STATISTICAL ANALYSIS PLAN

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

An Open-Label, 12-Month Study to Evaluate the Safety and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine

Clinical Study Protocol No. STS101-003

Final v4 September 19, 2022

Prepared by
Shelia Ligozio
Instat Clinical Research

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SIGNATURE PAGE

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Michelle Secic (Sep 23, 2022 14:48 EDT)	Sep 23, 2022
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CRF	case report form
CSR	clinical study report
DHE	dihydroergotamine
ECG	electrocardiogram
e-Diary	electronic diary
FIS	Functional Impairment Scale
HIT-6	Headache Impact Test
HR	heart rate
max	maximum
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
mITT	Intent-to-Treat
n	number of subjects
PGI	Patient Global Impression
PRN	pro re nata
PT	preferred term
QTcF	QT corrected with the Fridericia's formula
TEAE	treatment emergent adverse event
SAP	statistical analysis plan
SD	standard deviation
SIT	Smell Identification Test
SOC	system organ class
WHO Drug	World Health Organization Drug Dictionary
24-MQoL	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 objective of the study is to assess the safety and tolerability of STS101 in the acute treatment of migraine attacks over 12 months.

The secondary objective of this study is to describe the efficacy of STS101 in the acute treatment of migraine attacks over 12 months.

1.2. Study Design

This study will be a multi-center, multiple dose (PRN), open-label, 12-month study in approximately 480 subjects with migraine (ages 18 to 65 years). An amendment to the protocol allowed for subjects of the original cohort (enrolled before June 30, 2021) to continue use of study medication for an additional 6 months after completion of the original 12-month period. Only safety data will be collected during this period.

After establishing eligibility, the study participants will use STS101 (DHE nasal powder) on a PRN basis to treat migraine attacks for 12 months. Study participants will be able to use up to 2 doses of STS101 to treat a single migraine attack within 24 hours and can use up to 12 doses of STS101 per month for 12 months.

The study participants will document the pain severity of their migraine attacks, presence and severity of symptoms (photophobia, phonophobia, nausea) and functionality status over the 48-hour period after study drug administration. Specifically, headache pain severity data and symptom presence will be collected at the onset of the migraine attack, immediately before drug administration (time 0), 30 and 60 minutes, 2, 4, 24, and 48 hours after study drug administration.

Migraine attacks not treated with study medication will also be documented. Use of rescue medication is allowed, but triptans or other DHE products as rescue medications should be avoided for 24 hours after study drug administration (24 hours after the second dose if a repeat dose of STS101 is administered).

Adverse events, nasal and physical examination data, safety laboratory data, vital sign data and electrocardiogram (ECG) will be recorded to describe the tolerability and safety of STS101. Additionally, subjective and objective nasal symptom assessments and the Smell Identification Test (SIT) will be documented during the treatment period.

1.3. Study Visits and Procedures

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

Table 1: Schedule of Evaluations

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
	Screening	**Baseline**									**Final/ Early Term Visit**
Timing of Visit/ Allowable Visit Window (± days)	Day -30 to -1	Day 0	Month 1 (7 days)	Month 2 (7 days)	Month 3 (7 days)	Month 4 (7 days)	Month 5 (7 days)	Month 6 (7 days)	Month 8 (14 days)	Month 10 (14 days)	Month 12 (14 days)
Informed Consent Form	X										
Demographics/ Medical history	X										
Physical examination[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X	X[a]	X[a]	X
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X
Hematology, clinical chemistry, urinalysis	X	X			X			X			X
Serum pregnancy test	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X
12-lead ECG	X	X			X			X			X
Nasal Examination & Objective Assessment of Nasal Symptoms	X	X	X	X	X	X	X	X	X	X	X
Subjective Assessments of Nasal Symptoms	X	X			X			X			X
HIT-6 Questionnaire		X			X			X			X
Sheehan Suicidality Tracking Scale	X	X	X	X	X	X	X	X	X	X	X
Smell Identification Test™		X									X
Subject Impression Questions					X			X			X
Determine / review eligibility	X	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Health Care Resource Utilization		X	X	X	X	X	X	X	X	X	X
STS101 Device training/Collection	X	X	X	X		X	X		X	X	X
Handheld Device (eDiary) Training/ Dispensing/Review/ Collection		X	X	X	X	X	X	X	X	X	X
Study drug supply/Drug Accountability	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

a. Focused neurological examination
b. Height and BMI calculation only at Screening (Visit 1)
c. Females of childbearing potential only

Table 1 (cont'd): Schedule of Evaluations for Subjects continuing for 6 months after Visit 11

Visit	12	13	14
			Final/Early Term Visit
Timing of Visit/ Allowable Visit Window (± days)	Month 14 (14 days)	Month 16 (14 days)	Month 18 (14 days)
Physical examination[a]	X[a]	X[a]	X
Vital signs[b]	X	X	X
Hematology, clinical chemistry, urinalysis	X	X	X
Serum pregnancy test	X[c]	X[c]	X
12-lead ECG	X	X	X
Nasal Examination & Objective Assessment of Nasal Symptoms	X	X	X
Subjective Assessments of Nasal Symptoms			X
Sheehan Suicidality Tracking Scale	X	X	X
Smell Identification Test™			X
Concomitant medications	X	X	X
Study drug supply/Drug Accountability	X	X	X
Paper Diary Training/Dispensing/Review/Collection	X	X	X
Adverse events	X	X	X

2. STUDY POPULATIONS

The analysis populations to be used in the study are defined below. The safety data will be analyzed using six different populations: 6-Month Completers Mk2 (Cohort 1), 12-Month Completers Mk2 (Cohort 2), All Subjects Mk2 (Cohort 3), 6-Month Completers Mk1/Mk2 (Cohort 4), 12-Month Completers Mk1/Mk2 (Cohort 5), and All Subjects Mk1/Mk2 (Cohort 6). The efficacy data will be analyzed using the Modified Intent-to-Treat (mITT) population. Some efficacy endpoints may be analyzed on the 6-Month Completers Mk2 and 12-Month Completers Mk2 populations. An additional analysis population, Cohort 7, will also be used to summarize select efficacy and safety endpoints. These will be specified in the appropriate sections of the document. The table below gives a summary of the safety populations.

Table 2: Safety Populations Summary

Study Cohort	Population	Definition
1	6-Month Completers Mk2	Treated at least 12 migraines with study medication from the Mk2 device over a 6-month continuous period
2	12-Month Completers Mk2	Treated at least 24 migraines with study medication from the Mk2 device, completed the study, and did not enter extension or entered extension and treated at least 24 migraines with study medication from the Mk2 device over a 12-month continuous period
3	All Subjects Mk2	Treated at least one migraine with study medication from the Mk2 device
4	6-Month Completers Mk1/Mk2	Treated at least 12 migraines with either study medication device over a 6-month continuous period
5	12-Month Completers Mk1/Mk2	Treated at least 24 migraines with either study medication device, completed the study, and did not

Study Cohort	Population	Definition
		enter extension or entered extension and treated at least 24 migraines with either study medication device over a 12-month continuous period
6	All Subjects Mk1/Mk2	Treated at least one migraine with either study medication device
7	All Expansion Subjects	All subjects who enrolled in the expansion phase of the study (Mk2 device was the only study medication device dispensed)

The primary analysis will be conducted on the 6-Month Completers Mk2 safety population (Cohort 1). It is defined as all subjects who used study medication from the Mk2 device on average ≥ 2 times per month (minimum of 12 treated migraine attacks) over a 6-month continuous period. The 6-Month Completers Mk1/Mk2 safety population (Cohort 4) is defined as all subjects who used study medication from either the Mk1 or Mk2 device on average ≥ 2 times per month over a 6-month continuous period.

Six months of exposure will be defined as: last kit return date – day 0 visit date +1 ≥ 173. Subjects who meet these criteria will be considered for population inclusion. Study medication uses will be summed over a 187-day period starting at day 1 and increasing in increments of 1 day until day 187. The first 6-month period checked will be days 1 to 187. If a subject has 12 treated migraine attacks, the subject is included in the population. For subjects who do not have 12 treated migraine attacks, the next 6-month period, days 2 to 188, will be checked. This will continue until the last interval, days 366 to 552 (545+7 days), has been checked. The last day interval may be increased if subjects have data greater than day 552 and there are still subjects who could potentially be included in the population.

The 12-Month Completers Mk2 safety population (Cohort 2) is defined as all subjects who completed 12 months of study participation and used study medication from the Mk2 device on average ≥ 2 times per month (minimum of 24 treated migraine attacks in the 12-month duration). The 12-Month Completers Mk1/Mk2 safety population (Cohort 5) is defined as all subjects who completed 12 months of study participation and used study medication from either the Mk1 or Mk2 device on average ≥ 2 times per month. 12-Month study participation will be defined completing the Month 12 (Visit 11) visit as reported in the database for subjects who did not participate in the extension. Since the extension was added while the study was ongoing, subjects who continued into the extension, will be have a 12 month exposure defined and the number of treated attacks checked for each similar to the method described above for the 6 month exposure. Twelve months of exposure will be defined as: last kit return date – day 0 visit date = 1 ≥ 358 days. Study medication uses will be summed over a 372-day period starting at day 1. The final interval will be 180 to 552 days. The final interval may increase depending on available data.

The All Subjects Mk2 safety population (Cohort 3) is defined as all subjects who treat at least one migraine attack with study medication from the Mk2 device. The All Subjects Mk1/Mk2 safety population (Cohort 6) is defined as all subjects who treat at least one migraine attack with either the Mk1 or Mk2 device.

All available study medication information (from drug accountability and e-diary data) will be used to determine the number of doses taken.

The exposure and adverse event summaries for Cohorts 1-3 will only include the data on the Mk2 device.

The Modified Intent-to-Treat population is defined as all subjects who treated at least one migraine attack and who reported at least one post-treatment efficacy data in the After Treatment Diaries at any time point.

The All Expansion Subjects population is defined as all subjects who enrolled in the expansion phase of the study. These subjects are denoted in the database with a subject number starting with the digit 3 after the site number (i.e., 001-301).

3. DEFINITIONS AND DERIVED VARIABLES

- The reference start date will be derived using the maximum of the first dose date recorded by the subject in the eDiary or the first kit dispense date where drug was used according to drug accountability.

- The reference end date will be derived using the maximum of the last dose date recorded by the subject in the eDiary or the last kit dispense date where drug was used according to drug accountability.

- 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.

- Body mass index (BMI) will be derived from the recorded height at screening and weight at screening/baseline (last non-missing measurement). 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.

- Free from headache pain (0=None, 1=Mild, 2=Moderate, 3=Severe) is defined as mild (1), moderate (2) or severe (3) headache pain at time 0 becoming none (0).

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

- Sustained Freedom from Headache Pain up to a time point (e.g., 24, or 48 hours) is defined as a headache pain score of 0 from the 2 hours post dose time point to the time point of interest, e.g., 24 hours, with no use of rescue medication or a second dose of

study medication. All non-missing scores at the time points between the 2 and 24 or 48 hours post dose must be 0.

- Headache relapse is defined as the return of headache of any severity within the specified hours of the endpoint (e.g., 48 hours), when the patient was pain-free at 2 hours after investigational drug administration. The endpoint of interest, e.g., 48 hours must be non-missing.

- Most Bothersome Symptom (MBS) is defined as the most bothersome symptom (photophobia, phonophobia, or nausea) as reported prior to dosing. If only one symptom is present, then that symptom will be considered the MBS.

- Sustained Freedom from MBS up to a time point (24 or 48 hours) is defined as freedom from MBS at 2 hours post dose time point to the time point of interest, e.g., 24 hours, with no use of rescue medication or a second dose of study medication. All non-missing scores at the time points between the 2 and 24 or 48 hours post dose must be 0.

- Rescue medication is defined as any medication taken to treat migraine headaches after dosing with study medication. This will be derived from the headache medication diary.

- 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).

- 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 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.

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

- Duration of exposure is defined as last study medication dose date minus first study medication dose date plus one.

- Study duration is defined as the date of completion/discontinuation as recorded on the End of Study case report form (CRF) minus the informed consent date plus one. If the completion/discontinuation date is unknown or missing, the last available date the subject reported data will be used.

4. SAFETY PARAMETERS

- Mean drug exposure duration (overall and by device)
- Frequency and percentage of subjects taking one and two doses (overall and by device)
- Number of attacks treated with study medication (overall and by device)
- Number of attacks treated with second dose of study medication (overall and by device)
- Frequency and percentages in Treatment Emergent Adverse Events (TEAEs) based on subjects (overall and by device)
- Frequency and percentages in Treatment Emergent Adverse Events (TEAEs) based on attacks (overall and by device)
- Frequency and percentages in TEAE with a second dose within 2 hours of first dose based on subjects (overall and by device)
- Frequency and percentages in Cardiovascular TEAE based on subjects (overall and by device)
- Frequency and percentages in Treatment Emergent Adverse Events (TEAEs) based on attacks (overall and by device) by study month (3 month intervals)
- Frequency and percentages in Cardiovascular TEAE based on subjects (overall and by device) by study month (3 month intervals)
- Frequency and percentages in Cardiovascular TEAE based on attacks (overall and by device)
- Frequency and percentages in Local TEAE based on subjects (overall and by device)
- Frequency and percentages in Local TEAE based on attacks (overall and by device)
- Frequency and percentages in Local TEAE based on subjects with history of allergic rhinitis (overall and by device)
- Frequency and percentages in Local TEAE by timing of second dose based on subjects (Mk2 device only)
- Frequency and percentages in Local TEAE by timing of second dose based on attacks (Mk2 device only)
- Mean Change in Subjective nasal symptom assessment by study visit
- Shifts in Objective nasal symptom evaluation by study visit
- Mean Change in Smell Identification Test (SIT)

- Observed Mean in Sheehan Suicidality Tracking Scale by study visit
- Mean Change in blood tests for hematology, serum chemistry, and quantitative urinalysis by study visit
- Mean Change in Vital signs, including weight by study visit
- Mean Change in 12-lead ECG by study visit
- Frequency and percentages in Concomitant Medications taken

5. EFFICACY PARAMETERS

- Proportion of attacks with freedom from headache pain at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with freedom from most bothersome symptom at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with relief from headache pain at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with freedom from photophobia at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with freedom from phonophobia at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with freedom from nausea at 30 minute, 1, 2, 4, 24, and 48 hours post dose
- Proportion of attacks with sustained freedom from headache pain 2- 24 and 2-48 hours post dose
- Proportion of attacks with sustained freedom from most bothersome symptom 2- 24 and 2-48 hours post dose
- Proportion of attacks with freedom from headache pain at 30 minutes and 1, 2, 4, 24, and 48 hours post dose by study month
- Proportion of attacks with freedom from most bothersome symptom at 30 minutes, 1, 2, 4, 24, and 48 hours post dose by study month
- Proportion of attacks with relief from headache pain at 30 minutes 1, 2, 4, 24, and 48 hours post dose by study month
- Proportion of attacks with sustained freedom from headache pain at 2-24 and 2-48 hours post dose by study month
- Proportion of attacks with sustained freedom from most bothersome symptom at 2-24 and 2-48 hours post dose by study month
- Proportion of attacks with use of rescue medication within 24 and 48 hours post dose

- Proportion of attacks with use of second dose of study medication within 24 and 48 hours post dose
- Frequency of migraine attacks treated with STS101 by study month
- Frequency of migraine attacks by study month
- Proportion of attacks with headache relapse within 24 and 48 hours post dose
- FIS distribution for attacks at 30 minutes, 1, 2, 4, 24, and 48 hours post dose
- Mean total score on 24-hour Migraine Quality of Life Questionnaire (24-MQoL) at 24 hours post dose by study month
- Frequency and percentages of responses to satisfaction with treatment questions
- Mean change from baseline in HIT-6
- Mean change from baseline in Healthcare Resource Utilization

6. STATISTICAL METHODOLOGY

6.1. Statistical and Analytical Issues

6.1.1. Statistical Methods

All study data will be summarized 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 frequency counts and percentages. Missing values will not be considered in percentages unless otherwise noted in a footnote.
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).

No formal hypothesis testing will be performed, and as such, there will be no adjustments for multiplicity. Any statistical analyses performed will be exploratory, conducted at a significance level of 0.05, and described fully within that section.

6.1.2. Handling of Dropouts and Missing Data

Missing data will not be imputed. Summaries will be based on the available data only.

For incomplete dates needed in derivations (i.e., 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.

Missing dates will not be imputed.

6.1.3. Pooling of Investigator Sites

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

6.1.4. Determination of Sample Size

A total of approximately 480 adult male and female subjects (18 to 65 years of age) with migraine will be enrolled. At least 150 and 50 subjects are anticipated to complete at least 6 and 12 months, respectively. This sample size is expected to adequately characterize the safety and tolerability of STS101 in the acute treatment of migraine. A formal sample size calculation was not performed. However, it is assumed that a sample size of 480 subjects is sufficient to detect clinically important adverse events with an event rate of 1% or higher.

6.2. Subject Characteristics

6.2.1. Subject Disposition

The number of all enrolled subjects, number and percentage of subjects in each analysis population along with reasons for population exclusion, and number of subjects previously enrolled in STS101-002/STS101-007 study will be presented. In addition, number of subjects who completed/prematurely discontinued and reason for discontinuation will also be presented for each analysis population.

6.2.2. Protocol Deviations

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

6.2.3. Background and Demographic Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, height, weight, BMI) will be summarized descriptively for the seven safety population cohorts. The childbearing potential, smoking classification, alcohol use, and caffeine use will also be included in the summary.

6.2.4. Medical History

Medical history will be coded using MedDRA version 23.1 and listed by System Organ Class (SOC), Preferred Term (PT), and verbatim term. Medical history will be summarized using frequencies and percentages according to the SOC and PT on all safety population cohorts.

6.2.5. Migraine History

Migraine history, including the number of years experiencing migraine, less than 15 headache days per month in the 3 months prior to screening, migraine history of 4-12 attacks per month in the 3 months prior to screening, presence of associated symptoms in migraines during screening (aura, nausea, photophobia, phonophobia, allodynia), triptan use, and pain relief with triptan use, will be summarized. For the subjects of the expansion cohort, migraine history will include the mean number of migraine attacks and headache days in the three months prior to screening. The number of migraine attacks and headache days prior to screening are reported on the CRF. Migraine history will be summarized for all safety population cohorts.

6.2.6. Baseline Attack Symptoms

The baseline (time 0) responses to pain severity, photophobia, phonophobia, and nausea for all treated attacks will be summarized by treatment for the mITT and Cohort 7 population.

6.3. Safety Analysis

The primary safety population will be the 6-Month Completers Mk2 safety population (Cohort 1). Safety analyses will be conducted on all six safety population cohorts as defined in Section 2. All available data for subjects will be summarized for each population, i.e., if a subject is included in the 6-Month Completers Mk2 safety population but has data through Month 8 of the study, all of the data will be summarized for that subject. Selected clinical safety and tolerability data will be reported by treated migraine attacks. Selected clinical safety and tolerability data will be reported by use of STS101 Mk1 and Mk2 device.

No inferential statistics will be performed; only summary statistics will be provided unless otherwise noted. All safety data reported/captured at a clinic visit will use the visit assigned in the database. No windows around the month will be applied. However, if the data is captured in the diary, then the study month windows will be used.

All clinical safety and tolerability data will be listed by subject.

6.3.1. Treatment Exposure

Subjects may use up to 2 doses to treat a single migraine attack within 24 hours and can use up to 12 doses per month. There were also 2 study drug devices (Mk1 and Mk2) used during this study. All exposure summaries will be summarized by device and overall.

Treatment exposure will be summarized as follows:

- Duration of exposure to treatment as defined in Section 3 using descriptive statistics
- Study duration as defined in Section 3 using descriptive statistics
- Frequency and percentage of subjects by treatment duration by month according to Table 2 of Section 6.4.1.

The number of doses taken will be summarized as follows:

- The total number of doses of study medication from the Drug Accountability CRF
- The total number of doses of study medication from the Drug Accountability CRF by visit month
- The total number of doses of study medication from the eDiary
- The total number of doses of study medication from the eDiary by study month

The number of migraine attacks will be summarized as follows:

- The total number of migraine attacks treated with study medication (either 1 or 2 doses) during the study
- The number of treated migraine attacks (either 1 or 2 doses) by study month
- The number of migraine attacks treated with one dose during the study
- The number of migraine attacks treated with one dose by study month
- The number of migraine attacks treated with a second dose during the study
- The number of migraine attacks treated with a second dose by study month

Subjects with a second dose within 2 hours of the first dose will be summarized for each cohort and broken out into occurring either in the first hour (≤ 1 hour) or 1 – 2 hours.

The average number of treated migraine attacks per month will be derived for each subject based on their population inclusion. Therefore, the denominator for the 6-Month Completers safety populations will be 6 months, and the denominator for the 12-Month Completers safety populations will be 12 months. For the All Subjects safety populations, the denominator will be the difference in days between the reference end date and reference start date plus one and converted to months using 30.4375 (365.25/12). The subjects' average number of treated migraine attacks per month will be summarized using frequencies and percentages.

Also summarized will be the distribution of subjects by maximum number of treated attacks in one month.

A listing of the number of treated attacks per month by subject will also be provided along with a table summarizing the average number of treated attacks by month.

Study month definitions will be based on the windowing found in Table 3 of Section 6.4.1. Study drug administration and drug accountability will be listed by subject.

6.3.2. Adverse Events

Reported adverse events will be coded using MedDRA version 23.1.

A treatment emergent adverse event is defined as an AE that begins after the dosing of study drug. When determining treatment emergent adverse events, if the start date is missing and the event is ongoing at the time of dosing, then the event will be considered treatment emergent.

Treatment emergent adverse events will be summarized based on the number of subjects in each population. Multiple occurrences of an AE are counted only once per subject per system organ class and preferred term for summary tables. Treatment emergent AEs will also be summarized based on the number of treated migraine attacks for the subjects in each population. This summary will include the total number of events by SOC and PT. Therefore, all occurrences of an AE are counted per system organ class and preferred term.

An overview of adverse events will be presented, which will include the number and percent of subjects who had at least one AE, TEAE, Serious TEAE, TEAE related to study drug, and maximum severity of TEAE. The same summary will be done for the number of events.

The following TEAEs will be summarized by SOC, PT, and use of Mk1 and Mk2 device:

- Incidence of all TEAEs
- Local TEAEs (derived from a searchable list of preferred terms)
- Cardiovascular TEAEs (derived from a searchable list of preferred terms)
- 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 early discontinuation from study
- Incidence of TEAEs leading to drug interruption

For the 6-Month Completers (Mk1/Mk2) safety population (Cohort 4), subjects with a TEAE who used both Mk1 and Mk2 devices will be summarized using frequencies and percentages. The proportions of subjects with a TEAE on Mk1 and Mk2 will be analyzed using McNemar's test.

Treatment emergent adverse events and local TEAEs will also be summarized over the time in study by months. The start date of the event will be used to determine when the event occurred within the study using Table 3 in Section 6.4.1. The summary will be displayed using the following intervals: 0 – < 3 months, 3 - < 6 months, 6 - < 9 months, and 9 - < 12 months, and 12+ months. This summary will be performed for all six cohort safety populations.

Local TEAEs in subjects with a history of allergic rhinitis will be presented for all cohort safety populations also. History of allergic rhinitis is defined as subjects with any of the following medical history terms that are ongoing at the time of baseline:

- Rhinitis
- Rhinitis Allergic
- Rhinitis Chronic

A subset of treatment emergent adverse events in subjects who dosed twice within 2 hours will also be tabulated. Local treatment emergent adverse events will also be summarized by the number of doses taken and the timing of the second dose for Cohorts 1-3 only.

The following AE tables will be summarized on Cohort 7:

- Overview of AEs
- TEAEs by SOC/PT
- Related TEAEs.

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

6.3.3. Assessment of Nasal Symptoms

Observed and change from baseline values of Subjective Assessment of Nasal Symptoms will be summarized by visit (Month 3, 6, 12) using descriptive statistics. Shifts in Objective Assessment of Nasal Symptoms will be summarized at each visit (Months 1-6, 8, 10, 12) as compared to baseline.

6.3.4. Physical Examination

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

6.3.5. Vital Signs

Observed data at each visit and the change from baseline at the post baseline visit (Months 1-6, 8, 10, 12) for vital signs will be summarized.

Normal ranges for each vital sign parameter will be used to categorize the results as low (below the lower limit), normal (within the normal range), or high (above the upper limit). Frequency counts and percentages will be presented 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: 97.7-99.5 degrees F (36.5-37.5 degrees C) (inclusive)

6.3.6. Electrocardiogram

Electrocardiogram data is recorded in triplicate at each visit and will be averaged for summary purposes. Observed data at each visit and the change from baseline at the post baseline at Months 3, 6, 8, 10, and 12 in ECG parameters, heart rate (HR), RR, PR, QRS, and QT corrected with the Fridericia's formula (QTcF), will be summarized.

The ECG findings, as reported on the CRF, is also recorded in triplicate at each time point. For summary purposes, the worst finding will be selected. The number and percentage of subjects with clinically significant ECG findings as previously described will also be summarized at each post baseline visit in a shift table.

6.3.7. Laboratory Parameters

The observed data and change from baseline at the post baseline visits (Months 3, 6, 8, 10, and 12) in hematology, serum chemistry and quantitative urinalysis test results will be summarized.

For hematology and serum chemistry including calculated creatinine clearance, 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). The flags provided in the vendor dataset will be used for summary.

For qualitative urinalysis tests, the results will be tabulated as frequency counts and percentages.

In addition, shifts from baseline to post baseline for each parameter will be summarized.

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").

6.3.8. Smell Identification Test

The olfactory function will be assessed using the SIT at baseline and Month 12. The test consists of 4 booklets of 10 odors each for a total of 40 items. The score is the number of odors correctly identified. Observed and change from baseline values will be summarized using descriptive statistics. The number of subjects with an absolute change from baseline of 5 or more will be summarized using frequencies and percentages.

6.3.9. Sheehan Suicidality Tracking Scale

The Sheehan Suicidality Tracking Scale will be performed at every visit in the study. A baseline score of 0 was needed to enter the study. This questionnaire was not included in the original schedule of evaluations; therefore, data will not be available on all subjects. The total score (as

reported in the database) will be summarized using descriptive statistics for each post baseline visit.

6.3.10. Prior and Concomitant Medications and Therapies

Concomitant medications and migraine prevention medication usage (as defined in Section 3) will be summarized using frequencies and percentages. Migraine prevention medication use is defined using the indication response of 'Migraine Prevention'. 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. Prior and concomitant medications will be summarized separately. Concomitant migraine prevention medications will be summarized also.

The World Health Organization Drug Dictionary (WHO Drug) version B3 September 2020 will be used to classify prior and concomitant medications by therapeutic class and generic name based on anatomical therapeutic chemical (ATC) class code level 3. If the ATC level 3 code is not available, then the next available ATC level will be used (i.e., ATC level 2 or 1). Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject.

Concomitant procedures and non-drug therapies will be listed by subject.

6.4. Efficacy Analysis

The efficacy parameters will be recorded in an e-diary by the subjects. Subjects may have several treated migraine attacks, and subjects may take a second dose after 2 hours for any attack.

All efficacy analyses are exploratory, and there are no specified primary or secondary efficacy variables for this study. Definitions, summaries, and analyses for the efficacy parameters listed in Section 4 will be described in this section. The analysis for all endpoints will be based on the observed data for the mITT population. Since subjects may treat more than one migraine attack during the study, response rates or percentages will be based on the number of migraine attacks treated.

6.4.1. Freedom from Headache Pain

Headache pain severity will be collected at the onset of each migraine attack immediately before drug administration, at 30 minutes post dose, and at 1, 2, 4, 24, and 48 hours post dose. The 30 minute and 1 hour time points were added after the start of the study and not all attacks have data at these timepoints.

The endpoints for freedom from headache pain are:

- Attacks with freedom from headache pain at 30 minutes, 1, 2, 4, 24 and 48 hours post dose
- Attacks with freedom from headache pain at 30 minutes, 1, 2, 4, 24, and 48 hours post dose by month

The proportion of attacks free from headache pain at 2 hours post dose will be defined as attacks where the following is available: a baseline pain severity response, a non-missing response at 2 hours post dose, freedom from headache pain as defined in Section 3, and no use of rescue medication or a second dose of study medication prior to 2 hours post dose. The percentage will be based on the number of treated migraine attacks with a response, i.e., a subject may be counted more than once in the summary.

Freedom from headache pain at 30 minutes, 1, 4, 24, and 48 hours post dose will be defined in the same as 2 hours post dose; however, if a subject dosed a second time for an attack prior to the time point of interest (30 minute, 1, 4, 24, 48) then the subject's migraine attack is not included in subsequent analyses.

The proportion of migraine attacks at each time point will also be summarized by month (1-12). Month will be derived using a window based on the Day 0 or Baseline visit date (Visit 2). Months 1 through 5 will be defined using 30-day increments with an additional 7-day allowance from the baseline date. Months 6 through 12 will be defined using 30-day increments with an additional 14-day allowance. The table below outlines the windows.

Table 3: Month Window

Month	**Target Day**	**Window in Days**
1	30	0 - 37
2	60	38-67
3	90	68-97
4	120	98-127
5	150	128-157
6	180	158-194
7	210	195-224
8	240	225-254
9	270	255-284
10	300	285-314
11	330	315-344
12	360	345-374
13	390	375-404
14	420	405-434
15	450	435-464
16	480	465-494
17	510	495-524
18	540	>524

Migraine attacks will be slotted into each month based on the dates of the attacks.

The proportion of pain free migraine attacks by month will also be summarized in the 6-Month Completers Mk2, 6-Month Completers Mk1/Mk2, 12-Month Completers Mk2, 12-Month Completers Mk1/Mk2 safety, and All Expansion Subjects populations.

6.4.2. Freedom from MBS

Most bothersome symptom will be collected at the onset of each migraine attack immediately before drug administration, at 30 minutes post dose, and at 1, 2, 4, 24, and 48 hours post dose. The 30 minute and 1 hour time points were added after the start of the study, and therefore, not all attacks will have these time points.

The endpoints for freedom from MBS are:

- Attacks with freedom from MBS at 30 minutes, 1, 2, 4, 24 and 48 hours post dose
- Attacks with freedom from MBS at 30 minutes, 1, 2, 4, 24, and 48 hours post dose by month

The proportion of attacks free from MBS at 2 hours post dose will be defined as attacks where the following is available: a baseline MBS response (photophobia, phonophobia, or nausea), the symptom selected at baseline is not present at 2 hours post dose, and no rescue medication use or a second dose of study medication prior to 2 hours post dose. The percentage will be based on the number of treated migraine attacks, i.e., a subject may be counted more than once in the summary.

Freedom from MBS at 30 minutes, 1, 4, 24, and 48 hours post dose will be defined and summarized in the same manner as 2 hours post dose; however, if a subject dosed a second time for an attack prior to the time point of interest (30 minute, 1, 4, 24, 48) then the subject's migraine attack is not included in subsequent analyses. Summaries by study month will use the derived month windows described in section 6.4.1.

The proportion of MBS free migraine attacks by month will also be summarized in the 6-Month Completers Mk2, 6-Month Completers Mk1/Mk2, 12-Month Completers Mk2, 12-Month Completers Mk1/Mk2 safety, and All Expansion Subjects populations.

6.4.3. Relief from Headache Pain

Relief from headache pain will be derived from headach pain severity which is collected as noted in Section 6.4.1. Relief from headache pain at 2 hours post dose will be defined as attacks where the following is available: a baseline pain severity response, a non-missing response at 2 hours post dose, relief from headache pain as defined in Section 3, and no use of rescue medication or a second dose of study medication prior to 2 hours post dose. The percentage will be based on the

number of treated migraine attacks, i.e., a subject may be counted more than once in the summary.

The endpoints for relief from headache pain are:

- Attacks with relief from headache pain at 30 minutes, 1, 2, 4, 24 and 48 hours post dose
- Attacks with relief from headache pain at 30 minutes, 1, 2, 4, 24, and 48 hours post dose by month

Relief from headache pain at 30 minutes, 1, 4, 24, and 48 hours post dose will be defined and summarized in the same manner as relief from headache pain at 2 hours; however, if a subject dosed a second time for an attack prior to the time point of interest (30 minute, 1, 4, 24, 48) then the subject's migraine attack is not included in subsequent analyses. Summaries by study month will use the derived month windows described in section 6.4.1.

The proportion of relief from headache pain migraine attacks by month will also be summarized in the 6-Month Completers Mk2, 6-Month Completers Mk1/Mk2, 12-Month Completers Mk2, 12-Month Completers Mk1/Mk2 safety, and All Expansion Subjects populations.

6.4.4. Freedom from Photophobia, Phonophobia, and Nausea

Presence of photophobia, phonophobia, and nausea will be collected at the onset of each migraine attack immediately before drug administration (time 0), at 30 minutes post dose, and at 1, 2, 4, 24, and 48 hours post dose. The 30 minute and 1 hour time points were added after the start of the study, and therefore, not all attacks will have these time points.

The proportion of attacks with freedom from photophobia, phonophobia, and nausea will be summarized individually for each time point (30 minute, 1, 2, 4, 24, and 48 hours post dose).

6.4.5. Sustained Freedom from Headache Pain and MBS

Sustained freedom from headache pain is defined as free from headache pain at 2 hours post dose (as defined in Section 6.4.1) and remaining free of headache pain at 24 or 48 hours (as defined in Section 3). Rescue medication use will be based on observed data; therefore, if the subjects has no recorded rescue medications, then the subject is assumed to have no rescue medication use. Sustained freedom from headache pain at 24 and 48 hours will be analyzed overall and summarized by month using the windows described in Section 6.4.1.

Sustained freedom from MBS is defined and summarized in the same manner as above using the derivation of freedom from MBS as described in Section 6.4.2.

The proportion of sustained freedom from headache pain and MBS migraine attacks will also be summarized in the 6-Month Completers Mk2, 6-Month Completers Mk1/Mk2, 12-Month Completers Mk2, and 12-Month Completers Mk1/Mk2 safety populations.

6.4.6. Rescue Medications

Rescue medications will be reported in the e-diary under the Headache Medication Diary category throughout the study. The number of subjects using rescue medications and the number of migraine attacks requiring rescue medications within 24 and 48 hours post dose will be summarized using frequencies and percentages.

The number of subjects and the number of migraine attacks using a second dose of study medication within 24 and 48 hours post dose will also be summarized.

These summaries will also be performed on the All Expansion Subjects Population.

6.4.7. Frequency of Migraine Attacks

Migraine attacks are logged in the subjects' diaries throughout the study. The number and percentage of migraine attacks treated with STS101, as well as the total number of migraine attacks reported will be summarized by month using the windows described in Table 2, Section 6.4.1.

6.4.8. Relapse in Headache Pain

Headache relapse within 24 and 48 hours post dose will be defined as described in Section 3. Rescue medication or second dose use will not be considered a relapse.

6.4.9. Functional Impairment Scale

FIS will be collected at the onset of each migraine attack immediately before drug administration, at 30 minutes post dose, and at 1, 2, 4, 24, and 48 hours post dose. The 30 minute and 1 hour time points were added after the start of the study; therefore, data prior to the 2-hour time point will not be available for all subjects.

The endpoints of interest for FIS are:

- FIS distribution of attacks at 30 minutes, 1, 2, 4, 24, and 48 hours post dose
- FIS distribution of attacks at 30 minutes, 1, 2, 4, 24, and 48 hours post dose by month

The FIS distribution of attacks at each post dose time point will be summarized by month using the windows described in Table 2 of Section 6.4.1.

6.4.10. 24-hour Migraine Quality of Life Questionnaire

24-MQoL will be collected 24 hours after drug administration for one treated migraine attack per month. The questionnaire has 5 domains. They are work functioning, social functioning, energy/vitality, migraine symptoms, and feelings/concerns. The total score and domain

algorithms are defined in Section 3. The total score and domain scores will be summarized using descriptive statistics by month using the windows described in Section 6.4.1.

6.4.11. Subject Impression Questions

Subject impression questions were asked at Months 3, 6, and 12 and are listed below.

- Patient Global Impression (PGI)
- Ease of Use
- Patient Likelihood of Use of Study Medication if it were available
- Comparison of Study Medication with Previously Used Migraine Medication
- Consistency of Study Medication Effect (Month 12 only)

Responses to these questions will be summarized at each evaluation month using frequencies and percentages.

6.4.12. Headache Impact Test

The HIT-6 questionnaire will be performed at baseline, Months 3, 6, and 12 to assess the impact of the headaches on daily life. The total score will be derived as described in Section 3. The HIT-6 score will be summarized using descriptive statistics for observed and change from baseline values at baseline and each evaluation month.

The HIT-6 total score will also be derived as a categorical variable as defined in Section 3. The shifts in impact from baseline will also be summarized for each month.

6.4.13. Healthcare Resource Utilization

Healthcare resource utilization questions will be asked at baseline and at each post baseline visit. Subjects reported the number of times they used the following resources for migraines:

- office-based consultations
- office-based consultations with a specialist
- visits to urgent care, emergency department, or infusion center
- hospitalizations, overnight hospital/emergency department stays
- diagnostic services, i.e., MRI, CT, other

Each of these questions will be summarized using descriptive statistics. The change from baseline at each post baseline visit will also be included. Subject responses will be presented in a data listing.

6.4.14. Subgroup Analyses

Subgroup analyses will be conducted on the efficacy analyses of the freedom from headache pain at 2 hours, freedom from MBS at 2 hours, and relief from headache pain at 2 hours to gain insight of the nature and consistency of the treatment effect. Baseline migraine severity (Mild, Moderate, Severe) is the only planned subgroup. However, analysis by additional subgroups may be considered.

6.5. Interim Analysis

Two interim analyses are planned for this study. The first interim analysis will be conducted based on a data cut date of December 31, 2021. The second interim analysis will be conducted based on a data cut date of June 30, 2022.

There are no formal statistical analyses performed in this study since it is an open-label study; therefore, there is no impact on the final analysis.

7. TABLES, LISTINGS, AND FIGURES

Data listings will be sorted by subject number 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 treatment. Descriptive statistics such as mean, median, minimum, and maximum will generally 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, if applicable, 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.

Satsuma STS101-003 Final SAP 19Sep2022

Final Audit Report 2022-09-23

Created:	2022-09-20
By:	Shelia Ligozio (shelia.ligozio@instat.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAuCwGxdwtMjpV9GLCg0wsTD9rxrRZPcTI

"Satsuma STS101-003 Final SAP 19Sep2022" History

Document created by Shelia Ligozio (shelia.ligozio@instat.com)
2022-09-20 - 1:26:35 PM GMT

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Signature Date: 2022-09-20 - 1:27:52 PM GMT - Time Source: server

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Document e-signed by Michelle Secic (consult@secicstats.com)
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