CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 202-278 SN000
Drug Name:	Zelrix™ (NP101, sumatriptan succinate, a Sumatriptan Iontophoretic Transdermal Patch)
Indication(s):	Acute Migraine
Applicant:	NuPathe
Date(s):	Date of Document: October 29, 2010
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Biometrics Division:	Division of Biometrics I (DBI)
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Keywords: Logistic regression, Key secondary endpoints

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1 EXECUTIVE SUMMARY

Based on the results of NP101-007, there is evidence that Zelrix (Sumatriptan Iontophoretic Transdermal Patch) is effective as compared to placebo in acute migraine for adults, as assessed by the primary endpoint headache pain free and three key secondary endpoints, photophobia free, phonophobia free and nausea free.

NP101-007 is the only pivotal efficacy study for this submission. This is a randomized, parallel-group, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of NP101 for the treatment of acute migraine. A total of 530 subjects were randomized into the study through 38 centers in United States.

The primary objective of this study was to assess the proportion of subjects who were headache pain free at two hours after patch activation. The three key secondary objectives were to assess the proportion of subjects who were photophobia free, phonophobia free, and nausea free at two hours after patch activation.

All efficacy analyses were based on logistic regression models for intent-to-treat (ITT) population. For the primary endpoint, the proportion of subjects who were headache pain free at two hours, the model included treatment group as a main effect and randomization stratum (race) as a factor. For the analyses of the key secondary endpoints, including the proportion of subjects who were photophobia free, and phonophobia free and nausea free, a three-factor model was used. This model included treatment group as a main effect, randomization stratum (race) as a factor and the baseline value of the symptom as a second covariate; the additional term was included to account for the fact that not all subjects had the symptom at baseline. Last-observation-carried-forward (LOCF) was used to handle missing data.

For the primary endpoint and the three key secondary endpoints, NP101 was significantly better than placebo (LOCF analysis). The results of OC (observed case) analysis and BCF (baseline-carried-forward) are consistent with those of LOCF analysis. For acute migraine, the Agency requires the primary endpoint and the three key secondary endpoints are all statistically significant at 0.05 level (two-sided) for an efficacy claim.

This reviewer conducted subgroup analyses based on age (above/below observed median of 41 years), race (white vs. non-white) and sex (male vs. female) for the primary endpoint and key secondary endpoints. Results were summarized in Table 8, Table 9, Table 10, and Table 11. Please refer to Section 4.1.1 for details. For the subgroups investigated, the point estimates of the treatment effects are all in the same direction. However, it appears that the proportion of subjects who were headache pain free in NP101 group was numerically larger than that in Placebo group.

2 INTRODUCTION

2.1 Overview

Migraine is a condition that affects approximately 28 million people in the United States (U.S.). Females more frequently suffer from migraine headache than males (18% versus 6%, respectively).

Mild migraine can often be effectively treated with over-the-counter medications. Triptans are the mainstay of abortive treatment for acute migraine of moderate to severe intensity. Seven different triptans have been approved and are currently marketed. In the U.S., triptans are available in a variety of formulations (oral, dissolvable, nasal spray, and injectable). Non-oral formulations are recommended for patients with gastrointestinal (GI) symptoms.

In the U.S., sumatriptan is the most frequently prescribed triptan for the treatment of migraine. Sumatriptan is indicated for the acute treatment of migraine attacks, with or without aura, in adults. In the U.S. sumatriptan is currently available in three formulations – oral tablets, subcutaneous injection, and nasal spray.

The goal of the NP101 development program is to address unmet needs of the current sumatriptan formulations. NP101 will provide an alternative solution for migraine sufferers who experience nausea with current formulations and provide consistency of delivery with fewer triptan induced adverse events. NP101 employs iontophoretic technology to deliver sumatriptan. NP101 is a thin, disposable, single-use patch with a self-contained electronic controller and a battery power source designed to deliver sumatriptan transdermally. Iontophoresis is a non-invasive drug delivery method that, using low electrical current, moves solubilized drugs across the skin to the underlying tissue.

Four previous safety and pharmacokinetic clinical trials (NP101-001, NP101-002, NP101-004, and NP101-005) have been conducted with related but different prototype iontophoretic systems designed to deliver sumatriptan transdermally. In addition, a safety and pharmacokinetic clinical trial (NP101-006) has been conducted with the same iontophoretic system as used with the NP101-007 study.

NP101-007 is the only pivotal efficacy study for this submission. This is a randomized, parallel-group, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of NP101 for the treatment of acute migraine. A total of 530 subjects were randomized into the study through 38 centers in United States.

2.2 Data Sources

The sponsor's original electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA202278\0000 of the center's electronic document room. Both tabulations datasets (SDTM) and analysis datasets were provided.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During the review process, this reviewer did not encounter data quality problems with both tabulation data and analysis data.

3.2 Evaluation of Efficacy

Study NP101-007 is the only pivotal efficacy study for this submission.

3.2.1 STUDY NP101-007

3.2.1.1 Study Objectives

The primary objective of this study was to assess the proportion of subjects who were headache pain free at two hours after patch activation.

The key secondary objectives were to assess:

- the proportion of subjects who were nausea free at two hours after patch activation;
- the proportion of subjects who were photophobia free at two hours after patch activation;
- the proportion of subjects who were phonophobia free at two hours after patch activation.

Other secondary objectives were to assess:

- the proportion of subjects who were headache pain free at each time point (0.5, 1, 3, 4, 6, 12, and 24 hours) after patch activation;
- the proportion of subjects who experienced headache pain relief at each time point (0.5, 1, 2, 3, 4, 6, 12, and 24 hours) after patch activation; pain relief is defined as headache scores equal to zero (0) or 1 (mild pain);
- the proportion of subjects who were nausea free at each time point (0.5, 1, 3, 4, 6, 12, and 24 hours) after patch activation;
- the proportion of subjects who were photophobia free at each time point (0.5, 1, 3, 4, 6, 12, and 24 hours) after patch activation;
- the proportion of subjects who were phonophobia free at each time point (0.5, 1, 3, 4, 6, 12, and 24 hours) after patch activation;
- the proportion of subjects who were migraine free (no headache pain, no nausea, no photophobia, and no phonophobia) at two hours after patch activation;
- the proportion of subjects with a sustained headache pain-free response (defined as a 2- to 24-hour period) following patch activation without the use of rescue medication;
- the proportion of subjects who did not use rescue medication within a 24-hour period following patch activation.

3.2.1.2 Study Design

This study used a randomized, parallel-group, double-blind, placebo-controlled design to compare the efficacy and tolerability of NP101 to a placebo iontophoretic transdermal patch.

Dose timing (t = 0) for both the NP101 patch and placebo patch began when the patch was applied and a button was depressed causing a small red light-emitting diode (LED) light to come on indicating that the patch had been activated. Subjects wore the active or placebo patch for four hours.

Adult subjects who met the enrollment criteria were randomized in a 1:1 ratio and stratified by race [white and non-white] via an Interactive Voice Response System (IVRS) into one of two treatment groups. The two treatment groups were:

- NP101 sumatriptan iontophoretic transdermal patch, or
- Placebo iontophoretic transdermal patch.

At the Randomization Visit, subjects were instructed by the Investigational Site Personnel on how to apply the iontophoretic transdermal patch and how to complete their Migraine Study Diary. Upon experiencing a qualifying migraine headache, subjects initiated the study procedures as directed. Study patches were to remain in place for four hours and subjects were to record their responses to diary questions at 0.5, 1, 2, 3, 4, 6, 12, and 24 hours (or beyond, if their skin assessment results dictated) post patch activation.

Subjects stayed in the study until they had treated one migraine headache with a study patch or two months after randomization, whichever occurred first.

3.2.1.3 Efficacy Measures

The primary efficacy endpoint was the proportion of subjects who were headache pain free at two hours after patch activation.

The key secondary efficacy endpoints were:

- the proportion of subjects who were nausea free at two hours after patch activation;
- the proportion of subjects who were photophobia free at two hours after patch activation;
- the proportion of subjects who were phonophobia free at two hours after patch activation.

3.2.1.4 Statistical Analysis Plan

Planned Statistical Analysis

Four analysis populations were defined in this study:

- Randomized Population: All subjects who were randomized via the IVRS to a treatment assignment.
- Safety Population: All subjects who applied the study patch.
- Intent-to-Treat (ITT) Population: All subjects who applied and activated (defined as light continuously on for any length of time) the study patch and who had at least one post

baseline assessment for pain. The definition of the ITT population was further defined before database unblinding to exclude subjects who only applied patches where the medication pads failed to transfer.

- Per-Protocol (PP) Population: All ITT subjects who did not have any major protocol violations during the study.

The ITT population was the primary efficacy population. Analysis based on the PP population was to be performed if 10% or more ITT subjects were excluded from the PP population.

Missing data for the headache pain severity score (0-3, with 0 being pain free and 3 being severe pain) and nausea, photophobia, and phonophobia, at the two-hour post patch activation time point were imputed using two methods for analyses, a last observation carried forward (LOCF) method and, as part of one of the sensitivity analyses, a baseline carried forward (BCF) method was used for imputing missing values in these parameters.

All efficacy analyses were based on logistic regression models. For the primary endpoint, the proportion of subjects who were headache pain free at two hours, the model included treatment group as a main effect and randomization stratum (race) as a covariate. The same two-factor model was used to analyze the proportion of responder subjects in several secondary endpoints including: migraine free, use of rescue medication, pain relief, sustained pain free, and sustained pain relief. For the analyses of the remaining secondary endpoints, including the proportion of subjects who were nausea free, photophobia free, and phonophobia free, a three-factor model was used. This model included treatment group as a main effect, randomization stratum (race) as a covariate and the baseline value of the symptom as a second covariate; the additional term was included to account for the fact that not all subjects had the symptom at baseline.

For the headache pain severity score and the nausea, photophobia, and phonophobia scores at the two-hour post patch activation time point, missing values were imputed using a last observation carried forward (LOCF) method and two sets of sensitivity analyses were carried out to assess the impact of the imputation methodology, one based on a baseline carried forward (BCF) method and one based on observed cases (OC) only. No imputation, i.e. OC methodology, was used in the analyses of any of the remaining endpoints.

For all primary and secondary efficacy endpoints, the adjusted odds ratio (adjusted for covariates) and the corresponding 95% confidence intervals (95% CIs) and the nominal *p* value for the comparison between the NP101 and placebo groups for each endpoint were provided in the analysis summary tables.

Changes to Planned Analyses

Minor changes were made to the planned analyses, but they don’t impact the interpretation of the efficacy results.

3.2.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 530 subjects were randomized, of which 61 subjects were not treated, i.e., patch not applied within two months after randomization. This proportion of non-treated subjects (11.5%; 61 of 530 randomized subjects) is comparable to that reported in other recent large-scale migraine studies. A total of 469 subjects applied the study patch and were included in the safety analysis population.

Overall, 448 (95.5%) of the 469 subjects in the safety analysis population completed the study and a total of 21 subjects (4.5%) discontinued the study. The most common reasons for discontinuation in the NP101 treatment group were AEs (five subjects, 2.1%) and lost to follow-up (four subjects, 1.7%). The most common reasons for discontinuation in the placebo treatment group were failed/improper functioning study patch (four subjects, 1.7%) and AEs (three subjects, 1.3%). Two subjects in the NP101 treatment group discontinued treatment due to 'other' reasons, one due to a problem with patch adherence and the other as a result of not transferring the patch medication pads.

The subject disposition is presented in Table 1. Subject disposition between the two treatment groups was similar.

Table 1: Subject Disposition

Disposition	NP101	Placebo	Total
Randomized	265	265	530
Randomized, not treated	31	30	61
Safety analysis population[a]	234 (100)	235 (100)	469 (100)
Intent-to-treat analysis population[b]	226 (96.6)	228 (97.0)	454 (96.8)
Per protocol analysis population[c]	220 (94.0)	226 (96.2)	446 (95.1)
Completed study	222 (94.9)	226 (96.2)	448 (95.5)
Discontinued study	12 (5.1)	9 (3.8)	21 (4.5)
Did not experience qualifying migraine headache	0	1 (0.4)	1 (0.2)
Failed/improper functioning study patch	1 (0.4)	4 (1.7)	5 (1.1)
Adverse event	5 (2.1)	3 (1.3)	8 (1.7)
Lost to follow-up	4 (1.7)	1 (0.4)	5 (1.1)
Other	2 (0.9)	0	2 (0.4)

[a] Subjects applied study patch.
[b] Subjects applied and activated study patch with pad transfer and had at least one post baseline assessment for each migraine symptom (pain, photophobia, phonophobia, and nausea).
[c] Intent-to-treat subjects who did not have any major protocol violations as defined prior to database lock.
Source: Tables 14.1.1 and 14.1.1a

Source: Table 10 of Clinical Study Report

Demographic and Baseline Characteristics

A summary of selected demographics and baseline characteristics of the 469 subjects comprising the Safety population is provided in Table 2. No notable differences in baseline characteristics were observed between the two treatment groups.

Table 2: All Safety Subject Demographics – Safety Population

	NP101 N=234 (%)	**Placebo N=235 (%)**	**Total N=469 (%)**
Age (yrs): Mean (SD)	40.5 (11.20)	41.2 (11.06)	40.8 (11.12)
Minimum (yrs)	18	19	18
Maximum (yrs)	66	65	66
Sex: n (%)			
Male: n (%)	37 (15.8)	34 (14.5)	71 (15.1)
Female: n (%)	197 (84.2)	201 (85.5)	398 (84.9)
Race: n (%)			
White	192 (82.1)	190 (80.9)	382 (81.4)
Black (African American)	36 (15.4)	33 (14.0)	69 (14.7)
Asian[a]	3 (1.3)	8 (3.4)	11 (2.3)
American Indian/Alaska Native	2 (0.9)	2 (0.9)	4 (0.9)
Pacific Islander/Native Hawaiian	1 (0.4)	2 (0.9)	3 (0.6)

	NP101 N=234 (%)	Placebo N=235 (%)	Total N=469 (%)
Weight (kg): Mean (SD)	75.3 (19.98)	75.4 (18.96)	75.3 (19.45)
Minimum (kg)	41	41	41
Maximum (kg)	159	150	159
Height (cm): Mean (SD)	166.3 (8.51)	166.7 (9.06)	166.5 (8.78)
Minimum (cm)	152	142	142
Maximum (cm)	191	196	196
BMI (kg/m^2): Mean (SD)	27.16 (6.804)	27.07 (6.316)	27.12 (6.557)
Minimum (kg/m^2)	14.4	16.3	14.4
Maximum (kg/m^2)	63.2	53.6	63.2
Sumatriptan Use			
No	51 (21.8)	67 (28.5)	118 (25.2)
Yes	183 (78.2)	168 (71.5)	351 (74.8)
Sumatriptan Route			
Oral tablet	111 (60.7)	101 (60.1)	212 (60.4)
Nasal spray	8 (4.4)	1 (0.6)	9 (2.6)
Subcutaneous injection	3 (1.6)	5 (3.0)	8 (2.3)
Oral/Nasal	16 (8.7)	14 (8.3)	30 (8.5)
Oral/Nasal/Subcutaneous	17 (9.3)	22 (13.1)	39 (11.1)
Oral/Subcutaneous	28 (15.3)	25 (14.9)	53 (15.1)

[a] Subcategories for Asian subjects are reported in the source table.
Source: Table 14.1.4.1

Source: Table 12 of Clinical Study Report

An overall summary of the migraine history is presented in Table 3. The findings were similar between the treatment groups.

Table 3: Summary of Migraine History –Safety Population

	NP101 N=234 (%)	Placebo N=235 (%)	Total N=469 (%)
Subjects with a migraine history assessment	234 (100)	235 (100)	469 (100)
Years experienced migraine headache (yrs)			
Mean (SD)	21.6 (11.93)	20.6 (11.62)	21.1 (11.77)
Minimum, Maximum	2, 51	1, 49	1, 51
Duration of treated migraine headache (hrs)			
Median	11.0	12.0	12.0
Minimum, Maximum	1, 144	1, 72	1, 144
Average number of migraine headaches per month			
Mean (SD)	3.9 (1.49)	4.0 (1.35)	4.0 (1.42)
Minimum, Maximum	1, 11	1, 6	1, 11
Migraine classification (n [%])			
Migraine headache with aura	15 (6.4)	23 (9.8)	38 (8.1)
Migraine headache without aura	156 (66.7)	135 (57.4)	291 (62.0)
Both	63 (26.9)	77 (32.8)	140 (29.9)

Source: Table 14.1.5.2

Source: Table 14 of Clinical Study Report

The baseline migraine headache characteristics for the ITT population are presented in Table 4. The majority of subjects had headaches of moderate severity at baseline. A slightly higher proportion of NP101 subjects had headaches of moderate severity than reported by the placebo subjects at baseline. There were some differences between the two treatment groups with respect to presence of nausea at baseline (NP101: 42.5% vs. placebo: 52.2%).

Table 4: Summary of Migraine Headache Characteristics at Baseline: ITT Population

	NP101 N=226 (%)	Placebo N=228 (%)
Headache severity		
None	1 (0.4)[a]	0
Mild	0	0
Moderate	175 (77.4)	170 (74.6)
Severe	48 (21.2)	57 (25.0)
Missing	2 (0.9)	1 (0.4)
Photophobia		
Absent	38 (16.8)	30 (13.2)
Present	188 (83.2)	197 (86.4)
Missing	0	1 (0.4)
Phonophobia		
Absent	46 (20.4)	45 (19.7)
Present	180 (79.6)	182 (79.8)
Missing	0	1 (0.4)
Nausea		
Absent	130 (57.5)	109 (47.8)
Present	96 (42.5)	119 (52.2)
Description		
Unilateral	139 (61.5)	142 (62.3)
Bilateral	87 (38.5)	85 (37.3)
Missing	0	1 (0.4)
Pain worse with movement	196 (86.7)	190 (83.3)
Aura present	40 (17.7)	49 (21.5)

[a] Subject 137-1417 had a moderate severity headache at baseline that was indicated as None due to a CRF error.
Source: Tables 14.2.1 and 14.2.2, and Appendix 16.2.20.1

Source: Table 16 of Clinical Study Report

3.2.1.6 Sponsor's Primary Efficacy Results

The primary efficacy endpoint was the proportion of subjects who were headache pain free at two hours after patch activation. It was analyzed by a logistic regression model with treatment group as a main effect and randomization stratum (race) as a covariate.

There was a significantly (p = 0.0092) greater proportion of subjects who were headache pain free at two hours post treatment in the NP101 treatment group than in the placebo treatment group with missing data imputed using the LOCF method (see Table 5). A total of 40 of the 226 subjects (17.7%) who were treated with NP101 reported no headache pain at two hours compared with 21 of the 228 subjects (9.2%) who were treated with placebo.

Table 5: Analysis of Primary Endpoint (ITT Population)

Two Hours After Patch Activation	Number (%) Subjects		Treatment Difference (%)	Logistic Regression Analysis[a]	
	NP101 N=226 (%)	Placebo N=228 (%)		Odds Ratio (95%CI)	*p* value
Headache pain free – LOCF analysis	40/226 (17.7)	21/228 (9.2)	8.5	2.1 (1.20, 3.72)	0.0092
Headache pain free – OC analysis	40/225 (17.8)	21/227 (9.3)	8.5	2.1 (1.20, 3.72)	0.0092
Headache pain free – BCF analysis	40/226 (17.7)	21/228 (9.2)	8.5	2.1 (1.20, 3.72)	0.0092

LOCF = Last Observation Carried Forward.
OC = Observed Cases.
[a] The logistic regression model for headache free includes main effect of treatment and a covariate of randomization stratum. Odds ratio is the ratio of the odds to be a responder after treating with a NP101 patch vs. treating with a placebo patch.
Source: Tables 14.2.3.1.1, 14.2.3.2.1, and 14.2.3.3.1

Source: Table 17 of sponsor's Clinical Study Report

The results of OC analysis and BCF analysis are consistent with those of LOCF analysis.

3.2.1.7 Sponsor's Secondary Efficacy Results

The three key secondary endpoints were the proportion of subjects who were photophobia free, who were phonophobia free, and who were nausea free at two hours after patch activation and they were analyzed by a logistic regression model with treatment group as a main effect and randomization stratum (race) and the baseline value of the symptom as covariates.

For the three key secondary endpoints, NP101 was significantly better than placebo as shown in Table 6.

Table 6: Analysis of Secondary Efficacy Endpoints – LOCF Analysis; ITT Population

Two Hours After Patch Activation	Number (%) Subjects		Treatment Difference (%)	Logistic Regression Analysis[a]	
	NP101 N=226 (%)	Placebo N=228 (%)		Odds Ratio (95%CI)	*p* value
Photophobia free	116 (51.3)	83 (36.4)	14.9	1.9 (1.24, 2.86)	0.0028
Phonophobia free	125 (55.3)	89 (39.0)	16.3	2.2 (1.46, 3.40)	0.0002
Nausea free	189 (83.6)	144 (63.2)	20.4	3.0. (1.84, 4.83)	<0.0001

[a] The logistic regression models for photophobia, phonophobia, and nausea free include the main effect of treatment and two covariates of randomization stratum and baseline score. Odds ratio is the ratio of the odds to be a responder after treating with a NP101 patch vs. treating with a placebo patch.

Source: Table 14.2.3.1.2

Source: Table 18 of sponsor's Clinical Study Report

The results of OC analysis and BCF analysis are consistent with those of LOCF analysis.

3.2.1.8 Sponsor's Other Secondary Efficacy Results

Pain Relief by Time Point

The results of analyses of the proportion of subjects who had headache pain relief at each time point after patch activation are shown in Table 7. A numeric treatment effect is noted from the one-hour time point to the 12-hour time point. At the one-hour time point, 28.9% of subjects in the NP101 treatment group and 18.9% of subjects in the placebo treatment group had headache pain relief. By the 24-hour time point, 87.8% of subjects in the NP101 treatment group and 85.1% in the placebo treatment group had headache pain relief.

Table 7: Proportion of Subjects Who Had Headache Pain Relief: ITT Population

Time point	NP101 N=226 (%)	Placebo N=228 (%)	% Difference (NP101-placebo)
0.5 hour	29/226 (12.8)	21/228 (9.2)	3.6
1 hour	65/225 (28.9)	43/227 (18.9)	10.0
2 hours	119/225 (52.9)	65/227 (28.6)	24.3
3 hours	153/225 (68.0)	93/227 (41.0)	27.0
4 hours	175/224 (78.1)	125/227 (55.1)	23.0
6 hours	186/223 (83.4)	147/222 (65.0)	18.4
12 hours	207/224 (92.4)	183/222 (82.4)	10.0
24 hours	195/222 (87.8)	189/222 (85.1)	2.7

Source: Excerpt from Table 20 of sponsor's Clinical Study Report

Sustained Pain Relief

Sustained pain relief is defined as subjects having scores of none or mild at all time points from 2 through 24 hours and who had taken no rescue medication from time point 0 through 24 hours. The proportion of subjects with sustained pain relief in the NP101 group (33.9%) was numerically higher than observed in the placebo treatment group (20.6%).

3.2.2 REVIEWER'S ANALYSIS

This reviewer has confirmed the efficacy analysis results presented in this review.

This reviewer conducted subgroup analyses based on age (above/below observed median of 41 years), race (white vs. non-white) and sex (male vs. female) for the primary endpoint and key secondary endpoints. Results were summarized in Table 8, Table 9, Table 10 and Table 11. Please refer to Section 4.1.1 for details. For the subgroups investigated, the point estimates of the treatment effects are all in the same direction. However, it appears that the proportion of subjects who were headache pain free in NP101 group was numerically larger than that in Placebo group.

3.3 Evaluation of Safety

Please read Dr. Todd's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

4.1.1 STUDY NP101-007

Subgroup analyses based on age (above/below observed median of 41 years), race (white vs. non-white) and sex (male vs. female) were conducted for the primary endpoint and key secondary endpoints. Results were summarized in Table 8, Table 9, Table 10 and Table 11. This study was conducted in United States only, thus the subgroup analysis by geographic region is not necessary.

Table 8: Summary of Subgroup Analysis of Headache Pain Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	10 (9)	7 (6)
>41 yrs	30 (25)	14 (12)
Race Group		
White	35 (19)	16 (9)
Non-white	5 (13)	5 (11)
Sex		
Male	4 (11)	3 (9)
Female	36 (19)	18 (9)

Source: Reviewer's Analysis

Table 9: Summary of Subgroup Analysis of Photophobia Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	46 (43)	35 (31)
>41 yrs	70 (59)	48 (42)
Race Group		
White	97 (52)	67 (36)
Non-white	19 (48)	16 (36)
Sex		
Male	16 (44)	15 (47)
Female	100 (53)	68 (35)

Source: Reviewer's Analysis

Table 10: Summary of Subgroup Analysis of Phonophobia Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	58 (54)	37 (32)
>41 yrs	67 (57)	52 (46)
Race Group		
White	103 (55)	74 (40)
Non-white	22 (55)	16 (36)
Sex		
Male	22 (61)	15 (47)
Female	103 (54)	74 (38)

Source: Reviewer's Analysis

Table 11: Summary of Subgroup Analysis of Nausea Free: LOCF Analysis for ITT Population

Subgroup	NP101: Number (%)	Placebo: Number (%)
Age Group		
<=41 yrs	90 (83)	69 (61)
>41 yrs	99 (84)	75 (66)
Race Group		
White	156 (84)	111 (60)
Non-white	33 (83)	33 (75)
Sex		
Male	32 (89)	18 (56)
Female	157 (83)	126 (64)

Source: Reviewer's Analysis

For the subgroups investigated, the point estimates of the treatment effects are all in the same direction. However, it appears that the proportion of subjects who were headache pain free in NP101 group was numerically larger than that in Placebo group.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

NP101-007 is the only pivotal efficacy study for this submission. This is a randomized, parallel-group, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of NP101 for the treatment of acute migraine.

A total of 530 subjects were randomized, of which 61 subjects were not treated, i.e., patch not applied within two months after randomization. A total of 469 subjects applied the study patch and were included in the safety analysis population. Overall, 448 (95.5%) of the 469 subjects in the safety analysis population completed the study and a total of 21 subjects (4.5%) discontinued the study.

The primary objective of this study was to assess the proportion of subjects who were headache pain free at two hours after patch activation. The three key secondary objectives were to assess the proportion of subjects who were photophobia free, phonophobia free, and nausea free at two hours after patch activation.

All efficacy analyses were based on logistic regression models for intent-to-treat (ITT) population. For the primary endpoint, the proportion of subjects who were headache pain free at two hours, the model included treatment group as a main effect and randomization stratum (race) as a factor. For the analyses of the key secondary endpoints, including the proportion of subjects who were photophobia free, and phonophobia free and nausea free, a three-factor model was used. This model included treatment group as a main effect, randomization stratum (race) as a factor and the baseline value of the symptom as a second covariate; the additional term was included to account for the fact that not all subjects had the symptom at baseline. Last-observation-carried-forward (LOCF) was used to handle missing data.

For the primary endpoint, there was a significantly ($p = 0.0092$) greater proportion of subjects who were headache pain free at two hours post treatment in the NP101 treatment group than in the placebo treatment group with missing data imputed using the LOCF method. A total of 40 of the 226 subjects (17.7%) who were treated with NP101 reported no headache pain at two hours compared with 21 of the 228 subjects (9.2%) who were treated with placebo. For the three key secondary endpoints, NP101 was also significantly better than placebo (LOCF analysis). The results of OC (observed case) analysis and BCF (baseline-carried-forward) are consistent with those of LOCF analysis. For acute migraine, the Agency requires the primary endpoint and the three key secondary endpoints are all statistically significant at 0.05 level (two-sided) for an efficacy claim.

This reviewer conducted subgroup analyses based on age (above/below observed median of 41 years), race (white vs. non-white) and sex (male vs. female) for the primary endpoint and key secondary endpoints. Results were summarized in Table 8, Table 9, Table 10, and Table 11. Please refer to Section 4.1.1 for details. For the subgroups investigated, the point estimates of the treatment effects are all in the same direction. However, it appears that the proportion of subjects who were headache pain free in NP101 group was numerically larger than that in Placebo group.

5.2 Conclusions and Recommendations

The results of NP101-007 suggest that Zelrix (Sumatriptan Iontophoretic Transdermal Patch) is effective as compared to placebo in acute migraine for adults, based on the primary endpoint headache pain free and three key secondary endpoints, photophobia free, phonophobia free and nausea free.

CHECK LIST

Number of Pivotal Studies:

Trial Specification

Specify for each trial:

Protocol Number (s): NP101-007
Protocol Title (optional):
Phase: 3
Control: Placebo/Control
Blinding: Double-Blind/Open-Label
Number of Centers: 38
Region(s) (Country): US
Duration: patient treats one migraine headache within 2 months of randomization
Treatment Arms: Placebo/NP101
Treatment Schedule: (b) (4) mg iontophoretic transdermal patch during an acute migraine attack
Randomization: Yes
Ratio: 1:1
Method of Randomization: Central via an IVRS
Primary Endpoint: Headache pain free at 2 hours
Primary Analysis Population: ITT
Statistical Design: Superiority
Adaptive Design: No
Primary Statistical Methodology: Logistic regression
Interim Analysis: No
Sample Size: 530 subjects were randomized.
Sample Size Determination: Was it calculated based on the primary endpoint variable and the analysis being used for the primary variable?

Statistic = Chi-square test
Power= 90
Δ= 15%
α = 0.05 two-sided

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No.
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the **Covariates** pre-specified in the protocol? Yes.
- Did the Applicant perform **Sensitivity Analyses**? Yes.
- How were the **Missing Data** handled? LOCF
- Was there a **Multiplicity** involved? Yes.

  If yes,

  Multiple Arms (Yes/No)? No.

Multiple Endpoints (Yes/No)? Yes.

Which method was used to control for type I error? For acute migraine, the primary endpoint and all three key secondary endpoints are all required to be statistically significant at 0.05 (two-sided) for an efficacy claim.

- **Multiple Secondary Endpoints**: Are they being included in the label? If yes, method to control for type 1 error. Yes, but all secondary endpoints are required to be positive at 0.05 two-sided for efficacy claim.

Were Subgroup Analyses Performed (Yes/No)? Yes.

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes.

APPEARS THIS WAY ON ORIGINAL

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

/s/

JINGYU J LUAN
05/16/2011

KUN JIN
05/17/2011
I concur with this review.

KOOROS MAHJOOB
05/17/2011
The review was discussed and my views are incorporared. A concur with this review.