CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206099Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	206-099 SN000
Drug Name:	Onzetra® (Sumatriptan Nasal Powder, AVP-825)
Indication(s):	Acute Migraine with or without Aura
Applicant:	Avanir Pharmaceuticals
Date of Submission:	1/27/2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jingyu (Julia) Luan, Ph.D. (HFD-710)
Concurring Reviewers:	Kun Jin, Ph.D. (HFD -710) H.M. James Hung, Ph.D. (HFD -710)
Medical Division:	Division of Neurology Product (HFD -120)
Clinical Team:	Suhail Kasim, M.D. (HFD-120) Nicholas Kozauer, M.D. (HFD-120)
Project Manager:	Vandna Kishore (HFD-120)
Keywords: Migraine, Chi-square test, Sensitivity Analysis	

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1 EXECUTIVE SUMMARY

This submission includes a single phase III pivotal efficacy study OPN-SUM-MIG-3301. The results of this study suggest that (b) (4) SUMATRIPTAN is effective, as compared to placebo, in adults with Acute Migraine with or without Aura, based on the primary endpoint Headache Relief.

Study OPN-SUM-MIG-3301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III study evaluating the efficacy and safety of a single 20 mg dose of sumatriptan powder delivered intranasally with the bi-directional device in adults with acute migraine with or without aura. The expected maximum duration of subject participation was up to 12 weeks. The study contained a pretreatment screening phase for up to 3 weeks; a double-blind treatment phase until a subject treated a single migraine episode or up to 8 weeks after randomization, whichever was reached first; and an end-of-study visit occurring between 48 hours up to 7 days after treatment of a single migraine episode. Two hundred thirty (230) subjects were randomized in a 1:1 ratio to either 20 mg sumatriptan or placebo. The Full Analysis Dataset (FAD) consisted of 212 subjects (212/230=92%).

The primary efficacy endpoint was the proportion of subjects who had headache relief at 120 minutes after treatment with study drug. Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1). A significantly greater proportion of subjects in the 20 mg (b) (4) SUMITRIPTAN group, 73 (67.6%) subjects, reported pain relief at 120 minutes versus the placebo group, 47 (45.2%) subjects (p=0.0016).

In the section of Disposition of Subjects, the sponsor presented “Completers Dataset” as a subset of “Randomized Dataset” instead of a subset of “Full Analysis Dataset”. It is more sensible to show how many subjects in the Full Analysis Dataset (FAD) completed the study. Based on the data, there is only one patient in the Full Analysis Dataset (n=212) discontinued from the study.

In the primary efficacy analysis, the sponsor used LOCF to handle missing data. According to the publication, “*The prevention and treatment of missing data in clinical trials*” by the National Academies, LOCF as a primary analysis is discouraged. However, since only one subject in FAD discontinued from the study and needed LOCF imputation, the results of LOCF and completer analysis are virtually the same.

2 INTRODUCTION

2.1 Overview

Migraine is a common, disabling primary headache disorder. Epidemiological studies have documented its high prevalence and high socioeconomic and personal impacts. An overall US prevalence of migraine has been reported to be 17.5% among females and 8.6% among males. Migraine attacks are recurrent and associated with moderate to severe headache that are usually associated with gastrointestinal, neurologic, and autonomic symptoms. Migraine attacks

generally occur several times per month, typically last 4 to 72 hours, and are characterized by moderate to severe headaches, often unilateral, and with a pulsating quality. Migraines are often associated with nausea and/or vomiting, phonophobia, and/or photophobia. Approximately 30% of headaches also have associated aura, which is characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache.

The most commonly used medications for the treatment of acute migraine are triptans, with sumatriptan being the most commonly prescribed medication of the class. Intranasal formulations of some triptans (sumatriptan and zolmitriptan) have been developed with the intent of achieving faster absorption and producing an earlier onset of headache relief than oral formulations without the need for injection of parenteral formulations.

AVP-825 is a drug-device product used for nasal delivery of a powder form of sumatriptan succinate (active pharmaceutical ingredient) via a proprietary breath-powered delivery device. AVP-825 is intended for the acute treatment of migraine headache with or without aura. The device consists of a flexible mouthpiece and a specially shaped sealing nosepiece connected via a closed communication shell.

AVP-825 is being filed as a 505(b) (2) NDA and relies on previous findings pertaining to sumatriptan safety and efficacy {Imitrex® Nasal Spray (NDA 020626 [local exposure and efficacy]), Imitrex® oral tablet (NDA 020132 [systemic exposure]) and Imitrex® injectable, subcutaneous (NDA 020080 [systemic exposure])}, submitted by GlaxoSmithKline, for which Avanir Pharmaceuticals has not received right of reference.

The US clinical program for AVP-825 was conducted under IND 110,090. The core clinical development program supporting the evidence of efficacy of AVP-825 for the treatment of migraine with and without aura consists of supportive phase 2 trial OPTUK-MSPP PRO 002 and the pivotal phase 3 study OPN-SUM-MIG-3301. This review is for the pivotal phase 3 study OPN-SUM-MIG-3301.

This study was a double-blind, placebo-controlled, parallel-group study. Subjects randomized to a treatment continued until they treated a single attack or until 8 weeks after randomization, whichever occurred first. The study included a pretreatment screening phase, a double-blind phase, and a post treatment follow-up phase. Subjects were randomized in a 1:1 ratio (20 mg sumatriptan or placebo). Rescue medication (excluding ergotamine) was permitted 120 minutes after the dose of study drug if symptom relief was inadequate. The first patient was enrolled on December 20, 2011 and the last patient completed on May 31, 2012.

2.2 Data Sources

The sponsor's electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA206099 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality is generally acceptable. The analyses conducted by this reviewer were based on raw data.

3.2 Evaluation of Efficacy

3.2.1 PROTOCOL OPN-SUM-MIG-3301

3.2.1.1 Study Objectives

The primary objective for this study was to compare headache relief (defined as a reduction from moderate [Grade 2] or severe [Grade 3] pain to none [Grade 0] or mild [Grade 1] pain) at 120 minutes following a dose of 20 mg of (b) (4) SUMATRIPTAN with placebo in the acute treatment of a single migraine attack.

The secondary objective was to compare the efficacy of 20 mg (b) (4) SUMATRIPTAN with placebo on:

- Headache relief at 10, 15, 30, 45, 60, and 90 minutes after treatment
- Complete relief (i.e., pain free, defined as moderate [Grade 2] or severe [Grade 3] reduced to none [Grade 0]) at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment
- Headache severity changes from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment
- Clinical disability changes from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment, as measured by the Clinical Disability Scale
- Sustained pain-free plus no adverse events (SPFNAE) at 120 minutes after treatment and through 24, and 48 hours
- Presence of nausea, photophobia, phonophobia, or vomiting at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment
- Meaningful relief (subject-reported interpretation) and time to meaningful relief within 120 minutes of treatment
- Maintenance of headache relief over 24 and 48 hours following treatment, where maintenance of headache relief was defined as moderate (Grade 2) or severe (Grade 3) headache pain at baseline going to none (Grade 0) or mild (Grade 1) pain at 2 hours after dosing with no recurrence of headache or rescue medication up to 24 and 48 hours
- Time to recurrence of headache, defined as an increase from none (Grade 0) or mild (Grade 1) pain to moderate (Grade 2) or severe (Grade 3) pain within 24 hours of treatment
- Use of and time to rescue medication

3.2.1.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III study evaluating the efficacy and safety of a single 20 mg dose of sumatriptan powder delivered intranasally with the bi-directional device in adults with acute migraine with or without aura.

The planned enrollment was approximately 200 subjects (100 in each treatment group). The expected maximum duration of subject participation was up to 12 weeks. The study contained a pretreatment screening phase for up to 3 weeks; a double-blind treatment phase until a subject treated a single migraine episode or up to 8 weeks after randomization, whichever was reached first; and an end-of-study visit occurring between 48 hours up to 7 days after treatment of a single migraine episode.

3.2.1.3 Efficacy Measures

The primary efficacy endpoint was the comparison of the percentage of subjects in each treatment group who had headache relief at 120 minutes after treatment with study drug. Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1).

The secondary efficacy endpoints for this study were:

- The percentage of subjects in each treatment group with headache relief at 10, 15, 30, 45, 60, and 90 minutes after treatment;
- The percentage of subjects with complete relief at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment;
- Median time to complete relief within 120 minutes of treatment;
- Mean change in Headache Severity Score from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment (Grade from 0 [None] to 3 [Severe]);
- Mean change in Clinical Disability Scale from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after treatment (Grade from 0 [no disability] to 3 [cannot do all or most things]);
- Percentage of responses for each category on Clinical Disability Scale at each time point
- Percentage of subjects with SPFNAE at 120 minutes, over 24 and 48 hours after treatment;
- Percentage of subjects with nausea, phonophobia, photophobia, or vomiting at each time point;
- Percentage of subjects with meaningful relief (subject-reported interpretation) within 120 minutes of treatment;
- Median time to meaningful relief within 120 minutes of treatment;
- Percentage of subjects who maintained headache relief over 24 and 48 hours after treatment;
- Percentage of subjects who experienced a recurrence of headache within 24 hours and within 48 hours of treatment;
- Time to recurrence of headache within 24 hours and within 48 hours of treatment;
- Time to rescue medication after treatment.

3.2.1.4 Statistical Analysis Plan

The Full Analysis Dataset (FAD) included all subjects who were randomized, received study drug, and recorded at least one post-treatment assessment of pain severity. The treatment group assignment in this population was designated according to the treatment received. The FAD served as the basis for the analysis of efficacy.

The primary efficacy endpoint of this study was the percentage of subjects who had headache relief at 120 minutes after treatment with study drug. The primary efficacy analysis compared the 20 mg of (b) (4) SUMATRIPTAN treatment group to the placebo treatment group using a chi-square test (continuity-corrected).

Descriptive statistics were presented for baseline Headache Severity and Clinical Disability Scale values as well as for the changes from baseline at 10, 15, 30, 45, 60, 90, and 120 minutes after dosing. The treatment comparison for the change from baseline was performed with analysis of covariance (ANCOVA) models using treatment and center as main effects and the baseline value of the variable as a covariate. Treatment comparison for the dichotomous secondary efficacy points was analyzed with a two-group continuity-corrected chi-square test. For the longitudinal secondary efficacy endpoints, treatment comparisons were carried out by an estimate of the survival function constructed using the Kaplan-Meier method.

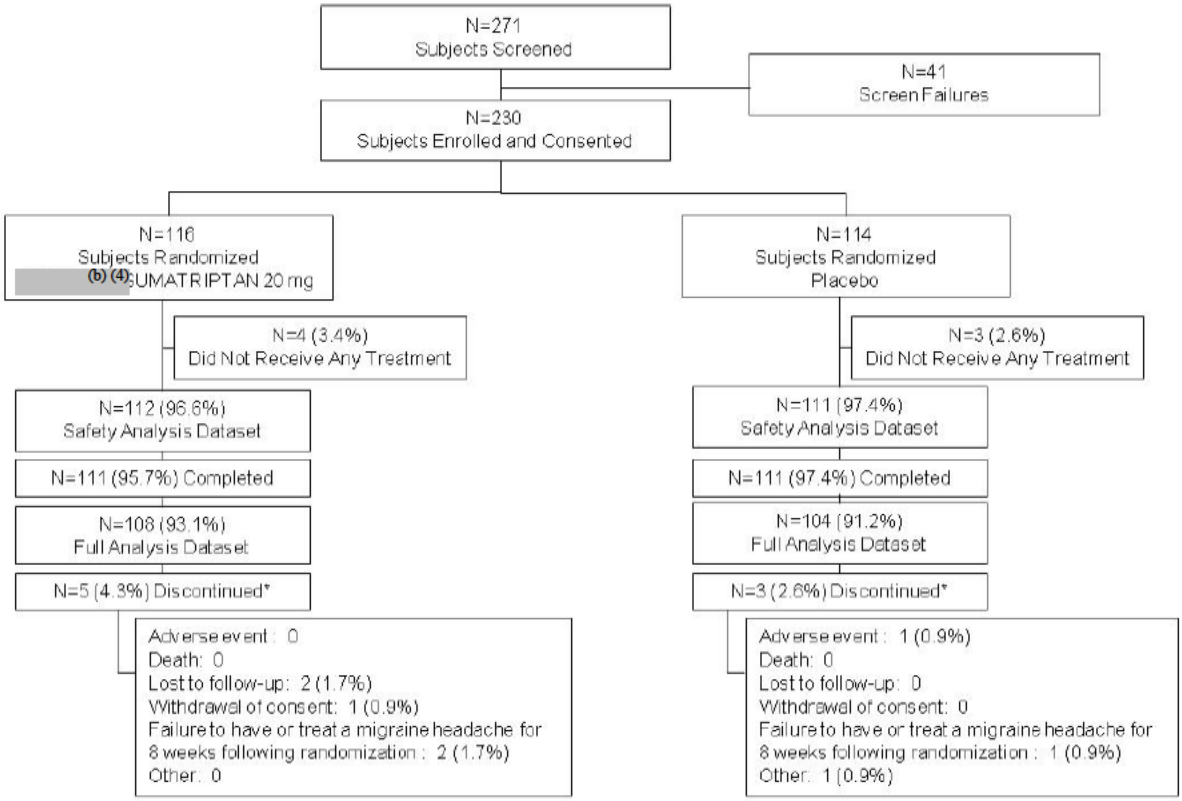
The changes in the planned analyses were very minor, which don't impact the interpretation of the study results.

3.2.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A diagram of subject disposition by treatment group and analysis population is provided in Figure 1. Subject disposition was similar in the two treatment groups. A total of 271 subjects were screened and 230 subjects were randomized. Seven randomized subjects were not treated resulting in 223 subjects in the Safety Population. Eleven of these subjects were excluded from the FAD population. Three subjects randomized to (b) (4) SUMATRIPTAN and seven subjects randomized to placebo took study medication before completing their baseline diary and did not record post-baseline assessments. Another (b) (4) SUMATRIPTAN subject did not record any post baseline pain assessments, resulting in a total of 212 subjects who were analyzed for efficacy. Five subjects (4 untreated) discontinued in the 20 mg (b) (4) SUMATRIPTAN group, while 3 subjects (all untreated) discontinued in the placebo group. One subject in the placebo group discontinued due to an AE (pregnancy). However, this subject had not taken any study medication.

Figure 1: Subject Disposition (All Subjects)



Source: Figure 10.1 of sponsor's CSR

Reviewer's Comments:

The sponsor presented "Completers Dataset" as a subset of "Randomized Dataset" instead of a subset of "Full Analysis Dataset". It is more sensible to see how many subjects in the Full Analysis Dataset completed the study. For revised presentation of Disposition of Subjects, please refer to 3.2.2 Reviewer's Analysis.

Demographics and Other Baseline Characteristics

Demographic data and other baseline characteristics for FAD are summarized in Table 1. It appears that the two treatment groups were balanced with respect to demographic and baseline characteristics. The mean (SD) age in the combined treatment groups was 42.0 (10.50) years and 83.5% of subjects were female. A large majority of subjects (85.8%) were white. Subjects had a mean (SD) of 4.5 (1.89) migraine attacks per month. The baseline severity for the migraine headache treated in this study was moderate for 83% of subjects and severe for 17% of subjects.

Table 1: Demographic and Other Baseline Characteristics (FAD Population)

	20 mg (b) (4) SUMATRIPTAN (N=108)	Placebo (N=104)	Total (N=212)
Age (years)			
n	108	104	212
Mean	41.9	42.0	42.0
SD	10.33	10.73	10.50
Median	44.0	43.0	43.0
Min, Max	19, 64	19, 63	19, 64
Sex			
Male	17 (15.7%)	18 (17.3%)	35 (16.5%)
Female	91 (84.3%)	86 (82.7%)	177 (83.5%)
Race			
American Indian or Alaska Native	1 (0.9%)	1 (1.0%)	2 (0.9%)
Asian	1 (0.9%)	1 (1.0%)	2 (0.9%)
Black or African American	15 (13.9%)	9 (8.7%)	24 (11.3%)
Hawaiian/other Pacific Islander	0	0	0
White	90 (83.3%)	92 (88.5%)	182 (85.8%)
Other	1 (0.9%)	1 (1.0%)	2 (0.9%)
Ethnicity			
Hispanic or Latino	4 (3.7%)	2 (1.9%)	6 (2.8%)
Not Hispanic or Latino	104 (96.3%)	102 (98.1%)	206 (97.2%)
Height (cm)			
n	108	104	212
Mean	166.580	165.327	165.965
SD	8.3522	9.5110	8.9402
Median	165.100	164.800	165.100
Min, Max	151.00, 187.96	144.00, 193.04	144.00, 193.04
Weight (kg)			
n	108	104	212
Mean	79.639	79.105	79.377
SD	20.4184	18.7133	19.5559
Median	75.000	74.455	74.775
Min, Max	45.00, 170.91	45.45, 131.60	45.00, 170.91
Average number of attacks per month [1]			
n	108	104	212
Mean	4.3	4.8	4.5
SD	1.91	1.86	1.89
Median	4.0	4.0	4.0
Min, Max	1, 8	1, 8	1, 8
Baseline Headache Severity			
No Pain	0	0	0
Mild	0	0	0
Moderate	90 (83.3%)	86 (82.7%)	176 (83.0%)
Severe	18 (16.7%)	18 (17.3%)	36 (17.0%)

SD=Standard Deviation; Min=minimum; Max=maximum ; [1] Applies to 12 months prior to study entry
Source Data: End of Text Table 14.1.2.2

Source: Table 11.1 of sponsor's CSR

3.2.1.6 Sponsor's Primary Efficacy Results

The primary efficacy endpoint was the proportion of subjects who had headache relief at 120 minutes after treatment with study drug. Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1). A comparison of treatment groups for the proportion of subjects with headache relief at 120 minutes after study treatment is presented in Table 2. A statistically significantly greater proportion of subjects in the 20 mg [(b) (4)] SUMITRIPTAN group, 73 (67.6%) subjects, reported pain relief at 120 minutes versus the placebo group, 47 (45.2%) subjects (p=0.0016).

Table 2: Proportion of Subjects with Headache Relief at 120 Minutes (FAD Population)

	[(b) (4)] SUMATRIPTAN 20 mg (N = 108)	Placebo (N = 104)
Headache relief		
Yes	73 (67.6%)	47 (45.2%)
No	35 (32.4%)	57 (54.8%)
Estimates of the Relative Risk		
Odds Ratio [1]	2.53	
95% CI [1]	(1.45, 4.42)	
P-Value [2]	0.0016	

Headache relief is defined as a reduction from moderate(Grade 2) or Severe (Grade 3) pain to none (Grade 0) or mild (Grade 1) pain.
CI = confidence interval.
The Last Observation Carried Forward (LOCF) imputation was used.
[1] Odds Ratio and 95% CIs were estimated by SAS FREQ procedure.
[2] P-value was calculated by chi-square test (continuity-corrected).
Source Data: End-of-Text Table 14.2.1.

Source: Table 11.3 of sponsor's CSR

Reviewer's Comments:
LOCF was used to impute missing data. Please refer to Section 3.2.2 Reviewer's Analysis for additional comments regarding missing data handling.

3.2.1.7 Sponsor's Secondary Efficacy Results

Headache Relief over Time

A comparison of treatment groups for the proportion of subjects with headache relief by time point after study treatment is presented in Table 3. At 30 minutes after dosing, 45 (41.7%) subjects showed pain relief in the 20 mg [(b) (4)] SUMATRIPTAN group versus 28 (26.9%) subjects in the placebo group. The proportion of subjects with pain relief in the 20 mg [(b) (4)] SUMATRIPTAN group increased with each time point to a maximum of 73 (67.6%) at 120 minutes. Subjects in the placebo group showed smaller increases in the proportion of subjects showing pain relief to a maximum of 47 (45.2%) at 120 minutes.

Table 3: Proportion of Subjects with Headache Relief by Time Point (FAD Population)

Time Point after Study Treatment	(b) (4) SUMATRIPTAN 20 mg (N=108)	Placebo (N=104)	Odds Ratio[1]
10 minutes			
Yes	11 (10.2%)	10 (9.6%)	1.06
No	93 (86.1%)	90 (86.5%)	
Missing	4 (3.7%)	4 (3.8%)	
Total	108 (100.0%)	104 (100.0%)	
15 minutes			
Yes	21 (19.4%)	15 (14.4%)	1.42
No	86 (79.6%)	87 (83.7%)	
Missing	1 (0.9%)	2 (1.9%)	
Total	108 (100.0%)	104 (100.0%)	
30 minutes			
Yes	45 (41.7%)	28 (26.9%)	1.94
No	62 (57.4%)	75 (72.1%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
45 minutes			
Yes	51 (47.2%)	34 (32.7%)	1.85
No	56 (51.9%)	69 (66.3%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
60 minutes			
Yes	60 (55.6%)	38 (36.5%)	2.18
No	47 (43.5%)	65 (62.5%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
90 minutes			
Yes	72 (66.7%)	43 (41.3%)	2.84
No	36 (33.3%)	61 (58.7%)	
Total	108 (100.0%)	104 (100.0%)	
120 minutes			
Yes	73 (67.6%)	47 (45.2%)	2.53
No	35 (32.4%)	57 (54.8%)	
Total	108 (100.0%)	104 (100.0%)	

Source: Excerpt from Table 11.4 of sponsor's CSR

Complete Relief over Time

Complete Relief was defined as a reduction in pain from moderate (Grade 2) or severe (Grade 3) to none (Grade 0). The proportion of subjects with complete relief by time point after study treatment is presented by treatment group in Table 4. As with headache relief, the proportion of subjects with complete relief in the 20 mg (b) (4) SUMATRIPTAN group increased with time to a maximum of 37 (34.3%) subjects at 120 minutes. The proportion of subjects in the placebo group with complete relief increased to only 18 (17.3%) at 120 minutes.

Table 4: Proportion of Subjects with Complete Relief by Time Point (FAD Population)

(b) (4)

Time Point after Study Treatment	SUMATRIPTAN 20 mg (N=108)	Placebo (N=104)	Odds Ratio[1]
10 minutes			
Yes	0	0	N/A
No	104 (96.3%)	100 (96.2%)	
Missing	4 (3.7%)	4 (3.8%)	
Total	108 (100.0%)	104 (100.0%)	
15 minutes			
Yes	2 (1.9%)	3 (2.9%)	0.63
No	105 (97.2%)	99 (95.2%)	
Missing	1 (0.9%)	2 (1.9%)	
Total	108 (100.0%)	104 (100.0%)	
30 minutes			
Yes	6 (5.6%)	4 (3.8%)	1.47
No	101 (93.5%)	99 (95.2%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
45 minutes			
Yes	16 (14.8%)	7 (6.7%)	2.41
No	91 (84.3%)	96 (92.3%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
60 minutes			
Yes	23 (21.3%)	11 (10.6%)	2.29
No	84 (77.8%)	92 (88.5%)	
Missing	1 (0.9%)	1 (1.0%)	
Total	108 (100.0%)	104 (100.0%)	
90 minutes			
Yes	28 (25.9%)	15 (14.4%)	2.08
No	80 (74.1%)	89 (85.6%)	
Total	108 (100.0%)	104 (100.0%)	
120 minutes			
Yes	37 (34.3%)	18 (17.3%)	2.49
No	71 (65.7%)	86 (82.7%)	
Total	108 (100.0%)	104 (100.0%)	

Source: Excerpt from Table 11.5 of sponsor's CSR

Clinical Disability Scores over Time

The Clinical Disability Score was on a scale of 0 to 3, with 0=no disability, 1= performance of daily activities mildly impaired, can still do everything but with difficulty, 2=performance of daily activities moderately impaired, unable to do some things, 3= performance of daily activities severely impaired, cannot do all or most things, bed rest may be necessary.

A comparison of change from baseline Clinical Disability Scores by time point and treatment group is presented in Table 5. The mean (SD) Clinical Disability Score at baseline was 1.6 (0.64) in the 20 mg (b) (4) SUMATRIPTAN group and 1.6 (0.70) in the placebo group. The baseline median in both groups was 2.0. There was a decrease in Clinical Disability with time in both groups. However, the 20 mg (b) (4) SUMATRIPTAN group showed greater improvement than placebo starting at 45 minutes post dose with a mean (SD) decrease of -0.5 (0.71) for 20 mg (b) (4) SUMATRIPTAN versus -0.3 (0.61) in the placebo group. At 120 minutes there was a mean decrease of -0.8 (0.89) in the 20 mg (b) (4) SUMATRIPTAN group versus -0.4 (0.87) in the placebo group.

Table 5: Clinical Disability Scores Comparison of Mean Change from Baseline by Time Point (FAD Population)

	(b) (4) SUMATRIPTAN 20 mg (N=108)		Placebo (N=104)	
Time Point After Study Treatment	Actual	Change from Baseline	Actual	Change from Baseline
0 (Pre-Dose)				
n	108		104	
Mean	1.6		1.6	
SD	0.64		0.70	
Median	2.0		2.0	
Min, Max	0, 3		0, 3	
10 Minutes				
n	104	104	100	100
Mean	1.5	-0.1	1.5	-0.1
SD	0.71	0.42	0.72	0.34
Median	2.0	0.0	1.5	0.0
Min, Max	0, 3	-1, 1	0, 3	-2, 1
15 Minutes				
n	107	107	102	102
Mean	1.5	-0.1	1.5	-0.1
SD	0.72	0.53	0.75	0.46
Median	1.0	0.0	2.0	0.0
Min, Max	0, 3	-2, 1	0, 3	-2, 1
30 Minutes				
n	107	107	103	103
Mean	1.3	-0.3	1.4	-0.2
SD	0.82	0.67	0.78	0.57
Median	1.0	0.0	1.0	0.0
Min, Max	0, 3	-2, 1	0, 3	-2, 1
45 Minutes				
n	107	107	103	103
Mean	1.1	-0.5	1.3	-0.3
SD	0.81	0.71	0.79	0.61
Median	1.0	0.0	1.0	0.0
Min, Max	0, 3	-2, 1	0, 3	-2, 1

Time Point After Study Treatment	(b) (4) SUMATRIPTAN 20 mg (N=108) Actual	Change from Baseline	Placebo (N=104) Actual	Change from Baseline
60 Minutes				
n	107	107	103	103
Mean	1.0	-0.6	1.3	-0.3
SD	0.82	0.73	0.85	0.72
Median	1.0	-1.0	1.0	0.0
Min, Max	0, 3	-2, 1	0, 3	-3, 1
90 Minutes				
n	108	108	104	104
Mean	0.9	-0.8	1.2	-0.4
SD	0.83	0.79	0.86	0.79
Median	1.0	-1.0	1.0	0.0
Min, Max	0, 3	-3, 1	0, 3	-3, 1
120 Minutes				
n	108	108	104	104
Mean	0.8	-0.8	1.2	-0.4
SD	0.87	0.89	0.91	0.87
Median	1.0	-1.0	1.0	0.0
Min, Max	0, 3	-3, 1	0, 3	-3, 2

Source: Excerpt from Table 11.8 of sponsor's CSR

Individual Migraine Related Symptoms over Time

Comparisons between treatment groups for the proportion of subjects with each of the migraine symptoms at 120 minutes post dose is presented in Table 6. Except for the very low incidence of vomiting, the proportion of patients with migraine related symptom was numerically lower in the 20 mg (b) (4) SUMATRIPTAN group than in the placebo group.

Table 6: Comparison of Proportion of Subjects with Individual Symptom between Treatment Groups at 120 Minutes (FAD Population)

Timepoint after Study Treatment (minutes)	(b) (4) SUMATRIPTAN 20 mg (N=108)	Placebo (N=104)	Odds Ratio[1]	95% CIs[1]	P-Value[2]
Nausea					
120 minutes					
Yes	20 (18.5%)	22 (21.2%)	0.85	(0.43, 1.67)	0.7574
No	88 (81.5%)	82 (78.8%)			
Total	108 (100.0%)	104 (100.0%)			
Photophobia					
120 minutes					
Yes	52 (48.1%)	62 (59.6%)	0.63	(0.37, 1.08)	0.1245
No	56 (51.9%)	42 (40.4%)			
Total	108 (100.0%)	104 (100.0%)			
Phonophobia					
120 minutes					
Yes	35 (32.4%)	46 (44.2%)	0.60	(0.35, 1.06)	0.1031
No	73 (67.6%)	58 (55.8%)			
Total	108 (100.0%)	104 (100.0%)			
Vomiting					

120 minutes					
Yes	2 (1.9%)	0	N/A	N/A	0.4941
No	106 (98.1%)	104 (100.0%)			
Total	108 (100.0%)	104 (100.0%)			

Source: Excerpt from Table 14.2.8, 14.2.9, 14.2.10 and 14.2.11 of sponsor's CSR

Reviewer's Comments:
Usually, the p-values for secondary endpoints are not presented. However, since nausea, photophobia and phonophobia were traditionally considered as the co-primary endpoints, the numerical p-values were presented only for comparison purpose.

3.2.2 REVIEWER'S ANALYSIS

This reviewer verified sponsor's efficacy analyses presented in this review. The analyses shown in this session were conducted by this reviewer.

3.2.2.1 Disposition of Subjects

In Section 3.2.1.5, the sponsor presented Disposition of Subjects. However, the sponsor presented "Completers Dataset" as a subset of "Randomized Dataset" instead of a subset of "Full Analysis Dataset". It is more sensible to show how many subjects in the Full Analysis Dataset (FAD) completed the study. The following description was provided by the sponsor:

> "*Five subjects (4 untreated) discontinued in the 20 mg* (b) (4) *SUMATRIPTAN group, while 3 subjects (all untreated) discontinued in the placebo group. One subject in the placebo group discontinued due to an AE (pregnancy). However, this subject had not taken any study medication.*"

Based on this statement and data, there is only one patient in the Full Analysis Dataset discontinued from the study (the patient who was treated in the 20 mg (b) (4) SUMATRIPTAN group, but discontinued from the study). The patients who were untreated or didn't take study medication should not be included in the Safety Dataset and Full Analysis Dataset.

Table 7: Revised Presentation of Subject Disposition

Dataset	(b) (4) SUMATRIPTAN 20 mg	Placebo
Randomized Dataset	116	114
Safety Dataset	112	111
Full Analysis Dataset	108	104
Completer Dataset	107	104

Source: Reviewer's Analysis

3.2.2.2 Last Observation Carried Forward (LOCF) Analysis versus Completer Analysis

In the primary efficacy analysis, the sponsor used LOCF to handle missing data. According to the publication, "*The prevention and treatment of missing data in clinical trials*" by the National Academies, LOCF as a primary analysis is discouraged. However, since only one subject in FAD

discontinued from the study and needed LOCF imputation, the results of LOCF and completer analysis are virtually the same (Table 8).

Table 8: LOCF Analysis versus Completer Analysis for Headache Relief

	(b) (4) SUMATRIPTAN 20 mg	Placebo	P-value*
LOCF Analysis	73 (67.6%)	47 (45.2%)	0.0016
Completer Analysis	72 (67.3%)	47 (45.2%)	0.0020

*: P-value was calculated by Chi-square test (continuity-corrected).
Source: Reviewer's Analysis

3.3 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

4.1.1 STUDY OPN-SUM-MIG-3301

Table 10 presents the results of subgroup analysis by sex, race and age group. It seems that the point estimates of the treatment effects are in the right direction for sex and age. For race, the point estimates of treatment effect were very similar for white and non-white subjects. However, this doesn't raise concerns since there are only 14% (30/212) non-white subjects in this study.

Table 9: Subgroup Analysis by Sex, Race and Age (FAD Population)

Subgroup	(b) (4) SUMATRIPTAN 20 mg (N=108)	Placebo (N=104)
Female	61 (67%)	40 (47%)
Male	12 (71%)	7 (39%)
White	60 (67%)	38 (41%)
Non-white	13 (72%)	9 (75%)
Age <= 40	27 (68%)	16 (43%)
Age 40-55	40 (69%)	28 (50%)
Age >=55	6 (60%)	3 (27%)

Source: Reviewer's Analysis

This study was conducted in US only, thus there is no subgroup analysis by geographic regions.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This submission includes a single phase III pivotal efficacy study OPN-SUM-MIG-3301.

Study OPN-SUM-MIG-3301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III study evaluating the efficacy and safety of a single 20 mg dose of sumatriptan powder delivered intranasally with the bi-directional device in adults with acute migraine with or without aura. The expected maximum duration of subject participation was up to 12 weeks. The study contained a pretreatment screening phase for up to 3 weeks; a double-blind treatment phase until a subject treated a single migraine episode or up to 8 weeks after randomization, whichever was reached first; and an end-of-study visit occurring between 48 hours up to 7 days after treatment of a single migraine episode. Two hundred thirty (230) subjects were randomized in a 1:1 ratio to either 20 mg sumatriptan or placebo. The Full Analysis Dataset (FAD) consisted of 212 subjects (212/230=92%).

The primary efficacy endpoint was the proportion of subjects who had headache relief at 120 minutes after treatment with study drug. Headache relief was defined as a reduction in headache severity from moderate (Grade 2) or severe (Grade 3) to none (Grade 0) or mild (Grade 1). A significantly greater proportion of subjects in the 20 mg (b) (4) SUMITRIPTAN group, 73 (67.6%) subjects, reported pain relief at 120 minutes versus the placebo group, 47 (45.2%) subjects (p=0.0016).

In the section of Disposition of Subjects, the sponsor presented “Completers Dataset” as a subset of “Randomized Dataset” instead of a subset of “Full Analysis Dataset”. It is more sensible to show how many subjects in the Full Analysis Dataset (FAD) completed the study. Based on the data, there is only one patient in the Full Analysis Dataset (n=212) discontinued from the study.

In the primary efficacy analysis, the sponsor used LOCF to handle missing data. According to the publication, “The prevention and treatment of missing data in clinical trials” by the National Academies, LOCF as a primary analysis is discouraged. However, since only one subject in FAD discontinued from the study and needed LOCF imputation, the results of LOCF and completer analysis are virtually the same.

5.2 Conclusions and Recommendations

The results of study OPN-SUM-MIG-3301suggest that (b) (4) SUMATRIPTAN is effective, as compared to placebo, in adults with Acute Migraine with or without Aura, based on the primary endpoint Headache Relief.

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/s/

JINGYU J LUAN
08/29/2014

KUN JIN
08/29/2014
I concur with the review.

HSIEN MING J HUNG
08/29/2014