CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-239

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY

MEMO FOR THE RECORD

NDA:	22-239	REVIEWER:	Carol Noory
DRUG:	Sumatriptan Succinate Needle-free Delivery System, 6 mg/0.5 mL	TEAM LEADER:	Veneeta Tandon, Ph.D.
SUBMISSION DATE(S):	December 28, 2007, June 18, 2008 September 12, 2008	SPONSOR: OCP DIVISION: OND DIVISION:	Zogenix Inc. DCP-1, HFD-860 Neurology HFD-120

EVALUATION OF THE RESULTS OF THE ESTABLISHMENT INSPECTION REPORT

On October 15, 2008, the Division of Scientific Investigation completed their review of the results of the establishment inspection report (EIR) for NDA 22-239, Intraject Sumatriptan, sponsored by Zogenix, Inc. The clinical site [Covance Global Clinical Research Unit, Inc., Dallas, TX] was inspected between 6/16-19/2008 and analytical site (b) (4) was inspected between 9/22-25/2008. Following the inspections Forms 483 were issued citing several items. Three items which might have an impact on the PK data of four subjects were evaluated by this reviewer.

ITEM 1:

The first item involved two subjects, 1053 and 2042. These subjects received the last dose of the previous trial 6 days before receiving the first dose on the following trial when 30 days were required between trials. The deviation is reported in the submission.

REVIEWER COMMENT:

The second sequence for both subject 1053 and subject 2042 was the arm. Since the arm was eliminated as a site of injection, this does not impact the final outcome of the study.

ITEM 2:

The 5 original samples from subject 1009 were reassayed because the original results were above the upper quantitation limit. The sponsor speculated that the samples were contaminated. Although the reassay confirmed the original data, the data from the subject 1009 were excluded from PK analysis.

REVIEWER COMMENT:

The 5 samples in question were from the TEST dose in the Arm (Sequence D, Period 3). In Sequence D, Subject 1009 received doses in the abdomen (TEST then REFERENCE) followed by dosing in the arm (TEST then REFERENCE) (TABLE 1). Each dose administration was followed by a washout period. Any possible contamination of the blood

samples from the ARM should not affect the data from the Abdomen, which was dosed first. Since the arm was eliminated as a site of injection, this does not impact the study which evaluated only the Abdomen and the Thigh.

Table 1: Assigned Treatment Sequences

Sequence	Period I (Study Day 1)	Wash-out	Period II (Study Day 2)	Wash-out	Period III (Study Day 3)	Wash-Out	Period IV (Study Day 4)
A	IMITREX–abdomen	→	Intraject–abdomen	→	IMITREX–thigh	→	Intraject–thigh
B	Intraject–abdomen	→	IMITREX–abdomen	→	Intraject–thigh	→	IMITREX–thigh
C	Intraject–abdomen	→	IMITREX–abdomen	→	Intraject–arm	→	IMITREX–arm
D	IMITREX–abdomen	→	Intraject–abdomen	→	IMITREX–arm	→	Intraject–arm
E	IMITREX–arm	→	Intraject–arm	→	IMITREX–thigh	→	Intraject–thigh
F	Intraject–thigh	→	IMITREX–thigh	→	Intraject–arm	→	IMITREX–arm

REF: **Appendix 16.1.1.1**

ITEM 3:

The firm stated that period 1 samples for subject 1042 were reassayed to investigate possible mislabeling between subjects 1042 and 2042. The firm stated that the reassayed data for subject 1042 were reported because they confirmed the original data.

REVIEWER COMMENT:

In the submission, the firm stated that subject 1042 withdrew prematurely and was excluded from all PK analysis.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the DSI establishment inspection report (EIR) for NDA 22-239, Intraject Sumatriptan, sponsored by Zogenix, Inc. The issues found during the inspection were determined not to impact the bioequivalence evaluation of Intraject Sumatriptan in the abdomen and the thigh.

SIGNATURES

Reviewer: Carol Noory Date: _____

Acting Team Leader: Veneeta Tandon Date: _____

cc list:

DFS: NDA 22-165
HFD-860: (NooryC, UppoorR, MehtaM, TandonV)
HFD-120: (ChenL, KatzR, BastingsE, HarrisR)

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

/s/

Carol Noory
10/28/2008 11:33:23 AM
BIOPHARMACEUTICS

Veneeta Tandon
10/29/2008 06:54:27 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-239
Submission Date(s):	December 28, 2007, June 18, 2008 and September 12, 2008
Brand Name:	(b) (4) DosePro™
Generic Name:	Sumatriptan Succinate
Dosage Form:	Intraject® needle-free drug delivery system
Dosage Strengths:	6 mg
Indication:	Acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes
NDA type:	505B(2)
Sponsor:	Zogenix Inc. 3929 Point Eden Way Hayward, CA 94545
IND:	71,275
Reviewer:	Carol Noory
Team Leader:	Veneeta Tandon, Ph.D.
OCP Division:	DCP-1, HFD-860
OND Division:	Neurology HFD-120

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I. EXECUTIVE SUMMARY

The sponsor is seeking approval for Intraject® sumatriptan for the same indications as the reference product, IMITREX® STAT dose, which is indicated for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes. The IMITREX® STAT dose delivers sumatriptan subcutaneously with a needle-based injection device. Intraject® is a needle-free delivery device which will be used to administer sumatriptan subcutaneously.

In support of the Clinical Pharmacology section of the application, the Sponsor has included one acceptable pivotal BA/BE study conducted in the US and three pilot studies conducted in Australia (not reviewed). The sponsor has also submitted PLR labeling for the product.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 1 has reviewed the Clinical Pharmacology information submitted on December 28, 2007, June 18, 2008 and September 12, 2008 under NDA 22-239. Pending an acceptable DSI inspection, DCP1 finds the Clinical Pharmacology information acceptable provided that a mutual agreement can be reached between the Agency and the Sponsor regarding recommended changes in the labeling. The reviewer's labeling changes shown by track changes are given on pages 15 to 23 (See III.).

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Sumatriptan succinate is a migraine-specific triptan agent with proven clinical benefits. The sponsor is submitting this New Drug Application (NDA) for sumatriptan needle-free injection, 6 mg, under Section 505(b)(2) using IMITREX STATdose, 6 mg, as the referenced product (NDA 20-080). Intraject® sumatriptan, was developed as an alternative dosage form of the reference listed product.

The IMITREX STATdose delivery system consists of an auto-injector with a needle and drug- filled cartridges. Intraject® sumatriptan (sumatriptan succinate), is a drug-device combination product which uses a needle-free drug delivery system. Both systems administer a subcutaneous 0.5 mL dose of sumatriptan succinate equivalent to 6 mg of sumatriptan as the base. The sponsor is seeking approval for the same indication as IMITREX, the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

A list of the pivotal and pilot pharmacokinetic studies submitted by the sponsor is shown in the following table.

Table 1. Pilot and Pivotal PK/BA Studies						
Study	**Country**	**Study Population**	**Injection / Sites**	**Study Design**	**Nominal No. Injections Per Injection Site[a]**	**Total Nominal No. of Injections[a]**
Pivotal PK/BE Study ZX001-0601	U.S. (IND)	N=54 healthy adult M/F subjects.	Clinician injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=36	N=108
Pilot PK Study SUM-04-01	Australia	N=18 healthy adult M/F subjects.	Clinician injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=12	N=36
Pilot Self-injection PK Study ARD-2100-0501	Australia	N=24 healthy adult M/F subjects.	Self-injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=16	N=48
Total N=96 Subjects	**Total nominal no. of Intraject® injectionsa N=192**					
a The number of nominal injections represent the number of planned injections per product Intraject® sumatriptan or IMITREX/Imigran Mk II, per injection site and may have differed from the actual number of injections administered during the study.						

The three pilot studies were conducted in Australia using the sumatriptan injectable product approved in Australia as the Reference. These studies were not reviewed and will not be used to support the approval of the clinical pharmacology portion of the application. Approval will rely on the results of the pivotal study conducted with the U.S. approved product as the reference.

Pivotal Study

STUDY ZX001-0601, was a Phase 1, randomized, open-label, single-dose, 4-way crossover in an incomplete-block treatment design in 54 healthy adult male and female subjects between the ages of 18 and 55. Each subject received the **TEST** (Intraject® sumatriptan, 6 mg) and the **REFERENCE**, (Imitrex® STATdose System, 6 mg) in two of the three possible injection sites (i.e., abdomen, arm, and/or thigh). The injections were made by a clinician. Each subject was randomly assigned to receive four of six treatment/administration site combinations in one of the following sequences:

	Period I (Study Day 1)	Wash-out	**Period II** (Study Day 2)	Wash-out	**Period III** (Study Day 3)	Wash-out	**Period IV** (Study Day 4)
Sequence A →	IMITREX-abd	→	Intraject-abd	→	IMITREX-thigh	→	Intraject-thigh
Sequence B →	Intraject-abd	→	IMITREX-abd	→	Intraject-thigh	→	IMITREX-thigh
Sequence C →	Intraject-abd	→	IMITREX-abd	→	Intraject-arm	→	IMITREX-arm
Sequence D →	IMITREX-abd	→	Intraject-abd	→	IMITREX-arm	→	Intraject-arm
Sequence E →	IMITREX-arm	→	Intraject-arm	→	IMITREX-thigh	→	Intraject-thigh
Sequence F →	Intraject-thigh	→	IMITREX-thigh	→	Intraject-arm	→	IMITREX-arm

Statistical Analysis Plan (SAP)

The sponsor developed a Statistical Analysis Plan (SAP) for assessing the bioequivalence of the Intraject® sumatriptan product compared to the IMITREX product. This plan failed to determine bioequivalence at any of the three sites of injection. The sponsor determined that the variability and low doses in the arm was responsible for the failures. They removed subjects (2 from the abdomen

group and ten from the arm group) identified as having received an incomplete dose (Visual Analog Scale (VAS) of less than 2) and then reanalyzed the data. The results indicated bioequivalence at all three sites of injection.

Bioequivalence:

The sponsor did a post-hoc analysis to determine the relative bioavailability independently at each injection site. This is the appropriate method since the variability of each injection site is different. This analysis included the 12 subjects previously eliminated due to incomplete injections. The summary PK parameters are shown in the following table. The sponsor also determined the area under the curve until the 15 minute time point. [AUC(0-15)] to determine bioequivalence during early exposure. The sponsor also analyzed the thigh and abdomen pooled data and determined bioequivalence.

Table 2. Summary Pharmacokinetic Parameters by Site of Injection

Parameter (units)	Test[a] (Intraject®)	Reference[a] (IMITREX)	Test/ Ref (%) [b]	90% Confidence Interval [c]	P-Value[d]	Within Subject CV%	Power %
Abdomen (n=35)							
Cmax (ng/mL)	76.9	85.3	90.1	83.92, 96.80		17.8%	86.9%
AUCt (ng*hr/mL)	93.2	102	91.0	87.12, 94.97		10.7%	>99%
AUCinf (ng*hr/mL)	94.3	104	91.0	87.17, 94.99		10.6%	>99%
AUC0-15 (ng*hr/mL)	14.4	14.2	101	92.03, 111.43	—		
Tmax (hr)	0.200	0.200	—	-0.150, 0.100	0.0355		
Thigh (n=32)							
Cmax (ng/mL)	70.6	66.5	106	100.82,112.01		12.5%	>99%
AUCt (ng*hr/mL)	91.0	98.5	92.3	90.93, 93.79		3.7%	>99%
AUCinf (ng*hr/mL)	92.1	99.8	92.3	90.91, 93.72		3.6%	>99%
AUC0-15 (ng*hr/mL)	13.1	11.4	115	105.55, 124.99	—		
Tmax (hr)	0.200	0.225	—	-0.183- 0.150	0.0470		
Arm (deltoid) N=34)							
Cmax (ng/mL)	59.2	81.6	72.5	52.88, 99.49		89.9%	0%
AUCt (ng*hr/mL)	51.7	97.4	53.0	34.28, 82.06		1448.4%	0%
AUCinf (ng*hr/mL)	72.7	98.5	73.8	58.69, 92.71		58.1%	0%
AUC0-15 (ng*hr/mL)	11.0	14.9	74.0	52.42, 104.48	—		
Tmax (hr)	0.150	0.175	—	-0.183, 0.050	<0.0001		

a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e. geometric means). Medians are presented for Tmax.

b Ratio of parameter means for ln-parameter (expressed as a percentage). Natural log-transformed ratios were transformed back to linear scale.

c 90% confidence interval for ratio of parameter means of ln-transformed parameter (expressed as a percentage). Natural log-transformed confidence limits were transformed back to linear scale.

d Wilcoxon's signed-rank test.

The mean plasma concentrations of sumatriptan (log scale) versus time for the abdomen, thigh, and arm (deltoid) are shown in the following figures.

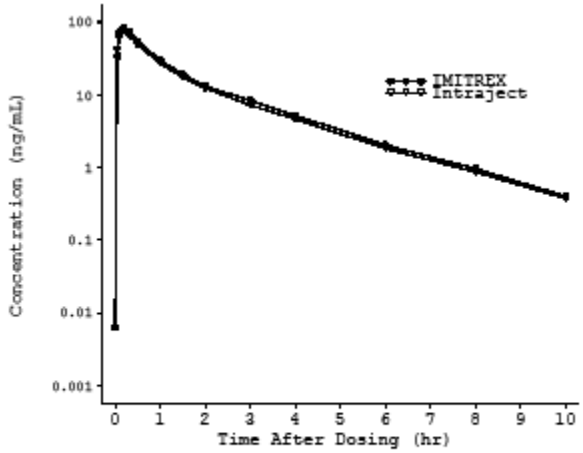


Figure 11-2. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Abdomen

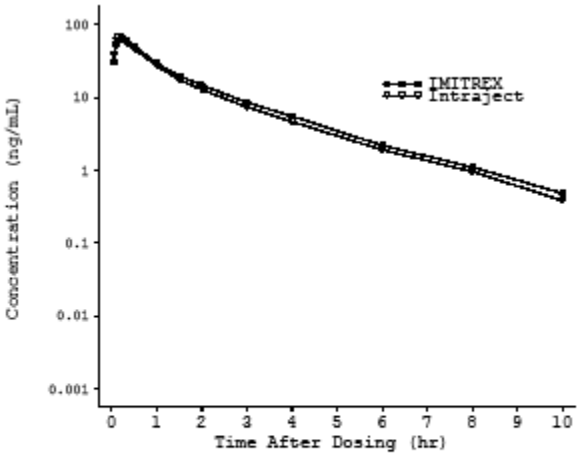


Figure 11-3. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Thigh

REF: Table 14.2.1-1b

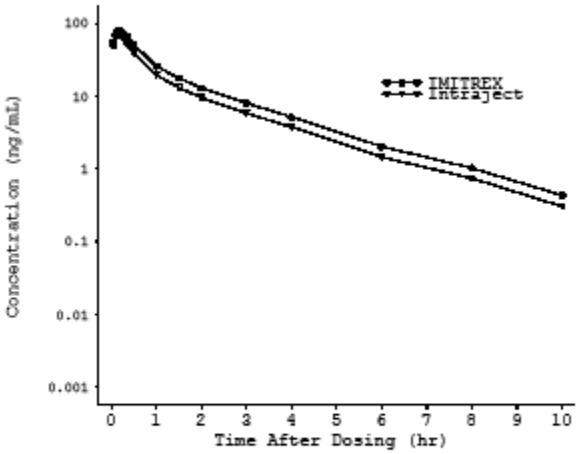


Figure 11-4. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Arm (Deltoid)

REF: Table 14.2.1-1c

The following conclusions can be drawn from the study based on the independent analysis of relative bioavailability at each site:

Abdomen:

- **AUC 0-∞:** Following single injections in the abdomen, Intraject® sumatriptan, 6 mg and Imitrex® STATdose System, 6 mg have similar AUC 0-∞. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. Imitrex® STATdose System, 6 mg were 91.0% (87.17%, 94.99%).

- **Cmax**: Peak sumatriptan concentrations following administration of Intraject® sumatriptan, 6 mg in and IMITREX® STATdose System, 6 mg in the abdomen were similar. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. IMITREX® STATdose System, 6 mg were 90.1 (83.92, 96.80).

- **Tmax:** The median Tmax for Intraject® sumatriptan, 6 mg was the same [0.2 hours (range 0.10-0.33)] as that of IMITREX® STATdose System, 6 mg [0.2(range 0.10-0.50)].

Thigh:

- **AUC 0-∞:** Following single injections in the thigh, Intraject® sumatriptan, 6 mg and Imitrex® STATdose System, 6 mg have similar AUC 0-∞. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. Imitrex® STATdose System, 6 mg were 92.3 (90.91, 93.72)

- **Cmax**: Peak sumatriptan concentrations following administration of Intraject® sumatriptan, 6 mg, and IMITREX® STATdose System, 6 mg in the thigh were similar. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. IMITREX® STATdose System, 6 mg were 106% (100.82, 112.01%). The 90% CI for Cmax was within the acceptable limit of 80-125%.

- **Tmax:** The median Tmax for Intraject® sumatriptan, 6 mg was [0.2 hours (range 0.067-0.333)] compared to that of IMITREX® STATdose System, 6 mg [0.225 hours (range 0.100-0.500)].

Arm (Deltoid):

- **AUC 0-∞:** Following single injections in the arm, AUC 0-∞ for Intraject® sumatriptan, 6 mg is 26.2% lower than Imitrex® STATdose System, 6 mg. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. IMITREX® STATdose System, 6 mg were 73.8% (58.69, 92.71). The lower limit of the 90% confidence interval is below the acceptable range (80-125%). Intraject® sumatriptan, 6 mg AUC 0-∞ is not bioequivalent to the IMITREX® STATdose System, 6 mg.

- **Cmax**: Peak sumatriptan concentrations following administration of Intraject® sumatriptan, 6 mg in the arm is 27.5% lower than peak concentrations of IMITREX® STATdose System, 6 mg. The geometric mean ratio and 90% confidence intervals for Intraject® sumatriptan, 6 mg vs. IMITREX® STATdose System, 6 mg were 72.5% (52.88, 99.49%). The 90% CI for Cmax was below the lower acceptable limit of 80-125%.

- **Tmax:** The median Tmax for Intraject® sumatriptan, 6 mg was [0.150 hours (range 0.050-0.250)] compared to that of IMITREX® STATdose System, 6 mg [0.175 hours (range 0.100-0.33)].

Safety:
According to the Sponsor, safety was assessed throughout the study by monitoring AEs and changes from baseline in clinical laboratory tests, vital signs, and ECGs for both Intraject and IMITREX. There were fewer TEAEs following administration to the thigh than administration to the abdomen or arm. According to the Sponsor, there were no clinically significant differences between Intraject® and IMITREX in clinical laboratory findings, vital signs, ECG findings, or other safety findings.

Local Injection Site Assessments:
According to the Sponsor, a higher incidence of swelling was observed at the local injection site for Intraject® injection. With the exception of the localized transient swelling, the local injection site signs that occurred were similar for both delivery systems. No subject discontinued the study due to an injection site reaction.

Reviewer Comments:

Bioequivalence: The reviewer calculated the relative bioavailability of Intraject® sumatriptan, 6 mg compared to Imitrex® STATdose System, 6 mg for each site as a two-way crossover using all subjects. The PK parameters, GSMean ratio and 90% CI support the Sponsor's conclusion that the Intraject® sumatriptan is bioequivalent to the IMITREX STATdose sumatriptan in the abdomen and the thigh. The arm will not be recommended as a site of injection. The sponsor's SAP was not used in this determination.

Safety: Intraject® and IMITREX STATdose have similar safety profiles.

Local Site Reactions: With exception of the localized transient swelling, the Intraject® system has local injection site signs that are similar to IMITREX STATdose. The differences should be explained in the labeling.

Pooled Bioequivalence Evaluation: The pooled bioequivalence will not be used to support approval of the NDA.

1.4. SIGNATURES

Reviewer: Carol Noory Date: _____

Acting Team Leader: Veneeta Tandon Date: _____

cc list:
DFS: NDA 22-165
HFD-860: (NooryC, UppoorR, MehtaM, TandonV)
HFD-120: (ChenL, KatzR, LaughrenT, HeimannM, FreedL, BastingsE, HarrisR)

II. QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES OF THE DRUG

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

Sumatriptan injection was first approved for marketing in the United States on 28 December 1992 (NDA 20-080) for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes. Triptans can be administered subcutaneously by self-injection, orally (including by orally disintegrating tablets) or as a nasal spray. IMITREX Injection remains the only injectable triptan available to patients. A list of approved triptans and their approval dates is provided in Table 3.

Table 3. Triptan Therapies Approved for Use in the U.S.

Trade	(generic) Name	Route of Delivery	NDA	Approval Date
IMITREX Tablets	(sumatriptan) Injection	Subcutaneous injection	20-080	December 28, 1992
IMITREX®	(sumatriptan)	Tablet	20-132	June 1, 1995
IMITREX® Nasal Spray	sumatriptan)	Nasal spray	20-626	August 26, 1997
Zomig®	(zolmitriptan)	Tablet	20-768	November 25, 1997
Amerge®	(naratriptan)	Tablet	20-763	February 10, 1998
Maxalt® /Maxalt-MLT®	/(rizatriptan)	Tablet/ ODT	20-864/ 20-865	June 29, 1998
Zomig-ZMT®	(zolmitriptan)	Orally dissolvable tablet	21-231	February 13, 2001
Axert®	(almotriptan)	Tablet	21-001	May 7, 2001
Frova®	(frovatriptan)	Tablet	21-006	November 8, 2001
Relpax®	(eletriptan)	Tablet	21-016	December 26, 2002
Zomig®	(zolmitriptan)	Nasal spray	21-450	September 30, 2003

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

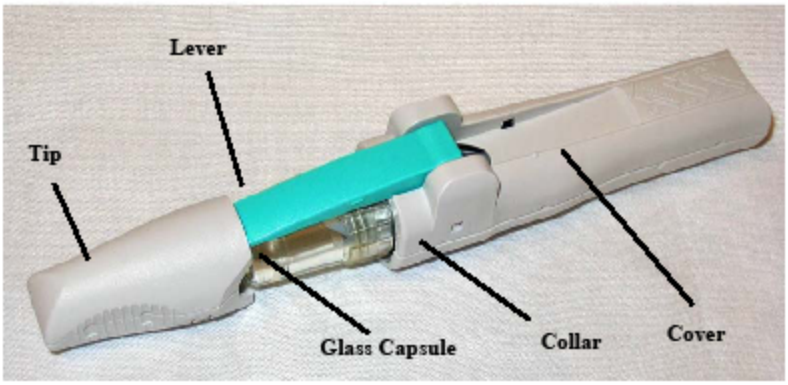
Drug:

Sumatriptan succinate is a migraine-specific acute triptan with proven statistical and clinical benefit. The proposed strength is the same as the approved IMITRIX injectable product which is 6 mg of sumatriptan/0.5 mL dose.

Dosage Form:

The dosage form is a single-use, disposable, needle-free delivery system, Intraject®, which combines a compressed nitrogen gas power source, an activation mechanism, and a prefilled glass drug capsule to simplify subcutaneous dosing. The Intraject® system (figure 4) provides a needle-free alternative for patients with concerns about using a needle injector.

Figure 4: Intraject® Sumatriptan Drug Product



Indication:

The indication is the same as the approved IMITREX sumatriptan injectable product.

- Acute treatment of migraine attacks with or without aura
- Acute treatment of cluster headache episodes

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

The 0.5 mL of solution with 6 mg sumatriptan (base) as the succinate drug is delivered subcutaneously with the Intraject® drug delivery system.

2.2. GENERAL CLINICAL PHARMACOLOGY

2.2.1. What are the design features of the Clinical Pharmacology Study used to Support the Dosing or Claims?

Bioequivalence:

The sponsor evaluated the relative bioavailability of Intraject® compared to IMITREXSTATdose at three sites, the arm, the abdomen and the thigh. **STUDY ZX001-0601,** was a Phase 1, randomized, open-label, single-dose, 4-way crossover in an incomplete-block treatment design in 54 healthy adult male and female subjects between the ages of 18 and 55. Each subject received the **TEST** (Intraject® sumatriptan, 6 mg) and the **REFERENCE**, (Imitrex® STATdose System, 6 mg) in two of the three possible injection sites (i.e., abdomen, arm, and/or thigh). The injections were made by a clinician. Each subject was randomly assigned to receive four of six treatment/administration site combinations in one of the following sequences:

Sequence A: IMITREX-abdomen → Intraject®-abdomen → IMITREX-thigh → Intraject®-thigh
Sequence B: Intraject®-abdomen → IMITREX-abdomen → Intraject®-thigh → IMITREX-thigh
Sequence C: Intraject®-abdomen → IMITREX-abdomen → Intraject®-arm → IMITREX-arm
Sequence D: IMITREX-abdomen → Intraject®-abdomen → IMITREX-arm → Intraject®-arm
Sequence E: IMITREX-arm → Intraject®-arm → IMITREX-thigh → Intraject®-thigh
Sequence F: Intraject®-thigh → IMITREX-thigh → Intraject®-arm → IMITREX-arm

The Sponsor also evaluated the safety and injection site reactions with both treatments.

2.2.2. Can the dose and dosing regimen be justified based on the studies conducted?

The dose and dosing regimen are based on the established dose and dosing regimen for IMITREXSTATdose, 6 mg.

2.3. PHARMACOKINETIC CHARACTERISTICS

2.3.1. What are the single-dose pharmacokinetics of Intraject® succinate?

The single dose pharmacokinetic parameters of Intraject® sumatriptan succinate are comparable to the PK parameters of IMITREXSTATdose at the abdomen, arm and the thigh sites and are shown in the following table.

Table 11-5. Summary of Additional Analysis of Mean Sumatriptan Pharmacokinetic Parameters. PK Analytic Population

Treatment, Site/ Parameter	C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-15} (ng*hr/mL)	AUC_t (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	T_{half} (hr)	K_{el} (1/hr)
Intraject, abdomen							
Mean	79.9	0.200	15.0	96.0	97.1	1.71	0.41
(SD)	(17.0)	(0.100, 0.333)	(3.75)	(12.3)	(12.4)	(0.206)	(0.049)
N	33	33	33	33	33	33	33
IMITREX, abdomen							
Mean	86.1	0.200	14.5	102	103	1.70	0.42
(SD)	(18.5)	(0.100, 0.500)	(4.24)	(12.0)	(12.1)	(0.254)	(0.061)
N	33	33	33	33	33	33	33
Intraject, arm							
Mean	87.6	0.150	17.0	89.2	90.3	1.71	0.42
(SD)	(19.1)	(0.0500, 0.250)	(3.98)	(11.6)	(11.4)	(0.275)	(0.061)
N	24	24	24	24	24	24	24
IMITREX, arm							
Mean	81.9	0.150	15.2	94.4	95.7	1.73	0.41
(SD)	(18.7)	(0.100, 0.333)	(4.55)	(11.0)	(10.6)	(0.290)	(0.062)
N	24	24	24	24	24	24	24
Intraject, thigh							
Mean	71.9	0.200	13.4	91.8	92.9	1.72	0.42
(SD)	(14.4)	(0.0667, 0.333)	(3.05)	(12.6)	(12.8)	(0.365)	(0.072)
N	32	32	32	32	32	32	32
IMITREX, thigh							
Mean	68.3	0.225	12.1	99.4	101	1.71	0.41
(SD)	(16.3)	(0.100, 0.500)	(4.20)	(13.5)	(13.6)	(0.226)	(0.052)
N	32	32	32	32	32	32	32

Note: All subjects with a VAS score ≤2 were excluded from analyses.
* Median (min, max) presented for T_{max}.
REF: Table 14.2.2-1b.

2.3.2 General ADME Characteristics of the Drug

The absorption, distribution, metabolism, and excretion of sumatriptan as a molecular entity are described in the label for the reference listed drug, IMITREX STATdose, 6 mg, (NDA 20-080). The labeling for Intraject® sumatriptan should be changed to reflect the PK data from the pivotal study.

Pharmacokinetic parameters following a 6-mg subcutaneous dose of Intraject® sumatriptan into the thigh were determined in 32 subjects (males and females). The maximum serum concentration (Cmax) was *(mean ± standard deviation)* 70.6 ± 14.4 ng/mL; the time to peak concentration *(Tmax)* was 0.2 hours after injection *(range, 0.067 to 0.33 hours);* and the terminal half-life was 1.72 ± 0.365 hours..

Pharmacokinetic parameters following a 6-mg subcutaneous dose of Intraject® sumatriptan into the abdomen were determined in 36 subjects (males and females). The maximum serum concentration (Cmax) was *(mean ± standard deviation)* 76.9 ± 17.3 ng/mL ; the time to peak concentration *(Tmax)* was 0.2 hours after injection *(range, 0.1 to 0.33 hours);* and the terminal half-life was 1.70 ± 0.207 hours.

2.3.2 What is the inter-subject variability used to determine sample size compared to the inter-subject variability in PK parameter?

Based on previous studies, the maximum inter-subject coefficient of variation (%CV) for log-transformed ratios was up to 25%. The Sponsor estimated that 26 subjects were required to provide ≥90% power at an alpha=0.051. In the pivotal study, at least 32 subjects completed the study, the within subject %CV was less than 18% and the power was greater than 86%.

2.4. GENERAL BIOPHARMACEUTICS

2.4.1. What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The formulation used in the pivotal trial is the same as the to-be-marketed formulation.

2.4.2. What is the relative bioavailability of the Intraject® sumatriptan compared to the marketed Imitrex STATdose?

The relative bioavailability of Intraject® sumatriptan was within the 90% confidence intervals limits for AUC and Cmax for both the abdomen and thigh site of injection. The Tmax at both sites was similar. Injection in the arm was not comparable. The arm was eliminated as a recommended injection site for Intraject® sumatriptan because injection into the lateral arm was associated with wet or incomplete injections, which resulted in a failure to establish bioequivalence. The abdomen and the thigh will be recommended as injection sites.

Table 4. Post Hoc Primary Bioequivalence Analysis

Parameter (units)	Test[a] (Intraject®)	Reference[a] (IMITREX)	Test/ Ref (%) [b]	90% Confidence Interval [c]
Abdomen (n=35)				
Cmax (ng/mL)	76.9	85.3	90.1	83.92, 96.80
AUCt (ng*hr/mL)	93.2	102	91.0	87.12, 94.97
AUCinf (ng*hr/mL)	94.3	104	91.0	87.17, 94.99
AUC0-15 (ng*hr/mL)	14.4	14.2	101	92.03, 111.43
Tmax (hr)	0.200	0.200	—	-0.150, 0.100
Thigh (n=32)				
Cmax (ng/mL)	70.6	66.5	106	100.82,112.01
AUCt (ng*hr/mL)	91.0	98.5	92.3	90.93, 93.79
AUCinf (ng*hr/mL)	92.1	99.8	92.3	90.91, 93.72
AUC0-15 (ng*hr/mL)	13.1	11.4	115	105.55, 124.99
Tmax (hr)	0.200	0.225	—	-0.183- 0.150

Arm (deltoid) N=34)				
Cmax (ng/mL)	59.2	81.6	72.5	52.88, 99.49
AUCt (ng*hr/mL)	51.7	97.4	53.0	34.28, 82.06
AUCinf (ng*hr/mL)	72.7	98.5	73.8	58.69, 92.71
AUC0-15 (ng*hr/mL)	11.0	14.9	74.0	52.42, 104.48
Tmax (hr)	0.150	0.175	—	-0.183, 0.050
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e. geometric means). Medians are presented for Tmax.				
b Ratio of parameter means for ln-parameter (expressed as a percentage). Natural log-transformed ratios were transformed back to linear scale.				
c 90% confidence interval for ratio of parameter means of ln-transformed parameter (expressed as a percentage). Natural log-transformed confidence limits were transformed back to linear scale.				

2.4.3 Was the Intraject® drug delivery system acceptable for patient usage?

The drug was administered by the clinician in the pivotal study. The sponsor has completed a usability study in migraine patients where the drug is self-injected.

2.5. ANALYTICAL

2.5.1. Were the correct moieties identified and properly measured?

Yes, the active moiety, Sumatriptan, and the concomitant medications, acetaminophen and ibuprofen were identified and measured. The lower limit of quantitation for sumatriptan was 0.200 ng/mL.

2.5.2. What bioanalytical methods are used to assess concentrations?

Sumatriptan in human plasma with lithium heparin as anticoagulant was analyzed using a validated liquid chromatography (LC) with tandem mass spectrometric (MS/MS) detection. The method was validated over the concentration range of 0.200 to 200 ng/mL using a sample volume of 0.100 mL. Sumatriptan and the internal standard (ISTD), sumatriptan-d6, were extracted from human plasma by liquid-liquid extraction. After evaporation of the organic layer under nitrogen, the residue was reconstituted and analyzed using LC with MS/MS detection. Results were calculated using peak area ratios, and calibration curves were generated using a weighted (1/x) linear least-squares regression. The method demonstrated acceptable precision and accuracy. Details of the analytical method are summarized in the following table.

Table 5. Analytical Method Parameters

Validation Study Number:	2100-839
Mnemonic:	SUMHPC
Analyte/Metabolite Name(s):	Sumatriptan
Internal Standard Name(s):	Sumatriptan-d6
Species/Matrix:	Human Plasma
Anticoagulant (if applicable):	Lithium Heparin
Sample Volume:	0.100 mL
Curve Range(s):	0.200 to 200 ng/mL for Sumatriptan
Extraction Type:	Liquid-Liquid Extraction
Automation (if applicable):	96-Well Format, Tomtec
Instrumentation/Detection:	LC-MS/MS (API 3000, ESI+)
Cycle Time:	2.5 minutes
Sample Storage Temperature:	-10 to -30°C
Freeze/Thaw Matrix Stability:	Four cycles
Room Temperature Matrix Stability:	At least 26 hours
Processed-Sample Viability:	At least 90 hours at 2 to 8°C
Frozen Matrix Stability:	At least 176 days at -10 to -30°C At least 176 days at -60 to -80°C
Stock Standard Solution Stability:	Sumatriptan: At least 172 days at 2 to 8°C
Intermediate Standard Solution Stability:	Sumatriptan: At least 82 days at 2 to 8°C
Special Storage/Treatment Requirements:	NA
Method Developed By:	(b) (4)

REFERENCE:

Ricksecker, K., "Validation of a Method for the Determination of Sumatriptan in Human Plasma by HPLC with MS/MS Detection," method validation report, (b) (4) Study No. 2100-839.

III. DETAILED LABELING RECOMMENDATIONS

Several changes, as indicated by track changes, have been recommended in Section 7 (DRUG INTERACTIONS); Section 8 (SPECIFIC POPULATIONS) and Section 12 (CLINICAL PHARMACOLOGY).

(b) (4)

8 pages of draft labeling withheld immediately after this page as B4 (TS/CCI)

IV. PIVOTAL STUDY

Study ZX001-0601 (Pivotal PK Study)

Title of Study: A Randomized, Open-Label, Single-Dose, Four-Way Crossover Study to Evaluate the Pharmacokinetics and Bioequivalence of Sumatriptan Delivered via the Intraject® System Versus the IMITREXSTATdose System® at Three Injection Sites in Healthy Adult Subjects [Protocol No. ZX001-0601]

Investigator: Patricia A. Chandler, MD,
Medical Director,
Covance Global Clinical Pharmacology

Study center: Covance Global Clinical Pharmacology,
1341 West Mockingbird Lane, Suite 400E,
Dallas, TX 75247

Studied period: November 20, 2006 Phase 1-December 23, 2006
Phase of development: 1

Objectives:

- *Primary:* To evaluate the pharmacokinetics of sumatriptan delivered subcutaneously [Intraject® (TEST) compared to IMITREX STATdose System® (REFERENCE)] at each of three injection sites (abdomen, thigh, and arm [deltoid]).
- *Secondary:* To evaluate the bioequivalence during early exposure of sumatriptan delivered by the Intraject® system (TEST) compared to the IMITREX STATdose System (REFERENCE) at three injection sites (abdomen, thigh, and arm [deltoid]),.
- *Other:*
  - To evaluate the bioequivalence of the Intraject® system (TEST) compared to the IMITREX STATdose System (REFERENCE) pooled across three injection sites (abdomen, thigh, and arm [deltoid]).
  - To evaluate injection site reactions (bleeding, swelling, erythema and bruising)

Design: This was a randomized, open-label, single-dose, partial-block, four-period, four-way crossover study conducted in 54 healthy men and women at a single US site.

Treatment: Each subject was assigned to four of the six sequences.

Sequence A: IMITREX-abdomen → Intraject®-abdomen → IMITREX-thigh → Intraject®-thigh
Sequence B: Intraject®-abdomen → IMITREX-abdomen → Intraject®-thigh → IMITREX-thigh

Sequence C: Intraject®-abdomen → IMITREX-abdomen → Intraject®-arm → IMITREX-arm
Sequence D: IMITREX-abdomen → Intraject®-abdomen → IMITREX-arm → Intraject®-arm
Sequence E: IMITREX-arm → Intraject®-arm → IMITREX-thigh → Intraject®-thigh
Sequence F: Intraject®-thigh → IMITREX-thigh → Intraject®-arm → IMITREX-arm

- **Study Products:**
  - **Test**: Intraject® sumatriptan; each injector delivers 0.5 mL of sterile, isotonic solution of 6 mg sumatriptan (base) as the succinate salt; subcutaneous administration; lot number PD05141.
  - **Reference**: IMITREX STATdose System; each injector contained 0.5 mL of solution of 6 mg sumatriptan (base) as the succinate salt; subcutaneous administration; lot number C255698.

- **Blood Samples**: Blood samples for PK analysis were collected 15 minutes before dosing and at 3, 6, 9, 12, 15, 20, and 30 minutes and at 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after dosing on each of 4 treatment days.

Statistical methods:
Demographics and baseline characteristics: Demographics were summarized overall and by treatment sequence. Baseline physical examination and medical history data were listed.

Table 11-3. Demographic and Baseline Data, Pharmacokinetic Analysis Population

Demographic/ Statistic	Randomly Assigned Treatment Sequence						All Subjects
	A	B	C	D	E	F	
	(n=9)	(n=9)	(n=9)	(n=9)	(n=9)	(n=9)	(n=54)
Age, years							
Mean (SD)	33 (11.3)	38 (9.6)	29 (8.3)	33 (11.2)	42 (8.0)	40 (12.1)	36 (10.8)
Min-max	21-53	22-51	20-47	22-52	30-50	21-55	20-55
Weight, kg							
Mean (SD)	74.7 (10.9)	74.5 (8.9)	74.2 (10.0)	69.7 (12.1)	77.9 (12.1)	72.0 (8.7)	73.9 (10.4)
Min-max	63.0-88.6	58.1-88.7	58.4-87.0	52.6-91.6	58.7-98.7	54.8-83.3	52.6-98.7
Height, cm							
Mean (SD)	168 (3.7)	168 (11.4)	169 (8.0)	168 (5.5)	170 (10.2)	168 (5.5)	168 (7.5)
Min-max	163-174	153-184	162-186	161-176	150-182	158-176	150-186
BMI, kg/m^2							
Mean (SD)	26.5 (4.3)	26.7 (3.6)	26.2 (4.1)	24.6 (3.9)	27.0 (3.7)	25.7 (3.5)	26.1 (3.8)
Min-max	22.1-33.1	19.9-30.5	21.6-33.2	19.9-32.8	21.3-31.1	19.2-29.9	19.2-33.2
Gender, n (%)							
Female	6 (66.7%)	6 (66.7%)	5 (55.6%)	7 (77.8%)	5 (55.6%)	5 (55.6%)	34 (63.0%)
Male	3 (33.3%)	3 (33.3%)	4 (44.4%)	2 (22.2%)	4 (44.4%)	4 (44.4%)	20 (37.0%)
Ethnicity, n (%)							
Hispanic or Latino	1 (11.1%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	2 (22.2%)	2 (22.2%)	9 (16.7%)
Race, n (%)							
Black or African-American	2 (22.2%)	3 (33.3%)	3 (33.3%)	3 (33.3%)	4 (44.4%)	3 (33.3%)	18 (33.3%)
White or Caucasian	7 (77.8%)	6 (66.7%)	6 (66.7%)	6 (66.7%)	5 (55.6%)	6 (66.6%)	36 (66.7%)
Fitzpatrick Skin Typing Test							
I	0 (0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)
II	1 (11.1%)	0 (0%)	2 (22.2%)	2 (22.2%)	0 (0%)	0 (0%)	5 (9.3%)
III	4 (44.4%)	5 (55.6%)	2 (22.2%)	4 (44.4%)	3 (33.3%)	5 (55.6%)	23 (42.6%)
IV	3 (33.3%)	4 (44.4%)	3 (33.3%)	3 (33.3%)	4 (44.4%)	4 (44.4%)	21 (38.9%)
V to VI	1 (11.1%)	0 (0%)	1 (11.1%)	0 (0%)	2 (22.2%)	0 (0%)	4 (7.4%)

REF: Appendices 16.2.4-2, 16.2.4-4, and 16.2.12 and Table 14.1-2b

***Pharmacokinetics/Bioequivalence*:** Plasma sumatriptan concentrations were measured using a validated assay method. AUCs [AUCt, partial $AUC_{(0\text{-}15\ min)}$, AUCinf], Cmax, Tmax, Thalf, and Kel were determined. Point estimates for each of the mean ratios were obtained from the antilogs of the mean differences of the log-transformed data. The 90% confidence intervals were obtained from the antilogs of the lower and upper bounds of the 90% confidence intervals for the differences in the means of the log-transformed data.

Analytical:
Study samples were stored in a freezer set to maintain -10 to -30°C prior to analysis. Sumatriptan and the internal standard (ISTD), sumatriptan-d6, were extracted from human plasma by liquid-liquid extraction. After evaporation of the organic layer under nitrogen, the residue was reconstituted and analyzed using LC with MS/MS detection.

Results were calculated using peak area ratios, and calibration curves were generated using a weighted (1/x) linear least-squares regression. The method demonstrated acceptable precision and accuracy. No interfering peaks were found in the areas of interest that were determined to significantly impact the data. The analytical summary information is given in the following table.

Report Number	**6538-542**
Laboratory	(b) (4)
Dates of Analysis	Dec. 15, 2006 to March 7, 2007
Drug Name	Sumatriptan
Internal Standard	Sumatriptan d6
Matrix	Human Plasma
Anticoagulant	Lithium Heparin
Extraction type	Liquid-Liquid
Method	LC-MS/MS (API 3000, ESI+)
Sample volume	0.1 ng/mL
Standard Range	0.2 to 200 ng/mL
Correlation Coefficient n=57	0.9995
Precision	1.4 to 5.8
Quality Control Samples	0.6, 30.0, and 160 ng/mL
Accuracy (%) n=114	91.7-100.7
Precision	2.1 to 5.0
Stability-Freezer	-10 to -30 for 41 days
Room Temperature	26 hours

Results:

A total of 57 subjects were enrolled in the study. Subjects were randomized to the six sequences as follows:

A	B	C	D	E	F	**Total**
9	10	10	10	9	9	**57**

The injections in the abdomen were in Sequence A, B, C, and D: n=39
Injections in the arm were in Sequences C, D, E, and F: n = 38
Injections in the Thigh were in Sequences A, B, E, and F: n=37

Subjects excluded from the PK analysis and the reason they were excluded is shown in the following table:

Table 11-13. Exclusions from PK Statistical Analyses

Subject	Sequence	Period/ Site	Reason for and Type of Exclusion
Excluded from PK Analysis Population and All Subsequent Analyses[a]			
1021	B	Period 1/ Abdomen	Withdrew prematurely and was excluded from the PK analysis population.
1022	D	Period 2/ Abdomen	Was withdrawn prematurely and excluded from the PK analysis population.
1042	C	Period 1/ Abdomen	Withdrew prematurely and was excluded from the PK analysis population.
Excluded from PK Analysis Population and All Subsequent Analyses for One Injection Site			
1009	C	Period 3/ Arm	This subject had plasma sumatriptan concentration data inconsistent with the maximum deliverable dose (possibly through sample contamination), without an exaggerated pharmacological effect, and was excluded from the PK analysis for the arm. Specifically, the subject had much higher concentrations compared to other subjects in the same treatment group (Intraject, arm). A spike in the concentration-time profile was also observed between the 9-, 12-, 15-, and 20-minute timepoints. The concentrations for this subject were confirmed by reassay.
1010	D	Period 1/ Abdomen	Missing concentration values at the 0.2-hour (12-minute) timepoint. This subject was excluded from the PK analysis for the abdomen.
1011 1012 1019	F	Period 1/ Thigh	These subjects had scheduled timepoints with duplicate actual collection times at 3, 6, 12, and/or 15 minutes; as they were missing plasma concentration data near the expected T_{max} of 9-12 minutes, they were excluded from the PK analysis for the thigh.
1032	D	Period 3/ Arm	Missing concentration values at the 0.2-hour (12-minute) timepoint. This subject was excluded from the PK analysis for the arm.
1051	B	Period 3/ Thigh	This subject did not receive a complete injection with Intraject in the thigh (VAS = 2) and was excluded from the PK analysis for the thigh.
Included in PK Analysis but Excluded from One or More Subsequent Analyses for One Injection Site			
1044	E	Period 2/ Arm	This subject had an AUC% extrapolated of > 30%. As a result, the AUC_{inf} value for this subject was not reported. No deviations occurred during dosing. As a result, this subject was included in the PK analysis for the arm, but excluded from the additional statistical analysis due to the AUC_{inf} value not reported for this subject.
1045	D	Period 4/ Arm	This subject had very low concentrations that only went out to 0.2 hours (12 minutes) postdose, while the other concentrations were below the limit of quantification. A spike in concentration was also observed at 0.15 hours (9 minutes) postdose. No deviations occurred during dosing. As a result, this subject was included in the PK analysis but excluded from the additional statistical analysis for the arm due to the lack of a discernable elimination phase required to determine AUC_{inf}.

[a] Individual plasma concentrations for these excluded subjects are listed in **Tables 14.2.1-1a, 14.2.1-1b,** and **14.2.1-1c** and portrayed graphically in **Appendix 16.2.5-3.**
REF: **Appendices 16.2.2** and **16.2.5-1** and data on file.

The final number of subjects by injection site is shown in the following table. Bioequivalence was determined by post-hoc analysis of the different injection sites on an independent basis.

Table 11-1. Subject Population Summary, by Injection Site

Number of Subjects	Arm		Thigh		Abdomen	
	Intraject	IMITREX	Intraject	IMITREX	Intraject	IMITREX
Enrolled and treated (safety population) [a]	38	38	37	37	39	39
Withdrew [b]	2	2	1	1	3	3
Completed all study procedures	36	36	36	36	36	36
Included in PK parameters analysis	34 [c]	34 [c]	32 [d]	32 [d]	35 [e]	35 [e]
Included in descriptive and inferential statistics (planned primary and secondary analyses) [f]	34 [g] /32 [h]	34 [g] /32 [h]	32	32	35	35
Included in post hoc primary and secondary analyses [f]	34	34	32	32	35	35
Included in additional primary statistical analysis [f,i]	24 [j]	24 [j]	32	32	33 [k]	33 [k]

[a] Three replacement subjects were enrolled: 2021, 2022, and 2042.
[b] Subjects 1021, 1022, and 1042 withdrew and were excluded from the PK parameters analysis.
[c] Subjects 1009 and 1032 were excluded.
[d] Subjects 1011, 1012, 1019, and 1051 were excluded.
[e] Subject 1010 was excluded.
[f] All subjects that were excluded from the PK parameters analysis were excluded from all subsequent statistical analyses.
[g] The primary analyses consisted of AUC_t, C_{max} and AUC_{inf}. For the arm, 34 subjects were included in the AUC_t and C_{max} analyses and 32 subjects were included in the AUC_{inf} analysis for both Intraject and IMITREX (34/32).
[h] Subjects 1044 and 1045 were excluded.
[i] All subjects with a VAS ≤2 were excluded in addition to those excluded from the PK analyses.
[j] Subjects 1009, 1011, 1012, 1026, 1028, 1029, 1032, 1044, 1045, 1047, 2022, and 2042 were excluded.
[k] Subjects 1010, 1047, and 2022 were excluded.
REF: **Appendix 16.2.1, Table 14.1-2a.**

The descriptive summary statistics for the key kinetic parameters by treatment and injection site are shown in the following table:

Table 11-4. Summary of Mean Sumatriptan Pharmacokinetic Parameters: PK Analytic Population

Treatment, Site/ Parameter	C_{max} (ng/mL)	T_{max}[a] (hr)	AUC_{0-15} (ng*hr/mL)	AUC_t (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	T_{half} (hr)	K_{el} (1/hr)
Intraject, abdomen							
Mean	78.6	0.200	14.8	94.3	95.3	1.70	0.42
(SD)	(17.3)	(0.100, 0.333)	(3.72)	(14.0)	(14.2)	(0.207)	(0.050)
N	35	35	35	35	35	35	35
IMITREX, abdomen							
Mean	87.3	0.200	14.9	103	104	1.69	0.42
(SD)	(18.7)	(0.100, 0.500)	(4.47)	(12.5)	(12.6)	(0.249)	(0.059)
N	35	35	35	35	35	35	35
Intraject, arm							
Mean	76.6	0.150	14.9	76.6	82.5	1.65	0.49
(SD)	(30.4)	(0.0500, 0.250)	(6.13)	(29.6)	(23.2)	(0.441)	(0.34)
N	34	34	34	34	32	33	33
IMITREX, arm							
Mean	83.4	0.175	15.5	98.2	99.3	1.72	0.41
(SD)	(17.5)	(0.100, 0.333)	(4.24)	(12.6)	(12.9)	(0.269)	(0.059)
N	34	34	34	34	32	33	33
Intraject, thigh							
Mean	71.9	0.200	13.4	91.8	92.9	1.72	0.42
(SD)	(14.4)	(0.0667, 0.333)	(3.05)	(12.6)	(12.8)	(0.365)	(0.072)
N	32	32	32	32	32	32	32
IMITREX, thigh							
Mean	68.3	0.225	12.1	99.4	101	1.71	0.41
(SD)	(16.3)	(0.100, 0.500)	(4.20)	(13.5)	(13.6)	(0.226)	(0.052)
N	32	32	32	32	32	32	32

[a] Median (min, max) presented for T_{max}
REF: Table 14.2.2-1a

Bioequivalence: The sponsor's attempt to determine primary bioequivalence using the Statistical Analysis Plan that they developed, resulted in a failure to demonstrate bioequivalence at all three injection sites. A Post-Hoc analysis of the data comparing each injection site independently was completed and based on mean ratio analyses of AUCt, AUCinf, and Cmax, Intraject® sumatriptan was found bioequivalent to reference IMITREX STATdose at the abdomen and thigh injection sites, but not at the arm (deltoid). Lack of bioequivalence at the arm was associated with an increased incidence of incomplete injections for Intraject® at this injection site, resulting in low mean values and high variance estimates for Cmax, AUCt, and AUCinf sumatriptan PK parameters. The Sponsor also evaluated the bioequivalence of the partial AUC to 15 minutes to determine equivalence during early exposure. The results are shown in the following table.

Post-Hoc Bioequivalence Analysis: Intraject® Sumatriptan vs. IMITREX STATdose				
Parameter (units)	**Test[a] (Intraject®)**	**Reference[a] (IMITREX)**	**Test/ Ref (%) [b]**	**90% Confidence Interval [c]**
Abdomen (n=35)				
Cmax (ng/mL)	76.9	85.3	90.1	83.92, 96.80
AUCt (ng*hr/mL)	93.2	102	91.0	87.12, 94.97
AUCinf (ng*hr/mL)	94.3	104	91.0	87.17, 94.99
AUC0-15 (ng*hr/mL)	14.4	14.2	101	92.03, 111.43
Tmax (hr)	0.200	0.200	—	-0.150, 0.100
Thigh (n=32)				
Cmax (ng/mL)	70.6	66.5	106	100.82,112.01
AUCt (ng*hr/mL)	91.0	98.5	92.3	90.93, 93.79
AUCinf (ng*hr/mL)	92.1	99.8	92.3	90.91, 93.72
AUC0-15 (ng*hr/mL)	13.1	11.4	115	105.55, 124.99
Tmax (hr)	0.200	0.225	—	-0.183- 0.150
Arm (deltoid) N=34)				
Cmax (ng/mL)	59.2	81.6	72.5	52.88, 99.49
AUCt (ng*hr/mL)	51.7	97.4	53.0	34.28, 82.06
AUCinf (ng*hr/mL)	72.7	98.5	73.8	58.69, 92.71
AUC0-15 (ng*hr/mL)	11.0	14.9	74.0	52.42, 104.48
Tmax (hr)	0.150	0.175	—	-0.183, 0.050
a Least-squares mean from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (i.e. geometric means). Medians are presented for Tmax.				
b Ratio of parameter means for ln-parameter (expressed as a percentage). Natural log-transformed ratios were transformed back to linear scale.				
c 90% confidence interval for ratio of parameter means of ln-transformed parameter (expressed as a percentage). Natural log-transformed confidence limits were transformed back to linear scale.				

The mean plasma concentrations of sumatriptan (log scale) versus time for the abdomen, thigh, and arm (deltoid) are shown in the following figures.

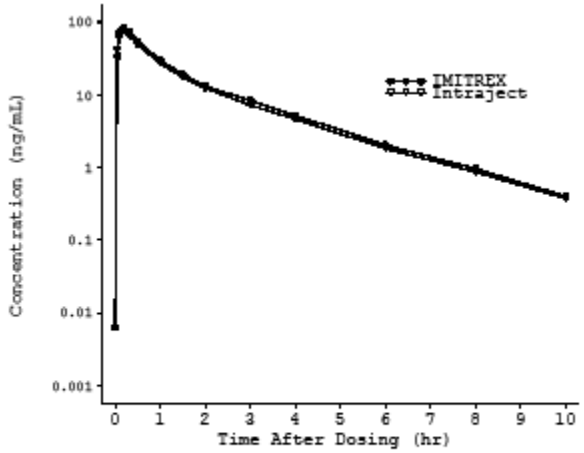


Figure 11-2. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Abdomen

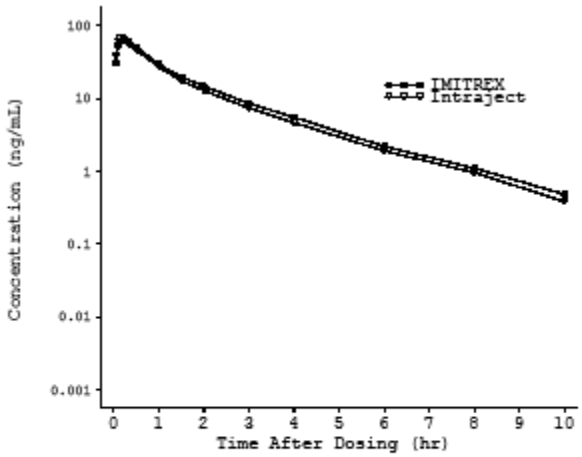


Figure 11-3. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Thigh

REF: Table 14.2.1-1b

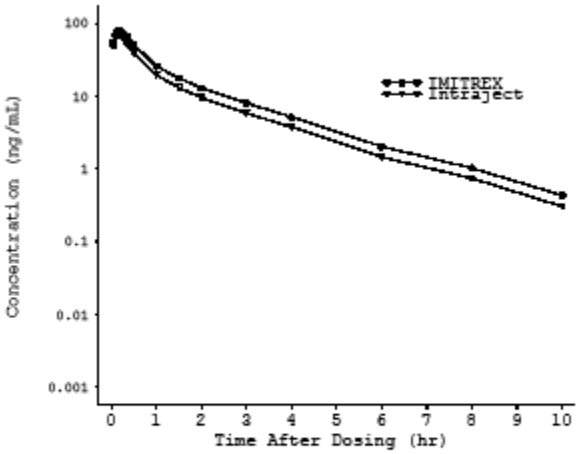


Figure 11-4. Geometric Mean Concentration-Time Profile for Intraject Sumatriptan vs. IMITREX STATdose in Plasma on the Log-Linear Scale Following Single Injection in the Arm (Deltoid)

REF: Table 14.2.1-1c

Pooled Bioequivalence: Bioequivalence was demonstrated for the Intraject® system relative to IMITREX STATdose for pooled abdomen and thigh sumatriptan concentration data based on mean ratio analyses of AUCt, AUCinf, and Cmax.

Supportive Bioequivalence Analysis: Intraject® vs. IMITREX STATdose						
Parameter (units)	N Test	N Ref	Test Mean **(Intraject®)**	Ref. Mean **(IMITREX)**	Mean Ratio T/R	90% CI
Cmax (ng/mL)	51	53	74.1	76.6	96.7	(91.77, 101.99)
AUCt (ng*hr/mL)	51	53	92.8	102	90.8	(88.14, 93.49)
AUCinf (ng*hr/mL)	51	53	93.9	103	90.8	(88.19, 93.50)
a Geometric means						

Safety: According to the Sponsor, safety was assessed throughout the study by monitoring adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examination findings. Overall, treatment-emergent adverse events (TEAEs) were reported by 75.4% of the subjects. A total of 95 TEAEs were reported following administration of Intraject®, of which 86.3% were considered possibly or probably related to study treatment, and 100 TEAEs were reported following administration of IMITREX, of which 90.0% were considered possibly or probably related to study treatment. The most frequently reported TEAEs for either treatment were headache, non-cardiac chest pain, paraesthesia, vertigo, hypoaesthesia oral, and nasal discomfort. All TEAEs were mild and

transient. There were no clinically significant differences between Intraject® and IMITREX in clinical laboratory findings, vital signs, ECG findings, or other safety findings.

Injection Site Reactions: According to the Sponsor, injection sites were assessed for signs of erythema, swelling, bleeding, and bruising reactions immediately following injection and at 1, 8, and 24 hours following injection. A higher incidence of swelling was observed for Intraject® injection.

V. SPONSOR'S PROPOSED LABELING

DRAFT LABELING TEXT

Draft Labeling Text

35 pages of draft labeling withheld immediately after this page as B4 (CCI/TS)

VI. FILING FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22239	Brand Name	Intraject® Sumatriptan
OCPB Division (I, II, III)	DCP-1	Generic Name	Sumatriptan Succinate
Medical Division	HFD-120	Drug Class	Antimigraine Drug
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Acute Treatment of Migraine with or without Aura and Acute Treatment of Cluster Headache
OCPB Team Leader	Ramana Uppoor	Dosage Form	Injectable
Date of Submission	12/28/2007	Dosing Regimen	6 mg
Estimated Due Date of OCPB Review	8/31/2008	Route of Administration	Subcutaneous Injection
PDUFA Due Date	10/31/2008	Sponsor	Zogenix Inc.
Division Due Date	9/29/2008	Priority Classification	S

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of Intraject® Sumatriptan (sumatriptan succinate) subcutaneous injection using Imitrex Statdose (sumatriptan injection), 6 mg, as the reference product (based on BE, no clinical efficacy trials)

Sumatriptan Intraject is a subcutaneous injection (6 mg) of sumatriptan succinate delivered subcutaneously using the needle free Intraject drug delivery system (DDS). Development of the Intraject sumatriptan DP was performed under investigational new drug application (IND) No. 71-275.

Prior to the submission of the U.S IND and the conduct of the Pivotal Pharmacokinetic/ Bioequivalence (PK/BE) Study ZX001-0601, three non-IND active-controlled pharmacokinetic studies ("Pilot PK Studies") were conducted in Australia under Protocol Nos. SUM-04-01, ARD-2100-0501 and ARD-2100-0504. These studies compared the safety, tolerability, pharmacokinetics, and bioequivalence of Intraject sumatriptan (6 mg/0.5 mL) to the reference product, sumatriptan injection as Imigran Injection (using the MK II Injector; 6 mg/0.5 mL) at three potential injection sites: abdomen, arm, and thigh. Imigran Injection marketed in Australia employs the Mk II auto-injector that is the same device as the auto-injector (called STATdose System) used for IMITREX Injection in the U.S. All four studies evaluated single doses of 6 mg sumatriptan/0.5 mL when administered by the Intraject Drug Delivery System (DDS) or the Imigran/IMITREX drug delivery system (i.e., Mk II Injector or STATdose System).

This submission includes bioavailability data from 4 completed studies including 1 pivotal bioequivalence study and 3 pilot studies. A summary table of clinical pharmacology studies is included in the Appendix.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			

Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	3	-	Pilot PK/BE Studies. Two studies include 3 injection sites (arm, thigh and abdomen). One of the studies tested arm as the only injection site.
multiple dose:				
Patients-				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		Pivotal PK/BE study Includes 3 injection sites 1) Arm 2) Thigh 3) Abdomen
replicate design; single / multi dose:				
Food-drug interaction studies:	-			

Dissolution:	-	-	-	
(IVIVC):				
Bio-waiver request based on BCS	-	-	-	
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			54 References
Total Number of Studies		5		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	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)	Is BE shown between Intraject and Imitrex? Is BE shown with different administration sites (arm, thigh and abdomen)?	
Other comments or information not included above	Request for DSI inspection: Pivotal pharmacokinetic/bioequivalence Study ZX001-601 Clinical Research Organization (CRO): (b) (4) Analytical Laboratory: (b) (4)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22239 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Ramana Uppoor, Mehul Mehta)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Subject Participation	Total Intraject Injections	Study Status; Type of Report
PK/BE (Pivotal Active controlled study)	ZX001-0601	Module 5, Section 5.3.1.2	To evaluate the pharmacokinetics and bioequivalence of Intraject® sumatriptan vs. IMITREX® Injection at three injection sites in healthy adult subjects	Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh)	Intraject needle-free injector using sumatriptan vs. marketed reference product, IMITREX Injection; 2 Intraject and 2 IMITREX injections; physician administered; subcutaneous	54 planned and randomized, 48 completed and evaluable	Healthy adult subjects	6 days, total	111	Completed; Full CSR
Clinical performance assessment (Device evaluation with saline injection)	P095-002	Module 5, Section 5.3.5.1	To establish best design configuration of Intraject by evaluating injection performance of different design configurations in a large group of subjects	Single-group study of subjects receiving 12 saline injections to the abdomen at multiple injection sites	Different design configurations of a needle-free injector (Intraject) using saline; 12 saline injections; subcutaneous	300 planned, 300 completed (9 patients received injections with "near-final device)	Generally healthy male and female adults aged 18-80 years	10 days, total	302 in near-final device (total exposure =3612)	Completed; Full CSR
Clinical performance verification (CPV) (Device evaluation with saline injection)	ARDM-02A00-0104	Module 5, Section 5.3.5.1	To verify device design by evaluating injection performance in a large group of subjects	Single-group study of subjects receiving saline injections to the abdomen at multiple (6) injection sites	Intraject needle-free injector using saline; 4 saline injections; subcutaneous	200 planned, 191 completed	Generally healthy male and female adults	4 days, total	764	Completed; Full CSR
Pilot PK (Active controlled study)	SUM-04-01	Module 5, Section 5.3.5.1	Pilot study to evaluate the pharmacokinetics and bioequivalence of Intraject sumatriptan vs. marketed reference product at 3 injection sites	Single-dose, open-label, 4-way crossover PK study using a balanced incomplete block design	Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Injection; 2 Intraject and 2 Imigran physician administered; subcutaneous	18 planned, 18 completed	Generally healthy male and female adult subjects	4 days, total	36	Completed; Full CSR
PK (Active controlled study)	ARD-2100-0501	Module 5, Section 5.3.5.1	To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites	Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh)	Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Injection; 2 Intraject and 2 Imigran self-injections; subcutaneous	24 planned, 24 completed	Healthy adult subjects	6 days, total	48	Completed; Full CSR
PK (Active controlled study)	ARD-2100-0504	Module 5, Section 5.3.5.1	To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites	Single center, randomized, single-dose, open-label, three-way crossover study	Intraject needle-free injector using sumatriptan vs. marketed reference product Imigran Injection; 2 Intraject and 1 Imigran; self-injections; subcutaneous	24 planned, 24 completed	Healthy adult subjects	5 days, total	48	Completed; Full CSR
In Vitro/In Vivo Correlation (ZED Trial)	PNF8800-1137	Module 5, Section 5.3.5.4	To further understand if certain skin attributes affect the performance of the Intraject®	Single center study of the skin characteristics of subjects that previously participated in study P095-002	N/A; no test material used	40 planned, 40 completed	Healthy adult subjects	1 day, total	0	Completed; Report
Naïve User Study	ARDM-02A00-0204	Module 1, Section 1.14.1.4	To evaluate the experience of naïve users as they were exposed to a progressive iteration of instruction followed by the opportunity to snap off the cap, prime and actuate the Intraject configured with the priming mechanism and snap-off cap	Single center, three-group, open-label study of subjects using instructional material to complete an injection into a foam pad	Intraject needle-free injector filled with sterile saline; 2 injections per subject; 2 subjects injected a third time	102 planned, 102 completed	Healthy adult subjects	1 day, total	0*	Completed; Report
Pilot Usability Study	ZX000-0702	Module 1, Section 1.14.1.4	To create instructions for use for Intraject sumatriptan simple enough to be understood by patients experiencing a migraine attack.	Single center, two-group, open-label study of subjects using only the test instructional material as a guide to complete an injection into a foam pad	Intraject needle-free injector filled with non-sterile saline; 1 injection per subject	20 planned, 19 completed	Healthy adult subjects	1 day, total	0*	Completed; Report

*206 injections into a foam pad were completed during the Naïve User study (ARDM-02A00-0204). 20 injections into a foam pad were completed during the Pilot Usability study (ZX000-0702).

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

/s/

Carol Noory
10/14/2008 02:00:49 PM
BIOPHARMACEUTICS

Veneeta Tandon
10/14/2008 02:20:15 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22239**	**Brand Name**	**Intraject® Sumatriptan**
OCPB Division (I, II, III)	**DCP-1**	**Generic Name**	**Sumatriptan Succinate**
Medical Division	**HFD-120**	**Drug Class**	**Antimigraine Drug**
OCPB Reviewer	**Jagan Mohan Parepally**	**Indication(s)**	**Acute Treatment of Migraine with or without Aura and Acute Treatment of Cluster Headache**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**Injectable**
Date of Submission	**12/28/2007**	**Dosing Regimen**	**6 mg**
Estimated Due Date of OCPB Review	**8/31/2008**	**Route of Administration**	**Subcutaneous Injection**
PDUFA Due Date	**10/31/2008**	**Sponsor**	**Zogenix Inc.**
Division Due Date	**9/29/2008**	**Priority Classification**	**S**

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of Intraject® Sumatriptan (sumatriptan succinate) subcutaneous injection using Imitrex Statdose (sumatriptan injection), 6 mg, as the reference product (based on BE, no clinical efficacy trials)

Sumatriptan Intraject is a subcutaneous injection (6 mg) of sumatriptan succinate delivered subcutaneously using the needle free Intraject drug delivery system (DDS). Development of the Intraject sumatriptan DP was performed under investigational new drug application (IND) No. 71-275.

Prior to the submission of the U.S IND and the conduct of the Pivotal Pharmacokinetic/ Bioequivalence (PK/BE) Study ZX001-0601, three non-IND active-controlled pharmacokinetic studies ("Pilot PK Studies") were conducted in Australia under Protocol Nos. SUM-04-01, ARD-2100-0501 and ARD-2100-0504. These studies compared the safety, tolerability, pharmacokinetics, and bioequivalence of Intraject sumatriptan (6 mg/0.5 mL) to the reference product, sumatriptan injection as Imigran Injection (using the MK II Injector; 6 mg/0.5 mL) at three potential injection sites: abdomen, arm, and thigh. Imigran Injection marketed in Australia employs the Mk II auto-injector that is the same device as the auto-injector (called STATdose System) used for IMITREX Injection in the U.S. All four studies evaluated single doses of 6 mg sumatriptan/0.5 mL when administered by the Intraject Drug Delivery System (DDS) or the Imigran/IMITREX drug delivery system (i.e., Mk II Injector or STATdose System).

This submission includes bioavailability data from 4 completed studies including 1 pivotal bioequivalence study and 3 pilot studies. A summary table of clinical pharmacology studies is included in the Appendix.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			

Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:	**-**	**-**	**-**	
Isozyme characterization:				
Blood/plasma ratio:	**-**	**-**	**-**	
Plasma protein binding:	**-**	**-**	**-**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**3**	**-**	Pilot PK/BE Studies. Two studies include 3 injection sites (arm, thigh and abdomen). One of the studies tested arm as the only injection site.
multiple dose:				
Patients-				
single dose:	**-**	**-**	**-**	
multiple dose:	**-**	**-**	**-**	
Dose proportionality -				
fasting / non-fasting single dose:	**-**	**-**	**-**	
fasting / non-fasting multiple dose:	**-**	**-**	**-**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**-**	**-**	**-**	
In-vivo effects of primary drug:	**-**	**-**	**-**	
In-vitro:				
Subpopulation studies -				
ethnicity:	**-**	**-**	**-**	
gender:	**-**	**-**	**-**	
pediatrics:	**-**	**-**	**-**	
geriatrics:				
renal impairment:	**-**	**-**	**-**	
hepatic impairment:	**-**	**-**	**-**	
PD:				
Phase 2:	**-**	**-**	**-**	
Phase 3:	**-**	**-**	**-**	
PK/PD:				
Phase 1 and/or 2, proof of concept:	**-**	**-**	**-**	
Phase 3 clinical trial:	**-**	**-**	**-**	
Population Analyses -				
Data rich:	**-**	**-**	**-**	
Data sparse:	**-**	**-**	**-**	
II. Biopharmaceutics				
Absolute bioavailability:	**-**	**-**	**-**	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		Pivotal PK/BE study Includes 3 injection sites 1) Arm 2) Thigh 3) Abdomen
replicate design; single / multi dose:				
Food-drug interaction studies:	**-**			

Dissolution:	-	-	-	
(IVIVC):				
Bio-waiver request based on BCS	-	-	-	
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			54 References
Total Number of Studies		5		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	X	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)	Is BE shown between Intraject and Imitrex? Is BE shown with different administration sites (arm, thigh and abdomen)?	
Other comments or information not included above	Request for DSI inspection: Pivotal pharmacokinetic/bioequivalence Study ZX001-601 **Clinical Research Organization (CRO):** **(b) (4)** **Analytical Laboratory:** **(b) (4)**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22239 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Ramana Uppoor, Mehul Mehta)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Subject Participation	Total Intraject Injections	Study Status; Type of Report
PK/BE (Pivotal Active controlled study)	ZX001-0601	Module 5, Section 5..3.1.2	To evaluate the pharmacokinetics and bioequivalence of Intraject® sumatriptan vs. IMITREX® Injection at three injection sites in healthy adult subjects	Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh)	Intraject needle-free injector using sumatriptan vs. marketed reference product, IMITREX Injection; 2 Intraject and 2 IMITREX injections; physician administered; subcutaneous	54 planned and randomized, 48 completed and evaluable	Healthy adult subjects	6 days, total	111	Completed; Full CSR
Clinical performance assessment (Device evaluation with saline injection)	P095-002	Module 5, Section 5..3.3.1	To establish best design configuration of Intraject by evaluating injection performance of different design configurations in a large group of subjects	Single-group study of subjects receiving 12 saline injections to the abdomen at multiple injection sites	Different design configurations of a needle-free injector (Intraject) using saline; 12 saline injections; subcutaneous	300 planned, 300 completed (9 patients received injections with "near-final device)	Generally healthy male and female adults aged 18-80 years	10 days, total	102 in near-final device (total exposure =3612)	Completed; Full CSR
Clinical performance verification (CPV) (Device evaluation with saline injection)	ARDM-02A00-0104	Module 5, Section 5..3.3.1	To verify device design by evaluating injection performance in a large group of subjects	Single-group study of subjects receiving saline injections to the abdomen at multiple (6) injection sites	Intraject needle-free injector using saline; 4 saline injections; subcutaneous	200 planned, 191completed	Generally healthy male and female adults	4 days, total	764	Completed; Full CSR
Pilot PK (Active controlled study)	SUM-04-01	Module 5, Section 5..3.3.1	Pilot study to evaluate the pharmacokinetics and bioequivalence of Intraject sumatriptan vs. marketed reference product at 3 injection sites	Single-dose, open-label, 4-way crossover PK study using a balanced incomplete block design	Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Injection; 2 Intraject and 2 Imigran physician administered; subcutaneous	18 planned, 18 completed	Generally healthy male and female adult subjects	4 days, total	36	Completed; Full CSR
PK (Active controlled study)	ARD-2100-0501	Module 5, Section 5..3.3.1	To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites	Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh)	Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Injection; 2 Intraject and 2 Imigran self-injections; subcutaneous	24 planned, 24 completed	Healthy adult subjects	6 days, total	48	Completed; Full CSR
PK (Active controlled study)	ARD-2100-0504	Module 5, Section 5..3.3.1	To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites	Single center, randomized, single-dose, open-label, three-way crossover study	Intraject needle-free injector using sumatriptan vs. marketed reference product Imigran Injection; 2 Intraject and 1 Imigran; self-injections; subcutaneous	24 planned, 24 completed	Healthy adult subjects	5 days, total	48	Completed; Full CSR
In Vitro/In Vivo Correlation (ZED Trial)	P/N 8800-1137	Module 5, Section 5..3.5.4	To further understand if certain skin attributes affect the performance of the Intraject®	Single center study of the skin characteristics of subjects that previously participated in study P095-002	N/A; no test material used	40 planned, 40 completed	Healthy adult subjects	1 day, total	0	Completed; Report
Naïve User Study	ARDM-02A00-0204	Module 1, Section 1.14.1.4	To evaluate the experience of naïve users as they were exposed to a progressive iteration of instruction followed by the opportunity to snap off the cap, prime and actuate the Intraject configured with the priming mechanism and snap-off cap	Single center, three-group, open-label study of subjects using instructional material to complete an injection into a foam pad	Intraject needle-free injector filled with sterile saline; 2 injections per subject; 2 subjects injected a third time	102 planned, 102 completed	Healthy adult subjects	1 day, total	0*	Completed; Report
Pilot Usability Study	ZX000-0702	Module 1, Section 1.14.1.4	To create instructions for use for Intraject sumatriptan simple enough to be understood by patients experiencing a migraine attack.	Single center, two-group, open-label study of subjects using only the test instructional material as a guide to complete an injection into a foam pad	Intraject needle-free injector filled with non-sterile saline; 1 injection per subject	20 planned, 19 completed	Healthy adult subjects	1 day, total	0*	Completed; Report

*206 injections into a foam pad were completed during the Naïve User study (ARDM-02A00-0204). 20 injections into a foam pad were completed during the Pilot Usability study (ZX000-0702).

Table 2.5-4. Summary of Pivotal and Pilot Pharmacokinetic/Bioequivalence Clinical Studies of Single-Dose Subcutaneous Injection, Intraject Sumatriptan (6 mg/0.5 mL) vs. IMITREX STATdose/Imigran Mk II Injector (6 mg/0.5 mL).

Study	Country	Study Population	Injection / Sites	Study Design	Nominal No. Injections Per Injection Site[a]	Total Nominal No. of Injections[a]
Pivotal PK/BE Study ZX001-0601	U.S. (IND)	N=54 healthy adult M/F subjects.	Clinician injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=36	N=108
Pilot PK Study SUM-04-01	Australia	N=18 healthy adult M/F subjects.	Clinician injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=12	N=36
Pilot Self-injection PK Study ARD-2100-0501	Australia	N=24 healthy adult M/F subjects.	Self-injected to abdomen, arm, and/or thigh.	4-way crossover, incomplete block.	N=16	N=48
Total N=96 Subjects			**Total nominal no. of Intraject injections[a] N=192**			

[a] The number of nominal injections represent the number of planned injections per product Intraject sumatriptan or IMITREX/Imigran Mk II, per injection site and may have differed from the actual number of injections administered during the study.

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/s/

Jagan Parepally
2/7/2008 12:30:25 PM
PHARMACOLOGIST

Ramana S. Uppoor
2/7/2008 01:24:37 PM
BIOPHARMACEUTICS
Project manager should send the DSI consult as requested in this filing memo.