CLINICAL STUDY PROTOCOL

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

Study Number: STS101-003

Investigational Drug: STS101 (Dihydroergotamine Nasal Powder)

IND Number: 136585

Sponsor: Satsuma Pharmaceuticals, Inc.
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Version History:

Version 6	November 24, 2021
Version 5	June 30, 2021
Version 4	November 6, 2020
Version 3	September 25, 2020
Version 2	May 11, 2020
Version 1	March 31, 2020

SIGNATURE PAGE (SPONSOR)

I have read and understand the contents of this protocol and agree to meet all obligations of Satsuma Pharmaceuticals, Inc. as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Principal Investigator is informed of all relevant information that becomes available during the conduct of the study.

Detlef Albrecht, MD

Digitally signed by Detlef Albrecht, MD
Date: 2021.12.08 08:59:49 -08'00'

Detlef Albrecht, MD **Date**
Chief Medical Officer
Satsuma Pharmaceuticals, Inc.

PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with ICH Good Clinical Practices (GCP) and all other applicable regulations. I will inform all who assist me in the conduct of this study of their responsibilities and obligations. Furthermore, I understand that the Sponsor and the Institutional Review Board/Ethics Committee (IRB/EC) must approve any changes to the protocol in writing before implementation, unless a deviation is required to eliminate an immediate safety hazard to a subject. In such cases the Sponsor and the IRB/EC will be notified as soon as possible.

Principal Investigator Signature **Date**

Principal Investigator Name (print)

Site Name

PROTOCOL SYNOPSIS

Sponsor/Company	Satsuma Pharmaceuticals, Inc.
Investigational Product	STS101 (Dihydroergotamine nasal powder)
Active Ingredient	Dihydroergotamine mesylate
Protocol Number	STS101-003
Title of Study	An Open-Label, 12-Month Study to Evaluate the Safety and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine
Study center(s)	Approximately 50 US sites
Objectives	***Primary*** • To assess the safety and tolerability of STS101 in the acute treatment of migraine attacks over 12 months. ***Secondary*** • To describe the efficacy of STS101 in the acute treatment of migraine attacks over 12 months.
Methodology	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). 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. Subjects of the original cohort (enrolled before June 30, 2021) will be offered to continue use of study medication for another 6 months after the completion of the original 12-month period. Only safety data will be collected during this addtioanal period. 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 ECGs 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.
Number of subjects (planned)	A total of approximately 480 adult male and female subjects (18 to 65 years of age) with migraine. At least 150 and 50 subjects are planned to complete at least 6 and 12 months, respectively. Approximately 20 subjects are expected to complete 18 months.
Inclusion criteria	1. Males or females, 18-65 years of age at the time of Screening Visit 2. Signed Informed Consent Form 3. Subject has at least 1-year history of migraines (with or without aura), according to the International Classification of Headache Disorder, 3rd Edition (ICHD3), including the following: a. Migraine onset before the age of 50 years b. History of 4 - 12 migraine attacks per month in each of the 3 months prior to Screening Visit c. History <15 headache days per month in each of the 3 months prior to Screening Visit 4. Female subjects will be included if they are post-menopausal (at least 1 year since last menses with an FSH >40 IU/mL) or surgically sterilized; or if they are of childbearing potential, they are not breastfeeding, have a negative pregnancy test, have no intention of becoming pregnant during the course of the study, and are using one of the following medically acceptable contraceptive methods during the course of this study: a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to screening (Visit 1) b. Simultaneous use of male condom with intravaginally applied spermicide and diaphragm c. Simultaneous use of male condom and hormonal contraceptives started at least 4 weeks prior to screening (Visit 1) d. Surgical sterilization of their partner(s) at least 6 months prior to screening (Visit 1) 5. Intact nasal mucosa (Appendix C), Objective Assessment of Nasal Symptoms: no ulceration; no bleeding; no or mild erythema, no or mild swelling and no or mild rhinorrhea) at baseline (Visit 2) 6. Willing and able to comply with the requirements of the protocol and follow directions from the clinic staff

Exclusion criteria	1. Pregnant or breast-feeding women 2. Women of child-bearing potential not using or not willing to use highly effective contraception 3. Diagnosis of headache conditions other than migraine with or without aura, including but not limited to diagnosis of basilar migraine (aka migraine with brainstem aura) or hemiplegic migraines, medication overuse headache or cluster headache 4. Clinically significant abnormal physical findings at the screening or baseline examination which would interfere with the objectives of the study 5. History of coronary artery disease, coronary artery vasospasm (including Printz-metals' angina), clinically significant arrhythmia or, peripheral vascular disease, ischemic disease (e.g., Raynaud's syndrome, ischemic bowel syndrome, angina pectoris, myocardial infarction, or documented silent ischemia); percutaneous coronary intervention, or cardiac surgery for complications from ischemic heart disease 6. History of cerebrovascular disease, including but not limited to stroke, transient ischemic attack, cerebral hemorrhage, subarachnoid hemorrhage 7. Presence of two or more of the following cardiovascular risk factors: a. Diagnosis of hypertension or receiving antihypertensive medication for treatment of hypertension b. Diagnosis of hypercholesteremia, or LDL >159 mg/dL or receiving cholesterol lowering medication c. Obesity (BMI > 31) d. Diabetes mellitus e. Family history of premature coronary artery disease (in male first-degree relatives < 55 years or female first-degree relatives < 65 years) f. Females who are surgically or physiologically postmenopausal g. Males over age 45 8. Clinically significant abnormal laboratory values (as determined by the Principal Investigator) at screening (Visit 1) or Baseline (Visit 2). 9. Severely impaired hepatic function (liver function tests ALT or AST greater than 2 times upper limit of normal) or renal function (serum creatinine greater than 1.5 times the upper limit of normal) at screening (Visit 1) or Baseline (Visit 2).

	10. Screening 12-lead ECG showing any clinically significant abnormalities at screening (Visit 1) or Baseline (Visit 2). 11. Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, at screening (Visit 1) or Baseline (Visit 2). 12. Diagnosis of major depression with current symptoms, psychosis, alcohol abuse or dependence, drug abuse or dependence, major psychiatric conditions (e.g., schizophrenia, psychosis or Bipolar disorder), or dementia. Other significant neurological or psychiatric disorders (including other pain syndromes or risk of suicide) that in the opinion of the investigator might interfere with study participation and assessments or subject safety 13. Any clinically significant symptoms or conditions, including but not limited to central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic or gastrointestinal conditions or history of such conditions that, in the opinion of the investigator might interfere with study assessments or subject safety 14. Participation in another drug research study within 30 days of screening (Visit 1) or within less than 5 half-lives of tested drug (whichever is longer). Note: Subjects who have participated in study STS101-002 are exempt from this. 15. Concomitant use of potent CYP3A4 inhibiting medications, for example protease inhibitors (e.g., ritonavir, nelfinavir, indinavir, saquinavir, tipranavir, lopinavir, atazanavir, darunavir), macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin), or strong imidazole antifungals (e.g., ketoconazole, and itraconazole) 16. Previously shown hypersensitivity to ergot alkaloids or the inactive ingredients of STS101 (microcrystalline cellulose, hydroxypropyl methylcellulose, mannitol) 17. Concomitant use of more than two preventive migraine medications 18. Concomitant daily use of peripheral and central vasoconstrictors including but not limited to amphetamines, phenylephrine, pseudoephedrine, propranolol and nicotine (from smoking, vaping or smokeless products) 19. Score of >0 on any of the questions 1-14 of the Sheehan Suicidality Tracking Scale
Investigational product, dosage and mode of administration	STS101 (DHE nasal powder) as 5.2 mg STS101

Duration of study	• Screening period: Up to 30 days • Treatment & follow up period: Up to 12 months; Subjects of the original cohort (enrolled before June 30, 2021) will be offered to continue use of study medication for another 6 months after the completion of the original 12-month period for a total of up to 18 months.
Criteria for evaluation	***Efficacy Endpoints*** • Proportion of subjects free from headache pain (defined as moderate or severe headache pain becoming none on a 4-point scale) at 30 and 60 minutes, 2, 4, 24 and 48 hours post dose • Proportion of subjects free from most bothersome symptom (MBS) (defined as the MBS identified prior to dosing being absent) at 30 and 60 minutes, 2, 4, 24 and 48 hours post dose • Proportion of subjects with relief from headache pain at 30 and 60 minutes, 2, 4, 24 and 48 hours post dose (defined as reduction in headache pain from moderate or severe [2 or 3 on a 4-point scale]) to mild or none [0 or 1 on a 4-point scale]) • Proportion of subjects free from headache pain at 30 and 60 minutes, 2, 4, 24 and 48 hours post dose by study month • Proportion of subjects free from most bothersome symptom (MBS) (defined as the MBS identified prior to dosing being absent) at 30 and 60 minutes, 2, 4, 24 and 48 hours post dose by study month • Proportion of subjects with headache relief at 2 hours post dose by study month • Proportion of subjects free from headache pain at 2 hours post dose and remain headache free at 24 hours post dose by study month • Frequency of migraine headaches treated with STS101 by study month • Frequency of migraine headaches by study month • Proportion of subjects with headache relapse within 48 hours post dose (defined as the return of headache of any severity within 48 hours after administration of the investigational drug, when the patient was pain-free at 2 hours after investigational drug administration) • Mean change in scores on Functional Impairment Scale (FIS) by study month. • Mean change in scores on 24-hour Migraine Quality of Life Questionnaire by study month. • Satisfaction with treatment questions • Mean change from baseline in HIT-6

	Safety Endpoints The following endpoints will be analyzed: • Physical examination • Vitals signs and body weight • 12-lead ECG • Subjective nasal symptom assessment • Objective nasal symptom evaluation • Smell Identification Test • Blood tests for hematology and biochemistry analysis (including liver function, renal function, thyroid function, electrolytes) • Urinalysis • Adverse events (AEs) • Documentation of concomitant medications
Statistical methods	***Efficacy*** Efficacy data will be summarized using descriptive statistics. Unless otherwise specified, for numeric data, 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., proportion of responders) will be presented using absolute and relative frequency counts and percentage. No formal hypotheses testing is planned for this study. When appropriate, exploratory hypotheses testing may be conducted at the significance level of 0.05. No adjustment for multiplicity will be employed. Data from all investigator center will be pooled. Missing data will not be imputed. For categorical efficacy endpoints (#1 - #10, and #13 as numbered in Section 8.3.2.1), frequencies and percentages of each category will be tabulated. For endpoints #1 - #7, and #10, the analysis will be a responder analysis with the responder defined by meeting the criteria for respective endpoints. For responder analysis, the proportions of responders and their 95% confidence intervals will be presented. For continuous efficacy endpoints #11, #12, and #14, the change from baseline will be summarized descriptively. Exploratory hypothesis testing of the mean change from baseline may be conducted using the paired t-test.

	Safety All adverse events and serious adverse events will be collected starting with the signining of the Informed Consent Form at Visit 1. All adverse events reported or observed will be listed, documenting course, severity, start and stop date, possible relationship to study medication, action taken, and outcome. Verbatim terms will be classified to preferred terms and related system organ class using the MedDRA dictionary. All reported adverse events will be summarized by the number and percentage of subjects reporting adverse events, system organ class, preferred term, severity and relationship to study drug. Descriptive statistics will be used to summarize safety labs including complete blood count (CBC), chemistry and urinalysis, physical and nasal exams, vital signs and 12-lead ECG, subjective nasal symptom assessment and the Smell Identification Test. Tabulations of out-of-range findings and changes from pre-dose to post-dose will be provided.

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List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Explanation
24-MQoL	24-hour Migraine Quality of Life Questionnaire
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAT	computer assisted tomography
CBC	Complete Blood Count
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence Interval
CM	Concomitant Medication
C_{max}	Maximum Observed Plasma Concentration
CRF	Case Report Form
DHE	Dihydroergotamine
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e-diary	Electronic diary in handheld device
FDA	Food and Drug Administration
FIS	Functional Impairment Scale
FIS	Functional Impairment Scale
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HPMC	Hydroxypropyl Methylcellulose
HR	heart rate
ICF	Informed Consent Form
ICHD-3	International Classification of Headache Disorders, 3rd edition
IM	Intramuscular
IN	Intranasal
IRB	Institutional Review Board
ITT	The intent-to-treat
IV	Intravenous

Abbreviation or specialist term	Explanation
MBS	most bothersome symptom
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
Mitt	modified intent-to-treat
MRI	magnetic resonance imaging
NOAEL	No Observed Adverse Effect Level
PK	Pharmacokinetic
PP	per protocol
PT	Preferred Term (in MedDRA dictionary)
QTcF	QT corrected with the Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SIT	Smell Identification test
SOC	System Organ Class (in MedDRA dictionary)
S-STS	Sheehan Suicidality Tracking Scale
$T_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Events
T_{max}	Time to reach C_{max}
VAS	Visual Analog Scale
WHO Drug	World Health Organization Drug Dictionary

STUDY PROTOCOL REVISION HISTORY

Changes in Version 6 (November 24, 2021)

- **Synopsis, Methodology (page 4-5 & 8); Section 2 Study Objectives and Purpose (page 31) Section 3.1 Overall Study Design and Plan (page 32); Section 3.2 Study Procedure Description (pages 32-36); Section 3.3 Schedule of Observations and Procedures (pages 40-42); Section 4 Selection and Withdrawal of Subjects (page 43); Section 6.1 Efficacy Evaluation Parameters (page 49); Section 8.1 Sample Size Determination (page 57); Appendix A Schedule of Evaluations (pages 67-68)**

Allow subjects of the original cohort (enrolled and Visit 2 date before June 30, 2021) to continue study for another 6 months after completion of 12-month study.

Rationale:

Satsuma would like to collect addtional safety data for up to 18 months. Moreover, 12-month data in at least 50 subjects using the second generation STS101 device on average 2 times per month may be required by the FDA for approval. Subjects of the original cohort who already switched to the second generation device before June 20, 2021 have a high likelihood of providing that data in time for the STS101 NDA.

Changes in Version 5 (June 30, 2021)

- **Synopsis, Methodology (page 4); Number of Subjects (page 5); Section 3.1 Overall Study Design and Plan (page 32); Section 4 Selection & Withdrawal of Subjects (page 41); Section 8.1 Sample Size Determination (page 55)**

Number of enrolled subjects changed from 300 to 480.

Rationale:

The FDA requested from Satsuma in December 2018 to provide repeated use data for STS101 for at least 150 subjects using STS101 on average 2 times per month for at least 6 months. Due to a higher than expected drop out rate a 6 six months, and the introduction of a second generation device an additional 180 subjects need to be enrolled and assigned study study medication.

- **Synopsis (page 7) and Section 4.2 Subject Exclusion Criteria (page 43)**

Added Exclusion Criteria #19: Score of >0 on any of the questions 1-14 of the Sheehan Suicidality Tracking Scale

Rationale:

FDA requirement to explore treatment emergent suicidal ideation and behavior for drugs in neurological indications.

- **Section 3.2.15 Sheehan Suicidality Tracking Scale (page 36); Section 3.3.1 Screening Visit (page 36); Section 3.3.2 Baseline Visit (page 37); Section 3.3.3 Visits 3 & 4 (page 38); Section 3.3.4 Visit 5 (page 38); Section 3.3.5 Visits 6 & 7 (page 39); Section 3.3.6 Visit 8 (page 39); Section 3.3.7 Visits 9 & 10 (page 40); Section 3.3.8 Final Visit/Early Termination (page 40); Section 7.1.1.7 Sheehan Suicidality Tracking Scale (page 51); Section 8.3.3.8 Safety Analysis - Sheehan Suicidality Tracking Scale (page 58); Appendix A Schedule of Evaluations (page 65); Appendix F Sheehan Suicidality Tracking Scale (page 72)**

Added completion of Sheehan Suicidality Tracking Scale at all study visits and analysis of data in safety analysis.

- **Section 5.3 Investigational Product Storage (page 45)**

Changed storage temperature from 15-25°C or 59°F-77 to 2-30ºC or 36-86°F.

Rationale:

Company expanded storage temperature range based on new data from long term stability studies.

- **Section 3.2.7 Vital Signs (page 33); Section 3.3.1 Screening Visit (Visit 1; Day-30 to Day -1) (page 36); Section 3.3.2 Baseline Visit (Visit 2; Day 0) (page 37); Section 3.3.3 Visits 3 & 4 (Month 1 and 2) (page 38); Section 3.3.4 Visit 5 (Month 3) (page 38); Section 3.3.5 Visits 6 & 7 (Month 4 & 5) (page 39); Section 3.3.6 Visit 8 (Month 6) (page 39); Section 3.3.7 Visits 9 & 10 (Month 8 & 10) (page 40); Section 3.3.8 Final Visit/Early Termination (Visit 11; Month 12) (page 40); Section 7.1.1.3 Vital Signs (page 50)**

Deleted oral as method for measuring body temperature.

Rationale:

No contact temperature taking allowed due to COVID-19 pandemic.

Changes in Version 4 (November 6, 2020)

- **Synopsis, Methodology, page 4; Efficacy Endpoints, page 8; Section 3.1 Overall Study Design and Plan, page 30; Section 6.1.1 Migraine Headache Pain Severity, page 45; Section 6.1.2 Most Bothersome Symptom, page 45; Section 6.1.4.1 Functional Impairment Scale, page 46**

Added evaluations of migraine headache pain severity, most bothersome symptom and functional impairment scale at 30 and 60 minutes after dosing

- **Section 6.2.1 Patient Global Impression, page 46**

Added evaluation at Visit 5 (Month 3)

- **Section 6.2.2 Ease of Use Impression, page 46**

Added evaluation at Visit 5 (Month 3)

- **Section 6.2.3 Likelihood of Use Question, page 46**

Added evaluation at Visit 5 (Month 3)

- **Section 6.2.4 Consistency of Study Medication Question, page 47**

Changed section name to **6.2.4 Comparison of study medication with previously used migraine medication**. Replaced original question with this text:

The study subjects will be asked to compare the effects of the study medication with their previously used migraine medication after 3, (Visit 5), 6 (Visit 8), and 12 (Visit 11/early term) months with answers to these four statements:

Compared to my previous migraine medication, STS101 (the study medication)

1. Allows me to return to normal faster
2. More consistently treats my Migraine
3. Works faster
4. Keeps migraine from coming back

The answer options for all four statements are: strongly agree; agree; neutral; disagree; strongly disagree

Changes in Version 3 (September 25, 2020)

- **Synopsis, Investigational Product, page 7; Section 1.5, Rationale for Dosing Frequency, pages 25-27; Section 5.1 Description of Investigational Product and Packaging, page 41; Section 5.2 Investigational Product Labeling, page 41; Section 5.9.1 Subject Randomization, page 43**

3.9 mg dose strength dropped from study.

Rationale: Phase 3 efficacy study STS101-002 showed better efficacy for the 5.2 mg dose strength versus the 3.9 mg dose strength without significant differences in adverse events.

- **Section 5.1 Description of Investigational Product and Packaging, page 41; Section 3.3.3 Visits 3 & 4 (Month 1 & 2), page 35; Section 5.4 Investigational Product Administration and Training, page 42; Schedule of Evaluations, page 62**

Investigational Product administration training added at Visits 3 and 4

Rationale: Additional training is expected to result in better administration technique and fewer IP administration errors.

- **Section 3.2.11 Clinical Laboratory Test, page 32; Section 3.3.2 Baseline Visit (V2, Day 0), page 34**

Added clarification that subject should be instructed to withhold study medication until the site has reviewed the Visit 2 laboratory results and confirmed the subject's eligibility.

Rationale: Avoid study drug use by subjects who are not eligible

- **Synopsis, Statistical Methods Safety, page 10; Section 3.3.1 Screening Visit (V1, Day30 to Day -1), page 33; Section 3.3.2 Baseline Visit (V2, Day 0), page 34; Section 7.2. Adverse Events, page 49; Section 8.3.3.2 Safety Analysis - Adverse Events, page 54; Schedule of Evaluations, page 62**

AE collection will begin after the signing of the Informed Consent Form (Visit 1)

Rationale: Subjects will administer placebo/MCC filled devices during administration training starting at Visit 1.

Changes in Version 2 (May 11, 2020)

- **Synopsis, Number of Subjects, page 5; Section 4, Selection and Withdrawal of Subjects, page 36; Section 8.1, Sample Size Determination (page 52)**

Clarification that at least 150 and 50 subjects are planned to complete 6 and 12 months of treatment, respectively.

- **Synopsis, Exclusion Criteria, page 7; Section 4.2, Exclusion Criteria, page 38**

Changed note in Exclusion criterion #14 to clarify that subjects who have participated in study STS101-002 are exempt from this exclusion.

- **Synopsis, Duration of study, page 7); Section 3.3.1, Screening Visit, page 31; Appendix A, Schedule of Evaluations (page 62)**

Changed maximum duration of screening period to 30 days.

- **Section 1.5, Rationale for Dosing Frequency, pages 24 and 25**

Added 2 times 3.9 mg STS101 to dosing frequency rationale.

- **Section 3.3.2, Baseline Visit (Visit 2; Day 0), page 33**

"Weight" and "Documentation of Health Care resource utilization (HCRU) in 6 months before screening" was added to list of procedures. Both procedures were inadvertently omitted in previous version.

- **Section 3.3.3, Visits 3 & 4 (Month 1 and 2), page 32; Section 3.3.4, Visit 5 (Month 3), page 33; Section 3.3.5, Visits 6 & 7 (Month 4 and 5), page 33; Section 3.3.6, Visit 8 (Month 6), page 34; Section 3.3.7, Visits 9 & 10 (Month 8 and 10), page 34; Section 3.3.8, Final Visit/Early Termination Visit (Visit 11; Month 12), page 35**

"Weight" and "Documentation of Health Care resource utilization since last visit (HCRU)" was added to list of procedures. Both were inadvertently omitted in previous version. Both procedures were inadvertently omitted in previous version.

- **Section 3.3.1, Screening Visit (Visit 1; Day-15 to Day -1), page 31; Section 3.3.2, Baseline Visit (Visit 2; Day 0); Section 3.3.4, Visit 5 (Month 3), page 33; Section 3.3.6, Visit 8 (Month 6), page 34, and Section 3.3.8, Final Visit/Early Termination Visit (Visit 11; Month 12), page 35**

Deleted "Urine drug and alcohol screen" since this procedure is not part of the protocol.

- **Section 3.3.3, Visits 3 & 4 (Month 1 and 2), page 32**

Added "Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments" to list of procedures. Procedure was inadvertently omitted in previous version.

- **Section 3.3.7, Visits 9 & 10 (Month 8 and 10), page 34**

Added "Clinical laboratory tests and urinalysis" to list of procedures. Procedures were inadvertently omitted in previous version.

- **Appendix A, Schedule of Evaluations, page 62**

"Health Care Resource Utilization" added to Schedule of Evaluations

1. BACKGROUND INFORMATION

1.1. Introduction

Satsuma Pharmaceuticals, Inc. (Satsuma) is developing STS101 (dihydroergotamine nasal powder), a drug-device combination of a dihydroergotamine (DHE) mesylate dry powder formulation prefilled in a single use delivery device for nasal administration. DHE mesylate is currently indicated for the acute treatment of migraine headaches with or without aura and the acute treatment of cluster headache episodes. DHE mesylate is available as a solution for subcutaneous (SC), intramuscular (IM), or intravenous (IV) administration and as a nasal spray (IN) (D.H.E. 45® Prescribing Information 2017; Migranal® Prescribing Information 2017).

DHE mesylate is a semi-synthetic derivative of ergotamine tartrate that has been used effectively to treat migraine since 1945 (Silberstein 2003) and was first approved in U.S. in 1946. The antimigraine activity of DHE mesylate is likely related to the agonist activity at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors (Dahlöf 2012). Additionally, DHE mesylate can cause vasoconstriction by blocking CGRP release, by stimulating adrenergic $\alpha_{2A/2c}$ and 5-HT_{2A} receptors and may inhibit neurogenic inflammation in peripheral meningeal tissues and nociceptive neuronal transmission centrally in the trigeminal nucleus caudalis (Burstein 2004; Dahlöf 2012; González-Hernández 2018; Hoskin 1996; Silberstein 2003;). The DHE mesylate-related side effects of nausea and vomiting are likely related to activation of central 5-HT_{1A} receptors and dopamine D_2 receptors (Silberstein 2003).

DHE mesylate is listed as first-line treatment in migraine treatment guidelines from the American Academy of Neurology (Marmura 2015). The effectiveness of DHE mesylate via intravenous, intramuscular, subcutaneous, intranasal and orally inhaled administration routes has been demonstrated (Aurora 2011; Carleton 1998; Edwards 2001; Gallagher 1996; Raskin 1986; Winner 1996). In these studies, treatment with DHE mesylate has consistently resulted in headache relief in 50 to 70% of the treated patients at 2 hours after administration.

However, patient acceptance of DHE mesylate has been limited due to these shortcomings:

- D.H.E.45® (Injectable DHE mesylate solution)
  - Inconvenience and side effects of administration by injection (IV, IM, SC)
  - DHE mesylate-related side effects, especially nausea, which is likely related to rate of administration (IV) and C_{max} and has been reported to occur less frequently when plasma concentrations remain below 6-10 ng/mL (Cook 2009)
- Migranal® (DHE mesylate intranasal spray)
  - Inconvenient multi-step procedure of vial opening, spray device-to-vial assembly, and priming (Migranal® Administration Instructions 2017)
  - Inconvenient administration procedure requiring four 0.125 mL sprays (two in each nostril, repeated after 15 minutes) (Migranal® Prescribing Information 2017) and Migranal® Administration Instructions 2017)

- Low and variable bioavailability (Migranal® Prescribing Information 2017; Tfelt-Hansen 2013)
- Slow onset of action (Tfelt-Hansen 2013)
- Drug run off into the pharynx and out of the nose (Djupesland 2013)
- Side effect of bad or altered sense of taste (Migranal® Prescribing Information 2017; van der Kuy 1999).

STS101 (DHE nasal powder) is designed and being developed to address the shortcomings of the injectable and intranasal DHE mesylate formulations:

- STS101 is designed to be easy and convenient for patients to quickly self-administer during a migraine attack.
- STS101 is rapidly and consistently absorbed with T_{max}, C_{max} and AUC values falling within ranges that have previously been established to be effective for DHE mesylate.
- Consistent with DHE mesylate effectiveness data reported in multiple studies, STS101 treatment is expected to be effective in early and late treatment of migraines, in attacks with and without allodynia, and to result in high 24-hour pain-free and low 24-hour recurrence rates.

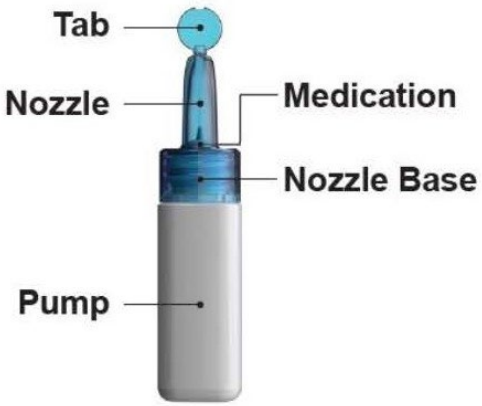
1.2. STS101 Description

STS101 is a drug-device combination product consisting of a powder formulation of DHE mesylate prefilled in a single use delivery device for intranasal (IN) administration.

1.2.1. STS101 Device

STS101 will be delivered by a pre-filled single use device, which is a manually operated and air driven device specifically designed for IN drug delivery (Figure 1).

Figure 1. STS101 Device



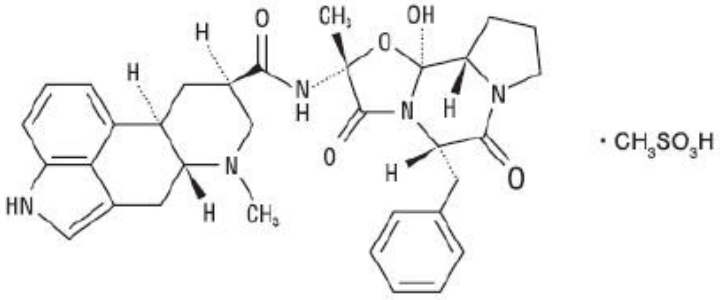
1.2.2. STS101 Powder Formulation

STS101 is a white to off-white powder formulation containing DHE mesylate, microcrystalline cellulose (MCC), hypromellose (hydroxypropyl methylcellulose, HPMC), and mannitol.

1.2.2.1. DHE Mesylate Information

DHE mesylate is a semi-synthetic derivative of ergotamine tartrate and is known chemically as ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl)-,(5′α)-,monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is $C_{34}H_{41}N_5O_8S$. The chemical structure is shown in Figure 2.

Figure 2. Dihydroergotamine mesylate chemical structure



1.2.3. DHE Mechanism of Action in the Treatment of Migraine

The antimigraine activity of DHE is likely related to the agonist activity at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors (Dahlöf 2012). Additionally, DHE can cause vasoconstriction via blocking CGRP release, by stimulating adrenergic $\alpha_{2A/2c}$ and 5-HT_{2A} receptors and may inhibit neurogenic inflammation in peripheral meningeal tissues and nociceptive neuronal transmission centrally in the trigeminal nucleus caudalis (Burstein 2004; Dahlöf 2012; González-Hernández 2018; Hoskin 1996; Silberstein 2003). The DHE mesylate-related side effects of nausea and vomiting are likely related to activation of central 5-HT_{1A} receptors and dopamine D_2 receptors (Silberstein 2003). Because of slow diffusion from the receptor biophase, the effects of DHE mesylate last far longer than can be expected from plasma concentrations (Dahlöf 2012; Tfelt-Hansen 2013).

1.2.4. STS101 DHE Pharmacokinetics

In a 2-part, three period, cross-over Phase 1 study, 15 healthy subjects were dosed with ascending doses of 1.3, 2.6 and 5.2 mg STS101 (equivalent to 1.5, 3.0, and 6.0 mg DHE mesylate USP). STS101 demonstrated dose dependent plasma concentrations. Table 1 shows selected PK parameters of Part 1 of the study.

Table 1. DHE PK Parameters, mean (±SD); STS101-001, Part 1

Parameter	STS101 (1.3 mg)	STS101 (2.6 mg)	STS101 (5.2 mg)
C_{max} (pg/mL)	645 (418)	1243 (576)	1870 (823)
T_{max} (h)	0.7 (0.28)	0.7 (0.47)	0.4 (0.12)
$AUC_{0\text{-}30min}$ (h*pg/mL)	188 (137)	362 (225)	606 (295)
$AUC_{0\text{-}2hr}$ (h*pg/mL)	956 (591)	1683 (719)	2549 (1132)
$AUC_{0\text{-}inf}$ (h*pg/mL)	4172 (1860)	7022 (2557)	10150 (3814)
$T_{1/2}$ (h)	12.9 (2.1)	12.6 (1.3)	12 (1.6)

Source: STS101-001 Data Tables, February 2019

In Part 2 of the study, 27 healthy subjects were dosed with 5.2 mg STS101 (equivalent to 6.0 mg DHE mesylate USP), 1.0 mg IM DHE mesylate, and 2.0 mg intranasal DHE mesylate spray in a randomized order. Table 2 shows selected PK parameters.

Table 2. DHE PK Parameters, mean (±SD); STS101-001, Part 2

Parameter	IM DHE Mesylate (1.0 mg)	Migranal (IN DHE Mesylate Spray 2.0 mg)	STS101 (DHE Nasal Powder 5.2 mg (Equivalent to 6.0 mg DHE Mesylate USP)
C_{max} (pg/mL)	3368 (840)	961 (727)	2175 (884)
T_{max} (h)	0.37 (0.3)	1.04 (0.4)	0.6 (0.4)
$AUC_{0\text{-}30min}$ (h*pg/mL)*	1357 (389)	152 (131)	686 (326)
$AUC_{0\text{-}2hr}$ (h*pg/mL)*	4791 (908)	1316 (990)	2979 (1147)
$AUC_{0\text{-}inf}$ (h*pg/mL)	13650 (2143)	6498 (3551)	12030 (4716)
$T_{1/2}$ (h)	11.2 (1.93)	12.7 (2)	11.8 (2.2)

Source: STS101-001 Data Tables, February 2019

Adverse events reported with STS101 use were all mild and mostly local nasal events such as discomfort, burning, or rhinorrhea, and taste sensations such as bitter or sour taste.

Additional information including detailed adverse event data may be found in the STS101 Investigator's Brochure.

1.2.5. DHE Clinical Experience

Migranal® (DHE mesylate intranasal liquid) and D.H.E. 45® (DHE mesylate injectable solution), approved in the United States in 1998 and 1946, respectively, have been prescribed to a large number of patients with migraine headaches. A detailed summary of human experience with marketed DHE mesylate formulations and other data regarding Migranal and DHE mesylate Injectable solution can be found in the STS101 Investigator's Brochure.

1.2.6. DHE Mesylate Pregnancy Category

DHE mesylate may cause fetal harm when administered to a pregnant woman. There are no adequate studies of DHE mesylate in human pregnancy, but developmental toxicity has been demonstrated in experimental animals. DHE mesylate possesses oxytocic properties and, therefore, should not be administered during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. DHE mesylate is designated Pregnancy Category X in the U.S (D.H.E. 45® Prescribing Information 2017; Migranal® Prescribing Information 2017).

1.3. Summary of Nonclinical Data

The nonclinical toxicology program for STS101 was designed to supplement the known nonclinical studies in support of the general safe use of DHE mesylate. In a GLP 14-day intranasal toxicology study with a 14-day recovery period conducted in dog, the presumed No Observed Adverse Effect Level (NOAEL) of DHE mesylate dose given to dogs (the most sensitive species) was approximately 49-fold more than the planned highest clinical dose of STS101 on a dose/weight (mg/kg) basis and 5-fold more based on a normalized nasal cavity surface area comparison. The results of the dog 14-day study support the presumption that the STS101 DHE mesylate formulation yields no new or unexpected significant toxicity at the highest feasible concentrations possible. The large safety multiples based on the NOAEL provide reassurance that the proposed human clinical dosing is reasonable and safe. The study is summarized in detail in the STS101 Investigator's Brochure.

1.4. Rationale for the Study

In the Phase 1 Study STS101-001, STS101 showed DHE plasma concentrations and PK parameters comparable to those previously reported for other DHE mesylate formulations and routes of administration (Humbert 1996; Schran 1994; Shrewsbury 2008). Based on the reported clinical efficacy data for these other DHE mesylate formulations and routes of administration, the PK profile of STS101 is assumed to be predictive of at least comparable clinical efficacy (Aurora 2011; Gallagher 1996; Winner 1996).

This study is being conducted as part of the clinical development program for STS101 to demonstrate the safety and tolerability of repeat dose use of STS101 for up to 12 months in the treatment of acute migraine attacks with or without aura.

1.5. Rationale for Dosing Frequency

The DHE dose of STS101 in study STS101-003 (5.2 mg, which is equivalent to 6.0 mg DHE mesylate, USP, respectively) is the dose selected for efficacy and safety evaluation in Phase 3. The dosing frequency takes into consideration the following:

- Plasma Exposure (PK) of DHE when administered as STS101
- Maximum daily/weekly doses per Prescribing Information for DHE by all routes
- Toxicology evaluations for systemic and local effects

The dosing schedule in Study STS101-003 will allow subjects to administer up to 2 doses of STS101 5.2 mg within a 24-hour period and up to 12 doses per month.

This use frequency is primarily based on the comparison of the plasma concentrations after STS101 5.2 mg with those after IV and IM injection of D.H.E 45® solution.

The table below provides comparison of the dosing frequency and PK data for STS101 5.2 mg and IV and IM DHE.

Table 3. Dosing frequency and PK data for STS101 5.2 mg, IV/IM/SC and IN DHE

Route of Administration	**IV**	**IM/SC**	**IN**	**STS101**
Dose per administration	1 mg	1 mg	2 mg	5.2 mg
Maximum dose per day/month	2/24 mg	3/24 mg	3/16 mg	2 x 5.2 mg 12 x 5.2 mg
Single dose C_{max} (pg/mL)	54,189	3368	961	2175
Single dose $AUC_{0\text{-}inf}$ (h*pg/mL)	12,894	13650	6498	12030

Source: STS101-001 Data Tables, February 2019; D.H.E. 45® Prescribing Information 2017; Kellerman 2013

The plasma concentrations and PK parameters after 5.2. mg STS101, specifically C_{max} and AUC, fall within boundaries of the PK of the approved injectable (IV, IM & SC) DHE regimen. Specifically, the maximum DHE plasma concentrations after 5.2 mg STS101 were below those for 1.0 mg DHE mesylate IM in Study STS101-001 (C_{max} of 2175 vs 3368 pg/mL, respectively) and well below maximum plasma concentrations reported after IV DHE mesylate (Kellerman 2013), providing a large margin of safety.

The Phase 1 study, STS101-001, did not identify any unexpected adverse events after administration of up to 5.2 mg STS101. As expected, most of the adverse events after STS101 were localized in the nose, rated as mild, transient, and not considered clinically relevant. The low scores in the subjective nasal symptom assessments and no significant findings in the objective nasal assessments further demonstrate the local tolerability of STS101. The incidences of DHE-related adverse events in the nose and taste sensations for 5.2 mg STS101 are comparable to those previously reported for Migranal (Migranal® Prescribing Information 2017).

In support of repeated dosing, the concentration-time profiles and pharmacokinetic parameters have been projected. The estimated C_{max} following 2 times 5.2 mg (re-dosed at 2 hours) is 3060 pg/mL compared to the observed C_{max} of 2175 pg/mL and 3368 pg/mL, after single doses of 5.2 mg STS101 and 1.0 mg IM DHE, respectively (STS101-001).

The estimated $AUC_{0\text{-}4h}$ following 2 times 5.2 mg (re-dosed at 2 hours) is 7800 pg*h/mL compared to the observed $AUC_{0\text{-}4h}$ (based on mean concentration-time profile) of 4810 and 7214 pg*h/mL following single doses of 5.2 mg STS101 and 1.0 mg IM DHE, respectively (STS101-001 Clinical Study Report, 2019 and subsequent simulations).

A total of two 5.2 mg administrations in a 24-hour period is therefore within the exposures that have been demonstrated to be safe and well tolerated with the approved injectable DHE product. DHE mesylate-related side effects, especially nausea, are unlikely to occur, as peak plasma concentrations are expected to not exceed 6000 pg/mL (Cook et al., 2009).

Additionally, repeated dosing of STS101 is within the margins of safety as established by a 2-week (i.e. 14 consecutive days) intranasal study in dogs (>20-fold based on mg/kg/day, ~5-fold based on DHE plasma AUC, and ~2-fold based on nasal cavity surface exposure; Study FY18-020b; see the Investigator's Brochure for more details on the nonclinical safety overages). Additionally, a 6-month toxicity study in dogs via nasal-only inhalation at doses up to 0.825 mg/kg/day resulted in minimal treatment related effects (Armer 2011).

When the total daily and total weekly allowances with approved DHE products and routes of administration are compared, the DHE mesylate amount for daily and weekly proposed frequency for STS101 is no greater than for oral DHE dosing (10 mg/day and 70 mg/week) Dihydergot Prescribing Information, 2011.

In conclusion, STS101 dosing of up to 2 times 5.2 mg STS101 within 24 hours and up to 12 times 5.2 mg per month is supported by the safety profile of single dosing at the proposed dose levels, the projected DHE systemic exposure that is within the range of injectable DHE products with repeated dosing, and the repeat dose toxicology NOAELs for systemic and local effects. The total number of doses per month will be limited to 12.

2. STUDY OBJECTIVES AND PURPOSE

The objectives of this study are:

Primary

- To assess the safety and tolerability of STS101 in the acute treatment of migraine attacks over 12 months and up to 18 months in a sub-set of subjects.

Secondary

- To describe the efficacy of STS101 in the acute treatment of migraine attacks over 12 months.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

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). 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. Subjects of the original cohort (enrolled before June 30, 2021) will be offered to continue use of study medication for another 6 months after the completion of the original 12-month period. Only safety data will be collected during this additional 6-month period.

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 ECGs 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.

3.2. Study Procedures Descriptions

The following list is a description of the procedures to be completed at screening and during the study:

3.2.1. Informed Consent

An Ethics Committee (EC)/Investigational Review Board (IRB)-approved informed consent form (ICF) must be signed and dated by each study subject prior to any study procedures being performed and a copy must be given to the subject. Subjects continuing for another 6 months after the original 12-month treatment period will need to sign an additional informed consent form.

3.2.2. Assignment of Subject Identification Number

Each subject will be assigned an individual subject identification number. The first three digits will identify the study site (ranging from 001 to 999) and last three digits will identify the subject as a running number starting with 001. As an example, the first subject entering screening at site 001 would receive the subject identification number 001-001, the second subject 001-002 etc.

3.2.3. Inclusion and Exclusion Criteria Assessment

All subjects must qualify for the study based on the inclusion and exclusion criteria specified in Section 4.1 and Section 4.2, respectively.

3.2.4. Medical History, Demographics, Concomitant and Prior Medications

A complete medical history will be obtained including a review of all major organ systems, and a history of alcohol, tobacco and caffeine use. Demographics will include gender, date of birth race and ethnicity. Prior medications will include all medications taken for 30 days prior to Screening. The medical history, demographics and a list of concomitant and prior medications will be documented at the screening visit.

In female subjects who menstruate the following additional information will be documented at the Baseline visit (Visit 2) and throughout the study:

- Timing and duration of last menstruation

Previous or current triptan use will be documented. Subjects who have or are currently using triptans will be asked to estimate how often they experience(d) pain relief (moderate or severe pain becoming mild to no pain) with triptan use:

- >75% of the time; >50 to 75% of the time; >25 to 50% of the time; <25% of the time

3.2.5. Headache Impact Test (HIT-6^{TM})

At the Baseline Visit (Visit 2) and at Visits 5, 8 and 11, subjects will complete the 6-question Headache Impact Test (Appendix E), a tool for assessing the impact of headache on daily life in subjects with migraine (Yang 2010).

3.2.6. Physical Examination

A full physical examination will be performed at Screening (Visit 1), Baseline (Visit 2), at 6 months (Visit 8), and at the Follow-up/early termination visit. The examination will include all major body systems with the exception of genitourinary. Site Personnel performing the physical exams must be qualified by training and licensure. A focused neurological exam (motor and sensory skills, hearing and speech, vision, coordination, and balance) will be done at Visits 3-7, 9 and 10. Examination of other body organ systems at Visits 3-7, 9 and 10 should be done as appropriate at the discretion of the investigator, e.g., to evaluate sequelae of adverse events. In subjects continuing for another 6 months after the original 12-month treatment period: focused neurological exam at Visits 12 and 13 and full physical examination at Visit 14.

3.2.7. Vital Signs

Vital signs will be obtained at Screening (Visit 1), Baseline (Visit 2), at each of the Visits 3-10 and at the Final/Early termination visit. Vital signs will include temperature, sitting blood pressure

(to be taken after 5 minutes of sitting), and pulse rate. In subjects continuing for another 6 months after the original 12-month treatment period: vital signs will be collected at Visits 12-14.

3.2.8. Weight, Height and Body Mass Index (BMI)

Subjects will be weighed in street clothes after removing shoes, coat or jacket. Weight will be measured at Screening, Baseline, all visits and the final/early termination visits. Subject height will only be measured at the Screening Visit without shoes. Subjects will have their BMI calculated at the Screening Visit (Visit 1) using the following formula: BMI = weight (kg)/height (m^2).

3.2.9. Evaluations of Effects in the Nose

3.2.9.1. Subjective Assessment of Nasal Symptoms

This is an 8-item questionnaire to be completed by the study subject with each item having to do with various aspects of nasally related signs and symptoms (e.g., nasal burning, itching, and pain). The questionnaire and completion instructions are shown in Appendix B.

The subjective assessment of nasal symptoms will be performed at the following times: Screening (Visit 1), Baseline (Visit 2), Visits 5, Visit 8 and at the Final/early termination Visit (Visit 11). In subjects continuing for another 6 months after the original 12-month treatment period: subjective assessment of nasal symptoms will be performed at Visit 14.

All VAS assessments will be converted to a numerical value in millimeters (range 0-100).

3.2.9.2. Objective Assessment of Symptoms

This is a 5-item assessment to be completed by a qualified physician or physician assistant. Using categorical scales ranging from “none” to “severe”, the physician will rate various aspects of the findings on physical examination of the nasal cavity. The questionnaire and detailed instructions for completion are shown in Appendix C.

The objective assessment of nasal symptoms will be performed at the following times: Screening (Visit 1), Baseline (Visit 2), Visits 3 through 10 and at the Final/early termination Visit. In subjects continuing for another 6 months after the original 12-month treatment period: objective assessment of nasal symptoms will be performed at Visits 12-14. Assessment sheets must be retained for all subjects. The person performing the assessments should be the same at all visits.

3.2.10. Smell Identification Test™

The Smell Identification Test™ (SIT) is our comprehensive 40-item test of olfactory function. The SIT will be administered according to the Smell Identification Test Administration Manual (Sensonics International; Haddon Heights, NJ, USA) at the following times: Baseline (Visit 2) and at the Final/early termination Visit (Visit 11). In subjects continuing for another 6 months after the original 12-month treatment period: SIT will be administered at Visit 14.

3.2.11. Clinical Laboratory Tests

A designated central laboratory will perform the hematology, biochemistry, urinalysis and diagnostic tests as specified in Table 4.

Samples for clinical laboratory tests will be taken at Screening (Visit 1), Baseline (Visit 2), Visits 5, 8-10 and at the Final/early termination visit (Visit 11). In subjects continuing for another 6 months after the original 12-month treatment period: clinical laboratory tests will be taken at Visits 12-14. All samples will be collected in accordance with the Study Laboratory Manual and shipped to the designed central laboratory.

The subjects should be instructed to withhold study medication until the site has confirmed that the laboratory test results at Visit 2 meet study eligibility criteria. The serum pregnancy test (HCG) will be performed in all female subjects at Screening (Visit 1) and at the Final/early termination visit (Visit 11). The serum pregnancy test (HCG) will be performed at every visit (Visit 1 through 11) in women of childbearing potential.

Laboratory reports will be reviewed by the investigator and out of range values will be identified and may be repeated at the Investigator's discretion. The Investigator will determine if any out of range values are clinically-significant and require recording as adverse events (AEs) in the electronic Case Report Form (eCRF). All clinically-significant out of range laboratory values obtained at the Baseline Visit or Follow-up visit will be followed until they return to normal or become medically stable.

Table 4. Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
Hematocrit Hemoglobin MCV Red Blood Cell Count Platelet Count White Blood Cell Count (*with Differential*)	Albumin Alkaline Phosphatase Alanine Transaminase (ALT) Aspartate Transaminase (AST) Blood Urea Nitrogen (BUN) Calcium Chloride Cholesterol profile Creatine phosphokinase Creatinine Gamma Glutamyl Transferase Glucose Lactate Dehydrogenase Potassium Sodium Direct and Total Bilirubin Total Protein Thyroid function tests (TSH, total T3 & T4) Serum pregnancy test (HCG) FSH	Appearance Color pH Specific Gravity Protein Glucose Ketones Occult Blood Nitrites Urobilinogen Leukocytes Bilirubin Urine microscopy, *if necessary*

Note: If deemed medically necessary, repeats of laboratory tests may be granted by the Medical Monitor.

3.2.12. Electrocardiogram

A 12-lead ECG will be performed at Screening (Visit 1), Baseline (Visit 2), Visits 5, 8-10 and at the Final/early termination Visit (Visit 11). In subjects continuing for another 6 months after the original 12-month treatment period: ECGs will be performed at Visits 12-14. All ECGs will be done in triplicate and reviewed by the investigator or a qualified delegate to assure subject eligibility and safety.

3.2.13. Adverse Events Recording

Adverse events will be recorded and assessed as specified in Section 7.

3.2.14. Electronic Headache Diary

Study participants will receive a handheld device for collection of electronic diary data. At the Baseline visit (Visit 2), study participants will receive training in the use of the device.

During the treatment period, the study participants will document signs and symptoms identifying a migraine headache, the pain severity of their treated migraine attack, presence and severity of symptoms (e.g., photophobia, phonophobia, nausea), rescue medication use and functional status over the 48-hour period after study drug administration in the e-diary.

The complete content and the training procedures for the electronic diary device will be described in separate documents.

3.2.15. Sheehan Suicidality Tracking Scale (S-STS)

All study subjects will complete the Sheehan Suicidality Tracking Scale (S-STS) (Appendix F) at all visits.

3.3. Schedule of Observations and Procedures

Appendix A shows the procedure for the study. The following assessments should be completed at the designated time period(s).

3.3.1. Screening Visit (Visit 1; Day-30 to Day -1)

Screening procedures to determine if subjects qualify for the study include:

a. Signing of informed consent
b. Review of inclusion/exclusion criteria
c. Recording of demographic data
d. Medical history, including concomitant medications
e. Full physical examination

f. Adverse Event Recording
g. Vital signs (including pulse rate, sitting blood pressure and temperature)
h. Body weight, height and BMI calculation
i. Nasal examination including Objective Assessment of Nasal Symptoms
j. Subjective Assessment of Nasal Symptoms
k. Completion of Sheehan Suicidality Tracking Scale
l. STS101 device training
m. Clinical laboratory tests
n. Urinalysis
o. Serum pregnancy test (all females)
p. 12-lead ECG (in triplicate)

3.3.2. Baseline Visit (Visit 2; Day 0)

a. Review of eligibility criteria
b. Full physical examination
c. Vital signs (including pulse rate, sitting blood pressure and temperature)
d. Weight
e. Concomitant medication review
f. Adverse Event Recording
g. Clinical laboratory tests and urinalysis
h. Serum pregnancy test (females of childbearing potential only)
i. 12-lead ECG (in triplicate)
j. Nasal examination including Objective Assessment of Nasal Symptoms
k. Subjective Assessment of Nasal Symptoms
l. Completion of Sheehan Suicidality Tracking Scale
m. Smell Identification test
n. Completion of HIT-6 instrument
o. Documentation of Health Care resource utilization (HCRU) in 6 months before screening

Any subject that no longer qualifies for study participation based on findings in any of the procedures will be withdrawn from the study as a screen failure and the reasons recorded on the screen failure log.

If the subject still meets all eligibility criteria for study participation, the following procedures will be done:

a. STS101 device and administration training
b. Dispense Investigational Product
c. Electronic headache diary use training and dispensation of electronic diary
d. Instruct subject to withhold study medication until the site has confirmed that the laboratory test results at Visit 2 meet study eligibility criteria.

3.3.3. Visits 3 & 4 (Month 1 and 2)

a. Focused neurological examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Nasal examination including Objective Assessment of Nasal Symptoms
e. Completion of Sheehan Suicidality Tracking Scale
f. Concomitant medication review
g. Adverse Event Recording
h. STS101 device and administration training
i. Serum pregnancy test (females of childbearing potential only)
j. Documentation of Health Care resource utilization (HCRU) since last visit
k. Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments. Counsel subject as needed Adverse Event recording
l. Study drug supply/Drug Accountability

3.3.4. Visit 5 (Month 3)

a. Focused neurological examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Concomitant medication review
e. Clinical laboratory tests and urinalysis
f. Serum pregnancy test (females of childbearing potential only)
g. 12-lead ECG (in triplicate)
h. Nasal examination including Objective Assessment of Nasal Symptoms
i. Subjective Assessment of Nasal Symptoms

j. Completion of Sheehan Suicidality Tracking Scale

m. Completion of HIT-6 instrument

n. Documentation of Health Care resource utilization (HCRU) since last visit

o. Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments. Counsel subject as needed.

m. Adverse Event recording

n. Study drug supply/Drug Accountability

3.3.5. Visits 6 & 7 (Month 4 & 5)

a. Focused neurological examination

b. Vital signs (including pulse rate, sitting blood pressure and temperature)

c. Weight

d. Nasal examination including Objective Assessment of Nasal Symptoms

e. Completion of Sheehan Suicidality Tracking Scale

f. Concomitant medication review

g. Serum pregnancy test (females of childbearing potential only)

h. Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments. Counsel subject as needed.

i. Documentation of Health Care resource utilization (HCRU) since last visit

j. Adverse Event recording

k. Study drug supply/Drug Accountability

3.3.6. Visit 8 (Month 6)

a. Full physical examination

b. Vital signs (including pulse rate, sitting blood pressure and temperature)

c. Weight

d. Concomitant medication review

e. Clinical laboratory tests and urinalysis

f. Serum pregnancy test (females of childbearing potential only)

g. 12-lead ECG (in triplicate)

h. Nasal examination including Objective Assessment of Nasal Symptoms

i. Subjective Assessment of Nasal Symptoms

j. Completion of Sheehan Suicidality Tracking Scale

k. Completion of HIT-6 instrument
l. Subject Impression of Study Medication Questions (see Section 6.2)
m. Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments. Counsel subject as needed.
n. Documentation of Health Care resource utilization (HCRU) since last visit
o. Adverse Event recording
p. Study drug supply/Drug Accountability

3.3.7. Visits 9 & 10 (Month 8 & 10)

a. Focused neurological examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Nasal examination including Objective Assessment of Nasal Symptoms
e. Completion of Sheehan Suicidality Tracking Scale
f. 12 Lead ECG (in triplicate)
g. Concomitant medication review
h. Clinical laboratory tests and urinalysis
i. Serum pregnancy test (females of childbearing potential only)
j. Review electronic diary and confirm subject properly recorded headache and migraine information and post treatment assessments. Counsel subject as needed.
k. Documentation of Health Care resource utilization (HCRU) since last visit
l. Adverse Event recording
m. Study drug supply/Drug Accountability

3.3.8. 12-Month Visit/Early Termination (Visit 11; Month 12)

At the final visit/early termination procedures will comprise the following:

a. Full physical examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Concomitant medication review
e. Clinical laboratory tests and urinalysis
f. Serum pregnancy test (All females)
g. 12-lead ECG (in triplicate)
h. Nasal examination including Objective Assessment of Nasal Symptoms
i. Subjective Assessment of Nasal Symptoms

j. Completion of Sheehan Suicidality Tracking Scale
k. Smell Identification Test
l. Completion of HIT-6 instrument
m. Subject Impression of Study Medication Questions (see Section 6.2)
n. Documentation of Health Care resource utilization (HCRU) since last visit
o. Adverse Event recording
p. Collect electronic diary device
q. For subjects assigned study medication (Visit 2) before June 30, 2021, check if subject wants to continue study for another 6 months. If subject agrees, they will sign the appropriate informed conenst form.
r. In subjects **not** continuing: Collect used and unused Investigational Product (STS101 devices)/Drug Accountability
s. In subjects continuing: Study drug supply/Drug Accountability

3.3.9. Visits 12 & 13 (Month 14 & 16)

a. Focused neurological examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Nasal examination including Objective Assessment of Nasal Symptoms
e. Completion of Sheehan Suicidality Tracking Scale
f. 12 Lead ECG (in triplicate)
g. Concomitant medication review
h. Clinical laboratory tests and urinalysis
i. Serum pregnancy test (females of childbearing potential only)
j. Adverse Event recording
k. Study drug supply/Drug Accountability

3.3.10. Final Visit/Early Termination (Visit 14; Month 18)

At the final visit/early termination procedures will comprise the following:

a. Full physical examination
b. Vital signs (including pulse rate, sitting blood pressure and temperature)
c. Weight
d. Concomitant medication review
e. Clinical laboratory tests and urinalysis
f. Serum pregnancy test (All females)
g. 12-lead ECG (in triplicate)

h. Nasal examination including Objective Assessment of Nasal Symptoms
i. Subjective Assessment of Nasal Symptoms
j. Completion of Sheehan Suicidality Tracking Scale
k. Smell Identification Test
l. Completion of HIT-6 instrument
t. Adverse Event recording
u. Collect used and unused Investigational Product (STS101 devices)/Drug Accountability

4. SELECTION AND WITHDRAWAL OF SUBJECTS

A total of approximately 480 adult male and female subjects aged 18 to 65 years with episodic migraine headaches. At least 150 and 50 subjects are planned to complete at least 6 and 12 months, respectively. Approximately 20 subjects are expected to complete 18 months.

4.1. Subject Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria applied:

1. Males or females, 18-65 years of age at the time of Screening Visit
2. Signed informed consent
3. Subject has at least 1-year history of migraines (with or without aura), according to the International Classification of Headache Disorder, 3rd Edition (ICHD3), including the following:
   a. Migraine onset before the age of 50 years
   b. History of 4 - 12 migraine attacks per month in each of the 3 months prior to Screening Visit
   c. History <15 headache days per month in each of the 3 months prior to Screening Visit
4. Female subjects will be included if they are post-menopausal (at least 1 year since last menses with an FSH >40 IU/mL) or surgically sterilized; or if they are of childbearing potential, they are not breastfeeding, have a negative pregnancy test, have no intention of becoming pregnant during the course of the study, and are using one of the following medically acceptable contraceptive methods during the course of this study:
   a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to screening (Visit 1)
   b. Simultaneous use of male condom with intravaginally applied spermicide and diaphragm
   c. Simultaneous use of male condom and hormonal contraceptives started at least 4 weeks prior to screening (Visit 1)
   d. Surgical sterilization of their partner(s) at least 6 months prior to screening (Visit 1)
5. Intact nasal mucosa (Appendix C, Objective Assessment of Nasal Symptoms: no ulceration; no bleeding; no or mild erythema, no or mild swelling and no or mild rhinorrhea) at baseline (Visit 2)
6. Willing and able to comply with the requirements of the protocol and follow directions from the clinic staff

4.2. Subject Exclusion Criteria

1. Pregnant or breast-feeding women
2. Women of child-bearing potential not using or not willing to use highly effective contraception
3. Diagnosis of headache conditions other than migraine with or without aura, including but not limited to diagnosis of basilar migraine (aka migraine with brainstem aura) or hemiplegic migraines, medication overuse headache or cluster headache

4. Clinically significant abnormal physical findings at the screening or baseline examination which would interfere with the objectives of the study
5. History of coronary artery disease, coronary artery vasospasm (including Printz-metals' angina), clinically significant arrhythmia or, peripheral vascular disease, ischemic disease (e.g., Raynaud's syndrome, ischemic bowel syndrome, angina pectoris, myocardial infarction, or documented silent ischemia); percutaneous coronary intervention, or cardiac surgery for complications from ischemic heart disease
6. History of cerebrovascular disease, including but not limited to stroke, transient ischemic attack, cerebral hemorrhage, subarachnoid hemorrhage
7. Presence of two or more of the following cardiovascular risk factors:
    a. Diagnosis of hypertension or receiving antihypertensive medication for treatment of hypertension
    b. Diagnosis of hypercholesteremia, or LDL >159 mg/dL or receiving cholesterol lowering medication
    c. Obesity (BMI > 31)
    d. Diabetes mellitus
    e. Family history of premature coronary artery disease (in male first-degree relatives < 55 years or female first-degree relatives < 65 years)
    f. Females who are surgically or physiologically postmenopausal
    g. Males over age 45
8. Clinically significant abnormal laboratory values (as determined by the Principal Investigator) at screening (Visit 1) or Baseline (Visit 2).
9. Severely impaired hepatic function (liver function tests ALT or AST greater than 2 times upper limit of normal) or renal function (serum creatinine greater than 1.5 times the upper limit of normal) at screening (Visit 1) or Baseline (Visit 2).
10. Screening 12-lead ECG showing any clinically significant abnormalities at screening (Visit 1) or Baseline (Visit 2).
11. Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, at screening (Visit 1) or Baseline (Visit 2).
12. Diagnosis of major depression with current symptoms, psychosis, alcohol abuse or dependence, drug abuse or dependence, major psychiatric conditions (e.g., schizophrenia, psychosis or Bipolar disorder), or dementia. Other significant neurological or psychiatric disorders (including other pain syndromes or risk of suicide) that in the opinion of the investigator might interfere with study participation and assessments or subject safety
13. Any clinically significant symptoms or conditions, including but not limited to central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic or gastrointestinal conditions or history of such conditions that, in the opinion of the investigator might interfere with study assessments or subject safety
14. Participation in another drug research study within 30 days of screening (Visit 1) or within less than 5 half-lives of tested drug (whichever is longer). Note: Subjects who have participated in study STS101-002 are exempt from this.

15. Concomitant use of potent CYP3A4 inhibiting medications, for example protease inhibitors (e.g., ritonavir, nelfinavir, indinavir, saquinavir, tipranavir, lopinavir, atazanavir, darunavir), macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin), or strong imidazole antifungals (e.g., ketoconazole, and itraconazole)
16. Previously shown hypersensitivity to ergot alkaloids or the inactive ingredients of STS101 (microcrystalline cellulose, hydroxypropyl methylcellulose, mannitol)
17. Concomitant use of more than two preventive migraine medications
18. Concomitant daily use of peripheral and central vasoconstrictors including but not limited to amphetamines, phenylephrine, pseudoephedrine, propranolol and nicotine (from smoking, vaping or smokeless products)
19. Score of >0 on any of the questions 1-14 of the Sheehan Suicidality Tracking Scale

4.3. Subject Withdrawal Criteria

Subjects will be informed that they are free to withdraw from the study at any time. The Investigator or the Medical Monitor may exercise his/her medical judgment to terminate a subject's participation in the study due to compliance, medical or behavioural reasons. All data normally collected at completion of the study (Visit 11 must be collected as soon as possible once a subject is withdrawn. The primary reason for discontinuation of treatment should be noted in the CRF and source data using the following categories:

a. **Adverse Event:** The subject has experienced an AE that, in the opinion of the Investigator, requires early termination. If a subject is discontinued from the study due to an AE, the Investigator is required to follow the subject until the AE is resolved or declared medically stable or the subject is lost to follow up.
b. **Non-compliance:** The subject did not adhere to protocol requirements in a fashion that would impair the data integrity or subject safety.
c. **Withdrawal of Consent:** The subject wishes to withdraw from the study.
d. **Death.** The event causing the death will be an SAE and will be documented.
e. **Investigator Discretion:** In the Investigator's judgment, continued participation in the study would not be in the best interest of the subject or the study.
f. **Study Termination:** The Sponsor, or IRB terminates the study.
g. **Lost to follow up.** Every effort should be expended to contact the subject and have them return for follow up assessments and return of Investigational Product (used or unused) and the electronic diary device.
h. **Inadequate number of migraine attacks:** Subjects may be discontinued from the study if they experience and treat less than two migraine attacks on average per month over the first three months of the study.
i. **Other:** If subject is discontinued from the study for any reason not applicable to the reasons stated above, this category should be used. The specific reason should then be indicated in the subject's source documents and the appropriate CRF.

5. TREATMENT OF SUBJECTS

5.1. Description of Investigational Product and Packaging

STS101 is a drug-device combination product consisting of a powder formulation of DHE mesylate prefilled in a single use delivery device for IN administration. The STS101 drug constituent contains a formulation of DHE mesylate, microcrystalline cellulose, mannitol and hydroxypropyl methylcellulose (HPMC).

DHE mesylate is a white or off-white powder. DHE mesylate is known chemically as ergotaman-3′,6′,18-trione,9,10-dihydro-12′-hydroxy-2′-methyl-5′-(phenylmethyl)-,(5′α)-,monomethanesulfonate. Its molecular weight is 679.80 and its empirical formula is $C_{34}H_{41}N_5O_8S$. Further information can be found in the Investigator's Brochure.

The investigational product will be made available as:

- 5.2 mg STS101 dose strengths (equivalent to 6.0 mg DHE mesylate USP) as unit dose in a labeled foil wrap.

The non-investigational product will be made available for training during the following Visits: Visit 1, 2, 3, and 4

- STS101 Empty Training Devices (empty STS101 Device).
- STS101 Filled Training Devices (STS101 Device containing microcrystalline cellulose).

5.2. Investigational Product Labeling

The foil wrap will be labeled with a label designating:

- STS101 dose strength (5.2 mg)
- Protocol number
- Lot number
- Kit Number
- Name and address of study sponsor
- Recommended storage conditions
- Investigational use only
- Directions: Use as directed following the Instructions for Use
- Warning: For nasal use only
- Blank spaces for: Date dispensed & Subject Number (to be completed by site personnel at time of dispensing)

5.3. Investigational Product Storage

Investigational Product supplies are to be stored under secure conditions in a dry, locked, limited access cabinet, at controlled room temperature. All Investigational Product must be stored at room temperature (2-30ºC or 36-86°F).

The study site pharmacist or designee will maintain an inventory and acknowledge receipt of all shipments of the Investigational Product. Accurate storage and dispensation records must be kept for drug accountability. Supplies of the investigational products will be checked and accountability records will be reviewed at each monitoring visit. A copy of all completed drug accountability forms will be collected by the monitor.

5.4. Investigational Product Administration & Training

STS101 will be self-administered by the subjects using the delivery device according to the Instructions for Use.

At Visits 1, 2, 3, and 4 study personnel will train the subject in the study drug preparation and administration. Instructions for Use, an instructional video, STS101 Empty Training Devices and STS101 Filled Training Devices will be used for training of the study subject at all of these visits.

For the treatment at home, the study subject will record the following information in the electronic diary:

- Time of dosing (defined as time of last intranasal delivery device actuation).
- The nostril (right or left) into which study drug was administered.

Subjects will be instructed to:

- Place Nozzle Tab and Nasal Device into the plastic bag provided.
- Place the plastic bag and Foil wrap into the carton.
- Return the carton to the clinical site.

5.5. Investigational Product Accountability

The Investigational Product will be prescribed by a licensed medical doctor.

The Investigator must maintain accurate records accounting for the receipt and dispensing of the investigational materials. This should consist of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and the return of study drug/devices.

All Investigational Products dispensed to and taken by subjects must be accurately recorded on an appropriate drug accountability record maintained at the site and reviewed by the study monitor.

All Investigational Products designated for this clinical study must not be administered to any subjects other than those enrolled in this study and may not be utilized for any laboratory or animal research.

5.6. Investigational Product Handling and Disposal

Site study staff will retain used and unused Investigational Product at the study site. At the end of the study, all used and unused Investigational Product will be reconciled by the Sponsor's designee. At the end of the study, all used and unused STS101 devices will be returned to the Sponsor or if requested by sponsor, destroyed at the study site in compliance with the rules and regulations set forth by the institution conducting the study, and in observance with the rules and regulations of federal agencies concerning prescription only drug products.

5.7. Concomitant Medications

Use of any concomitant medications will be documented and reported.

Triptans and ergot alkaloids are not allowed within 24 hours before and after study drug administration.

The concomitant use of potent CYP3A4 inhibiting medications, for example protease inhibitors (e.g., ritonavir, nelfinavir, indinavir, saquinavir, tipranavir, lopinavir, atazanavir, darunavir), macrolide antibiotics (e.g., erythromycin, clarithromycin, troleandomycin), or strong imidazole antifungals (e.g., ketoconazole, and itraconazole) are not allowed.

The concomitant use of more than two prevention medications for migraine is not allowed.

The concomitant use of a peripheral and central vasoconstrictive medication is not allowed.

5.8. Treatment Compliance

All used or unused Investigational Product will be returned to the site at each study visit at which time the dispensed Investigational Product will be reconciled in the drug accountability log.

5.9. Randomization and Blinding

5.9.1. Subject Randomization

There is no randomization. All subjects will be assigned to receive 5.2 mg STS101.

5.9.2. Blinding & Unblinding Procedures

This is an open label study.

6. ASSESSMENT OF EFFICACY

6.1. Efficacy Evaluation Parameters

The following efficacy evaluation parameters will be programmed in an electronic handheld device (e-Diary) that the study subjects will use to provide their information. Note: No efficacy data will be collected in subjects who continue for another 6 months after the original 12-month treatment period.

6.1.1. Migraine Headache Pain Severity

The study participants will be prompted to document the pain severity of the treated migraine attack by this request: *"Please rate the pain severity of your current migraine headache."*

The subject's rating will be documented on a four-point scale from no pain (= 0), mild pain (= 1), moderate pain (= 2) to severe pain (= 3).

Headache pain severity ratings will be collected at the onset of the migraine attack, immediately before drug administration (time 0), at 30 and 60 minutes, 2, 4, 24, and 48 hours after study drug administration.

6.1.2. Most Bothersome Symptom

The study participants will be prompted to document the presence of three symptoms, photophobia, phonophobia and nausea during the treated migraine attack by these requests:

For photophobia: *"Do you have sensitivity to light?"*
For phonophobia: *"Do you have sensitivity to sound?"*
For nausea: *"Do you have nausea?"*

For each of the three symptoms, the subject will respond with "Yes" (if symptom present) or "No" (if symptom absent).

Immediately before study drug administration (time 0), the study subjects will be prompted to declare the most bothersome symptom among the symptoms present by this request: "Please indicate which of the symptoms that you have at (sensitivity to light, sensitivity to sound or nausea) bothers you the most at this time."

The presence of the three symptoms will be recorded at the onset of the migraine attack, immediately before drug administration (time 0), at 30 and 60 minutes, 2, 4, 24, and 48 hours after study drug administration.

6.1.3. Use of Rescue Medication

Rescue medication is defined as any medication taken to treat the migraine headache after study drug administration.

Any use of medications to treat the migraine headache will be recorded for 48 hours after study drug administration.

6.1.4. Evaluation of Function & Subjective Impressions

6.1.4.1. Functional Impairment Scale

The study subjects will be prompted to record their functional status using the Functional Impairment Scale (FIS): *"Please rate how much your current migraine headache impacts your ability to function right now."*

The subject's rating will be documented on a four-point scale from no impairment (=0; able to function normal)), mild impairment (= 1; able to perform all activities of daily living but with some difficulty), moderate impairment (= 2; unable to perform certain activities of daily living) to severe impairment (= 3; unable to perform most to all activities of daily living or requiring bed rest).

The FIS will be recorded at the onset of the migraine attack, immediately before drug administration (time 0), at 30 and 60 minutes, 2, 4, 24, and 48 hours after study drug administration.

6.1.4.2. 24-hour Migraine Quality of Life Questionnaire

For one treated attack per month, the study subjects will be prompted to complete the 24-hour Migraine Quality of Life Questionnaire (24-MQoL) (Appendix D) at 24 hours after drug administration.

6.2. Other Evaluations at Office Visits

6.2.1. Patient Global Impression

The study subjects will be asked to rate the global impression of the study treatment at Visit 5 (Month 3), Visit 8 (Month 6) and Visit 11/Early Term (Month 12) with this question: "What is your global impression of the study treatment?"

The subject's rating will be documented on a five-point verbal Likert scale with these response options: very good, good, no opinion, poor, very poor.

6.2.2. Ease of Use Impression

The study subjects will be asked to rate the ease of use of the study medication at Visit 5 (Month 3), Visit 8 (Month 6), and Visit 11/Early Term (Month 12) with this question: "How easy was the administration of the study medication?"

The subject's rating will be documented on a five-point verbal Likert scale with these response options: very easy, easy, no opinion, not easy, not easy at all.

6.2.3. Patient Likelihood of Use

The study subjects will be asked to rate the likelihood of using the study medication at Visit 5 (Month 3), Visit 8 (Month 6) and Visit 11/Early Term (Month 12) months with this question:

"How likely is it that you would use the study medication to treat your migraine if it were available?"

The subject's rating will be documented on a five-point verbal Likert scale with these response options: very likely, likely, no opinion, unlikely, very unlikely.

6.2.4. Comparison of Study Medication with Previously Used Migraine Medication

The study subjects will be asked to compare the effects of the study medication with their previously used migraine medication after 3, (Visit 5), 6 (Visit 8), and 12 (Visit 11/early term) months with answers to these four statements:

Compared to my previous migraine medication, STS101 (the study medication)

1. Allows me to return to normal faster
2. More consistently treats my Migraine
3. Works faster
4. Keeps migraine from coming back

The answer options for all four statements are: strongly agree; agree; neutral; disagree; strongly disagree

6.2.5. HIT-6

The subjects will complete the HIT-6 instrument at Visit 2 (baseline), Visit 5 (3 months), Visit 8 (6 months), and Visit 11/early term (12 months).

6.3. Healthcare Resource Utilization

Subjects will be asked at baseline (Visit 2) to provide information on their healthcare resource utilization over the prior 6 months. This should include:

- Any migraine specific office-based consultations (primary care, nurse practitioner/physician assistant, neurologist)
- Any visits to pain clinic, headache clinic, mental health clinic and chiropractor/alternative medicine, urgent care or emergency department
- Any hospitalizations or overnight hospital/emergency department stays
- Any diagnostic services including computer assisted tomography (CAT) scans, magnetic resonance imaging (MRI).

At each follow up visit the subjects will be asked to provide information reg. their healthcare resource utilization over the period since their last visit.

7. ASSESSMENT OF SAFETY

7.1. Safety Parameters

The following evaluations and assessments will be conducted during the course of the study (Refer to the Schedule of Assessments in Appendix A).

7.1.1. Examinations

7.1.1.1. Physical Examinations

A physical examination will include the following body systems: HEENT, Lymphatic, Cardiovascular, Respiratory, Gastrointestinal, Dermatologic, Musculoskeletal, Neurologic and Other.

New physical examination observations that meet the definition of an AE will be recorded on the AE form.

7.1.1.2. Height, Weight, and BMI

Subjects will be weighed in street clothes after removing coat or jacket and shoes at the Screening Visit, Baseline visit, and follow-up or early termination visit. At the Screening Visit, subject height will be measured without shoes. Subjects will have their BMI calculated using the following formula: BMI = weight (kg)/height (m^2).

7.1.1.3. Vital Signs

Vital signs consist of the subject's resting sitting blood pressure, pulse rate, and temperature.

The subject should rest for at least 5 minutes prior to recording the vital signs. The Investigator will review the vital signs and comment on all clinically significant abnormalities.

7.1.1.4. Nasal Symptom Assessments/Nasal Exam

An assessment of subjective nasal symptoms will be performed based on data recorded with the Subjective Assessment of Nasal Symptoms form (Appendix B). A nasal exam will be completed along with an assessment of objective nasal symptoms will be performed based on data recorded with the Objective Assessment of Nasal Symptoms form (Appendix C).

7.1.1.5. Smell Identification Test

Olfactory function will be assessed based on the Smell Identification Test.

7.1.1.6. Electrocardiogram (ECG)

Standard 12-lead ECG will be performed in triplicate approximately 1 minute apart. All ECGs will be reviewed by a competent physician who will comment on any abnormal findings.

Clinically significant findings if found at Screening (Visit 1) or Baseline (Visit 2) may be a reason to exclude the subject.

In subjects who report chest related symptoms or adverse events, an ECG (in triplicate) should be recorded if symptoms are reported to the site within 48 hours of onset.

7.1.1.7. Sheehan Suicidality Tracking Scale

The S-STS is a 16-item scale that assesses the seriousness of suicidality risk using a 5-point Likert scale from "not at all" (0) to "extremely" (4) (Sheehan 2014). The S-STS will be completed by all subjects at all study visits.

7.1.2. Laboratory Assessments

Central laboratory tests results will be reviewed for any clinically significant abnormalities by a qualified physician. Labs can be reviewed by a Physician Assistant (PA) or Nurse Practitioner (NP); however, they should be signed/dated by an MD. If any clinically significant findings are present at Screening (Visit 1) or Baseline (Visit 2), the subject will be considered a screen failure and ineligible for study participation.

7.1.2.1. Hematology

Complete blood count (CBC) with differential including: white blood cell count with differential, red blood cell count, hemoglobin, hematocrit, MCV, and platelet count.

7.1.2.2. Serum Chemistry

Serum chemistry including: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (direct and total), blood urea nitrogen (BUN), calcium, chloride, cholesterol profile, creatine phosphokinase, creatinine, gamma glutamyl transferase, glucose, lactate dehydrogenase, potassium, sodium, thyroid function tests (TSH, total T3 & T4), and total protein.

7.1.2.3. Urinalysis

Urinalysis examination including: Appearance, color, pH, specific gravity, protein, glucose, ketones, occult blood, nitrites, urobilinogen, leukocytes, bilirubin and if necessary, urine microscopy.

7.1.2.4. Serum Pregnancy Test & FSH

Serum HCG pregnancy & FSH tests results in female subjects.

7.1.2.5. Lab Testing for Chest Related Symptoms or Adverse Events

In subjects who report chest related symptoms or adverse events, the following markers should be evaluated (if symptoms are reported to the site within 48 hours of onset): total creatine kinase

(CK), CK-myocardial band (CK- MB), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), cardiac troponins (Troponin T; Troponin I), and myoglobin. A blood sample for analysis of DHE plasma concentration should also be drawn.

7.2. Adverse Events

An adverse event (AE) is defined as: "Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. Treatment emergent adverse events (TEAE) are defined as adverse events recorded after dosing of the investigational product.

AEs will be recorded as volunteered by the subject or solicited through indirect questioning. **AE collection will begin after the signing of the Informed Consent Form (Visit 1) and continue until the final/early termination visit .**

AEs will be solicited at the times indicated in the schedule of assessments by asking a question such as: "Since you were last seen, have you felt unwell or different from usual in any way?" AEs may also be reported spontaneously.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory values are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (e.g., increased liver enzymes in hepatitis), the diagnosis only should be reported as an AE.

Any adverse events, signs, and symptoms will be fully recorded on the AE form including date of onset, date of resolution, frequency, severity, seriousness, relationship to the drug, treatments administered and outcome. AEs may also be reported spontaneously at any time.

All AEs must be recorded in the source data and the CRF. Any ongoing AEs at the subject's last visit will be followed, until it resolves, stabilizes or returns to baseline levels.

7.2.1. AE Relationship to Study Drug

An AE will be considered 'related" or "not related" to the use of the investigational product based on the criteria listed in Table 5. Assessment of the causal relationship between any Serious Adverse Event (SAE) and study drug administration will be performed by both the Investigator and the Sponsor. If at least one of the parties assesses the event as related, it will be reported expeditiously as required to the appropriate authorities.

Table 5. Adverse Event Relationship to Study Drug

Related:	There is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causality). Individual AE reports will be considered "related" to the use of the product if the "not related" criteria are not met.
Not Related:	There is an unreasonable temporal relationship between administration of the product and the onset of the AE (i.e., the event occurred either before, or too long after administration of the product for it to be considered product-related); The causal relationship between the product, and the AE is biologically implausible (i.e., death of a passenger in an automobile accident); There is a clearly more likely alternative explanation for the AE (i.e., typical adverse reaction to a concomitant drug and/or typical disease-related event).

7.2.2. Assessment of Adverse Event Severity

Table 6 shows the guidelines for rating severity of AEs may be used:

Table 6. Assessment of Adverse Event Severity

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.
Moderate:	Discomfort enough to cause interference with or modification of usual activities.
Severe:	Incapacitating, with inability or notable impairment in work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may be stopped, and treatment for the event may be required.

7.2.3. Serious Adverse Events (SAEs) Recording and Reporting

The Investigator must decide whether each AE meets the definition of an SAE. An SAE is any untoward medical occurrence that at any dose:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Is considered medically significant by the Investigator or requires intervention to prevent any one of the outcomes above.

For fatal events, the cause of death is reported whenever known. If an autopsy was performed, an autopsy report should be provided. Death should be reported as the outcome of a specific SAE.

Life-threatening, in the definition of serious, refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Reports for hospitalization of elective procedures do not need to be reported as SAEs if there are no precipitating signs/symptoms or worsening of the pre-existing condition that necessitated the procedure. However, SAEs must be reported for any medical complications that prolonged the hospitalization.

Medically significant events are those events considered important in the Investigator's opinion that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

Any SAE will be reported within 24 hours of knowledge by the Investigator. Investigator should not delay reporting while waiting for clarification or supporting medical information.

The Investigator must complete the required information fields for SAE documentation and reporting in the electronic CRF (AE eCRF and SAE eCRF) and provide any supportive documents available (hospital summaries, diagnostic test results, laboratory test results, etc.). Any subject identifying information must be redacted prior to uploading. The investigator should not wait for these supporting documents in order to notify the medical monitor if doing so would place the notification outside the 24-hour window. All SAEs will also be reported on the AE eCRF and SAE eCRF and concomitant medications (CM) administered in association with the serious AE will be documented on the CM eCRF.

For any information not available at the time of the first report that becomes available later, the Investigator should add this information to both the source documentation and the initial SAE section of the eCRFs, and provide any additional written documentation to the Safety Group immediately or within 1 working day of receipt.

The Sponsor or designee is responsible for notifying regulatory agencies of SAEs that require reporting as per the governing regulations.

It is the responsibility of the Investigator to report to the relevant IRB/EC in accordance with the IRB/EC's reporting specific reporting requirements for SAEs.

All SAEs must be followed up until the event is resolved, returns to the baseline condition, or is declared medically stable with no further change expected or the subject is lost to follow up.

SAEs Occurring after the Follow-Up Visit: If an SAE comes to the attention of the Investigator after study termination within 30 days of the last dose of study drug(s), and it is considered related to study drug, it must be recorded and followed up in the same way as the SAEs occurring during the study.

Any report of pregnancy identified for any female subject or for a female partner of a male subject should be reported immediately (within 24 hours of being informed) to the medical monitor. Pregnancies will be considered 'events of special interest' and will not be captured as serious adverse events (SAEs). The Pregnancy Report Form will be utilized to obtain follow-up information. Pregnancies will be followed to termination or eight weeks post- delivery for determination of resolution to the event. Subjects who become pregnant during treatment must immediately be withdrawn from the study (classified as early termination).

8. STATISTICS

8.1. Sample Size Determination

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 and about 20 subjects to complete 18 months. With a sample size of 300 subjects, there is a 95% probability to detect clinically important adverse events with event rate of 1% or higher. This sample size is expected to adequately characterize the safety and tolerability of STS101 in the acute treatment of migraine.

8.2. Subject Populations

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

8.2.1. Safety Population

The safety population will include all subjects who have received the study medication. This population will be the primary analysis population for the study.

8.2.2. Efficacy Population

The efficacy population will include all subjects who received the study drug to treat at least one episode and reported a post-treatment efficacy evaluation for at least 1 time point.

8.3. Statistical Analysis

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 absolute and relative frequency counts and percentage.

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

A detailed Statistical Analysis Plan (SAP) will be provided in a separate document.

8.3.1. Demographic and Baseline Variables

Demographics and baseline characteristics will be summarized descriptively for the safety and efficacy populations.

8.3.2. Efficacy Analysis

8.3.2.1. Efficacy Endpoints

The following efficacy endpoints will be analyzed.

1. Proportion of subjects free from headache pain (defined as moderate or severe headache pain becoming none on a 4-point scale) at 2, 4, 24 and 48 hours post dose
2. Proportion of subjects free from most bothersome symptom (MBS) (defined as the MBS identified prior to dosing being absent) at 2, 4, 24 and 48 hours post dose
3. Proportion of subjects with relief from headache pain at 2, 4, 24 and 48 hours post dose (defined as reduction in headache pain from moderate or severe [2 or 3 on a 4-point scale]) to mild or none [0 or 1 on a 4-point scale])
4. Proportion of subjects free from headache pain at 2, 4, 24 and 48 hours post dose by study month
5. Proportion of subjects free from most bothersome symptom (MBS) (defined as the MBS identified prior to dosing being absent) at 2, 4, 24 and 48 hours post dose by study month
6. Proportion of subjects with headache relief at 2, 4, 24 and 48 hours post dose by study month
7. Proportion of subjects free from headache pain at 2 hours post dose and remain headache free at 24 and 48 hours post dose by study month
8. Frequency of migraine headaches treated with STS101 by study month
9. Frequency of migraine headaches by study month
10. Proportion of subjects with headache relapse within 48 hours post dose (defined as the return of headache of any severity within 48 hours after administration of the investigational drug, when the patient was pain-free at 2 hours after investigational drug administration)
11. Mean change in scores on Functional Impairment Scale (FIS) by study month.
12. Mean change in scores on 24-hour Migraine Quality of Life Questionnaire by study month.
13. Satisfaction with treatment questions
14. Mean change from baseline in HIT-6

8.3.2.2. Hypotheses Testing and Significance Level

No formal hypotheses testing is planned for this study. When appropriate, exploratory hypotheses testing may be conducted at the significance level of 0.05. No adjustment for multiplicity will be employed.

8.3.2.3. Handling of Missing Data

For the analysis of the efficacy endpoints, data will be summarized descriptively with available data. Missing data will not be imputed.

8.3.2.4. Pooling of Centers

Data from all investigational centers will be pooled for analysis. The analyses will not be performed by center and will not include adjustment for centers.

8.3.2.5. Analysis Methods for Efficacy Endpoints

For efficacy endpoints #1 - #10, and #13 as numbered in Section 8.3.2.1, frequencies and percentages of each category will be tabulated. For endpoints #1 - #7, and #10, the analysis will be a responder analysis with the responder defined by meeting the criteria for respective endpoints. For responder analysis, the proportions of responders and their 95% confidence intervals will be presented.

For efficacy endpoints #11, #12, and #14, the change from baseline will be summarized descriptively. Exploratory hypothesis testing of the mean change from baseline may be conducted using the paired t-test.

8.3.3. Safety Analysis

Safety analyses will be conducted for the safety population. All reported adverse events will be coded using MedDRA 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. Missing safety data will not be imputed.

8.3.3.1. Extent of Exposure

The number of subjects exposed to the study medication will be summarized. The frequency and duration of exposure will also be summarized.

8.3.3.2. Adverse Events

A TEAE is defined as an AE that begins after the dosing of study drug. Adverse events reported after the administration of the filled training devices during Visits 1 – 4 will be summarized in separate tables.

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/Suspected to study drug, TEAE related/Suspected to study procedure, maximum severity of TEAE.

Multiple occurrences of an AE are counted only once per subject per SOC and PT for summary tables.

The following TEAEs will be summarized by SOC, PT:

- Incidence of all TEAEs
- Nasal 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 early discontinuation withdrawn from study

All data collected in the AE case report form (CRF) will be listed in by-subject listings.

8.3.3.3. Assessment of Nasal Symptoms

The data from the Subjective and Objective Assessment of Nasal Symptoms will be summarized.

8.3.3.4. Laboratory Evaluations

The observed data at each time point and change from baseline (Visit 2) at each post-baseline time point in hematology, serum chemistry and quantitative urinalysis test results will be summarized. Frequency counts and percentages of out-of-range alerts will be summarized over time. Shift-tables from baseline to each post-baseline time point will be presented.

8.3.3.5. Vital Signs

Observed data at each time point and the change from baseline (Visit 2) at each post-baseline time point for vital signs will be summarized.

Normal ranges for each vital sign parameter 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 over time by for these categorical data.

8.3.3.6. ECG Evaluations

Observed data at each time point and the change from baseline (Visit 2) at each post-baseline time point in ECG parameters, heart rate (HR), RR, PR, QRS, and QT corrected with the Fridericia's formula (QTcF), will be summarized.

The number and percentage of subjects with other clinically significant ECG findings will also be summarized at each post baseline time point.

8.3.3.7. Concomitant Medications

Concomitant medication usage will be summarized. The World Health Organization Drug Dictionary (WHO Drug) will be used to classify prior and concomitant medications by therapeutic class and generic name based on ATC code level 3. Subjects will only be counted one time in each unique ATC Class and generic name if multiple drugs are used by a subject.

8.3.3.8. Sheehan Suicidality Tracking Scale

Reported data at each time point and the change from baseline (Visit 1) at each study visit will be summarized by treatment groups.

8.3.4. Interim Analysis

An interim analysis is planned for this study at the time when 150 subjects have completed 6 months of treatment. This data is intended for the STS101 NDA submission.

9. DATA HANDLING AND RECORDKEEPING

9.1. Case Report Forms (CRFs)

All clinical study data will be collected by the clinical investigator and staff, recorded on source documents and captured electronically in the electronic CRF.

The populated electronic CRFs will be monitored against source documents by the Sponsor's representative and any subsequent data discrepancies identified will be recorded and communicated to the investigative site for resolution.

Completion of the electronic CRF should occur within approximately 24 hours of a subject's visit.

9.2. Retention of Records

The Investigator must maintain adequate records for the study including all source documentation, completed CRFs, logs, medical records, laboratory reports, signed ICFs, investigational product disposition records, adverse event reports, information regarding subjects who discontinued, all correspondence with the EC and the Sponsor (or designee) and other pertinent data.

The study site will maintain adequate study records for at least 2 years after product approval for marketing or until instructed by the Sponsor in writing. After that period, the Sponsor may be contacted to determine whether the study records will be forwarded to the Sponsor, destroyed or kept at another facility for a longer period of time at the Sponsor's expense.

To avoid any possible errors, the Investigator must contact Satsuma (or designee) prior to the destruction of any study records. The Investigator will also notify Satsuma (or designee) in the event of accidental loss or destruction of any study records.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Study Monitoring

The study will be monitored by the Sponsor's representatives at all stages of study conduct from inception to completion in accordance with current Good Clinical Practice (GCP) guidelines. This monitoring will be in the form of site visits and other communication and will include review of original source documents and CRFs. The Sponsor's monitor or representative will notify the Principal Investigator prior to conducting any investigational site visit. The frequency of these visits will depend upon the progress of the study, and will include monitoring to assess facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, investigational product accountability, AE reporting and other factors.

10.2. Audits and Inspections

The clinical site will be subject to audit and inspection by the Sponsor or representative during and/or at the end of the study as appropriate.

The Investigator will permit representatives of Satsuma or representative or FDA auditors to inspect facilities and records relevant to this study, including the subject’s original medical records for verification of study-related procedures and data.

11. ETHICS

11.1. Ethics Review

The Ethics Committee/Institutional Review Board will review and approve the study protocol, the ICF and other relevant substantive information or documents before the study is initiated. If an Investigator chooses to advertise for subjects for this study, whether in professional or consumer publications, radio, or television or any digital media, all advertising copy and language must be approved by Satsuma and the EC/IRBs prior to initiation.

A copy of the EC/IRB approval letter for the protocol and the consent form/subject information sheet, which specifically identifies the protocol name and the Satsuma protocol number, must be sent to Satsuma (or designee) prior to initiating the study. Subsequently, the Investigator is responsible for keeping the EC/IRB advised of the progress of the study as deemed appropriate but, in any case, at least once a year during the course of the study and for keeping the EC/IRB informed of any significant study change or adverse reactions per EC/IRB specific guidelines.

11.2. Ethical Conduct of the Study

This study will be conducted in strict compliance with the Declaration of Helsinki, ICH, GCP, EC/IRB and other relevant regulatory requirements and laws.

The Investigator must ensure that each subject's anonymity is maintained as described within this protocol. On the CRFs or other documents submitted to Satsuma, or its designee, subjects must be identified only by their initials and a subject number. Documents that are not for submission to Satsuma, and/or its designee, (i.e., signed ICFs) should be kept in strict confidence by the Investigator, in compliance with Federal regulations and ICH and GCP Guidelines. The Investigator is obligated to inform the subject in the ICF that his/her study-related records will be reviewed by the above-named study sponsor and representatives.

11.3. Written Informed Consent

Prior to any study procedures being performed, each study participant will be required to read, sign and date an EC/IRB -approved ICF, explaining the nature, purpose, possible risks and benefits, and the duration of the study. Each participant will be given a copy of the fully executed ICF.

The ICF must be written in English or Spanish, and all subjects must be fluent in English or Spanish (speaking, writing, and reading). The Investigator or designee shall give the subject, adequate time to read the ICF and consider study participation and have all questions answered. They should also express understanding of the information presented regarding the trial before it is signed and dated.

Each subject's signed ICF must be kept on file by the Investigator and be available for possible inspection by regulatory authorities, and/or the study Sponsor or designee, or the EC/IRB. Documentation of the informed consent and subject information discussion must appear in the subject's medical record and/or the subject's study file and be available for verification by monitors at any time.

11.4. Disclosure of Data

Individual subject medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted below is prohibited.

However, at the request of the subject such medical information may be given to the subject's personal physician, or to other appropriate medical personnel responsible for the subject's welfare.

In addition, data generated during this study are to be available for inspection upon request by FDA auditors, the Sponsor's monitors or by the EC/IRB. Therefore, absolute confidentiality cannot be guaranteed.

The sponsor is planning a publication of the complete study data. No publication of an individual site's data may occur before that publication and no publications may occur without the sponsor's written approval.

12. REFERENCES

Dihydergot Prescribing Information, 2011.

Armer TA, Lynch M, Moutvic R, Singer A. Toxicological assessment of dihydroergotamine after chronic inhalation in dogs. Toxicol Pathol. 2011;39(3):544-52. doi: 10.1177/0192623311399786.

Aurora SK, Silberstein SD, Kori SH, Tepper SJ, Borland SW, Wang M, Dodick DW. MAP0004, orally inhaled DHE: a randomized, controlled study in the acute treatment of migraine. Headache. 2011;51(4):507-17. doi: 10.1111/j.1526-4610.2011.01869.x.

Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol. 2004;55(1):19-26. doi: 10.1002/ana.10786.

Carleton SC, Shesser RF, Pietrzak MP, Chudnofsky CR, Starkman S, Morris DL, Johnson G, Rhee KJ, Barton CW, Chelly JE, Rosenberg J, Van Valen MK. Double-blind, multicenter trial to compare the efficacy of intramuscular dihydroergotamine plus hydroxyzine versus intramuscular meperidine plus hydroxyzine for the emergency department treatment of acute migraine headache. Ann Emerg Med. 1998;32(2):129-38.

Cook RO, Shrewsbury SB, Ramadan NM. Reduced adverse event profile of orally inhaled DHE (MAP0004) vs IV DHE: potential mechanism. Headache. 2009;49(10):1423-34. doi: 10.1111/j.1526-4610.2009.01510.x.

D.H.E. 45® Prescribing Information. Bridgewater (NJ): Valeant Pharmaceuticals; 2017 Nov.

Dahlöf C, Maassen Van Den Brink A. Dihydroergotamine, ergotamine, methysergide and sumatriptan - basic science in relation to migraine treatment. Headache. 2012;52(4):707-14. doi: 10.1111/j.1526-4610.2012.02124.x.

Djupesland PG, Messina JC, Mahmoud RA. Breath powered nasal delivery: a new route to rapid headache relief. Headache. 2013;53 Suppl 2:72-84. doi: 10.1111/head.12186.

Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. Headache. 2001;41(10):976-80.

Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. Dihydroergotamine Working Group. Arch Neurol. 1996;53(12):1285-91.

González-Hernández A, Lozano-Cuenca J, Marichal-Cancino BA, MaassenVanDenBrink A, Villalón CM. Dihydroergotamine inhibits the vasodepressor sensory CGRPergic outflow by prejunctional activation of α2-adrenoceptors and 5-HT1 receptors. The Journal of Headache and Pain. 2018;19(1):40. doi: 10.1186/s10194-018-0869-8.

Hartmaier SL, Santanello NC, Epstein RS, Silberstein SD. Development of a brief 24-hour migraine-specific quality of life questionnaire. Headache. 1995;35(6):320-9.

Hoskin KL, Kaube H, Goadsby PJ. Central activation of the trigeminovascular pathway in the cat is inhibited by dihydroergotamine. A c-Fos and electrophysiological study. Brain. 1996;119 (Pt 1):249-56.

Humbert H, Cabiac MD, Dubray C, Lavene D. Human pharmacokinetics of dihydroergotamine administered by nasal spray. Clin Pharmacol Ther. 1996;60(3):265-75. doi: 10.1016/s0009-9236(96)90053-3.

Kellerman DJ, Forst A, Combs DL, Borland S, Kori S. Assessment of the consistency of absorption of dihydroergotamine following oral inhalation: pooled results from four clinical studies. J Aerosol Med Pulm Drug Deliv. 2013;26(5):297-306. doi: 10.1089/jamp.2012.0999.

Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the american headache society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20. doi: 10.1111/head.12499.

Migranal® Administration Instructions. Valeant Pharmaceuticals.

Migranal® Prescribing Information. Aliso Viejo (CA): Valeant Pharmaceuticals.

Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. Neurology. 1986;36(7):995-7.

Schran HF, Tse FLS, Chang C-T, Hunt TL, Saxe MA, Ventura DF, Diserio FJ, Hendler J. Bioequivalence and safety of subcutaneously and intramuscularly administrred dihydroergotamine in healthy volunteers. Current Therapeutic Research. 1994;55(12):1501-8. doi: https://doi.org/10.1016/S0011-393X(05)80758-1.

Sheehan DV, Giddens JM, Sheehan IS. Status Update on the Sheehan-Suicidality Tracking Scale (S-STS) 2014. Innovations in clinical neuroscience. 2014;11(9-10):93-140.

Shrewsbury SB, Cook RO, Taylor G, Edwards C, Ramadan NM. Safety and pharmacokinetics of dihydroergotamine mesylate administered via a Novel (Tempo) inhaler. Headache. 2008;48(3):355-67. doi: 10.1111/j.1526-4610.2007.01006.x.

Silberstein SD, McCrory DC. Ergotamine and dihydroergotamine: history, pharmacology, and efficacy. Headache. 2003;43(2):144-66.

Tfelt-Hansen PC. Relatively slow and long-lasting antimigraine effect of dihydroergotamine is most likely due to basic pharmacological attributes of the drug: a review. Cephalalgia. 2013;33(13):1122-31. doi: 10.1177/0333102413483372.

van der Kuy PH, Lohman JJ, Hooymans PM, Ter Berg JW, Merkus FW. Bioavailability of intranasal formulations of dihydroergotamine. Eur J Clin Pharmacol. 1999;55(9):677-80.

Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol. 1996;53(2):180-4.

Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6) across episodic and chronic migraine. Cephalalgia. 2010;31(3):357-67. doi: 10.1177/0333102410379890.

Appendix A. Schedule of Evaluations

Visit #	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
	Screening	**Baseline**									**Final (12-Month) / Early Term**
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	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	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 (S-STS)	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							
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 & BMI calculation only at Screening (Visit 1). Weight at all visits; [c] Females of childbearing potential only

Appendix A. Schedule of Evaluations (continued)

For original cohort subjects continuing for 6 months after Visit 11

Visit #	12	13	14
			Final / Early Term
Timing of Visit Allowable Visit Window (±days)	**Month 14** (14 days)	**Month 16** (14 days)	**Month 18** (14 days)
Informed Consent Form			
Demographics/Medical history			
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 (S-STS)	X	X	X
Smell Identification Test™			X
Concomitant medications	X	X	X
Study drug supply/Drug Accountability	X	X	X
Adverse events	X	X	X

[a] Focused neurological examination; [b] Height & BMI calculation only at Screening (Visit 1). Weight at all visits; [c] Females of childbearing potential only

Appendix B. Subjective Assessment of Nasal Symptoms

On the rating scale below, identify how much you are bothered by the **BOLD** symptom by placing a vertical line (|) on the line from "none" (left edge) to "worst imaginable" (right edge).

1. Please rate your overall **nasal discomfort**.

   none ├──────────────────────────────────────┤ worst imaginable

2. Please rate your **nasal burning**.

   none ├──────────────────────────────────────┤ worst imaginable

3. Please rate your **nasal itching**.

   none ├──────────────────────────────────────┤ worst imaginable

4. Please rate your **nasal pain**.

   none ├──────────────────────────────────────┤ worst imaginable

5. Please rate your **nasal blockage or obstruction**.

   none ├──────────────────────────────────────┤ worst imaginable

6. Please rate how much **abnormal taste** you experience.

   none ├──────────────────────────────────────┤ worst imaginable

7. Please rate how much **runny nose** you experience.

   none ├──────────────────────────────────────┤ worst imaginable

8. Please rate how much **sneezing** you experience.

   none ├──────────────────────────────────────┤ worst imaginable

Check marks on the VAS will be converted to numerical values in millimeters (0-100 mm) within the database.

Appendix C. Objective Assessment of Nasal Symptoms

A total of 5 questions are listed in this assessment sheet. On the numerical rating scale below, identify the degree of the presence of the **BOLD** physical finding by choosing a number from 0: none, 1: mild, 2: moderate, 3: severe. This sheet will be completed by the qualified physician or physician assistant or nurse practitioner who performs the examination.

1. **Nasal Erythema** (please circle)

0 (none)	1 (mild)	2 (moderate)	3 (severe)

Mild = redness limited to < 20 % of visible nasal mucosa
Moderate = redness 20-50 % of visible nasal mucosa
Severe = redness > 50 % of visible nasal mucosa

2. **Nasal Edema** (please circle)

0 (none)	1 (mild)	2 (moderate)	3 (severe)

Mild = localized swelling < 20 % of visible nasal mucosa
Moderate = area of swelling 20-50 % of visible nasal mucosa
Severe = swelling affects > 50 % of visible nasal mucosa

3. **Rhinorrhea** (please circle)

0 (none)	1 (mild)	2 (moderate)	3 (severe)

Mild = blows nose < 3 times in 1 hour
Moderate = blows nose 4-7 times in 1 hour
Severe = blows nose 8 or greater number of times in 1 hour

(continued on next page)

4. **Nasal Bleeding** (please circle)

0 (none)	1 (mild)	2 (moderate)	3 (severe)

Mild = blood streaking on tissue
Moderate = less than 5 mL (1 teaspoon) estimated bleeding
Severe = greater than or equal to 5 mL (1 teaspoon) estimated bleeding

5. **Nasal Ulceration** (please circle)

0 (none)	1 (mild)	2 (moderate)	3 (severe)

Mild = mucosal erosion < 2 mm in diameter
Moderate = mucosal erosion 3-5 mm in diameter
Severe = mucosal erosion/ulceration 6 mm or greater in diameter

Signature of Investigator **Date (dd/mm/yyyy)**

Appendix D. 24-Hour Migraine Quality of Life Questionnaire

24-HOUR MIGRAINE QUALITY OF LIFE QUESTIONNAIRE

Only the patient (subject) should enter information onto this questionnaire.

The following questions are to be completed 24 HOURS after you take your first dose of medication for your migraine headache, and ask how your quality of life was affected.

In the past 24 HOURS after you took your first dose of medication for your migraine headache, how much of the time did you:
(Please check <u>one</u> box for each question)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
	1	2	3	4	5	6	7
1. have increased sensitivity to light and/or noise	☐	☐	☐	☐	☐	☐	☐
2. have nausea	☐	☐	☐	☐	☐	☐	☐
3. have throbbing head pain	☐	☐	☐	☐	☐	☐	☐
4. feel upset about having migraine headaches	☐	☐	☐	☐	☐	☐	☐
5. feel physically uncomfortable	☐	☐	☐	☐	☐	☐	☐
6. feel concerned that your migraine medication wouldn't relieve your migraine headache symptoms	☐	☐	☐	☐	☐	☐	☐

24-HOUR MIGRAINE QUALITY OF LIFE QUESTIONNAIRE

In the past 24 HOURS after you took your first dose of medication, how much of the time did your migraine headache and accompanying symptoms limit your ability to:
(Please check one box for each question)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
	1	2	3	4	5	6	7
7. do normal everyday work (job outside the home, schoolwork, housework)	☐	☐	☐	☐	☐	☐	☐
8. stay alert	☐	☐	☐	☐	☐	☐	☐
9. operate machinery or a motor vehicle (including home appliances and office equipment)	☐	☐	☐	☐	☐	☐	☐
10. enjoy life	☐	☐	☐	☐	☐	☐	☐

In the past 24 HOURS after you took your first dose of medication, how much did your migraine headache and accompanying symptoms negatively affect your:
(Please check one box for each question)

	A very great deal	A great deal	A good deal	A moderate amount	Some	Very little	None
	1	2	3	4	5	6	7
11. interactions with people who are close to you	☐	☐	☐	☐	☐	☐	☐
12. interactions with other people	☐	☐	☐	☐	☐	☐	☐
13. energy level	☐	☐	☐	☐	☐	☐	☐
14. ability to have a good night's sleep	☐	☐	☐	☐	☐	☐	☐
15. mood	☐	☐	☐	☐	☐	☐	☐

E

Reference: Hartmaier 1995

Appendix E. Headache Impact Test (HIT-6™)

HIT-6™ HEADACHE IMPACT TEST

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

3. When you have a headache, how often do you wish you could lie down?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

Appendix F. Sheehan Suicidality Tracking Scale (S-STS)

SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS)

INSTRUCTIONS: PLEASE USE DATA FROM ALL SOURCES AND CONSIDER SEVERITY, FREQUENCY, TIME SPENT AND TIME FRAME IN YOUR RESPONSES. THE RESPONSE "NOT AT ALL" TO ANY QUESTION MEANS "NONE" AND MEANS THAT THE THOUGHT, EXPERIENCE OR BEHAVIOR "DID NOT OCCUR AT ALL". THROUGHOUT THE SCALE, THE WORDS *INTENT / INTEND* MEAN ANY INTENT GREATER THAN ZERO. SCORE THE MOST SERIOUS EVENT THAT OCCURRED FOR EACH ITEM BELOW.

In the past (timeframe):

1. did you have any accident? (this includes taking too much of your medication accidentally) IF NO, SKIP TO QUESTION 2. IF YES, GO TO QUESTION 1a: — NO ☐ YES ☐

	Not at all	A little	Moderately	Very	Extremely
1a. how seriously did you plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose? IF THE ANSWER TO QUESTION 1a IS 0 (= Not at all), SKIP TO QUESTION 2. IF THE SCORE IS 1 OR HIGHER, GO TO QUESTION 1b:	0	1	2	3	4

1b. did you intend to die as a result of any accident? — NO ☐ YES ☐

In the past (timeframe), **how seriously did you:**	Not at all	A little	Moderately	Very	Extremely
2. think (even momentarily) that you would be better off dead, need to be dead or wish you were dead? How many times? ____	0	1	2	3	4
3. think (even momentarily) about harming or hurting or injuring yourself – with at least some intent or awareness that you might die as a result – or think about suicide (killing yourself)? How many times? ____	0	1	2	3	4
4. have a voice or voices telling you to kill yourself or have dreams with any suicidal content? mark either or both: ☐ a voice or voices ☐ a dream	0	1	2	3	4
5. have any suicide method in mind (i.e. how)? #	0	1	2	3	4
6. have any suicide means in mind (i.e. with what)? #	0	1	2	3	4
7. have any place in mind to attempt suicide (i.e. where)? * #	0	1	2	3	4
8. have any date / timeframe in mind to attempt suicide (i.e. when)?*#	0	1	2	3	4
9. intend to act on thoughts of killing yourself? mark either or both: did you intend to act: ☐ at the time ☐ at some time in the future	0	1	2	3	4
10. intend to die as a result of a suicidal act? mark either or both: did you intend to die: ☐ at the time ☐ at some time in the future	0	1	2	3	4
11. feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later? mark either or both: was this: ☐ to kill yourself ☐ to plan to kill yourself; mark either or both: was this: ☐ largely unprovoked ☐ provoked	0	1	2	3	4
12. take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)?	0	1	2	3	4
13. injure yourself on purpose without intending to kill yourself? How many times? ____	0	1	2	3	4
14. attempt suicide (try to kill yourself)?	0	1	2	3	4

"A suicide attempt is a potentially self-injurious behavior, associated with at least some intent (> 0) to die as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury." (FDA 2012 definition[1,2]). * Note: Items 7 & 8 on S-STS ("a plan for suicide") means not going beyond ideas or talking about a plan for suicide. If actual behaviors occurred, the event should not be coded on item 7 or 8, but as "preparatory behavior" (item 12). Both events can occur separately over the same timeframe. # Note: clinician should ask for details.

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SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS) - EVENTS REPORT

15. IF ANSWER 14 IS POSITIVE ASK:

In the past (timeframe), how many times did you attempt suicide? ____

	When? dd/MMM/yyyy	How?	How serious was each attempt? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Attempt (halted by self, by another person or event, or not at all)
Level **1**: You started the suicide attempt, but then **you decided to stop** and did not finish the attempt.
Level **2**: You started the suicide attempt, but then **you were interrupted** and did not finish the attempt.
Level **3**: You went through the suicide attempt **completely** as you meant to.

16. IF ANSWER 12 IS POSITIVE ASK:

In the past (timeframe), how many times did you take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)? ____
(Include only the times when you stopped short of making an actual suicide attempt.)

	When? dd/MMM/yyyy	How?	How serious was each preparation? Not at all	A little	Moderately	Very	Extremely	Level
1.			0	1	2	3	4	
2.			0	1	2	3	4	
3.			0	1	2	3	4	
4.			0	1	2	3	4	
5.			0	1	2	3	4	

Add rows as needed.

Levels of Preparation
Level **1**: You took active steps to prepare to kill yourself, but you did not start the suicide attempt.
Level **2**: You were about to try to kill yourself, but then **you stopped yourself** just before harming yourself.
Level **3**: You were about to try to kill yourself, but then **someone or something stopped you** just before harming yourself.

TIME SPENT PER DAY WITH ANY SUICIDAL IMPULSES, THOUGHTS OR ACTIONS OVER THE PAST (TIMEFRAME):
Usual time spent per day: ____ hours ____ minutes.
Least amount of time spent in any day: ____ hours ____ minutes.
Most amount of time spent in any day: ____ hours ____ minutes.

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SHEEHAN-SUICIDALITY TRACKING SCALE (S-STS) - CLINICIAN USE ONLY

Complete this section only *if the patient does not return for the scheduled follow up visit* **and** is not available to permit completion of pages 1 and 2. Only one response can be selected from 17 through 22.

FOR CLINICIAN USE ONLY

	NO	YES
17. Missed appointment - reason: subject died from a completed suicide?	0	100
18. Missed appointment - reason: subject died, but not enough information to code as a suicide?	0	**
19. Missed appointment - reason: subject died from cause(s) other than suicide?	0	**
20. Missed appointment - reason: subject alive, but not available because of a suicide attempt?	0	56
21. Missed appointment - reason: subject alive, but not available for known reasons other than suicide?	0	**
22. Missed appointment - reason: subject alive, but not available, for uncertain reasons, or "lost to follow up"?	0	**

Total Scale Score	Add scores from Questions 1a (only if 1b is coded YES), + 2 through 11 + [the highest of 12 or any row of 16] + [the highest of 14 or any row of 15] or (only if applicable 17 or 18 or 19 or 20 or 21 or 22 [page 3]). ** = enter total S-STS score from prior visit only if this response is applicable.	TOTAL	

☐ I have reviewed the answers on Pages 1 and 2 with the patient.

_____ _____
Clinician Signature dd/MMM/yyyy

☐ I have reviewed the answers on Pages 1 and 2 with my doctor or clinician.

_____ _____
Patient Signature dd/MMM/yyyy

References

1. Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. August 2012. Revision 1. U.S Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Silver Spring, MD 20992-0002. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm/ Direct download from www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf
2. Posner K, Oquendo MA et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. C-CASA Definitions in Table 2, page 1037. Am J Psychiatry 2007; 164:1035-1043

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