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APPLICATION NUMBER:

202278Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA	202-278 (Resubmission)
Applicant:	NuPathe
Proposed Trade name:	Zecuity™
Stamp Date	July 16, 2012
Amendment Date	November 19, 2012; December 14, 2012
Established Name:	Sumatriptan
Dosage Form:	Transdermal Iontophoretic System
Route of Administration:	Topical
Indication:	Migraine
Reviewer:	Tapash Ghosh

Background: The proposed Sumatriptan Transdermal Iontophoretic System (also know as Zecuity ™) is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks. Sumatriptan (Imitrex®, GlaxoSmithKline) is available in the United States (U.S.) in three formulations; oral tablets, subcutaneous injection, and as a nasal spray. Sumatriptan (Sumavel™ DosePro™, Zogenix) is available as a needleless subcutaneous injection. Generic sumatriptan oral tablets, nasal spray, and injection are also available. The proposed product, if approved, will be the first transdermal sumatriptan product.

The sumatriptan iontophoretic transdermal system, is a disposable, single-use co-packaged drug/device combination product that delivers sumatriptan transdermally for the treatment of acute migraine attacks. The drug component portion of Zecuity is referred to as the reservoir card and consists of two separate reservoir pads imbibed with either (b) (4) g of sumatriptan formulation (b) (4) sumatriptan succinate containing (b) (4) mg equivalent to 86 mg of sumatriptan base) or (b) (4) g of salt solution ((b) (4) sodium chloride). The device portion of Zecuity is the Electrode Patch (E-Patch) containing a positively charged (b) (4) electrode and a negatively charged (b) (4) electrode.

The terms below are those used by the Applicant to describe the drug product unless otherwise noted.

NP101 Drug/Device Combination	Unassembled but commercially packaged reservoir cards and electrode card
NP101 Drug Product*	Consists of two reservoir cards, Drug Reservoir Card (DRC) and the Salt Reservoir Card (SRC)
Electrode Card/E-Card	Two electrodes and controller manufactured to form a single component
NP101 Device/E-Patch	E-Card laminated to a transdermal patch

Figure 1: (b) (4)

Drug delivery is approximately four hours (b) (4) after which time the system is automatically deactivated by the pre-[4] programmed circuit. The quality of the system is controlled by several tests including *in-vitro* drug release. The reservoir card pads are (b) (4) .

Regulatory History:

In the Biopharmaceutics Review of the original submission dated October 29, 2010, a comple reponse was recommended citing several deficiencies in the applicant's proposed *in-vitro* release method (see Biopharmaceutics review in DARRT dated June 22, 2011). Those deficiencies were captrured in the Agency's CR letter dated August 29, 2011. In this resubmission, the applicat addressed those deficiencies which have been reviewed here.

The Biopharmaceutics deficiencies listed in the 29-AUG-2011 CR Letter (as mentioned below) are reviewed below.

Item #22 Establish a test and acceptance criteria for in vitro release on stability.

NuPathe Response

In vitro assay has been developed and acceptance criteria established for release and stability.

Reviewer Evaluation: A modified *in vitro* release method developed and validated by (b) (4) was submitted in this resubmission and was reviewed. Item #22 has been adequately addressed.

Items #36 – 42 are related to issues specific to the original method submitted in the original submission.

NuPathe Response
In vitro assay has been developed and acceptance criteria established for release and stability.

Reviewer Evaluation: A modified *in vitro* release method developed and validated by [redacted] (b) (4) was submitted in this resubmission and was reviewed. Items *#36 – 42* have been adequately addressed.

RECOMMENDATION

ONDQA-Biopharmaceutics has reviewed the overall *in-vitro* release information and from the Biopharmaceutics view point NDA 202-278 for Zelrix™ (Sumatriptan) iontophoretic transdermal system is recommended for approval.

The following points need to be conveyed to the sponsor:

1. The Agency recommended *in-vitro* release specifications which are accepted by the applicant, will be used [redacted] (b) (4)

2. [redacted] (b) (4)

3. The applicant's *in-vitro* release method appears complex and requires thorough understanding. The method is recommended for approval [redacted] (b) (4) from the date of approval of the product.

4. Once all the information are received and reviewed by the Agency, a decision on the *in-vitro* release method and specifications will be negotiated with the applicant.

For Internal Action (Not to be conveyed to the Applicant)

Following approval, the reviewer plans to [redacted] (b) (4) to gain a thorough understanding of the test methodology.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Richard T. Lostritto, Ph. D.
Acting Biopharmaceutics Lead
Office of New Drug Quality Assessment

Biopharmaceutics Review:

In Vitro Method Description

In response to the the Biopharmaceutics deficiencies listed in the 29-AUG-2011 CR Letter, a modified *in vitro* release method developed and validated by [redacted] (b) (4) was submitted in this resubmission and was reviewed.

The goal of the *in vitro* assay test is to evaluate drug release with respect to the rate of delivery (I.e. flux) at each stage and the total drug delivered by a NP101 E-Patch over the duration of patch operation.

The *in vitro* test system is designed to allow the device to operate normally, with minimal change to the typical operating conditions, including current density, resistance, and non-passive diffusion. The system is based on a [redacted] (b) (4) The membrane system limits passive diffusion, while providing sufficient resistance to allow the E-Patch to operate within its design specifications and deliver the drug. The interface between the anode electrode, drug pad, and membrane system is designed to allow the entire anode electrode to be exposed during the test and, therefore, operate at full electrochemical capacity throughout the test.

This test was developed to assess the quality of the product with respect to three parameters – Flux (b) (4), during [redacted] (b) (4), and total drug released at 4 hours.

The *in vitro* drug release method was validated for precision, accuracy, current discrimination and sample solution stability and passed the validation acceptance criteria set forth within the protocol VP-120-001-006. [redacted] (b) (4) in the test method did meet acceptance criteria showing that the method is robust with respect to bracketed component concentrations [redacted] (b) (4) The method showed acceptable inter-day and inter-analyst repeatability and demonstrated its ability to discriminate inactive patches from the NP1 01 E-patches. In conclusion, this method has shown to be suitable for its intended use.

[Full Test Method TM 120-001-06 (June 6, 2012) and Test Method Validation Report VR-120-001-006 (July 09, 2012) both by [redacted] (b) (4). can be found in the resubmission dated July 16, 2012]

During review of the method and the proposed in-vitro release specifications, the following information request (IR) was e-mailed to the applicant on November 13, 2012:

Provide in-vitro release data obtained from the to be marketed batch (s) (mention full batch information) used to generate your proposed in-vitro dissolution specification. If you have generated more data with more batches since you submitted your CR response, include them as well.

The applicant responded on November 19, 2012 as follows:

At the time of NDA resubmission on July 16, 2012, *in vitro* analysis data from one drug product lot, comprised of the Drug Reservoir Card (DRC) lot 7013362 and Salt Reservoir Card (SRC) lot 7013352, and one E-Patch lot 9901152 was presented in the NDA in Sections 3.2.P.5.2.4.2 and 3.2.P.5.6.2.1.3 (see (b) (4) Method report TM-120-001-006).

Since NDA resubmission on July 16, 2012, three additional drug product lots and one different E-Patch lot have been tested. Batch information for all lots is provided in Table 2. Summary of in vitro analysis from all lots are presented in Tables 3, 4, and 5 below. Detailed results are presented in Table 6 below. Both sets of data were also presented in the 2012 IND 74,877 Annual Report, Section B.7.3 (Summary) and in Appendix D (Detailed).

Table 2: Batch Information

Batch	Drug Product (DRC/SRC)			E-Patch		
	Lot (DRC/SRC)[1]	Manufacturer	Purpose	Lot	Manufacturer	Purpose
1	7013362/7013352	(b) (4)	Supplies (GMP)	9901152	(b) (4)	Design Validation (GMP)
2	9900580		Tech Transfer	9901152		Design Validation (GMP)
3	9900590		Tech Transfer	9901152		Design Validation (GMP)
4	9900600		Tech Transfer	9901152		Design Validation (GMP)
5	7013362/7013352		PQ	9901702		Supplies (GMP)

[1] Drug reservoir card lot 7013362 and salt reservoir card lot 7013352 were manufactured as (b) (4) (b) (4) (b) (4) Drug lots 9900580, 900590, and 990060 were manufactured as (b) (4) (b) (4)

Table 3: Summary Data - *In Vitro* Data, Flux (b) (4) mg/cm²/hour)

Drug Product Lot (DRC/SRC)[1]	Patch Lot	Numbers Tested	Flux (b) (4) (mg/cm²/hour)		
			Mean (mg/cm²/hour)	STDEV[2]	RSD[3] (%)
7013362/7013352	9901152	44	0.294	0.019	6.5
9900580	9901152	12	0.311	0.019	6.0
9900590	9901152	12	0.327	0.021	6.3
9900600	9901152	12	0.319	0.027	8.3
7013362/7013352	9901702	12	0.317	0.020	6.3
Pooled Data[4]		92	0.307	0.024	7.8

[1] Drug lot 7013362/7013352 was manufactured as (b) (4). Drug lots 9900580, 9900590, and 990060 were manufactured as (b) (4)

[2] Standard deviation
[3] Relative standard deviation
[4] Assay results from each individual sample tested were pooled.

Table 4: Summary Data: *In Vitro* Data, Flux (b) (4) (mg/cm²/hour)

Drug Product Lot (DRC/SRC)[1]	Patch Lot	Numbers Tested	Flux (b) (4) (mg/cm²/hour)		
			Mean (mg/cm²/hour)	STDEV[2]	RSD[3] (%)
7013362/7013352	9901152	44	0.112	0.009	8.2
9900580	9901152	12	0.118	0.013	11.4
9900590	9901152	12	0.121	0.007	5.7
9900600	9901152	12	0.122	0.011	8.9
7013362/7013352	9901702	12	0.122	0.005	4.3
Pooled Data[4]		92	0.116	0.010	8.8

[1] Drug lot 7013362/7013352 was manufactured as (b) (4). Drug lots 9900580, 9900590, and 990060 were manufactured as (b) (4)

[2] Standard deviation
[3] Relative standard deviation
[4] Assay results from each individual sample tested were pooled.

Table 5: Summary Data: *In Vitro* Data, Total Drug (mg)

Drug Product Lot (DRC/SRC)[1]	Patch Lot	Numbers Tested	Total Drug (mg)		
			Mean (mg)	STDEV[2]	RSD[3] (%)
7013362/7013352	9901152	44	11.28	0.73	6.5
9900580	9901152	12	11.80	0.16	1.3
9900590	9901152	12	12.33	0.73	5.9
9900600	9901152	12	12.24	1.00	8.2
7013362/7013352	9901702	12	12.20	0.54	4.4
Pooled Data[4]		92	11.73	0.90	7.6

[1] Drug lot 7013362/7013352 was manufactured as (b) (4) Drug lots 9900580, 9900590, and 990060 were manufactured as (b) (4)

[2] Standard deviation
[3] Relative standard deviation
[4] Assay results from each individual sample tested were pooled.

Table 6: Detailed *In Vitro* Data

		Flux (b) (mg/cm²/hr)						Flux (b) mg/cm²/hr)						Total Drug (mg)					
		Sample (Individual Patches)						Sample (Individual Patches)						Sample (Individual Patches)					
Drug Lot (DRC/SRC)[1]	Patch Lot	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
7013362/ 7013352	9901152	0.301	0.293	0.289	0.300	0.295	0.312	0.108	0.110	0.106	0.106	0.102	0.123	11.41	11.28	10.87	11.23	10.94	12.24
7013362/ 7013352	9901152	0.261	0.322	0.287	0.292	0.277	0.265	0.114	0.117	0.119	0.118	0.113	0.115	10.63	11.88	11.64	11.63	11.18	10.84
7013362/ 7013352	9901152	0.285	0.270	0.313	0.286	0.284	0.298	0.091	0.099	0.118	0.111	0.108	0.114	10.03	10.21	11.98	11.02	10.82	11.44
7013362/ 7013352	9901152	0.312	0.305	0.305	0.255	0.315	0.296	0.117	0.108	0.100	0.094	0.116	0.099	11.74	11.14	10.88	9.61	11.96	10.72
7013362/ 7013352	9901152	0.280	0.311	0.247	0.296	0.314	0.293	0.116	0.119	0.092	0.122	0.118	0.116	11.08	11.97	9.36	11.81	11.99	11.45
7013362/ 7013352	9901152	0.268	0.319	0.321	0.32	0.316	0.304	0.115	0.13	0.116	0.124	0.111	0.122	11.06	12.93	11.94	12.31	11.56	11.95
7013362/ 7013352	9901152	0.298	0.300	0.267	0.309	0.286	0.312	0.119	0.109	0.109	0.113	0.096	0.127	11.58	11.24	10.6	11.59	10.36	12.37
7013362/ 7013352	9901152	0.266	0.288	N/A	N/A	N/A	N/A	0.108	0.117	N/A	N/A	N/A	N/A	10.54	11.27	N/A	N/A	N/A	N/A
9900580	9901152	0.329	0.296	0.317	0.323	0.333	0.279	0.128	0.118	0.107	0.122	0.133	0.111	12.7	11.68	11.46	12.25	13.04	10.77
9900580	9901152	0.32	0.323	0.294	0.29	0.294	0.329	0.128	0.125	0.088	0.106	0.111	0.133	12.48	12.47	9.93	10.71	11.18	12.94

		Flux (b) mg/cm²/hr)						Flux (b) (mg/cm²/hr)						Total Drug (mg)					
		Sample (Individual Patches)						Sample (Individual Patches)						Sample (Individual Patches)					
Drug Lot (DRC/SRC)[1]	Patch Lot	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
9900590	9901152	0.352	0.32	0.341	0.337	0.36	0.32	0.134	0.115	0.12	0.121	0.127	0.119	13.49	11.93	12.43	12.51	13.38	12.12
9900590	9901152	0.326	0.301	0.3	0.303	0.347	0.314	0.13	0.116	0.117	0.114	0.128	0.113	12.83	11.59	11.53	11.51	13.03	11.6
9900600	9901152	0.288	0.318	0.338	0.306	0.284	0.339	0.11	0.128	0.127	0.117	0.102	0.126	11.08	12.58	12.87	11.76	10.62	12.84
9900600	9901152	0.282	0.324	0.328	0.375	0.325	0.323	0.107	0.125	0.12	0.14	0.129	0.128	10.83	12.56	12.38	14.14	12.66	12.57
7013362/ 7013352	9901702	0.314	0.313	0.357	0.352	0.316	0.319	0.123	0.113	0.134	0.122	0.122	0.126	12.27	11.68	13.49	12.74	12.23	12.47
7013362/ 7013352	9901702	0.314	0.317	0.312	0.309	0.289	0.288	0.127	0.117	0.122	0.119	0.120	0.121	12.29	11.90	12.13	11.89	11.51	11.74

[1] Drug lot 7013362/7013352 was manufactured as (b) (4) Drug lots 9900580, 9900590, and 990060 were manufactured as (b) (4)

The following proposed *in vitro* acceptance criteria were included in NDA resubmission Sections 3.2.P.5.1.3 based on a [redacted] (b) (4), using data from drug product lot 7013362/7013352 and E-Patch lot 9901152. Post NDA resubmission on July 16, 2012, an error was identified in the [redacted] (b) (4) calculation used to determine the proposed acceptance criteria [redacted] (b) (4), and total drug delivery). This calculation error has been corrected. As a result of this correction, the revised proposed acceptance criteria are included below in Table 7.

Table 7: Proposed *In Vitro* Acceptance Criteria

Acceptance Criteria Proposed in the Resubmission	Proposed Interim Acceptance Criteria
[redacted] (b) (4)	

In reviewing the applicant's proposed *in-vitro* release specifications, the following IR was sent to the applicant on December 12, 2102:

Based on data you provided, the Agency suggests that you report your interim in-vitro release acceptance criteria as per the Tabular/ USP/NF format.

The applicant responded on December14, 2012 as follows:

NuPathe accepts proposed **interim** *in vitro* release acceptance criteria as recommended by the Agency. The following acceptance criteria replace the NP101 *in vitro* Release criteria previously in Section 3.2.P.5.1.3 of the NDA.

Stage (L) *(b) (4) systems are analyzed at Level (b) (4) acceptance criteria are met if (b) (4) individual value lies outside each of the stated ranges as described below in (b) (4) Criteria Table:*

L1 Criteria

Parameters	Flux
(b) (4) mA (b) (4)	(b) (4) mg/cm²/hr
mA	mg/cm²/hr
Total Drug	ng

Stage (L) *(b) (4) If the (b) (4) criteria are not met, then (b) (4) additional systems are analyzed at Level (b) (4) The (b) (4) criteria are met if these (b) (4) conditions are met, as described below in (b) (4) Criteria Table:*

1. The average value of the (b) (4) systems lies within each of the stated ranges;

2. (b) (4) of the (b) (4) systems is more than (b) (4) percent of labeled content outside each of the stated ranges.

(b) (4) **Criteria**

Parameters	(b) (4) mA flux (b) (4) (mg/cm²/hr)	(b) (4) mA flux (b) (4) (mg/cm²/hr)	Total Drug (mg)
Average	(b) (4)		
Individual System			

Stage (L) *(b) (4) If the (b) (4) criteria are not met, then (b) (4) additional systems are tested at level (b) (4) (b) (4)). The (b) (4) criteria are met if these (b) (4) conditions are met, as described below in (b) (4) Criteria Table:*

1. *The average value of the (b) (4) systems lies within each of the stated ranges;*
2. *Not more than (NMT) (b) (4) systems are more than (b) (4) percent of labeled content outside each of the stated ranges;*
3. *(b) (4) of the (b) (4) systems is more than (b) (4) percent of labeled content outside each of the stated ranges.*

(b) (4) Criteria

Parameters	(b) (4) mA flux (b) (4) (mg/cm²/hr)	(b) (4) mA flux (b) (4) (mg/cm²/hr)	Total Drug (mg)
Average	(b) (4)		
Individual System	NMT (b) (4) systems are outside the range of (b) (4) *and* (b) (4) individual system is outside the range of (b) (4)	NMT (b) (4) systems are outside the range of (b) (4) *and* (b) (4) individual system is outside the range of (b) (4)	NMT (b) (4) systems are outside the range of (b) (4) *and* (b) (4) individual system is outside the range of (b) (4)

Reviewer's Comments:

1. The Agency recommended *in-vitro* release specifications which are accepted by the applicant, will be used (b) (4)

2. (b) (4)

3. The applicant's *in-vitro* release method appears complex and requires thorough understanding. The method is recommended for approval (b) (4) from the date of approval of the product.

4. Following approval, the reviewer plans to (b) (4) to gain a thorough understanding of the test methodology.

5. Once all the information are received and reviewed by the Agency, a decision on the *in-vitro* release method and specifications will be negotiated with the applicant.

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/s/

TAPASH K GHOSH
12/17/2012

RICHARD T LOSTRITTO
12/18/2012

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Sumatriptan Succinate
NDA:	202-278 (0031)
PRODUCT (Brand Name):	Zecuity™
DOSAGE FORM:	Iontophoretic Transdermal Patch
INDICATION:	Acute treatment of migraine attacks, with or without aura, in adults
NDA TYPE:	Response to CR
SPONSOR:	NuPathe Inc.
IND :	74,877
REVIEWER:	Michael Bewernitz, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	Division 1 (DCP 1)
OND DIVISION:	Neurology (DNP)

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

The sponsor seeks approval of NP101 (Sumatriptan Succinate) iontophoretic transdermal patch, which is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally. The proposed indication is acute treatment of migraine attacks, with or without aura, in adults. NP101 patch was designed to deliver approximately 6.5 mg sumatriptan which is similar to the dose for IMITREX STAT subcutaneous injection (up to 6 mg SC, according to the current IMITREX STAT label). The proposed dosing regimen includes application of single transdermal patch to upper arm or thigh. The maximum recommended dose that may be given in 24 hours is two patches. The second patch may be applied as early as 2 hours after initial patch activation.

The Sponsor received a complete response (CR) on August 29 2011 regarding NDA 202,278. In the letter, the clinical pharmacology team stated that the data from the bioequivalence study (NP101-013) were not acceptable for review and that the study needed to be repeated. The Sponsor repeated study NP101-013 under the name NP101-023.

The current submission contains 3 bioequivalence (BE) studies to assess the BE of 1) a modified form of the NP101 patch versus the patch that demonstrated efficacy, 2) the modified patch and the to-be-marketed version of the patch (with the pad-detection system, or PDS), 3) patches manufactured at two different locations, assess the bioequivalence of patches assembled with two different electrode manufacturing techniques, and assess the impact of heat on the PK of the modified form of the NP101 patch. Safety and tolerability data was also obtained from the studies.

For additional information, please refer to the clinical pharmacology review of NDA 202,278 dated June 29, 2011.

A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 20-2278. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view. The labeling recommendations had been conveyed to the Sponsor in the original review cycle and there are no further labeling changes at this time from a clinical pharmacology perspective.

B. Phase IV Commitment

None.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

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

Bioequivalence:

- The modified version of the patch (Gen2) that was used in both studies 023 and 026 was considered bioequivalent to the patch (Gen1) used in the Phase 3 efficacy and safety study, NP101-007 (based on results of study 023).

- Sumatriptan succinate delivered by the to-be-marketed version of the NP101 patch (with the PDS, Gen3) was considered bioequivalent to the modified version of the patch (Gen2) first used in study 023 (based on results from study 026).

- The patches manufactured in [redacted] (b) (4) are BE. The patch pharmacokinetics are not significantly affected by [redacted] (b) (4) manufacturing method (study NP101-018, [redacted] (b) (4)).

A direct comparison between the to-be-marketed patch Gen3 and Gen1 was not feasible as the supplies from the Gen1 patch were expired. Furthermore, [redacted] (b) (4) In this scenario, it seems unlikely that the differences between the modified patch (Gen2) and the Gen patch will result in significant differences in exposure.

- The pharmacokinetics of the patch are not significantly affected by heat (study NP101-024, heat supplied by a therapeutic heat wrap vs. no heat).

- Race effect on PK (Study NP101-024): the results from limited data analysis (n=5 white, and n=7 non-white), suggest that C_{max} may be greater (p=0.0354) for white subjects (26.56 ng/mL) than non-white subjects (20.49 ng/mL) receiving Gen2 patch without heat wrap. The study results did not show evidence of statistically significant differences between white and non-white population for either $AUC_{0\text{-inf}}$ or $AUC_{0\text{-last}}$.

- In addition, Sponsor demonstrated that application of the patch without subsequent activation resulted in plasma concentrations of sumatriptan that were below the limit of quantification (<0.200 ng/mL) for all PK time points (Treatment C, study NP101-024).

For additional biopharmaceutical findings, please refer to the clinical pharmacology review of NDA 202,278 dated June 29, 2011.

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II. QUESTION BASED REVIEW

A. General Attributes

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

Drug:

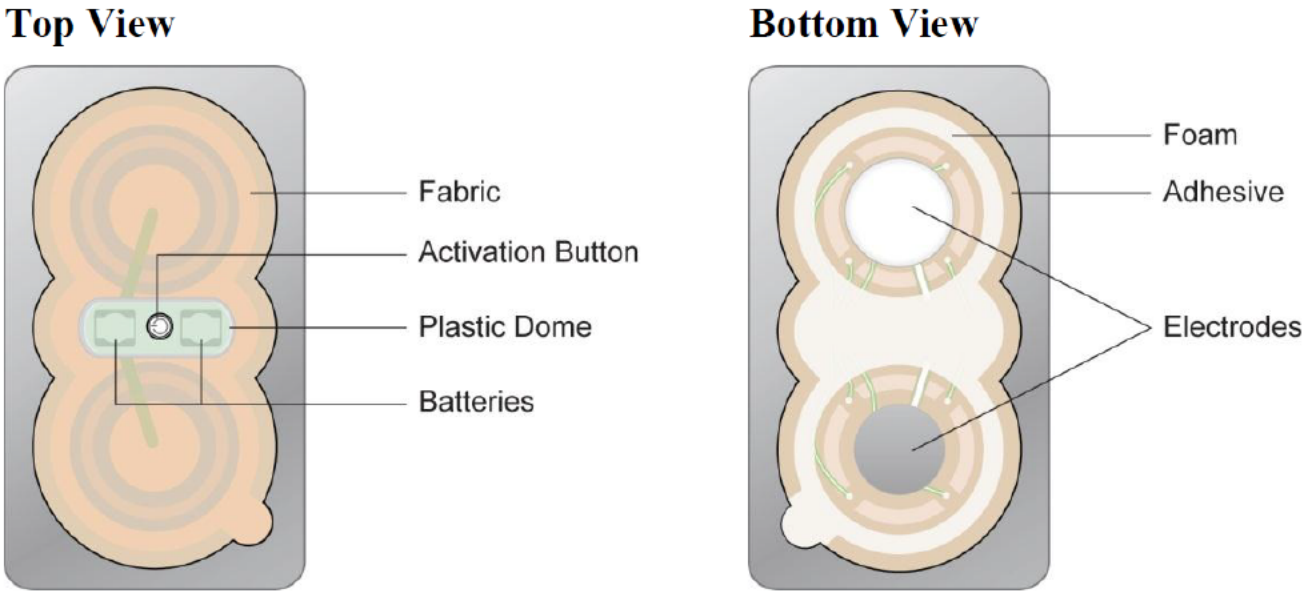
Sumatriptan succinate is a migraine-specific acute triptan with proven statistical and clinical benefit. NP101 (sumatriptan succinate) is an iontophoretic transdermal patch designed to deliver 6.5 mg sumatriptan over 4 hours of application.

Dosage Form (With Newly-added PDS):

NP101 is a disposable, single-use, transdermal patch, drug/device combination product that utilizes iontophoretic technology.

Each patch contains (b) (4) mg sumatriptan (base) as the succinate salt in an aqueous formulation. The patch, upon activation, delivers through intact skin 6.5 mg of sumatriptan over 4 hours. The technology employs the use of two electrodes with nonwoven pads placed on top of each electrode with one containing the drug compound (anode), and the other containing a salt solution (cathode). The patch is comprised of a medical grade adhesive fabric and foam and a plastic dome that contains an activation button, batteries, and electronics.

Figure 1: Top and Bottom Views of the To-Be-Marketed Version of the Patch



(source: label-draft-annotated, page 24/47)

In addition, NP101 is equipped with a pad detection system (PDS) which consists of [redacted] (b) (4). The PDS is a safety feature that prohibits patch activation if the drug or salt pad(s) are not correctly aligned or absent. The PDS was added to NP101 in order to prevent the occurrence of burns and subsequent scars, which were observed in some subjects during the Phase 3 studies in instances where patches with misaligned or absent medication pad(s) were applied and activated. An illustration of the PDS [redacted] (b) (4) is presented in Figure 2.

[redacted] (b) (4)

(*source: CSR study 026, page 20/197*)

The sponsor has researched three versions of the patch throughout the NP101 development program (each designed to deliver 6.5 mg of sumatriptan). The versions are:

- **Generation 1 (Gen1) NP101** – Patch used in NP101-007 (pivotal Phase 3 study).
- **Generation 2 (Gen2) NP101** – Generation 1 patch with the following modifications: batteries changed from (b) (4), (b) (4)
- **Generation 3 (Gen3) NP101** – To-be marketed patch with the addition of the pad detection system to the Generation 2 patch.

Indication:

NP101 (sumatriptan succinate) is indicated for the acute treatment of migraine attacks, with or without aura, in adults.

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

NP101 employs iontophoretic technology to deliver sumatriptan transdermally. Iontophoresis is a non-invasive drug delivery method that uses low electrical current to move ionized drugs across the skin to the underlying tissue and blood vessels.

The total time of drug delivery and patch operation is approximately four hours (b) (4) after which time the patch is automatically deactivated. Approximately 6.5 mg of sumatriptan is delivered to the patient.

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 a single efficacy study conducted by the sponsor to support the approval of the NP101 are summarized below:

Table 1: Pad Detection System Test Points (TP)

Type of Study and Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	n	Healthy or Patients
NP101-007 Efficacy study.	Evaluate the efficacy and safety of NP101 for the treatment of acute migraine.	Randomized, single-dose, parallel-group, double-blind, placebo-controlled, multicenter study.	NP101 patch applied to upper arm with a 4 h wear time ((b) (4) mA*min). Control treatment: placebo patch containing a salt formation.	469	Healthy and acute migraine patients.
NP101- 018. BE study	Assess the BE of NP101 drug product manufactured at two different sites, evaluate PK of NP101 patches with electrodes having (b) (4)	Open-label, randomized, singledose, 4-way crossover study. (up to four treatment periods)	NP101 patch Treatment A: drug product made by (b) (4) Treatment B: drug product made by (b) (4) Treatment C: E-Patch with (b) (4) g Treatment D: E-Patch with (b) (4)	30	Healthy
NP101- 023. BE study. (repeat of Study NP101- 013)	Assess the BE of the NP101 patch used in Study NP101- 007 and a modified NP101 patch compared to oral Imitrex®.	Open-label, randomized, singledose, 3-way crossover study vs. sumatriptan oral tablet (Imitrex®). (up to three treatment periods)	NP101 patch Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Modified patch (NP101B) Treatment C: 100 mg oral sumatriptan tablet.	32	Healthy
NP101- 024. Relative BA study.	Evaluate the effect of local heat on PK of the NP101 patch; to assess patch conformability	Open label, single center, single-dose 2-way cross-over study conducted in healthy adultvolunteers. Treatments A and B were randomized. (up to three treatment periods)	NP101 patch Treatments A and B: 2- way crossover (2 patch applications to upper arm) Treatment C: patch applied to forearm and not activated.	12	Healthy
NP101- 026. BE study.	Assess the BE of the modified NP101 patch used in Study NP101-023 and the final proposed commercial NP101 patch with the PDS.	Open-label, randomized, singledose, 2-waycrossover study. Treatments A and B were randomized. (up to three treatment periods)	NP101 patch Treatment A: Modified patch used in Study NP101-023 Treatment B: Enhanced patch with PDS Treatment C: Same patch as Treatment B but applied with pads misaligned or absent to validate PDS.	32	Healthy

(tabular listing of all clinical studies, page 2/9-7/9)

C. Intrinsic Factors

Effect of Race on NP101 Pharmacokinetics

Sponsor performed a sub-group analysis to assess the effect of race on pharmacokinetics in both treatment groups (study NP101-024). This study utilized the Gen2 patch. The results are shown in the Table 2.

Table 2: Pharmacokinetic Parameters Summary by Race For Sub-Group Analysis Conducted on Study NP101-024 Subjects.

				Non-White vs. White	
Parameter	Heat Status	Race Group	Geometric Mean (95%CI)	Ratio of Geometric Means (95%CI)	p-value
C_{max}, ng/mL	Patch without heat	White	26.56 (22.15, 31.85)	0.77 (0.61, 0.98)	0.0354
		Non-White	20.49 (17.58, 23.89)		
	Patch with heat	White	23.47 (19.43, 28.34)	0.82 (0.64, 1.05)	0.1068
		Non-White	19.28 (16.44, 22.62)		
$AUC_{0\text{-last}}$, hr*ng/mL	Patch without heat	White	129.45 (104.41, 160.50)	0.82 (0.62, 1.09)	0.1555
		Non-White	106.61 (88.90, 127.85)		
	Patch with heat	White	114.20 (94.83, 137.53)	0.89 (0.70, 1.13)	0.3088
		Non-White	101.58 (86.81, 118.86)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Patch without heat	White	130.68 (106.22, 160.79)	0.84 (0.64, 1.10)	0.1818
		Non-White	109.73 (92.09, 130.74)		
	Patch with heat	White	115.54 (96.04, 139.00)	0.90 (0.71, 1.15)	0.3526
		Non-White	103.93 (88.90, 121.50)		

All estimates derived from a 1-way ANCOVA model of race effect on log transformed parameter value. There were n=5 white subjects and n=7 non-white subjects.

(CSR – Study NP101-024, page 53/136)

Based on analysis of limited information (n=5 white subjects and n=7 non-white subjects), analyses suggest that C_{max} may be greater (p=0.0354) for white subject (26.56 ng/mL) versus non-white subjects (20.49 ng/mL) receiving Treatment A (patch without heat wrap). However, this increase in C_{max} is not expected to produce a clinically significant safety concern considering that the C_{max} of the approved Imitrex 100 mg oral tablet is 51 ng/mL. The analysis suggests that there is no significant difference between white and non-white population for either $AUC_{0\text{-inf}}$ or $AUC_{0\text{-last}}$.

For additional information regarding intrinsic factors, please refer to the clinical pharmacology review of NDA 202,278 dated June 29, 2011.

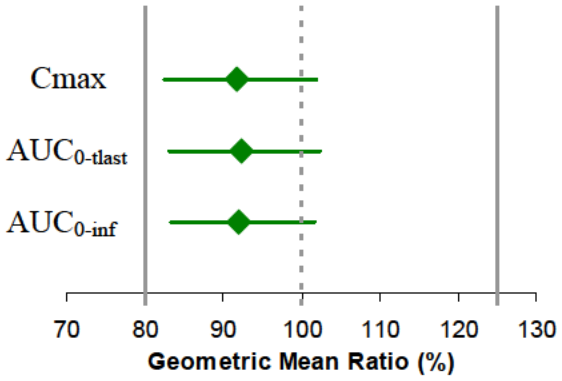
D. Extrinsic Factors

Does local heat affect pharmacokinetics?

In Study NP101-024, the Sponsor assessed the effect of local heat on the pharmacokinetics of the Gen2 patch in n=12 health adult subjects. Local heat may affect the exposure of transdermal drug delivery

systems that rely on passive diffusion. The Sponsor assessed the bioequivalence of the Gen2 patch with a therapeutic heat wrap applied for the entire 4-hour treatment duration with the Gen2 patch without external heat applied. The patch applied with the therapeutic heat wrap was bioequivalent to the patch without external heat according to all exposure metrics as is shown in the figure below. The GMR (90% CI) for C_{max} was 91.7 (82.5, 101.9) %. The GMR (90% CI) for $AUC_{0\text{-tlast}}$ was 92.3 (83.1, 102.4) %. The GMR (90% CI) for $AUC_{0\text{-inf}}$ was 92.0 (83.3, 101.7) %. The local heat has no significant impact on the pharmacokinetics of the Gen2 patch.

Figure 3: Bioequivalence Assessment of the Gen2 Patch With Heat Compared to the Gen2 Patch Without Heat (Study NP101-024).



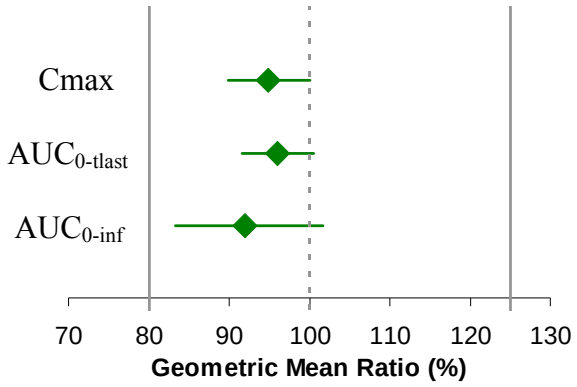
For additional information regarding extrinsic factors, please refer to the clinical pharmacology review of NDA 202,278 dated June 29, 2011.

E. General Biopharmaceutics

Is the NP101 patch (Gen1) used in Study NP101-007 (efficacy study) bioequivalent to the modified NP101 patch (Gen2) used in Study NP101-023?

Study NP101-023 assessed bioequivalence between the NP101 patch (Gen1) version previously used in the NP101-007 study (a Phase 3 study that demonstrated the efficacy and safety of NP101) and the NP101 patch version with modifications (Gen2), in n=32 healthy adult volunteers. The modifications include changing the (b) (4) battery to the (b) (4) battery, (b) (4) [redacted]. The Gen1 patch is bioequivalent to the Gen2 patch according to all three exposure metrics as is shown in the figure below. The GMR (90% CI) for C_{max} was 94.8 (89.9, 100.0) %. The GMR (90% CI) for $AUC_{0\text{-tlast}}$ was 96.0 (91.6, 100.5) %. The GMR (90% CI) for $AUC_{0\text{-inf}}$ was 96.0 (91.7, 100.4) %.

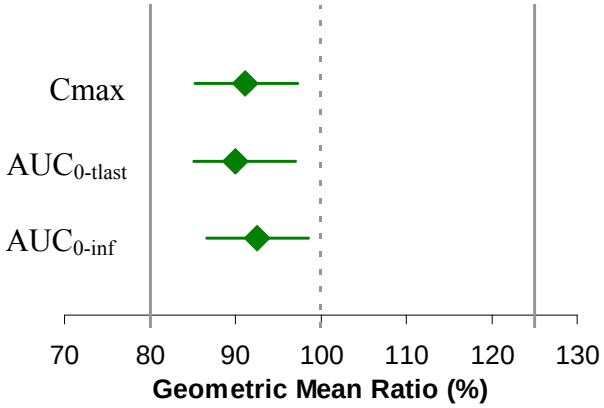
Figure 4: Bioequivalence Assessment of the NP101 Patch (Gen1) Used in Study NP101-007 (Efficacy Study) Compared to the Modified NP101 Patch (Gen2).



Is the modified NP101 patch used in Study NP101-023 (Gen2) bioequivalent to the final proposed commercial NP101 patch with the PDS (Gen3)?

Study NP101-026 assessed the bioequivalence of the modified NP101 patch used in study NP101-023 (Gen2) with the to-be-marketed version (with the PDS, Gen3) in n=31 healthy adult volunteers. The analysis results demonstrate bioequivalence of Gen2 patch with the to-be-marketed Gen3 patch as is shown in the figure below. The GMR (90% CI) for C_{max} was 91.1 (85.3-97.3) %. The GMR (90% CI) for $AUC_{0\text{-tlast}}$ was 90.9 (85.2- 97.0) %. The GMR (90% CI) for $AUC_{0\text{-inf}}$ was 92.5 (86.7-98.6) %.

Figure 5: Bioequivalence Assessment for the modified NP101 patch used in Study NP101-023 (Gen2) versus the final proposed commercial NP101 patch (Gen3) with the PDS.



Is the final proposed commercial NP101 patch (Gen3) with the PDS bioequivalent to the patch (Gen2) used in Study NP101-007 (efficacy study)?

The sponsor utilized a bioequivalence "bridging" approach in order to claim bioequivalence between the final proposed commercial NP101 patch with the PDS (Gen3) to the patch (Gen1) used in Study NP101-007 (efficacy study).In other words, if patch Gen2 is bioequivalent to patch Gen1, and patch Gen3 is bioequivalent to patch Gen2, then the Sponsor concludes that patch Gen3 is bioequivalent to patch Gen1.

Ideally, a BE study should be conducted to assess BE between patches Gen1 used in the pivotal study and the to-be-marketed patches Gen3. However, the Sponsor stated that a direct comparison between patch "Gen3" and "Gen1" was not feasible as the supplies from the Gen1 patch were expired. Furthermore, the PDS in the Gen3 patch [redacted] (b) (4) [redacted]. In this scenario, it seems unlikely that the differences between the Gen2 and Gen3 patches will result in significant differences in exposure.

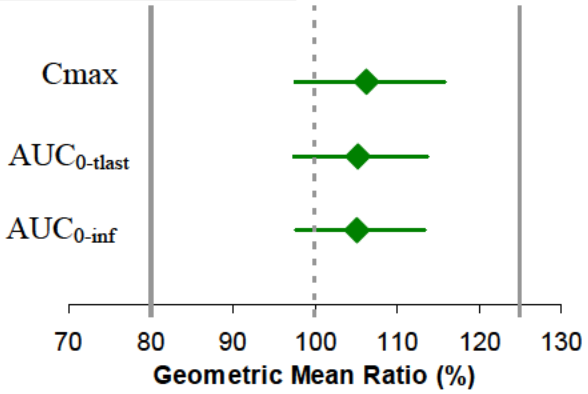
Also, the difference in exposures is not expected to be clinically significant. While the exposures obtained from the to-be-marketed Gen3 patch are lower ($AUC_{0\text{-}inf}$ was 109.73 hr*ng/mL and C_{max} was 21.89 ng/mL in study NP101-026) than the exposures obtain from the Gen1 patch ($AUC_{0\text{-}inf}$ was 128.31 hr*ng/mL and C_{max} was 24.01 ng/mL), the Gen3 patch produces exposures which are similar to the approved IMITREX STAT dosage form. The approved IMITREX STAT (6 mg subcutaneous) product produces an $AUC_{0\text{-}inf}$ of 105.0 hr*ng/mL and the Gen3 version of the patch produces an $AUC_{0\text{-}inf}$ of 109.73 hr*ng/mL. For the reasons above, it reasonable accept the claim of bioequivalence between the Gen1 patch and Gen3 patch

Does manufacturing location affect pharmacokinetics?

Sponsor reports that prior to study NP101-018, the drug product for NP101 was manufactured at the [redacted] (b) (4) The Sponsor conducted the NP101-018 study to determine drug product bioequivalence between the [redacted] (b) (4) [redacted] in order to qualify two viable drug product manufacturing facilities for NP101.

In study NP101-018, the bioequivalence of the patch manufactured at a site in the [redacted] (b) (4) versus a patch assessed in [redacted] (b) (4) was assessed in n=30 healthy adult volunteers. This study utilizes the modified version of the patch (Gen2). The patch assembled in the [redacted] (b) (4) is equivalent to the patch assembled in [redacted] (b) (4) as is shown in the figure below. The GMR (90% CI) for C_{max} was 106.3 (97.6-115.8) %. The GMR (90% CI) for $AUC_{0\text{-}tlast}$ was 105.3 (97.5-113.7) %. The GMR (90% CI) for $AUC_{0\text{-}inf}$ was 105.2 (97.7-113.3) %.

Figure 6: Bioequivalence Assessment for Gen2 Patches Assembled using Parts Manufactured at Different Locations: [redacted] (b) (4).

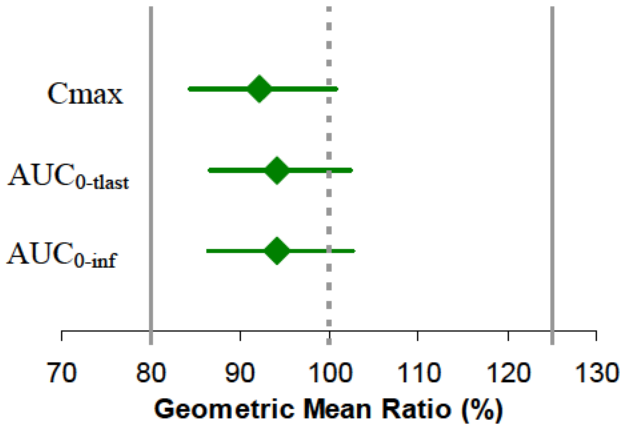


In addition, study NP101-018 also assessed the bioequivalence of the Gen2 patch which utilized the [redacted] (b) (4) n=30 healthy adult volunteers. The Sponsor makes the following statement regarding the rationale for the manufacturing bioequivalence comparison:

"*To date, NP101 supplies have used* [redacted] (b) (4) *(source: study 018 CSR, page 22/269)*

The Gen2 patch assembled with the [redacted] (b) (4) is bioequivalent to the patch which utilized the [redacted] (b) (4) as is demonstrated in the figure below. The GMR (90% CI) for C_{max} was 92.2 (84.4, 100.7) %. The GMR (90% CI) for $AUC_{0\text{-tlast}}$ was 94.2 (86.7, 102.5) %. The GMR (90% CI) for $AUC_{0\text{-inf}}$ was 94.2 (86.4, 102.7) %.

Figure 7: Bioequivalence Assessment for Gen2 Patches With Different Electrode Manufacturing Techniques.



F. Analytical

Have the analytical methods been sufficiently validated?

Yes.

For additional information regarding analytical methods validation, please refer to the clinical pharmacology review of NDA 202,278 dated June 29, 2011.

III. Labeling Recommendations

There are no labeling recommendations at this time.

APPEARS THIS WAY ON ORIGINAL

IV. Appendix

A Individual Study Synopsis

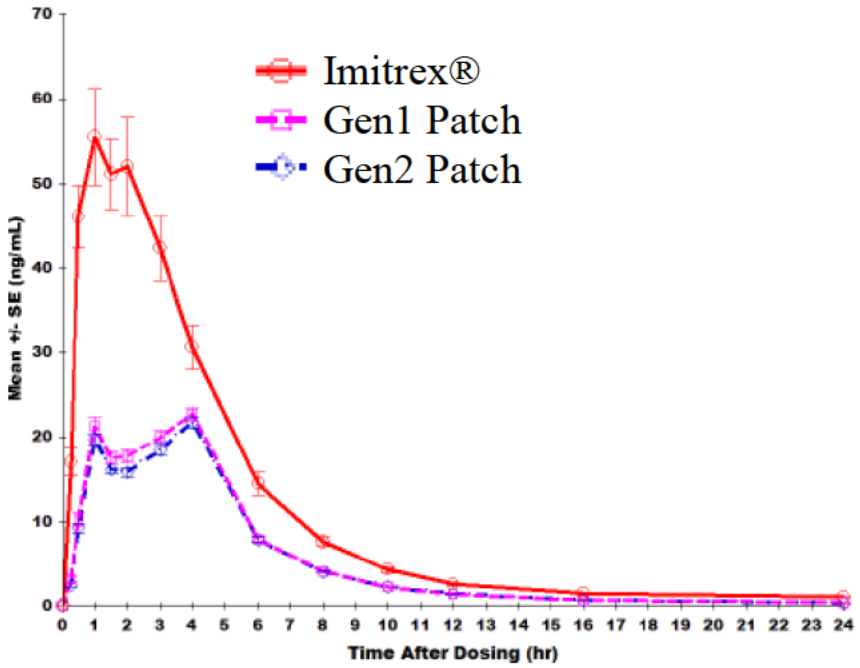
NP101-023: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioequivalence of Two NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments With an Oral Formulation of Imitrex® in Healthy Volunteers.

Objectives	1. to evaluate the bioequivalence between NP101 patches previously used in the NP101-007 study (a Phase 3 study that demonstrated the efficacy and safety of NP101) and NP101 patches with minor modifications, in healthy adult volunteers 2. to compare the pharmacokinetics of NP101 with the currently approved oral formulation of Imitrex® in healthy adult volunteers.
Study Design	This was a Phase I, single center, open label, randomized, single-dose, three-way crossover study. Three treatments were administered according to a randomized sequence in Periods 1 through 3: 1. Treatment A: "Generation 1" (Gen1) patch previously used in the NP101-007 study applied to the upper arm and left in place for 4 hours. The "Tx A" patch is designed to deliver ≈6.5 mg of sumatriptan (utilizing [redacted] (b) (4), for a total of [redacted] (b) (4) mA*minutes). 2. Treatment B: "Generation 2" (Gen2) Patch for long term studies and commercial use (*modifications from the* [redacted] (b) (4)), applied to the upper arm and left in place for 4 hours. The "Tx B" patch is designed to deliver ≈6.5 mg of sumatriptan (utilizing [redacted] (b) (4), for a total of [redacted] (b) (4) mA*minutes). 3. Treatment C: Imitrex® (100 mg sumatriptan succinate oral tablet).
Study Population	n=36 healthy adult volunteers were planned for enrollment. 33 subjects were enrolled. All 33 subjects were included in safety analysis, and 32 subjects were included in PK Evaluable Population. Age(years): 20 – 62, mean 30.6; Weight(kg): 46.9 – 90, mean 68.0; Sex: Male (56.3 %); Race: Majority non-hispanic (97 %)
PK Sampling	Blood samples were obtained at the following times: pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose.
Bioanalytical Method	

Sumatriptan Bioanalytical Method	
Method	HPLC with MS/MS
Internal Standard	sumatriptan-d_6, [redacted] (b) (4)
LOQ (ng/mL)	0.2
Calibration Concentrations Assay Range (ng/mL)	0.2, 0.4, 0.7, 2.5, 8, 30, 80, 100 0.200 to 100
Quality Controls (ng/mL)	0.5, 1.25, 4.5, 15, 75
Accuracy (% difference from theoretical)	-1.19 – 1.30 %
Precision (%CV)	2.94 – 6.45 %

PK Assessments	The Sponsor estimated the following PK parameters from the sumatriptan plasma concentration-time data: 1) area under the plasma concentration-time curve from time zero to the last quantifiable concentration post-dose (***AUC0–last***), 2) area under the plasma concentration-time curve from time zero to infinity (***AUC0-inf***), 3) maximum plasma concentration after dosing (***Cmax***), 4) time to maximum plasma concentration (***Tmax***), 5) first order terminal elimination rate constant (***λz***), and 6) terminal half-life (***t½***).
Safety Endpoints	1. Adverse events (AEs). 2. 12-lead electrocardiogram (ECG) recordings at Screening, 4.5 hours post-dose on Day 1 of each treatment period, and at End of Study visit 3. Vital signs pre-dose and 4.5 hours post-dose on Day 1 of each treatment period. 4. Findings from the patch adherence evaluation and skin irritation examinations following NP101 patch Treatments A and B.
PK Results	

Figure 8. Mean (+/-SD) Sumatriptan Plasma Concentration Versus Time for all Treatments



Bioequivalence Comparison: Gen2 Patch vs. Gen1 Patch

The PK results support bioequivalence between Gen1 patch (used in pivotal efficacy trial 007) and Gen2 patch (patch with modifications) for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$).

Bioequivalence Comparison: Gen1 Patch vs. Oral Imitrex

The PK results do not support bioequivalence between Gen1 (patch used in pivotal efficacy trial 007) and Imitrex® (100 mg sumatriptan succinate oral tablet) for any of the exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$).

Bioequivalence Comparison: Gen2 Patch vs. Oral Imitrex

The PK results do not support bioequivalence between Gen2 patch (patch with modifications) and Imitrex® (100 mg sumatriptan succinate oral tablet) for any of the exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$).

Table 3: Results of Bioequivalence Computations

Parameter	Treatment	N	Geometric Mean (90% CI)	Comparison	Ratio (%) (90% CI)
C_{max}, ng/mL	Gen1	32	23.3 (22.0, 24.8)	Gen2 vs Gen1	94.8 (89.9, 100.0)
	Gen2	32	22.1 (20.8, 23.5)		
$AUC_{0\text{-last}}$, hr*ng/mL	Gen1	32	122.8 (116.1, 129.8)	Gen2 vs Gen1	96.0 (91.6, 100.5)
	Gen2	32	117.8 (111.4, 124.6)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Gen1	32	125.0 (118.2, 132.1)	Gen2 vs Gen1	96.0 (91.7, 100.4)
	Gen2	32	119.9 (113.4, 126.8)		
C_{max}, ng/mL	Gen1	32	23.3 (21.4, 25.3)	Gen1 vs Imitrex®	39.2 (35.4, 43.4)
	Imitrex®	32	59.4 (54.6, 64.7)		
$AUC_{0\text{-last}}$, hr*ng/mL	Gen1	32	122.6 (112.5, 133.6)	Gen1 vs Imitrex®	48.0 (43.1, 53.5)
	Imitrex®	32	255.4 (234.4, 278.3)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Gen1	32	124.9 (114.7, 135.9)	Gen1 vs Imitrex®	47.4 (42.6, 52.8)
	Imitrex®	32	263.4 (242.0, 286.7)		
C_{max}, ng/mL	Gen2	32	22.1 (20.3, 24.0)	Gen2 vs Imitrex®	37.1 (33.4, 41.1)
	Imitrex®	32	59.6 (54.8, 64.8)		
$AUC_{0\text{-last}}$, hr*ng/mL	Gen2	32	117.7 (108.1, 128.2)	Gen2 vs Imitrex®	45.9 (41.5, 50.8)
	Imitrex®	32	256.3 (235.3, 279.1)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Gen2	32	119.8 (110.1, 130.4)	Gen2 vs Imitrex®	45.3 (41.0, 50.2)
	Imitrex®	32	264.2 (242.8, 287.5)		

Table 4. Summary PK parameters of Sumatriptan (PK Evaluable Population, n=32)

Parameter	Gen1 Patch	Gen2 Patch	Imitrex®
C_{max} (ng/mL), mean(sd)	24.01 (5.752)	22.52 (3.793)	64.17 (31.507)
T_{max}, median (min-max)	4.00 (1.00, 4.03)	4.00 (1.00, 4.03)	1.00 (0.50, 3.00)
$AUC_{0\text{-inf}}$ (hr*ng/mL), mean(sd)	128.31 (27.007)	122.03 (20.025)	310.22 (138.203)
$AUC_{0\text{-last}}$ (hr*ng/mL) , mean(sd)	126.09 (26.875)	119.90 (19.612)	274.54 (123.449)
$t_{½}$ (hr), median (min-max)	3.15 (2.20, 6.22)	3.22 (2.16, 6.70)	3.57 (2.49, 10.34)

Safety Result	Nine (27.3%) subjects experienced a total of 14 treatment emergent AEs with Gen1 patch, five (15.2%) subjects experienced seven treatment emergent AEs with Gen2 patch, and three (9.1%) subjects experienced a total of three treatment emergent AEs with Imitrex®. All adverse events were mild or moderate in severity. There were no deaths, serious adverse events, or discontinuations due to adverse events. The most frequently reported AEs following Gen1 and Gen2 patches were headache (12.1% and 6.1%, respectively) and application site conditions (application site cold feeling, application site pain, application site paraesthesia, application site pruritus, and application site reaction). Application site AEs were reported for three (9.1%) subjects following Gen1 patch and three (9.1%) subjects following Gen2 patch. All of these events were mild in severity and all resolved within one day.

	Sponsor reports that there were no clinically significant changes in vital signs or clinically significant ECG findings observed during study.
Conclusion	All three exposure metrics (AUC_{0-last}, $AUC0_{-inf}$ and C_{max}) satisfied the bioequivalence criteria for the comparison between Gen1 patch (used in pivotal efficacy trial 007) and Gen2 patch (with modifications). Therefore, bioequivalence between Gen1 patch and Gen2 patch is established. The C_{max}, AUC_{0-last}, $AUC0_{-inf}$ for the Gen1 patch and Gen1 patch were estimated to be 37-39%, 46-48%, and 45-47% of the approved oral formulation of Imitrex®, respectively.

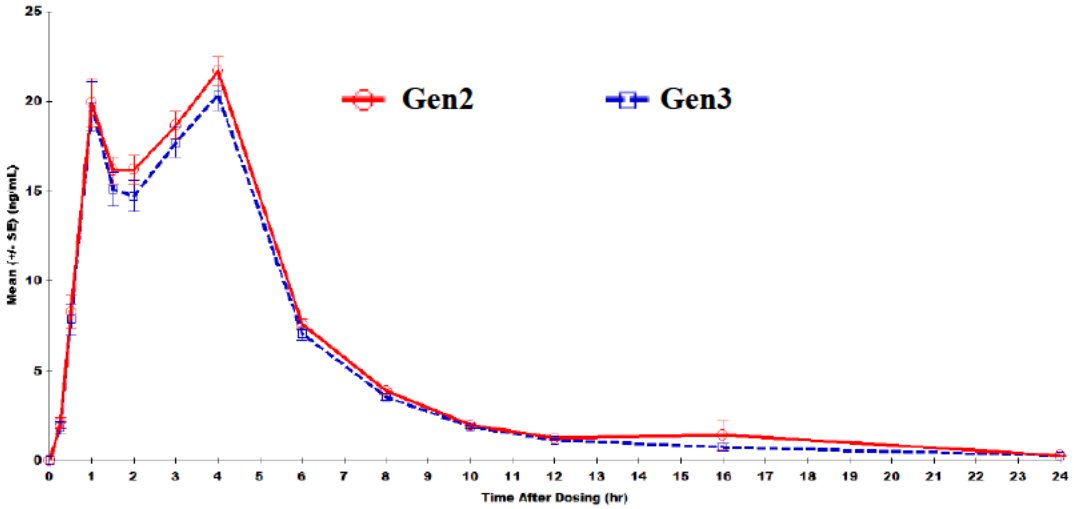
NP101-026: A Phase 1, Single Center, Open Label, Randomized, Single-Dose, Two-Way Crossover Study to Compare the Pharmacokinetics and Bioequivalence of Two NP101 (Sumatriptan Iontophoretic Transdermal System) Patches and Validation Testing of the NP101 Pad Detection System.

Objectives	1. To compare the bioequivalence between NP101 patches previously used in the NP101-023 study (previously demonstrated to be bioequivalent to patches used in the NP101-007 Phase 3 study that demonstrated the efficacy and safety of NP101) and NP101 patches with modifications, in healthy adult volunteers; 2. To validate that the electronic patch pad detection system (PDS) prohibited the patches from entering active dosing mode when medication pads were misaligned or absent.
Study Design	This was a Phase 1, single center, open label, randomized, single-dose, two-way crossover study conducted in healthy adult volunteers 4. Treatment A: "Generation 2" (Gen2) patch. The "modified" patch first used in study 023. 5. Treatment B: "Generation 3" (Gen3) patch. The to-be-marketed final version of the patch. Similar to Gen2 patch, but with the addition of the pad detection system (PDS)*. 6. Treatment C: Same as Gen3 but with misaligned and absent pads ($Gen3_{no\ pads}$). This arm is included in order to assess the PDS functionality. **The PDS is comprised of* [redacted] (b) (4) *to detect misaligned or absent drug or salt pads. The PDS is designed to prohibit the patch from turning on (entering active dosing mode) when it detects that no pads are present or the pads are misaligned.*
Study Population	n=32 healthy adult volunteers were enrolled. 31 subjects completed Gen2 patch arm, 32 completed Gen3 patch arm, and 32 completed the $Gen3_{no\ pads}$ patch arm. Age(years): 18–64, mean 32.3; Weight(kg): 51–86, mean 67.2; Sex: Male (48.4%); Race: Majority non-hispanic (87.1 %)
PK Sampling	Blood samples were obtained at the following times: pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose.
Bioanalytical Method	**Sumatriptan Bioanalytical Method** Method: HPLC with MS/MS Internal Standard: Sumatriptan-d_6, [redacted] (b) (4)

LOQ (ng/mL)	0.2
Calibration Concentrations	0.2, 0.4, 0.7, 2.5, 8, 30, 80, and 100
Assay Range (ng/mL)	0.200 to 100
Quality Controls (ng/mL)	0.5, 1.25, 4.5, 15, and 75
Accuracy (% difference from theoretical)	0.248 – 2.38%
Precision (%CV)	2.29 - 3.25%

PK Assessments	The Sponsor estimated the following PK parameters from the sumatriptan plasma concentration-time data: 1) area under the plasma concentration-time curve from time zero to the last quantifiable concentration post-dose (***AUC0–last***), 2) area under the plasma concentration-time curve from time zero to infinity (***AUC0-inf***), 3) maximum observed plasma concentration after dosing (***Cmax***), 4) time to maximum plasma concentration (***Tmax***), 5) first order terminal elimination rate constant (***λz***), and 6) terminal half-life (***t½***).
Safety Endpoints	1. Adverse events (AEs). 2. 12-lead electrocardiogram (ECG) findings at Screening, 4-5 hours post-dose on Day 1 for Gen2 and Gen3, and at End of Study visit (if clinically indicated). 3. Vital signs pre-dose and 4.5 hours post-dose for Gen2 and Gen3. 4. Skin irritation examinations at pre-dose and at 4 hours (immediately following patch removal), 24, 48, and 72 hours following patch removal for Gen2 and Gen3. Skin irritation examinations were not collected post-patch application for $Gen3_{no\ pads}$.
PK Results	

Figure 9. Mean (+/-SD) Sumatriptan Plasma Concentration Versus Time for Gen2 and Gen3



Relative Bioavailability Comparison: Gen3 Patch vs. Gen2 Patch: The 90% confidence intervals of the geometric mean ratios fall entirely within the 80% to 125% boundary for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$). Thus, the bioequivalence criteria is met for all three exposure metrics.

Table 5: Results of Bioequivalence Computations

Parameter	Treatment	N	Geometric Mean (90% CI)	Comparison	Ratio (%) (90% CI)
C_{max}, ng/mL	Gen2	31	23.2 (21.6, 24.9)	Gen3 vs Gen2	91.1 (85.3, 97.3)
	Gen3	31	21.1 (19.6, 22.7)		
$AUC_{0\text{-last}}$, hr*ng/mL	Gen2	31	116.7 (108.1, 126.0)	Gen3 vs Gen2	90.9 (85.2, 97.0)
	Gen3	31	106.1 (98.3, 114.5)		
$AUC_{0\text{-inf}}$, hr*ng/mL	Gen2	31	117.6 (108.5, 127.4)	Gen3 vs Gen2	92.5 (86.7, 98.6)
	Gen3	31	108.7 (100.4, 117.7)		

All estimates derived from the ANOVA model on natural logarithmic transformed data with subject (sequence) as a random effect.

Table 6. Summary PK parameters of Sumatriptan (PK Evaluable Population, n=31)

Parameter	Gen2 Patch	Gen3 Patch
C_{max} (ng/mL), mean(sd)	23.61 (4.56)	21.89 (6.15)
T_{max}, median (min-max)	3.00 (1.00-16.0)	1.08 (0.97-4.00)
$AUC_{0\text{-inf}}$ (hr*ng/mL), mean(sd)	121.21 (24.676)	109.73 (26.100)
$AUC_{0\text{-last}}$ (hr*ng/mL), mean(sd)	119.10 (23.842)	110.22 (28.723)
$t_{½}$ (hr), median (min-max)	3.00 (1.62-4.98)	2.86 (1.55-4.71)

PDS Functionality Assessment ($Gen3_{no\ pads}$): The Sponsor's clinical results demonstrate 100% accuracy of the PDS to prohibit the patch from turning on (entering active dosing mode) when medication pads were misaligned or absent.

Safety Result

Treatment	Sponsor's safety findings
Gen2	One (3.2%) subject experienced one treatment emergent AE with the Gen2 patch
Gen3	four (12.5%) subjects experienced six treatment emergent AEs with the Gen3 patch
$Gen3_{no\ pads}$	No treatment-emergent AEs were reported for the $Gen3_{no\ pads}$ patch.

All adverse events were mild in severity. There were no deaths, serious adverse events, or discontinuations due to adverse events.

The most frequently reported AEs were application site conditions including:

- application site pain (two subjects),
- application site reaction (three subjects)
- application site rash (one subject)

All of these events were mild in severity and all resolved within one day.

Skin irritation scores were all ≤ 2 following patch administration, i.e., only minimal (score 1) or moderate (score 2) erythema. No subject had moderate erythema at 24 hours post patch

	application, and no erythema was observed at 72 hours post-dose. Sponsor reports that there were no clinically meaningful differences between the two patch treatments with respect to skin irritation scores.
Conclusion	The bioequivalence criteria for the Gen3 patch vs. Gen2 patch comparison is met for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$).

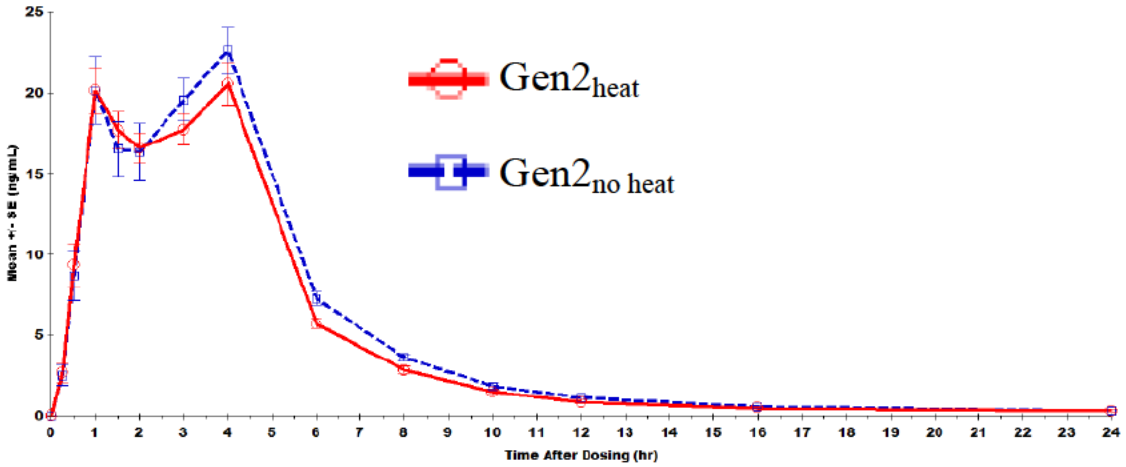
NP101-024: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Two-Way Crossover Study to Compare the Pharmacokinetics of Two NP101 Patch (Sumatriptan Iontophoretic Transdermal System) Applications With and Without Controlled Heat, and Evaluate Pharmacokinetics of a Non-activated Patch During Conformability Testing, in Healthy Volunteers

Objectives	1. to evaluate the pharmacokinetic effect of local heat administration on the NP101 patch in healthy adult volunteers, 2. to perform conformability testing to comply with IEC 60601-2-2 requirements, and 3. to evaluate the pharmacokinetics of a non-activated patch during conformability testing.
Study Design	This was a Phase I, single center, open label, single-dose study conducted in healthy adult volunteers. Periods 1 and 2 (Treatments A and B) were randomized. Period 3 (Treatment C) was not randomized. 1. Treatment A: "Generation 2" patch without local heat ($Gen2_{no\ heat}$). The Gen2 patch is the modified patch from study 023 (*modifications include* [redacted] (b) (4), applied to the upper arm and left in place for 4 hours. The patch is designed to deliver ≈6.5 mg of sumatriptan (utilizing [redacted] (b) (4) for a total of [redacted] (b) (4) mA*minutes). 2. Treatment B: "Generation 2" patch with local heat ($Gen2_{heat}$). Same as Treatment A but with a heat wrap applied around the patch for the entire 4 hour duration. 3. Treatment C: "Generation 2" patch that is applied but never activated ($Gen2_{deactivated}$). Same as Treatment A, but the patch is never activated.
Study Population	n=12 healthy adult volunteers Age(years): 18–58, mean 30.8; Weight(kg): 52.1–86.2, mean 67.3; Sex: Male (50 %); Race: Majority non-hispanic (100 %)
PK Sampling	Blood samples were obtained at the following times: • Periods 1 and 2: Pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. • Period 3: Pre-dose (within 15 minutes prior to dosing) and at 0.50, 1, 4, and 6 hrs post-dose.
Bioanalytical Method	

Sumatriptan Bioanalytical Method	
Method	HPLC with MS/MS
Internal Standard	sumatriptan-d_6, [redacted] (b) (4)
LLOQ (ng/mL)	0.2
Calibration Concentrations	0.2, 0.4, 0.7, 2.5, 8, 30, 80, and 100
Assay Range (ng/mL)	0.200 to 100
Quality Controls (ng/mL)	0.5, 1.25, 4.5, 15, and 75
Accuracy (% difference from theoretical)	-1.53% - 3.81%
Precision (%CV)	2.17% - 7.26%

PK Assessments	The Sponsor estimated the following PK parameters from the sumatriptan plasma concentration-time data: 1) area under the plasma concentration-time curve from time zero to the last quantifiable concentration post-dose (***AUC0–last***), 2) area under the plasma concentration-time curve from time zero to infinity (***AUC0-inf***), 3) maximum plasma concentration after dosing (***Cmax***), 4) time to maximum plasma concentration (***Tmax***), 5) first order terminal elimination rate constant (***λz***), and 6) terminal half-life (***t½***).
Safety Endpoints	1. Adverse events (AEs). 2. 12-lead electrocardiogram (ECG) findings at Screening, 4.5 hours post-dose on Day 1 of each treatment period for $Gen2_{no\ heat}$ patch and $Gen2_{heat}$ patch and at End of Study visit (if clinically indicated). 3. Vital signs at Screening, Day -1, and pre-dose and 4.5 hours post-dose on Day 1 of each treatment period for $Gen2_{no\ heat}$ and $Gen2_{heat}$. 4. Findings from the patch adherence evaluation ($Gen2_{no\ heat}$ and ($Gen2_{deactivated}$) and skin irritation examinations ($Gen2_{no\ heat}$ and $Gen2_{heat}$).
PK Results	

Figure 10. Mean (+/-SD) Sumatriptan Plasma Concentration Versus Time for $Gen2_{no\ heat}$ patch and $Gen2_{heat}$ patch



Bioequivalence Comparison: $Gen2_{heat}$ Patch vs. $Gen2_{no\ heat}$ Patch

The PK results support bioequivalence between $Gen2_{no\ heat}$ (patch with modifications without heat) and $Gen2_{heat}$ (patch with modifications with heat) for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$).

Table 7: Results of Bioequivalence Computations

Parameter	Treatment	N	Geometric Mean (90% CI)	Comparison	Ratio (%) (90% CI)
C_{max}, ng/mL	$Gen2_{no\ heat}$	12	22.8 (20.4, 25.6)	$Gen2_{heat}$ vs. $Gen2_{no\ heat}$	91.7 (82.5, 101.9)
	$Gen2_{heat}$	12	20.9 (18.7, 23.4)		
$AUC_{0\text{-last}}$, hr*ng/mL	$Gen2_{no\ heat}$	12	115.6 (103.4, 129.2)	$Gen2_{heat}$ vs. $Gen2_{no\ heat}$	92.3 (83.1, 102.4)
	$Gen2_{heat}$	12	106.7 (95.4, 119.2)		
$AUC_{0\text{-inf}}$, hr*ng/mL	$Gen2_{no\ heat}$	12	118.0 (106.0, 131.4)	$Gen2_{heat}$ vs. $Gen2_{no\ heat}$	92.0 (83.3, 101.7)
	$Gen2_{heat}$	12	108.6 (97.6, 120.9)		

Table 8. Summary PK parameters of Sumatriptan (PK Evaluable Population, n=12)

Parameter	$Gen2_{no\ heat}$	$Gen2_{heat}$
C_{max} (ng/mL), mean(sd)	23.33 (5.047)	21.35 (4.549)
T_{max}, median (min-max)	4.00 (1.00-4.00)	2.75 (1.00-4.00)
$AUC_{0\text{-}inf}$ (hr*ng/mL), mean(sd)	120.61 (26.399)	110.30 (19.841)
$AUC_{0\text{-}last}$ (hr*ng/mL) , mean(sd)	118.38 (27.070)	108.37 (19.914)
$t_{½}$ (hr), median (min-max)	3.02 (1.77-4.28)	3.13 (1.69-6.09)

Pharmacokinetic Results from $Gen2_{deactivated}$ (non-activated patch application):

During Period 3 ($Gen2_{deactivated}$), study patches were worn on the forearm for 4 hours for purposes of conformability testing. The patches were not activated. Five PK samples were collected for each subject in Period 3 at 0, 0.5, 1, 4 and 6 hours after patch application.

The Sponsor reports that initially, they showed measureable concentrations from patients that were $Gen2_{deactivated}$ (non-activated patch application), which was not supposed to deliver the drug. The Sponsor identified a source for sample contamination. The sponsor revised the study protocol in a manner that addressed the potential source of contamination and repeated this portion of the study. Only three of the six subjects (Subjects 001, 003 and 007) were able to return for the repeat application where it was confirmed that plasma concentrations of sumatriptan were below the limit of quantification (<0.200 ng/mL) for all PK time points.

Effect of Race on Pharmacokinetics: The Sponsor performed an analysis of the effect of race on pharmacokinetics. Comparisons were made between white (n=5) and non-white subjects (n=7). The results suggest that C_{max} may be greater for white versus non-white subjects receiving $Gen2_{no\ heat}$ patch. The analysis suggests there may not be significant differences between white and non-white population for either $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}last}$ for either $Gen2_{no\ heat}$ patch or $Gen2_{heat}$

Safety Result

Sponsor reports that there were no serious adverse events and no discontinuations due to AEs. In addition, Sponsor reports that there were no clinically significant changes in vital signs or ECG findings observed during study.

Treatment	Sponsor's Safety Findings	
$Gen2_{no\ heat}$	One mild AE (vessel puncture site hematoma, unrelated to study drug) was reported following $Gen2_{no\ heat}$ patch.	Following $Gen2_{no\ heat}$ patch and $Gen2_{heat}$ patch, there were no skin irritation scores greater than 2 (moderate erythema). There were no observations of moderate erythema beyond 24 hours post patch application, and no erythema was observed by 10 days post-dose for either treatment. There were no clinically meaningful differences between the two patch treatments (with and without heat wrap) with respect to skin irritation scores.
$Gen2_{heat}$	Two mild AEs were reported following $Gen2_{heat}$: application site reaction ("burning not painful") considered related to study drug; epistaxis considered unrelated to study drug.	
$Gen2_{deactivated}$	There were no AEs reported for $Gen2_{deactivated}$ patch.	

Conclusion

Application of the heat wrap over the patch for four hours does not affect pharmacokinetics in

	terms of AUC_{0-last}, $AUC0_{-inf}$, or C_{max}.

NP101-018: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Four-Way Crossover Study to Compare the Pharmacokinetics and Bioequivalence of Drug Product From Two Manufacture Locations and Exploratory Pharmacokinetics of Two NP101 (Sumatriptan Iontophoretic Transdermal System) Patches.

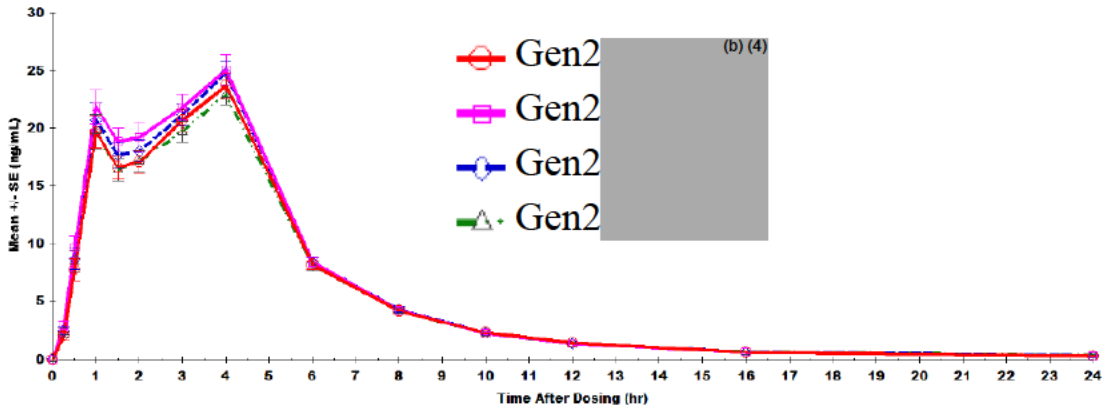
Objectives	1. to assess the bioequivalence between drug product previously used in the NP101-013 study (manufactured by [redacted] (b) (4)) with drug product manufactured by [redacted] (b) (4), in healthy adult volunteers; 2. exploratory testing to compare the pharmacokinetics of NP101 used in the NP101-013 study with new electrodes having [redacted] (b) (4).
Study Design	This was a Phase 1, single center, open label, randomized, single-dose, four-way crossover study conducted in 32 healthy adult volunteers. All arms use the "Generation 2" (Gen2) patch which is the "modified patch" previously used in the NP101-013 study. 1. Treatment A: Gen2 patch with drug product manufactured by [redacted] (b) (4) (Gen2 [redacted] (b) (4). 2. Treatment B: Gen2 patch with drug product manufactured by [redacted] (b) (4) (Gen2 [redacted] (b) (4) [redacted] (b) (4)). 3. Treatment C: Gen2 patch with [redacted] (b) (4); drug product manufactured by [redacted] (b) (4) (Gen2 [redacted] (b) (4)). 4. Treatment D: Gen2 patch with [redacted] (b) (4); drug product manufactured by [redacted] (b) (4) (Gen2 [redacted] (b) (4)).
Study Population	n=32 subjects were enrolled. The patch deactivated early in 2 subjects and Sponsor excluded them from the PK evaluable population. (n=30). Age(years): 18–58, mean 29.4; Weight(kg): 51–87.7, mean 64.6; Sex: Male (50%); Race: Majority non-hispanic (100%)
PK Sampling	Blood samples were obtained at the following times: pre-dose (within 15 minutes prior to dosing).
Bioanalytical Method	

Sumatriptan Bioanalytical Method	
Method	HPLC with MS/MS
Internal Standard	Sumatriptan-d_6, [redacted] (b) (4)
LOQ (ng/mL)	0.2
Calibration Concentrations	0.2, 0.4, 0.7, 2.5, 8, 30, 80, 100
Assay Range (ng/mL)	0.200 to 100
Quality Controls (ng/mL)	0.5, 1.25, 4.5, 15, 75
Accuracy (% difference from theoretical)	-1.79 – 2.60%
Precision (%CV)	1.49 – 3.04%

PK Assessments	The Sponsor estimated the following PK parameters from the sumatriptan plasma concentration-time data: 1) area under the plasma concentration-time curve from time zero to the last quantifiable concentration post-dose (***AUC0–last***), 2) area under the plasma concentration-time curve from

	time zero to infinity (***AUC0-inf***), 3) maximum observed plasma concentration after dosing (***Cmax***), 4) time to maximum plasma concentration (***Tmax***), 5) first order terminal elimination rate constant (***λz***), and 6) terminal half-life (***t½***).
Safety Endpoints	5. Adverse events (AEs). 6. 12-lead electrocardiogram (ECG) findings at screening and post-dose for all treatments. 7. Vital signs pre-dose and post-dose for all treatments. 8. Skin irritation and patch adherence examinations following NP101 patch treatments.
PK Results	

Figure 11. Mean (+/-SD) Sumatriptan Plasma Concentration Versus Time



Relative Bioavailability Comparison: Gen2 [redacted] (b) (4) (manufactured in [redacted] (b) (4)) vs. Gen2 [redacted] (b) (4) (manufactured in [redacted] (b) (4)): All estimates derived from the ANOVA model on natural logarithmic transformed data with subject (sequence) as a random effect. The 90% confidence intervals of the geometric mean ratios fall entirely within the 80% to 125% boundary for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$). Thus, the bioequivalence criteria is satisfied for all three exposure metrics (see table 1).

Table 9: Results of Bioequivalence Computations For Comparison of Manufacturing Sites

Parameter	Manufacturing Site	N	Geometric Mean (90% CI)	Comparison	Ratio (%) (90% CI)
C_{max}, ng/mL	[redacted] (b) (4)	30	23.6 (21.8, 25.7)	[redacted] (b) (4)	106.3 (97.6, 115.8)
		30	25.1 (23.2, 27.3)		
$AUC_{0\text{-last}}$, hr*ng/mL		30	122.7 (113.0, 133.2)		105.3 (97.5, 113.7)
		30	129.1 (118.9, 140.2)		
$AUC_{0\text{-inf}}$, hr*ng/mL		30	125.1 (115.3, 135.7)		105.2 (97.7, 113.3)
		30	131.5 (121.3, 142.7)		

Relative Bioavailability Comparison: Gen2 [redacted] (b) (4) (manufactured using [redacted] (b) (4)) vs. Gen2 [redacted] (b) (4) (manufactured using [redacted] (b) (4)): The 90% confidence intervals of the geometric mean ratios fall entirely within the 80% to 125% boundary for all three exposure metrics (C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$). Thus, the bioequivalence criteria is satisfied for all three exposure metrics (see table 2).

Table 10: Results of Bioequivalence Computations for Comparison of Manfacturing Methods

Parameter	Electrode (b) (4) Technique	N	Geometric Mean (90% CI)	Comparison	Ratio (%) (90% CI)
C_{max}, ng/mL	(b) (4)	30	25.1 (23.2, 27.1)	(b) (4)	92.2 (84.4, 100.7)
		30	23.1 (21.4, 25.0)		
$AUC_{0\text{-last}}$, hr*ng/mL		30	127.5 (117.2, 138.6)		94.2 (86.7, 102.5)
		30	120.1 (110.4, 130.6)		
$AUC_{0\text{-inf}}$, hr*ng/mL		30	130.0 (119.7, 141.2)		94.2 (86.4, 102.7)
		30	122.5 (112.8, 133.0)		

Table 11. Summary PK parameters of Sumatriptan (PK Evaluable Population, n=31)

Parameter	Gen2 (b) (4)	Gen2 (b) (4)	Gen2 (b) (4)	Gen2 (b) (4)
C_{max} (ng/mL), mean(sd)	24.37 (6.163)	26.03 (6.969)	25.58 (5.499)	23.76 (5.576)
T_{max}, median (min-max)	4.00 (1.00-4.05)	4.00 (1.00-4.02)	4.00 (1.00-4.05)	4.00 (1.00-4.30)
$AUC_{0\text{-inf}}$ (hr*ng/mL), mean(sd)	128.55 (31.318)	136.55 (38.526)	133.39 (32.241)	126.48 (31.848)
$AUC_{0\text{-last}}$ (hr*ng/mL), mean(sd)	126.20 (31.344)	134.16 (38.263)	130.98 (32.439)	124.15 (31.885)
$t_{½}$ (hr), median (min-max)	3.22 (1.94-5.88)	3.01 (2.23-5.76)	2.84 (2.30-5.22)	3.08 (2.31-4.94)

Safety Result

Treatment	Sponsor's Safety findings Related to Treatment
Gen2 (b) (4)	Application site paraesthesia (verbatim term: "stinging, not painful") was reported by one subject during Gen2 (b) (4) and was considered probably related to treatment
Gen2	Application site reaction ("tenderness, not painful") was reported by one subject during Gen2 (b) (4) and was considered possibly related to treatment.
Gen2	Sponsor did not attribute any AEs as being related to Gen2 (b) (4)
Gen2	Sponsor did not attribute any AEs as being related to Gen2

According to the Sponsor, all other AEs were unrelated to study treatment.There were no deaths or serious adverse events, and no adverse events leading to discontinuation. Six subjects (18.8%) experienced a total of seven AEs during study.

According to the Sponsor, the type and incidence of adverse events was similar to that observed in previous NP101 studies. There was one AE of moderate severity (diarrhea); all other AEs were mild. The majority of events were resolved within a few hours after onset; all events were resolved by the following day.

Conclusion: Patches manufactured in (b) (4) are bioequivalent to patches manufactured in (b) (4).

	Patches with [redacted] (b) (4) are bioequivalent to patches with [redacted] (b) (4)

B OCP Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	202278-0031	**Brand Name**	Zecuity™
OCP Division (I, II, III)	DCP-I	**Generic Name**	Sumatriptan (internal code name NP101)
Medical Division	DNP/ HFD-120	**Drug Class**	Selective serotonin receptor agonist
OCP Reviewer	Michael Bewernitz	**Indication(s)**	Acute treatment of migraine attacks, with or without aura, in adults
OCPB Team Leader	Angela Men	**Dosage Form**	Iontophoretic transdermal system
		Dosing Regimen	6.5 mg of sumatriptan is delivered over 4 hours. The maximum recommended dose that may be given in 24 hours is two patches. The second patch may be applied as early as 2 hours after initial patch activation.
Date of Submission	07/16/2012	**Route of Administration**	Transdermal
Estimated Due Date of OCP Review	11/ 26/2012	**Sponsor**	NuPathe Inc.
Division Due Date	11/30/2012	**Priority Classification**	S
PDUFA Due Date	01/17/2013		

Clin. Pharm. and Biopharm. Information

This application for Zecuity™ (sumatriptan) iontophoretic transdermal system (internal code name NP101) is being submitted as a 505(b)(2) submission for Acute treatment of migraine attacks, with or without aura, in adults.

In October 2010, the Sponsor submitted NDA 202-278 following the 505(b)(2) pathway for the Zecuity system. The reference product was the oral formulation of Imitrex® (sumatriptan succinate). The Sponsor received a complete response letter from the Agency on August 29th, 2011. The clinical pharmacology component of the complete response letter provided the following comment regarding study NP101-013 (a bioequivalence study):

"The clinical portion of Study NP101-013 (which was designed to assess the bioequivalence of the NP101 patch used in pivotal efficacy Study NP101-007 and that intended for commercial use, compared to oral Imitrex) is not acceptable for review, because Prism Research failed to randomly select and retain reserve samples for the test and reference products used in this study, as required by 21 CFR 320.38 (Retention of bioavailability samples). Due to the absence of reserve samples at Prism Research, authenticity of the test and reference products used in Study NP101-013 cannot be assured. Since the data from NP101-013 generated at Prism Research are not acceptable for review, the results obtained from the pivotal BE Study NP101-013 are not acceptable. That study must therefore be repeated."

The current NDA is a resubmission containing the Sponsor's responses to the comments listed in the complete response letter. The sponsor provided the following response in the current submission regarding the clinical pharmacology comment from the complete response letter in the preceding paragraph:

"Study NP101-013 was repeated as study NP101-023, located in Section 5.3.1.2 of the NDA. As stated in Section 7.4.2.2 of the protocol, sufficient reserve samples were randomly selected and retained by the study site for the test and reference products used in the study, as required by 21 CFR 320.38. This study confirmed the bioequivalence shown in NP101-013. However, after study NP101-023, NP101 was slightly modified by adding the Pad Detection System (PDS) design enhancement. Study NP101-026 subsequently confirmed the bioequivalence of the NP101 patches used in Study NP101-023 to those intended for commercial use."

The current submission contains the repeated bioequivalence study (NP101-023) as well as the subsequent bioequivalence study (NP101-026) performed using the device with the updated PDS.

This NDA consists of

Phase 1 Pharmacokinetic Studies

NP101-018 is *a manufacturing BE study*. The objective was to assess the BE of NP101 drug product manufactured at two different sites and evaluate the PK of NP101 patches with electrodes having [redacted] (b) (4) in healthy volunteers.

NP101-023 is *a formulation bridging BE study*. The objective was to assess the BE of the NP101 patch used in Study NP101-007 (efficacy study) and a modified NP101 patch compared to the approved oral formulation of Imitrex® in healthy volunteers. Study NP101-023 is a repeat of study NP101-013 performed as a result of the clinical pharmacology comment in the complete response letter.

NP101-024 is *a relative BA study*. The objective was to evaluate the effect of local heat on the pharmacokinetics of NP101 in healthy volunteers.

NP101-026 is *a formulation bridging BE study*. The objective of the study was to assess the BE of the modified NP101 patch used in Study NP101-023 and the final proposed commercial NP101 patch with the PDS in healthy volunteers.

Other Studies

NP101-022 was conducted to assess the residual sumatriptan succinate following NP101 treatment application to the upper arm or thigh.

NP101-025 was conducted to collect data when medication pads were aligned, not aligned, and absent and to verify that the PDS prohibited the patch from turning on when medication pads were misaligned or absent.

Please refer to the clinical pharmacology filing review for NDA-202278-0028 (January 4th 2011) for information regarding clinical studies previously included in the prior submission.

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	-	-	
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	-	-	
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-vitro:	-	-	-	
Subpopulation studies -				
ethnicity:	X	-	-	A pooled analysis of Phase 1 study data was performed to evaluate the effect of race on NP101 PK.
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:	X	1	-	Sponsor assessed the effect of local heat on PK (NP101-024)
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	-	NP101-018, NP101-023, NP101-026
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	-	-	
Total Number of Studies	X	4	-	
		4 PK		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)	1. Is the NP101 patch used in Study NP101-007 (efficacy study) bioequivalent to the modified NP101 patch used in Study NP101-023? 2. Is the modified NP101 patch used in Study NP101-023 bioequivalent to the final proposed commercial NP101 patch with the PDS? 3. Is the final proposed commercial NP101 patch with the PDS bioequivalent to the patch used in Study NP101-007 (efficacy study)? 4. Does local heat affect pharmacokinetics? 5. Does manufacturing location affect pharmacokinetics?	
Other comments or information not included above	DSI inspection request for clinical and bioanalytical portions of the study NP101-023 and NP101-026 will be sent to the project manager.	
Primary reviewer Signature and Date	Michael Bewernitz	
Secondary reviewer Signature and Date	Angela Men	

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Electronic data sets are

					available
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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
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	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
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	
	General				
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			x	

	another language needed and provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

We will request that the sponsor provide their rationale for their formulation bridging approach to bioequivalence rather than a direct comparison. In other words, why they compare the to-be-marketed final commercial version of the patch to the modified version of the patch (in study 026) instead of comparing the to-be-marketed final commercial version of the patch to the version of the patch that was used to show efficacy (in study 007)?

Note to the Project manager: We will submit a DSI inspection request for clinical and bioanalytical portions of study NP101-023 and study NP101-026.

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

/s/

MICHAEL A BEWERNITZ
11/23/2012
updated the formatting and did another overall check on the document.

YUXIN MEN
11/23/2012

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	202278-0031	**Brand Name**	Zecuity™
OCP Division (I, II, III)	DCP-I	**Generic Name**	Sumatriptan (internal code name NP101)
Medical Division	DNP/ HFD-120	**Drug Class**	Selective serotonin receptor agonist
OCP Reviewer	Michael Bewernitz	**Indication(s)**	Acute treatment of migraine attacks, with or without aura, in adults
OCPB Team Leader	Angela Men	**Dosage Form**	Iontophoretic transdermal system
		Dosing Regimen	6.5 mg of sumatriptan is delivered over 4 hours. The maximum recommended dose that may be given in 24 hours is two patches. The second patch may be applied as early as 2 hours after initial patch activation.
Date of Submission	07/16/2012	**Route of Administration**	Transdermal
Estimated Due Date of OCP Review	11/ 26/2012	**Sponsor**	NuPathe Inc.
Division Due Date	11/30/2012	**Priority Classification**	S
PDUFA Due Date	01/17/2013		

Clin. Pharm. and Biopharm. Information

This application for Zecuity™ (sumatriptan) iontophoretic transdermal system (internal code name NP101) is being submitted as a 505(b)(2) submission for Acute treatment of migraine attacks, with or without aura, in adults.

In October 2010, the Sponsor submitted NDA 202-278 following the 505(b)(2) pathway for the Zecuity system. The reference product was the oral formulation of Imitrex® (sumatriptan succinate). The Sponsor received a complete response letter from the Agency on August 29th, 2011. The clinical pharmacology component of the complete response letter provided the following comment regarding study NP101-013 (a bioequivalence study):

"The clinical portion of Study NP101-013 (which was designed to assess the bioequivalence of the NP101 patch used in pivotal efficacy Study NP101-007 and that intended for commercial use, compared to oral Imitrex) is not acceptable for review, because Prism Research failed to randomly select and retain reserve samples for the test and reference products used in this study, as required by 21 CFR 320.38 (Retention of bioavailability samples). Due to the absence of reserve samples at Prism Research, authenticity of the test and reference products used in Study NP101-013 cannot be assured. Since the data from NP101-013 generated at Prism Research are not acceptable for review, the results obtained from the pivotal BE Study NP101-013 are not acceptable. That study must therefore be repeated."

The current NDA is a resubmission containing the Sponsor's responses to the comments listed in the complete response letter. The sponsor provided the following response in the current submission regarding the clinical pharmacology comment from the complete response letter in the preceding paragraph:

"Study NP101-013 was repeated as study NP101-023, located in Section 5.3.1.2 of the NDA. As stated in Section 7.4.2.2 of the protocol, sufficient reserve samples were randomly selected and retained by the study site for the test and reference products used in the study, as required by 21 CFR 320.38. This study confirmed the bioequivalence shown in NP101-013. However, after study NP101-023, NP101 was slightly modified by adding the Pad Detection System (PDS) design enhancement. Study NP101-026 subsequently confirmed the bioequivalence of the NP101 patches used in Study NP101-023 to those intended for commercial use."

The current submission contains the repeated bioequivalence study (NP101-023) as well as the subsequent bioequivalence study (NP101-026) performed using the device with the updated PDS.

This NDA consists of

Phase 1 Pharmacokinetic Studies

NP101-018 is *a manufacturing BE study*. The objective was to assess the BE of NP101 drug product manufactured at two different sites and evaluate the PK of NP101 patches with electrodes having [redacted] (b) (4) in healthy volunteers.

NP101-023 is *a formulation bridging BE study*. The objective was to assess the BE of the NP101 patch used in Study NP101-007 (efficacy study) and a modified NP101 patch compared to the approved oral formulation of Imitrex® in healthy volunteers. Study NP101-023 is a repeat of study NP101-013 performed as a result of the clinical pharmacology comment in the complete response letter.

NP101-024 is *a relative BA study*. The objective was to evaluate the effect of local heat on the pharmacokinetics of NP101 in healthy volunteers.

NP101-026 is *a formulation bridging BE study*. The objective of the study was to assess the BE of the modified NP101 patch used in Study NP101-023 and the final proposed commercial NP101 patch with the PDS in healthy volunteers.

Other Studies

NP101-022 was conducted to assess the residual sumatriptan succinate following NP101 treatment application to the upper arm or thigh.

NP101-025 was conducted to collect data when medication pads were aligned, not aligned, and absent and to verify that the PDS prohibited the patch from turning on when medication pads were misaligned or absent.

Please refer to the clinical pharmacology filing review for NDA-202278-0028 (January 4th 2011) for information regarding clinical studies previously included in the prior submission.

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

ethnicity:	X	-	-	A pooled analysis of Phase 1 study data was performed to evaluate the effect of race on NP101 PK.
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:	X	1	-	Sponsor assessed the effect of local heat on PK (NP101-024)
Bioequivalence studies -				
traditional design; single / multi dose:	X	3	-	NP101-018, NP101-023, NP101-026
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	-	-	
Total Number of Studies	X	4	-	
		4 PK		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)	1. Is the NP101 patch used in Study NP101-007 (efficacy study) bioequivalent to the modified NP101 patch used in Study NP101-023? 2. Is the modified NP101 patch used in Study NP101-023 bioequivalent to the final proposed commercial NP101 patch with the PDS? 3. Is the final proposed commercial NP101 patch with the PDS bioequivalent to the patch used in Study NP101-007 (efficacy study)? 4. Does local heat affect pharmacokinetics? 5. Does manufacturing location affect pharmacokinetics?	
Other comments or information not included above	DSI inspection request for clinical and bioanalytical portions of the study NP101-023 and NP101-026 will be sent to the project manager.	
Primary reviewer Signature and Date	Michael Bewernitz	
Secondary reviewer Signature and Date	Angela Men	

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Electronic data sets are available
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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
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	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired			x	

	and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?				
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	
	General				
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_____

We will request that the sponsor provide their rationale for their formulation bridging approach to bioequivalence rather than a direct comparison. In other words, why they compare the to-be-marketed final commercial version of the patch to the modified version of the patch (in study 026) instead of comparing the to-be-marketed final commercial version of the patch to the version of the patch that was used to show efficacy (in study 007)?

Note to the Project manager: We will submit a DSI inspection request for clinical and bioanalytical portions of study NP101-023 and study NP101-026.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Appendix: Tabular listing of all clinical studies

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	NP101-005	5.3.1.1	Compare the PK of NP101 with currently approved formulations of Imitrex®.	Open-label, randomized, single-dose, 5-way crossover study vs. sumatriptan sc injection, oral tablet, and nasal spray formulations.	NP101 patch Treatment F (b)(4) g formulation in drug reservoir (b)(4) mg sumatriptan applied to subject]) Treatment G (b)(4) g formulation in drug reservoir) Treatment B: 100 mg oral Treatment C: 6 mg SQ Treatment D: 20 mg intranasal	25	Healthy	Single dose (up to seven treatment periods)	Complete; Full CSR
BA	NP101-012	5.3.1.1	Assess the BA of NP101 applied to two different sites; and assess the PK of NP101 in elderly subjects.	Group I: Open-label, randomized, single-center, single-dose, 3-way crossover study vs. sumatriptan sc injection in subjects 18-45 yrs. of age. Group II: Open-label, single-center, single-dose study in subjects >65 yrs. of age.	NP101 patch (b)(4) mg sumatriptan applied to subject) Group I: patch applied to upper arm (Treatment A) patch applied to thigh (Treatment B) 6 mg sc injection (Treatment C) Group II: Treatment A	Group I: 25 Group II: 08	Healthy	Group I: single-dose (up to three treatment periods) Group II: single dose	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE Study was repeated as Study NP101-023 due to lack of retained samples at study site.	NP101-013	5.3.1.2	Assess the BE of the NP101 patch used in Study NP101-007 and a modified NP101 patch (initially intended for commercial use) compared to the currently approved oral formulation of Imitrex®.	Open-label, randomized, single-center, single-dose, 3-way crossover study (one additional Group added per amendment) vs. sumatriptan oral tablet (Imitrex®).	NP101 patches ([redacted] mg sumatriptan applied to subject), applied to upper arm with a 4 h wear time [redacted] mA min Group 1: Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Patch for commercial use (NP101B) Treatment C: 100 mg oral tablet Group 2: Treatment A: Patch used in NP101-007 (NP101A) Treatment D: Patch for commercial use (NP101D) Treatment C: 100 mg oral tablet	63	Healthy	Single dose (up to four treatment periods)	Complete; Full CSR
BE	NP101-018	5.3.1.2	Assess the BE of NP101 drug product manufactured at two different sites and evaluate the PK of NP101 patches with electrodes having [redacted]	Open-label, randomized, single-dose, 4-way crossover study.	NP101 patch ([redacted] mg sumatriptan applied to subject) Treatment A: drug product made by [redacted] Treatment B: drug product made by [redacted] Treatment C: E-Patch with [redacted] Treatment D: E-Patch with [redacted]	30	Healthy	Single dose (up to four treatment periods)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	NP101-023	5.3.1.2	Assess the BE of the NP101 patch used in Study NP101-007 and a modified NP101 patch compared to the currently approved oral formulation of Imitrex®.	Open-label, randomized, single-dose, 3-way crossover study vs. sumatriptan oral tablet (Imitrex®).	NP101 patch (b) (4) mg sumatriptan applied to subject) Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Modified patch (NP101B) Treatment C: 100 mg oral sumatriptan tablet.	32	Healthy	Single dose (up to three treatment periods)	Complete; Full CSR
BE	NP101-026	5.3.1.2	Assess the BE of the modified NP101 patch used in Study NP101-023 and the final proposed commercial NP101 patch with the PDS.	Open-label, randomized, single-dose, 2-way crossover study. Treatments A and B were randomized.	NP101 patch (b) (4) mg sumatriptan applied to subject) Treatment A: Modified patch used in Study NP101-023 Treatment B: Enhanced patch with PDS Treatment C: Same patch as Treatment B but applied with pads misaligned or absent to validate PDS.	32	Healthy	Single dose (up to three treatment periods)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-001 (b) (4)	5.3.3.1	Evaluate the PK profile and relative bio-availability of prototype NP101 patches.	Open-label, randomized, single-center, single-dose, crossover study vs. sumatriptan sc injection and oral tablet.	NP101 patch treatments (containing (b) (4) mg sumatriptan in aqueous solution) applied to upper back: NP101.01: (b) (4) NP101.02: NP101.03: NP101.04: Control treatments: 6 mg sc injection; 50 mg oral tablet (Imigran FTab)	8	Healthy	Single dose (total of six treatment periods)	Complete; Abbrev. CSR
PK	NP101-002 (b) (4)	5.3.3.1	Evaluate the tolerability and PK profile of prototype NP101 patches applied for different wear times and to different body locations.	Open-label, randomized, single-center, single-dose, 6-period crossover study vs. sumatriptan oral tablet.	NP101 patch treatments (containing up to (b) (4) mg sumatriptan in aqueous solution): NP101.05: (b) (4) formulation applied to upper back (Period 1) or upper arm (Period 3): (b) (4) (b) (4) formulation applied to upper arm (Period 4) for (b) (4) mA min NP101.06: (b) (4) formulation, upper arm, (b) (4) mA min (Period 5) NP101.06A: (b) (4) formulation, upper arm, (b) (4) mA min (Period 6) Control treatment (Period 2): 50 mg oral tablet (Imigran FTab)	17	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-004 (Legacy)	5.3.3.1	Evaluate the PK profile of prototype NP101 patches compared to that of oral sumatriptan succinate.	Open-label, single-center, single-dose, 5-period crossover study vs. sumatriptan oral tablet.	NP101 patch treatments (b) (4) mg applied subject) applied to upper arm (Treatments A and C) or upper back (Treatments D and E) and with an anode electrode size of (b) cm^2 (Treatment A) or (b) (4) cm^2 (Treatments C, D, and E): A: (b) (4) mA min C: mA min D: mA min E: mA min Control treatment (Treatment B): 100 mg oral tablet (Imigran FTab)	9	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR
PK	NP101-006	5.3.3.1	Compare the PK profiles among five NP101 patches.	Open-label, single-center, single-dose, 5-period crossover study.	NP101 patch (b) (4) mg applied subject) applied to upper arm (Periods 1, 2, 3, 4) or upper thigh (Period 5); with a pad transfer ring (Periods 1, 3, 5) or without a pad transfer ring (Periods 2, 4); and containing either an (b) (4) Design (Period 1, 2, 5) or (b) (4) Design (Period 3, 4) microprocessor	4	Healthy	Single dose (total of five treatment periods)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-011	5.3.3.3	Compare the PK of NP101 during an acute migraine attack and during a non-migraine period.	Open-label, single-center, single-dose, 4-way crossover study (two additional periods added per amendment) vs. sumatriptan oral tablet (Imitrex®).	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to the upper arm during a migraine (Periods 3 and 6) or during a non-migraine period (Periods 4 and 5) Control treatment: 50 mg oral tablet administered during a migraine (Period 1) or during a non-migraine period (Period 2)	23	Healthy/ Acute migraine headache	Single dose (up to six treatment periods)	Complete, Full CSR
Tolera-bility	NP101-014	5.3.3.3	Evaluate the potential of NP101 transdermal patch to cause skin irritation. The secondary objective was to collect patch adherence data, and to assess the PK of sumatriptan.	Randomized, placebo-controlled, repeat patch test study that compares the NP101 patch to a placebo patch.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm with a 4 h wear time (b) (4) mA min. and placebo patch containing a salt formulation.	10	Healthy	Maximum 21 days	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-024	5.3.3.4	Evaluate the effect of local heat administration PK on the NP101 patch; and a non-activated patch application to forearm to assess PK and patch conformability.	Open label, single center, single-dose 2-way cross-over study conducted in healthy adult volunteers. Treatments A and B were randomized.	NP101 patch (b) (4) mg sumatriptan applied to subject) Treatments A and B: 2-way crossover (2 patch applications to upper arm) Treatment C applied to forearm and not activated.	12	Healthy	Single dose (up to three treatment periods)	Complete; Full CSR
Efficacy	NP101-007	5.3.5.1	Evaluate the efficacy and safety of NP101 for the treatment of acute migraine.	Randomized, parallel-group, double-blind, placebo-controlled, multicenter study.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm with a 4 h wear time (b) (4) mA min. Control treatment: Placebo patch containing a salt formulation.	469 (NP101: 234; placebo: 235)	Healthy/ Acute migraine headache	Single dose	Complete, Full CSR
Safety	NP101-008	5.3.5.2	Evaluate the safety and efficacy of NP101 in the treatment of acute migraine over 12 months.	Open-label, multicenter study in subjects previously enrolled and treated (patch activation) in Study NP101-007.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm or upper thigh with a 4 h wear time (b) (4) mA min.	198	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	NP101-009	5.3.5.2	Evaluate the safety of NP101 in the treatment of acute migraine over 12 months.	Open-label, multicenter study.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm or upper thigh with a 4 h wear time (b) (4) mA min.	514	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Complete; Full CSR
Other	NP101-022	5.3.5.4	Single-dose study to determine residual sumatriptan succinate following NP101 treatment: patch applied to upper arm or thigh.	Open-label, randomized, single center, single-dose study.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm or thigh with a 4 h wear time (b) (4) mA min.	13	Healthy	Single treatment	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Other	NP101-025	5.3.5.4	Collect data when medication pads were aligned, not aligned, and absent and to verify that the PDS prohibited the patch from turning on when medication pads were misaligned or absent.	Open label, single center, multiple application study.	NP101 patch (b) (4) mg sumatriptan applied to subject), applied to upper arm or thigh: Period 1: pads transferred aligned – 4 patches each worn for 30 min. Period 2: pads transferred misaligned – 4 patches each worn for 30 min. Period 3: pads transferred aligned and misaligned – 4 or 5 patches each worn for 10 min. Period 4: pads transferred aligned, misaligned, and absent – 6 to 9 patches each worn for 10 min. Patches did not deliver medication.	26	Healthy	Single dose (four treatment periods)	Complete; Full CSR

BA = bioavailability; BE = bioequivalence; CSR = clinical study report; g = grams, h = hour; HPMC = hydroxypropylmethylcellulose; mA = milliamp; min = minutes; mg = milligrams, PDS = pad detection system, PK = pharmacokinetic; (b) (4); sc = subcutaneous; yrs. = years

(*source: NDA 202278-0031, "tabular listing.pdf", pages 1 to 9*)

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/s/

MICHAEL A BEWERNITZ
11/21/2012

YUXIN MEN
11/21/2012

ADDENDUM TO CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#	**202278**
Generic Name:	Sumatriptan Succinate
Formulation:	Iontophoretic transdermal Patch
Sponsor:	NuPathe, Inc.
Reviewer:	Jagan Mohan Parepally, Ph.D.
Submission Type:	Addendum to Clinical Pharmacology Review

BACKGROUND

This addendum is in response to the Office of Scientific Investigations (OSI) results. The following information reflects update on the pivotal bioequivalence (BE) study NP101-013 in the Clinical Pharmacology review for NDA 202278, which was finalized in DARRTs on June 29, 2011. At the request of Division of Neurology Products, the Office of Scientific Investigations conducted audits of the following pivotal BE study:

Study # NP101-013: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioavailability of Three NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments With an Oral Formulation of Imitrex® in Healthy Volunteers and to Collect Resistance Data During Application of NP101

The clinical portion of the study was conducted at Prism Research, Saint Paul, MN and the analytical portion of the study at (b) (4) respectively. Following the inspections at (b) (4) and Prism Research, Form 483s (Inspectional Observations) were issued. The clinical and analytical audit was based on 100% audit of source data.

OSI evaluated the Establishment Inspection Reports (EIR) recommends that the clinical portion of Study NP101-013 be not acceptable for review due to following issue:

- Prism Research failed to randomly select and retain reserve samples for the test and reference products used in this study, as required by 21 CFR 320.38 (Retention of bioavailability samples). Due to the absence of reserve samples at Prism Research, authenticity of the test and reference products used in Study NP101-013 cannot be assured.

OSI also evaluated the (b) (4) response to the Form 483 (Objectionable Observations) and associated exhibits related to objectionable observations and concluded that the firm adequately responded to the violations and recommended that the bioanalytical portion be accepted for review.

Since the data from NP101-013 generated at Prism Research are not acceptable for review. OCP concludes that the results obtained from the pivotal BE Study NP101-013 are not acceptable.

RECOMMENDATION

Pivotal study establishing bioequivalence of the transdermal patch used in Study NP101-007 (efficacy study) and that intended for commercial use is not acceptable.

_____ _____

Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

_____ _____

Angela Men M.D., Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 NDA 202278
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Parepally

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/s/

JAGAN MOHAN R PAREPALLY
07/19/2011

YUXIN MEN
07/19/2011

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Sumatriptan Succinate
NDA:	20-2278
PRODUCT (Brand Name):	NP101
DOSAGE FORM:	Iontophoretic Transdermal Patch
INDICATION:	Acute treatment of migraine attacks with or without aura (b) (4)
NDA TYPE:	505 (b)(2)
SPONSOR:	NuPathe Inc.
IND :	74,877
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP 1, HFD-860
OND DIVISION:	Neurology HFD 120

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

The sponsor is seeking approval of NP101 (Sumatriptan Succinate) iontophoretic transdermal patch, which is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally [redacted] (b) (4) reference IMITREX® STAT dose System (NDA 20-080), Imitrex® tablets, Imitrex® nasal spray products. Sumatriptan is a selective agonist for the 5-HT_{1B} and 5-HT_{1D} receptors indicated for the acute treatment of migraine attacks, with or without aura, and the acute treatment of cluster headache episodes. NP101 patch was designed to deliver approximately 6.5 mg sumatriptan similar to sumtriptan subcutaneous injection dose currently marketed as IMITREX STAT dose. The proposed dosing regimen includes application of single transdermal patch to upper arm or thigh. The maximum recommended number of patches that may be given in 24 hours is two, separated by at least 2 hours.

The sponsor conducted eight studies including an acceptable pivotal BA/BE study and relative BA study supporting interchangeability of application site and three pilot studies in support of the Clinical Pharmacology section of the application. The sponsor also included an efficacy study, NP101-007 conducted in 469 migraine patients. The proportion of subjects who were migraine free at two hours

after patch activation in the NP101 treatment group was significantly higher than that of the placebo treatment group. Safety and tolerability data was also obtained from three studies.

A. Recommendation

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the clinical Pharmacology and Biopharmaceutics sections of NDA 20-2278. The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view. However, Chemistry, Manufacturing, and Controls (CMC) review division sent an information request letter dated 5/16/2011 indicating that "the fundamental design of NP101 is not acceptable. Specifications cannot be established per 21.CFR.314.50 to adequately assure identity, strength, quality, purity, potency and bioavailability of the product. A lack of uniformity of drug formulation distribution, and issues with drug formulation containment, safe disposal procedures, and patient usability raise concerns about the safety and efficacy of the product". Since the product design is not acceptable, NP101will not be approved. Therefore, no further labeling recommendation will be made and labeling recommendations are not outlined in the Detailed Labeling Recommendations section of the review.

Clinical Pharmacology briefing was held on 6/22/11 and the attendees were Drs. Mehul Mehta, Ramana Uppoor, Eric Bastings, Nushin Todd, Angela Men, Raman Baweja and Xinning Yang.

B. Phase IV Commitment

None.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

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

Bioequivalence:

Sumatriptan delivered by NP101 (iontophoretic transdermal patch) intended for commercial use was considered bioequivalent to NP101 used in the Phase 3 efficacy and safety study (NP101-007). The 90% CIs for maximum plasma concentration (Cmax) ranged from 79.8 to 95.8 with a geometric mean ratio (GMR) of 87.4. For $AUC_{inf,}$ 90% CI ranged from 85 to 97.2 with a GMR of 90.9.

Although the 90% CI of the GMR for the Cmax was not within the prespecified intervals of 80-125%, this minor difference in C_{max} is not considered clinically significant. The Imitrex® nasal spray formulation, approved based on effectiveness and safety in clinical trials, results in relatively lower C_{max} and AUC_{inf} when compared to that of NP101. Therefore, comparative bioavailability of sumatriptan delivered by NP101 patch intended for commercial is acceptable. However, if there are any significant modifications to the device and or the formulation in response to CR letter, new BE studies may be needed.

Interchangeability of application site:

NP101 application sites, upper arm and thigh, are interchangeable as the relative bioavailability of sumatriptan following application of patch to these two sites were comparable. The 90% CI for C_{max} were (78 to 91%) out of 80 to 125% bioequivalence limits. Minor differences in C_{max} are acceptable for the reasons mentioned above. The 90% CIs for the AUC_{inf} ranged from 83 to 96 with a GMR of 89. Transdermal patch applied to upper arm delivered approximately 6.85 mg of sumatriptan, and NP101 patch applied to upper thigh delivered approximately 6.13 mg of sumatriptan.

Effect of age on pharmacokinetics:

The Cmax in healthy elderly subjects was 104 % of that observed in young subjects (24.5 ng/mL versus 23.3 ng/mL). The $AUC_{0\text{-}inf}$ observed in elderly subjects was 115 % of that observed in young subjects (130.8 hr*ng / mL versus113.4 hr*ng/mL). Per the Imitrex® Package Insert (PI), the use of sumatriptan in elderly subjects is not recommended because of decreased hepatic function and risk of coronary artery disease and hypertension.

Effect of gender on pharmacokinetics:

No significant differences in AUC and Cmax were observed between male and female subjects after NP101, oral, nasal or subcutaneous treatments of Imitrex®.

Effect of migraine on pharmacokinetics of sumatriptan:

There were no differences in mean sumatriptan Cmax or $AUC_{0\text{-}4}$ observed following NP101 treatment during a migraine compared to that observed following NP101 treatment during a migraine-free period.

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 three formulations – oral tablets, subcutaneous injection, and nasal spray.

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

Injection: Sumatriptan is available as Imitrex® 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.

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. NP101 (sumatriptan succinate) is an iontophoretic transdermal patch designed to deliver 6.5 mg sumatriptan over 4 hours of application.

Dosage Form:

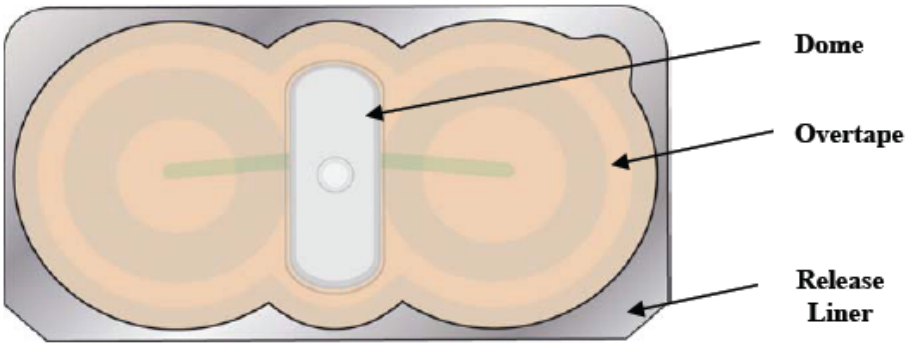
NP101 is a disposable, single-use, transdermal patch, co-packaged drug/device combination product that utilizes iontophoretic technology.

The drug product component of NP101 is referred to as the reservoir card and consists of two separate reservoirs. One reservoir contains a nonwoven pad imbibed with (b) (4) g of sumatriptan formulation ((b) (4)% sumatriptan succinate containing 86 mg of sumatriptan). A second reservoir contains a nonwoven pad imbibed with (b) (4) g of salt formulation (b) (4)% sodium chloride). Each reservoir is sealed separately.

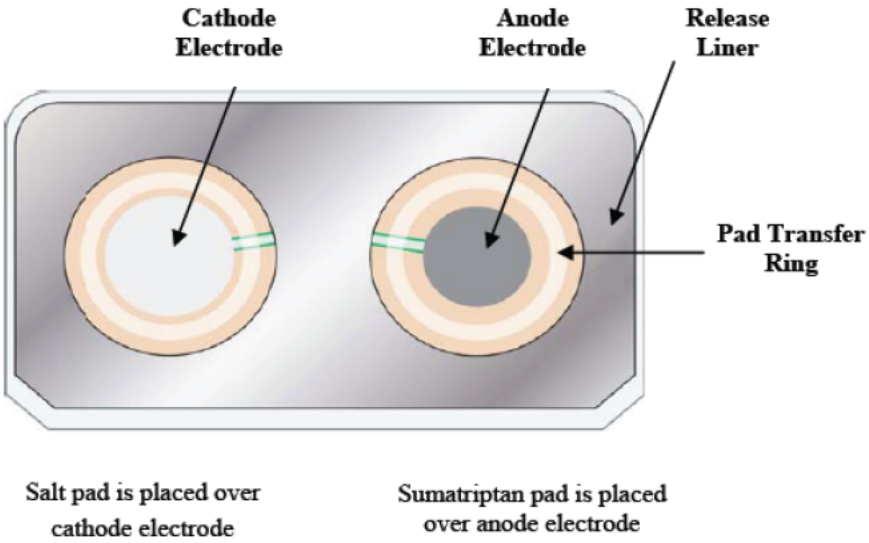
The device portion of NP101 consists of two electrodes, one positive, (the anode) and one negative (the cathode).

Description and Composition of the Drug Product

Top View of Electrode Patch



Bottom View of Electrode Patch



Indication:

NP101 (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?

NP101 employs iontophoretic technology to deliver sumatriptan transdermally. Iontophoresis is a non-invasive drug delivery method that uses low electrical current to move ionized drugs across the skin to the underlying tissue and blood vessels.

The total time of drug delivery and patch operation is approximately four hours [redacted] (b) (4) after which time the patch is automatically deactivated by the firmware embedded on the pre-programmed circuit. Approximately 6.5 mg of sumatriptan is delivered to the patient.

What is the proposed mechanism (s) of action?

Sumatriptan is a serotonin agonist for a vascular 5 hydroxytryptamine1D ($5\text{-}HT_{1D}$) receptor subtype (a member of the $5\text{-}HT_1$ family), and has only weak affinity for $5\text{-}HT_{1A}$ receptors and no significant activity (as measured using standard radioligand binding assays) or pharmacological activity at $5\text{-}HT_2$, $5\text{-}HT_3$, $5\text{-}HT_4$, $5\text{-}HT_{5A}$, or $5\text{-}HT_7$ receptor subtypes, or at alpha1, alpha2, 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 $5\text{-}HT_{1D}$ 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 a single efficacy study conducted by the sponsor to support the approval of the NP101 are summarized below:

Type of Study and Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy or Patients
BA NP101-005	Compare the PK of NP101 with currently approved formulations of Imitrex®	Open-label, randomized, single-center, single-dose, 5-way crossover study (2 additional periods added per amendment) vs. sumatriptan sc injection, oral tablet, and nasal spray formulations	NP101 (Zelrix™) patch Treatments A, E, F, G sumatriptan succinate in polyamine formulation, applied to upper arm with a 4 h wear time/ (b) (4) mA min Control treatments: B: 100 mg oral tablet C: 6 mg sc injection D: 20 mg intranasal	25	Healthy
BE NP101-013	Assess the BE of the NP101 patch used in Study NP101-007 and that intended for commercial use compared to the currently approved oral formulation of Imitrex®	Open-label, randomized, single-center, single-dose, 3-way crossover study (one additional Group added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patches containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time (b) (4) mA min Group 1: Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Patch for commercial use (NP101B) Treatment C: 100 mg oral tablet Group 2: Treatment A: Patch used in NP101-007 (NP101A) Treatment D: Patch for commercial use (NP101D) Treatment C: 100 mg oral tablet	63	Healthy

BA NP101-012	Assess the BA of NP101 applied to two different sites; and assess the PK of NP101 in elderly subjects	Group I: Open-label, randomized, single-center, single-dose, 3-way crossover study vs sumatriptan sc injection in subjects 18-45 yrs of age Group II: Open-label, single-center, single-dose study in subjects >65 yrs of age	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm (Group I, Treatment A and Group II) or upper thigh (Group I, Treatment B) with a 4 h wear time (b) (4) mA min Control treatment (Group I only): 6 mg sc injection (Imitrex®)	Group I: 25 Group II: 08	Healthy
PK NP101-011	Compare the PK of NP101 during an acute migraine attack and during a non-migraine period	Open-label, single-center, single-dose, 4-way crossover study (two additional periods added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation applied to the upper arm during a migraine (Periods 3 and 6) or during a non-migraine period (Periods 4 and 5) Control treatment: 50 mg oral tablet administered during a migraine (Period 1) or during a non-migraine period (Period 2)	23	Healthy/ Acute migraine headache
Efficacy NP101-007	Evaluate the efficacy and safety of NP101 for the treatment of acute migraine	Randomized, parallel-group, double-blind, placebo-controlled, multicenter study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time (b) (4) mA min Control treatment: Placebo patch containing a salt formulation	469 (NP101: 234; placebo: 235)	Healthy/ Acute migraine headache

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® (sumatriptan succinate) injection NDA 20-080.

Effect of Race on NP101 Pharmacokinetics

The sponsor evaluated the effect of race on the pharmacokinetics of sumatriptan delivered by NP101 in Study NP101-005. White subjects had significantly higher AUC and Cmax values than those of non-white subjects ($p \leq 0.0041$). Other PK parameters were not significantly different as shown in the table below for the patch treatments.

Table 1: Pharmacokinetic Parameters Summary by Race Group – Subjects Who Received Patch Treatments F and G

Parameter	Group	Estimate (95%CI) Non-white (N=8)	Estimate (95%CI) White (N=9)	GM Ratio (95%CI) (Non-white / White)	Difference p-value
AUC0-inf (hr*ng/mL)	Nasal	35.80 (20.80 - 61.63)	47.80 (28.65 - 79.76)	0.75 (0.36 - 1.58)	0.4222
	Oral	228.03 (183.79 - 282.92)	265.66 (216.78 - 325.57)	0.86 (0.64 - 1.15)	0.2894
	SQ	107.90 (95.70 - 121.66)	114.70 (102.43 - 128.44)	0.94 (0.80 - 1.11)	0.4421
	Patch F	89.86 (78.78 - 102.49)	131.74 (116.38 - 149.13)	0.68 (0.57 - 0.82)	0.0004
	Patch G	97.64 (87.32 - 109.18)	124.57 (112.12 - 138.41)	0.78 (0.67 - 0.91)	0.0041
Cmax (ng/mL)	Nasal	9.65 (6.19 - 15.04)	12.24 (8.05 - 18.60)	0.79 (0.43 - 1.45)	0.4198
	Oral	42.35 (32.71 - 54.82)	58.77 (46.07 - 74.96)	0.72 (0.51 - 1.03)	0.0677
	SQ	74.70 (63.98 - 87.22)	84.21 (72.77 - 97.46)	0.89 (0.72 - 1.10)	0.2488
	Patch F	19 34 (16.82 - 22.23)	28.92 (25.35 - 32.98)	0.67 (0.55 - 0.81)	0.0004
	Patch G	19.23 (16.85 - 21.95)	25.89 (22.85 - 29.33)	0.74 (0.62 - 0.89)	0.0033
t1/2 (hr)	Nasal	2.54 (1.97 - 3.26)	1.83 (1.44 - 2.32)	1.39 (0.98 - 1.96)	0.0616
	Oral	4.34 (3.31 - 5.69)	4.01 (3.10 - 5.17)	1.08 (0.75 - 1.57)	0.6555
	SQ	2.24 (2.01 - 2.49)	1.85 (1.67 - 2.04)	1.21 (1.05 - 1.40)	0.0135
	Patch F	2.85 (2.48 - 3.28)	2 94 (2.58 - 3.35)	0.97 (0.80 - 1.18)	0.7486
	Patch G	2.92 (2.55 - 3.35)	2.73 (2.40 - 3.10)	1.07 (0.89 - 1.29)	0.4573
Tmax (hr)	Nasal	1.15 (0.76 – 1.54)	1.69 (0.75 – 2.63)	NA	0.4293
	Oral	1.94 (1.47 – 2.41)	2.44 (1.40 – 3.49)	NA	0.5478
	SQ	0.23 (0.16 - 0.30)	0.29 (0.24 – 0.35)	NA	0.1147
	Patch F	2.00 (0.82 – 3.18)	1.33 (0.57 – 2.10)	NA	0.2697
	Patch G	3.25 (2.28 – 4.22)	1.89 (0.84 – 2.94)	NA	0.0489

Patch F: NP101 patch with (b) (4)g of formulation
Patch G: NP101 patch with (b) (4)g of formulation

The result of this study showed that Cmax and AUC of sumatriptan were lower in the Non-white subjects, but the half-life observed was similar comparing to the White.

Reviewer's Comment:

The above Study (NP101-005) was conducted in fewer subjects (13 Males and 12 females but only 17 finished and N=9 for White and 8 for non-White) to draw any conclusions. The current Imitrex® PI for

for oral and injectable sumatriptan shows that the systemic clearance and Cmax of sumatriptan were similar in black and Caucasian healthy male subjects (nasal has not been evaluated).

Effect of Gender on NP101 Pharmacokinetics

According to the Imitrex® (sumatriptan) PI, in a study comparing males and females, no pharmacokinetic differences were observed for AUC, Cmax, Tmax, and half-life following oral administration of sumatriptan. Similarly, in Study NP101-005, no significant differences in AUC and Cmax were observed between male and female subjects after oral, nasal or subcutaneous treatments as shown in the table below.

Table 2: Pharmacokinetic Parameters Summary by Gender

			-- Geometric Means--		
Parameter	Treatment	Subset	Estimate (95%CI)	Ratio (95%CI)	Difference between Subgroup p-value*
AUCinf	Nasal	Sex=FEMALE	51.74 (31.57 - 84.81)	1.58 (0.77 - 3.25)	0.1961
		Sex=MALE	32.75 (19.39 - 55.32)		
	Oral	Sex=FEMALE	264.08 (215.21 - 324.05)	1.15 (0.85 - 1.55)	0.3328
		Sex=MALE	229.57 (184.78 - 285.22)		
	Patch F	Sex=FEMALE	108.19 (89.48 - 130.82)	0.96 (0.73 - 1.27)	0.7860
		Sex=MALE	112.15 (91.69 - 137.17)		
	Patch G	Sex=FEMALE	109.49 (95.25 - 125.87)	0.97 (0.79 - 1.19)	0.7531
		Sex=MALE	112.89 (97.38 - 130.87)		
	SQ	Sex=FEMALE	118.86 (107.20 - 131.79)	1.15 (0.99 - 1.33)	0.0718
		Sex=MALE	103.66 (92.90 - 115.66)		
Cmax	Nasal	Sex=FEMALE	11.81 (7.73 - 18.04)	1.18 (0.63 - 2.18)	0.5843
		Sex=MALE	10.04 (6.41 - 15.74)		
	Oral	Sex=FEMALE	51.71 (39.39 - 67.88)	1.06 (0.71 - 1.57)	0.7691
		Sex=MALE	48.91 (36.64 - 65.27)		
	Patch F	Sex=FEMALE	23.00 (18.86 - 28.04)	0.92 (0.69 - 1.23)	0.5441
		Sex=MALE	25.02 (20.27 - 30.88)		
	Patch G	Sex=FEMALE	22.83 (19.31 - 26.99)	1.03 (0.81 - 1.31)	0.7991
		Sex=MALE	22.16 (18.55 - 26.47)		
	SQ	Sex=FEMALE	78.17 (67.13 - 91.03)	0.96 (0.77 - 1.20)	0.7179
		Sex=MALE	81.23 (69.11 - 95.46)		
t 1/2	Nasal	Sex=FEMALE	2.06 (1.58 - 2.69)	0.93 (0.63 - 1.37)	0.6819
		Sex=MALE	2.22 (1.68 - 2.94)		
	Oral	Sex=FEMALE	4.35 (3.37 - 5.61)	1.10 (0.76 - 1.59)	0.5995
		Sex=MALE	3.96 (3.02 - 5.19)		
	Patch F	Sex=FEMALE	2.79 (2.45 - 3.17)	0.92 (0.76 - 1.11)	0.3557

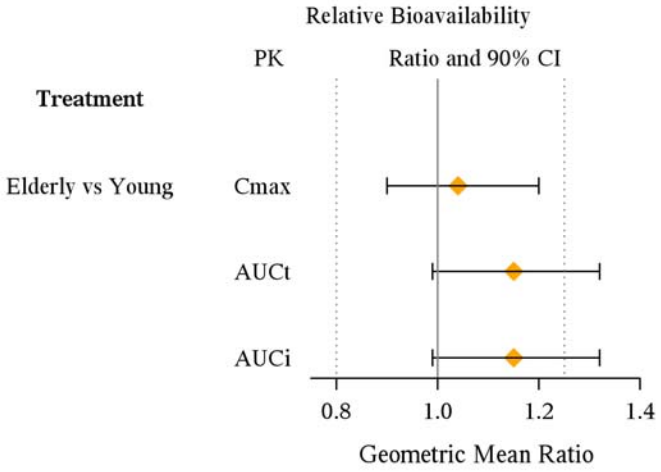
		Sex=MALE	3.03 (2.65 - 3.47)		
	Patch G	Sex=FEMALE	2.72 (2.39 - 3.09)	0.93 (0.77 - 1.12)	0.4149
		Sex=MALE	2.93 (2.56 - 3.35)		
	SQ	Sex=FEMALE	1.99 (1.76 - 2.25)	0.97 (0.81 - 1.16)	0.6876
		Sex=MALE	2.06 (1.81 - 2.35)		

Male n=8, Female n=9

Exposure in Geriatric Population

The sponsor has provided information on relative bioavailability of NP101 in healthy elderly cohort and in healthy adult cohort in Study NP101-012. The Cmax in healthy elderly subjects was 104 % of that observed in young subjects (24.5 ng/mL versus 23.3 ng/mL). The $AUC_{0\text{-}inf}$ observed in elderly subjects was 115 % of that observed in young subjects (130.8 hr*ng / mL versus 113.4 hr*ng/mL). Forest plot below represents geometric mean ratios with upper and lower 95% CI's. Per the PI, the use of sumatriptan in elderly subjects is not recommended because of decreased hepatic function and risk of coronary artery disease and hypertension.

Figure 1: Analysis of Relative Bioavailability for Treatment Groups: Elderly vs. Young Subjects



D. Extrinsic Factors

Is there any drug-drug interaction between zolpidem and other drugs?

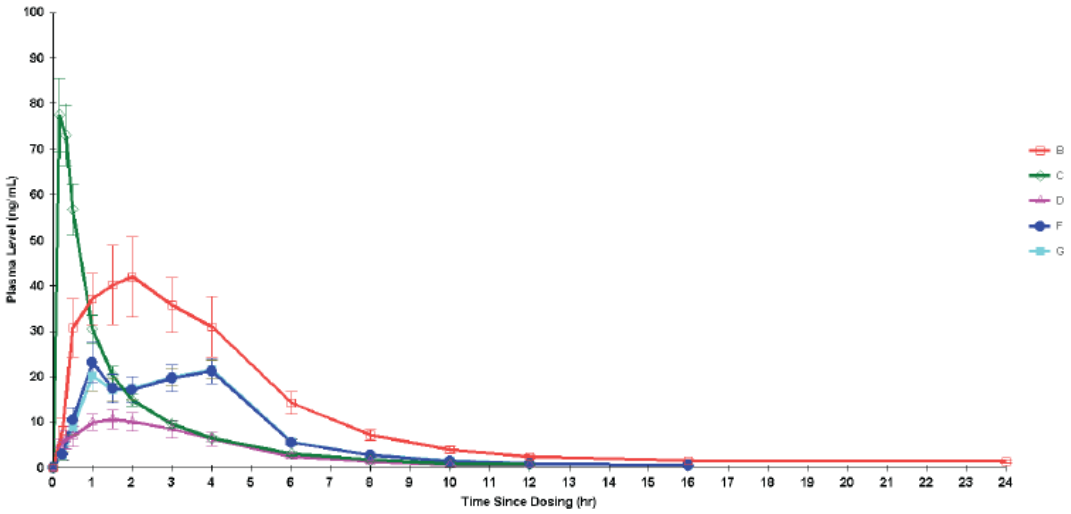
No drug-drug interaction studies were conducted with NP101 patch. Drug-drug interaction information related to sumatriptan succinate is provided in the original NDA for this drug. Please see Clinical Pharmacology reviews for Imitrex® (sumatriptan succinate) injection NDA 20-080.

E. General Biopharmaceutics

How does the PK profile of NP101 compare to different formulations of Imitrex®?

The mean plasma concentration over time profiles are shown in Figure below for the five formulations evaluated in Study NP101-005 (subcutaneous, oral, intranasal and NP101 patch Treatments F and G). The maximum plasma concentrations of sumatriptan obtained with NP101 (25 ng/mL) are intermediate between those obtained with 20 mg sumatriptan nasal spray and 100 mg sumatriptan oral tablets. The Cmax of NP101 was approximately 30% of s.c. injection. The mean AUC0-inf values intermediate between those obtained with 100 mg oral and 6 mg nasal spray formulations, and were similar to that obtained with a 6 mg subcutaneous dose.

Figure 2: Mean Sumatriptan Plasma Concentration (95%CI) Over Time



Treatment B (n=23): 100 mg sumatriptan oral tablet
Treatment C (n=23): 6 mg sumatriptan subcutaneous injection
Treatment D (n=23): 20 mg sumatriptan nasal spray
Treatment F (n=17): NP101 patch F (NP101 patch contains (b) (4) of formulation)
Treatment G (n=17): NP101 patch G (NP101 patch contains (b) (4) g of formulation)

What is the effect of food on the bioavailability of NP101?

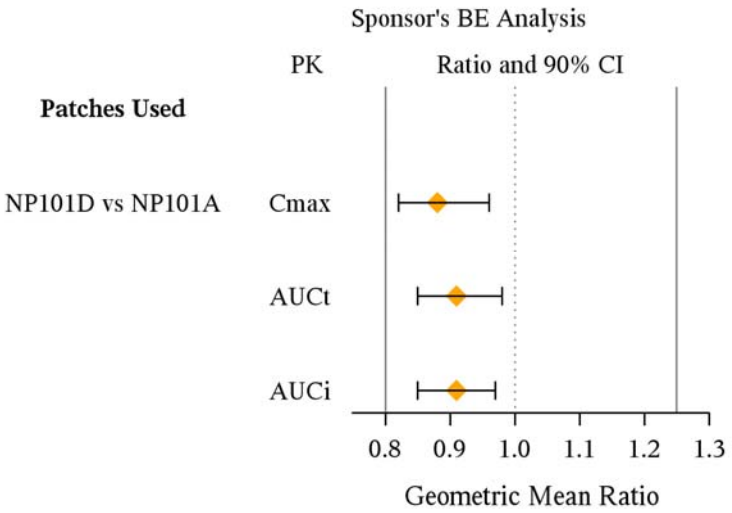
Food effect on bioavailability is not applicable as the route of administration for NP101 is transdermal.

Is NP101 used in the Phase 3 efficacy and safety study (NP101-007) and that intended for commercial use bioequivalent?

The bioequivalence of the NP101 used in the Phase 3 efficacy and safety study (NP101-007) and that intended for commercial use was determined in study NP101-013. The C_{max} and AUC_{inf} of sumatriptan transdermal patch used in the efficacy study and final commercial patch were comparable as shown in the figure below (the sponsor's analysis, N=30).

The figure below provides a summary of geometric mean ratios with 90% CI of the pharmacokinetic parameters for treatment groups.

Figure 3: Analysis of Bioequivalence for Treatment Groups: Commercial Product vs. Phase III Product



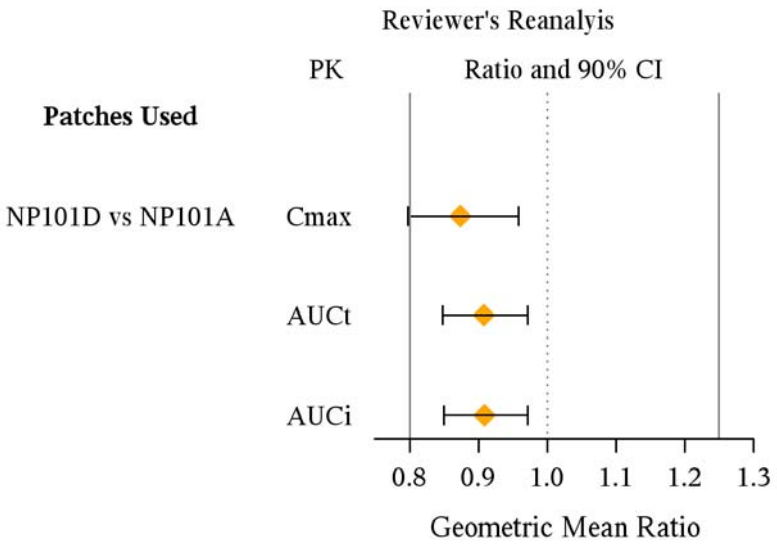
Reviewer's reanalysis:

For reanalysis, subjects 2 and 28 were also included since these subjects completed at least 2 treatments. Subject 4 was excluded since the subject just completed one treatment.

The 90% CIs for maximum plasma concentration (Cmax) ranged from 79.8 to 95.8 with a GMR) of 87.4. For $AUC_{inf,}$ 90% CI ranged from 85 to 97.2 with a GMR of 90.9.

Although the 90% CI of the GMR for the Cmax was not within the prespecified intervals of 80-125%, this minor difference in C_{max} is not considered clinically significant. The Imitrex nasal spray formulation, approved based on effectiveness and safety in clinical trials, results in relatively lower C_{max} and AUC_{inf} when compared to that of NP101. Therefore, comparative bioavailability of sumatriptan delivered by NP101 intended for commercial is acceptable.

Figure 4: Reanalysis of Bioequivalence for Treatment Groups: Commercial Product vs. Phase III Product



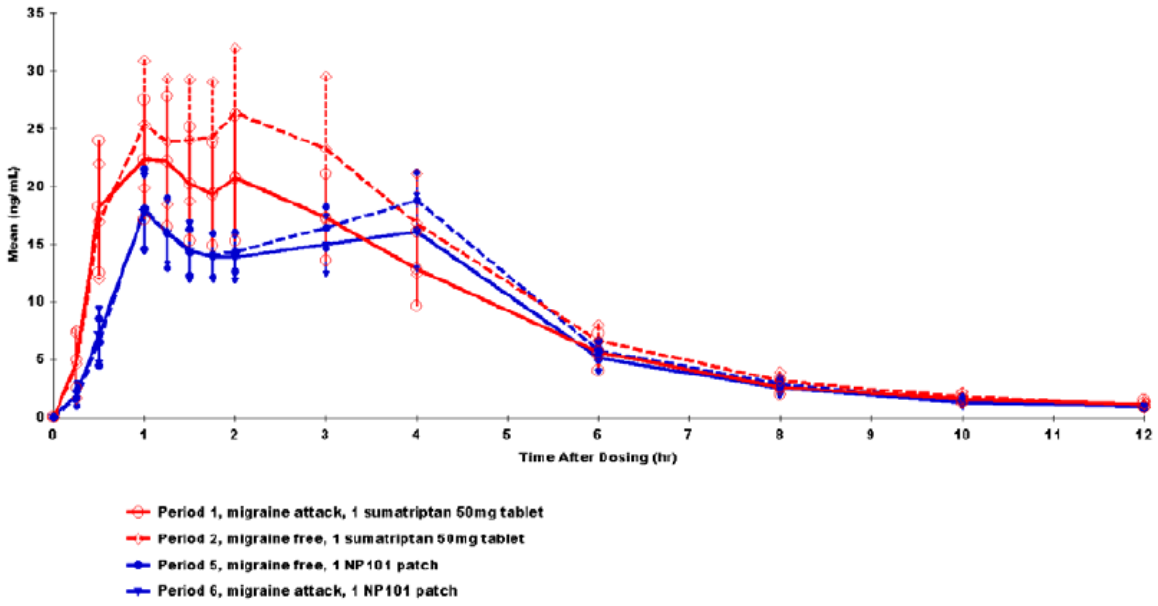
NP101A: patch previously used in the Phase 3 efficacy and safety study (NP101-007)
NP101D patch for long term studies and commercial use

Is there a difference in pharmacokinetics of sumatriptan during migraine attack and during a migraine-free period after NP101 treatment and after oral sumatriptan administration?

Yes. The effect of migraine on pharmacokinetics of sumatriptan after oral administration and NP101 treatment was evaluated in study NP101-011. Following oral administration of 50 mg sumatriptan, approximately 40% of subjects exhibited a migraine effect on sumatriptan pharmacokinetics during an acute migraine attack compared to during a non-migraine period. In these subjects, mean sumatriptan Cmax and AUC_{0-4} were decreased by 48% and 45%, respectively, following oral administration during a migraine compared to a migraine-free period.

There were no differences in mean sumatriptan Cmax or AUC_{0-4} observed following NP101 treatment during a migraine compared to that observed following NP101 treatment during a migraine-free period.

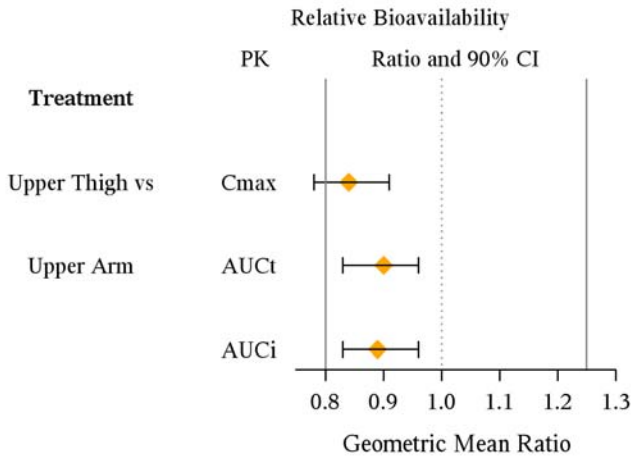
Figure 5: Sumatriptan Mean (95% CI) Plasma Concentration – Time Profile by Treatment and Period (N=18)



NP101 is indicated to be applied on upper arm or thigh. Is the patch placement site interchangeable?

Relative bioavailability of sumatriptan following NP101 applied to upper arm and thigh was compared in study NP101-012. NP101 application site is interchangeable as relative bioavailability of sumatriptan following application of patch to upper arm and thigh were comparable as shown in the plot below. The 90% CI for Cmax were (78 to 91%) out of 80 to 125% bioequivalence limits. Minor differences in Cmax are not clinically significant. The 90% CIs for the AUC_{inf} ranged from 83 to 96 with a GMR) of 89. Transdermal patch applied to upper arm delivered approximately 6.85 mg of sumatriptan, and NP101 applied to upper thigh delivered approximately 6.13 mg of sumatriptan.

Figure 6: Analysis of Relative Bioavailability for Treatment Groups With Different Application Site: Upper Arm vs. Thigh



F. Analytical

Have the analytical methods been sufficiently validated?

Yes.

Method: Sumatriptan and the internal standard were isolated through [redacted] (b) (4) using an [redacted] (b) (4). The eluate is [redacted] (b) (4). The final extract is analyzed via [redacted] (b) (4). The lower limit of quantitation was nominally 0.200 ng/mL for sumatriptan.

Pre-Study Bioanalytical Method Validation

Information Requested	Data
Analyte	Zolpidem
Internal standard (IS)	[redacted] (b) (4)
Method description	HPLC-[redacted] (b) (4) chromatography with MS/MS detection
Limit of quantitation	1.0 ng/mL
Average recovery of drug (%)	70.8%
Average recovery of IS (%)	69.2%
Standard curve concentration range (ng/mL)	0.2-100 ng/mL
Standards Accuracy Range (%)	98.2%-100.5%
Standards precision range (%)	1.3%-7.7%
QC concentrations (ng/mL)	LQC = 0.2 ng/mL MQC = 0.5 ng/mL MQC2 = 7.5 ng/mL HQC = 75 ng/mL
QC precision range (%)	1.1%-7.9%
QC accuracy range (%)	93%-98%
Bench-top stability (hrs)	26 hours at room temperature.

Stock stability (days)	63 days
Stock Solution stability (hrs) (Short Term)	28 days in frozen matrix
Wet Extract Stability	127 hours @ Ambient temperature.
Freeze-thaw stability (cycles)	4 cycles.
Long-term storage stability (days)	506 days
Dilution integrity	4 fold
Selectivity	No interfering peaks noted in blank plasma samples

Office of Scientific Investigations Audit:

At the request of Division of Neurology Products, the Office of Scientific Investigations conducted audit of the following pivotal bioequivalence study:

Study # NP101-013: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioavailability of Three NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments With an Oral Formulation of Imitrex® in Healthy Volunteers and to Collect Resistance Data During Application of NP101

The clinical and analytical portions of the studies were conducted at Prism Research, Saint Paul, MN and (b) (4) respectively. Following the inspections at (b) (4) and Prism Research, Form 483s (Inspectional Observations) were issued. The clinical and analytical audit was based on 100% audit of source data.

OSI evaluated the (b) (4) response to the Form 483 and associated exhibits related to objectionable observations and concluded that the firm adequately responded to the violations and recommended that the bioanalytical data be accepted for review.

III. Labeling Recommendations

Since the product design is not acceptable from a CMC perspective, NP101will not be approved. Therefore, no further labeling recommendation will be made and labeling recommendations are not outlined in the Detailed Labeling Recommendations section of the review at this point.

IV. Appendix

A Individual Study Synopsis

NP101-005: A Phase I, Single Center, Open Label, Randomized, Crossover Study to Compare the Pharmacokinetics of NP101 (Sumatriptan Iontophoretic Transdermal Patch) with Three Formulations of Imitrex® in Healthy Volunteers

Objectives:

- The primary objective was to compare the pharmacokinetics (PK) of NP101 (sumatriptan iontophoretic transdermal patch) with the currently approved oral, subcutaneous injection and nasal spray formulations of Imitrex® in healthy volunteers and to assess the bioavailability relative to the 6 mg subcutaneous injection.
- The secondary objective was to evaluate the safety of NP101 in healthy volunteers.

<table>
<tr><td>Study Design</td><td colspan="2">Single-centre, open, randomized, crossover trial. Subjects were to receive five study treatments in sequence according to the randomization schedule.</td></tr>
<tr><td>Study Population</td><td colspan="2">Healthy male (n=13) and female (n=12)
Age: 18-65 years
BMI: 18.0- 30 kg/m^2
25 subjects were randomized, and 16 completed the study</td></tr>
<tr><td>Treatment Groups</td><td colspan="2">
<table>
<tr><th>Treatment</th><th>Worn</th><th>Wear Time (hr)</th><th>Waveform</th><th>mA Min</th><th>Anode Reservoir Formulation</th><th>Cathode Reservoir Formulation</th></tr>
<tr><td>A, F</td><td>Upper arm</td><td>4</td><td>(b) (4)</td><td>(b) (4)</td><td>(b) g of sumatriptan gel solution (b) % polyamine and (b) sumatriptan succinate) containing (b) (4) mg of sumatriptan succinate</td><td>(b) (4) Hydroxypropylcellulose (HPC) and NaCl</td></tr>
<tr><td>E, G</td><td>Upper arm</td><td>4</td><td>(b) (4)</td><td></td><td>(b) g of sumatriptan gel solution (b) (4) polyamine and (b) sumatriptan succinate) containing 104 mg of sumatriptan succinate</td><td>(b) (4) Hydroxypropylcellulose (HPC) and NaCl</td></tr>
</table>
Note: Dosing with Treatment A and E was discontinued after nine subjects were treated. Possible patch performance issues were investigated and modified patches (Treatment F and G) were subsequently used.

NP101 patches studied in this trial are described below. The patches were designed to deliver a theoretical dose of 10 mg.
</td></tr>
<tr><td>Dosage and Administration</td><td>
Reference: Each subject was to receive three formulations of Imitrex®:
• Treatment B -100 mg oral tablet
• Treatment C - 6 mg subcutaneous injection
• Treatment D - 20 mg intranasal spray
</td><td>
Test: NP101 patches
Treatment A, F:
(b) (4) g of sumatriptan gel solution ((b) (4)% polyamine and (b) (4) sumatriptan succinate) containing 120 mg of sumatriptan succinate
Treatment E, G: (b) (4) g of sumatriptan gel solution ((b) (4)%
</td></tr>
</table>

		polyamine and (b) (4) sumatriptan succinate) containing (b) (4) mg of sumatriptan succinate
Sampling: Blood	Blood samples were collected as follows for **Treatments A, E, F and G** (NP101): pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 16 hours post-dose. **Treatment B** (oral): pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose. **Treatment C (SQ) and Treatment D (IN):** pre-dose (within 15 minutes prior to dosing) and at 0.17, 0.33, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. **Reviewer's Comment:** Blood samples were collected upto16 hrs postdose for patch treatment groups and upto12 hrs postdose for SQ and IN treatment when compared to 24 hrs in oral treatment group. Sampling scheme is adequate for characterizing PK parameters including peak plasma concentration and terminal half-life (AUC_{0-t} was >98% of AUC0-inf in all treatment groups).	
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_6 as an internal standard and a lower limit of quantification of 0.2 ng/mL.	

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 1.25, 4.5, 15, and 75 ng/mL	0.2, 0.4, 0.7, 2.5, 8, 30, 80 and 100 ng/mL
Between Batch accuracy	103.2 to 104.5	87.7 to 101.1
Between Batch Precision (%CV)	1.67 to 3.84	1.46 to 6.05
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9998	
Linear Range (ng/mL)	0.2 to 100 ng/mL	
Sensitivity (LLOQ, ng/mL)	0.2 ng/mL	

PK Assessments	The following PK parameters were determined: C_{max}, T_{max}, λz, t½, AUC_{0-last}, AUC_{0-inf} and total body clearance (Cl/F). The bioavailability (F) of the non-parenteral formulations was assessed relative to the subcutaneous injection. The dose delivered during iontophoretic application was calculated using the following equation: F*Dose delivered = AUC_{0-inf} iontophoretic * $Clearance_{sc}$ [F = fraction of dose absorbed into systemic circulation.]
PD Assessments	None
Statistical Methods	Pharmacokinetics: PK parameters for sumatriptan were calculated from the actual plasma concentration-time data using non-compartmental method with the computer program WinNonlin™. PK parameters for each treatment were reported along with descriptive statistics. The relative bioavailability of subcutaneous sumatriptan was almost 100% and therefore, this route (Treatment C) was used as reference for determination of the non-parenteral bioavailabilities (Treatments A, B, D, E, F and G). The relative bioavailability (F) after non-parenteral routes (np) were calculated as: F=AUC_{inf} (np). (Dose) SQ /(AUC_{inf})SQ.(Dose)np. Analysis of variance (ANOVA) was used to compare AUC_{0-inf} and C_{max} values between treatments. The relative bioavailability was assessed by the 2 1-sided test procedure via 90% confidence intervals obtained within the framework of the ANOVA for dose normalized ln(C_{max}) and ln(AUC_{0-inf}) for each of the non-parenteral formulations (Treatments A, B, D, E, F and G) against sumatriptan subcutaneous injection (Treatment C). The relative bioavailability of the patch was assessed both using the theoretical dose of 10 mg and the calculated dose delivered to the systemic circulation. AUC_{0-last}, T_{max} and $t_{1/2}$ were summarized descriptively. Race (white or nonwhite) and sex (male or female) effects on PK parameters were evaluated and PK parameters were also tabulated by race and sex subgroups.

RESULTS:

The mean amount of drug delivered by NP101 Treatments F and G was 6.11 mg and 6.09 mg respectively (95%CI was 5.33 to 6.88 mg for Treatment F and 5.52 to 6.66 mg for Treatment G).

The table below provides a summary of arithmetic means of the pharmacokinetic parameters for each treatment group.

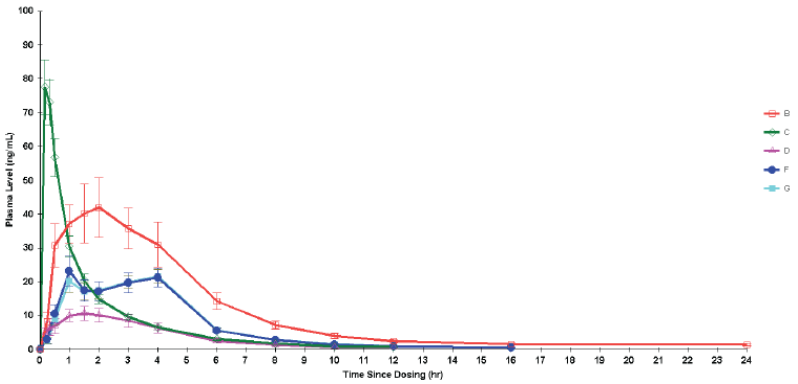
Table 3: Pharmacokinetic Parameters for Each Treatment Group.

Treatment Group	AUC0-inf (hr*ng/mL)	AUC0-last (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	t1/2 (hr)	Lambda_z (/hr)	Cl/F (mL/hr)
SQ (n=23)	113.60	111.42	82.24	0.25	2.21	0.31	53938
Nasal (n=23)	50.25	48.72	12.49	1.45	2.24	0.31	600884
Oral (n=23)	247.14	237.40	51.61	2.24	4.82	0.16	434641
Treatment F (n=17)	113.45	111.51	24.76	1.65	2.94	0.22	93886
Treatment G (n=17)	112.92	111.01	23.05	2.53	2.86	0.23	91636

Treatment groups: B = Oral, C = SQ, D = Nasal, F = Patch Treatment F, and G = Patch Treatment G

The geometric mean sumatriptan plasma concentration (95%CI) vs time profiles are presented by treatment formulation in the figure below.

Figure 7: Mean sumatriptan (95% CI) plasma concentrations (ng/mL) vs time profiles



Treatment groups: B = Oral, C = SQ, D = Nasal, F = Patch Treatment F, and G = Patch Treatment G

Table below presents the dose delivered during iontophoretic application using the following equation:

F*Dose delivered = $AUC_{0\text{-}inf}$ iontophoretic * $Clearance_{sc}$
[F = fraction of dose absorbed into systemic circulation.]

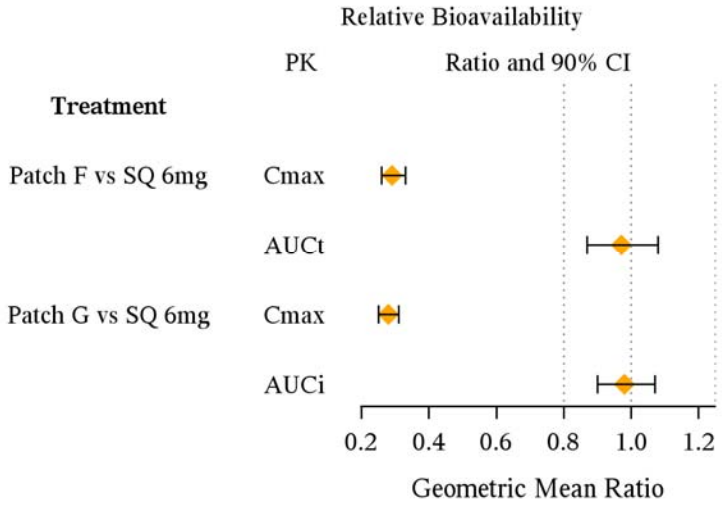
Table 4: Dose Delivered During Iontophoretic Application

Parameter	N	Arithmetic Mean (95% CI)			Min	Max	Median	CV (%)
		Mean	Lower	Upper				
Treatment F dose delivered	17	6.11	5.33	6.88	3.47	9.07	6.26	24.7
Treatment G dose delivered	17	6.09	5.52	6.66	3.67	7.50	6.05	18.2

Relative Bioavailability

Figure below presents the estimates of relative bioavailability and corresponding 90% confidence intervals for each patch formulation vs. subcutaneous injection estimated by the 2 1-sided test procedure obtained within the framework of the ANOVA.

Figure 8: Analysis of Relative Bioavailability of two NP101 Products With Respect to Subcutaneous Injection



Race Effect

Table below represents pharmacokinetic parameters summarized by race (white or non-white) for each treatment group in the subjects who had patch Treatments F and G.

Table 5: Pharmacokinetic Parameters Summary by Race Group – Subjects Who Received Patch Treatments F and G

Parameter	Group	Estimate (95%CI) Non-white	Estimate (95%CI) White	GM Ratio (95%CI) (Non-white / White)	Difference p-value
AUC0-inf (hr*ng/mL)	Nasal	35.80 (20.80 - 61.63)	47.80 (28.65 - 79.76)	0.75 (0.36 - 1.58)	0.4222
	Oral	228.03 (183.79 - 282.92)	265.66 (216.78 - 325.57)	0.86 (0.64 - 1.15)	0.2894
	SQ	107.90 (95.70 - 121.66)	114.70 (102.43 - 128.44)	0.94 (0.80 - 1.11)	0.4421
	Patch F	89.86 (78.78 - 102.49)	131.74 (116.38 - 149.13)	0.68 (0.57 - 0.82)	0.0004
	Patch G	97.64 (87.32 - 109.18)	124.57 (112.12 - 138.41)	0.78 (0.67 - 0.91)	0.0041
AUC0-last	Nasal	33 92 (19.26 - 59.73)	46.12 (27.05 - 78.63)	0.74 (0.34 - 1.60)	0.4129

(hr*ng/mL)	Oral	216.54 (174.12 - 269.28)	259.03 (210.90 - 318.13)	0.84 (0.62 - 1.13)	0.2218
	SQ	105.91 (93.92 - 119.43)	113 56 (101.40 - 127.18)	0.93 (0.79 - 1.10)	0.3822
	Patch F	88 21 (77.35 - 100.59)	129.60 (114.50 - 146.69)	0.68 (0.57 - 0.82)	0.0004
	Patch G	95.59 (85.56 - 106.80)	122.86 (110.67 - 136.40)	0.78 (0.67 - 0.91)	0.0032
Cmax (ng/mL)	Nasal	9.65 (6.19 - 15.04)	12.24 (8.05 - 18.60)	0.79 (0.43 - 1.45)	0.4198
	Oral	42.35 (32.71 - 54.82)	58.77 (46.07 - 74.96)	0.72 (0.51 - 1.03)	0.0677
	SQ	74.70 (63.98 - 87.22)	84.21 (72.77 - 97.46)	0.89 (0.72 - 1.10)	0.2488
	Patch F	19 34 (16.82 - 22.23)	28.92 (25.35 - 32.98)	0.67 (0.55 - 0.81)	0.0004
	Patch G	19.23 (16.85 - 21.95)	25.89 (22.85 - 29.33)	0.74 (0.62 - 0.89)	0.0033
t1/2 (hr)	Nasal	2.54 (1.97 - 3.26)	1.83 (1.44 - 2.32)	1.39 (0.98 - 1.96)	0.0616
	Oral	4.34 (3.31 - 5.69)	4.01 (3.10 - 5.17)	1.08 (0.75 - 1.57)	0.6555
	SQ	2.24 (2.01 - 2.49)	1.85 (1.67 - 2.04)	1.21 (1.05 - 1.40)	0.0135
	Patch F	2.85 (2.48 - 3.28)	2.94 (2.58 - 3.35)	0.97 (0.80 - 1.18)	0.7486
	Patch G	2.92 (2.55 - 3.35)	2.73 (2.40 - 3.10)	1.07 (0.89 - 1.29)	0.4573
Tmax (hr)	Nasal	1.15 (0.76 – 1.54)	1.69 (0.75 – 2.63)	NA	0.4293
	Oral	1.94 (1.47 – 2.41)	2.44 (1.40 – 3.49)	NA	0.5478
	SQ	0.23 (0.16 - 0.30)	0.29 (0.24 – 0.35)	NA	0.1147
	Patch F	2.00 (0.82 – 3.18)	1.33 (0.57 – 2.10)	NA	0.2697
	Patch G	3.25 (2.28 – 4.22)	1.89 (0.84 – 2.94)	NA	0.0489

N=9 white; N= 8 non-white

Race differences in AUC, C_{max}, and T_{max} were not statistically significant after oral, nasal and subcutaneous administration of sumatriptan.

White subjects had relatively shorter $t_{1/2}$ than non-white subjects after subcutaneous treatment with sumatriptan (p=0.0135).

According to the package insert (PI) for oral and injectable sumatriptan, the systemic clearance and Cmax of sumatriptan were similar in non-white and Caucasian healthy male subjects (nasal has not been evaluated).

Reviewer's Comment:

Even though bioavailability of sumatriptan decreased in non-white subjects the half-life observed was similar. Therefore, this change cannot be attributed to melanin binding. The above Study (NP101-005) was conducted in fewer subjects (13 Males and 12 females only 17 completed, n=9 for white and n=8 for non-white) to draw any conclusions.

Minor difference in half-life of sumatriptan was not observed in previous studies conducted for Imitrex s.c injection. According to the PI systemic clearance and Cmax of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

Table 6: Pharmacokinetic Parameters Summary by Gender

			-- Geometric Means--		
Parameter	Treatment	Subset	Estimate (95%CI)	Ratio (95%CI)	Difference between Subgroup p-value*
AUCinf	Nasal	Sex=FEMALE	51.74 (31.57 - 84.81)	1.58 (0.77 - 3.25)	0.1961
		Sex=MALE	32.75 (19.39 - 55.32)		
	Oral	Sex=FEMALE	264.08 (215.21 - 324.05)	1.15 (0.85 - 1.55)	0.3328
		Sex=MALE	229.57 (184.78 - 285.22)		
	Patch F	Sex=FEMALE	108.19 (89.48 - 130.82)	0.96 (0.73 - 1.27)	0.7860
		Sex=MALE	112.15 (91.69 - 137.17)		
	Patch G	Sex=FEMALE	109.49 (95.25 - 125.87)	0.97 (0.79 - 1.19)	0.7531
		Sex=MALE	112.89 (97.38 - 130.87)		
	SQ	Sex=FEMALE	118.86 (107.20 - 131.79)	1.15 (0.99 - 1.33)	0.0718
		Sex=MALE	103.66 (92.90 - 115.66)		
Cmax	Nasal	Sex=FEMALE	11.81 (7.73 - 18.04)	1.18 (0.63 - 2.18)	0.5843
		Sex=MALE	10.04 (6.41 - 15.74)		
	Oral	Sex=FEMALE	51.71 (39.39 - 67.88)	1.06 (0.71 - 1.57)	0.7691
		Sex=MALE	48.91 (36.64 - 65.27)		
	Patch F	Sex=FEMALE	23.00 (18.86 - 28.04)	0.92 (0.69 - 1.23)	0.5441
		Sex=MALE	25.02 (20.27 - 30.88)		
	Patch G	Sex=FEMALE	22.83 (19.31 - 26.99)	1.03 (0.81 - 1.31)	0.7991
		Sex=MALE	22.16 (18.55 - 26.47)		
	SQ	Sex=FEMALE	78.17 (67.13 - 91.03)	0.96 (0.77 - 1.20)	0.7179
		Sex=MALE	81.23 (69.11 - 95.46)		
t 1/2	Nasal	Sex=FEMALE	2.06 (1.58 - 2.69)	0.93 (0.63 - 1.37)	0.6819
		Sex=MALE	2.22 (1.68 - 2.94)		
	Oral	Sex=FEMALE	4.35 (3.37 - 5.61)	1.10 (0.76 - 1.59)	0.5995
		Sex=MALE	3.96 (3.02 - 5.19)		
	Patch F	Sex=FEMALE	2.79 (2.45 - 3.17)	0.92 (0.76 - 1.11)	0.3557
		Sex=MALE	3.03 (2.65 - 3.47)		
	Patch G	Sex=FEMALE	2.72 (2.39 - 3.09)	0.93 (0.77 - 1.12)	0.4149
		Sex=MALE	2.93 (2.56 - 3.35)		
	SQ	Sex=FEMALE	1.99 (1.76 - 2.25)	0.97 (0.81 - 1.16)	0.6876
		Sex=MALE	2.06 (1.81 - 2.35)		

Male n=8, Female n=9

CONCLUSIONS

- Treatments F and G delivered approximately 6.11 mg sumatriptan.
- Based on this delivered dose, the $AUC_{0\text{-}inf}$ calculated for NP101 were about 99% to 100% of $AUC_{0\text{-}inf}$ of the subcutaneous injection, the C_{max} of the patches was about 28% to 30% of the C_{max} of the subcutaneous injection.
- There was no statistically significant difference in the mean PK parameters between Treatments F and G.
- No statistically significant differences were observed between male and female subjects in PK parameters after patch applications.

NP101-006: A Phase I, Single Center, Open Label, Single-Dose, Five-Period Study to Compare the Pharmacokinetics of NP101 (Sumatriptan Iontophoretic Transdermal Patch) in Healthy Volunteers

Objectives:

- The primary objective was to compare the pharmacokinetics (PK) profiles among five NP101 patches in healthy volunteers.
- The secondary objective was to evaluate the safety of NP101 in healthy volunteers.

<table>
<tr><td>Study Design</td><td>Single-centre, open-label, single-dose, five period study. Treatment periods were separated by a minimum three-day washout period.</td></tr>
<tr><td>Study Population</td><td>Healthy male and female
Age: 18-45 years
BMI: 18.0- 30 kg/m^2
4 subjects were enrolled in the study</td></tr>
<tr><td>Treatment Groups</td><td>The study treatments were as follows:
<table>
<tr><th>Period</th><th>Placement</th><th>NP101 Patch Design</th></tr>
<tr><td>Period 1</td><td>Upper Arm</td><td>S1V design, with pad transfer ring used in patch</td></tr>
<tr><td>Period 2</td><td>Upper Arm</td><td>S2N design, with no pad transfer ring used in patch</td></tr>
<tr><td>Period 3</td><td>Upper Arm</td><td>C1V design, with pad transfer ring used in patch</td></tr>
<tr><td>Period 4</td><td>Upper Arm</td><td>C2N design, with no pad transfer ring used in patch</td></tr>
<tr><td>Period 5</td><td>Upper Thigh</td><td>S1V design, with pad transfer ring used in patch</td></tr>
</table>
The NP101 designs administered in the study are described using the following definitions:
S design = (b) (4) firmware programming
C design = (b) (4) firmware programming
1V = with pad transfer ring</td></tr>
</table>

	2N = without pad transfer ring
Sampling: Blood	Blood samples at each of Periods 1–5, a total of 13 blood samples were collected at the following time points for the determination of sumatriptan concentrations in plasma: pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 16 hrs 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_6 as an internal standard and a lower limit of quantification of 0.2 ng/mL.

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 1.25, 4.5, 15, and 75 ng/mL	0.2, 0.4, 0.7, 2.5, 8, 30, 80 and 100 ng/mL
Between Batch accuracy	98.6 to 101	99.2 to 102.2
Between Batch Precision (%CV)	-0.68 to 2.48	2.6 to 3.64
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9998	
Linear Range (ng/mL)	0.2 to 100 ng/mL	
Sensitivity (LLOQ, ng/mL)	0.2 ng/mL	

PK Assessments	The following PK parameters for sumatriptan included AUC_{0-last}, AUC_{0-inf}, C_{max}, T_{max}, first order terminal elimination rate constant (λz), and terminal half-life ($t_{1/2}$).
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:

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

PK Parameter Mean (SD) – Excluding Subjects 002 and 003 from Period 2

Treatment	S1V	SIV	S2N [1]	C1V	C2N
Period	1	5	2	3	4
λ_z,	0.263 (0.029)	0.279 (0.035)	0.275 (0.036)	0.261 (0.020)	0.264 (0.020)
$T_{1/2}$ (hr)	2.66 (0.296)	2.51 (0.337)	2.55 (0.336)	2.67 (0.207)	2.64 (0.183)
T_{max} (hr)	2.50 (1.732)	2.50 (1.732)	4.00 (0)	3.25 (1.500)	2.50 (1.732)
C_{max}	22.35 (4.455)	20.80 (3.207)	27.00 (1.697)	23.78 (4.140)	26.88 (5.222)
AUC_{last} (hr.ng/mL)	124.58 (31.660)	112.77 (20.479)	152.08 (9.926)	123.35 (29.326)	141.36 (31.433)
AUC_{inf} (hr.ng/mL)	126.31(32.560)	114.221 (20.975)	154.22 (10.597)	125.87 (30.490)	143.72 (32.484)

[1] Subjects 002 and 003 were excluded from Period 2 summaries due to patch early removal.

Reviewer's Comment: This is a pilot exploratory study conducted in four subjects during the preliminary development. Two subjects were excluded from period 2 due to patch malfunction.

CONCLUSIONS

- Patches without the pad transfer ring appeared to have a relatively higher mean C_{max} and AUC when compared to the patches with a pad transfer ring (Treatment S2N vs. S1V or C2N vs. C1V).
- C_{max} and AUC appeared to be relatively higher when patch S1V was applied to the upper arm compared to upper thigh application.
- Patches with different microprocessors (Treatment SIV vs. CIV or S2N vs. C2N) appeared to have similar pharmacokinetic profiles.

NP101-011: A Phase I, Open Label, Single-Dose, Four-Way Crossover Study [total of six study periods per amended protocol] Comparing the Pharmacokinetics of NP101 (Sumatriptan Iontophoretic Transdermal Patch) with an Oral Formulation of Imitrex® (50 mg) in Migraine Subjects During an Acute Migraine Attack and During a Non-Migraine Period

Objectives:

The primary objective of this Phase I study was to compare the pharmacokinetics (PK) of NP101 with a currently approved oral formulation of Imitrex® in migraine subjects during an acute migraine attack and during a non-migraine period.

Study Design	Single-centre, open-label, single-dose, four-way crossover study.
Study Population	Healthy male and female Age: 18-65 years

	A total of 23 subjects were enrolled in study
Treatment Groups	Treatment A: Sumatriptan Succinate Oral (50 mg) Tablet Treatment B: NP101
NP101 Formulation	<table><tr><th>Treatment</th><th>Formulation Anode Reservoir</th><th>Formulation Cathode Reservoir</th></tr><tr><td>B</td><td>3.0 g of sumatriptan gel solution (10% polyamine and 4% sumatriptan succinate) containing 120 mg of sumatriptan succinate</td><td>3.0 g of 2% Hydroxypropylcellulose (HPC) and 0.9% sodium chloride (NaCl)</td></tr></table>
Sampling: Blood and Urine	Blood Samples: Period 1to 4 15 blood samples for PK analysis were obtained at the following time points: 0 (within 15 minutes prior to dosing), 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose. Period 5 and 6 14 blood samples for PK analysis were obtained at the following time points: 0 (within 15 minutes prior to dosing), 0.25, 0.5, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12 hours post-dose. **Reviewer's Comment:** Blood sampling scheme is adequate for characterizing PK parameters including peak plasma concentration and terminal half-life. Urine Samples: A 24 hour urine sample was collected from all subjects who participated in Periods 2, 4 and 5 in order to compare the metabolic profile of sumatriptan over the 24-hour period following oral and NP101 treatments. Urine samples were analyzed for sumatriptan and metabolites using LC/MS/MS in different detection modes.
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_6 as an internal standard and a lower limit of quantification of 0.2 ng/mL. <table><tr><th>Parameter</th><th>Quality Control Samples</th><th>Standard Curve Samples</th></tr><tr><td>Quality Control or Standard Curve Concentration (ng/mL)</td><td>0.5, 1.25, 4.5, 15, and 75 ng/mL</td><td>0.2, 0.4, 0.7, 2.5, 8, 30, 80 and 100 ng/mL</td></tr><tr><td>Between Batch accuracy</td><td>98.4 to 106.4</td><td>98.4 to 103.1</td></tr><tr><td>Between Batch Precision (%CV)</td><td>0.85 to 2.93</td><td>0.5 to 3.05</td></tr><tr><td>Linearity</td><td colspan="2">Weighted linear equation ($1/X^2$), mean r=</td></tr></table>

	0.9997
Linear Range (ng/mL)	0.2 to 100 ng/mL
Sensitivity (LLOQ, ng/mL)	0.2 ng/mL

Reviewer's Comment: The performance of the assay method during study sample analysis is acceptable.

PK Assessments	The following PK parameters for sumatriptan were calculated from the actual plasma concentration-time data: AUC_{0-last}, AUC_{0-inf}, C_{max}, T_{max}, λz, t½. Amount and percent of drug excreted in urine unchanged or as sumatriptan metabolites over a 24-hour period were calculated from the 24-hour urine collection data during the non-migraine periods. Metabolic profiling and identification was also conducted on pooled urine samples.
PD Assessments	None
Statistical Methods	Pharmacokinetics: **Initial Planed Analysis** PK parameters for sumatriptan were calculated from the actual plasma concentration-time data using non-compartmental methods with WinNonlin. Analysis of variance (ANOVA) was used to compare AUC0-inf and Cmax values between treatments. AUC0-last, Tmax, t1/2 were summarized descriptively. **Changes to Planned Analyses** The protocol specified that plasma PK parameters (C_{max} and AUCs) and drug excretion parameters were to be analyzed using a mixed model analysis of variance (ANOVA) with treatment (NP101 vs oral sumatriptan) and period (migraine vs non-migraine) as fixed effects and subject as a random effect. The interaction between treatment and period was also to be examined. The differences of T_{max} were to be examined using the Wilcoxon Rank Sum test. Summary tables were to include adjusted geometric means and the corresponding 95% confidence intervals (95% CIs), and inferential statistics from the ANOVA for AUCs and C_{max} and the Wilcoxon Rank Sum test for T_{max}. However, these analyses were not performed.

RESULTS:

According to the sponsor the blood samples for PK analysis collected during the time that NP101 patches were being worn in Periods 3 and 4 may have been contaminated due to leakage from some of these patches. Therefore, the summaries of PK results presented were based only on data collected in Periods 1 and 2 and Periods 5 and 6.

Mean (SD) C_{max} and AUC Values by Period and Treatment: PK Evaluable Subjects (N=18)

According to the sponsor migraine effect on PK is defined as follows:
Migraine Effect = Yes if AUC_{0-4}(migraine)/AUC_{0-4}(migraine free) <0.80 and Cmax (migraine)/Cmax(migraine free) <0.80 after oral dosing.

Table 6: Mean (SD) Cmax and AUC Values by Period and Treatment for Subgroups of Subjects With Migraine Effect (N=7) and Without Migraine Effect (N=11) Following Oral Sumatriptan Treatment: PK Evaluable Subjects

	C_{max} (ng/mL)		**AUC_{0-4} (hr*ng/mL)**		**AUC_{0-12} (hr*ng/mL)**		**AUC_{0-inf} (hr*ng/mL)**	
Period (Treatment/	**Migraine Effect**		**Migraine Effect**		**Migraine Effect**		**Migraine Effect**	
Migraine Effect)	Yes	No	Yes	No	Yes	No	Yes	No
Period 1 (Oral/ Migraine)	19.1 (10.76)	30.9 (10.30)	51.7 (35.36)	79.2 (18.16)	87.0 (53.22)	111.7 (28.92)	96.5(64.91)	123.1 (34.69)
Period 2 (Oral/ Migraine-free)	36.8 (13.20)	30.5 (11.77)	93.2 (34.44)	76.7 (24.48)	143.7 (39.95)	111.6 (39.68)	156.8 (45.69)	125.4 (47.59)
Period 5 (NP101/ Migraine-free)	21.1 (2.59)	21.1 (5.74)	54.6 (8.20)	56.0 (16.67)	96.4 (12.19)	94.8 (27.63)	99.5 (12.87)	97.5 (28.61)
Period 6 (NP101/ Migraine)	19.4 (3.14)	20.4 (6.66)	56.1 (12.28)	50.5 (17.21)	92.6 (23.63)	84.3 (31.00)	94.8 (24.31)	87.7 (32.80)
Migraine Effect = Yes if $AUC_{0-4(migraine)}$/$AUC_{0-4(migraine\ free)}$ <0.80 and $C_{max\ (migraine)}$/$C_{max(migraine\ free)}$ <0.80 after oral dosing.								
One subject was excluded of AUC_{0-inf} summary due to poor linearity of the terminal phase (%AUC_{0-inf}) extrapolation >20%.								

Figure 9: Sumatriptan Mean (95% CI) Plasma Concentration – Time Profile by Treatment and Period (N=18)

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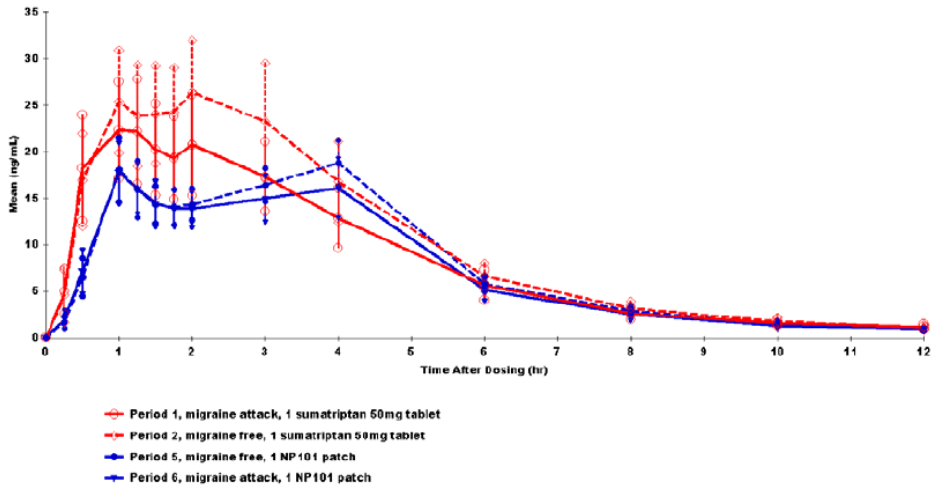


Reviewer's Comments: Two individual subjects had slightly lower plasma concentration during migraine attack following NP101 treatment.

Imitrex® PI indicates that Cmax is similar during a migraine attack and during a migraine-free period, but the Tmax is slightly later during the attack, approximately 2.5 hours compared to 2.0 hours.

Urinary Excretion

Unchanged sumatriptan excreted in urine on an average was lower after NP101 treatment (Period 5) than after oral sumatriptan 50-mg tablet treatment. The percent of dose excreted as unchanged sumatriptan was higher in Period 5 (11%, based on calculated dose delivered by patch treatment) than in Period 2 (2%).

Three metabolites of sumatriptan were identified in both Period 2 and Period 5: M1-oxidative deamination, M2-demethylation, and M5-hydroxylation. There was no difference in metabolite profile from Period 2 and Period 5.

The average percent of the metabolite, M1 (indol acetic acid), to the unchanged sumatriptan peak area ratio was higher in Period 5 (68.7%) than in Period 2 (38.1%). The absolute quantity of Ml in urine samples was not determined.

CONCLUSIONS

- Plasma concentration time profile for seven subjects out of 18 had decreased sumatriptan absorption (subjects are experiencing a migraine headache) compared to that observed when the same subjects are migraine headache free in Imitrex® 50 mg tablet treatment group.

- Two subjects in NP101 treatment group had decreased sumatriptan absorption during migraine attack when compared to migraine free group.

- Percentage of sumatriptan excreted unchanged to the dose delivered was higher for patch treatment when compared to oral treatment. However, there was no difference in metabolite profile from both treatments.

NP101-012: A Phase I, Single Center, Open-Label, Randomized, Single-Dose Study Encompassing: Three-Way Crossover Study to Compare the Pharmacokinetics of NP101 (Sumatriptan Iontophoretic Transdermal Patch) Applied to Two Different Application Sites with Subcutaneous Formulation of Imitrex® in Healthy Volunteers, and NP101 Pharmacokinetics in Healthy Elderly Volunteers Compared to NP101 Pharmacokinetics in Healthy Adult Volunteers

Objectives:

The primary objectives were:

- to assess bioavailability of NP101 applied to two different patch application sites: upper arm and upper thigh;
- to compare the pharmacokinetics of NP101 with the currently approved subcutaneous formulation of Imitrex® in healthy young adult volunteers by assessing the relative bioavailability of NP101 to the 6 mg subcutaneous injection; and
- to assess the pharmacokinetics of NP101 in healthy young vs. healthy elderly volunteers.

Study Design	Single-centre, open-label, randomized, single-dose study. Treatment periods were separated by three-day washout period.
Study Population	Healthy young and healthy elderly volunteers >65 years old (male and female) Age: 18-45 years and >65 years BMI: Group I 18.0- 25 kg/m^2; Group II 18.0- 27.6 kg/m^2 A total of 25 subjects were enrolled in Group I and 8 subjects in Group II
Treatment Groups	Group I: Group I subjects were healthy young adult volunteers between the ages of 18-45 years old. Each subject received two NP101 treatments and an Imitrex® 6 mg subcutaneous injection in sequence according to the randomization schedule. The treatments were separated by a three-day washout period. The three treatments received by Group I subjects were as follows: • Treatment A: NP101 applied to the upper arm and left in place for 4 hours • Treatment B: NP101 applied to the upper thigh and left in place for 4

	hours (b) (4) [redacted] atriptan utilizing mA minutes). • Treatment C: Imitrex® 6 mg sumatriptan (as the succinate salt) subcutaneous (SQ) injection Group II: Group II subjects were healthy elderly volunteers >65 years old, who were gender-matched and race-matched to a subgroup of healthy young adult volunteers between the ages of 18-45 years old from Group I. Group II subjects received a single NP101 treatment (Treatment A).
Duration of Treatment	Group I subjects who participated in all three crossover periods received two NP101 patch, one applied to the upper arm (Treatment A) and one applied to the upper thigh (Treatment B), and one Imitrex® SQ injection (Treatment C), each separated by at least a three-day washout period. Group II subjects received a single NP101 treatment applied to the upper arm (Treatment A).
Sampling: Blood	Blood samples (4 mL per sample) for PK analysis were collected for all treatments by catheter or venipuncture into ethylenediamine tetra acetic acid (EDTA) collection tubes at the following times for the determination of sumatriptan concentrations in plasma for each treatment: Pre-dose (within 15 minutes prior to dosing) and at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. **Reviewer's Comment:** Blood sampling scheme is adequate for characterizing PK parameters including peak plasma concentration and terminal half-life.
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_6 as an internal standard and a lower limit of quantification of 0.2 ng/mL.

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 1.25, 4.5, 15, and 75 ng/mL	0.2, 0.4, 0.7, 2.5, 8, 30, 80 and 100 ng/mL
Between Batch accuracy	95.9 to 97.4	98.9 to 108.4
Between Batch Precision (%CV)	3.05 to 7.06	2.06 to 6.87

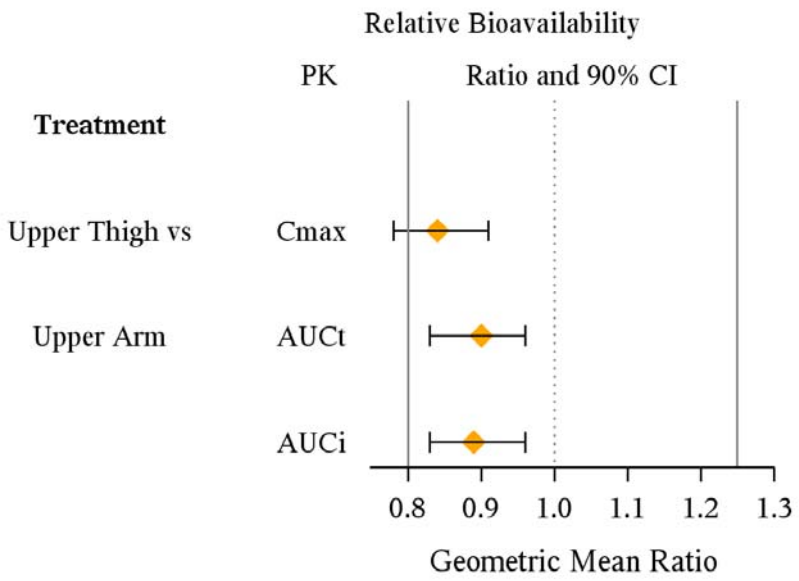
	<table><tr><td>Linearity</td><td>Weighted linear equation ($1/X^2$), mean r= 0.9997</td></tr><tr><td>Linear Range (ng/mL)</td><td>0.2 to 100 ng/mL</td></tr><tr><td>Sensitivity (LLOQ, ng/mL)</td><td>0.2 ng/mL</td></tr></table> **Reviewer's Comment:** The performance of the assay method during study sample analysis is acceptable.
Urine	None
Feces	None
PK Assessments	The following PK parameters for sumatriptan were calculated from the actual plasma concentration-time data: AUC_{0-last}, AUC_{0-inf}, C_{max}, T_{max}, λz, t½, and Cl/F.
Statistical Methods	Pharmacokinetics: PK parameters for sumatriptan were calculated from the actual plasma concentration-time data using non-compartmental methods with WinNonlin. Pharmacokinetic parameters for each treatment were reported along with descriptive statistics. Sumatriptan plasma concentration profiles were presented graphically by treatment, period, and subject. Analysis of variance (ANOVA) was used to compare AUC_{0-inf} and C_{max} values between treatments. AUC_{0-last}, T_{max}, $t_{1/2}$, and Cl/F were summarized descriptively. Period effects and sequence effects were evaluated. The relative bioavailability (F) was assessed by the 2 1-sided test procedure via 90% confidence intervals obtained within the framework of the ANOVA for ln(Cmax) and ln(AUC0-inf). As the dose delivered by NP101 application is estimated to be the same as the 6 mg subcutaneous formulation, no dose normalization was performed. The following four bioavailability assessments were provided: • F between Treatment B (patch applied to upper thigh) and Treatment A (patch applied to upper arm), where Treatment A is the reference treatment. • F between Treatment A (patch applied to upper arm) and Treatment C, where Treatment C (SQ) is the reference treatment. • F between Treatment B (patch applied to upper thigh) and Treatment C, where Treatment C (SQ) is the reference treatment. • F between Group II (healthy elderly subjects) and Group I (gender and race matched healthy young adults) after Treatment A, where Group I (healthy young adults) is the reference treatment.

	Summary tables included ratios and corresponding 90% confidence intervals (90% CIs). The dose delivered during NP101 (Treatments A and B) was calculated using the following equation: F*dose delivered=$AUC_{0\text{-}inf}$ iontophoretic * $Clearance_{sc}$ [F = fraction of dose absorbed into systemic circulation.]

PHARMACOKINETIC RESULTS

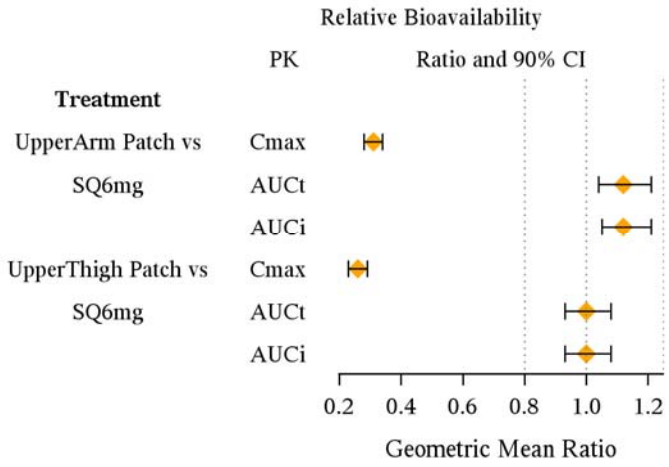
The bioavailability of the NP101 applied to the upper thigh (Treatment B) was compared to the NP101 applied to the upper arm (Treatment A) based on C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$. The results of this analysis are presented in the figure below.

Figure 10: Analysis of Relative Bioavailability for Treatment Groups With Different Application Site: Upper Arm vs. Thigh



The bioavailability of NP101 Treatment A and Treatment B were assessed relative to Treatment C (Imitrex® SQ injection) as shown in the figure below.

Figure 11: Analysis of Relative Bioavailability of NP101 Applied to Upper Arm and Thigh With Respect to Subcutaneous Injection



The bioavailability of the NP101 applied to the upper arm (Treatment A) was compared for elderly subjects (Group II) versus paired gender- and race-matched young adult subjects from Group I. The results of this analysis are shown in the figure below.

Figure 12: Analysis of Relative Bioavailability for Treatment Groups: Elderly vs. Young Subjects

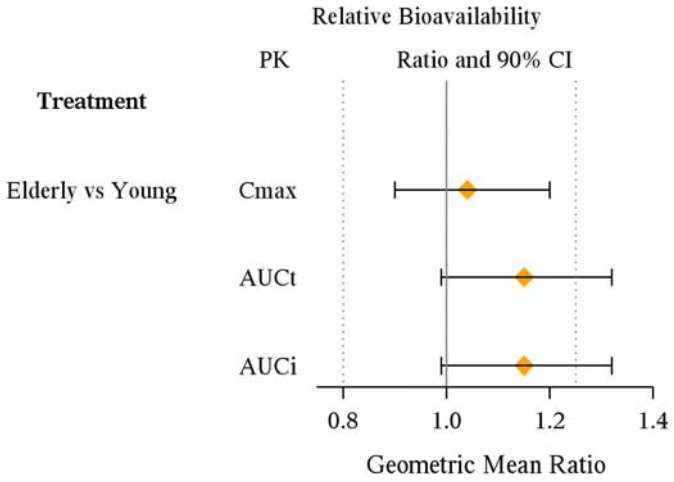
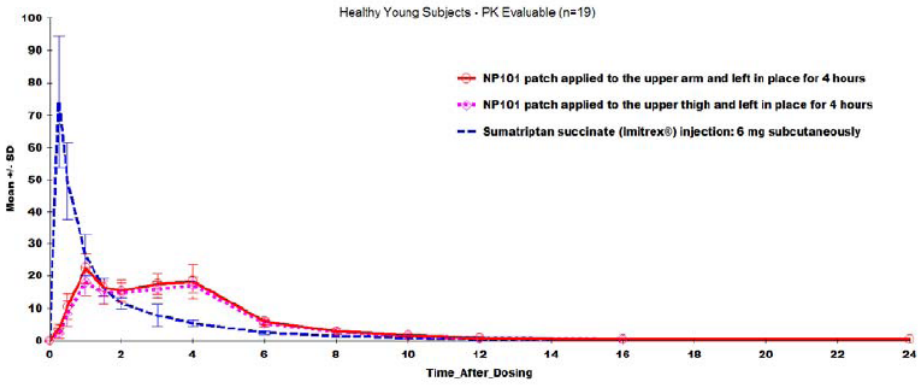


Figure 13: Mean (±SD) Sumatriptan Plasma Concentration vs Time Profile



CONCLUSIONS

- NP101 Treatment A (applied to upper arm) delivered approximately 6.85 mg of sumatriptan, and NP101 Treatment B (applied to upper thigh) delivered approximately 6.13 mg of sumatriptan.
- The C_{max} and $AUC_{0\text{-}inf}$ observed after NP101 application to the upper thigh (Treatment B) was comparable to that observed after application to the upper arm (Treatment A). However, 90% CI for Cmax were (78 to 91%) out of 80 to 125% BE limits. The 90% CIs for the AUC_{inf} ranged from 83 to 96 with a geometric mean ratio (GMR) of 89.
- The $AUC_{0\text{-}inf}$ of sumatriptan provided by the two NP101 treatments was comparable to that of subcutaneous injection of sumatriptan (6 mg); however, Cmax following NP101 administration was approximately 30% of that produced by subcutaneous injection.
- The overall exposure ($AUC_{0\text{-}inf}$) to sumatriptan following NP101 in elderly subjects was approximately 15% higher when compared to young adult subjects.

Labeling Recommendation: Application site can be interchanged as needed.

NP101-013: A Phase I, Single Center, Open Label, Randomized, Single-Dose, Three-Way Crossover Study to Compare the Pharmacokinetics and Bioavailability of Three NP101 (Sumatriptan Iontophoretic Transdermal Patch) Treatments With an Oral Formulation of Imitrex® in Healthy Volunteers and to Collect Resistance Data During Application of NP101

Objectives:

The primary objectives were:

- to compare the bioequivalence between NP101s previously used in the NP101-007 study (a Phase 3 study that demonstrated the efficacy and safety of NP101) and NP101s with minor modifications, in healthy adult volunteers;
- to compare the pharmacokinetics of NP101 with the currently approved oral formulation of Imitrex® in healthy adult volunteers;

Study Design	Single-centre, open-label, randomized, three-way, crossover study. Treatment periods were separated by a two- or three-day washout period.
Study Population	Healthy male (n=41) and female (n=22) Age: 18-65 years BMI: 18.0- 25 kg/m^2 63 subjects were enrolled, and 59 were included in the PK Evaluable Population
Treatment Groups	The study treatments were as follows: • Treatment A: NP101A patch previously used in the Phase 3 efficacy and safety study (NP101-007) applied to the upper arm and left in place for 4 hours. The NP101A patch was designed to deliver 6.5 mg of sumatriptan utilizing (b) (4) mA minutes). • Treatment B: NP101B patch for long term studies and commercial use (minor modifications from the NP101A patch including battery changed from two (b) (4) batteries to two (b) (4) batteries and (b) (4) l), applied to the upper arm and left in place for 4 hours. The NP101B patch was designed to deliver 6.5 mg of sumatriptan utilizing (b) (4) mA minutes). • Treatment C: RT Technology™ Imitrex® (100 mg oral sumatriptan succinate tablet). • Treatment D: NP101D patch for long term studies and commercial use (minor modifications from the NP101A patch including battery changed from two (b) (4) batteries to two (b) (4) 2 batteries, new (b) (4) [same as NP101B], with addition of a (b) (4) applied to the upper arm and left in place for 4 hours. The NP101D patch was designed to deliver 6.5 mg of sumatriptan utilizing (b) (4) mA minutes).
Duration of Treatment	Group 1 subjects who participated in all three crossover periods (Periods 1-3) received two NP101 patches (Treatments A and B) and one Imitrex® oral tablet, each separated by at least a three-day washout period; subjects who participated in Period 4 received one NP101 (Treatment B). Group 2 subjects who participated in all three crossover periods (Periods 1-3) received two NP101 patches (Treatments A and D), and one Imitrex® oral tablet, each separated by a two-day washout period.
Sampling: Blood	Blood samples were collected prior to study drug administration (0.25, 0.50, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs post-dose in each period.

	Reviewer's Comment: Blood sampling scheme is adequate for characterizing PK parameters including peak plasma concentration and terminal half-life (AUC_{0-t} was >95% of AUC_{0-inf} in all treatment groups).
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_6 as an internal standard and a lower limit of quantification of 0.2 ng/mL.

Parameter	**Quality Control Samples**	**Standard Curve Samples**
Quality Control or Standard Curve Concentration (ng/mL)	0.5, 1.25, 4.5, 15, and 75 ng/mL	0.2, 0.4, 0.7, 2.5, 8, 30, 80 and 100 ng/mL
Between Batch accuracy	95.6 to 98	96.3 to 102
Between Batch Precision (%CV)	2.78 to 5.36	1.86 to 6.11
Linearity	Weighted linear equation ($1/X^2$), mean r= 0.9997	
Linear Range (ng/mL)	0.2 to 100 ng/mL	
Sensitivity (LLOQ, ng/mL)	0.2 ng/mL	

Reviewer's Comment: The performance of the assay method during study sample analysis is acceptable.

PK Assessments	The following PK parameters for sumatriptan were calculated from the actual plasma concentration-time data: AUC_{0-last}, AUC_{0-inf}, C_{max}, T_{max}, λz, and t½.
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. Analysis of variance (ANOVA) was used to compare AUC_{0-last}, AUC_{0-inf}, and C_{max} values between treatments. T_{max}, and $t_{1/2}$ were summarized descriptively. Period effects and sequence effects were evaluated. The relative bioavailability (F) of Treatment D compared to Treatment A was assessed by the 2 1-sided test procedure; 90% confidence intervals (90% CIs) were obtained within the framework of the ANOVA for ln(Cmax), ln (AUC0-last), and ln(AUC0-inf). Treatment A (NP101A patch that was used in the Phase 3 efficacy and safety study [NP101-007]) was the reference

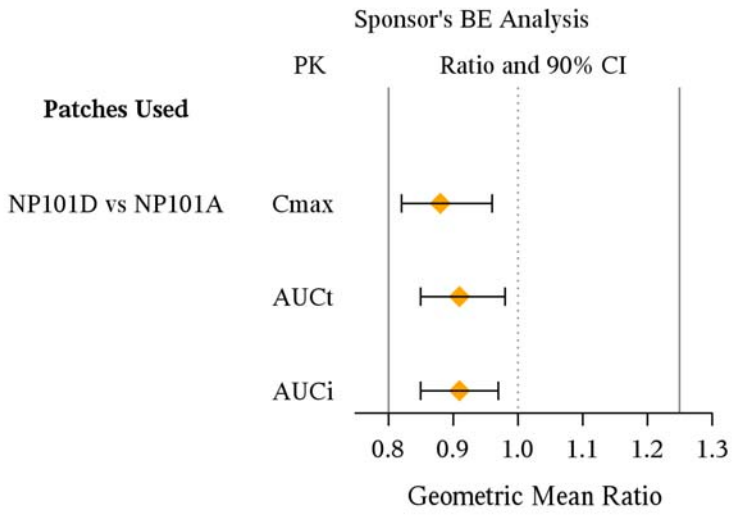
	drug and Treatment D was the test drug in this analysis. The relative bioavailability of NP101 Treatments A and D compared to Treatment C (oral) was assessed by the 2 1- sided test procedure; 90% CIs were obtained within the framework of the ANOVA. Treatment C was the reference drug and Treatments A and D were the test drugs in this analysis. Summary tables included ratios and the corresponding 90% CIs.

PHARMACOKINETICS RESULTS

The sponsor's assessment of the bioequivalence of the NP101D patch and the NP101A patch was based on C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$.

The figure below provides a summary of geometric mean ratios with 90% CI of the pharmacokinetic parameters for treatment groups.

Figure 14: Analysis of Bioequivalence for Treatment Groups: Commercial Product vs. Phase III Product



According to the sponsor's study report:

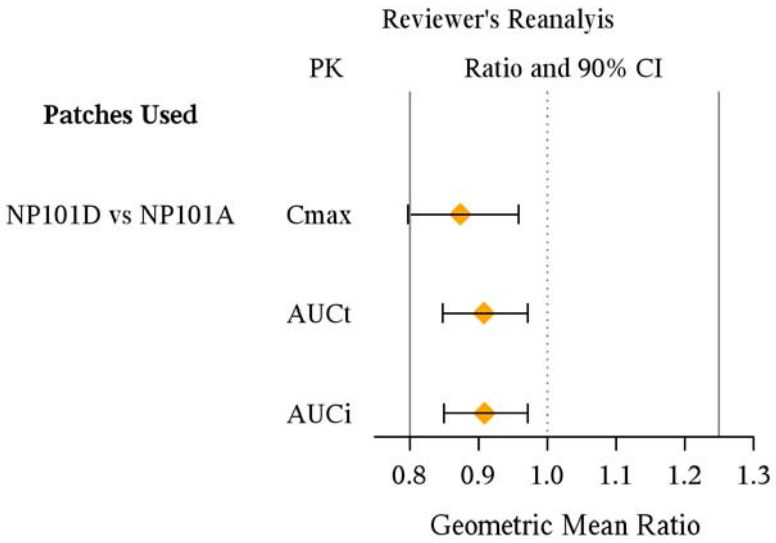
Thirty (30) subjects in Group 2 who received all three treatments (A, C, and D) and did not have any major protocol violations that may have confounded the interpretation of PK results were included in the PK Evaluable Population. This was the primary population for bioavailability/bioequivalence analysis.

Reviewer's Comment: Exclusion of subjects based on completion of all three treatments was not pre-specified in the study protocol. The sponsor excluded three subjects from PK analysis (subjects 2, 4 and 28). Subject 2 and 28 completed 2 treatments; subject 4 completed only one treatment.

Reviewer's reanalysis indicated that 90% CIs for Cmax ranged from 79.8 to 95.8 with a GMR of 87.4 and for AUCinf ranged from 85 to 97.2 with a GMR of 90.9.

For reanalysis, subjects 2 and 28 were also included since these subjects completed at least 2 treatments. Subject 4 was excluded since the subject just completed one treatment.

Figure 15: Reanalysis of Bioequivalence for Treatment Groups: Commercial Product vs. Phase III Product



The table below provides a summary of PK parameters by treatment group.

Table 7: Summary of PK Parameters by Treatment

Parameter	**PK Evaluable Population (N=30)**		
Statistic	**Treatment A**	**Treatment D**	**Treatment C**
C_{max}, ng/mL			
Mean (SD)	21.20 (6.101)	18.72 (4.848)	51.25 (14.796)
Median	20.00	18.50	49.95
Minimum, Maximum	9.96, 42.40	8.44, 33.30	21.20, 90.80
T_{max}, hr			
Median	1.00	1.00	1.00

Minimum, Maximum	1.00, 4.00	0.97, 4.00	0.50, 6.00
$AUC_{0\text{-}inf}$, hr*ng/mL			
Mean (SD)	106.85 (28.378)	97.42 (26.205)	221.50 (53.801)
Median	100.45	93.94	223.89
Minimum, Maximum	61.30, 179.27	53.94, 178.31	86.62, 325.21
$AUC_{0\text{-}last}$, hr*ng/mL			
Mean (SD)	105.01 (28.047)	95.90 (25.943)	216.82 (52.643)
Median	99.22	91.96	221.09
Minimum, Maximum	60.25, 177.65	52.77, 175.76	84.91, 320.43
$t_{1/2}$, hr			
Mean (SD)	3.12 (1.146)	3.08 (1.257)	4.83 (2.965)
Median	2.68	2.61	3.47
Minimum, Maximum	2.16, 6.15	2.02, 6.81	1.77, 13.52

SD = standard deviation; Treatment A = NP101 used in Study NP101-007; Treatment C = Imitrex 100 mg oral tablet; Treatment D = final modified NP101.

Relative bioavailability of NP101 Treatment A and Treatment D to Treatment C (Imitrex® 100 mg oral tablet) is shown in the figure below.

Figure 16: Analysis of Relative Bioavailability of two NP101 Products With Respect to 100 mg Sumatriptan Tablets

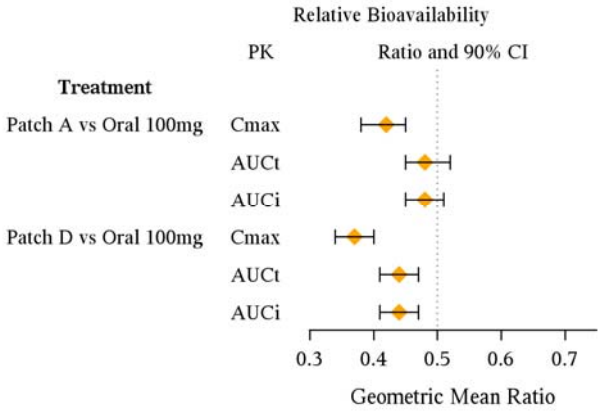
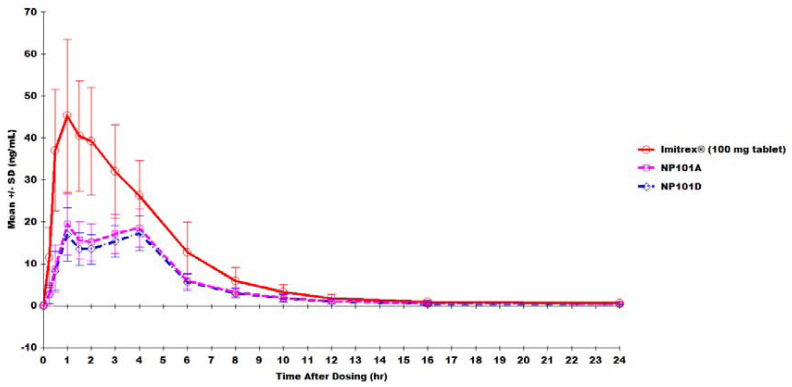


Figure 17: Mean (±SD) Sumatriptan Plasma Concentration vs Time Profile



CONCLUSIONS

- The 90% CIs for Cmax ranged from 79.8 to 95.8 with a GMR of 87.4. However, AUCinf ranged from 85 to 97.2 with a GMR of 90.9.
- The C_{max} and AUC of sumatriptan transdermal patch used in the efficacy study and final commercial patch were comparable.
- The Cmax of sumatriptan achieved by two NP101 treatments was approximately 37% to 42% of that produced by oral administration of sumatriptan (100 mg); and the $AUC_{0\text{-}inf}$ following NP101 administration was approximately 44% to 48% of that produced by oral administration.

B OCP Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	**202278**	**Brand Name**	**Zelrix™**
OCPB Division (I, II, III)	**DCP-1**	**Generic Name**	**Sumatriptan**
Medical Division	**HFD-120**	**Drug Class**	**5-HT Agonist**
OCPB Reviewer	**Jagan Mohan Parepally**	**Indication(s)**	**Treatment of Migraine**
OCPB Team Leader	**Angela Men**	**Dosage Form**	**Iontophoretic Transdermal Patch**
Date of Submission	**10/29/2010**	**Dosing Regimen**	**Maximum Recommended 2 Patches separated by 2hrs in 24 hrs**
Estimated Due Date of OCP Review	**7/28/2011**	**Route of Administration**	**Transdermal**
PDUFA Due Date	**8/29/2011**	**Sponsor**	**NuPathe Inc.**

Division Due Date	8/9/2011	Priority Classification	S

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA to support the marketing approval of NP101 (Sumatriptan) Iontophoretic transdermal patch, which is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally. This product is intended for the acute treatment of migraine attacks with or without aura [redacted] (b) (4) [redacted]. Imitrex® STATdose System (NDA 20-080), Imitrex® tablets, Imitrex® nasal spray are used as reference products. NP101™ employs iontophoretic technology to deliver sumatriptan transdermally. Iontophoresis is a non-invasive drug delivery method that uses low electrical current to move ionized drugs across the skin to the underlying tissue and blood vessels.

The total time of drug delivery and patch operation is approximately four hours [redacted] (b) (4) [redacted] after which time the patch is automatically deactivated by the firmware embedded on the pre-programmed circuit. Approximately 6.5 mg of sumatriptan is delivered to the patient.

The present submission contains a bioavailability (BA), formulation bridging bioequivalence (BE), efficacy, safety and tolerability studies as listed below. Comparative BA studies indicate that $AUC_{0\text{-}inf}$ of sumatriptan provided by the two NP101 patch treatments (upper arm and thigh) was approximately 100% to 112% of that produced by subcutaneous injection of sumatriptan (6 mg); however, Cmax was only 26% to 31% of that produced by subcutaneous injection.

NP101-007 was the only efficacy study conducted (randomized, parallel-group, double-blind, placebo-controlled, multicenter study) in 469 migraine patients. The proportion of subjects who were migraine free at two hours after patch activation was significantly higher in the NP101 treatment group than in the placebo treatment group ($p = 0.0135$), with a 7.6% treatment difference (15.5% for the NP101 treatment group compared with 7.9% for the placebo treatment group).

Pharmacokinetic Studies

NP101-005 is a comparative BA study comparing the PK of NP101 with currently approved formulations of Imitrex®.

NP101-006 is a comparative BA study comparing the PK profiles among five NP101 patches

NP101-013 is a formulation bridging BE study the objective of the study is to assess the BE of the transdermal patch used in Study NP101- 007 (efficacy study) and that intended for commercial use compared to the currently approved oral formulation of Imitrex®.

NP101-012 is a comparative BA study comparing the PK of NP101 applied to two different sites; and assess the PK of NP101 in elderly subjects.

NP101-011 is a PK study comparing the PK of NP101 during an acute migraine attack and during a nonmigraine period with control treatment: 50 mg oral tablet administered during a migraine or during a non-migraine period.

Efficacy Study

NP101-007 is an efficacy study the primary objective was to evaluate the efficacy and safety of NP101 for the treatment of acute migraine. Control treatment: Placebo patch containing a salt formulation.

Tolerability and Safety Studies

NP101-014 is a tolerability study the primary objective was to evaluate the potential of NP101 transdermal patch to cause skin irritation. The secondary objective was to collect patch adherence data, and to assess the PK of sumatriptan.

NP101-008 is a safety study to evaluate the safety of NP101 in the treatment of acute migraine over 12 months in subjects previously enrolled and treated in Study NP101-007 (efficacy study).

NP101-009 is a safety study to evaluate the safety of NP101 in the treatment of acute migraine over 12 months.

Pilot Studies:

These studies were conducted to evaluate prototype transdermal patches. Studies include NP101-001, NP101-002, and NP101-004.

	"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	2		Method Validation NUP-R1105 NUP-R1111: Metabolite profiling from NP101-011
I. Clinical Pharmacology				

Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-	-	-	
multiple dose:				
Patients-				
single dose:	**X**	-	-	
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 1:	**X**	-	-	
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 -	**X**	**7**		Comparative BA studies NP101-005, NP101-006, NP101-012 and NP101-011 Pilot Studies NP101-001, NP101-002, NP101-004
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		1) Bridging study for IND and commercial formulation (NP101-013)
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	-	-	
Total Number of Studies		10		

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)	How does PK of Zelrix™ compare with approved formulations of Imitrex® (reference)? Is final commercial product bioequivalent to IND formulation used? Is there a difference in BA when transdermal patch is applied to two different sites (upper arm and thigh)?	
Other comments or information not included above	DSI inspection request for clinical and bioanalytical portions of the study NP101-013 was sent to the project manager.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Electronic data sets available
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			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				

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	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
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			
	General				
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 202278 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Veneeta Tandon, Ramana Uppoor, Mehul Mehta)

Table 1: Listing of Clinical Studies

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	NP101-005	5.3.1.1	Compare the PK of NP101 with currently approved formulations of Imitrex®	Open-label, randomized, single-center, single-dose, 5-way crossover study (2 additional periods added per amendment) vs sumatriptan sc injection, oral tablet, and nasal spray formulations	NP101 (Zelrix™) patch Treatments A, E, F, G sumatriptan succinate in polyamine formulation, applied to upper arm with a 4 h wear time/ (b) (4) mA min Control treatments: B: 100 mg oral tablet C: 6 mg sc injection D: 20 mg intranasal	25	Healthy	Single dose (up to seven treatment periods)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	NP101-013	5.3.1.2	Assess the BE of the NP101 patch used in Study NP101-007 and that intended for commercial use compared to the currently approved oral formulation of Imitrex®	Open-label, randomized, single-center, single-dose, 3-way crossover study (one additional Group added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patches containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time (b) (4) mA min Group 1: Treatment A: Patch used in NP101-007 (NP101A) Treatment B: Patch for commercial use (NP101B) Treatment C: 100 mg oral tablet Group 2: Treatment A: Patch used in NP101-007 (NP101A) Treatment D: Patch for commercial use (NP101D) Treatment C: 100 mg oral tablet	63	Healthy	Single dose (up to four treatment periods)	Complete; Full CSR
BA	NP101-012	5.3.1.1	Assess the BA of NP101 applied to two different sites; and assess the PK of NP101 in elderly subjects	Group I: Open-label, randomized, single-center, single-dose, 3-way crossover study vs sumatriptan sc injection in subjects 18-45 yrs of age Group II: Open-label, single-center, single-dose study in subjects >65 yrs of age	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm (Group I, Treatment A and Group II) or upper thigh (Group I, Treatment B) with a 4 h wear time (b) (4) mA min Control treatment (Group I only): 6 mg sc injection (Imitrex®)	Group I: 25 Group II: 08	Healthy	Group I: single-dose (up to three treatment periods) Group II: single dose	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-001	5.3.3.1	Evaluate the PK profile and relative bio-availability of prototype NP101 patches	Open-label, randomized, single-center, single-dose, crossover study vs sumatriptan sc injection and oral tablet	NP101 (Zelrix™) patch treatments (containing (b) (4) mg sumatriptan in aqueous solution) applied to upper back: NP101.01: (b) (4) NP101.02: NP101.03: NP101.04: Control treatments: 6 mg sc injection; 50 mg oral tablet (Imigran FTab)	8	Healthy	Single dose (total of six treatment periods)	Complete; Abbrev. CSR
PK	NP101-002	5.3.3.1	Evaluate the tolerability and PK profile of prototype NP101 patches applied for different wear times and to different body locations	Open-label, randomized, single-center, single-dose, 6-period crossover study vs sumatriptan oral tablet	NP101 (Zelrix™) patch treatments (containing up to (b) (4) mg sumatriptan in aqueous solution): NP101.05: (b) (4) formulation applied to upper back (Period 1) or upper arm (Period 3) (b) (4) (b) (4) formulation applied to upper arm (Period 4) for (b) (4) mA min NP101.06: (b) (4) formulation, upper arm, (b) (4) mA min (Period 5) NP101.06A: (b) (4) formulation, upper arm, (b) (4) mA min (Period 6) Control treatment (Period 2): 50 mg oral tablet (Imigran FTab)	17	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	NP101-004	5.3.3.1	Evaluate the PK profile of prototype NP101 patches compared to that of oral sumatriptan succinate	Open-label, single-center, single-dose, 5-period crossover study vs sumatriptan oral tablet	NP101 (Zelrix™) patch treatments (containing up to 86 mg sumatriptan in polyamine formulation) applied to upper arm (Treatments A and C) or upper back (Treatments D and E) and with an anode electrode size of 5 cm^2 (Treatment A) or 10 cm^2 (Treatments C, D, and E): A: (b) (4) mA min C: mA min D: mA min E: mA min Control treatment (Treatment B): 100 mg oral tablet (Imigran FTab)	9	Healthy	Single dose (at least two treatment periods)	Complete; Abbrev. CSR
PK	NP101-006	5.3.3.1	Compare the PK profiles among five NP101 patches	Open-label, single-center, single-dose, 5-period crossover study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation applied to upper arm (Periods 1, 2, 3, 4) or upper thigh (Period 5); with a pad transfer ring (Periods 1, 3, 5) or without a pad transfer ring (Periods 2, 4); and containing either an S Design (Period 1, 2, 5) or C Design (Period 3, 4) microprocessor	4	Healthy	Single dose (total of five treatment periods)	Complete; Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Tolera-bility	NP101-014	5.3.3.3	Evaluate the potential of NP101 transdermal patch to cause skin irritation. The secondary objective was to collect patch adherence data, and to assess the PK of sumatriptan.	Randomized, placebo-controlled, repeat patch test study that compares the NP101 patch to a placebo patch	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time (b) (4) mA min. and placebo patch containing a salt formulation	10	Healthy/ Acute migraine headache	Maximum 21 days	Complete; Full CSR
PK	NP101-011	5.3.3.3	Compare the PK of NP101 during an acute migraine attack and during a non-migraine period	Open-label, single-center, single-dose, 4-way crossover study (two additional periods added per amendment) vs sumatriptan oral tablet (Imitrex®)	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation applied to the upper arm during a migraine (Periods 3 and 6) or during a non-migraine period (Periods 4 and 5) Control treatment: 50 mg oral tablet administered during a migraine (Period 1) or during a non-migraine period (Period 2)	23	Healthy/ Acute migraine headache	Single dose (up to six treatment periods)	Complete, Full CSR

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/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	NP101-007	5.3.5.1	Evaluate the efficacy and safety of NP101 for the treatment of acute migraine	Randomized, parallel-group, double-blind, placebo-controlled, multicenter study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm with a 4 h wear time/ (b) (4) mA min Control treatment: Placebo patch containing a salt formulation	469 (NP101: 234; placebo: 235)	Healthy/ Acute migraine headache	Single dose	Complete, Full CSR
Safety	NP101-008	5.3.5.2	Evaluate the safety and efficacy of NP101 in the treatment of acute migraine over 12 months	Open-label, multicenter study in subjects previously enrolled and treated (patch activation) in Study NP101-007	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm or upper thigh with a 4 h wear time/ (b) (4) mA min	198	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Complete; Full CSR
Safety	NP101-009	5.3.5.2	Evaluate the safety of NP101 in the treatment of acute migraine over 12 months	Open-label, multicenter study	NP101 (Zelrix™) patch containing 86 mg sumatriptan in polyamine formulation, applied to upper arm or upper thigh with a 4 h wear time/ (b) (4) mA min	514	Healthy/ Acute migraine headache	Up to six treatments per month (total of 12 months)	Ongoing, Interim Report

BA = bioavailability; BE = bioequivalence; CSR = clinical study report; h = hour; HPMC = hydroxypropylmethylcellulose; mA = milliamp; min = minutes; PK = pharmacokinetic; (b) (4); sc = subcutaneous; yrs = years

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/s/

JAGAN MOHAN R PAREPALLY
06/29/2011

YUXIN MEN
06/29/2011

ONDQA (Biopharmaceutics) Review

NDA	202-278 (000)
Applicant:	NuPathe
Proposed Tanami:	Zelrix™
Stamp Date	October 29, 2010; March 31, 2011
Established Name:	Sumatriptan
Dosage Form:	Transdermal Iontophoretic System
Route of Administration:	Topical
Indication:	Migraine
Reviewer	Tapash Ghosh

Background: The proposed Sumatriptan Transdermal Iontophoretic System (also know as NP101 and Zelrix™) is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks. Sumatriptan (Imitrex®, GlaxoSmithKline) is available in the United States (U.S.) in three formulations; oral tablets, subcutaneous injection, and as a nasal spray. Sumatriptan (Sumavel™ DosePro™, Zogenix) is available as a needleless subcutaneous injection. Generic sumatriptan oral tablets, nasal spray, and injection are also available. The proposed product, if approved, will be the first transdermal sumatriptan product.

The drug product component of NP101 is referred to as the reservoir card and consists of two separate reservoirs. One reservoir contains a nonwoven pad imbibed with (b) (4) g of sumatriptan formulation (b) (4) % sumatriptan succinate containing 86 mg of sumatriptan). A second reservoir contains a nonwoven pad imbibed with (b) (4) g of salt formulation (b) (4) % sodium chloride). Each reservoir is sealed separately. Upon use, the sumatriptan is placed on the positively charged electrode (anode) and the salt pad is placed on the negatively charged electrode (cathode) of the device. Application of a low electrical potential across the electrodes results in the movement of ionized sumatriptan molecules away from the electrode, through the skin, and into the tissue, where they are rapidly absorbed by the underlying blood vessels. The total time of drug delivery and patch operation is approximately four hours (b) (4) after which time the patch is automatically deactivated by the firmware embedded on the pre-programmed circuit. Approximately (b) (4) mg of sumatriptan is targeted to be delivered to the patient over 4 hours of application.

During discussion in the IND phase, in March 2010, the Agency instructed the sponsor to continue developing a discriminating *in vitro* method with the ability to evaluate drug permeation as a quality control tool to detect lot to lot variability (reject bad performance product). FDA's instruction went on to say that the NDA submission should provide the final report for the *in vitro* permeation test including all data collected during development and validation of the test. NuPathe (the sponsor) contracted (b) (4) to develop and optimize the *in-vitro* release method. The sponsor clarified (via e-mail dated June 02, 2011) that (b) (4) will also be performing the *in vitro* release test for commercial product.

According to the sponsor, as submitted during submission of the original NDA, an *in vitro* permeation method was developed and validated on the basis of data obtained during the course of validation and a quality control release and stability specification was established as described below:

NP101 *In-Vitro* Release	Stage 1: Six samples tested, each unit tested equals Q ± (b) (4)% If values are outside of acceptable range proceed to Stage 2. Stage 2: Six additional samples tested, average of 12 units is equal to Q ± (b) (4)% Q = mg	N/A	(b) (4) method 120-001-02

In response to the Agency's further querries and as a result of further developmental work, in a subsequent submission dated March 31, 2011, the sponsor submitted data to let the Agency know that the method was being optimized. The sponsor claimed that the method they proposed last is more robust than the initial method and therefore provides more consistent data. However, they also cautioned that additional evaluation of multiple lots of reservoir cards and E-Patches remains ongoing. The sponsor claims that the optimized method will be validated by performing supplemental steps to the original validation. Based on the data generated so far, the sponsor proposed (dated March 31, 2011) to change the previously proposed *in-vitro* release specification as follows:

Test	**Limit**		**Method**
	Release	**Shelf Life**	
NP101 *In-Vitro* Release	Stage 1: Six samples tested, each unit tested equals Q ± (b) (4) %. If values are outside of acceptable range proceed to Stage 2. Stage 2: Six additional samples tested, average of 12 units is equal to Q ± (b) (4)%. Q = (b) (4) mg	N/A	(b) (4) method 120-001-02

[1] Performed on each batch at a minimum one time per year.

While the method is still undergoing validation and optimization, the following parameters remain unresolved to assure robustness and reproducibility of the final method:

- Can the sampling area be reproducibly moved without disturbing the integrity of the system?
- Can the electronics be precisely controlled especially in changing the (b) (4) (b) (4)

- How is the total amount of drug delivered calculated?
- Is the system able to detect and precisely prevent passive transport of the drug?

A Product Quality and Manufacturing Memo for *in-vitro* release testing site (b) (4) of ZelrixTM (sumatriptan) iontophoretic transdermal system of NuPathe, Inc; Reservoir Card and Electrode Patch has been generated. Of note, it has been decided by the clinical division that the submission will receive a complete response (CR) in the first cycle of review.

In summary, a rigorous control over each batch's release performance is of paramount importance from a product quality control and assurance point of view. Therefore, careful evaluation of this complex *in-vitro* release procedure utilizing the sponsor's custom designed apparatus is necessary to validate its suitability to assure batch to batch uniformity of NP101.

Under this circumstance, the reviewer recommends that the review of *in-vitro* release method and specification will be deferred until (b) (4) is done with complete validation of the *in-vitro* release method and proposes a release and stability *in-vitro* specification. A decision on the acceptance of the sponsor's proposed method and specification will be reviewed upon submission of the data generated from clinical/bio batches.

Though the sponsor's proposed development and validation report (VP-120-001-002) will not be reviewed this time, based on a preliminary assessment, the following comments should be sent to the sponsor:

- Explain when approximately (b) (4) mg of sumatriptan is targeted to be delivered to the patient *in-vivo* over 4 hours of application, why your last *in-vitro* release specification proposes a Q = (b) (4) mg after 4 hour.

- Submit *in-vitro* release data/profiles generated using your final release method from clinical/biobatches for the Agency to review. More than one point specification is recommended for this product, especially at the juncture of changing the (b) (4) from (b) (4).

- The sponsor's proposed specification with a range of Q ± (b) (4) is not acceptable without an established IVIVC and/or supportive bioequivalence data. The Agency usually recommends a range of Q ± (b) (4). Please provide a justification for your choice of Q values.

- Explain how the sampling area be reproducibly moved without disturbing the integrity of the system.

- Explain how the electronics be precisely controlled especially in changing the (b) (4) ((b) (4)

- Explain how the total amount of drug delivered calculated.

- Explain how the system is able to detect and precisely prevent passive transport of the drug.

Recommendation: The proposed Sumatriptan Transdermal Iontophoretic System in vitro release testing (also know as NP101 and Zelrix™) as submitted is not acceptable from a Biopharmaceutics perspective.

The sponsor needs to address the following comments in future submissions:

- Explain when approximately (b) (4) mg of sumatriptan is targeted to be delivered to the patient *in-vivo* over 4 hours of application, why your last *in-vitro* release specification proposes a Q = (b) (4) mg after 4 hour.

- Submit *in-vitro* release data/profiles generated using your final release method from clinical/biobatches for the Agency to review. More than one point specification is recommended for this product, especially at the juncture of changing the (b) (4) from (b) (4).

- The sponsor's proposed specification with a range of Q ± (b) (4) is not acceptable without an established IVIVC and/or supportive bioequivalence data. The Agency usually recommends a range of Q ± (b) (4). Please provide a justification for your choice of Q values.

- Explain how the sampling area be reproducibly moved without disturbing the integrity of the system.

- Explain how the electronics be precisely controlled especially in changing the (b) (4) (b) (4)

- Explain how the total amount of drug delivered calculated.

- Explain how the system is able to detect and precisely prevent passive transport of the drug.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

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/s/

TAPASH K GHOSH
06/22/2011

PATRICK J MARROUM
06/22/2011