STATISTICAL ANALYSIS PLAN

Satsuma Pharmaceuticals, Inc.
400 Oyster Point Boulevard, Suite 221
South San Francisco, CA 94080

A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Single Doses of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine

Clinical Study Protocol No. STS101-007

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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	adverse event
ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
DHE	dihydroergotamine
ECG	electrocardiogram
e-diary	electronic diary
ET	early termination
FIS	Functional Impairment Scale
HIT-6	Headache Impact Test
HR	heart rate
LOCF	last observation carried forward
max	maximum
MBS	most bothersome symptom
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MI	multiple imputation
mITT	Modified Intent-to-Treat
n	number of subjects
PP	Per Protocol
PT	preferred term
QTcF	QT corrected with the Fridericia's formula
TEAE	treatment emergent adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	single imputation
SOC	system organ class
WHO Drug	World Health Organization Drug Dictionary
24-MQoLQ	24-hour Migraine Quality of Life Questionnaire

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to ensure the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives. Results obtained from the analyses outlined in this document will be the basis of the final clinical study report (CSR) for this protocol.

1.1 Study Objectives

The Primary Objectives of the study are:

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from most bothersome symptom at 2 hours after dosing

The Key Secondary Objectives of the study are:

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at 1 hour after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to avoid the use of rescue medication within 24 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve normal function at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve 2 to 48 hour sustained pain free status
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve 2 to 48 hour sustained freedom from most bothersome symptom status
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to avoid the use of rescue medication within 48 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve 2 to 24 hour sustained pain free status
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve 2 to 24 hour sustained freedom from most bothersome symptom status
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from photophobia at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from phonophobia at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from nausea at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to avoid headache pain relapse within 48 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve 2 to 24 hour sustained normal function status

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain at the following timepoints after dosing: 3, 4, 6, 12, and 24 hours
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain at 2 hours after dosing by allodynia status at time of dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from most bothersome symptom at 2 after dosing by allodynia status at time of dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain at 2 hours after dosing in subjects with severe headache at baseline
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from most bothersome symptom at 2 hours after dosing in subjects with severe headache at baseline

Additional Secondary Objectives of the study are:

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from headache pain at 48 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from most bothersome symptom at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve normal function at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to avoid headache pain relapse within 24 hours after dosing
- To estimate the probability of a subject to achieve freedom from pain during the 48-hour post dose period
- To estimate the probability of a subject to achieve freedom from the most bothersome symptom during the 48-hour post dose period
- To estimate the probability of a subject to achieve pain relief during the 48-hour post dose period
- To estimate the probability of a subject to achieve pain relief during the 2-hour post dose period
- To estimate the probability of a subject requiring rescue medication during the 48-hour post dose period
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from photophobia at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from phonophobia at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from nausea at various timepoints after dosing
- To evaluate the frequency of each rescue medication
- To evaluate the study subject's global impression of the study treatment as well as other subject impression responses

- To evaluate the efficacy of a single dose of 5.2 mg STS101 on Functional Impairment Scale scores
- To evaluate the time to onset of efficacy in subjects achieving freedom from headache pain
- To assess the safety and tolerability of a single dose of 5.2 mg STS101 in the treatment of acute migraine attacks

The Exploratory Objectives of the study are:

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at various timepoints after dosing by allodynia status at time of dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours and various timepoints after dosing in subjects who wake up with acute migraine attacks
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours and various timepoints after dosing in subjects with acute menstrual related migraine attacks
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at 2 hours and various timepoints after dosing in subjects with acute migraine attacks by allodynia status at time of treatment
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at 2 hours and various timepoints after dosing in subjects who wake up with acute migraine attacks
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve pain relief at 2 hours and various timepoints after dosing in subjects with acute menstrual related migraine attacks
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve both, freedom from pain **and** most bothersome symptom at 2 hours after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve both, freedom from pain **and** most bothersome symptom at various timepoints after dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from headache pain and most bothersome symptom (MBS) at 2 hours after dosing by baseline (Visit 2) HIT-6 score
- To evaluate the effects of a single dose of 5.2 mg STS101 on the 24-hour Migraine Quality of Life Questionnaire (24-MQoLQ)
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by baseline aura symptoms
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by preventative migraine medication use at screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve relief from headache pain at 2 hours after dosing by preventative migraine medication use at screening

- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by anti-CGRP antibody use at screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve relief from headache pain at 2 hours after dosing by anti-CGRP antibody use at screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by inadequate response to triptan medication before screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve relief from headache pain at 2 hours after dosing by inadequate response to triptan medication use before screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by inadequate response to gepant medication before screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve relief from headache pain at 2 hours after dosing by inadequate response to gepant medication use before screening
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by baseline headache severity
- To evaluate the efficacy of a single dose of 5.2 mg STS101 on the 24-MQoLQ scores on subjects with freedom from headache pain, freedom from MBS, and relief from headache pain at 2 and 24 hours post dose
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing by duration of migraine onset to study medication dosing
- To evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from pain, freedom from most bothersome symptom, and relief from headache pain at 2 hours after dosing by various subgroups

1.2 Study Design

This is a multi-center, single-dose, randomized, double-blind, placebo-controlled, parallel group study in approximately 1400 subjects with acute migraines (ages 18 to 65 years).

After establishing initial eligibility, the study participants will be trained in the use of the electronic diary (e-diary) to record their headache attacks for 15 days during the screening period. Attack pain severity, presence of symptoms (nausea, photophobia, or phonophobia) and impact on function status will be documented.

The study subjects will also be trained in the administration of study medication and use of the STS101 device, and undergo Placebo Response Reduction training, designed to improve discrimination between placebo and drug effects in clinical trials.

After establishing eligibility, the study participants will be randomized (1:1) to receive one of two treatments:

- 5.2 mg STS101 (equivalent to 6.0 mg of dihydroergotamine (DHE) mesylate USP)
- Placebo (matching nasal powder)

The randomization will be stratified by the use of migraine prevention medication. After the randomization, the study participants will treat their next qualifying migraine attack of at least moderate pain severity with the allocated blinded study medication within 4 hours of the onset of the attack.

The study participants will document the following symptoms of their treated migraine before and over 48 hours after study drug administration in an e-diary: migraine headache pain severity, presence of symptoms (photophobia, phonophobia, nausea), presence of allodynia and functionality status. Headache pain severity and symptom data will be documented immediately before drug administration (time 0), at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 14, and 48 hours after study drug administration. The subjects must select a most bothersome symptom from among photophobia, phonophobia, and nausea immediately before study drug administration.

If subjects require rescue medication, they will be encouraged to wait until the 2-hour post study drug administration data collection timepoint. The use of triptans or other DHE mesylate products as rescue medications should be avoided for 24 hours after study drug administration. The study participants will return to the study site within approximately one week of the treated migraine attack.

Adverse events, objective nasal evaluation data, safety laboratory data, vital sign data and ECGs will be recorded before and after treatment to evaluate the tolerability and safety of STS101.

A sufficient number of subjects will be screened to randomize approximately 1400 subjects in the study. The dropout rate is estimated to be less than 35%. Subjects who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of dropouts or number of subjects with missing data exceeds initial expectations, subjects who withdraw or are withdrawn may be replaced.

1.3 Study Timepoints

A complete description of procedures at each visit can be found in the protocol. The Schedule of Assessments is presented in Table 1 below.

Table 1: Schedule of Assessments

	Visit 1	Visit 2	Visit 3
	Screening	**Randomization**	**Follow-up/Early Termination (ET)**
Timing of Visit	**Day -30 to -1**	**Day 1**	**Within one week (±3 days) of use of study medication (no later than Study Day 66)**
Informed Consent	X		
Demographic Data/Medical History	X		
Physical Examination	X	X	X
Vital Signs	X	X	X
Body Weight and Height	X	X[a]	X[a]
BMI Calculation	X		
Hematology, Clinical Chemistry, Urinalysis[f]	X		X
Serum & Urine Pregnancy Screen (All Females)	X[g]	X	X[g]
Urine Drug and Alcohol Screen	X	X	
12-Lead ECG (in triplicate)	X		X
Determine/Review Eligibility	X	X	
HIT-6 Instrument		X	
Sheehan Suicidality Tracking Scale (S-STS)	X	X	X
Headache Diary Use Training & Review	X	X	X[d]
Headache Diary Event Recording	X[b]	X[c]	
Objective Assessment of Nasal Symptom	X	X	X
Placebo Response Reduction Training	X	X	
Patient Subjective Impression Questions (6.2)			X
Randomization		X	
Concomitant Medications	X	X	X
STS101 Administration Training	X	X	
Investigational Product Supply		X	X[e]
Adverse Events Recording	X	X	X

[a] Weight only
[b] Recording of headaches for 15 days
[c] Recording of headache severity & symptoms of treated attack
[d] Collect e-diary device
[e] Collect STS101 device
[f] FSH in menopausal females (surgical or physiologically menopausal)
[g] Serum Only

2. GENERAL ANALYSIS DEFINITIONS

2.1 Statistical Hypotheses

The hypothesis for the study objectives is that a single dose of 5.2 mg of STS101 is significantly superior to placebo in achieving freedom from headache pain and freedom from most bothersome symptom at 2 hours post dose.

2.2 Determination of Sample Size

A total of approximately 1400 subjects (approximately 700 in each treatment group) will be randomized.

For the co-primary endpoint of pain freedom at 2 hours post dosing of investigational drug, a therapeutic gain of 10%, assuming a 25% responder rate for STS101 and 15% for the placebo is targeted. Based on these assumptions, 700 subjects per arm can provide 99% power to detect the target treatment difference. For the co-primary endpoint of MBS freedom at 2 hours post investigational drug, a therapeutic gain of 10%, assuming a 45% responder rate for STS101 and 35% for the placebo is targeted. Based on these assumptions, 700 subjects per treatment group can provide 95% power to detect the target treatment difference. The sample size calculation is based on a chi-square test with a significance level of 0.05 and a 2-sided test.

The primary efficacy objective will be addressed by simultaneously testing the 2 co-primary endpoints of pain freedom and MBS freedom at 2 hours after drug administration at a significance level of 0.05. This sample size will provide an overall power of at least 94%.
All study data will be summarized by treatment using descriptive statistics. Unless otherwise specified, for numeric data (e.g., age, weight), descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). All categorical/qualitative data (e.g., gender, race) will be presented using absolute and relative frequency counts and percentages.

2.3 Study Populations

The analysis populations to be used in the study are defined below.

Modified Intent-to-Treat Population

For the purposes of efficacy data analysis, the modified intent-to-treat (mITT) population will be the primary analysis population. This population will include all randomized subjects who reported a qualifying migraine attack, received the study drug, and reported efficacy data in at least one post-treatment e-Diary. Data will be analyzed according to the treatment group each subject was randomized to receive.

Per-Protocol Population

The per protocol (PP) population will consist of all mITT subjects who do not have protocol deviations that could significantly affect the interpretation of the results for the primary

endpoints. Subjects' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who are randomized. Data will be analyzed according to the treatment each subject was randomized to receive.

Safety Population

The safety population will include all subjects who are randomized and have received the study drug. Data will be analyzed according to the treatment each subject actually received.

2.4 Pooling of Investigator Sites

Data for all sites will be pooled for analysis. The analyses will not be performed by sites and will not include adjustment for sites.

2.5 General Handling of Missing Data

For incomplete dates related to adverse events, concomitant medications, or onset date of migraine in migraine history, the dates will be imputed as follows:

If the incomplete date is a start/onset date:
(1) if the month and year are present, then the first day of the month will be used for day.
(2) if only the year is present, then the first day of January will be used for month and day.

If the incomplete date is an end date:
(1) if the month and year are present, then the last day of the month will be used for day.
(2) if only the year is present, then the last day of December will be used for month and day. If the reported year is the same as the informed consent year, then the informed consent date will be used.

Dates that are completely missing will not be imputed.

Baseline values that are missing will not be imputed. Subjects who have missing subgroup values will not be included in that particular subgroup analyses.

Missing data related to an efficacy parameter will be discussed in Efficacy Section 4.

3. SUBJECT CHARACTERISTICS

3.1 Subject Disposition

The number of randomized subjects and number/percentage of subjects in each analysis population, number of subjects who completed/discontinued the study, and reasons for discontinuations will be presented by treatment group for all subjects. In addition, this summary will also be presented by treatment group for each analysis population.

Reasons for population exclusion will be displayed in a data listing.

3.2 Protocol Deviations

Protocol violations/deviations will be collected, including the deviation category, classification, and the start date if possible. The deviations will be presented in a data listing for all randomized subjects.

3.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics (including social history) will be summarized descriptively by treatment group for the ITT Population, mITT Population, the Per-Protocol Population, and the Safety Population. See Section 4.3 for derived variable definitions. Exploratory hypotheses testing may be performed to assess the comparability of demographics and baseline characteristics among the treatment groups. No multiplicity adjustment will be applied to these tests.

3.4 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and listed by System Organ Class (SOC), Preferred Term (PT), and verbatim term. Medical history will also be summarized by treatment group using frequencies and percentages according to the SOC and PT.

3.5 Migraine History

Migraine history, including the number of years experiencing migraine, average number of migraine attacks with moderate or severe pain and headache days for the 3 months prior to screening, average duration of in hours of untreated moderate/severe migraine attack, typical symptoms in migraines during screening (aura, nausea, photophobia, phonophobia, allodynia), triptan use, pain relief with triptan use, gepant use, and pain relief with gepant use will be summarized by treatment group and listed by treatment group and subject as well. The definitions of the derived variables can be found in Section 4.3.

3.6 Headache Impact Test

The Headache Impact Test will be scored and categorized according to the derivations in Section 4.3. Descriptive statistics for the total score and frequency distributions for the total score and each question will be summarized by treatment group.

3.7 Treated Migraine Attack Baseline Symptoms

Baseline summaries of key efficacy parameters and subgroups will be summarized using descriptive statistics or frequency distributions. These summaries include: the severity of the baseline migraine (mild, moderate, severe), allodynia status (yes, no), aura symptoms (yes, no), nausea (yes, no), photophobia (yes, no), phonophobia (yes, no), most bothersome symptom

(nausea, photophobia, phonophobia), Functional Impairment Scale (FIS) (none, mild, moderate, severe), subjects taking anti-CGRP Antibody at screening (yes, no), subjects taking preventative migraine medication at randomization (yes, no), subjects taking preventative migraine medication during screening (yes, no), subjects who woke with migraine (yes, no), subjects with menstrual related attacks (yes, no), onset of migraine attacks compared to study medication dosing (≤30 minutes, >30 minutes – 1 hour, >1 - 2 hours, >2 – 4, >4 hours). See Section 4.3 for derivations.

3.8 Prior and Concomitant Medications and Therapies

Concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group. Prior medications are defined as medications that start and end before study drug dosing. Concomitant medications are defined as: (1) medications that start before study drug dosing and end after dosing or are ongoing at the time of dosing or (2) medications that start after study drug dosing. The World Health Organization Drug Dictionary (WHO Drug) version B3 Mar 1, 2020, will be used to classify prior and concomitant medications by therapeutic class and generic name based on ATC code level 3. If preferred coding level is not available, the next lowest level will be used. Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject. Preventative migraine concomitant medications and acute migraine concomitant medications will also be summarized by treatment. Preventative migraine and acute migraine medications will be determined by the indication selected on the case report form (CRF). Concomitant procedures and non-drug therapies will be listed by treatment group and subject.

4. EFFICACY

All efficacy parameters, except the Patient Subjective Impression Questions, will be recorded in an e-diary by the subjects. The data recorded in the e-diary will not be altered. All data is summarized as recorded by the subject. Patient Subjective Impression Questions will be recorded on the case report form.

All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

Throughout this document, p-values refer to 2-sided nominal p-values. To simplify the presentation of results, the statistical tables will present only nominal 2-sided p-values and unadjusted confidence intervals (CI).

A study-wise Type I error of 0.05 will be used for the study. A multiplicity strategy (See Section 4.5.1) will be taken into account when interpreting the nominal 2-sided p-values for the primary and key secondary endpoints.

4.1 Primary Efficacy Estimands

The primary efficacy objectives are to evaluate the efficacy of a single dose of 5.2 mg STS101 to achieve freedom from headache pain and most bothersome symptom at 2 hours after dosing. The

co-primary endpoints used to achieve this objective will be defined using composite estimands as follows:

Freedom from headache pain at 2 hours

- Population: Subjects in the mITT population who had moderate or severe headache pain at baseline.
- Variable: Proportion of headache pain response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects achieving freedom from headache pain at 2 hours

Freedom from MBS at 2 hours

- Population: Subjects in the mITT population who had a MBS at baseline.
- Variable: Proportion of MBS response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects achieving freedom from MBS at 2 hours

4.2 Key Secondary Efficacy Estimands

The secondary efficacy objectives are listed in Section 1.1. The secondary endpoints used to achieve these objectives will be defined using composite estimands as follows:

Achieving relief from headache pain at 2 hours

- Population: Subjects in the mITT population who had moderate or severe headache pain at baseline.
- Variable: Proportion of headache pain response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects achieving relief from headache pain at 2 hours

Relief from headache pain at 1 hour will follow the same estimand with the focus on the 1-hour timepoint.

Rescue medication use within 24 hours

- Population: Subjects in the mITT population.
- Variable: Proportion of rescue medication use
- Intercurrent event: If a subject has a missing response for any reason at the 24-hour timepoint, rescue medication use will be assumed at 24 hours.

- Population-level summary: Proportion of subjects using rescue medication within 24 hours

Rescue medication use within 48 hours will be defined using the same estimand above for rescue medication use within 24 hours but with the timepoint of interest being 48 hours post dose.

Achieve normal function at 2 hours

- Population: Subjects in the mITT population who had mild, moderate, or severe impairment in ability to function at baseline.
- Variable: Proportion of ability to function (FIS) response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects achieving normal function at 2 hours

Sustained freedom from headache pain for 2 to 24 hours

- Population: Subjects in the mITT population who had moderate or severe headache pain at baseline.
- Variable: Proportion of headache pain response
- Intercurrent event: If a subject took rescue medication at any time within 24 hours of dosing, non-response will be assumed. If a subject has a missing response for any reason at the 24-hour timepoint, non-response will be assumed. If a subject is missing responses between 2 - 24 hours, exclusive, no imputation will be made.
- Population-level summary: Proportion of subjects with freedom from headache pain at 2 hours and sustained to 24 hours

Sustained freedom from headache pain for 2 to 48 hours will follow the same estimand with the timepoint of interest at 48 hours.

Sustained freedom from MBS for 2 to 24 hours

- Population: Subjects in the mITT population who had a MBS at baseline.
- Variable: Proportion of MBS response
- Intercurrent event: If a subject took rescue medication at any time within 24 hours of dosing, non-response will be assumed. If a subject has a missing response for any reason at the 24-hour timepoint, non-response will be assumed. If a subject is missing responses between 2 - 24 hours, exclusive, no imputation will be made.
- Population-level summary: Proportion of subjects with freedom from MBS at 2 hours and sustained to 24 hours

Sustained freedom from MBS for 2 to 48 hours will follow the same estimand with the timepoint of interest at 48 hours.

Free from photophobia at 2 hours

- Population: Subjects in the mITT population who had photophobia at baseline.
- Variable: Proportion of photophobia response

- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects free from photophobia at 2 hours

Free from phonophobia at 2 hours

- Population: Subjects in the mITT population who had phonophobia at baseline.
- Variable: Proportion of phonophobia response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects free from phonophobia at 2 hours

Free from nausea at 2 hours

- Population: Subjects in the mITT population who had nausea at baseline.
- Variable: Proportion of nausea response
- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject has a missing response for any reason at the 2-hour timepoint, non-response will be assumed at 2 hours.
- Population-level summary: Proportion of subjects free from nausea at 2 hours

Headache relapse within 48 hours

- Population: Subjects in the mITT population and free from headache pain at 2 hours.
- Variable: Proportion of headache pain response
- Intercurrent event: If a subject has a missing response at the 48-hour timepoint, relapse will be assumed. If a subject is missing responses between 2 - 48 hours, exclusive, no imputation will be made. No imputation will be made if the subject takes a rescue medication.
- Population-level summary: Proportion of subjects with headache pain of any severity within 48 hours

Sustained Normal Function for 2 to 24 hours

- Population: Subjects in the mITT population who had mild, moderate, or severe impairment in ability to function at baseline.
- Variable: Proportion of ability to function (FIS) response
- Intercurrent event: If a subject took rescue medication at any time within 24 hours of dosing, non-response will be assumed. If a subject has a missing response for any reason at the 24-hour timepoint, non-response will be assumed. If a subject is missing responses between 2 - 24 hours, exclusive, no imputation will be made.
- Population-level summary: Proportion of subjects achieving normal function at 2 hours and sustained to 24 hours

Other key secondary endpoints that are variations of the estimands already presented are:

- Freedom from headache pain at 3-24 hours post dose
  - Follows the freedom from headache pain at 2 hours post dose estimand for each timepoint
- Freedom from headache pain at 2 hours post dose in subjects with allodynia at baseline
  - Follows the freedom from headache pain at 2 hours post dose estimand with the exception of the population, which is the subjects in mITT population who had allodynia at baseline
- Freedom from MBS at 2 hours post dose in subjects with allodynia at baseline
  - Follows the freedom from headache pain at 2 hours post dose estimand with the exception of the population, which is the subjects in mITT population who had allodynia at baseline
- Freedom from headache pain at 2 hours post dose in subjects with severe headache at baseline
  - Follows the freedom from headache pain at 2 hours post dose estimand with the exception of the population, which is the subjects in mITT population who had severe pain severity at baseline
- Freedom from MBs at 2 hours post dose in subjects with severe headache at baseline
  - Follows the freedom from MBS at 2 hours post dose estimand with the exception of the population, which is the subjects in mITT population who had a baseline MBS and had severe pain severity at baseline.

4.3 Definitions and Derived Variables

- The baseline measurement for a variable is defined as the last non-missing value from the baseline visit measured prior to the first dose of the study drug. If a subject has repeated measurements from the baseline visit, then the last repeated non-missing value will be used. The efficacy parameters (all collected in the e-diary) are measured just prior to study dosing (considered time 0) in the migraine report of the e-diary. These values are considered the baseline values for efficacy.

- Body mass index (BMI) will be derived from the recorded height and weight at the screening visit. It is calculated as weight in kilograms divided by height in meters squared.

- Age will be derived as the integer value of informed consent date minus birth date plus one, then divided by 365.25.

- The number of subjects with < 15 headache days per month for 3 months prior to screening will be derived by averaging the number of headache days over months 1-3 from the Migraine History CRF and dichotomizing the averages into Yes if the average is <15 and No if the average is >=15.

- The number of migraine attacks with moderate or severe pain for 3 months prior to screening will be derived by averaging over months 1-3, the number of migraine attacks

with moderate/severe pain prior to screening from the Migraine History CRF and dichotomizing the averages into Yes if the average is between 2-8 inclusive and No if the average does not fall in this range.

- Allodynia status is defined as present if a subject has at least 2 'yes' responses to the 6-question allodynia questionnaire [Ashkenazi 2007; Tepper, 2011]).

- The 4-point headache pain severity scale is as follows: 0=None, 1=Mild, 2=Moderate, and 3=Severe. Free from headache pain is defined as moderate or severe [2 or 3] headache pain at baseline [time 0] becoming none [0].

- Freedom from headache pain is defined as headache pain identified at baseline [time 0] being absent, or severity is none [0].

- Freedom from most bothersome symptom is defined as the MBS identified at baseline [time 0] being absent.

- Sustained pain freedom or remaining headache free up to a time point (e.g,. 24, or 48 hours) after investigational drug administration is defined as a score of 0 from the 2 hours post dose timepoint to the timepoint, e.g. 24 hours, with no use of rescue medication. The 2 and 24 or 48 hour post dose timepoints score must be 0 and the scores in between 2 and 24 or 48 hours must be 0 or missing.

- Sustained freedom from MBS or remaining free up to a time point (e.g,. 24, or 48 hours) after investigational drug administration is defined as the absence of the MBS at baseline (time 0) from the 2 hours post dose timepoint to the timepoint, e.g. 24 hours, with no use of rescue medication. The 2 and 24 or 48 hour post dose timepoints response must be absent and the responses between 2 and 24 or 48 hours must be absent or missing.

- Headache relapse is defined as the return of headache of any severity within the specified hours of the endpoint after administration of the investigational drug, when the patient was pain-free at 2 hours after investigational drug administration.

- Proportion of subjects who achieve normal function is defined as a rating of '0' on the FIS. For the sustaining normal function for 2-24 hour and 2-48 hour endpoints, the subjects must have a rating of '0' at the 2 and 24/48 hour time points and no non-zero responses in between the time interval (i.e., the responses in between the time interval can be missing).

- Relief from headache pain is defined as a reduction in headache pain from moderate or severe [2 or 3] to mild or none [1 or 0].

- Free from photophobia is defined as photophobia being absent post dose if present at baseline (time 0).

- Free from phonophobia is defined as phonophobia being absent post dose if present at baseline (time 0).

- Free from nausea is defined as nausea being absent post dose if present at baseline (time 0).

- Rescue medication is defined as any medication taken to treat migraine headaches after dosing. This will be derived from the electronic diary. Rescue medication use within 24 hours is defined as follows: a) the 24-hour response is missing, b) the 24-hour response is Yes, or c) any non-missing time points prior to 24 hours are Yes. No rescue medication use within 24 hours is defined as the 24-hour response is No and all non-missing time points prior to 24 hours are No. Rescue medication use within 48 hours is defined similarly.

- The definition of migraine headache during their menstruation period is taken from the Drug Accountability case report form in which the menstruation information was also collected. If the subject treated a migraine within 1 (+/- 2) days of menstruation, then the subject will be considered as having a menstruation related acute migraine attack.

- Prior or current triptan use and inadequate response to triptan medication will be derived from the Migraine History CRF where the response to pain relief with triptan use is reported as <=75% of the time.

- Prior or current gepant use and inadequate response to gepant medications will be derived from the Migraine History CRF where the response to pain relief with gepant use is reported as <=75% of the time.

- 24-hour Migraine Quality of Life Questionnaire domains are defined as: Work Functioning (questions 7, 8, 9), Social Functioning (questions 10, 11, 12), Energy/Vitality (questions 13, 14, 15), Migraine Symptoms (questions 1, 2, 3), and Feelings/Concerns (questions 4, 5, 6). The domain scores are derived by summing the values of the responses to the specified questions. The total score will be the sum of all domains. The values of the responses are the recorded numeric values in the electronic handheld device (e-diary).

- Number of years experiencing a migraine will be defined as the date of informed consent minus the date of migraine onset plus 1.

- Preventative migraine medication taken at screening is recorded in the Concomitant Medication CRF (“Migraine Prevention” checked as indication for concomitant medication use) and on the Randomization CRF (use of migraine prevention medication as stratification factor). The response on the Randomization CRF will be summarized along with the actual responses as provided in the Concomitant Medication CRF. All analyses of efficacy and tolerability and summaries by preventative migraine medication use will use the actual responses from the Concomitant Medication CRF.

- Subjects taking anti-CGRP antibody at screening will be derived from the concomitant medications using a list of searchable preferred terms. If the end date of the medication is greater than the informed consent date or reported as ongoing/missing and the start date is less than or equal to the first dose date, then the medication will be included.

- Onset of migraine attacks is broken into 4 categories: ≤30 minutes, >30 minutes – 1 hour, >1 - 2 hours, >2 – 4, and >4 hours as compared to time of dosing with study medication.

- Time to event derivations will compare the first time of the event (i.e., freedom from headache pain) to the time of dosing in hours. Data will be censored at 48 hours for freedom from headache pain, freedom from MBS, and pain relief if the subject did not have an event or if the subject took rescue medication. Rescue medication use will be censored at the last available non-missing time in hours.

- Subjects who woke up with migraine headaches will be defined as migraines that have a recorded onset time between midnight and 7:00am.

- Headache Impact Test (HIT-6) total score is calculated as the sum of the points for each response given by a subject. Points for each response are as follows: Never=6, Rarely=8, Sometimes=10, Very Often=11, and Always=13.

- The baseline HIT-6 overall score will be categorized into the following categories: Severe Impact, defined as a total score >=60, Substantial Impact, defined as a total score >=56 to <60, Some Impact, defined as a total score >=50 to <56, and Little or No Impact, defined as a total score <50.

- A responder on the Patient Global Impression Rating is defined as a good or very good response.

- Proportion of subjects who sustained pain relief for 2-24 hour and 2-48 hour is defined as the subjects must have pain relief (as defined previously) at 2 hours and a rating of ‘0’ or ‘1’ at the 24/48 hour time points and no responses of ‘2’ or ‘3’ in between the time interval (i.e., the responses in between the time interval can be missing) and no rescue medication use during the time period of interest.

- Non-response is defined as the unwanted response for a variable. For all endpoints except rescue medication use, it will be an imputed value of No or 0. For rescue medication use, the value will be Yes or 1.

4.4 Efficacy Variables

Primary Efficacy Endpoints:

- Proportion of subjects free from headache pain at 2 hours after dosing (defined as moderate or severe headache pain [2 or 3 on a 4-point scale] at baseline [time 0] becoming none [0] on a 4-point scale)

  Proportion of subjects free from most bothersome symptom among photophobia, phonophobia and nausea at 2 hours after dosing (defined as the MBS identified at baseline [time 0] being absent)

Key Secondary Efficacy Endpoints:

The key secondary efficacy parameters are listed below, but not in the statistical testing hierarchy that will be tested with the fixed-sequence method in order to protect the study-wise Type error under 0.05 (see Section 4.5.1 for the statistical testing hierarchy).

- Proportion of subjects who use rescue medication within 24 hours after dosing
- Proportion of subjects free from photophobia at 2 hours after dosing
- Proportion of subjects with relief from headache pain at 1 hour after dosing
- Proportion of subjects free from headache pain at 3, 4, 6, 12, and 24 hour time points after dosing
- Proportion of subjects who use rescue medication within 48 hours after dosing
- Proportion of subjects who achieve normal function at 2 hours after dosing
- Proportion of subjects free from headache pain at 2 hours after dosing and remaining headache free at 24 hours after dosing with no use of rescue medication and no relapse of any headache pain (defined as 2-24 hour sustained pain free)
- Proportion of subjects free from headache pain at 2 hours after dosing and remaining headache free at 48 hours after dosing with no use of rescue medication and no relapse of any headache pain (defined as 2-48 hour sustained pain free)
- Proportion of subjects free from most bothersome symptom at 2 hours after dosing and remaining MBS free at 24 hours after dosing with no use of rescue medication and no relapse of any MBS (defined as 2-24 hour sustained MBS free)
- Proportion of subjects free from most bothersome symptom at 2 hours after dosing and remaining MBS free at 48 hours after dosing with no use of rescue medication and no relapse of any MBS (defined as 2-48 hour sustained MBS free)
- Proportion of subjects with headache relapse within 48 hours after dosing
- Proportion of subjects free from phonophobia at 2 hours after dosing
- Proportion of subjects free from nausea at 2 hours after dosing

- Proportion of subjects with Sustained Normal Function based on FIS from 2 to 24 hours
- Proportion of subjects with baseline allodynia and free from headache pain at 2 hours post dose
- Proportion of subjects with baseline allodynia and free from MBS at 2 hours post dose
- Proportion of subjects with severe headache severity at baseline and free from headache pain at 2 hours post dose
- Proportion of subjects with severe headache severity at baseline and free from MBS at 2 hours post dose

Additional Secondary Efficacy Endpoints:

The secondary efficacy parameters will be analyzed but no formal hypotheses testing will be performed.

- Proportion of subjects with freedom from headache pain at 15, 30, 45 minutes, 1, 1.5, and 48 hours after dosing
- Proportion of subjects with freedom from MBS at 15, 30, 45 minutes, 1, 1.5, 3, 4, 6, 12, 24, and 48 hours after dosing
- Proportion of subjects who achieve relief from headache pain at 15, 30, 45 minutes, 1.5, 3, 4, 6, 12, 24, and 48 hours after dosing
- Proportion of subjects who achieve normal function at 1, 4, 24, and 48 hours after dosing
- Proportion of subjects with freedom from photophobia at 15, 30, 45 minutes, 1, 1.5, 3, 4, 6, 12, 24, and 48 hours after dosing
- Proportion of subjects with freedom from phonophobia at 15, 30, 45 minutes, 1, 1.5, 3, 4, 6, 12, 24, and 48 hours after dosing
- Proportion of subjects with freedom from nausea at 15, 30, 45 minutes, 1, 1.5, 3, 4, 6, 12, 24, and 48 hours after dosing
- Proportion of subjects with headache pain relapse within 24 hours after dosing
- Shift from baseline in FIS response
- Time to achieving headache relief
- Time to freedom from headache pain
- Time to freedom from MBS
- Time to rescue medication use
- Frequency of Rescue Medications
- Frequency of Patient Global Impression (very good, good, no opinion, poor, very poor)

- Patient global response (very good/good)
- Frequency of Ease of Use Impression (very easy, easy, no opinion, not easy, not easy at all)
- Comparison of Study Medication with Previously Used Migraine Medication:
    - Frequency of Return to Normal Faster (strongly agree, agree, neutral, disagree, strongly disagree)
    - Frequency of Consistently Treats Migraine (strongly agree, agree, neutral, disagree, strongly disagree)
    - Frequency of Works Faster (strongly agree, agree, neutral, disagree, strongly disagree)
    - Frequency of Keeps Migraine from Coming Back (strongly agree, agree, neutral, disagree, strongly disagree)
- Time to onset of freedom from headache pain as established by testing for statistical differences in descending order from 2 hours to 15 minutes

Exploratory Efficacy Endpoints:

The following exploratory endpoints will be analyzed if there are adequate number of subjects in the sub-population of interest.

- Proportion of subjects free from headache pain at various timepoints after dosing by allodynia status at baseline
- Proportion of subjects free from MBS at various timepoints after dosing by allodynia status at baseline
- Proportion of subjects with relief from headache pain at 2 hours after dosing by allodynia status at baseline
- Proportion of subjects with relief from headache pain at various timepoints after dosing by allodynia status at baseline
- Proportion of subjects free from both, headache pain and most bothersome symptom at 2 hours after dosing
- Proportion of subjects free from both, headache pain and most bothersome symptom at various time points after dosing
- Proportion of subjects free from headache pain at 2 hours after dosing in subjects who wake up with migraine headache
- Proportion of subjects free from most bothersome symptom at 2 hours after dosing in subjects who wake up with migraine headache
- Proportion of subjects free from headache pain at various timepoints after dosing in subjects who wake up with migraine headache

- Proportion of subjects free from most bothersome symptom at various timepoints after dosing in subjects who wake up with migraine headache
- Proportion of subjects with relief from headache pain at 2 hours after dosing in subjects who wake up with migraine headache
- Proportion of subjects with relief from headache pain at various timepoints after dosing in subjects who wake up with migraine headache
- Proportion of subjects free from headache pain at 2 hours after dosing by baseline HIT-6 score (severe, substantial, some, little/no impact)
- Proportion of subjects free from MBS at 2 hours after dosing by baseline HIT-6 score (severe, substantial, some, little/no impact)
- Proportion of subjects free from headache pain at 2 hours after dosing in subjects with menstrual related migraine attack
- Proportion of subjects free from most bothersome symptom at 2 hours after dosing in subjects with menstrual related migraine attack
- Proportion of subjects free from headache pain at various timepoints after dosing in subjects with menstrual related migraine attack
- Proportion of subjects free from most bothersome symptom at various timepoints after dosing in subjects with menstrual related migraine attack
- Proportion of subjects with relief from headache pain at 2 hours after dosing in subjects with menstrual related migraine attack
- Proportion of subjects with relief from headache pain at various timepoints after dosing in subjects with menstrual related migraine attack
- 24-hour Migraine Quality of Life Questionnaire total and domain scores (migraine symptoms, work functioning, social functioning, energy/vitality, feelings/concerns)
- Proportion of subjects free from headache pain at 2 hours post dose in subjects with/without aura symptoms
- Proportion of subjects free from MBS at 2 hours post dose in subjects with/without aura symptoms
- Proportion of subjects free from headache pain at 2 hours post dose for subjects who were taking a preventive migraine medication at Screening
- Proportion of subjects free from MBS at 2 hours post dose for subjects who were taking a preventive migraine medication at Screening
- Proportion of subjects with relief from headache pain at 2 hours post dose for subjects who were taking a preventive migraine medication at Screening
- Proportion of subjects free from headache pain at 2 hours post dose for subjects who were taking an anti-CGRP antibody at Screening

- Proportion of subjects free from MBS at 2 hours post dose for subjects who were taking an anti-CGRP antibody at Screening
- Proportion of subjects with relief from headache pain at 2 hours post dose for subjects who were taking an anti-CGRP antibody at Screening
- Proportion of subjects free from headache pain at 2 hours post dose for subjects who had inadequate response to triptan medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Proportion of subjects free from MBS at 2 hours post dose for subjects who had inadequate response to triptan medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Proportion of subjects with relief from headache pain at 2 hours post dose for subjects who had inadequate response to triptan medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Proportion of subjects free from headache pain at 2 hours post dose for subjects who had inadequate response to gepant medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Proportion of subjects free from MBS at 2 hours post dose for subjects who had inadequate response to gepant medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Proportion of subjects with relief from headache pain at 2 hours post dose for subjects who had inadequate response to gepant medication(s) before Screening; inadequate response is defined as having pain relief for less than or equal to 75% of the time.
- Association between total score and individual domain scores of 24-hour Migraine Quality of Life Questionnaire at 24 hours post dose and
    - Freedom from pain at 2 hours post dose
    - Freedom from pain at 24 hours post dose
    - Freedom from MBS at 2 hours post dose
    - Freedom from MBS at 24 hours post dose
    - Relief from pain at 2 hours post dose
    - Relief from pain at 24 hours post dose
- Proportion of subjects free from headache pain at 2 hours post dose in subjects by baseline headache severity
- Proportion of subjects free from MBS at 2 hours post dose in subjects by baseline headache severity
- Proportion of subjects free from headache pain at 2 hours post dose in subjects by migraine onset category

- Proportion of subjects free from MBS at 2 hours post dose in subjects by migraine onset category
- Proportion of subjects free from headache pain by subgroups defined in Section 4.5.7
- Proportion of subjects free from MBS by subgroups defined in Section 4.5.7
- Proportion of subjects who achieve relief from headache pain by subgroups defined in Section 4.5.7

4.5 Efficacy Analysis Methods

4.5.1 Multiplicity Strategy

A fixed-sequence method will be employed to control for the study-wise Type I error rate at alpha=0.05. The fixed-sequence method will test each endpoint at an alpha of 0.05 in the hierarchal order described below. The method is as follows:

If the first hypothesis test is significant at the 0.05 significance level (i.e. p-value < 0.05), the next hypothesis will be tested at the same 0.05 level. This process will continue according to the hierarchy defined below. The testing will stop when the p-value of the test is greater than or equal to 0.05. At that point, further hypotheses testing will be considered exploratory and the Type I error is not controlled under the study-wise 0.05 significance level.

The hierarchy for testing the primary and secondary efficacy endpoints on the primary analysis population (mITT population) is below.

1. **(P1) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 2 hours post dose
2. **(P2) 5.2 mg dose vs. Placebo** in the proportion of subjects free from MBS at 2 hours post dose
3. **(S1) 5.2 mg dose vs. Placebo** in the proportion of subjects with relief from headache pain at 2 hours post dose
4. **(S2) 5.2 mg dose vs. Placebo** in the proportion of subjects who achieve normal function at 2 hours after dosing
5. **(S3) 5.2 mg dose vs. Placebo** in the proportion of subjects who use rescue medication within 24 hours post dose
6. **(S4) 5.2 mg dose vs. Placebo** in the proportion of subjects free from photophobia at 2 hours post dose
7. **(S5) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 3 hours post dose
8. **(S6) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 4 hours post dose
9. **(S7) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 6 hours post dose
10. **(S8) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 12 hours post dose

11. **(S9) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 24 hours post dose
12. **(S10) 5.2 mg dose vs. Placebo** in the proportion of subjects free from phonophobia at 2 hours post dose
13. **(S11) 5.2 mg dose vs. Placebo** in the proportion of subjects free from MBS at 2 hours after dosing and remaining MBS free at 24 hours after dosing with no use of rescue medication and no relapse of any MBS
14. **(S12) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 2 hours post dose and remaining headache free for 24 hours post dose with no use of rescue medication and no relapse of any headache pain
15. **(S13) 5.2 mg dose vs. Placebo** in the proportion of subjects achieving pain relief at 1 hour post dose
16. **(S14) 5.2 mg dose vs. Placebo** in the proportion of subjects free from MBS at 2 hours after dosing and remaining MBS free at 48 hours after dosing with no use of rescue medication and no relapse of any MBS
17. **(S15) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 2 hours post dose and remaining headache free for 48 hours post dose with no use of rescue medication and no relapse of any headache pain
18. **(S16) 5.2 mg dose vs. Placebo** in the proportion of subjects free from nausea at 2 hours post dose
19. **(S17) 5.2 mg dose vs. Placebo** in the proportion of subjects who use rescue medication within 48 hours after dosing
20. **(S18) 5.2 mg dose vs Placebo** in the proportion of subjects with Sustained Normal Functioning (on FIS) from 2 to 24 hours
21. **(S19) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 2 hours post dose in attacks with allodynia at baseline
22. **(S20) 5.2 mg dose vs. Placebo** in the proportion of subjects free from MBS at 2 hours post dose in attacks with allodynia at baseline
23. **(S21) 5.2 mg dose vs. Placebo** in the proportion of subjects free from headache pain at 2 hours post dose in attacks with severe headache at baseline
24. **(S22) 5.2 mg dose vs. Placebo** in the proportion of subjects free from MBS at 2 hours post dose in attacks with severe headache at baseline
25. **(S23) 5.2 mg dose vs. Placebo** in the proportion of subjects with headache relapse within 48 hours after dosing

Statistical testing may be performed for other secondary and exploratory endpoints without adjustment of multiplicity. The consistency of the testing results will aid in the evaluation of the overall treatment benefit of STS101.

4.5.2 Primary Endpoint Analysis Methods

For the primary analysis of the co-primary endpoints, missing data will be imputed based on a single-imputation method. Subjects who do not have evaluable assessments at the 2-hour time point, or who received rescue medications prior to the 2-hour time point will be considered as non-responders. Although this is a single-imputation method, the approach is conservative and

does not impute a favorable outcome (i.e., pain-free or MBS-free status) for subjects with missing data.

The hypothesis test for the primary analysis is:

$$H_0: P_t = P_p \text{ vs } H_1: P_t \neq P_p$$

where P_t is the proportion of response for STS101, and P_p is the proportion of response for placebo.

A Chi-square test will be used to compare 5.2 mg STS101 to placebo using the multiplicity strategy described in Section 4.5.1. The number needed to treat (defined as the inverse of the treatment difference) will also be included in the table.

4.5.3 Key Secondary Endpoint Analysis Methods

The key secondary parameters are listed in Section 4.4. Missing data on the composite estimands will be imputed based on a single-imputation method in the same manner described for the primary endpoints.

The hypothesis test for the key secondary analyses is the same as the primary analyses.

A Chi-square test will be used to compare 5.2 mg STS101 to placebo using the multiplicity strategy described in Section 4.5.1.

4.5.4 Additional Secondary Endpoint Analysis Methods

The secondary efficacy endpoints (see Section 4.4) will be analyzed in the same manner as the estimands described for the primary/key secondary endpoints. No adjustment for multiplicity will be made on these analyses.

Missing data will not be imputed, unless noted otherwise in the definitions of the parameters. Endpoints that use observed data are the patient global response, frequency of rescue medications, patient global impression, ease of use, and comparison of study medication with previously used migraine medication ratings.

Time to event analyses will be performed for the following:

- Time to freedom from headache pain
- Time to freedom from MBS
- Time to achieving relief from headache pain
- Time to rescue medication use

Time to freedom from headache pain, MBS, and relief from headache pain will be censored at 48 hours if a subject uses rescue medication. If a subject does not have an event and does not use rescue medication, the subject will be censored at the last non-missing timepoint in the diary.

Time to rescue medication use will be censored at the last timepoint with a non-missing response. A log rank test (Kaplan-Meier method) will be used to compare treatment differences. A separate analysis will also be conducted on time to achieving relief from headache pain between 0 to 2 hours. If a subject uses rescue medication during the 2 hours, the subject will be censored at 2 hours. If a subject has not had relief from headache pain at 2 hours, the subject will be censored at the last non-missing timepoint with a maximum of 2 hours. A Kaplan-Meier curve will be produced for this analysis.

The Patient Impression Rating endpoints (patient global impression, ease of use, comparison of study medication with previously used migraine medication) will be analyzed using the Mantel-Haenszel test. A Chi-square test will be used to analyze all other endpoints.

Rescue medications taken during the study will be summarized by treatment using frequencies and percentages. A rescue medication will be counted once at most per subject in the summary.

To fully describe the treatment benefit of STS101, the proportion of subjects who achieve freedom from headache pain, freedom from MBS, and relief from headache pain at various timepoints after dosing will be displayed graphically to show the time course of effect.

To address the onset of efficacy, the Freedom from Headache Pain by Timepoint estimand will be used. The proportion of subjects achieving freedom from headache pain will be examined from the 2-hour time point towards the baseline in a sequential manner (i.e. 2 hours, 1.5 hours, 1 hour, 45 minutes, 30 minutes, 15 minutes). A significance level of 0.05 will be used for this analysis. If the treatment comparison between STS101 and placebo is significant at 0.05 level at 2 hours, the significance at 1.5 hours will be examined next. If the comparison is significant at 1.5 hours, then 1-hour timepoint will be examined next. The process will continue until the timepoint for which the significance level exceeds 0.05. The last timepoint for which the significant level is less than 0.05 is considered the timepoint of onset of efficacy.

Additionally, all secondary endpoints, including the primary and key secondary endpoints, will be analyzed using the mITT, PP, and ITT populations.

4.5.5 Exploratory Endpoint Analysis Methods

Exploratory endpoints are listed in Section 4.4. Endpoints that are derived in the primary or secondary key endpoints will follow the estimands for handling of intercurrent events. Missing data for these endpoints will be imputed based on a single-imputation method in the same manner described for the analysis on the primary endpoints, unless noted otherwise in the definitions of the parameters. Endpoints that use observed data are the 24-hour Migraine Quality of Life scores.

An analysis of variance (ANOVA) model with treatment as a factor will be used to test compare treatment differences for the 24-hour Migraine Quality of Life endpoints. The LS mean difference and 95% confidence interval will be presented in the table. A Chi-square test will be used to analyze the freedom from headache pain and MBS endpoints, and a Cochran-Mantel-

Haenszel test will be used to compare treatment differences for all other endpoints stratified by a baseline variable. No adjustment for multiplicity will be made on these analyses.

All exploratory endpoints will be analyzed using the mITT, PP, and ITT populations.

4.5.6 Sensitivity Analyses

Sensitivity analyses using additional single-imputation (SI), multiple-imputation (MI) with the tipping-point (TP) method, a worst-case scenario, and observed case analysis are planned. Another sensitivity analysis that will be conducted on the primary endpoints is the removal of subjects with a malfunction in their e-Diary. A description of the issue is below:

Due to a core software defect the 2-hour ATD was unable to be completed by some subjects. Data interruptions occurred for these subjects when a transmission and an alarm/notification fire occurred at the exact same time, causing the device to timeout and not save the form at completion.

The transmission/alarm amalgam issue was not caught in core testing as protocol STS101-007 utilizes custom alarm functions which alter the state and break of transmissions.

These subjects will be identified prior to database lock. All sensitivity analyses will be on the mITT population.

Depending on the extent of missing data, additional sensitivity analysis with other pattern-mixture model analyses may be considered. The inclusion of additional sensitivity analyses will be determined after the examination of the nature and the extent of missing data and before the unblinding of the study. Any additional analyses will be included in an addendum to the SAP.

4.5.6.1 *Additional Single-Imputation Method*

The additional SI method will be performed on the following endpoints:

- Freedom from headache pain at 2 hours
- Freedom from MBS at 2 hours
- Relief from headache pain at 2 hours
- Achieving normal function at 2 hours
- Freedom from photophobia at 2 hours
- Freedom from phonophobia at 2 hours
- Freedom from nausea at 2 hours

The estimands defined for each endpoint will be the same except for the Intercurrent event attribute. Intercurrent events will be handled as such:

- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours or the timepoint of interest. If a subject is missing the 2-hour timepoint for any reason, the last observed variable (from

the estimand) value prior to the 2-hour timepoint will be carried forward to the 2-hour timepoint (LOCF).

4.5.6.2 *Multiple Imputation Method*

Multiple imputation will be performed on the co-primary endpoints:

- Freedom from headache pain at 2 hours
- Freedom from MBS at 2 hours

Rubin's (1987) MI procedure will also be conducted to assess the impact of missing values in the co-primary endpoints. Instead of filling in a single value for each missing value, Rubin's procedure replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute.

Two MI methods are planned:

Markov chain Monte Carlo (MCMC) method (Schafer 1997):
For non-monotone missing data patterns, MCMC assumes multivariate normality and generates multiple imputations using simulations from a Bayesian prediction distribution for normal data.

Regression method:
For monotone missing data patterns, a logistic regression model is fitted for each variable with missing values. Based on the resulting model, a new logistic regression model is used to impute subsequent missing values for the variable. Since the data set has a monotone missing data pattern, the process is repeated sequentially for variables with missing values.

Based on these two MI methods, the missing data will be imputed using the following approaches.

Step 1: non-monotone missing data will be imputed using the MCMC method by treatment group (or if necessary, use treatment group as a factor).

Step 2: monotone missing data will be imputed using the regression method on the basis of the predicted future pattern.

One hundred (100) imputed datasets will be generated for each MI analysis. If the MCMC method is needed to achieve monotone missing data for Step 2, then this imputation will generate 100 imputed datasets and the regression method will be performed on each imputed dataset. The imputed values will range between 0 and 1. Imputed values greater than or equal to 0.5 will be categorized as a responder (1), and imputed values less than 0.5 will be categorized as a non-responder (0). Each imputed dataset will be analyzed separately using PROC GENMOD with a binomial distribution and logit link, treatment as a factor and response at the 2 hour-timepoint as the dependent variable. The final estimate of the treatment difference will be the average of the estimates based on the 100 individual imputed datasets. The pooling of the individual estimates

and inferences based on the combined estimate will be handled by SAS procedure MIANALYZE.

In addition to the above multiple imputation procedure, a tipping-point analysis will also be conducted where statistical significance occurs in the main analyses. A shift parameter, representing an adjustment of the effect size in the active treatment group, will be applied in the imputation of missing data. This shift parameter will be gradually increased towards the direction of reduced effect size, which imputes unfavorable outcomes for the missing data in the active treatment group. The shift parameter which results in a reversal of study conclusion (i.e. tipping point) will be identified and presented on the table. The plausibility of the shift parameter will inform the robustness of the study conclusion and the impact of the missing values.

The estimands defined for each co-primary endpoint will be the same except for the Intercurrent event attribute. Intercurrent events will be handled as such:

- Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours or the timepoint of interest. If a subject is missing the 2-hour timepoint for any reason, the variable (from the estimand) values from the 15, 30, and 45 minutes, and 1, 1.5, 2 hour timepoints will be used in estimated missing data via the multiple imputation methods described above.

4.5.6.3 *Worst Case Scenario*

The worst case scenario will be performed on the following endpoints:

- Freedom from headache pain at 2 hours
- Freedom from MBS at 2 hours
- Relief from headache pain at 2 hours
- Achieving normal function at 2 hours
- Freedom from photophobia at 2 hours
- Freedom from phonophobia at 2 hours
- Freedom from nausea at 2 hours

The estimands defined for each endpoint will be the same except for the Intercurrent event attribute. Intercurrent events will be handled as such:

Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours or the timepoint of interest. If a subject is missing the 2-hour timepoint for any reason and the randomized treatment is STS101, the 2-hour timepoint will be imputed as non-response. If a subject has missing data at 2 hours and the randomized treatment is Placebo, the 2-hour timepoint will be imputed as a responder.

4.5.6.4 *Observed Case Analysis*

The observed case analysis will be performed on the following endpoints:

- Freedom from headache pain at 2 hours
- Freedom from MBS at 2 hours
- Relief from headache pain at 2 hours
- Achieving normal function at 2 hours
- Freedom from photophobia at 2 hours
- Freedom from phonophobia at 2 hours
- Freedom from nausea at 2 hours

The estimands defined for each endpoint will be the same except for the Population and Intercurrent event attribute. Intercurrent events will be handled as such:

Population: Subjects in the mITT population who have a non-missing response at 2 hours.

Intercurrent event: If a subject took rescue medication at any time within the first 2 hours of dosing, non-response will be assumed at 2 hours. If a subject is missing the 2-hour timepoint for any reason, no imputation will be made. The observed data at the 2-hour timepoint will be used. Therefore, if a subject is missing data at the 2-hour timepoint, the subject will be excluded from the analysis.

4.5.6.5 *Primary Analysis with Subject Exclusion Due to e-Diary Software Defect*

The primary analysis with subject exclusion due to a software defect in the e-Diary will be performed on the co-primary endpoints:

- Freedom from headache pain at 2 hours
- Freedom from MBS at 2 hours

The estimands defined for each endpoint will be the same except for the population:

Population: Subjects in the mITT population who have a non-missing response at 2 hours and did not have a software defect in the e-Diary.

4.5.7 Subgroup Analyses

Subgroup analyses of the freedom from headache pain at 2 hours, freedom from MBS at 2 hours, and relief from headache pain at 2 hours will be conducted to gain insight of the nature and consistency of the treatment effect. Subgroups prospectively identified include:

1. age group (18-35 years, >35-50 years, >50-65 years)
2. gender (male, female)
3. race (white, other)
4. baseline severity of attack (time 0) (moderate, severe)
5. allodynia status (yes, no)
6. menstrual related migraine attacks (yes, no)
7. in subjects who wake up with migraine headache (yes, no)

8. baseline (Visit 2) HIT-6 score (severe impact, substantial impact, some impact, little/no impact)
9. ethnicity (Hispanic, Not Hispanic)
10. baseline weight (<=median, >median)

Among these subgroup analyses, several are also included in the secondary or exploratory endpoints; therefore, only those subgroups not already summarized will be tabulated.

Because of the smaller sample sizes for each subgroup, the objective of the analysis is to evaluate the consistency of efficacy results across these factors. Statistical tests will be performed. However, the interpretation of the p-values will take into account sample size and multiplicity issues. Forest plots with estimates and 95% confidence intervals of the treatment effect across different subgroups will be presented.

5. SAFETY

The safety objective is to assess the safety and tolerability of a single dose of 5.2 mg STS101 in the treatment of acute migraine attacks. This objective is assessed through adverse events, physical examinations, vital signs, objective nasal symptom assessments, electrocardiogram, and laboratory assessments.

Safety analyses will be conducted for the safety population, which will include all subjects who received at least one dose of study medication. Clinical safety and tolerability data will be summarized by treatment group in tables and listed by treatment group and by subject. Adverse events will be coded using MedDRA version 24.0 and listed by System Organ Class, Preferred Term, and verbatim term. No inferential statistics will be performed; only summary statistics will be provided unless otherwise noted.

5.1 Extent of Exposure

Because this is a single-dose study with PRN use, each subject is expected to receive one dose only. The number of subjects exposed to each treatment group is the number of subjects in the Safety Population; therefore, a table summarizing exposure is not displayed. Study drug dosing and reported compliance will be listed by treatment group and subject.

5.2 Adverse Events

A treatment emergent adverse event (TEAE) is defined as an adverse event (AE) that begins after the dosing of study drug.

An overview of adverse events will be presented by treatment group, which will include the number and percent of subjects who had at least one AE, TEAE, Serious TEAE, TEAE leading to discontinuation, TEAE related to study drug, and maximum severity of TEAE.

Multiple occurrences of an AE are counted only once per subject per system organ class and preferred term for summary tables.

The following TEAEs will be summarized by SOC, PT and treatment group:

- Incidence of all TEAEs
- Local TEAEs (will be updated based on actual events prior to unblinding)
- Cardiovascular TEAEs
- Incidence of all TEAEs by maximum severity (severe, moderate and mild) specified by investigators
- Incidence of TEAEs related to the study drug as determined by the investigators
- Incidence of serious TEAEs
- Incidence of TEAEs leading to discontinuation of study drug

The incidence of all TEAEs, Local TEAEs, Cardiovascular TEAEs and TEAEs by severity will also be summarized in subjects with preventative migraine medication use at screening.

All data collected in the AE CRF will be listed in by subject listings.

5.3 Assessment of Nasal Irritation

The Objective Assessment of Nasal Irritation is a 5-item assessment completed by the site to assess the effects of the study drug on the nose at Screening, Day 1, and Follow-up visits. Nasal symptoms assessed are Nasal Erythema, Nasal Edema, Rhinorrhea, Nasal Bleeding, and Nasal Ulceration. The responses are categorical and range from 0 (none) to 3 (severe). The shift in responses from baseline to follow-up will be summarized by treatment group. Exploratory hypothesis testing may be performed to compare treatment group by question. No multiplicity adjustment will be applied to these tests.

5.4 Physical Examination

Physical examination findings will be presented in data listings by treatment group and subject.

5.5 Vital Signs

Vital signs, including weight, are recorded on subjects at Screening, Day 1, and Follow-up visits. Observed data at baseline and follow-up visits and the change from baseline for vital signs will be summarized by treatment group.

Normal ranges for the following vital sign parameters will be used to categorize the results as low (lower than the lower limit), normal (within the normal range), or high (higher than the upper limit). Frequency counts and percentages will be presented at each visit by treatment group for these categorical data.

The following normal ranges will be used in the summary of vital signs.

- Systolic blood pressure: 90-160 mmHg (inclusive)
- Diastolic blood pressure: 50-90 mmHg (inclusive)

- Pulse: 50-100 beats/min.(inclusive)
- Temperature: 97.7-99.0 degrees F (36.5 - 37.5 degrees C, inclusive)

5.6 Electrocardiogram

Electrocardiogram (ECG) data is recorded in triplicate at Screening, Day 1, and Follow-up visits and will be averaged for summary purposes. Observed data at baseline and follow-up visits and the change from baseline in ECG parameters, heart rate (HR), RR, PR, QRS, and QT corrected with the Fridericia's formula (QTcF), will be summarized by treatment group.

The ECG findings, as reported on the CRF, is also recorded in triplicate. For summary purposes, the worst finding will be selected. The number and percentage of subjects with clinically significant ECG findings as previously described will be summarized as a shift from baseline to follow-up visit by treatment group.

5.7 Laboratory Evaluations

Laboratory evaluations will be conducted at Screening and Follow-up visits and pregnancy tests in females will be performed on Screening, Day 1, and Follow-up visits. The observed data and change from baseline (Visit 1 or if re-draw: qualifying value) to the final study visit (Visit 3) in hematology, serum chemistry and quantitative urinalysis test results will be summarized by treatment group.

For hematology and serum chemistry normal ranges for each parameter will be used to categorize the test results as low (value lower than the lower limit), normal (value within the normal range), or high (value higher than the upper limit).

For urinalysis, test results will be categorized as normal and abnormal. Frequency counts and percentages will be presented over time by treatment groups for these categorical data.

In addition, shifts from baseline (shift to maximum value, shift to minimum value) to the follow-up visit in quantitative laboratory tests with normal ranges will be summarized by treatment group.

If a continuous laboratory value is reported as either below or above the limits of quantification, the qualifiers should be dropped and the numeric value used in the analysis (e.g., "< 1" should be "1" and "> 100" should be "100").

5.8 Sheehan Suicidality Tracking Scale

The Sheehan Suicidality Tracking Scale (S-STS) will be performed at Screening, Day 1, and Follow-up Visit. The total score, as derived on the CRF, will be summarized using descriptive statistics by treatment group.

6. Interim Analysis

No interim analysis is planned for this study.

7. TABLES, LISTINGS, AND FIGURES

Data listings will be sorted by subject number, treatment group, and visit (if appropriate). All data recorded on the CRFs will be included in the listings as well as some derived information. The shells for the data listings will be primarily to show where specific data can be found. The variable spacing and overall presentation or layout of the listings may need to be altered once actual data is available.

Tables will generally be presented with the parameter in the first column followed by the active treatment group and placebo. Descriptive statistics such as mean, median, minimum, and maximum will be presented to one decimal place and standard deviation will be presented to two decimal places. The laboratory tables may vary for each test depending on the precision of the test. P-values will be presented to four decimal places. If a p-value is less than 0.0001 then it will be presented as <0.0001.

A list of the tables, listings, and figures will be maintained outside of this document and may be amended as needed.

8. REFERENCES

Ashkenazi A, Sholtzow M, Shaw JW, Burstein R, Young WB. Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia. 2007;27(2):111-7. doi: 10.1111/j.1468-2982.2006.01255.x.
Rubin D.B.: Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons, 1987

Schafer: Analysis of Incomplete Multivariate Data. Chapman & Hall, New York, 1997
Ware JE: SF-36 Health Survey update. Spine, 25(24):3130–3139, 2000

Tepper SJ, Kori SH, Goadsby PJ, Winner PK, Wang MH, Silberstein SD, Cutrer FM. MAP0004, orally inhaled dihydroergotamine for acute treatment of migraine: efficacy of early and late treatments. Mayo Clin Proc. 2011;86(10):948-55. doi: 10.4065/mcp.2011.0093.

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