STATISTICAL ANALYSIS PLAN

Study Title:	**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ZOLMITRIPTAN NASAL SPRAY FOR THE TREATMENT OF ACUTE MIGRAINE IN SUBJECTS AGES 6 TO 11 YEARS, WITH AN OPEN-LABEL EXTENSION**
Name of Test Drug:	IPX229 (zolmitriptan nasal spray)
Protocol Number:	IPX229-B16-01
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AE	adverse event
BMI	body mass index
bpm	beats per minute
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
FAS	full analysis set
GEE	generalized estimating equation
IWRS	interactive web response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	nonsteroidal anti-inflammatory drugs
OLE	open label safety extension
PedMIDAS	pediatric migraine disability assessment
QTc	corrected QT
QTcB	Bazett's corrected QT
QTcF	Fridericia's corrected QT
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TLFs	tables, listings, figures
WHO	World Health Organization
ZNS	zolmitriptan nasal spray

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, listings, and figures (TLFs) in the clinical study report (CSR) for Study IPX229-B16-01. This SAP is based on the study protocol amendment 3 dated 13Dec2017.

1.1. Study Designs and Objectives

The primary objective of the study is to evaluate the efficacy and safety of zolmitriptan nasal spray (ZNS) in the acute treatment of migraine headache in subjects ages 6 to 11 years.

This is a randomized, double-blind, placebo-controlled, 2-period, crossover outpatient study (See Figure 1). Within 2 weeks of screening, eligible subjects will return to the study site to begin a 6-week single-blind run-in period, during which a single migraine headache will be treated with 1 dose of placebo. Subjects will be instructed to treat a headache of moderate or severe pain intensity within approximately 20 minutes of onset of headache pain reaching moderate or severe intensity and to complete a diary capturing the headache severity using a 4-point headache pain intensity scale (severe = 3, moderate = 2, mild = 1 or none = 0), other associated symptoms, and use of rescue medication(s). Headaches occurring while the child is at school will not be treated with study drug. Adverse events (AEs) will also be collected. Diary entries are to be recorded immediately prior to treatment with study drug and after treatment at 30 minutes, 1 and 2 hours. If, after 2 hours, the migraine headache has not responded (ie, reduced to a pain intensity of mild or none), the subject is permitted to use protocol-allowed rescue medication(s). Any subsequent migraine episodes during the run-in period will be treated with the subject's protocol-allowed pre-study acute migraine medication. Subjects who have not treated a migraine headache with blinded placebo during the 6-week run-in period will be considered screen failures. Placebo challenge responders (defined as those subjects who treat a migraine attack of moderate (2) or severe (3) intensity and who achieve a mild (1) or none (0) response within 2 hours after dosing) will be discontinued from the study.

Eligible placebo non-responders will be randomized to one of two treatment sequences within their respective body weight stratum determined immediately prior to randomization: ZNS followed by placebo or placebo followed by ZNS (Table 1). Subjects weighing less than 50 kg will be allocated randomly to receive ZNS 2.5 mg or 1 mg in a 5:1 fashion during the ZNS treatment. Subjects weighing at least 50 kg will be allocated randomly to receive ZNS 5 mg or 2.5 mg in a 5:1 fashion during the ZNS treatment (Table 2). Following randomization, subjects will have up to 6 weeks to treat a migraine attack of moderate or severe intensity. During each treatment period, subjects will treat a single moderate to severe migraine attack with study drug within approximately 20 minutes of the headache pain reaching moderate or severe intensity. Headaches occurring while the child is at school will not be treated with study drug. Headache pain intensity will be assessed by the subjects immediately prior to treatment with study drug and at 30 minutes, 1, 2, and 24 hours postdose using a subject diary containing the 4-point headache pain intensity scale. Associated migraine symptoms will also be assessed at these time points. Subjects who do not obtain satisfactory relief of migraine pain by 2 hours after taking study drug will be permitted to treat with their protocol-allowed pre-study acute migraine medication (eg,

nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) at that time or at any time thereafter, if the headache does not resolve or if it recurs, with the exception that all triptans and ergot derivatives are prohibited for 24 hours following the dose of study treatment. After treating a migraine attack in the first treatment period, the subject will return to the study site to receive study drug for the second treatment period. Subjects will then have up to 6 weeks to treat a second migraine attack of moderate or severe intensity.

Subjects who successfully complete the double-blind portion of this study and continue to be eligible will be offered participation in a 6-month outpatient open-label safety extension (OLE; Part 2) where they will treat up to 4 moderate to severe migraine attacks per month with ZNS. The occurrence, continuance, or recurrence of migraine headache pain for up to 72 hours after the onset of a migraine attack is considered to be part of this attack and is not considered a separate attack, regardless of treatment. Headaches occurring while the child is at school will not be treated with study drug. During the OLE, subjects will assess their pain-free status immediately prior to treatment with ZNS and 2 hours after the first dose for each migraine attack treated with ZNS. Subjects who do not obtain satisfactory relief of migraine pain by 2 hours after taking study drug, or if the headache recurs after 2 hours, are permitted to treat with a second dose of their study drug and/or their protocol-allowed pre-study acute migraine medication (eg, NSAIDs or acetaminophen). For each migraine attack, diary entries will only be made for the first dose of study drug; a second dose of study drug may not be administered within 2 hours of the first dose and no more than 2 doses of study drug are permitted within a 24-hour period and for any single attack. Other triptans and ergot derivatives are prohibited for 24 hours following the last dose of study drug treatment. Migraine-associated disability, using the PedMIDAS questionnaire, will be assessed at the end of study.

Figure 1: Study Flow Chart
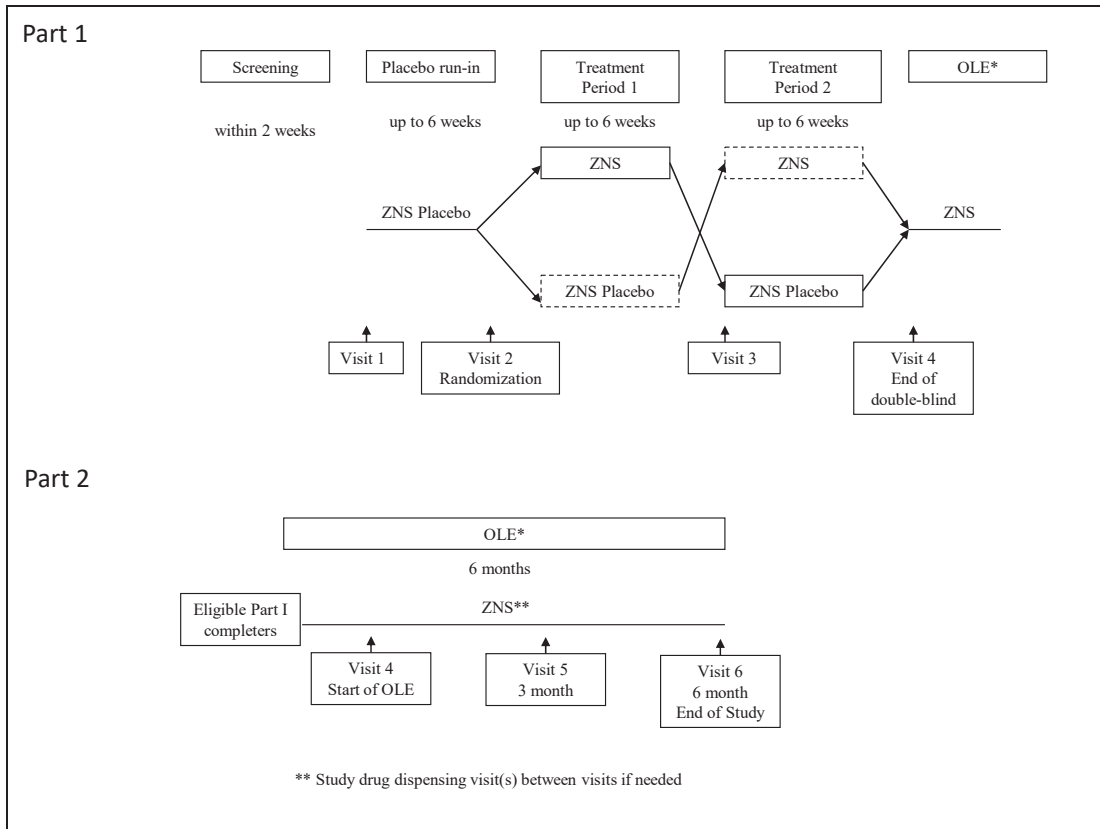
Table 1: Randomization Schedule for Study IPX229-B16-01

	Treatment Period 1	Treatment Period 2
Sequence 1	ZNS	ZNS Placebo
Sequence 2	ZNS Placebo	ZNS

Subjects weighing less than 50 kg will be allocated randomly to receive ZNS 2.5 mg or 1 mg in a 5:1 fashion during the ZNS treatment. Subjects weighing at least 50 kg will be allocated randomly to receive ZNS 5 mg or 2.5 mg in a 5:1 fashion during the ZNS treatment. The two dose levels are described in Table 2.

Table 2: Dose Levels during Double-Blind Treatment Period

	Dose Level (Number Randomized)	
Weight (kg)	Low (n=48)	High (n=240)
<50	1 mg	2.5 mg
≥50	2.5 mg	5 mg

During the OLE, all eligible subjects will receive ZNS. Subjects weighing <50 kg will receive 2.5 mg and those weighing at least 50 kg will receive 5 mg, with the option to reduce to 2.5 mg if tolerability is an issue.

1.2. Sample Size and Power

Part I of this study is a randomized, double-blind, placebo-controlled, 2-period, crossover outpatient study with a 6-week placebo run-in period.

Approximately 426 subjects will be enrolled to the placebo run-in period to randomize 288. With the 5:1 (high dose:low dose) randomization ratio for each of the two weight strata, it is estimated that 240 subjects will be randomized in the high-dose group and 48 subjects will be randomized to the lower dose level.

The sample size is based on detecting a difference in the percentage of subjects treated with a high dose (2.5 mg in the <50 kg weight stratum and 5 mg in the ≥50 kg weight stratum) who are pain free at 2 hours between ZNS and placebo. In this crossover trial, 240 high-dose-treated subjects will be adequate to detect a clinically relevant difference of 0.11 in the percentage of subjects who are pain free at 2 hours between ZNS and placebo as statistically significant (0.05, two tailed) with 90% power assuming a standard deviation of 0.5.

Approximately 48 subjects will be randomized in the low dose level (1 mg in the <50 kg weight stratum and 2.5 mg in the ≥50 kg weight stratum). The data from the low dose level will be summarized to explore dose-response relationship.

Based on other migraine crossover studies, dropout rates during the placebo run-in period ranged from 12% to 50%. Based on this, approximately 426 subjects will be enrolled into the placebo run-in period to randomize 288. This allows for approximately 32% dropout during placebo run-in period.

Approximately 100 subjects who complete the double-blind crossover phase will enter the 6-month OLE to enable at least 50 subjects to complete at least 6 months treating on average at least one migraine attack per month (treating up to 4 migraine attacks per month) with ZNS. Part II of the study is an OLE with subjects who successfully complete Part I of the study.

2. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Part1 of and 2 of the study will be analyzed separately. Separate sets of tables, listings and figures will be prepared for Part 1 and Part 2.

After all subjects have completed the double-blind phase of the study (Part I) or prematurely discontinued from the study, all data in Part I will be cleaned, the database will be frozen (soft lock), the study will be unblinded, and an analysis of Part I (double-blind) data will be performed. This will be the primary analysis of the study and a type I error rate (5%) will be allocated for this analysis.

All statistical tests will be 2-sided and performed at the 5% significance level, without multiplicity adjustment.

Likewise, after all subjects have completed Part II (OLE) of the study or prematurely discontinued from the study, all outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. This final analysis will mainly focus on the OLE.

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, descriptive statistics (the number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) will be presented.

2.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, listing, and figure.

2.1.1. Safety Analysis Set

The safety analysis set includes all enrolled subjects treated study drug (including placebo run-in). For each treatment period (run-in, period 1, period 2, open-label), subjects will be classified according to the treatment actually treated and by dose level (high dose and low dose according to the weight group):

- Placebo (run-in)
- ZNS 1 mg
- ZNS 2.5 mg for the low weight group
- ZNS 2.5 mg for the high weight group
- ZNS 2.5 mg combined
- ZNS 5 mg
- Placebo (double-blind)
- ZNS (open-label)

All safety analyses will be performed using the safety analysis set.

2.1.2.   Full Analysis Set

The full analysis set (FAS) includes all subjects who were randomized and administered at least one dose of post randomization study drug. The analysis of all efficacy variables will be performed using the FAS and will be analyzed separately for high dose and low dose groups.

2.1.3.   Double-Blind Completers Analysis Set

The completers analysis set includes all subjects treated with study drug during both periods (periods 1 and 2) and who complete the assessment of predose and 2-hour headache pain intensity ratings during each period.

2.1.4.   Open-Label Extension (OLE) Analysis Set

The OLE analysis set includes all subjects who completed the double-blind phase, were dispensed and used at least one dose of open-label drug. Subjects who complete the OLE will also be identified.

2.2.   Treatment Groups

Generally in analysis of Part 1 data will be summarized by weight group (<50 kg and >=50 kg) and whenever applicable by dose (<50 kg low dose (1 mg), <50 kg high dose (2.5 mg), >=50 kg low dose (2.5 mg), >=50 kg high dose (5 mg) and Placebo). All subjects taking 2.5 mg dose (<50 kg high dose and >=50 kg low dose together) will also be summarized whenever applicable. For summaries based on the Safety Analysis Set the group of subjects who were not randomized will also be presented.

In analysis of Part 2 data will be summarized by weight group and dose. Subjects in the <50 kg group will receive 2.5 mg dose, and subjects in >=50 kg group will initially receive 5 mg dose, but may down-titrate to 2.5 mg dose. All subjects receiving 2.5 mg dose and all subjects in the >=50 kg weight group will also be summarized. Since subjects may have different weight and receive different doses at different time points in the study, the assignment of subjects to treatment groups in Part 2 is not static. The following strategy will be used:

- For treatment-emergent adverse events: each TEAE will be assigned to the dose and its associated weight group based on AE onset date; see section 6.1.6 for details.

- For disposition: subject disposition will be summarized based on the last dose and its associated weight group in the study

- For baseline characteristics and findings: subjects will be summarized based on the first OLE dose that is dispensed to them at Visit 4.

- For findings collected at post-baseline visits: finding will be summarized based on the last dose and its associated weight group that the subject received prior to the visit. If the subject did not treat a migraine headache in Part 2 prior to the visit, the findings will be associated with the last dose dispensed to the subject at a prior visit. For Part 2 baseline the classification will be based on the dose dispensed at Visit 4.

- For concomitant medications: each concomitant medication will be associated with the study drug dose and its associated weight group that the subject took prior to the start of the concomitant medication and also with each study drug dose the subject took while taking this concomitant medication.

Details of specific treatment groups for each table are presented in the table shells document.

2.3.   Randomization

Subjects are randomly assigned to one of the two treatment sequences, stratified by weight and dose group, via the interactive web response system (IWRS). In each dose group, the assignment to the two treatment sequences (ZNS:placebo or placebo:ZNS) is in a 1:1 ratio. The randomizations scheme is as follows.

Figure 2:   **Planned Randomization Scheme**
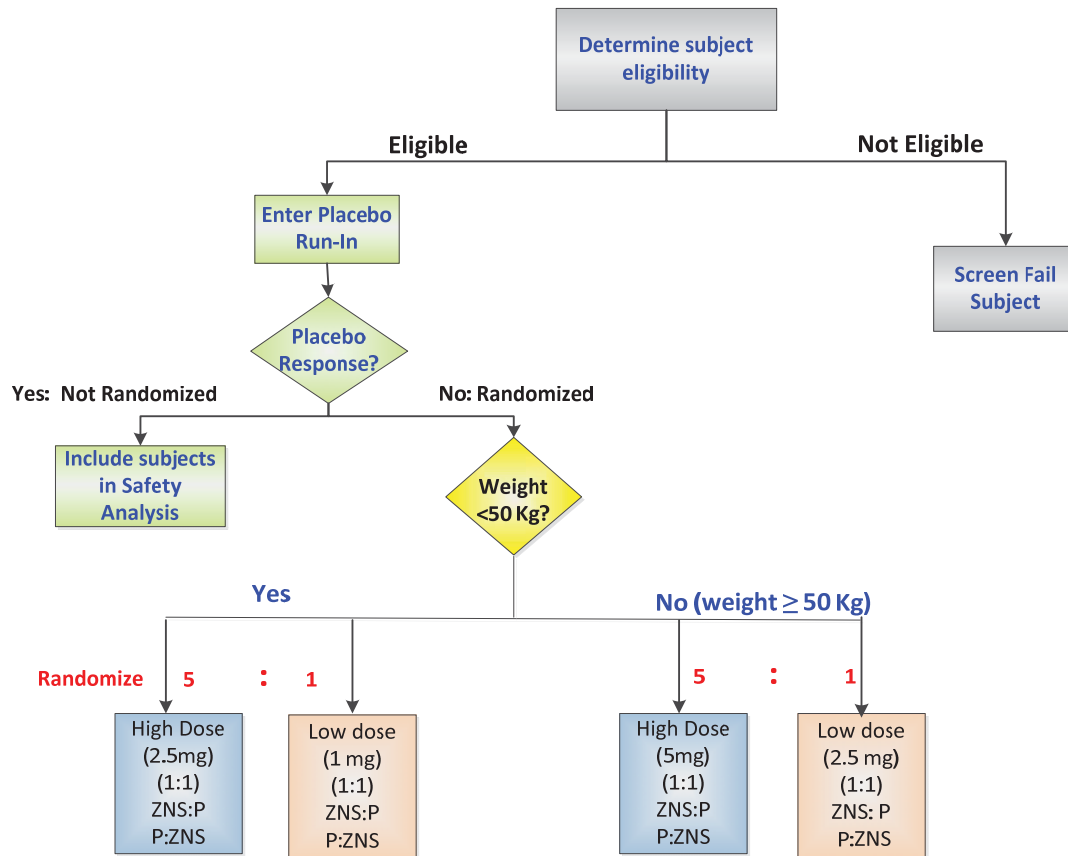
* Subjects who have not treated a migraine headache with blinded placebo during the 6-week run-in period will be considered screen failures.

2.4.   Examination of Subject Subgroups

Subgroup analyses will be performed to examine the consistency of responses for subjects in the following subgroups:

   a.   Sex: Males, females

   b.   Age: 6-8 years old, 9-11 years old (at screening)

   c.   Race: Caucasian, Asian, African American, Others

   d.   Type of migraine by history: with aura, without aura, mixed

   e.   BMI: dichotomize at median

2.5.   Missing Data and Outliers

2.5.1.   Missing Data

In general, missing data will not be imputed except for missing migraine headache diary data.

2.5.1.1.   Imputation Method for Migraine Headache Diary Data

1. If the predose diary is missing the pain intensity for a particular treatment period, then the subject is considered a non-responder for diary time points 0.5-hour, 1-hour, and 2-hour for that treatment period.

2. If all postdose pain intensity up to and including the 2-hour diary are missing for a particular treatment period, then the subject is considered a non-responder for those time points (0.5-hour, 1-hour, and 2-hour) for that treatment period.

3. If a subject receives rescue medication within 2 hours after dosing with study drug for a particular treatment period, the subject will be considered a non-responder for all the subsequent diary time points after rescue for that treatment period up to and including the 2-hour time point. Note: if subject diary includes records of rescue medication that started prior to the start of migraine, such medications will be ignored as incorrect diary entry. If rescue medications are recorded with missing start date/time, worse case will be assumed, i.e. that the rescue medication was taken at the same time as the migraine started.

4. If a subject naps or sleeps within 2 hours after dosing with study drug for a particular treatment period, the subject will be considered a non-responder for all diary time points up to and including the 2-hour diary time point for that treatment period.

5. No imputation will be done for the 24-hour time point (observed cases only).

6. Otherwise, missing diary data up to the 2-hour time point will be imputed by the last observation carried forward (LOCF).

2.5.2.   Outliers

All data will be included in the data analysis. No sensitivity analysis will be conducted with respect to any potential outliers.

2.6.   Center Pooling Algorithm

It is anticipated that some centers may randomize only a few patients. For the purpose of efficacy analyses, centers with less than 8 subjects in the FAS will be pooled with the closest center geographically until the number of subjects in the FAS after pooling is > 8. The pooled center will be used in models that adjust for center to minimize having a center where all subjects have the same treatment for the primary efficacy variable.

2.7.   Data Handling Conventions and Transformations

Selected by-subject listings will be presented for all subjects in the safety analysis set and sorted by subject ID number, treatment period, and study day (if applicable). Data collected on log forms, such as AEs and concomitant medications, will be presented in chronological order by preferred terms within subject.

2.8.   Definitions of Baseline and Study Day

2.8.1.   Definition of Baseline

There will be two definitions of baseline, for the Part 1 analysis and Part 2 analysis.

In the analysis of Part 1, baseline is defined as the last non-missing value before or at the run-in Visit 1 date.

In the analysis of Part 2, baseline is defined as the last non-missing value before or at the End of DB Period Visit 4 date.

2.8.2.   Definition of Study Day

Study day will be calculated differently in the analysis of Part 1 and Part 2.

For Part 1, study day for treated subjects will be calculated from the run-in visit date and derived as follows:

- For post Run-in Visit study days: Assessment Date – Run-in Visit Date + 1
- For days prior to the Run-in Visit: Assessment Date – Run-in Visit Date

Therefore, study day 1 in Part 1 is the day of the Run-in Visit.

For screen failures, study day will not be calculated.

For Part 2, study day for treated subjects will be calculated from the End of DB Period Visit 4 date and derived as follows:

- For post Visit 4 study days: Assessment Date –Visit 4 Date + 1
- For days prior to Visit 4: Assessment Date –Visit 4 Date

Therefore, study day 1 in Part 2 is the day of Visit 4.

2.9.   Analysis Windows

2.9.1.   Analysis Visit Windows for OLE

Subjects may not come to the visit in the OLE in accordance with the protocol schedule. For the purpose of analysis, visits will be assigned to the analysis visit windows as in Table 3.

Table 3:   Analysis Visit Windows for OLE

Visit	Nominal Time Point	Lower Limit (OLE Study Months)	Upper Limit (OLE Study Months)
Visit 4	--		0
Visit 5	Month 3	Month 3 - 1 month	Month 3 + 1 month
Visit 6	Month 6	Month 6 – 1 month	Month 6 + 1 month

OLE study month 0 is the start of the OLE visit day (Visit 4). Visits falling out of the above windows will not be assigned to a particular analysis visit. Data from these visits will be listed in listings.

- If multiple visits take place within a visit window, assignment of visits to visit window will be as follows:

  – The record closest to the nominal time point for that visit will be selected.

  – If there are 2 records that are equidistant from the nominal time point, the later one will be selected.

2.9.2.   Analysis Windows for Diary Data

Diary assessment may not occur exactly at the protocol-specified time points. For the purpose of analysis or Part 1, observations will be assigned to analysis windows.

The analysis windows for diary data in Part 1 are provided in Table 4.

Table 4:   Analysis Windows for Diary Data

Nominal Time Point	Lower Limit from Dosing Time (Minutes)	Upper Limit from Dosing Time (Minutes)
headache first became severe or moderate	-60	0
30-minute	1	45
1-hour (60 minutes)	46	90
2-hour (120 minutes)	91	150
24-hour (1440 minutes)	151	2160

Diary records falling out of the windows above will not be assigned and will only be listed in listings.

If multiple, valid, nonmissing diary data exist in an analysis window, records will be chosen based on the following rules:

- In general, the predose value will be the last nonmissing value prior to the dosing time of study drug.

- For postdose assessments:

- The record closest to the nominal time for that visit will be selected.

- If there are 2 records that are equidistant from the nominal time, the nominal record (the one recorded on the correct diary time point) will be selected.

  o However, if there are 2 records that are equidistant, one is the actual time and one is the imputed time (due to missing data), the assessment with actual time will be selected.

- If there are 2 records with identical times, the one recorded on the correct diary time point will be used.

In the analysis of Part 2 the diary observations will be analyzed according to the nominal timepoint recorded in the diary.

3. SUBJECT DISPOSITION

3.1. Subject Enrollment and Disposition

For Part 1 a summary of subject enrollment will present counts and percentages of subjects who were screened, enrolled, randomized and were treated with at least one dose of study drug post-randomization, completed double-blind phase and discontinued during the double-blind phase.

For Part 2 a summary of enrollment will present counts and percentages of subjects who entered OLE, were treated in OLE, completed OLE and discontinued during OLE..

A summary of subject disposition will be provided by treatment group and period for each study part. This summary will present the number of subjects who were dispensed, treated, discontinued treatment and the reasons for early discontinuation. The summary will be based on the safety analysis set for Part 1 and all subjects who entered Part 2 for Part 2.

3.2. Extent of Study Drug Exposure and Adherence

3.2.1. Duration of Exposure to Study Drug

Exposure to study drug in Part 1 will be summarized by frequencies and percentages based on the safety analysis set using the following categories:

- run-in
- double-blind
    - ZNS only
    - Placebo only
    - Both

In Part 2 subjects will be summarized by number of doses taken:

- < 4 doses
- 4 to < 8 doses
- 8 to < 12 doses
- 12 to < 24 doses
- 24 to < 36 doses
- >= 36 doses

Note that during the open-label period subjects are allowed to take a second dose of study drug within 72 hours of the start of this migraine headache. This dose counts towards the total count of study drug dose.

3.3. Protocol Deviations

Protocol deviations, such as subjects who did not meet eligibility criteria at study entry and those occurring after subjects entered the study, are documented during routine monitoring and are reviewed by the medical monitor. Details of protocol deviations for each study site will be provided by the Clinical Operations Group to the Statistics and Data Management Group prior to database finalization. All protocol deviations will be listed for both study parts.

4. BASELINE CHARACTERISTICS

4.1. Demographics

Subject demographic variables (age, sex, race, and ethnicity) will be summarized for Part 1 for the safety analysis and for Part 2 for the OLE analysis set using descriptive statistics. Age will be calculated at the appropriate study part baseline. Age will also be dichotomized into 6 to < 9 and 9 to 11 years. Proportion of female subjects who are postmenarcheal will also be provided.

A by-subject demographic listing will be provided by subject ID number in ascending order for each study part.

4.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), and body mass index (BMI; in kg/m^2) at baseline of each study part. Weight in pounds (lbs) will be converted to kg using the conversion factor 1 lb = 0.45359 kg. Height in inches will be converted to centimeters using the conversion factor 1 in = 2.54 cm. These baseline characteristics will be summarized for the safety analysis set for Part 1 and for the OLE analysis set for Part 2 using descriptive statistics. Weight will be dichotomized into < 50 kg and $\geq$ 50 kg.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order, along with the demographic information.

4.3. Migraine Headache Disease Characteristics and Measures

The age at onset of migraine attacks, average number of migraine headaches per month, average number of migraine headache days per month, and average number of non-migraine headache days/month will be summarized using descriptive statistics for Part 1 for the safety analysis set and for Part 2 for the OLE analysis set.

The following categorical variables will be summarized using the safety analysis set by frequencies and percentages: type of migraine (with aura, without aura, both), duration of typical untreated moderate/severe migraine (< 3 hours, $\geq$ 3 to 4 hours, > 4 to 6 hours, > 6 to 8 hours, > 8 hours), nausea (yes/no), light sensitivity (yes/no), sound sensitivity (yes/no), and vomiting (yes/no) with a typical migraine.

4.4. Medical History and Physical Findings

Summaries of clinically significant medical history and abnormal physical findings at screening will be provided for Part 1 for the safety analysis set and for Part 2 for the OLE analysis set.

5. EFFICACY ANALYSES

5.1. Primary Efficacy Endpoint in Part 1

A patient diary is used to collect the patients' self-assessment of headache pain intensity. Pain intensity is rated on a 4-point scale: severe (3), moderate (2), mild (1), and none (0).

The primary efficacy endpoint is the proportion of subjects with pain-free status at the 2-hour time point for the high dose group during the double-blind phase of the study. Pain-free status is defined as a reduction in the headache pain intensity rating from moderate (2) or severe (3) pain at predose to none (0) at 2-hour post dose, without using rescue medication and without napping/sleeping prior to the 2-hour assessment.

For the primary efficacy endpoint analysis, all high-dose subjects in the FAS are included.

The primary endpoint will be analyzed using a generalized estimating equation (GEE). The model includes treatment, period, sequence, weight group (at randomization), and predose (immediately prior to study drug administration) headache pain intensity. The logit link function is used with an unstructured within subject covariance matrix. Odds ratio, p-value for the treatment effect and the corresponding 95% confidence interval will be presented.

5.2. Sensitivity and Supportive Analyses of the Primary Efficacy Endpoint

5.2.1.1. Carryover Effect

The presence of a carryover effect will be estimated by the sequence effect. If the sequence effect is found to be significant at a 0.05 level, the following analyses will be conducted using data from Period 1 as corroborative evidence:

- Cochran-Mantel-Haenszel (CMH) test stratified by center.

  Although this comparison will be underpowered, consistent trend with the analysis from the primary analysis will be considered as corroborative evidence. In addition to the CMH test, the treatment difference, and 95% confidence interval, will be estimated for Period 1 via a logistic model with treatment, weight group, and predose severity score as factors.

- The percentage of patients achieving pain-free status by sequence and period will be summarized. This analysis will provide information on whether there is a differential dropout rate after each treatment and whether treatment by period interaction is evident.

In addition, McNemar's test for each sequence to compare ZNS with placebo will also be performed.

5.2.1.2. Completers Analysis

An analysis on the completers analysis set will also be performed as corroborative evidence.

5.2.1.3. Multiple Imputation Analysis

If the dropout rate is > 20%, a multiple imputation analysis will be performed. The analysis will be as follows:

a. Use logistic regression on Period 1 data to regress the response variable (0/1) on randomization weight group and treatment group.

$$logit(p) = \beta_0 + \beta_1 trtp + \beta_2 wtgrp$$

where $p_j = \Pr(R_j = 1|trtp, wtgrp)$ and R_j is the response of subject j.

b. For each observation with missing data in Period 2,

i. Calculate the predictive probability of response $R_j = 1$

$p_j = \frac{\exp(\mu_j)}{1+\exp(\mu_j)}$, where $\mu_j = \hat{\beta}_0 + \hat{\beta}_1 trtp + \hat{\beta}_2 wtgrp$.

ii. Draw a random uniform variable, u, between 0 and 1. If the value of $u < p_j$, impute $R_j = 1$; otherwise, impute $R_j = 0$.

iii. Draw a random uniform variable, v, between 0 and 1. If $v < 0.5$, then impute baseline severity = 3; otherwise, impute baseline severity = 2.

c. Analyze the data using the model as in primary analysis.

d. Repeat the steps b-c above 25 times.

e. Combine the results using Rubin's rule (Rubin 1987).

5.2.1.4. Tipping Point Analysis

In addition to the multiple imputation analysis, a tipping point analysis will be performed when the dropout rate is > 20%. The analysis will be carried out as follows:

a. Use logistic regression on Period 1 data to regress response (0/1) on randomization weight and treatment group.

$$logit(p) = \beta_0 + \beta_1 trtp + \beta_2 wtgrp$$

where $p_j = \Pr(R_j = 1|trtp, wtgrp)$.

b. For each observation with missing data in Period 2,

i. Calculate the predictive probability of $R_j = 1$

$p_j = \frac{\exp(\mu_j)}{1+\exp(\mu_j)}$, where $\mu_j = \hat{\beta}_0 + \hat{\beta}_1 trtp + \hat{\beta}_2 wtgrp$.

ii. Draw a random uniform variable, u, between 0 and 1.

- If the missing value is in ZNS arm and if the value of $u < p_j - \Delta$, impute $R_j = 1$; otherwise, impute $R_j = 0$, with Δ varies from 0 to p_j by an increment of .05. This effectively penalizes the ZNS arm by making it less likely to have a responder.

- If the missing value is in placebo arm and if the value $u < p_j$, impute $R_j =$ 1; otherwise, impute $R_j = 0$.

iii. Draw a random uniform variable, v, between 0 and 1. If $v < 0.5$, then impute baseline severity = 3; otherwise, impute baseline severity = 2.

c. Analyze the data using the model as in primary analysis.

d. Repeat the steps b-c above 25 times.

e. Combine the results using Rubin's rule (Rubin 1987).

5.2.1.5. Subgroup Analysis

Analysis of the primary endpoint as discussed in section 5.1 will also be performed for the subgroups defined in section 2.4.

5.2.1.6. Repeated Measures Analysis

The primary endpoint will also be analyzed using a generalized estimating equation (GEE) using results from all post-dose timepoints (0.5, 1, 2 and 24 hours). The model will include treatment, period, sequence, weight group (at randomization), predose (immediately prior to study drug administration) headache pain intensity, timepoint as time factor and treatment by timepoint interaction. The logit link function will be used with an unstructured within subject covariance matrix. Odds ratio, p-value for the treatment effect and the corresponding 95% confidence interval will be presented for each timepoint.If the model fails to converge due to the unstructured covariance matrix, a simpler covariance matrix will be employed in the order of 1) autoregressive (1) [SAS PROC GEE type = AR(1)], 2) exchangeable [type = EXCH]. The first covariance structure that does not have a convergence problem will be the one used for the analysis.

5.3.   Secondary Efficacy Endpoints in Part 1

Secondary efficacy endpoints include the following:

- Proportion of subjects with pain-free status 2-hour postdose for low dose group

- Proportion of subjects with pain-free status at 30 minutes, 1-hour, and 24-hour postdose (will also be performed for the subgroups defined in section 2.4 for the high dose group)

- Proportion of subjects without photophobia at 30 minutes, 1-hour, 2-hour, and 24-hour postdose

- Proportion of subjects without phonophobia at 30 minutes, 1-hour, 2-hour, and 24-hour postdose

- Proportion of subjects without nausea at 30 minutes, 1-hour, 2-hour, and 24-hour postdose

- Proportion of subjects with a headache response (defined as a reduction in headache severity from moderate (2) or severe (3) to mild (1) or none (0)) at 30 minutes, 1-hour, 2-hour, and 24-hour postdose (will also be performed for the subgroups defined in section 2.4 for the high dose group)

- Proportion of subjects who use rescue medication within 2, 3, 4 and up to 24 hours postdose. Note: if subject diary includes records of rescue medication that started prior to the start of migraine, such medications will be ignored as incorrect diary entry. If rescue medications are recorded with missing start date/time, worse case will be assumed, i.e. that the rescue medication was taken at the same time as the migraine started.

- Proportion of subjects with headache recurrence during 2 to 24 hours postdose for the subset of subjects who attained a 2-hour pain-free response

- Proportion of subjects with headache recurrence (with headache severity higher than that at 2 hours) during 2 to 24 hours postdose for the subset of subjects who attained a 2-hour headache response

- Proportion of subjects with sustained headache response 2 to 24 hours postdose defined as the proportion of subjects who attained a 2-hour headache response and who did not experience a headache recurrence (pain intensity moderate or severe) between 2 and 24 hours

- Proportion of subjects with sustained pain free response 2 to 24 hours postdose defined as the proportion of subjects who attained a 2-hour pain free response and who remained pain free between 2 and 24 hours

- Time to rescue medication. For those subjects who did not use rescue medication, the time to rescue medication is censored at 24 hours after dosing. Additionally, descriptive summary of time to rescue medication will be presented for those subjects who did take a rescue medication. Note: if subject diary includes records of rescue medication that started prior to the start of migraine, such medications will be ignored as incorrect diary entry. If rescue medications are recorded with missing start date/time, time to rescue medication will be imputed as zero.

For all proportion endpoints, a GEE model similar to the primary analysis will be conducted for the low dose group and high dose group separately.

For the time to use of rescue medication, a Cox proportional hazards model for crossover data (France et al 1991) with treatment, period, weight, and baseline headache pain intensity will be used.

Time to use of rescue medication will also be presented graphically using the Kaplan-Meier estimates.

5.4. Open-label Extension (OLE) Clinical Assessment Endpoints in Part 2

The following endpoints will be assessed during the OLE:

- Proportion of subjects with pain-free status at 2-hour postdose for each treated migraine headache that reached moderate to severe intensity. These descriptive summaries will be presented at each visit by weight group and dose during the OLE. If a subject did not experience a treated migraine headache between visits, he or she will be excluded in the summary for that particular visit.

- Change from randomization in the PedMIDAS total score will be summarized descriptively at the end of the study by weight group and dose based on the last dose received in the study.

- Proportion of subjects experiencing 2-hour pain free for ≥ 20%, 40%, 60%, and 80% of their treated moderate to severe migraine headaches. For each subject the proportion will be calculated as [Number of migraine headaches treated with the given dose level resolving to pain-free in 2 hour]/[Number of all migraine headaches treated with the given dose level]*100%. For subjects who received different dose levels or changed weight groups in the course of Part 2 of the study, the proportion will calculated separately for each weight group and dose level.

- Proportion of treated moderate to severe migraine headaches that reduce to pain free at 2 hours:

    o Descriptive summaries (mean, SD, median, min, max)

    o Categorical summaries of ≥ 20%, 40%, 60%, and 80% of treated headaches

5.5. Changes From Protocol-Specified Efficacy Analyses

If a subject naps or sleeps within 2 hours after dosing with study drug for a particular treatment period, the subject will be considered a non-responder for all diary time points up to and including the 2-hour diary time point for that treatment period.

The randomized population is replaced by the full analysis set. The completers population is further clarified as the double-blind completers analysis set.

The protocol inadvertently states that the McNemar's test was to be performed for Period 1 data. This SAP has corrected that the McNemar's test will be performed for each sequence.

Additional endpoints were added to the OLE endpoints to further elucidate the effect of ZNS:

- Proportion of subjects experiencing 2-hour pain free for ≥ 20%, 40%, 60%, and 80% of their treated moderate to severe migraine headaches.

- Proportion of treated moderate to severe migraine headaches that reduce to pain free at 2 hours:

    o Descriptive summaries (mean, SD, median, min, max)

    o Categorical summaries of ≥ 20%, 40%, 60%, and 80% of treated headaches

6. SAFETY ANALYSES

6.1. Adverse Events and Deaths

6.1.1. Adverse Event Dictionary

Reported AEs will be coded to standard terms using a standard dictionary (Medical Dictionary for Regulatory Activities [MedDRA]) latest version at the time of the database finalization.

6.1.2. Adverse Event Severity

Severity of adverse events will be determined by the investigator as mild, moderate, or severe. AEs with missing severity will be queried to resolution.

6.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related," "Possibly Related," or "Unlikely Related" on the AE case report form (CRF) to the question of "Relationship to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. AEs with missing relationship to study drug will be queried to resolution.

6.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Drug Safety database before data finalization.

6.1.5. Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as events with an onset date on the date of a study drug administration and up to 3 days after that date. If in the OLE period a second dose of study drug is administered within 72 hours of the start of the migraine headache, the window for TEAEs is extended by 3 more days. A worsening of previous illnesses or experience from baseline while on study drug is also considered a TEAE.

6.1.6. Assignment of Adverse Events to Study Parts and Treatment Groups

Each treatment-emergent adverse event by definition occurs within 3 days (with a possible extension if a second dose was taken in the OLE period) of a study drug dose. TEAEs will be assigned to study parts based on the dose they are thus associated with, i.e. TEAEs occurring after run-in or double-blind doses will be assigned to Part 1 and TEAEs occurring after OLE doses will be assigned to Part 2. TEAEs will also be assigned to the treatment group associated with the dose.

Non-treatment-emergent AEs will be assigned to study parts based on their onset date. Non-treatment-emergent AEs starting prior to the date of Visit 4 will be assigned to Part 1 and starting on or after the date of Visit 4 to Part 2. In case an AE has a partial start date that is ambiguous

and could have occured either before or after the date of Visit 4, such AE will be assigned to Part 1. Non-treatment-emergent AEs will not be assigned to treatment groups.

6.1.7.   Summaries of Adverse Events and Deaths

TEAEs will be summarized based on the safety analysis set for Part 1 and based on the OLE analysis set for Part 2. All TEAEs will be summarized by body system, and by preferred terms within a body system, by severity, and by relation to study medication. Each AE (based on preferred terminology) is counted only once for a given subject within a specified treatment or study period. If the same AE occurred on multiple occasions, the highest severity and least complimentary relationship will be assumed. If two or more AEs were reported as a unit, the individual terms will be reported as separate AEs.

6.2.   Laboratory Evaluations

Laboratory data are collected at Screening, Visit 4, and at End of Study for this study. Laboratory data collected will be summarized using the safety analysis set for Part 1 and using the OLE analysis set for Part 2. The analysis will be based on both values reported in SI units and in conventional units. Summaries in conventional units will be provided only for those parameters, for which conventional unit are different from the SI units.

A by-subject listings for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, chemistry, urinalysis, and urine drug test, and pregnancy test. Values falling outside the normal reference range will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

6.2.1.   Summaries of Numeric Laboratory Results

For Part 1, numeric laboratory results at Part 1 baseline and Visit4/End of Double-Blind Period as well as the change from baseline to end of double-blind period will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) by treatment group.

For Part 2 numeric laboratory results will be similarly summarized for Part 2 baseline and Month 6 visit.

The proportion of subjects with Low (below the lower limit of normal range), Normal (within the limit of normal range), High (above the upper limit of normal range) will be presented for both parts.

6.2.2.   Shifts Relative to the Baseline Value

Shift tables will be presented by showing changes in results from Part 1 baseline value (low, normal, and high) to the End of Double-Blind for Part 1 and from Part 2 baseline value to End of Study (Month 6) for hematology, blood chemistry, and urinalysis.

6.2.3. Other Laboratory Results

A summary of pregnancy results (positive/negative) will be provided for postmenarcheal female subjects in the safety analysis set for Part 1 and the OLE analysis set for Part 2.

A summary of urine drug test results (positive/negative) will be provided for subjects in the safety analysis set who were 9 years of age or older at Screening for Part 1 and End of Double-blind period for Part 2. The reason(s) for the positivity will also be listed.

6.3. Vital Signs

Descriptive statistics of systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oral body temperature will be provided at every visit for both study parts. The change from the corresponding part baseline will be summarized similarly for post-baseline visits.

Additionally, vital signs will be summarized by periods in the Double-Blind phase of Part 1. Summary at the period baseline, end of period and change from baseline to end of period will be summarized by the treatment in that period (each ZNS dose level and Placebo). Period baseline will be defined as the last assessment taken prior to the treatment in each of the two Double-Blind periods. End of period is defined as the next scheduled assessment after the treatment.

Proportions of subjects with clinically significant vital signs will also be summarized. Clinically significant vital signs are defined in Table 5.

Table 5: Definitions of Potentially Clinically Significant Vital Signs

Vital Sign	Criterion	Change from baseline
Systolic blood pressure	$\geq$ 131 mmHg; $\leq$ 90 mmHg	Increase and decrease $\geq$ 20 mmHg
Diastolic blood pressure	$\geq$ 83 mmHg; $\leq$ 46 mmHg	Increase $\geq$ 30 mmHg; Decrease $\geq$ 20 mmHg
Pulse rate	> 120 bpm; < 60 bpm	Increase $\geq$ 15 bpm; Decrease $\geq$ 15 bpm
Temperature	> 38.3°C	Change $\geq$ 1.11°C

6.4. Prior, Concomitant, and Rescue Medications

Prior and concomitant medications will be coded using the current version of World Health Organization (WHO) Drug Dictionary.

Prior medications are defined as medications taken and stopped prior to the first dosing date of study drug (placebo run-in). Concomitant medications for Part 1 are defined as medications taken while a subject took study drug in Part 1or prior to taking study drug and continued during Part 1, up to Visit 4 date. Concomitant medications for Part 2 are defined as medications taken at any time on or after the date of Visit 4. Use of concomitant medications will be summarized by ATC Level 2 class, preferred name, study period, and within the Double-Blind period by treatment, using the number and percentage of subjects in the safety analysis set for Part 1 and in the OLE analysis set for Part 2. A subject reporting the same medication more than once in the same period will be counted only once when calculating the number and percentage of subjects

who received that medication. The summary will be ordered alphabetically by medication class (WHODrug ATC 2 Term) and preferred term (WHODrug Product term).

No formal statistical testing is planned for prior and concomitant medications.

Rescue medications are defined as those used after the study drug treatment for further alleviation of pain associated with the migraine attack, and is recorded on the subject's diary. Note: if subject diary includes records of rescue medication that started prior to the start of migraine, such medications will be ignored as incorrect diary entry. The use of rescue medication in Part 1 will be summarized by ATC Level 2 class, preferred name and treatment using the number and percentages of subjects in the safety analysis set. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by medication class (WHODrug ATC 2 term) and preferred term (WHODrug Product term). The time to the use of rescue medication will also be summarized. Details are provided in Section 5.3.

6.5.   Electrocardiogram Results

Descriptive statistics of ventricular rate, PR interval, QRS interval, QT interval, corrected QT intervals (QTcF and QTcB), and RR interval will be provided at Part 1 baseline and End of Double-Blind period for Part 1 for the safety analysis set and also for Part 2 baseline and End of Study (Month 6) for the OLE analysis set. Change from the corresponding part baseline for these parameters will also be summarized.

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

Corrected QT (QTc) intervals will be derived using Bazett's correction (QTcB) as follows:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

ECG overall interpretation and rhythm assessment will also be summarized categorically by visit for both parts.

ECG results will also be summarized based on the following categories.

Table 6:   Definitions of Potentially Clinically Significant ECG Parameters

ECG parameter	Criterion	Change from baseline
Heart rate	> 120 bpm; < 60 bpm	Increase ≥ 15 bpm; Decrease ≥ 15 bpm
PR	≥ 200 msec	
QRS	≤ 50 msec ≥ 100 msec	
QT	≥ 500 msec ≤ 200 msec	Increase ≥ 60 msec
QTcB	≥ 450 msec	Increase 15% from baseline
QTcF	≥ 450 msec	Increase 15% from baseline

6.6.   Columbia-Suicide Severity Rating Scale

Suicidal ideation will be defined as "yes" answer to any one of the five suicidal ideation questions (Question 1-5) on the C-SSRS.

Suicidal behavior will be defined as "yes" answer to any one of the 5 suicidal behavior questions (Actual attempt, Interrupted attempt, Preparatory Acts or Behavior, Suicidal behavior, Complete suicide) on the C-SSRS.

The frequencies and percentages of suicidal behavior and suicidal ideation from the Columbia Suicidal Severity Rating Scale (C-SSRS) will be summarized by randomized treatment and by visit and overall (at least once post-baseline) using the safety analysis set for Part 1, and also using the OLE analysis set for Part 2.

The frequencies and percentages of suicidal behavior and suicidal ideation will also be summarized by periods in the Double-Blind phase of Part 1. Summary at the period baseline and end of period will be summarized by the treatment in that period (each ZNS dose level and Placebo). Period baseline will be defined as the last assessment taken prior to the treatment in each of the two Double-Blind periods. End of period is defined as the next scheduled assessment after the treatment.

6.7.   Physical Exam Results

The frequency distribution of abnormal physical findings at Part 1 baseline, and End of Double-Blind period will be tabulated for Part 1 using the safety analysis set, as well as at Part 2 baseline and at End of Study (Month 6) for Part 2 using the OLE analysis set.

6.8.   Duration of the OLE Period

Numbers and percentages of subjects who treated at least one migraine in each of the six OLE period months will be presented for the OLE Analysis Set by month, weight group and dose level. For the purposes of this summary, months will be defined as 30-days periods starting from the day of Visit 4.

Additionally, the counts and percentages meeting the following criteria will be presented:

- Subjects who completed all 6 months of the OLE period, i.e. those that completed the OLE period and had their Visit 6 at least 180 days after Visit 4

- Subjects who completed all 6 months of the OLE period and treated an average of at least 1 attack per month

- Subjects who completed all 6 months of the OLE period and treated an average of at least 1 attack per month and no more than 4 attacks in any month.

For this analysis subjects will be assigned to treatment groups based on the last dose they received in Part 2.

6.9.   Changes From Protocol-Specified Safety Analyses

There are no changes from the protocol-specified safety analyses.

7.   SOFTWARE

SAS® Software Version 9.4 or later. SAS Institute Inc., Cary, NC, USA.

8. CODE SAMPLES

8.1. Primary analysis GEE model

```sas
proc genmod data=…;
  class trtp aperiod trtseqp usubjid weightcat base;
  model avalc(event='Y') = trtp aperiod trtseqp weightcat base/ dist=binomial
link=logit type3;
  repeated subject=usubjid(trtseqp) / type=UN within=aperiod;
  lsmeans trtp / diff cl oddsratio ilink;
run;
```

The input dataset needs to include a record per each subject/treatment period. Explanation of variables:
1. TRTP: planned treatment at the time of assessment
2. APERIOD: treatment period number (1 or 2)
3. TRTSEQP: planned sequence of treatments (ZNS-Placebo or Placebo-ZNS)
4. USUBJID: unique subject identifier
5. WEIGHTCAT: weight category (<50 kg or >=50 kg)
6. BASE: pre-dose headache severity
7. AVALC: response variable (Y = response achieved, N = not achieved).

Odds ratios, their confidence intervals and p-values will be found in the Diffs ODS dataset.

8.2. Sensitivity Analysis Logistic Regression

```sas
proc logistic data=…;
  where aperiod = 1;
  class trtp weightcat base / param=ref;
  model avalc(event='Y') = trtp weightcat base;
run;
```

The input dataset needs to include a record per subject from treatment period 1 only.
The meaning of the variables is the same as in the primary analysis GEE model.

8.3. Sensitivity Analysis CMH Test

```sas
proc freq data=…;
  where aperiod = 1;
  tables sitegr1*trtp*avalc / cmh;
run;
```

The input dataset needs to include a record per subject from treatment period 1 only.
The meaning of the variables TRTP and AVALC is the same as in the primary analysis GEE model. SITEGR1 is pooled site.

8.4. Sensitivity Analysis McNemar Test

```
proc freq data=…;
  by trtseqp;
  tables avalc1*avalc2 / agree;
run;
```

The input dataset needs to include a record per subject with variables:
- AVALC1: responses in treatment period 1
- AVALC2: responses in treatment period 2
- TRTSEQP: planned sequence of treatments (ZNS-Placebo or Placebo-ZNS)

8.5. Sensitivity Analysis Repeated Measures Model

```
proc genmod data=…;
  class trtp aperiod trtseqp usubjid weightcat base atptn;
  model avalc(event='Y') = trtp aperiod atptn trtp*atptn weightcat base/
dist=binomial link=logit type3;
  repeated subject=usubjid(trtseqp) / type=UN within=aperiod*atptn;
  lsmeans trtp*atptn / diff cl oddsratio ilink;
run;
```

The input dataset needs to include a record per subject, period (1 or 2) and timepoint (0.5 hr, 1 hr, 2 hr or 24 hr post-dose).

The variables are the same as in the primary analysis GEE model, plus:

- ATPTN: timepoint number (0.5 hr, 1 hr, 2 hr or 24 hr post-dose).

In case of convergence problems type=AR(1) and type=EXCH will be tried.

8.6. Sensitivity Analysis with Multiple Imputations and Tipping-Point Analysis

Step 1. A dataset needs to be created with the following variables:

1. TRTP: planned treatment at the time of assessment
2. APERIOD: treatment period number (1 or 2)
3. TRTSEQP: planned sequence of treatments (ZNS-Placebo or Placebo-ZNS)
4. USUBJID: unique subject identifier
5. WEIGHTCAT: weight category (<50 kg or >=50 kg)
6. BASE: pre-dose headache severity
7. AVALC: response variable (Y = response achieved, N = not achieved).

The following rows need to be included:

1. Data for all subjects for the 2-hour timepoint in Period 1 with non-missing AVALC

2. Data for all subjects with missing AVALC for the 2-hour timepoint in Period 2. In these rows both BASE and AVALC will be missing.

Step 2. Use the dataset from Step 1 as input to perform logistic regression on Period 1 data and estimate the probability of response in Period 2:

```
proc logistic data=…;
  class trtp weightcat / param=ref;
  model avalc(event='Y') = trtp weightcat;
  output out=predicted p=pred_prob;
run;
```

In the output dataset PREDICTED the variable PRED_PROB will indicate the predicted probability of response.

Step 3. To ensure results are repeatable and amenable to validation by double-programming, a seed value 2291601 will be used in all random number generation functions below. The value was chosen arbitrarily based on the protocol number.

For each value of penalization factor Δ ranging from 0 to 1 in increments of 0.05 do the following.

For each subject with missing Period 2 result perform the following steps 25 times:

- Draw a random uniform variable, u, between 0 and 1 (i.e. u = ranuni(2291601))
- If the subject receives ZNS in Period 2 and if the value of u < PRED_PROB − Δ, impute response (AVALC = 'Y'); otherwise, impute no response (AVALC = 'N'). This effectively penalizes the ZNS treatment by making it less likely to have a responder.
- If the subject receives Placebo in Period 2 and if the value of u < PRED_PROB, impute response (AVALC = 'Y'); otherwise, impute no response (AVALC = 'N').
- Draw a random uniform variable, v, between 0 and 1 (i.e. v = ranuni(2291601)).
- If v < 0.5, then impute pre-dose headache severity = 'SEVERE'; otherwise, impute pre-dose headache severity = 'MODERATE'.
- Add thus imputed data for Period 2 to actual, observed data from Period 2. As the result all subjects in the FAS must now have a result, observed or imputed, for Period 2
- Analyze the dataset obtained above using the same method as in the primary analysis (section 8.1)

Step 4. After the previous steps we obtain Diffs ODS dataset for each value of the penalization factor and each of the 25 multiple imputations. Within each penalization factor value combine the results of the multiple imputations:

```
proc mianalyze data=Diffs;
  by penalization_factor;
  modeleffects Estimate;
  stderr StdErr;
run;
```

The input dataset is the Diffs ODS dataset from the previous step.

Step 5. Convert the estimates to odds ratios using the following data step code on the ParameterEstimates ODS dataset from the previous step:

```
OddsRatio = exp(Estimate);
z = probit(1-0.05/2);
UpperOR = OddsRatio*exp(z*StdErr);
LowerOR = OddsRatio*exp(-z*StdErr);
```

These results will be presented in the table.

8.7. Analysis of Time to Rescue Medication

Time to rescue medication quantiles:

```
proc lifetest data=…;
  time aval*cnsr(1);
  strata trtp;
run;
```

The input dataset needs to have a record per subject per treatment (ZNS or Placebo).
Explanation of variables:
1. TRTP: planned treatment at the time of assessment
2. AVAL: time to rescue medication (censored at 24 hours of subject does not take any rescue medication)
3. CNSR: censoring indicator (1 – time is censored, 0 – time is not censored)

Cox proportional hazards model:

```
proc phreg data=…;
  class trtp aperiod weightcat base;
  model aval*cnsr(1) = trtp aperiod weightcat base;
run;
```

Explanation of variables:
1. TRTP: planned treatment at the time of assessment
2. AVAL: time to rescue medication (censored at 24 hours of subject does not take any rescue medication)
3. CNSR: censoring indicator (1 – time is censored, 0 – time is not censored)
4. APERIOD: treatment period number (1 or 2)
5. WEIGHTCAT: weight category (<50 kg or >=50 kg)
6. BASE: pre-dose headache severity

9.   REFERENCES

France L, Lewis J, and Kay R. The analysis of failure time data in crossover studies. Statistics in Medicine 1991;10:1099-1113.

Rubin, DB. Multiple imputation in nonresponse in surveys. San Francisco, CA: Wiley; 1987.

Wang H, Chow SC. Sample size calculations for comparing proportions. In: Wiley Encyclopedia of Clinical Trials, San Francisco, CA: John Wiley & Sons, Inc.; 2007: 1-11.