal delivery of a powder form of sumatriptan succinate via a breath-powered delivery device (Xsail) as an acute treatment of migraine with or without aura. Sumatriptan is a selective agonist for the 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors indicated for the acute treatment of migraine attacks, with or without aura, (b) (4). Sumatriptan succinate is currently marketed under trade name Imitrex<sup>®</sup> in the form of s.c injection, nasal spray, oral tablets and Zecuity<sup>®</sup> transdermal patch. The sponsor seeks 505(b)(2) pathway using Imitrex<sup>®</sup> formulations as Reference Listed Drugs (RLD) for the approval of Onzetra.

The delivery device consists of a flexible mouthpiece and a specially shaped sealing nosepiece connected via a closed communication shell. The device is intended to deliver sumatriptan into the nasal cavity using the patient's exhaled breath and the device design to produce a balanced closure of the soft palate while the device is being used to deliver drug. The drug substance is sumatriptan succinate (15.4 mg per capsule; 11 mg base), with no excipients, loaded in a (b) (4) capsule that is contained within a disposable nosepiece. The proposed dosing regimen includes administration of 22 mg dose delivered through administration of two 11 mg nosepieces, one per nostril. If the migraine headache returns, a second 22 mg dose may be administered 2 hours after the first dose. The maximum recommended number of doses that may be given in 24 hours is two, separated by at least 2 hours.

The sponsor conducted four studies, two safety/efficacy studies, an acceptable pivotal relative BA study and a dose proportionality study to support of the application. The efficacy study demonstrated significant effectiveness compared with the placebo group. Sumatriptan exposure following 22 mg Onzetra administration was bracketed within the exposure of sumatriptan from approved 6 mg subcutaneous sumatriptan injection and 100 mg oral sumatriptan. The AUC of sumatriptan was similar to that of 20 mg Imitrex nasal spray.

### A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology sections of NDA 206099. The submission is acceptable from a Clinical Pharmacology point of view pending agreement of labeling recommendations in the package insert.

Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review should be conveyed to the sponsor.

### B. Phase IV Commitments

None.

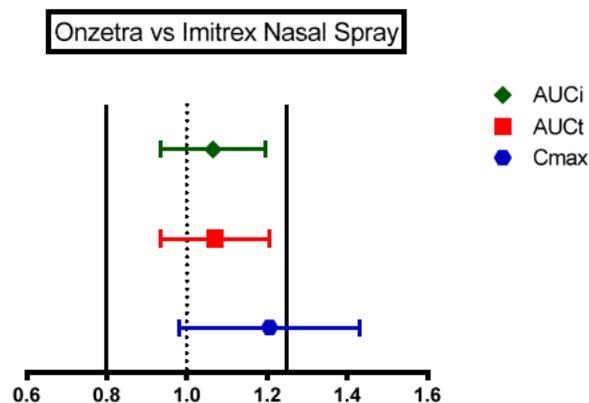
### C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

#### **Relative Bioavailability**

The sponsor conducted a pivotal relative bioavailability study (OPN-SUM-1302) comparing the proposed commercial drug product with the reference Imitrex<sup>®</sup> formulations to support marketing application. A single-center, open-label, randomized, single-dose, 4-way crossover study demonstrated that the systemic exposure of sumatriptan ( $AUC_{0-inf}$  and  $C_{max}$ ) after administration of Onzetra 22mg is well within the exposure of 6 mg of the Imitrex SC Injection and 100 mg Imitrex Oral Tablet and not less than 20 mg of the Imitrex Nasal Spray. This comparison allowed for the referencing of the systemic safety data from the Imitrex Injection and Tablet NDAs. Relative bioavailability ( $F_{rel}$ ), the fraction of the administered dose relative to Imitrex SC Injection adjusted for sumatriptan dose administered, was approximately 14% for all the treatments. The relative bioavailability was 13.8% for Onzetra 22 mg dose, 14.6% for Imitrex Nasal Spray group and 14.4% for 100 mg dose in the tablet group.

Following forest plot represents comparisons of PK parameter ratio following administration of 22 mg Onzetra, administered intranasally (Test) and 20 mg Imitrex<sup>®</sup> (Sumatriptan) Nasal Spray (Reference).



**Note:** Onzetra 22 mg dose is delivered through administration of two 11 mg nosepieces, one per nostril. However Imitrex<sup>®</sup> (Sumatriptan) nasal spray, 20 mg dose is administered to a single nostril.

The overall exposure ( $AUC_{0-inf}$ ) was comparable following 22 mg Onzetra when compared with 20 mg Imitrex<sup>®</sup> Nasal Spray (reference) with the 90% CIs of ln-transformed  $AUC_{0-inf}$  within the range of 80% - 125%. The sumatriptan peak plasma

concentration ( $C_{\max}$ ) was approximately 19% higher. However, this  $C_{\max}$  is much lower than that of SC injection. Therefore, no significant adverse effects are expected.

***Dose Proportionality***

Dose-proportionality study, conducted in France including 12 subjects, indicated that the Onzetra 11 mg dose was less than dose-proportional to Onzetra 22 mg with respect to sumatriptan PK parameters (AUC and  $C_{\max}$ ). Since the sample size in this study was limited and due to high variability in PK parameters (upto 70% CV), no meaningful conclusions could be drawn.

Jagan Mohan Parepally, Ph.D.

**Reviewer, Division of Clinical Pharmacology 1 (DCP1)**

Concurrence:

Angela Men, M.D, Ph.D. \_\_\_\_\_

**Team Leader, DCP1**

cc:     HFD-120     NDA 206099  
       HFD-860     Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Parepally

## II. QUESTION BASED REVIEW

### A. General Attributes

#### **Drug/Drug Product Information:**

***What pertinent regulatory background or history contributes to the current assessment of this drug?***

The Agency approved Sumatriptan in four formulations - oral tablets, subcutaneous injection, nasal spray and iontophoretic transdermal patch.

*Tablets:* Sumatriptan is available as sumatriptan succinate in 25 mg, 50 mg, and 100 mg Imitrex® tablets (GlaxoSmithKline).

*Subcutaneous (s.c) Injection:* Sumatriptan is available as Imitrex® s.c Injection 4 mg (8 mg/mL) and 6 mg (12 mg/mL) containing sumatriptan as the succinate salt (GlaxoSmithKline). When injected, sumatriptan is fast acting, but the effect lasts for a short time.

*Nasal Spray:* Sumatriptan is available as Imitrex nasal spray 5 mg and 20 mg (GlaxoSmithKline). The nasal spray is faster acting than the oral formulation.

*Iontophoretic Transdermal Patch:* Sumatriptan is available as Zecuity® an iontophoretic transdermal patch designed to deliver 6.5 mg sumatriptan over 4 hours of application.

***What are the highlights of the drug delivery system and the drug product as they relate to clinical pharmacology and biopharmaceutics evaluation?***

#### ***Drug Substance:***

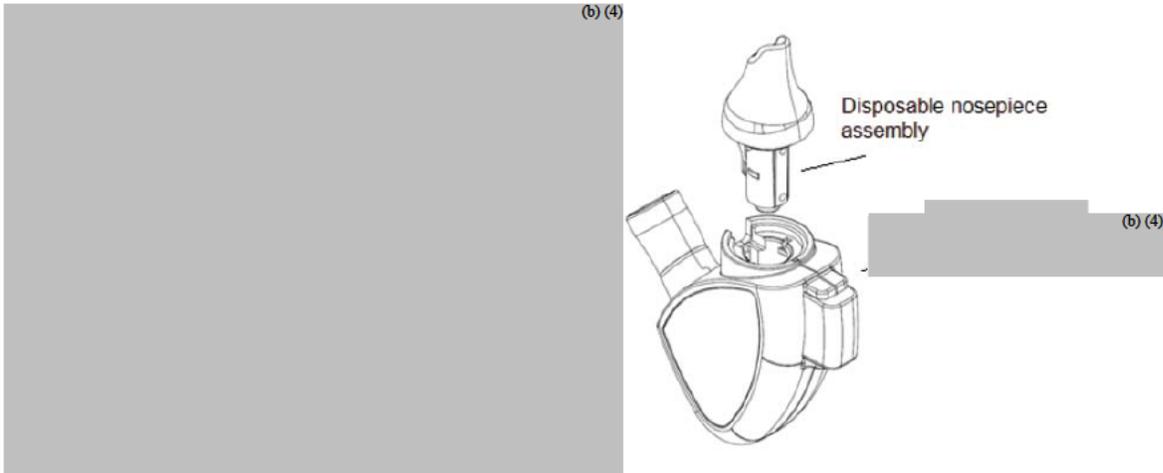
Sumatriptan succinate is a migraine-specific acute triptan with proven clinical benefit.

#### ***Dosage Form/Drug Product:***

Onzetra is a combination product comprised of a drug product and a nasal delivery device (Xsail). Drug product is comprised of a capsule filled with 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). No excipients are included in the drug product formulation. Following figures represent disposable nosepiece assembly and Xsail delivery device.

*Nose Piece Assembly*

*Drug Delivery Device*



***Proposed Indication:***

Onzetra (sumatriptan succinate) is indicated for acute treatment of migraine attacks with or without aura [redacted] (b) (4).

***What are the proposed dosage(s) and route of administration?***

Onzetra is intended for nasal drug delivery of sumatriptan succinate powder. Drug product is comprised of a capsule filled with 11 mg of sumatriptan base. One dose of 22 mg base equivalent of sumatriptan succinate administered as two 11 mg divided doses, each divided dose administered per nostril, to treat an acute migraine.

***What is the proposed mechanism (s) of action?***

Sumatriptan is a serotonin agonist for a vascular 5 hydroxytryptamine<sub>1D</sub> (5-HT<sub>1D</sub>) receptor subtype (a member of the 5-HT<sub>1</sub> family), and has only weak affinity for 5-HT<sub>1A</sub> receptors and no significant activity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5A</sub>, or 5-HT<sub>7</sub> receptor subtypes, or at alpha<sub>1</sub>, alpha<sub>2</sub>, or beta-adrenergic; dopamine or dopamine; muscarinic; or benzodiazepine receptors. The therapeutic activity of sumatriptan in migraine is generally attributed to its agonist activity at 5-HT<sub>1D</sub> receptors.

**B. General Clinical Pharmacology**

**What are the design features of the clinical pharmacology and efficacy studies used to support dosing or claims?**

The following clinical pharmacology studies and two efficacy studies, summarized below were conducted by the sponsor to support the approval of the Onzetra:

<b>Type of Study and Study Identifier</b>	<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>Number of Subjects</b>	<b>Healthy or Patients</b>
Bioavailability (BA) OPN-SUM-1302	Relative BA to Imitrex Oral Tablet, SC, and Nasal Spray	Open-label, randomized, single-center, single-dose, 4-way crossover study of Onzetra vs. Imitrex (sumatriptan) sc injection, oral tablet, and nasal spray formulations	Onzetra (sumatriptan succinate powder) 22 mg, SD, IN; Imitrex Nasal Spray 20 mg, SD, IN; Imitrex Injection 6 mg, SD, SC; Imitrex tablet 100 mg, SD, PO	20	Healthy
Bioavailability (BA) OPTUK MSPP IMP 001	Relative BA to Imitrex SC	Open-label, randomized, single-center, single-dose, 3-way crossover study of Onzetra 10 mg and 20 mg vs. Imitrex (sumatriptan) sc injection.	Onzetra (sumatriptan succinate powder) 20 mg, SD, IN; and 10 mg, SD, IN; Imitrex Injection 6 mg SC	12	Subjects with Migraine Headache
Efficacy and Safety OPN-SUM-MIG-3301	Headache relief 2 hrs after dosing	Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety	Onzetra single 22 mg dose (sumatriptan powder) delivered intranasally and placebo	230	Subjects who suffer regularly from acute migraine attacks
Efficacy and Safety OPTUK-MSPP PRO-002	Pain Free 2 hrs after dosing	Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety	Onzetra single 11 and 22 mg doses (sumatriptan powder) delivered intranasally and placebo	140	Subjects who suffer regularly from acute migraine attacks

The efficacy studies demonstrated significant effectiveness compared with the placebo group. In study OPN-SUM-MIG-3301, there was a statistically significant mean between-group treatment difference in the 22 mg Onzetra group, 73 (67.6%) subjects, who reported pain relief at 120 minutes versus the placebo group, 47 (45.2%) subjects (p=0.0016).

### **C. Intrinsic Factors**

The effects of various intrinsic factors (e.g., hepatic, renal) were provided in the original NDA. Please see Clinical Pharmacology reviews for Imitrex<sup>®</sup> (sumatriptan succinate) injection NDA 20-080.

### **D. Extrinsic Factors**

#### ***Is there a drug-drug interaction between sumatriptan and other drugs?***

No drug-drug interaction studies were conducted with Onzetra. Drug-drug interaction information related to sumatriptan succinate is provided in the original NDA for this drug.

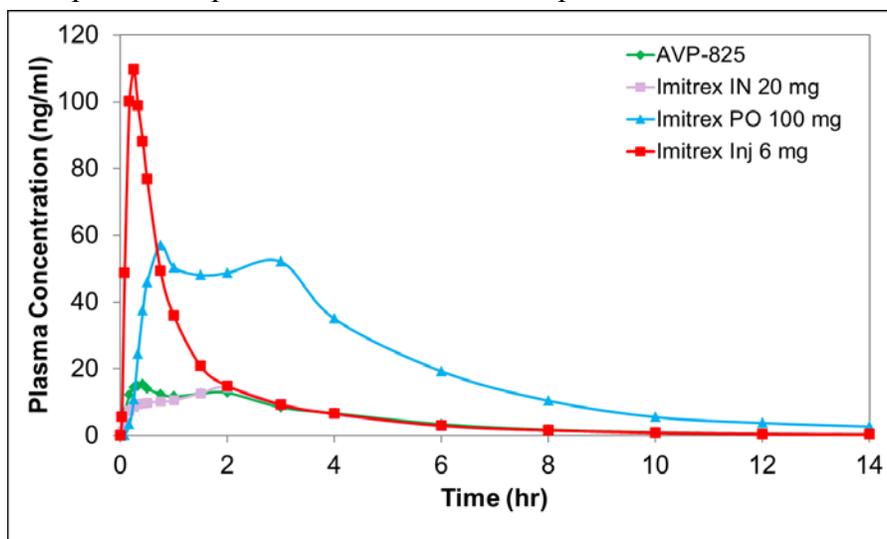
Please see Clinical Pharmacology reviews for Imitrex® (sumatriptan succinate) injection NDA 20-080.

### E. General Biopharmaceutics

#### *How does the PK profile of Onzetra compare to different formulations of Imitrex®?*

The mean plasma concentration over time profiles for the four formulations (22 mg Onzetra, 20 mg Imitrex® (sumatriptan) nasal spray, 100 mg Imitrex® (sumatriptan) oral tablet, and 6 mg Imitrex® (sumatriptan) subcutaneous (SC) injection) evaluated in a pivotal PK Study OPN-SUM-1302 are shown in Figure below. The maximum plasma concentration ( $C_{max}$ ) and  $AUC_{0-inf}$  of sumatriptan obtained following treatment with 22 mg Onzetra were below those obtained with 6 mg sumatriptan s.c injection and 100 mg sumatriptan oral tablets respectively. The  $C_{max}$  of 22 mg Onzetra was approximately 19% higher when compared to 20 mg Imitrex nasal spray. The mean  $AUC_{0-inf}$  values were similar to that obtained with 20 mg Imitrex nasal spray.

Figure: Sumatriptan mean plasma concentration-time profiles



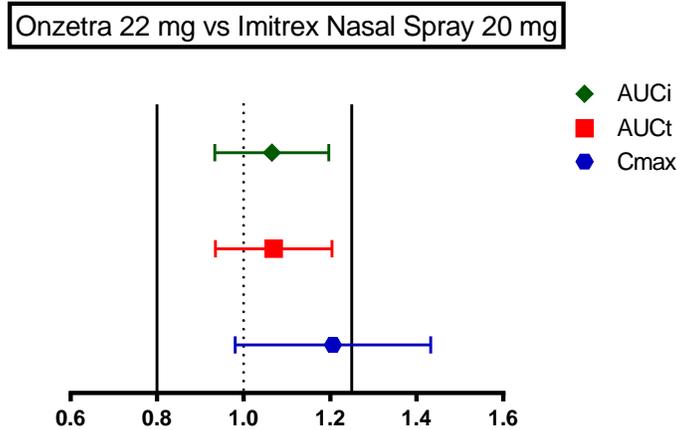
Treatment A = 22 mg Onzetra, administered intranasally (Test)

Treatment B = 20 mg IMITREX® (Sumatriptan) Nasal Spray (Reference)

Treatment C = 100 mg IMITREX® (Sumatriptan) Oral Tablet (Reference)

Treatment D = 6 mg IMITREX® (Sumatriptan) Subcutaneous Injection (Reference)

Following forest plot represents comparisons of PK parameter ratio following administration of 22 mg Onzetra, administered intranasally (Test) and 20 mg Imitrex® (Sumatriptan) Nasal Spray (Reference).



Sumatriptan succinate is a migraine-specific acute triptan with proven clinical benefit. Several sumatriptan products including 20 mg Imitrex<sup>®</sup> (sumatriptan) nasal spray, 100 mg Imitrex<sup>®</sup> (sumatriptan) oral tablet, and 6 mg Imitrex<sup>®</sup> (sumatriptan) subcutaneous (SC) injection had been approved.

During IND meetings with the sponsor, the Agency clarified that it would not be necessary to demonstrate statistical superiority to placebo on migraine symptoms in an efficacy study if exposure achieved with Onzetra were to be equal to 20 mg Imitrex nasal spray and less than 100 mg Imitrex<sup>®</sup> (sumatriptan) oral tablet, and 6 mg Imitrex<sup>®</sup> (sumatriptan) subcutaneous (SC) injection so that the effectiveness and safety of these reference products can be used to support Onzetra's efficacy and safety. Therefore the relative bioavailability Study OPN-SUM-1302 is considered as pivotal study for this application. In addition, the sponsor conducted two safety and efficacy studies to support the application.

Of note, at the request of Division of Neurology Products, the Office of Scientific Investigations (OSI) conducted audit of the clinical and bioanalytical portions of this pivotal relative bioavailability study conducted at Celerion, Neptune, New Jersey and (b) (4) respectively. The OSI concluded that reliability of source data generated in study OPN-SUM-1302 can be accepted for review.

***Are sumatriptan plasma concentrations dose proportional following administration of Onzetra 11 mg dose and Onzetra 22 mg dose?***

No. Dose-proportionality of the sumatriptan plasma concentrations resulting from the nasal administration of sumatriptan powder using Onzetra 11 mg dose and Onzetra 22 mg dose was determined in a non IND study (Study OPTUK MSPP IMP 001). This study was conducted in France including 12 subjects. The results indicated that the Onzetra 11 mg dose was less than dose-proportional to Onzetra 22 mg with respect to sumatriptan PK parameters as shown in the table below.

Pharmacokinetic parameters following administration of Onzetra 11 mg dose and Onzetra 22 mg dose. Data are expressed as means  $\pm$  SD and range (minimum; maximum)

	<b>11mg sumatriptan intranasal</b>	<b>22mg sumatriptan intranasal</b>
<b>C<sub>max</sub></b> (ng/mL)	10.8 ± 7.1 (3.4 ; 30.7)	15.3 ± 6.6 (4.1 ; 25.9)
<b>T<sub>max</sub></b> (min)	20 (10 ; 360)	20 (5 ; 240)
<b>t<sub>1/2</sub></b> (min)	178.1 ± 123.5 (57.7 ; 507.7)	148.8 ± 27.3 (120.3 ; 209.1)
<b>AUC<sub>0-t</sub></b> (ng.min/mL)	1865.5 ± 1171.4 (421.3 ; 4913.2)	2734.4 ± 917.6 (1071.3 ; 4018.7)
<b>AUC<sub>0-∞</sub></b> (ng.min/mL)	2219.9 ± 1605.2 (451.9 ; 6385.4)	2888.2 ± 946.9 (1143.7 ; 4307.0)

In this study, pharmacodynamic parameters were measured by wake EEG associated with GTN-induced headaches, were compared between the two routes of administration. Pretreatment with sumatriptan 6 mg s.c. completely prevented the excess in theta frequency bands (most sensitive marker) induced by sublingual GTN for 40 min. Similar to the active comparator theta induced by sublingual GTN resulted in depressed frequency bands for 40 min for 11 and 22 mg intranasal sumatriptan. However, theta bands increased beyond 40 min upto 4 hours timepoint in all the treatment groups. Among the different frequency bands tested, the most sensitive marker appeared to be theta band. The EEG findings showed that sumatriptan administered by intranasal route resulted in similar pattern in theta bands upto 4 hours.

***What is the effect of food on the bioavailability of Onzetra?***

Food effect on bioavailability is not applicable as the route of administration for Onzetra is intranasal.

***Are there any changes to drug product used during the clinical trials when compared to commercial product?***

During the clinical trials, the sponsor used drug device which has fixed nose piece and mouth piece during the development of the product. Following modification of the device to include flexible parts to the nose piece and mouth piece, an in vitro study was conducted to show similarity in drug delivery. The content of this study will be reviewed ONDQA reviewers.

***What is the proposed dose of Onzetra for the acute treatment of migraine? What are the Onzetra doses administered in clinical trials supporting the application?***

The proposed dose of Onzetra is 22 mg for the acute treatment of migraines in adults. The 22 mg dose is delivered through administration of two 11 mg nosepieces, one per nostril.

According to the sponsor, the amount of drug delivered from the device during in vitro testing is 10 mg. However, correcting for residual dose in device following administration, the calculated dose that was delivered to migraine patients treating a migraine episode in clinical trials was found to be  $7.5 \pm 1.2$  mg (n=40). The Agency requested the sponsor that the labeled dose should be based on the amount of dry powder sumatriptan base filled into a capsule (i.e., 11 mg), rather than on the amount of drug delivered from the device during in vitro testing (i.e., 10 mg) or in vivo by migraine patients ( $7.5 \pm 1.2$  mg).

## F. Analytical

### *Have the analytical methods been sufficiently validated?*

Yes.

*Method:* Sumatriptan and the internal standard were isolated through solid phase extraction. The final extract is analyzed via HPLC with MS/MS detection. The lower limit of quantitation was nominally 0.10 ng/mL for sumatriptan.

### Bioanalytical Method Validation Summary

Information Requested	Data
Validation Summary	(b) (4) Validation Study ZZ00872-02
Analyte	Sumatriptan
Internal Standard (IS)	d <sub>6</sub> -Sumatriptan
Limit of Quantitation (ng/mL)	0.100 ng/mL
Average Recovery of Drug (% Mean)	75% at 0.300 ng/mL 71% at 2.00 ng/mL 72% at 15.0 ng/mL
Average Recovery of IS (% Mean)	72%
Standard Curve Concentrations (ng/mL)	0.100, 0.200, 0.500, 2.00, 6.00, 12.0, 18.0, and 20.0 ng/mL
QC Concentrations (ng/mL)	LLOQ QC, 0.300, 2.00, and 15.0 ng/mL
QC Intra-Batch Precision Range (% CV)	1.3 to 4.4%
QC Intra-Batch Accuracy Range (% Bias)	-4.1 to 7.0%
QC Inter-Batch Precision Range (% CV)	1.5 to 6.0%
QC Inter-Batch Accuracy Range (% Bias)	-1.7 to 3.3%
Bench-Top Stability (Hrs)	Short-Term Stability: 27 hours in polypropylene tubes in an ice water bath under UV-shielded light; 23 hours in polypropylene tubes at ambient temperature under white light  Cumulative Short-Term Stability: 55 hours in polypropylene tubes in an ice water bath under UV-shielded light (total of all thaw cycles)
Stock Stability (Days)	Long-Term Stability for Stock Solutions (Stock): 2730 days at approximately 100 µg/mL in methanol in polypropylene tubes at -20°C

<b>Processed Stability (Hrs)</b>	Post-Preparative Stability: 121 hours in a polypropylene 96 well plate at 5°C Processed Sample Integrity: 134 hours in a polypropylene 96 well plate at 5°C		
<b>Freeze-Thaw Stability (Cycles)</b>	6 freeze (-20°C)-thaw (ice water bath) cycles in polypropylene tubes under UV-shielded light		
<b>Long-Term Storage Stability (Days)</b>	Long-Term Stability: 446 days in polypropylene tubes at -20°C		
<b>Dilution Integrity</b>	Up to 200 ng/mL, diluted 20-fold		
<b>Selectivity</b>	No significant interference at the retention time and mass transition of sumatriptan was observed from endogenous components in any of the 10 human plasma (EDTA) lots screened or of d <sub>6</sub> -sumatriptan (IS) in any of the 10 human plasma (EDTA) lots screened		
<b>Anticoagulant</b>	K <sub>2</sub> EDTA		
<b>Quantitation Method</b>	Peak area ratio		
<b>Quality Control Samples</b>		Precision (% CV)	Accuracy (% Bias)
<b>Inter-Batch</b>	<b>LLOQ</b>	6.0	0.0
	<b>Low</b>	3.6	-1.7
	<b>Medium</b>	1.5	0.0
	<b>High</b>	3.7	3.3
<b>Intra-Batch (Batch 2)</b> <b>Aliquot Method: Manual</b> <b>Extraction Method: Automated</b>	<b>LLOQ</b>	4.1	-4.1
	<b>Low</b>	4.4	-3.0
	<b>Medium</b>	1.3	0.5
	<b>High</b>	1.6	6.0
<b>Intra-Batch (Batch 3)</b> <b>Aliquot Method: Manual</b> <b>Extraction Method: Automated</b>	<b>LLOQ</b>	4.1	7.0
	<b>Low</b>	2.5	-1.0
	<b>Medium</b>	1.4	0.0
	<b>High</b>	3.2	2.7
<b>Intra-Batch (Batch 4)</b> <b>Aliquot Method: Manual</b> <b>Extraction Method: Automated</b>	<b>LLOQ</b>	2.6	2.0
	<b>Low</b>	1.7	0.0
	<b>Medium</b>	1.5	-1.5
	<b>High</b>	1.5	-2.0
<b>Matrix Effect</b>	No significant matrix effect was observed in any of the 10 human plasma (EDTA) lots that were fortified with sumatriptan at the concentration of the LLOQ (0.100 ng/mL) or in any of the 10 human plasma (EDTA) lots that were fortified with sumatriptan at the concentration of the high QC (15.0 ng/mL) samples		
<b>Hemolyzed Sample Integrity</b>	No significant interference for sumatriptan was observed in any of the 3 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the LLOQ (0.100 ng/mL) or in any of the 3 hemolyzed human plasma (EDTA) lots (fortified with 2% whole blood) that were fortified at the concentration of the high QC (15.0 ng/mL) samples		

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## IV. APPENDIX

### A Individual Study Review

OPN-SUM-1302: An Open-Label, Single-Dose, Randomized, Crossover Study to Compare the Bioavailability of the Intranasal Administration of 20 mg (b) (4) SUMATRIPTAN with 20 mg IMITREX® (sumatriptan) Nasal Spray, 100 mg IMITREX® (sumatriptan) Oral Tablet and 6 mg IMITREX® (sumatriptan) Subcutaneous Injection in Healthy Subjects

#### Objectives:

The primary objectives of this study were:

- To compare the single-dose pharmacokinetics (PK) of intranasal administration of 20 mg Onzeta with 20 mg IMITREX® (sumatriptan) Nasal Spray, 100 mg IMITREX® (sumatriptan) Oral Tablet, and 6 mg IMITREX® (sumatriptan) subcutaneous (SC) Injection, in healthy subjects.
- To estimate the relative bioavailability of single-dose intranasal administration of all the above products.

Study Design	This was a single-center, randomized, open-label, single-dose, 4-way crossover bioavailability study in healthy subjects.
Study Population	Healthy male and female Age: 18-55 years BMI: 18 - 32 kg/m <sup>2</sup> 20 subjects were enrolled and 20 completed the study
Treatment Groups	Each subject received the following treatments on 4 separate study days at approximately the same time in each period, with a 7-day washout between treatments: Treatment A: 20 mg (b) (4) SUMATRIPTAN, administered intranasally Treatment B: 20 mg IMITREX® (sumatriptan) Nasal Spray Treatment C: 100 mg IMITREX® (sumatriptan) Oral Tablet Treatment D: 6 mg IMITREX® (sumatriptan) SC Injection The subjects fasted from midnight on the day before dosing (at least 8 hours before dosing) and up to 4 hours postdose. The oral tablet (Treatment C 100 mg IMITREX®) was taken with 240 mL water.
Sampling: Blood	Blood samples were collected at the following time points for the determination of sumatriptan concentrations in plasma: pre-dose, 2, 5, 10, 15, 20, 25, 30, 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours post-dose.

Analysis	Sumatriptan concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with sumatriptan-d <sub>6</sub> as an internal standard and a lower limit of quantification of 0.1 ng/mL.		
	<b>Parameter</b>	<b>Quality Control Samples</b>	<b>Standard Curve Samples</b>
	Quality Control or Standard Curve Concentration (µg/mL)	0.3, 2.0, 15, and 80 ng/mL	0.1, 0.2, 0.5, 2, 6, 12, 18 and 20 ng/mL
	Between Batch Precision (%CV)	2.8 to 6.4	1.5 to 3.3
	% Bias	1.0 to 8.7	-1.6 to 1.0
	Linearity	Weighted linear equation (1/X <sup>2</sup> ), mean r= 0.9990	
	Linear Range (µg/mL)	0.1 to 20 ng/mL	
	Sensitivity (LLOQ, µg/mL)	0.1 ng/mL	
PK Assessments	The following PK parameters for sumatriptan included AUC <sub>0-last</sub> , AUC <sub>0-inf</sub> , AUC <sub>0-30</sub> , C <sub>max</sub> , T <sub>max</sub> , first order terminal elimination rate constant (λz), and terminal half-life (t <sub>1/2</sub> ) and F <sub>rel</sub> (%).		
PD Assessments	None		
Statistical Methods	Pharmacokinetics: Pharmacokinetic parameters for sumatriptan were calculated from the actual plasma concentration-time data using non-compartmental methods with WinNonlin. Pharmacokinetic parameters were summarized by treatment using descriptive statistics. Sumatriptan plasma concentration profiles were presented graphically by treatment, period, and subject.		

**RESULTS:**

Demographic Summary

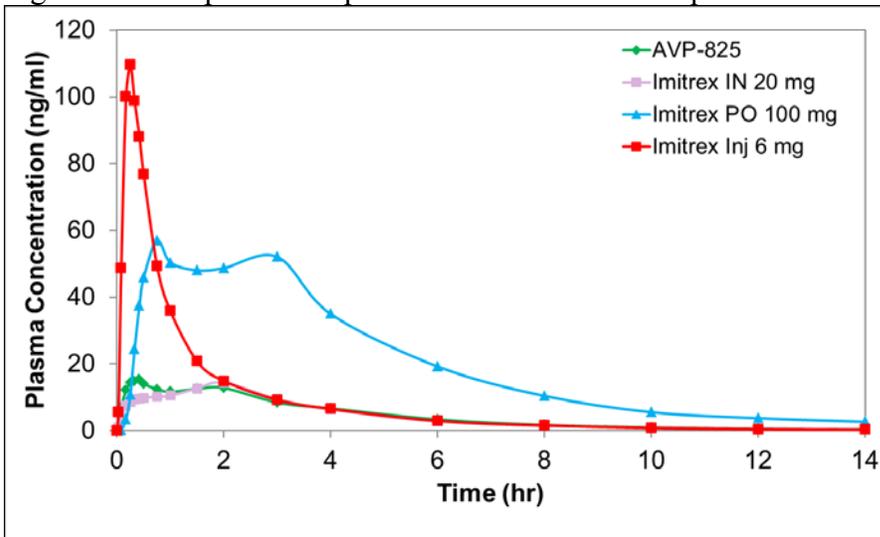
Trait		Treatment Sequence				Overall
		ABCD	BDAC	CADE	DCBA	
Gender	Female	1 ( 20%)	1 ( 20%)	1 ( 20%)	0 ( 0%)	3 ( 15%)
	Male	4 ( 80%)	4 ( 80%)	4 ( 80%)	5 (100%)	17 ( 85%)
Race	Black or African American	4 ( 80%)	3 ( 60%)	2 ( 40%)	3 ( 60%)	12 ( 60%)
	White	1 ( 20%)	2 ( 40%)	3 ( 60%)	2 ( 40%)	8 ( 40%)
Ethnicity	Hispanic or Latino	0 ( 0%)	1 ( 20%)	1 ( 20%)	0 ( 0%)	2 ( 10%)
	Not Hispanic or Latino	5 (100%)	4 ( 80%)	4 ( 80%)	5 (100%)	18 ( 90%)
Age (yrs)	N	5	5	5	5	20
	Mean	36.8	36.0	39.0	35.4	36.8
	SD	10.47	11.07	11.70	8.26	9.70
	Median	41.0	30.0	36.0	37.0	36.5
	Minimum	20	26	24	23	20
	Maximum	47	49	54	44	54

Weight (kg)	N	5	5	5	5	20
	Mean	84.46	83.10	79.82	83.48	82.72
	SD	13.514	12.538	10.162	9.801	10.803
	Median	89.50	85.00	83.90	81.80	84.45
	Minimum	61.3	67.9	68.8	71.5	61.3
Height (cm)	N	5	5	5	5	20
	Mean	171.2	171.6	171.0	179.2	173.3
	SD	5.26	10.14	5.57	2.49	6.91
	Median	173.0	171.0	170.0	181.0	173.5
	Minimum	162	159	166	176	159
	Maximum	175	184	180	181	184

**Reviewer’s Comment:** The study subjects were mostly healthy males (85%). However, sumatriptan clearance is not influenced by gender or racial differences per previous NDA review.

Following figure represents mean PK profiles of sumatriptan following administration of 22 mg Onzetra, 20 mg IMITREX® (sumatriptan) Nasal Spray, 100 mg IMITREX® (sumatriptan) Oral Tablet, and 6 mg IMITREX® (sumatriptan) subcutaneous (SC) Injection.

Figure: Sumatriptan mean plasma concentration-time profiles



Following table represents PK parameters obtained from the Study 1302.

Table: Pharmacokinetic parameters group means and standard deviation (SD) for each period are presented as follows:

Pharmacokinetic Parameters	Treatment A Mean ± SD (N=20)	Treatment B Mean ± SD (N=20)	Treatment C Mean ± SD (N=20)	Treatment D Mean ± SD (N=20)
C <sub>max</sub> (ng/mL)	20.787 ± 12.2	16.397 ± 5.70	70.170 ± 25.3	111.63 ± 21.6
t <sub>max</sub> (hr) <sup>a</sup>	0.7499 (0.167, 2.00)	1.500 (0.176, 2.00)	1.750 (0.502, 3.00)	0.2505 (0.167, 0.335)
AUC <sub>0-t</sub> (ng*hr/mL)	63.046 ± 20.2882	59.152 ± 17.7438	292.60 ± 87.5272	127.32 ± 17.3255
AUC <sub>0-inf</sub> (ng*hr/mL)	64.916 ± 20.5819	61.060 ± 17.7803	308.83 ± 92.3504	128.22 ± 17.3666

AUC <sub>0-30min</sub> (ng*hr/mL)	5.7967 ± 4.108	3.5999 ± 1.896	8.1118 ± 4.973	39.660 ± 7.098
t <sub>1/2</sub>	3.058 ± 0.56145	3.338 ± 0.92990	3.792 ± 1.7726	2.330 ± 0.38451
Lambda z	0.2338 ± 0.042134	0.2235 ± 0.066284	0.2114 ± 0.069614	0.3051 ± 0.049318
AUC% <sub>extrap</sub> (%)	3.002 ± 1.4393	3.378 ± 2.3477	5.163 ± 4.4749	0.7118 ± 0.31934
F <sub>rel</sub> (%)	<b>15.28 ± 4.6195</b>	14.58 ± 4.7175	14.43 ± 3.6905	

Treatment A = 22 mg Onzetra, administered intranasally (Test)  
 Treatment B = 20 mg IMITREX<sup>®</sup> (Sumatriptan) Nasal Spray (Reference)  
 Treatment C = 100 mg IMITREX<sup>®</sup> (Sumatriptan) Oral Tablet (Reference)  
 Treatment D = 6 mg IMITREX<sup>®</sup> (Sumatriptan) Subcutaneous Injection (Reference)  
<sup>a</sup>t<sub>max</sub> is presented as Median (Minimum, Maximum)

**Note:** The extrapolated AUC of sumatriptan is less than 6% following treatments A, B, C and D. F<sub>rel</sub> (%) was calculated using 20 mg Onzetra dose instead of 22 mg. Using 22 mg as administered dose the F<sub>rel</sub> (%) is 13.8 for Onzetra.

Following tables represent comparisons of PK parameters between different treatments.

**Comment:** Reviewer calculated mean ratios of C<sub>max</sub>, AUC and 90% CI's matched with that of sponsor's values as indicated in the tables below.

#### Statistical Comparisons of Plasma Sumatriptan Pharmacokinetic Parameters: Treatment A versus Treatment B

Parameter	Geometric LS Means		% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
	Treatment A (N=20)	Treatment B (N=20)			
C <sub>max</sub>	18.388	15.401	119.40	(98.92, 144.12)	36.71
AUC <sub>0-t</sub>	60.075	56.457	106.41	(93.78, 120.73)	24.20
AUC <sub>0-30min</sub>	4.755	3.131	151.90	(117.11, 197.02)	52.26
AUC <sub>0-inf</sub>	61.941	58.448	105.98	(93.61, 119.98)	23.77

Treatment A = 22 mg Onzetra, administered intranasally (Test)  
 Treatment B = 20 mg IMITREX<sup>®</sup> (Sumatriptan) Nasal Spray (Reference)  
 Parameters were ln-transformed prior to analysis.  
 Values for Treatment A and Treatment B are the exponentiated LS means from the ANOVA.  
 % Geometric Mean Ratio = 100\*exp(LS mean test - LS mean reference)  
 % Intra-subject CV = 100\*sqrt(exp(s<sup>2</sup>) - 1), where s<sup>2</sup> is the residual variance component from the ANOVA.

#### Statistical Comparisons of Plasma Sumatriptan Pharmacokinetic Parameters: Treatment A versus Treatment C

Parameter	Treatment A (N=20)	Treatment C (N=20)	% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
AUC <sub>0-t</sub>	60.075	280.894	21.39	(18.85, 24.27)	24.20
AUC <sub>0-30min</sub>	4.755	6.944	68.48	(52.80, 88.82)	52.26
AUC <sub>0-inf</sub>	61.941	296.516	20.89	(18.45, 23.65)	23.77

Treatment A = 22 mg Onzetra, administered intranasally (Test)  
 Treatment C = 100 mg IMITREX<sup>®</sup> (Sumatriptan) Oral Tablet (Reference)

Statistical Comparisons of Plasma Sumatriptan Pharmacokinetic Parameters:  
Treatment A versus Treatment D

Parameter	Treatment A (N=20)	Treatment D (N=20)	% Geometric Mean Ratio	90% Confidence Intervals	% Intra-subject CV
C <sub>max</sub>	18.388	109.633	16.77	(13.90, 20.24)	36.71
AUC <sub>0-t</sub>	60.075	126.193	47.61	(41.96, 54.01)	24.20
AUC <sub>0-30min</sub>	4.755	39.051	12.18	(9.39, 15.79)	52.26
AUC <sub>0-inf</sub>	61.941	127.098	48.73	(43.05, 55.17)	23.77

Treatment A = 22 mg Onzetra, administered intranasally (Test)

Treatment D = 6 mg IMITREX® (Sumatriptan) Subcutaneous Injection (Reference)

## CONCLUSIONS

- Sumatriptan peak plasma concentration (C<sub>max</sub>) was approximately 19% higher following 22 mg Onzetra when compared with 20 mg IMITREX® Nasal Spray (reference). However, the overall exposure (AUC<sub>0-inf</sub>) was comparable; the 90% CIs of ln-transformed AUC<sub>0-inf</sub> were within the range of 80% - 125%.
- The mean C<sub>max</sub> and AUC<sub>0-inf</sub> ratio (the peak and overall exposure) of sumatriptan following 22 mg Onzetra was approximately 28% and 21% respectively when compared with 100 mg IMITREX® (Sumatriptan) Oral Tablet (Reference).
- The mean C<sub>max</sub> and AUC<sub>0-inf</sub> ratio (the peak and overall exposure) of sumatriptan following 22 mg Onzetra was approximately 17% and 49% respectively when compared with 6 mg IMITREX® (Sumatriptan) Subcutaneous Injection (Reference).
- The C<sub>max</sub> and AUC of sumatriptan are bracketed within the PK profiles of the reference (oral, subcutaneous and nasal spray) formulations.

OPTUK-MSPP-IMP-001: An active treatment-controlled, 3-way cross-over design study to evaluate, in the glyceryltrinitrate (GTN) challenge, the effects on quantitative wake EEG of intranasal sumatriptan in subjects suffering from migraine.

**Objectives:**

Primary:

- To compare the effects of intranasal sumatriptan with a subcutaneous reference dose on glyceryltrinitrate (GTN)-induced migraine in subjects suffering from migraine by EEG.

Secondary

- To compare the plasma PK profiles, safety and tolerability of sumatriptan after the two routes of administration.
- To compare the PK/PD relationship between sumatriptan plasma concentrations and quantified wake EEG between the two routes of administration.
- To evaluate a potential dose effect of the two doses of intranasal sumatriptan by means of the quantified wake EEG.

Study Design	This was a single-center, randomized, open-label, active treatment controlled, 3-way crossover study in subjects suffering from migraine.
Study Population	Subjects suffering from migraine. Age: 18-40 years BMI: 18-29 kg/m <sup>2</sup> 12 subjects were enrolled and 12 completed the study
Treatment Groups	Sumatriptan: administration of 11 mg and 22 mg doses as intranasal powder delivered with the OptiNose powder delivery device. The 11 mg dose was administered to one nostril using one OptiNose powder delivery device. The 22 mg dose was administered to both nostrils using two OptiNose powder delivery devices. A wash-out period of at least 5 days was included between consecutive administrations GTN challenge: single sublingual administration of 0.9mg  Duration of treatment: Morning administration of intranasal (i.n.) or sub-cutaneously (s.c.) sumatriptan on Day 1 of each period, with a single GTN dose of 0.9 mg sublingually administered.  The administration was performed after an overnight fasting period (at least 10 h between last snack and the administration) and was followed 15 min later by a GTN administration (0.9 mg).
Sampling: Blood	Blood samples for plasma concentrations determination were drawn, on Day 1 at T0 (before treatment), every 10 min during the first 90 min, and then 2h, 4h, 6h, 8h and 12h after treatment. Additional samples were drawn at 5 and 15 min.

Analysis	Sumatriptan concentration was determined in plasma samples using a validated method for high performance liquid chromatography- with tandem mass spectrometric detection with sumatriptan-d <sub>6</sub> as an internal standard. The lower limit of quantification was 0.2 ng/mL.		
	<b>Parameter</b>	<b>Quality Control Samples</b>	<b>Standard Curve Samples</b>
	Quality Control or Standard Curve Concentration (µg/mL)	0.6, 40, 70, and 400 ng/mL	0.2, 0.5, 2, 10, 25, 50, 70 and 80 ng/mL
	Between Batch Precision (%CV)	5.3 to 7.8	4.3 to 9.4
	% Bias	0.3 to 10.9	-7.5 to 6.1
	Linearity	Weighted linear equation (1/X <sup>2</sup> ), mean r= 0.996	
	Linear Range (µg/mL)	0.2 to 80 ng/mL	
	Sensitivity (LLOQ, µg/mL)	0.2 ng/mL	
PK Assessments	The following PK parameters for sumatriptan included AUC <sub>0-last</sub> , AUC <sub>0-inf</sub> , AUC <sub>0-30</sub> , C <sub>max</sub> , T <sub>max</sub> , first order terminal elimination rate constant (λz), and terminal half-life (t <sub>1/2</sub> ) and F <sub>rel</sub> (%).		
PD Assessments	The EEGs were recorded based on a montage of 28 electrodes with linked ears as a reference. During the recording periods subjects were sitting in a quiet room with eyes closed (i.e. resting conditions). After a double baseline recording (i.e. 2 x 10 min in eyes closed conditions before sumatriptan and GTN administrations), a continuous recording period of the first 1.5 h post-dosing was performed. In addition, at time 2, 4, 6 and 8 h a 10 min EEG recording was recorded at each time point. The first 1.5 h post-dosing was broken down into 10 min periods (i.e. 9 periods of 10 min).		
Safety Assessments	<ul style="list-style-type: none"> <li>- Adverse events (throughout the study).</li> <li>- Physical examination (at screening, on Day-1, on Day 2, and at the end-of-study visit).</li> <li>- Vital signs (at screening, on Day-1, on Day 1, before and 15 min, 30 min, 45 min, 1 h, 1h30, 2h, 3h, 4h, 6h and 12h after administration, on Day 2, 24h after administration and at end-of-study visit).</li> <li>- ECG parameters (at screening, on Day-1, on Day 1 before and 2h after administration, on Day 2, 24h after administration and at end-of-study visit).</li> <li>- Laboratory tests (at screening, on Day-1, and at end-of-study visit).</li> </ul>		
Statistical Methods	<p>Pharmacokinetics: Differences between treatments are analyzed descriptively. A cross-over analysis of variance is performed on AUCs, C<sub>max</sub> and 90% confidence interval for the ratio of each dose of intranasal sumatriptan compared to the reference (s.c. sumatriptan). t<sub>max</sub> is analyzed by means of nonparametric tests.</p> <p>PK/PD relationships: The relationships between plasma concentrations and lead median of EEG parameters are based upon the descriptive analysis of graphs, for a selection of recording conditions and parameters which display most consistent modifications, and on common time measurements.</p>		

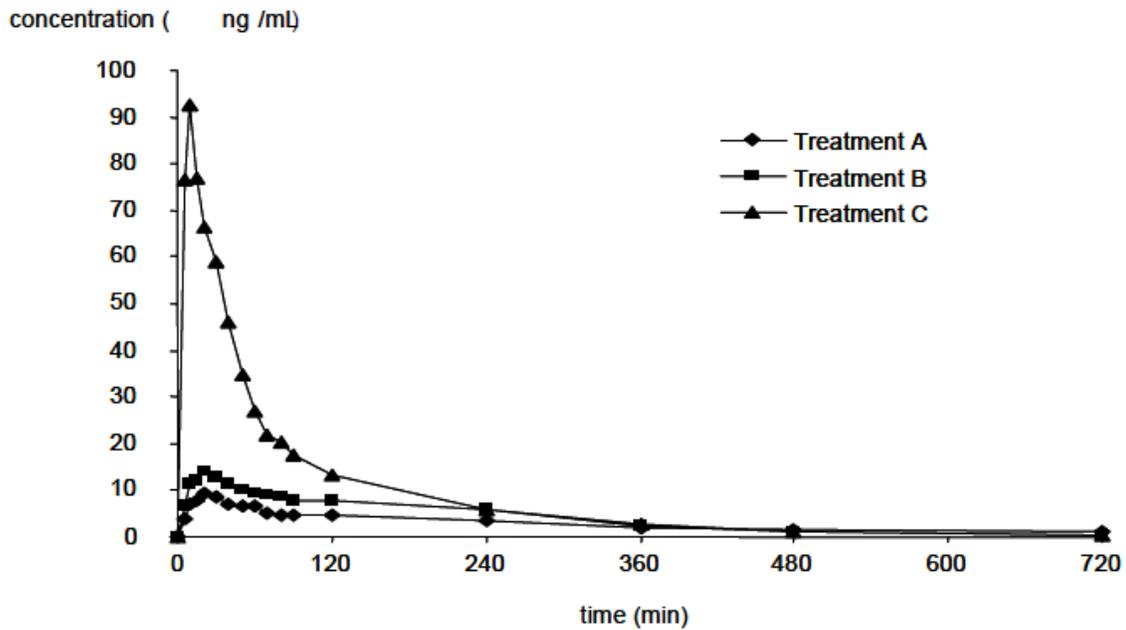
## Pharmacodynamic analysis

Standard frequency EEG band parameters, derived from mean spectra, were calculated for Resting (R) conditions for each of the 28 leads and subject. The analysis of brain maps was performed using a methodology developed by FORENAP Pharma called Statistical Decision Tree (SDT)

**RESULTS:**

Pharmacokinetics

Mean plasma concentration ( $\pm$ SD) profiles of sumatriptan determined after administration of 11 and 22 mg intranasal sumatriptan and 6 mg sumatriptan subcutaneous injection.



Values of pharmacokinetic parameters per formulation. Data are expressed as means  $\pm$  SD and range (minimum; maximum)

	11mg sumatriptan intranasal	22mg sumatriptan intranasal	6mg sumatriptan sub-cutaneous
<b>C<sub>max</sub></b> (ng/mL)	10.8 $\pm$ 7.1 (3.4 ; 30.7)	15.3 $\pm$ 6.6 (4.1 ; 25.9)	96.4 $\pm$ 25.4 (67.7 ; 143.0)
<b>T<sub>max</sub>*</b> (min)	20 (10 ; 360)	20 (5 ; 240)	10 ( 5 ; 30 )
<b>t<sub>1/2</sub></b> (min)	178.1 $\pm$ 123.5 (57.7 ; 507.7)	148.8 $\pm$ 27.3 (120.3 ; 209.1)	105.9 $\pm$ 30.8 (76.2 ; 172.2)
<b>AUC<sub>0-30 min</sub></b> (ng.min/mL)	207.7 $\pm$ 129.2	302.3 $\pm$ 155.9	1999.3 $\pm$ 410.8

	(47.9 ; 504.0)	(62.7 ; 577.8)	(1604.8 ; 2822.0)
<b>AUC<sub>0-t</sub></b> (ng.min/mL)	1865.5 ± 1171.4 (421.3 ; 4913.2)	2734.4 ± 917.6 (1071.3 ; 4018.7)	6300.0 ± 1826.3 (4087.1 ; 11196.2)
<b>AUC<sub>0-∞</sub></b> (ng.min/mL)	2219.9 ± 1605.2 (451.9 ; 6385.4)	2888.2 ± 946.9 (1143.7 ; 4307.0)	6400.1 ± 1823.8 (4290.0 ; 11239.9)

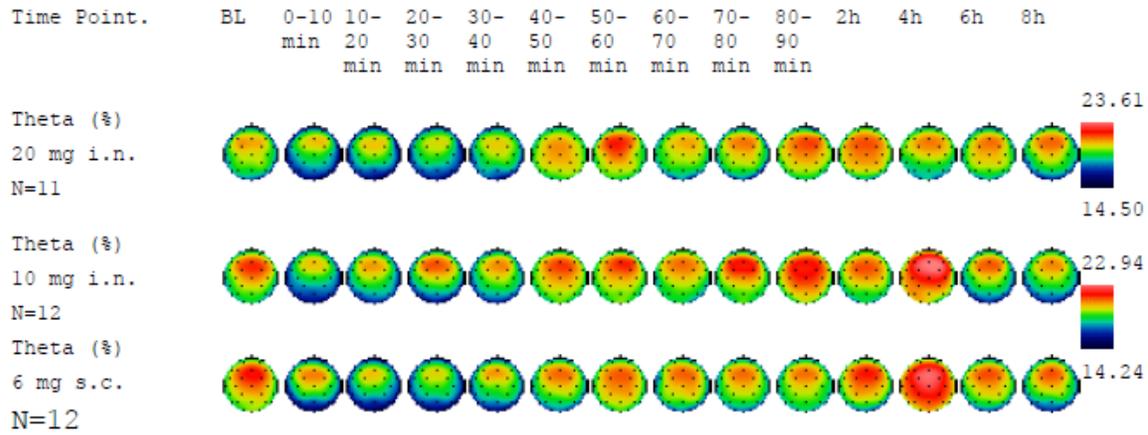
Parametric 90% confidence intervals with point estimates for comparison of test and reference formulations of sumatriptan 11 and 22 mg (n=12)

	<b>11 mg</b>	<b>22 mg</b>
	<b>ln</b>	<b>ln</b>
	<b>AUC<sub>0-∞</sub></b>	<b>AUC<sub>0-∞</sub></b>
LSM Formulation Sumatriptan i.n.	7.49	7.91
LSM Formulation 6mg s.c	8.73	8.73
MSE	0.290	0.0437
90% CI for Test/ Reference ratio	<b>19.3-42.8%</b>	<b>37.7-51.3%</b>
Point Estimate for Test/Reference ratio	<b>28.7%</b>	<b>44.0%</b>

### Pharmacodynamics

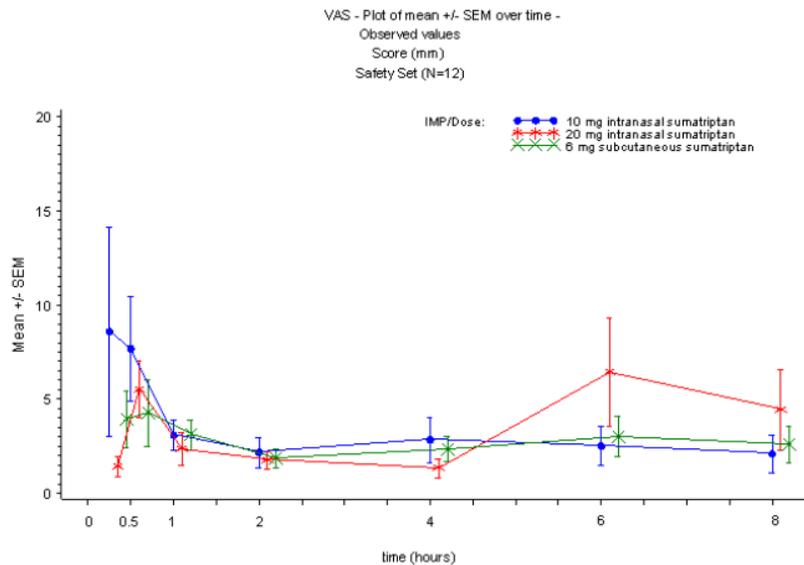
According to Thomaidis et al. 1996, main effects on the EEG associated with GTN-induced headaches are significant increases in relative values for the delta and theta frequency bands; decreases in alpha and beta did not reach significance.

Pretreatment with sumatriptan 6 mg s.c. completely prevented the excess in theta induced by sublingual GTN and resulted in depressed theta for 40 min (row 3) in the figure below. Similar to the active comparator theta induced by sublingual GTN resulted in depressed theta for 40 min for 11 and 22 mg intranasal sumatriptan. However, theta bands increased beyond 40 min upto 4 hours timepoint in all the treatment groups. The implication of this outcome should be reviewed by Clinical Division.



**Note:** In this study among the different frequency bands tested, the most sensitive marker appeared to be theta band. The EEG findings should be reviewed by the MO for the effects of sumatriptan on GTN challenge in the patients with migraine.

Time profiles of Headache using the VAS.



**Discussion**

GTN is a product of nitric oxide and induces headaches with some features similar to those of migraine.

This study is a non IND study conducted in France. The sample size (n=12) is not justified to evaluate the pharmacodynamics endpoints. High inter-subject variability was observed for PK parameters.

**CONCLUSIONS**

- The mean  $C_{max}$  and AUC of sumatriptan following 11 mg and 22 mg dose were not dose proportional.
  - The mean  $C_{max}$  and AUC of sumatriptan following intranasal administration were lower than that of sub-cutaneous administration as expected.
  - Most of subjects recorded no pain in the headache severity score with all the treatments. 20 mg sumatriptan IN resulted in relatively lower pain score when compared to 11 mg dose upto 4 hours post dose. However, the pain score were higher for 22 mg group beyond 4 hours.
- !

**B OCP Filing Memo**

Office of Clinical Pharmacology and Biopharmaceutics <b>NEW DRUG APPLICATION FILING AND REVIEW FORM</b>			
<b>General Information About the Submission</b>			
	Information		Information
NDA Number	206099	Brand Name	(b) (4) (AVP-825)
OCP Division (I, II, III)	DCP-1	Generic Name	Sumatriptan Succinate
Medical Division	HFD-120	Drug Class	Triptans
OCP Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Migraine
OCP Team Leader	Angela Men	Dosage Form	Nasal Powder
Date of Submission	1/27/2014	Dosing Regimen	22 mg
Estimated Due Date of OCP Review	10/23/2014	Route of Administration	Nasal
PDUFA Due Date	11/26/2014	Sponsor	Avanir Pharmaceuticals
Division Due Date	10/30/2014	Priority Classification	S

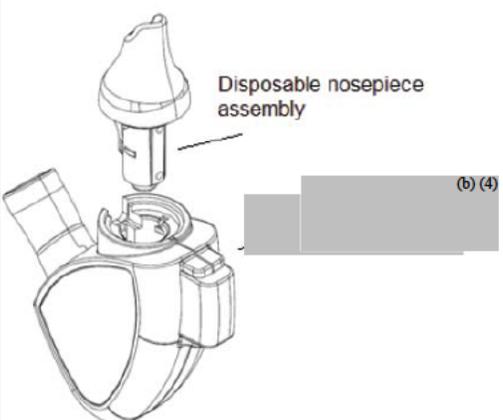
**Clin. Pharm. and Biopharm. Information**

**Summary:** This is a 505(b)(2) NDA to support the marketing approval of (b) (4) (sumatriptan succinate) nasal powder.

(b) (4) is a drug-device product used for nasal delivery of a powder form of sumatriptan succinate via a breath-powered delivery device (Xail) for the proposed indication of the acute treatment of migraine with or without aura. Sumatriptan succinate is currently marketed under trade name of Imitrex® in the form of s.c injection, nasal spray and tablets.

The device consists of a flexible mouthpiece and a specially shaped sealing nosepiece connected via a closed communication shell. The device is intended to deliver sumatriptan into the nasal cavity using the patient's exhaled breath and the device design to produce a balanced closure of the soft palate while the device is being used to deliver drug. The drug substance is sumatriptan succinate (15.4 mg per capsule; 11 mg base), with no excipients, loaded in a (b) (4) capsule that is contained within a disposable nosepiece.

(b) (4)



The clinical studies conducted to support the NDA are Phase 1 PK study OPN-SUM-1302, Phase 2 Study OPTUK-MSPP-IMP-001, OPTUK-MSPP-PRO002 and Phase 3 study OPN-SUM-MIG-3301 using drug delivery device.

**OPN-SUM-1302** was an open-label, single-dose, randomized, crossover study to compare the bioavailability of the intranasal administration of 20 mg AVP-825 with 20 mg Imitrex (sumatriptan) nasal spray, 100 mg Imitrex (sumatriptan) oral tablet and 6 mg Imitrex (sumatriptan) subcutaneous injection in healthy subjects

**OPTUK MSPP IMP 001** was a single center, open-label, active-treatment controlled, randomized, 3 way cross-over study. The primary objective of the study was to compare, by means of quantified wake EEG, the effects of AVP-825 versus a subcutaneous (SC) reference dose of sumatriptan, on migraine induced by glyceryltrinitrate (GTN, also known as nitroglycerin) in subjects diagnosed with chronic migraine.

Two efficacy trials were conducted in the AVP-825 clinical development program:

**OPN-SUM-MIG-3301** was a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of a single 20 mg dose of sumatriptan powder delivered intranasally with the bi-directional device in adults with acute migraine with or without Aura.

**OPTUK-MSPP-PRO002** was a multicentre, double-blind, placebo-controlled evaluation of intranasal sumatriptan delivered with the OptiNose powder device in the treatment of acute migraine.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	2		
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>	-	-	-	
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>	-	-	-	
<b>Plasma protein binding:</b>	-	-	-	
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>F. Healthy Volunteers-</b>				
single dose:	X	1	-	Relative BA Study
multiple dose:				
<b>1. Patients-</b>				
single dose:	X	1	-	Relative BA Study
multiple dose:	-	-	-	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	-	-	-	

fasting / non-fasting multiple dose:	-	-	-	
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
<b>PD:</b>				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
<b>Population Analyses -</b>				
Data rich:	-	-	-	
Data sparse:	-	-	-	
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>	-	-	-	
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:		-		
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>	-	-	-	
<b>(IVIVC):</b>				
<b>Bio-waiver request based on BCS</b>	-	-	-	
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>	-	-	-	
<b>Chronopharmacokinetics</b>	-	-	-	
<b>Pediatric development plan</b>	-	-	-	
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>4</b>		
<b>(b) Filability and QBR comments</b>				
	"X" if yes			
Application filable?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?				

QBR questions (key issues to be considered)	
<b>Other comments or information not included above</b>	Request for OSI inspection: Pivotal PK Study OPN-SUM-1302  <b>Clinical Research Organization (CRO):</b> Celerion Clinical Research Center, 1930 Heck Avenue, Neptune, NJ   (b) (4)
<b>Primary reviewer Signature and Date</b>	
<b>Secondary reviewer Signature and Date</b>	

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine			X	

	reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CC: NDA 206099 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Angela Men, Ramana Uppoor, Mehul Mehta)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAGAN MOHAN R PAREPALLY  
11/05/2014

YUXIN MEN  
11/05/2014

<b>BIOPHARMACEUTICS REVIEW</b> <b>Office of New Drugs Quality Assessment</b>			
<b>Application No.:</b>	NDA 206099	<b>Reviewer:</b> Sandra Suarez Sharp, Ph.D.	
<b>Division:</b>	DNP		
<b>Sponsor:</b>	(b) (4)	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Trade Name:</b>	(b) (4) Xsail	<b>Supervisor (acting):</b> Paul Seo, Ph.D.	
<b>Generic Name:</b>	Sumatriptan Nasal Powder	<b>Date Assigned:</b>	Jan 29, 2014
<b>Indication:</b>	Treatment of patients with epilepsy	<b>Date of Review:</b>	Oct 10, 2014
<b>Formulation/strength</b>	Nasal Power/22 mg (two nosepieces, each containing 11 mg sumatriptan base)		
<b>Route of Administration</b>	Intranasal		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<b>Submission dates</b>	<b>Date of informal/Formal Consult</b>	<b>PRIMARY REVIEW DUE DATE</b>	
Jan 27, 2014 April 40, 2014	Jan 29, 2014	Oct 23, 2014	
<b>Type of Submission:</b>	505(b)(2)		
<b>Type of Consult:</b>	• In vitro BE data supporting the manufacturing changes		
<b>SUMMARY OF BIOPHARMACEUTICS FINDINGS</b>			
<b>Background:</b>			
<p>The Applicant is seeking approval of Sumatriptan Nasal Spray, 22 mf for the acute treatment of migraine with or without aura. NDA 206099 for Sumatriptan Nasal Spray, aerosol powder is being filed as a 505(b)(2) submission and relies on previous findings pertaining to sumatriptan safety and efficacy of Imitrex® Nasal Spray (NDA 020626), Imitrex® oral tablet (NDA 020132, and Imitrex® injectable, subcutaneous (NDA 020080).</p> <p>Sumatriptan Nasal Spray is comprised of a nasal delivery device containing a capsule filled with 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder) drug substance. No excipients are included in the drug product formulation. The drug product-containing capsule is housed within the chamber and retained in place with a grid. The nozzle is pressed onto the chamber to complete the disposable nosepiece.</p> <p>The device (b) (4) used in the clinical studies had a rigid mouthpiece with a fixed position, whereas the proposed commercial finished product will contain a device with a flexible mouthpiece, which according to the Applicant improves its usability. In addition, it appears that the commercial product will be manufactured using (b) (4) a different plant, and will use (b) (4) (b) (4) packaging.</p>			
<b>Submission:</b>			
<p>In support of the approval of this NDA, the Applicant is relying on the results of the following studies:</p> <ol style="list-style-type: none"> <li>1. Study (OPN-SUM-1302) comparing the bioavailability of 20 mg AVP-825 with 20 mg Imitrex Nasal Spray, 100 mg Imitrex Oral Tablet, and 6 mg Imitrex Injection in healthy subjects.</li> <li>2. Study OPTUK-MSPP IMP 001 was conducted in France prior to the IND submission and is included</li> </ol>			

in this NDA as a supportive study.

These two studies are being reviewed by the Clinical Pharmacology Reviewer, OCP. In addition, this submission includes a request for a waiver of the requirements of evidence demonstrating *in-vivo* BE for the manufacturing changes between the fixed mouthpiece device used in clinical studies and the proposed flexible mouthpiece device intended for commercialization. Comparative in vitro testing evaluating emitted dose-particle size distribution (ED-PSD) and emitted dose-dose content uniformity (ED-DCU) using a population BE approach performed on three batches were included in support of the biowaiver.

**Review:**

This review evaluates, summarizes, and makes recommendations in terms of the acceptability of the in vitro characterization study supporting the BE waiver request.

**Reviewer's Assessment:**

**1. In Vitro Characterization Study Supporting the Waiver Request**

Two in vitro studies were conducted to evaluate the comparability between the OptiNose (b)(4) Assembly and OptiNose Flexible (b)(4) Assembly based on the emitted dose content uniformity (E-DCU) and the emitted dose particle size distribution (ED-PSD) determination of Sumatriptan Nasal Capsules. For each Reference and Test the dose content of sumatriptan free base in the emitted dose was assayed and reported. The arithmetic average for each pair of nosepieces was used as a single determination of E-DCU. Similarly, for ED-PSD, D10, D50, D90 and SPAN (SPAN is defined as  $(D_{90} - D_{10})/D_{50}$ ) were measured and reported for each nosepiece. The arithmetic average for each pair of nosepieces was used as a single determination of D50 and SPAN. A step-wise population bioequivalence statistical analysis and estimated the 95% upper confidence bound for linearized criteria were provided.

The 95% upper confidence bound derived from the analysis for E-DCU, D50, and SPAN was less than zero. Therefore, based on these results, the OptiNose Flexible (b)(4) Assembly and OptiNose (b)(4) Assembly are considered bioequivalent.

**Risk Assessment Evaluation:**

Refer to the CMC review for the quality risk assessment table of this product. From the Biopharmaceutics perspective, Sumatriptan Nasal Powder is considered a low risk drug product due to the following drug substance and drug product characteristics:

1. The drug substance is highly soluble;
2. The drug product is a powder for nasal administration with high bioavailability;
3. There are several products in the market (e.g., Imitrex Nasal Spray) which sumatriptan systemic exposure is higher than the exposure following the administration of Sumatriptan Nasal Powder.

**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 206-099 and its amendments submitted on Jan 29, 2014 and April 30, 2014. From the Biopharmaceutics perspective, Sumatriptan nasal Powder, 22 mg strength under NDA 206099 is recommended for **APPROVAL**.

Sandra  
Suarez -A

Digitally signed by Sandra Suarez -A  
DN: cn=Sandra Suarez -A, o=FDA, ou=People,  
c=US, email=Sandra.Suarez-A@FDA.gov, serial=12003001001.1-1.20147809  
Date: 2014.10.16 12:03:59 -0700

**Sandra Suarez Sharp, Ph. D.**  
Biopharmaceutics Reviewer  
Office of New Drugs Quality Assessment

**Angelica Dorantes, Ph. D.**  
Biopharmaceutics Team Leader  
Office of New Drugs Quality Assessment

cc : PSeo

## BIOPHARMACEUTICS ASSESSMENT

### BACKGROUND

The Applicant is seeking approval of Sumatriptan Nasal Spray, 22 mf for the acute treatment of migraine with or without aura. Sumatriptan Nasal Spray is an aerosol powder being filed as a 505(b)(2) NDA and relies on previous findings pertaining to sumatriptan safety and efficacy of Imitrex® Nasal Spray (NDA 020626), Imitrex® oral tablet (NDA 020132, and Imitrex® injectable, subcutaneous (NDA 020080).

In support of the approval of this NDA, the Applicant is relying on the results of the following studies:

1. Study (OPN-SUM-1302) comparing the bioavailability of 20 mg AVP-825 with 20 mg Imitrex Nasal Spray, 100 mg Imitrex Oral Tablet, and 6 mg Imitrex Injection in healthy subjects.
2. Study OPTUK-MSPP IMP 001 was conducted in France prior to the IND submission and is included in this NDA as a supportive study.

These two studies are being reviewed by OCP. In addition, the submission includes a request for a waiver of the requirements of evidence demonstrating *in-vivo* bioequivalence for the manufacturing changes between the fixed mouthpiece device used in clinical studies and the proposed flexible mouthpiece device intended for commercialization.

Comparative *in vitro* testing evaluating emitted dose-particle size distribution (ED-PSD) and emitted dose-dose content uniformity (ED-DCU) using a population BE approach performed on three batches were included in support of the biowaiver.

This review evaluates, summarizes, and makes recommendations in terms of the acceptability of the *in vitro* characterization study supporting the BE waiver request.

### CHEMISTRY

#### Drug Substance

Sumatriptan succinate, USP drug substance is freely soluble in water. The drug substance with the particle size distribution specified for this product (d90: (b) (4)) has been shown to dissolve (b) (4) in USP dissolution tests (b) (4). In addition, there are no excipients used in the product, so there is no possibility of excipients introducing any delay or variation in dissolution and absorption. According to the Applicant, the quality of the drug substance used in the clinical product and intended for commercial product is identical.

Data generated with human nasal administration of the proposed drug product (AVP-825) suggest that sumatriptan succinate has higher nasal permeability than with oral administration. The Applicant states that the higher nasal permeability is supported by the findings of higher bioavailability, faster entry into serum (increased AUC<sub>0-30</sub>) and faster T<sub>max</sub> (less than one hour) compared to oral administration on a dose-adjusted basis (adjusting for delivered dose). In general, sumatriptan succinate, USP is considered as a BCS class III drug substance (high solubility, low permeability).

### Drug Product

Sumatriptan Nasal Spray is comprised of a nasal delivery device containing a capsule filled with 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder) drug substance. No excipients are included in the drug product formulation. The drug product-containing capsule is housed within the chamber and retained in place (b) (4). The nozzle is pressed onto the chamber to complete the disposable nosepiece.

The device (b) (4) used in the clinical studies had a rigid mouthpiece with a fixed position, whereas the proposed commercial finished product will contain a device with a flexible mouthpiece, which according to the Applicant improves its usability (Figure 1).

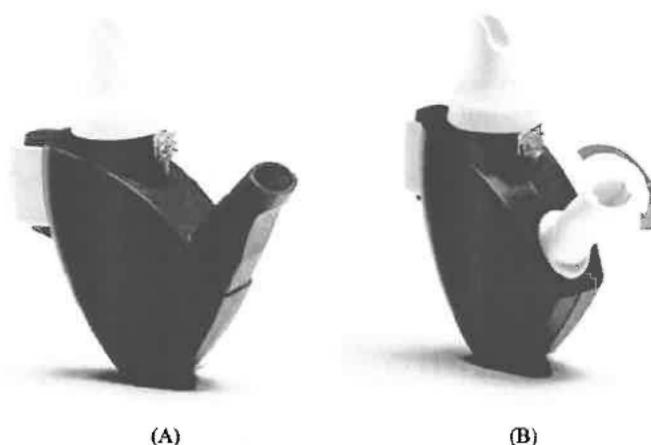


Figure 1. Fixed mouthpiece device (A) and flexible mouthpiece device (B).

In addition, it appears that the commercial product will be manufactured (b) (4) in a different plant, and will use (b) (4) packaging. Table 1 summarizes the changes implemented to the clinical trial drug product/device combination.

Table 1. Changes from clinical product to commercial product

#	Parameter	Clinical Studies	Commercial Product
1	Manufacturing site (capsule filling and nosepiece assembly)	(b) (4)	(b) (4)
2	Manufacturing equipment used to fill capsules		
3	Primary packaging material		
4	Design of the device (mouthpiece)	Fixed mouthpiece device	Flexible mouthpiece device*

The formulation of sumatriptan succinate contained in AVP-825 is given in Table 2.

**Table 2.** Formulation of the AVP-825 sumatriptan succinate Capsules

Ingredient and Material	AVP-825
Sumatriptan succinate, USP	15.4 mg of sumatriptan succinate (11 mg sumatriptan base equivalent)
Capsule (b) (4)	(b) (4)

**DATA SUPPORTING THE BIOWAIVER REQUEST**

Based on the discussion that took place during the IND stage, an agreement was reached with the Applicant that the following data/analysis should be included at the time of NDA filing in support of the BE waiver:

1. Emitted dose content uniformity (EDCU) and emitted dose particle size distribution (ED-PSD) using the PBE approach.
2. Effect of flow rate (i.e., 15, 20, 30, and 45 L/min) on EDCU, ED-PSD.
3. Pressure drop and resistance.
4. The extent of mouthpiece flexibility and orientation effects on the EDCU, ED-PSD and resistance should be discussed.

The biopharmaceutics review is focused on the assessment of the emitted dose content uniformity (EDCU) and emitted dose particle size distribution (ED-PSD) using the PBE approach. The effect of flow rate, pressure drop/resistance and the extent of mouthpiece flexibility and orientation effects on the EDCU, ED-PSD and resistance are being reviewed by the CMC team.

**Emitted Dose Content Uniformity (EDCU) and Emitted Dose Particle Size Distribution (ED-PSD) Using the PBE Approach**

Three (3) separate batches of the fixed mouthpiece device Assembly (Reference) and the flexible mouthpiece device assembly (Test) were evaluated. Twenty (20) devices were evaluated within each batch. A total of 240 nosepieces (batch# 0032R) were used for the study. The E-DCU and ED-PSD were determined from each nosepiece for each device assembly. The average result from each pair of nosepieces (from the full dose of 22 mg sumatriptan base) was calculated, giving a total of 120 observations between the six batches for the comparison analysis (Table 3). The arithmetic average for each pair of nosepieces (two nosepieces comprise one dose) was used as a single determination of E-DCU. Similarly, for ED-PSD, the measures D<sub>10</sub>, D<sub>50</sub>, D<sub>90</sub> and SPAN (SPAN is defined as (D<sub>90</sub> - D<sub>10</sub>)/D<sub>50</sub>) were measured and reported for each nosepiece. The arithmetic average for each pair of nosepieces was used as a single determination of D<sub>50</sub> and SPAN.

**Table 3.** Materials Required

Device	Batch Number	Sample Size
Fixed mouthpiece device (Reference)	111414/01	20
	131397/01	20
	131858/01	20
Flexible mouthpiece Device (Test)	13-001-2367	20
	13-002-2367	20
	13-003-2367	20

### Statistical Analysis

The comparison between the Reference and Test was analyzed with a linear fixed effects model. The estimates of the variance components for the Test and Reference were estimated with the model via a REPEATED statement in SAS® PROC MIXED. Kenward and Roger's method (as used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR)). The model was applied to natural log-transformed DCU, D50 and SPAN.

The geometric mean ratio (Test/Reference) along with the corresponding two-sided 90% confidence interval (CI) from exponential least-square means differences were calculated based on the above model. Also, the 95% upper confidence bounds were calculated from the comparison criterion formula:

$$\frac{(\mu_T - \mu_R)^2 + (\sigma_T^2 - \sigma_R^2)}{\max\{\sigma_0^2, \sigma_R^2\}} \leq \theta.$$

Where,  $\mu_T$  and  $\mu_R$  are the estimates of the least-square means for the Test and Reference,  $\sigma_T^2$  and  $\sigma_R^2$  are the estimate of the variance components for the Test and Reference,  $\sigma_0^2$  is the scaling variance criteria (set to 0.01) and  $\theta$  is the bioequivalence limit. The two products (Test and Reference) are bioequivalent if the ratio of the geometric least-square means is within 0.90 and 1.11 and the 95% confidence bound of  $\theta \leq 1.11$ .

### Reviewer's Comment

*It was noted that the Applicant did not follow the recommendations stated in the FDA guidance for population BE analysis. Therefore, the following comment was conveyed to the Applicant as part of the 74-day letter:*

- 1. FDA does not agree with the use of a 90% confidence intervals approach to establish bioequivalence based on vitro testing. Under the Population BE method, for each comparative in vitro test, FDA recommends the calculation of a 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion as a measure of equivalence between the test and reference products. The confidence interval is compared to an acceptance limit that is based on fixed statistical parameters. The 95% upper confidence bound for linearized criteria  $H_0$  must be  $\leq 0$  (refer to Draft Guidance on Budesonide Suspension for Inhalation published in Sep 2012 and the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data).*
- 2. Submit the complete set of data as SAS transport files for the batches used in the population BE analysis. We refer you to the Budesonide Suspension for Inhalation Guidance for Industry for recommendations in terms of format of the data and what constitutes a complete set of data to run the in vitro BE analysis between the Test and Reference products.*

The Applicant provided the requested information on March 30, 2014. Specifically, the step-wise population bioequivalence statistical analysis and estimated the 95% upper confidence bound for linearized criteria were provided. The results of this analysis are summarized in Tables 4 and 5.

**Table 4.** Statistical Estimates of Measures for OptiNose Flexible (b)(4) Assembly (Test) and OptiNose (b)(4) Assembly (Reference)

Measure	Geometric Mean			Geometric Mean Ratio	Estimate of Standard Deviation		$\hat{\sigma}_T / \hat{\sigma}_R$ Ratio
	OptiNose (b)(4) (Test)	Flexible Assembly	OptiNose (b)(4) Assembly (Reference)		$\hat{\sigma}_T$	$\hat{\sigma}_R$	
	E-DCU (%)	102.83			102.33	0.0187	
D50 ( $\mu\text{m}$ )	33.57		31.31	0.0429	0.0376	1.14	
SPAN	2.34		2.39	0.0222	0.0182	1.22	

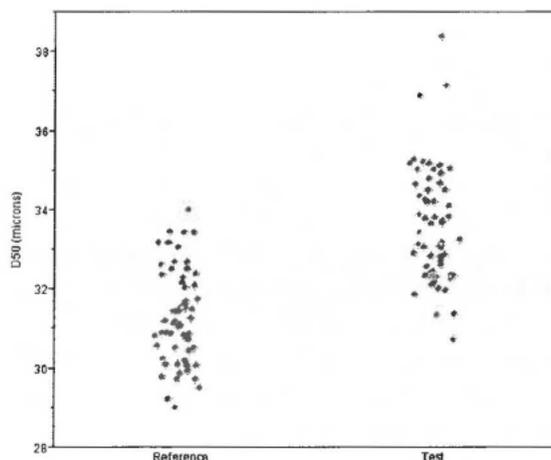
Geometric Mean Ratios are calculated by exponentiating the difference of LSMs.  $\hat{\sigma}_T$  = Estimate of the standard deviation for OptiNose Flexible (b)(4) Assembly (Test)  $\hat{\sigma}_R$  = Estimate of the standard deviation for OptiNose (b)(4) Assembly (Reference)

**Table 5.** Population Bioequivalence Results for OptiNose Flexible (b)(4) Assembly (Test) Versus OptiNose (b)(4) Assembly (Reference)

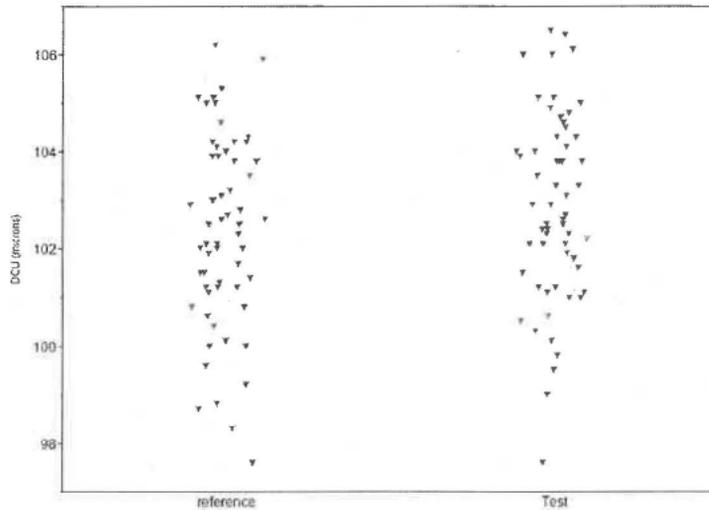
Measure	Scaled	Linearized Point Estimate	95% Upper Confidence Bound	Pass or Fail PBE
E-DCU (%)	Constant-scaled	-0.0209	-0.0207	Pass
D50 ( $\mu\text{m}$ )	Constant-scaled	-0.0156	-0.0136	Pass
SPAN	Constant-scaled	-0.0203	-0.0199	Pass

PBE = Population Bioequivalence  
 If  $\hat{\sigma}_R > 0.1$  (regulatory constant), then PBE is concluded by the reference-scaled procedure. If  $\hat{\sigma}_R \leq 0.1$  (regulatory constant), then PBE is concluded by the constant-scaled procedure. The 95% upper confidence bound for linearized criteria must be  $\leq 0$  to pass PBE.

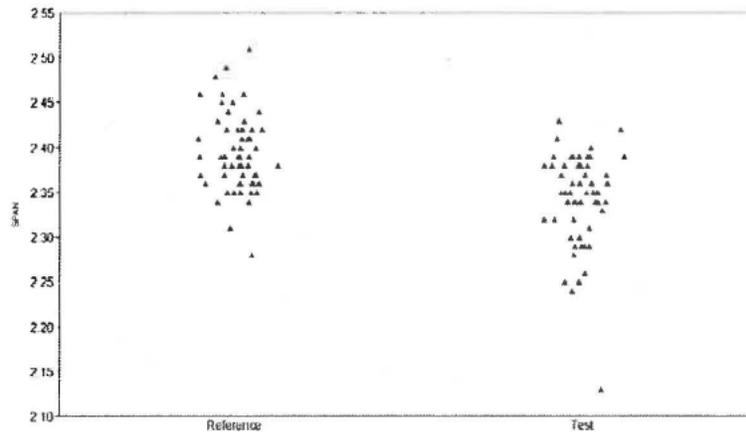
Figures 2-4 show the distribution for D50, DCU and SPAN as a function of the drug product-device combination.



**Figure 2.** Average D<sub>50</sub> for the refernde and test drug product/device combination. Constructed using the Applicnat provided data.



**Figure 3.** Average DCU for the refernde and test drug product/device combination. Constructed using the Applicnat provided data.



**Figure 4.** SPAN for the refernde and test drug product/device combination. Constructed using the Applicnat provided data.

#### Reviewer's Comments

Figure 2 shows that the D50 upper range is slightly higher than that for the reference product; however, this difference is not statistically significant as shown by the results of the BE study. To test for population bioequivalence, 95% upper confidence bound of either the reference-scaled or constant-scaled linearized are computed. For linearized  $\theta_p$ , if this upper bound is negative, population bioequivalence is concluded. If the upper bound is positive, population bioequivalence is not reached. Linearized tests are based on regulatory limit ( $\theta_p$ ) of 2.0891, scaling variance ( $\sigma^2_{T0}$ ) of 0.1 and variance terms offset ( $\epsilon_p$ ) equal to 0.01. If the estimate of  $\sigma_{R} > \sigma_{T0}$ , reference scaling is used. If  $\sigma_{R} < \sigma_{T0}$ , constant scaling used. If  $\sigma_{R} = 0.10$ , either reference scaling or constant scaling at either side of the changeover point (0.10) should be used. Table 4

*shows that the estimate of the standard deviation of the Reference was less than the regulatory constant (0.1) for E-DCU, D50, and SPAN; therefore, population bioequivalence determined from the constant-scaled procedure is appropriate.*

**Reviewer's Overall Assessment: ACCEPTABLE**

The 95% upper confidence bound derived from the analysis for E-DCU, D50, and SPAN was less than 0 (Table 5). Therefore, based on these results, the OptiNose Flexible <sup>(b) (4)</sup> Assembly and OptiNose <sup>(b) (4)</sup> Assembly is considered bioequivalent.