16.1.1 PROTOCOL AND PROTOCOL AMENDMENTS

The study protocol is provided on the following pages.

CLINICAL STUDY PROTOCOL

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

Study Number: STS101-002

Investigational Drug: STS101 (Dihydroergotamine Nasal Powder)

IND Number: 136585

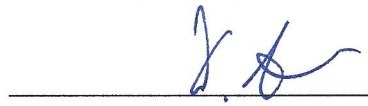
Sponsor: Satsuma Pharmaceuticals, Inc.
400 Oyster Point Boulevard, Suite 221
South San Francisco, CA 94080
Tel. No.: 408-857-5248

Medical Monitor: Detlef Albrecht, MD
Tel. No.: 408-857-5248

Version History: Original April 9, 2019

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.



April 9, 2019

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

Date

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	STS101-002
Title of Study	A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Single Doses of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine
Study center	Approximately 100 in the United States
Objectives	***Primary*** • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain at 2 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from most bothersome symptom at 2 hours after dosing in subjects with acute migraine attacks ***Secondary*** • To evaluate the efficacy of single doses of two strengths of STS101 to achieve 2 to 24 hour sustained pain free status in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve 2 to 48 hour sustained pain free status in subjects with acute migraine attacks • To evaluate the efficacy of single dose of two strengths of STS101 to avoid the use of rescue medication within 24 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single dose of two strengths of STS101 to avoid the use of rescue medication within 48 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at 2 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to avoid headache pain relapse within 24 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to avoid headache pain relapse within 48 hours after dosing in subjects with acute migraine attacks • To evaluate the effects of single doses of two strengths of STS101 on the Functional Impairment Scale (FIS) in subjects with acute migraine attacks • To evaluate the effects of single doses of two strengths of STS101 on the 24-hour Migraine Quality of Life Questionnaire (24-MQoLQ) in subjects with acute migraine attacks

	• To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain depending upon time elapsed from onset of migraine attack to time of dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain by allodynia status at time of dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with severe acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects who wake up with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with acute menstrually related migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at 2 hours after dosing in subjects with acute migraine attacks by allodynia status at time of treatment • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain at various timepoints after dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at various timepoints after dosing • To estimate the probability of a subject responding to treatment (freedom from pain) during the 24-hour post dose period • To estimate the probability of a subject requiring rescue medication during the 24-hour post dose period • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from photophobia at 2 hours after dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from phonophobia at 2 hours after dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from nausea at 2 hours after dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief depending upon time elapsed from onset of migraine to time of dosing • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with acute migraine attacks • To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at various timepoints after dosing in subjects with acute migraine attacks • To evaluate the study subject's global impression of the study treatment • To assess the safety and tolerability of single doses of two strengths of STS101 in the treatment of acute migraine attacks

Methodology	This is a multi-center, single-dose, randomized, double-blind, placebo-controlled, parallel group study in approximately 1140 subjects with acute migraine (ages 18 to 65 years). After establishing initial eligibility, the study participants will document their headache attacks for 28 days in an electronic diary. Attack frequency, duration, pain severity, presence of symptoms (nausea; photophobia, phonophobia) and impact on functional status will be documented. Study participants must have 2 to 8 migraine attacks, and fewer than 15 headache days during the 28-day screening period to be eligible for randomization. After establishing full eligibility, the study participants will be trained in the use of the STS101 device and randomized (1:1:1) to receive one of three treatments: • 3.9 mg STS101 (equivalent to 4.5 mg of DHE mesylate USP) • 5.2 mg STS101 (equivalent to 6.0 mg of DHE mesylate USP) • Placebo (matching nasal powder) After randomization, the study participants will treat their next qualifying migraine attack of at least moderate pain severity with the allocated blinded study medication at home. The subjects will be instructed to treat a qualifying migraine attack within 8 hours of the onset of the attack. The study participants will document the pain severity of their treated migraine attack, presence of symptoms (photophobia, phonophobia, nausea), presence of allodynia and functionality status over the 48-hour period after study drug administration in an e-diary. Headache pain severity and symptom data will be collected at the onset of the migraine attack, immediately before drug administration (time 0), at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours after study drug administration. The subjects must select a most bothersome symptom among photophobia, phonophobia, and nausea immediately before study drug administration. Additionally, subjective nasal irritation assessments will be documented during the treatment period. If subjects require rescue medication, they will be encouraged to wait until the 2-hour post study drug administration data collection timepoint. The use of triptans or other DHE mesylate products as rescue medications should be avoided for 24 hours after study drug administration. The study participants will return to the study site within one week of the treated migraine attack. Adverse events, objective nasal evaluation data, safety laboratory data, vital sign data and ECGs will be recorded before and after treatment to evaluate the tolerability and safety of STS101.
Number of subjects (planned)	A total of approximately 1140 evaluable adult male and female subjects aged 18 to 65 years with acute migraine headaches.

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. Migraine headache frequency of 2 to 8 attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period c. Fewer than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period d. Individual migraine attacks separated by at least 2 days of no headache pain 4. Subjects on preventive migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry and have no plans to change the dose during the study 5. Female subjects will be included if they are post-menopausal (at least 1 year since last menses) 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 adequate contraceptive drugs or devices during the course of this study. Medically acceptable methods of contraception that may be used by the subject and/or her partner are: a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to Screening Visit 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 d. Surgical sterilization of their partner(s) at least 6 months prior to Screening Visit 6. Intact nasal mucosa (no erythema, no inflammation, no ulceration, no swelling, no bleeding, no atrophy (severe local dryness and/or crusting), no septal perforation, and no other nasal conditions that may interfere with intranasal dosing 7. Willing and able to comply with the requirements of the protocol and follow directions from the clinic staff 8. Adequate compliance (≥80%) in the completion of the e-diary during the Screening Period

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 diagnosis of basilar or hemiplegic migraines or cluster headache 4. Abnormal physical findings of clinical significance 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 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. Receiving antihypertensive medication for treatment of hypertension b. Hypercholesteremia (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 the Screening Visit 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) 10. Screening 12-lead ECG showing any clinically significant abnormalities 11. Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, at the Screening Visit 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 or within less than 5 half-lives of tested drug (whichever is longer) 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 one preventive migraine medication. 18. Current use of opioids, barbiturates, or cannabis or cannabinoid containing products 19. Concomitant use of peripheral and central vasoconstrictors including propranolol and nicotine (from smoking, vaping or smokeless products)
Investigational product, dosage and mode of administration	• 3.9 & 5.2 mg STS101 dose strengths (equivalent to 4.5 and 6.0 mg of DHE mesylate USP; nasal powder) • Placebo (matching nasal powder) **For subject training** • STS101 Empty Training Devices • STS101 Filled Training Devices
Duration of study	• Screening period: Up to 35 days • Treatment & follow up period: Up to 56 days

Criteria for evaluation	***Efficacy*** *Primary Efficacy:* • Proportion of subjects free from headache pain at 2 hours post dose (defined as moderate or severe headache pain [2 or 3 on a 4-point scale] at baseline [time 0] becoming none [0] on a 4-point scale) • Proportion of subjects free from most bothersome symptom (MBS) among photophobia, phonophobia and nausea at 2 hours post dose (defined as the MBS identified at baseline [time 0] being absent) *Secondary Efficacy*: • Proportion of subjects free from headache pain at 2 hours post dose and remaining headache free at 24 hours post dose with no use of rescue medication and no relapse of any headache pain (defined as score of 0 on a 4-point scale from 2-24 hours) • Proportion of subjects free from headache pain at 2 hours post dose and remaining headache free at 48 hours post dose with no use of rescue medication and no relapse of any headache pain (defined as score of 0 on a 4-point scale from 2-48 hours) • Proportion of subjects who use rescue medication within 24 hours post dose • Proportion of subjects who use rescue medication within 48 hours post dose • Proportion of subjects with relief from headache pain at 2 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 2 hours post dose by allodynia status at baseline (allodynia status will be defined as "present" with at least 2 "yes" responses to the 6-question allodynia questionnaire [Ashkenazi 2007; Tepper 2011]) • Proportion of subjects with headache relapse within 24 hours post dose (defined as the return of headache of any severity within 24 hours post dosing of the investigational drug, when the subject was pain-free at 2 hours after dosing) • Proportion of subjects with headache relapse within 48 hours post dose (defined as the return of headache of any severity within 48 hours post dosing of the investigational drug, when the subject was pain-free at 2 hours after dosing) • Mean change in scores on Functional Impairment Scale (FIS) at various timepoints post dosing compared to baseline (time 0) • 24-hour Migraine Quality of Life Questionnaire summary scores at 24 hours post dose • Proportion of subjects free from headache pain at 2 hours post dose depending upon time elapsed from onset of migraine attack to time of dosing (investigational drug dosing ≤2 hours, 2-4 hours or >4 hours after onset of migraine attack)

	• Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post dose in subjects with severe headache • Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post dose in subjects who wake up with migraine headache • Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post dose in subjects with menstrually related migraine attack • Proportion of subjects with relief from headache pain at 2 hours post dose by allodynia status at baseline (time 0) (allodynia status will be defined as "present" with at least 2 "yes" responses to the 6-question allodynia questionnaire [Ashkenazi 2007; Tepper 2011]) • Proportion of subjects with headache relief at 2 hours post dose depending upon time elapsed from onset of migraine attack to time of dosing (investigational drug dosing ≤2 hours, 2-4 hours or >4 hours after onset of migraine attack) • Proportion of subjects free from headache pain at various time points after dosing • Proportion of subjects achieving headache relief at various time points after dosing • Proportion of subjects free from photophobia (defined as photophobia being absent at 2 hours post-dose if present at baseline [time 0]) • Proportion of subjects free from phonophobia (defined as phonophobia being absent at 2 hours post-dose if present at baseline [time 0]) • Proportion of subjects free from nausea (defined as nausea being absent at 2 hours post-dose if present at baseline [time 0]) • Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post-dose • Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at various time points post-dose • Patient Global Impression ratings ***Safety*** The following assessment and measurements will be conducted at screening, before randomization and at the final visit: • Physical examination • Vitals signs and body weight • Subjective nasal irritation assessment • Objective nasal irritation assessment • 12-lead ECG • 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	**Sample Size Determination** A total of approximately 1140 evaluable subjects is planned for the study. Given the 1:1:1 randomization ratio, approximately 380 subjects will be randomized to each treatment group. For the co-primary endpoint of pain freedom at 2 hours post dosing of investigational drug, a therapeutic gain of 15% is considered clinically meaningful and targeted. This is assuming a 30% responder rate for STS101 and 15% for the placebo. Based on these assumptions, 380 subjects per arm can provide 99% power to detect the target treatment difference. For the co-primary endpoint of MBS freedom at 2 hours post investigational drug, a therapeutic gain of 12.5%, assuming a 47.5% responder rate for STS101 and 35% for the placebo is targeted. Based on these assumptions, 380 subjects per arm can provide 95% power to detect the target treatment difference. The sample size calculation is based on a chi-square test with a significance level of 0.05 and a 2-sided test. The primary efficacy objective will be addressed by simultaneously testing the 2 co-primary endpoints of pain freedom and MBS freedom at 2 hours after drug administration at a significance level of 0.05. This sample size will provide an overall power of at least 94%. **Efficacy** A detailed Statistical Analysis Plan (SAP) including the final hierarchy of testing of primary and secondary endpoints will be created before data base lock and study unblinding. All study data will be summarized by treatment using descriptive statistics. Unless otherwise specified, for numeric data (e.g., age, weight), descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). All categorical/qualitative data (e.g., gender, race) will be presented using absolute and relative frequency counts and percentage. Data from all investigational centers will be pooled for analysis. For the primary analysis of the co-primary endpoints, missing data will be imputed based on a single-imputation method. Subjects who do not have evaluable assessments at the 2-hour time point, or who received rescue medications prior to the 2-hour time point will be considered as non-responders. The impact of missing data will be further investigated in a number of sensitivity analyses with other single and multiple-imputation approaches. A study-wise Type I error of 0.05 will be used for the study. A multi-family gate-keeping strategy will be employed to control for the study-wise Type I error rate at alpha=0.05. There are 2 families of hypotheses tests. The first family is the primary endpoints family for the 2 dose groups. The second family includes the hypotheses tests with respect to a subset of secondary endpoints for which the control of Type I error is planned. For both co-primary endpoints, the Chi-square test will be used to

	compare the active treatment groups and placebo. Chi-square test will also be used to test secondary endpoints consisting of proportion of responders. For analyses stratified by allodynia status, timing of treatment, the Cochran-Mantel-Haenszel test will be used. The Kaplan-Meier method will be used for time to use of rescue medications. Analysis of Covariance (ANCOVA) with treatment factor and baseline scores as a covariate, will be used for the analysis of FIS. The 24-hour Migraine Quality of Life Questionnaire assessments will be analyzed with the Analysis of Variance (ANOVA) models. The chi-square test will be used to analyze the Patient Global Impression ratings. Subgroup analyses of the key efficacy endpoints will be conducted to gain insight of the nature and consistency of the treatment effect. **Safety** Safety analyses will include all subjects who received at least one dose of study medication. All adverse events reported or observed will be listed, documenting severity, start and stop date and time, possible relationship to study medication, action taken, and outcome. Treatment emergent adverse events (TEAE) are defined as adverse events recorded after dosing of the investigational product. Verbatim terms will be classified to preferred terms (PT) and related system organ class (SOC) using the MedDRA dictionary. The preferred terms and system organ classes will be tabulated by treatment group. All reported adverse events will be summarized by the number of subjects reporting adverse events, system organ class, preferred term, severity and relationship to study drug. Safety labs including complete blood count (CBC), chemistry and urinalysis will be tabulated using descriptive statistics. A tabulation of by-subject abnormal/out-of-range findings and changes from pre-dose (baseline at Visit 2) to post-dose in all laboratory variables will be provided. Vital signs, objective and subjective evaluations of nasal irritation and standard 12-lead ECGs will be tabulated using descriptive statistics. A tabulation of by-subject abnormal/out-of-range findings and changes from pre-dose (baseline at Visit 2) to post-dose variables will be provided.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Explanation
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
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
CRO	Contract Research Organization
CV	Coefficient of Variation
DHE	Dihydroergotamine
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e-diary	Electronic diary in handheld device
ET	Ergotamine Tartrate
FIS	Functional Impairment Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRAS	Generally Recognized As Safe
hCG	Human Chorionic Gonadotropin
HPMC	Hydroxypropyl Methylcellulose
ICF	Informed Consent Form
IM	Intramuscular
IN	Intranasal
IRB	Institutional Review Board
IV	Intravenous
k_{el}	Terminal Rate Constant
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OTC	Over the Counter
PE	Physical Exam
PK	Pharmacokinetic
PT	Preferred Term (in MedDRA dictionary)

Abbreviation or specialist term	Explanation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class (in MedDRA dictionary)
SOP	Standard Operating Procedure
$T_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Events
TK	Toxicokinetic
T_{max}	Time to reach C_{max}
VAS	Visual Analog Scale

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 via 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 (Hoskin 1996; Burstein 2004; Silberstein 2003; Dahlöf 2012; González-Hernández 2018). 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 (Raskin 1986; Winner 1996; Gallagher 1996; Carleton 1998; Edwards 2001; Aurora 2011). 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 (Tfelt-Hansen 2013; Migranal® Prescribing Information 2017)
- 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.

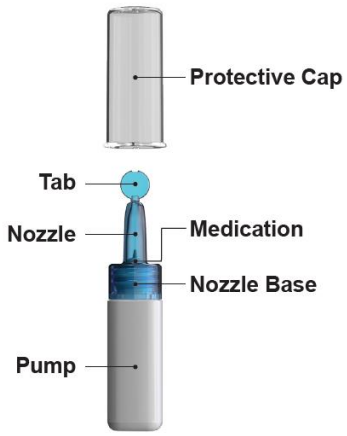
1.2. STS101 Description

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



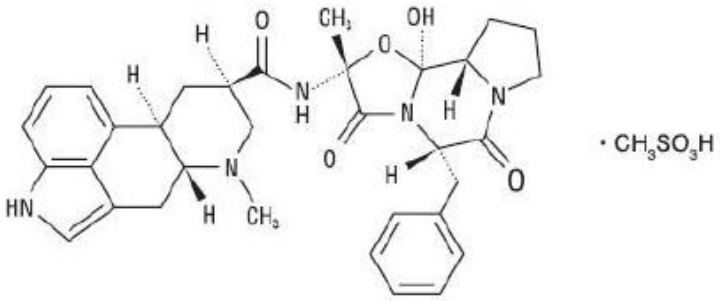
1.2.2. STS101 Powder Formulation

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 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 (Hoskin 1996; Burstein 2004; Silberstein 2003; Dahlöf 2012; González-Hernández 2018). 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 (Schran 1994; Humbert 1996; 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 (Gallagher 1996; Winner 1996, Aurora 2011).

This study follows the FDA Guidance[1] and the Guidelines of International Headache Society for acute migraine studies (Diener 2019) and is being conducted as part of the clinical development program for STS101 to demonstrate the efficacy, safety and tolerability of STS101 in the treatment of acute migraine attacks with or without aura.

[1] FDA Guidance for Industry. Migraine: Developing Drugs for Acute Treatment. February 2018.

2. STUDY OBJECTIVES AND PURPOSE

The objectives of this study are:

Primary

- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain at 2 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from most bothersome symptom at 2 hours after dosing in subjects with acute migraine attacks

Secondary

- To evaluate the efficacy of single doses of two strengths of STS101 to achieve 2 to 24 hour sustained pain free status in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve 2 to 48 hour sustained pain free status in subjects with acute migraine attacks
- To evaluate the efficacy of single dose of two strengths of STS101 to avoid the use of rescue medication within 24 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single dose of two strengths of STS101 to avoid the use of rescue medication within 48 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at 2 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to avoid headache pain relapse within 24 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to avoid headache pain relapse within 48 hours after dosing in subjects with acute migraine attacks
- To evaluate the effects of single doses of two strengths of STS101 on the Functional Impairment Scale (FIS) in subjects with acute migraine attacks
- To evaluate the effects of single doses of two strengths of STS101 on the 24-hour Migraine Quality of Life Questionnaire (24-MQoLQ) in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain depending upon time elapsed from onset of migraine attack to time of dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain by allodynia status at time of dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with severe acute migraine attacks

- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects who wake up with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with acute menstrually related migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at 2 hours after dosing in subjects with acute migraine attacks by allodynia status at time of treatment
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain at various timepoints after dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief at various timepoints after dosing
- To estimate the probability of a subject responding to treatment (freedom from pain) during the 24-hour post dose period
- To estimate the probability of a subject requiring rescue medication during the 24-hour post dose period
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from photophobia at 2 hours after dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from phonophobia at 2 hours after dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from nausea at 2 hours after dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve pain relief depending upon time elapsed from onset of migraine to time of dosing
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom at 2 hours after dosing in subjects with acute migraine attacks
- To evaluate the efficacy of single doses of two strengths of STS101 to achieve freedom from pain and most bothersome symptom over various timepoints after dosing in subjects with acute migraine attacks
- To evaluate the study subject’s global impression of the study treatment
- To assess the safety and tolerability of single doses of two strengths of STS101 in the treatment of acute migraine attacks

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This is a multi-center, single-dose, randomized, double-blind, placebo-controlled, parallel group study in approximately 1140 subjects with acute migraine (ages 18 to 65 years).

After establishing initial eligibility, the study participants will document their headache attacks for 28 days in an electronic diary. Attack frequency, duration, pain severity, presence of symptoms (nausea; photophobia, phonophobia) and impact on functional status will be documented. Study participants must have 2 to 8 migraine attacks, and fewer than 15 headache days during the 28-day screening period to be eligible for randomization.

After establishing full eligibility, the study participants will be trained in the use of the STS101 device and randomized (1:1:1) to receive one of three treatments:

- 3.9 mg STS101 (equivalent to 4.5 mg of DHE mesylate USP)
- 5.2 mg STS101 (equivalent to 6.0 mg of DHE mesylate USP)
- Placebo (matching nasal powder)

After randomization, the study participants will treat their next qualifying migraine attack of at least moderate pain severity with the allocated blinded study medication at home. The subjects will be instructed to treat a qualifying migraine attack within 8 hours of the onset of the attack.

The study participants will document the pain severity of their treated migraine attack, presence of symptoms (photophobia, phonophobia, nausea) presence of allodynia and functional status over the 48-hour period after study drug administration in an e-diary. Headache pain severity and symptom data will be collected at the onset of the migraine attack, immediately before drug administration (time 0), at 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours after study drug administration. The subjects must select a most bothersome symptom among photophobia, phonophobia, and nausea immediately before study drug administration. Additionally, subjective nasal irritation assessments will be documented during the treatment period.

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

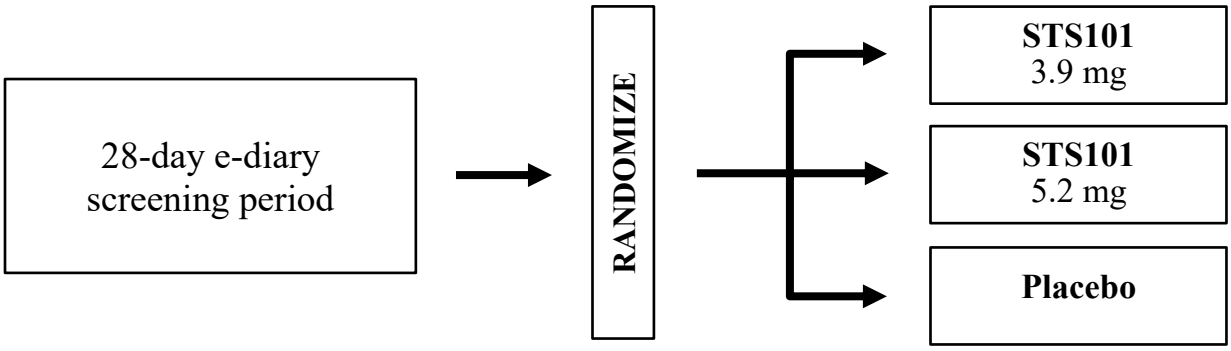
Adverse events, objective nasal evaluation data, safety laboratory data, vital sign data and ECGs will be recorded before and after treatment to evaluate the tolerability and safety of STS101.

Sufficient numbers of subjects will be screened to enroll approximately 1140 subjects in the study. The dropout rate is estimated to be less than 20%. Subjects who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of drop-

outs or number of subjects with missing data exceeds initial expectations, subjects who withdraw or are withdrawn might be replaced.

Figure 3 displays the study schematic design:

Figure 3. Study Schematic



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.

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 1 month (28 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 for the three months prior to the Screening Visit:

- Timing and duration of menstruation in each month
- Occurrence of migraine headaches on day 1 (± 2 days) of menstruation in each month

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™)

At the Randomization Visit (Visit 2), subjects will complete the 6-question Headache Impact Test (Appendix F), a tool for assessing the impact of headache on daily life in subjects with migraine (Yang 2010).

3.2.6. Physical Examination

A physical examination will be performed at Screening (Visit 1), Randomization (Visit 2) 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.

3.2.7. Vital Signs

Vital signs will be obtained at Screening (Visit 1), Randomization (Visit 2), and at the Follow-up/early termination visit. Vital signs will include oral temperature, sitting blood pressure (to be taken after 5 minutes of sitting), pulse rate, and respiration rate.

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, Randomization, and at the follow-up/early termination visit. Subject height will only be measured at screening, 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 Irritation

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 subject will check the severity of each item on a visual analog scale (VAS; range 0-100 mm) in the electronic diary. The questionnaire and completion instructions are shown in Appendix B.

The subjective assessment of nasal irritation will be performed at the following times: Screening (Visit 1), Randomization (Visit 2), immediately before and 15 and 60 minutes and 24 hours after study drug administration and at the Follow-up/early termination Visit (Visit 3).

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

3.2.9.2. Objective Assessment of Nasal Irritation

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 irritation will be performed during Screening (Visit 1), Randomization (Visit 2), and at the Follow-up/early termination Visit (Visit 3). Assessment sheets must be retained for all subjects. The person performing the assessments should be the same at all visits.

3.2.10. Clinical Laboratory Tests

A designated central laboratory will perform the hematology, biochemistry, urinalysis and diagnostic tests as specified in Table 3.

Samples for clinical laboratory tests will be taken at Screening (Visit 1), Randomization (Visit 2) and at the Follow-up/early termination visit (Visit 3). All samples will be collected in accordance with the Study Laboratory Manual and shipped to the designed central laboratory.

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 Randomization Visit or Follow-up visit will be followed until they return to normal or become medically stable.

Table 3. 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	Appearance Color pH Specific Gravity Protein Glucose Ketones Occult Blood Nitrites Urobilinogen Leukocytes Bilirubin Urine microscopy, *if necessary*
Diagnostic Screening		
Urine Alcohol & Drug Panel: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Opiates, PCP and Methadone		

3.2.11. Electrocardiogram

A 12-lead ECG will be performed at Screening (Visit 1), Randomization (Visit 2), and at the Follow-up/early termination Visit (Visit 3). At the Screening and Randomization Visits the investigator or a qualified delegate will review the ECG to assure subject eligibility. All ECGs will be done in triplicate.

3.2.12. Adverse Events Recording

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

3.2.13. Electronic Headache Diary

Study participants will receive a handheld device for collection of electronic diary data. At the Screening and Randomization Visits, study participants will receive training in the use of the device. During the Screening Period the study participants will document their headaches for 28 days. Headache frequency, and migraine attacks (including information on pain severity and symptoms identifying a migraine headache) will be documented. Study participants must have at

least 2 attacks but no more than 8 attacks of migraine and less than 15 headache days during the 28-day period to be eligible for randomization.

During the treatment period, the study participants will document sign and symptom symptoms identifying a migraine headache, the pain severity of their treated migraine attack, presence and severity of symptoms (photophobia, phonophobia, nausea, allodynia) and functional status over the 48-hour period after study drug administration in the e-diary. Additionally, subjective nasal irritation assessments will be documented during the treatment period.

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

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 Procedures

Initial screening will be performed at Study Entry, and it will determine whether subjects will qualify for the study.

3.3.2. Screening Visit & Period (Day-35 to Day -1)

Subject screening procedures and study entry procedures include:

a. Signing of informed consent
b. Review of inclusion/exclusion criteria
c. Recording of demographic data
d. Medical history, including concomitant medications
e. Physical examination
f. Vital signs (including pulse rate, respiration rate, sitting blood pressure and oral temperature)
g. Body weight, height and BMI calculation
h. Objective assessment of nasal irritation
i. Subjective assessment of nasal irritation
j. STS101 device training
k. Electronic headache diary use training
l. Clinical laboratory tests
m. Urinalysis

n. Serum pregnancy test (females only)
o. Urine drug and alcohol screen
p. 12-lead ECG (in triplicate)
q. Completion of Headache Diary by subject (28 days)

3.3.3. Randomization Visit (Visit 2)

Eligible subjects will be randomized to treatment on study Day 1

a. Review of 28-day migraine headache diary data
b. Review of eligibility criteria
c. Vital signs (including pulse rate, respiration rate, sitting blood pressure and oral temperature)
d. Physical examination
e. Weight
f. Concomitant medication review
g. Clinical laboratory tests and urinalysis
h. Serum pregnancy test (females only)
i. Urine drug and alcohol screen
j. 12-lead ECG (in triplicate)
k. Objective assessment of nasal irritation
l. Subjective assessment of nasal irritation
m. Completion of HIT-6 instrument

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. Randomization
b. STS101 device and administration training
c. Dispense Investigational Product
d. Electronic headache diary use training and dispensation of electronic diary

3.3.4. Final Visit/Early Termination (Visit 3)

Subjects will undergo final safety assessment procedures within one week (7 days ± 3days) after migraine treatment. The follow-up visit/early termination procedures will comprise the following:

a. Physical examination
b. Vital signs (including pulse rate, respiration rate, sitting blood pressure and oral temperature)
c. Weight
d. Concomitant medication review
e. Serum pregnancy test (females only)
f. Clinical laboratory tests
g. Urinalysis
h. 12-lead ECG (in triplicate)
i. Objective assessment of nasal irritation
j. Subjective assessment of nasal irritation
k. Patient Global Impression Question
l. Adverse events
m. Collect used Investigational Product (STS101 device)
n. Collect electronic diary device

4. SELECTION AND WITHDRAWAL OF SUBJECTS

A total of approximately 1140 adult male and female subjects aged 18 to 65 years with acute migraine headaches will be enrolled into the study.

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 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. Migraine headache frequency of 2 to 8 attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period
   c. Fewer than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period
   d. Individual migraine attacks separated by at least 2 days of no headache pain
4. Subjects on preventive migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry and have no plans to change the dose during the study
5. Female subjects will be included if they are post-menopausal (at least 1 year since last menses) 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 adequate contraceptive drugs or devices during the course of this study. Medically acceptable methods of contraception that may be used by the subject and/or her partner are:
   a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to Screening Visit
   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
   d. Surgical sterilization of their partner(s) at least 6 months prior to Screening Visit
6. Intact nasal mucosa (no erythema, no inflammation, no ulceration, no swelling, no bleeding, no atrophy (severe local dryness and/or crusting), no septal perforation, and no other nasal conditions that may interfere with intranasal dosing
7. Willing and able to comply with the requirements of the protocol and follow directions from the clinic staff
8. Adequate compliance (≥80%) in the completion of the e-diary during the Screening Period

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 diagnosis of basilar or hemiplegic migraines or cluster headache
4. Abnormal physical findings of clinical significance 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
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. Receiving antihypertensive medication for treatment of hypertension
   b. Hypercholesteremia (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 the Screening Visit
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)
10. Screening 12-lead ECG showing any clinically significant abnormalities
11. Systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, at the Screening Visit
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 or within less than 5 half-lives of tested drug (whichever is longer)
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 one preventive migraine medication
18. Current use of opioids, barbiturates, or cannabis or cannabinoid containing products.
19. Concomitant use of peripheral and central vasoconstrictors including propranolol and nicotine (from smoking, vaping or smokeless products)

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 3) 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. **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 almost white to faintly red powder or colourless crystals. 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:

- 3.9 and 5.2 mg STS101 dose strengths (equivalent to 4.5 and 6.0 mg DHE mesylate USP) as unit dose in a labeled foil wrap.
- Matching placebo as unit dose in a labeled foil wrap.

The non-investigational product will be made available for training during the Screening and Randomization Visits:

- STS101 Empty Training Devices (empty STS101 Device) in a foil wrap.
- STS101 Filled Training Devices (STS101 Device containing microcrystalline cellulose) in a foil wrap.

5.2. Investigational Product Labeling

The foil wrap will be labeled with a label designating:

- STS101 dose strength (3.9 mg, 5.2 mg, or placebo)
- 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 (15-25ºC or 59°F-77°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 Screening (Visit 1) and Randomization (Visit 2), study personnel will train the subject in the study drug preparation and administration. Instructions for Use (Appendix D), an instructional video, STS101 Empty Training Devices and STS101 Filled Training Devices will be used for training of the study subject at both 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.
- Whether or not there was any sneezing and/or nose blowing, within 30 minutes after dosing.

Subjects will be instructed to:

- Place clear Cap, Nozzle's 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 48 hours before and for 24 hours after study drug administration.

No other medication intended for treatment of the acute migraine attack should be taken within 24 hours before and for 2 hours after study drug administration.

Allowed rescue medication include NSAIDs, neuroleptics, corticosteroids, antiemetics, muscle relaxants, sleep medications, gabapentin.

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) is not allowed.

The concomitant use of more than one prevention medication for migraine is not allowed.

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

The concomitant use of opioids, barbiturates, or cannabis or cannabinoid containing products is not allowed.

5.8. Treatment Compliance

All used or unused Investigational Product will be returned to the site at Visit 3 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

After evaluation of the subject eligibility (including review of screening laboratories, 28-day headache diary data) and confirmation that subject meets the Inclusion and Exclusion criteria at the Randomization Visit, a study subject will be randomized in the IWRS system according to the pre-programmed randomization schedule. The randomization will be stratified for the use of migraine prevention medication. The randomization process will be described in a separate document.

5.9.2. Blinding

The study is a double-blind study of STS101 and matching placebo. No personnel directly involved with the conduct of the study will have knowledge of a subject's treatment assignment. This includes all personnel at the study site, at the sponsor and any CRO involved in the conduct and monitoring of the study. A randomization code will be generated by a statistician independent of the study and not be available to the analysis team until the clinical and data collection, entry, and cleaning processes are complete and database is locked for unblinded analysis.

5.9.3. Unblinding Procedures

Unblinding procedures will be described in a separate document.

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.

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 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 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 15, 30, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 24, and 48 hours after study drug administration.

6.1.3. Evaluation of Allodynia

The presence of allodynia (painful cutaneous sensations) will be assessed by prompting the study subjects to respond to these questions (Ashkenazi 2007; Tepper 2011):

1. Is your scalp tender to touch?
2. Does combing your hair bother you?
3. Does wearing your glasses or sunglasses bother you?

4. Does washing your face bother you?
5. Are your teeth and gums tender to touch?
6. Is your skin over the face tender to touch?

For each question, the possible responses are "Yes", "No" and for questions 2 and 3 also "Not applicable (NA)".

Study subjects answering "Yes" to at least 2 questions will be considered to have allodynia. The presence of allodynia will be assessed immediately before drug administration (time 0), at 2 and 4 hours after study drug administration.

6.1.4. 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. Study subjects will be encouraged to avoid use of any rescue medication until the 2-hour post study drug administration data collection timepoint.

6.1.5. Evaluation of Function

6.1.5.1. 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 1, 2, 4, 24, and 48 hours after study drug administration.

6.1.5.2. 24-hour Migraine Quality of Life Questionnaire

The study subjects will be prompted to complete the 24-hour Migraine Quality of Life Questionnaire (24-MQoL) (Appendix E) at 24 hours after drug administration.

6.2. Patient Global Impression

The study subjects will be asked to rate the global impression of the study treatment at Visit 3 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 poor, poor, no opinion, good, very good.

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, Randomization 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, respiration rate and oral 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 Mucosa Irritation Assessments

An assessment of subjective (subject questionnaire) and objective (investigator) nasal irritation assessment will be performed at the Screening, Randomization and follow-up visits.

7.1.1.5. Electrocardiogram (ECG)

Standard 12-lead ECG will be performed in triplicate. All ECGs will be reviewed by a competent physician who will comment on any abnormal findings. Clinically significant findings if found at screening or randomization may be a reason to exclude the subject.

7.1.2. Laboratory Assessments

Central laboratory tests results will be reviewed for any clinically significant abnormalities by a qualified physician or physician assistant. If any clinically significant findings are present at screening, 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. Urine Drug Screen

Alcohol & Drug Panel: Amphetamines, Barbiturates Benzodiazepines, Cannabinoids, Cocaine, Opiates, PCP and Methadone.

7.1.2.5. Serum Pregnancy Test

A serum hCG pregnancy test will be performed at Screening (Visit 1), Randomization (Visit 2) and the Follow-up/early termination visit in all female subjects.

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 Randomization Visit (Visit 2) and continue until the follow-up/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 AE will be followed, whenever possible, until it returns to the baseline condition, is declared medically stable with no further change expected or the subject is lost to follow up.

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 4. 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 4. 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 5 shows the guidelines for rating severity of AEs may be used:

Table 5. 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 ET).

8. STATISTICS

8.1. Sample Size Determination

A total of approximately 1140 evaluable subjects is planned for the study. Given the 1:1:1 randomization ratio, approximately 380 subjects will be randomized to each treatment group.

For the co-primary endpoint of pain freedom at 2 hours after drug administration, a therapeutic gain of 15% is considered clinically meaningful and is targeted. This is assuming a 30% responder rate for STS101 and 15% for the placebo. Based on these assumptions, 380 subjects per arm can provide 99% power to detect the target treatment difference. For the co-primary endpoint of MBS freedom at 2 hours after drug administration, a therapeutic gain of 12.5%, assuming a 47.5% responder rate for STS101 and 35% for the placebo is targeted. Based on these assumptions, 380 subjects per arm can provide 95% power to detect the target treatment difference. The sample size calculation is based on a chi-square test with a significance level of 0.05 and a 2-sided test.

The primary efficacy objective will be addressed by simultaneously testing the 2 co-primary endpoints of pain freedom and MBS freedom at 2 hours after drug administration at a significance level of 0.05. This sample size will provide an overall power of at least 94%.

8.2. Subject Populations

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

8.2.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized subjects who reported a qualifying migraine attack, received the study drug, and reported any post-treatment efficacy evaluation. Data will be analyzed according to the treatment group each subject is randomized to.

8.2.2. Modified Intent-to-Treat Population

For the purposes of efficacy data analysis, the modified intent-to-treat (mITT) population will be the primary analysis population. This population will include all randomized subjects who reported a qualifying migraine attack, received the study drug, and reported a post-treatment efficacy evaluation for at least 1 time point at or before the 2-hour time point. Data will be analyzed according to the treatment group each subject is randomized to.

8.2.3. Per-Protocol Population

The per protocol (PP) population will consist of all mITT subjects who do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. Subjects' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

8.2.4. Safety Population

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

8.3. Statistical Analysis

All study data will be summarized by treatment using descriptive statistics. Unless otherwise specified, for numeric data (e.g., age, weight), descriptive statistics will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). All categorical/qualitative data (e.g., gender, race) will be presented using absolute and relative frequency counts and 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. The SAP will include the final hierarchy for testing of the primary and secondary efficacy endpoints and will be finalized prior to database lock and unblinding of the study.

8.3.1. Demographic and Baseline Variables

Demographics and baseline characteristics (including HIT-6 and triptan response information) will be summarized descriptively by treatment group for the mITT Population, the ITT Population, the Per-Protocol Population, and the Safety Population. Exploratory hypotheses testing may be performed to assess the comparability of demographics and baseline characteristics among the treatment groups. No multiplicity adjustment will be applied to these tests.

8.3.2. Efficacy Analysis

8.3.2.1. Primary Efficacy Endpoints

- Proportion of subjects free from headache pain at 2 hours post dose (defined as moderate or severe headache pain [2 or 3 on a 4-point scale] at baseline [time 0] becoming none [0] on a 4-point scale)
- Proportion of subjects free from most bothersome symptom (MBS) among photophobia, phonophobia and nausea at 2 hours post dose (defined as the MBS identified at baseline [time 0] being absent)

8.3.2.2. Secondary Efficacy Endpoints

- Proportion of subjects free from headache pain at 2 hours post dose and remaining headache free at 24 hours post dose with no use of rescue medication and no relapse of any headache pain (defined as score of 0 on a 4-point scale from 2-24 hours)
- Proportion of subjects free from headache pain at 2 hours post dose and remaining headache free at 48 hours post dose with no use of rescue medication and no relapse of any headache pain (defined as score of 0 on a 4-point scale from 2-48 hours)
- Proportion of subjects who use rescue medication within 24 hours post dose
- Proportion of subjects who use rescue medication within 48 hours post dose
- Proportion of subjects with relief from headache pain at 2 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 2 hours post dose by allodynia status at baseline (time 0) (allodynia status will be defined as "present" with at least 2 "yes" responses to the 6-question allodynia questionnaire [Ashkenazi 2007; Tepper 2011])
- Proportion of subjects with headache relapse within 24 hours post dose (defined as the return of headache of any severity within 24 hours post dosing of the investigational drug, when the subject was pain-free at 2 hours after dosing)
- Proportion of subjects with headache relapse within 48 hours post dose (defined as the return of headache of any severity within 48 hours post dosing of the investigational drug, when the subject was pain-free at 2 hours after dosing)
- Mean change in scores on Functional Impairment Scale (FIS) at various timepoints post dosing compared to baseline (time 0)
- 24-hour Migraine Quality of Life Questionnaire summary scores at 24 hours post dose
- Proportion of subjects free from headache pain at 2 hours post dose depending upon time elapsed from onset of migraine attack to time of dosing (investigational drug dosing ≤2 hours, 2-4 hours or >4 hours after onset of migraine attack)
- Proportion of subjects free from headache pain and free from most bothersome symptom

(MBS) at 2 hours post dose in subjects with severe headache

- Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post dose in subjects who wake up with migraine headache
- Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post dose in subjects with menstrually related migraine attack
- Proportion of subjects with relief from headache pain at 2 hours post dose by allodynia status at baseline (time 0) (allodynia status will be defined as "present" with at least 2 "yes" responses to the 6-question allodynia questionnaire [Ashkenazi 2007; Tepper 2011])
- Proportion of subjects with headache relief at 2 hours post dose depending upon time elapsed from onset of migraine attack to time of dosing (investigational drug dosing ≤2 hours, 2-4 hours or >4 hours after onset of migraine attack)
- Proportion of subjects free from headache pain at various time points after dosing
- Proportion of subjects achieving headache relief at various time points after dosing
- Proportion of subjects free from photophobia (defined as photophobia being absent at 2 hours post-dose if present at baseline [time 0])
- Proportion of subjects free from phonophobia (defined as phonophobia being absent at hours post-dose if present at baseline [time 0])
- Proportion of subjects free from nausea (defined as nausea being absent at 2 hours post-dose if present at baseline [time 0])
- Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at 2 hours post-dose
- Proportion of subjects free from headache pain and free from most bothersome symptom (MBS) at various time points post-dose
- Patient Global Impression ratings

8.3.2.3. Hypotheses Testing and Significance Level

A study-wise Type I error of 0.05 will be used for the study. The multiplicity strategy will be taken into account when interpreting the nominal 2-sided p-values.

A multi-family gate-keeping strategy will be employed to control for the study-wise Type I error rate at alpha=0.05. There are 2 families of hypotheses tests. The first family is the primary endpoints family for the 2 dose groups. The second family includes the hypotheses tests with respect to a subset of secondary endpoints for which Type I error protection is planned.

To adjust for the multiplicity of having 2 dose groups in the primary endpoints family, the truncated Hochberg Step-up Procedure will be used. If both co-primary endpoints for both dose groups are significant at 0.05 level, the secondary endpoints family of hypotheses will be tested according to a pre-specified hierarchy at the 0.05 significance level. If both co-primary endpoints are significant for only one of the two dose groups, the secondary endpoints family of hypotheses will be tested according to a pre-specified hierarchy at the 0.025 significance level.

To adjust for the multiplicity for the endpoints in the secondary endpoints family, a fixed-sequence hierarchical testing procedure will be used. The secondary endpoints will be tested in a pre-defined order at the unused significance level passed on from the testing of the primary endpoints family. The multiplicity adjustment and the order of the secondary endpoints to be tested will be described in detail in the SAP.

8.3.2.4. Handling of Missing Data

For the primary analysis of the co-primary endpoints, missing data will be imputed based on a single-imputation method. Subjects who do not have evaluable assessments at the 2-hour time point, or who received rescue medications prior to the 2-hour time point will be considered as non-responders. The impact of missing data will be further investigated in a number of sensitivity analyses with other single and multiple-imputation approaches. The details of the sensitivity analyses will be described in the SAP.

8.3.2.5. 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.

8.3.2.6. Analysis Methods for Efficacy Endpoints

For both co-primary endpoints, the Chi-square test will be used to compare the active treatment groups and placebo. Chi-square test will also be used to test secondary endpoints consist of proportion of responders. For analyses stratified by allodynia status, timing of treatment, the Cochran-Mantel-Haenszel test will be used. The Kaplan-Meier method will be used for time to use of rescue medications. Analysis of Covariance (ANCOVA) with treatment factor and baseline scores as a covariate, will be used for the analysis of FIS. The 24-hour Migraine Quality of Life Questionnaire assessments will be analyzed with the Analysis of Variance (ANOVA) models. The chi-square test will be used to analyze the Patient Global Impression ratings.

To fully describe the treatment benefit of STS101, the proportion of subjects achieving “no headache pain” at various time points following treatment will be tested between the active treatment groups and placebo. The results will also be displayed graphically to show the time course of effect. To address the onset of efficacy, treatment difference vs. placebo will be examined from the 2 hour-timepoint towards the baseline in a sequential manner (i.e. 2 hours, 1.5 hours, 1 hour, 45 minutes, 30 minutes, 15 minutes). A significance level of 0.05 will be used for this analysis.

8.3.2.7. Subgroup Analysis of Efficacy Endpoints

Subgroup analyses of the key efficacy endpoints will be conducted to gain insight of the nature and consistency of the treatment effect. Subgroups prospectively identified include:

1. age group
2. gender
3. race
4. baseline severity of attack (time 0)
5. allodynia status
6. menstrually related migraine attacks
7. in subjects who wake up with migraine headache

Among these subgroup analyses, # 4, 5, 6, 7 are also included in the secondary endpoints. Analysis by additional subgroups may be considered. They will be specified in the SAP before the study is unblinded for analysis.

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

8.3.3. Safety Analysis

Safety analyses will be conducted for the safety population, which will include all subjects who received at least one dose of study medication. All clinical safety and tolerability data will be summarized by treatment group and listed by treatment group and by subject. 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 each treatment group will be summarized. Because this is a single-dose study, each subject is expected to receive one dose only.

8.3.3.2. Adverse Events

A TEAE is defined as an AE that begins after the dosing of study drug.

An overview of adverse events will be presented by treatment group, which will include the number and percent of subjects who had at least one AE, TEAE, Serious TEAE, TEAE 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 and treatment group:

- 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 Irritation

The data from the Subjective and Objective Assessment of Nasal Irritation will be summarized by treatment group. Exploratory hypothesis testing may be performed to compare treatment group by question. No multiplicity adjustment will be applied to these tests.

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 by treatment group.

For hematology and serum chemistry including calculated creatinine clearance, normal ranges for each parameter will be used to categorize the test result as low (value lower than the lower limit), normal (value within the normal range), or high (value higher than the upper limit). For urinalysis, test results will be categorized as normal and abnormal. Frequency counts and percentages will be presented over time by treatment groups for these categorical data. In addition, shifts from baseline (shift to maximum value, shift to minimum value) to each post-baseline time point and to any post-baseline time point for each parameter will be summarized by treatment group.

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

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 by treatment group.

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 treatment group 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 by treatment groups.

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

8.3.3.7. Concomitant Medications

Concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group. 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.

8.3.4. Interim analysis

No interim analysis is planned for this study.

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 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.

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.

The ICF must contain the subject's dated signature confirming the consent. In addition, a witness must also sign and date the ICF. The person who conducted the informed consent discussion will

also be sign and date the consent form. Each participant will be given a copy of the fully executed ICF.

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

Ashkenazi A, Sholtzow M, Shaw JW, Burstein R, Young WB. Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia. 2007;27(2):111-7. doi: 10.1111/j.1468-2982.2006.01255.x.

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. Valeant Pharmaceuticals; 2017.

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.

Diener HC, Tassorelli C, Dodick DW, Silberstein SD, Lipton RB, Ashina M, Becker WJ, Ferrari MD, Goadsby PJ, Pozo-Rosich P, Wang SJ, Mandrekar J, International Headache Society Clinical Trials Standing C. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia. 2019:333102419828967. doi: 10.1177/0333102419828967.

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.

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; 2017.

Migranal® Prescribing Information. Valeant Pharmaceuticals; 2017.

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.

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

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

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 Assessments

	Visit 1	Visit 2	Visit 3
	Screening	**Randomization**	**Follow-up / Early Termination**
Timing of Visit	**Day -35 to -1**	**Day 1**	**Day 1-56 (±3) days, but within one week of treatment**
Informed consent	X		
Demographic data / Medical history	X		
Physical examination	X	X	X
Vital signs	X	X	X
Body weight and height	X	X[a]	X[a]
BMI Calculation	X		
Hematology, clinical chemistry, urinalysis	X	X	X
Serum pregnancy screen (females only)	X	X	X
Urine Drug and Alcohol Screen	X	X	
12-lead ECG (in triplicate)	X	X	X
Determine / review eligibility	X	X	
HIT-6 Instrument		X	
Headache Diary use training & review	X	X	X[e]
Headache Diary event recording	X[b]	X[c]	
Subjective Nasal Irritation Assessment	X	X	X
Objective Nasal Irritation Assessment	X	X	X
Patient Global Impression Rating			X
Randomization		X	
Concomitant medications	X	X	X
STS101 Instructions for use training	X	X	
Investigational Product supply		X	X[f]
Adverse events recording		X[d]	X

[a] Weight only; [b] Recording of headaches for 28 days; [c] Recording of headache severity & symptoms of treated attack, [d] Starting after randomization visit; [e] Collect e-diary device; [f] Collect STS101 device

Appendix B. Subjective Assessment of Nasal Irritation

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 Irritation

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

* Assessment for this question will be based on the subject record of the number of nose blows as recorded in worksheet

(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. STS101 Instructions for Use


3
Break off tab
Break off tab
Hold the blue Nozzle's base. Break off the Nozzle's Tab by bending it back and forth.
Do NOT squeeze the white Pump yet.
4
Insert into nostril
Insert the blue Nozzle into one nostril as far as it will comfortably go.
5
3x
Deliver dose
a) While breathing in through your nose, quickly and fully squeeze the Pump until your fingers touch.
b) Squeeze 2 more times.
A full dose = 3 squeezes
6
Collect items
a) Place clear Cap, Nozzle's Tab and Nasal Device into the plastic bag provided.
b) Place bag and Foil wrap into the carton.
c) Return carton to the clinical site.

Appendix E. 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 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
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	☐	☐	☐	☐	☐	☐	☐

Reference: Hartmaier 1995

Appendix F. 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

August 12, 2019

TO: ADVARRA IRB

FR: Detlef Albrecht, MD
Satsuma Chief Medical Officer

Re.: STS101-002; Administrative Change #1 to Study Protocol dated 9 April 2019

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

Protocol Page 60 – Written Informed Consent

11.3 Written Informed Consent

In the third paragraph of this section the protocol states:

"The ICF must contain the subject's dated signature confirming the consent. In addition, a witness must also sign and date the ICF."

Revision to Page 60 – Subject Preference Question

Since neither the IRB nor the ICH guidelines or GCP process require the signature of a witness, the ICF does not contain a signature line for a witness and a witness signature will not be required.

Detlef Albrecht
Digitally signed by Detlef Albrecht
Date: 2019.08.12 12:42:49 -07'00'

October 10, 2019

TO: EMERGE Study Investigators

FR: Detlef Albrecht, MD
Satsuma Chief Medical Officer

Re.: STS101-002: Clarifications for Study protocol

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

1. Evaluation of intact nasal mucosa (Visits 1 and 2):

1.1 Study Protocol Inclusion Criterion # 6:

"Intact nasal mucosa (no erythema, no inflammation, no ulceration, no swelling, no bleeding, no atrophy (severe local dryness and/or crusting), no septal perforation, and no other nasal conditions that may interfere with intranasal dosing"

Interpretation and documentation

To meet Inclusion Criterion # 6, the nasal examinations at Visits 1 and 2 must be negative and the criteria "nasal erythema, nasal edema, nasal bleeding, nasal ulceration" in the Objective Assessment of Nasal Irritation (Appendix C) must be checked with "none" = 0. For "rhinorrhea", responses of "none" = 0 and "mild" = 1 in the Objective Assessment of Nasal Irritation are acceptable.

1.2 Objective Assessment of Nasal Irritation (Appendix C)

All five nasal symptoms should be evaluated based on visual inspection of the nose. Please note that the information marked with an asterisk under **3. Rhinorrhea** ("Assessment for this question will be based on the subject record of the number of nose blows as recorded in worksheet") does not apply in this study. The number of nose blows should be based on the information provided by the subject.

2. Contraception

Study Protocol Inclusion Criterion # 5:

"Female subjects will be included if they are post-menopausal (at least 1 year since last menses) 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 adequate contraceptive drugs or devices during the course of this study. Medically acceptable methods of contraception that may be used by the subject and/or her partner are:

a. Simultaneous use of male condom and intra-uterine contraceptive device placed at least 4 weeks prior to Screening Visit
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
d. Surgical sterilization of their partner(s) at least 6 months prior to Screening Visit"

Interpretation and documentation

1) Hysterectomy or bilateral tubal ligation fulfil the criteria "surgically sterilized"
2) All subjects of child bearing potential must agree to use one of the options listed, even if they practiced abstinence before the study, have a same sex partner or no sexual partner. The spirit of this criterion is that a medically acceptable method of contraception is practiced when the potential of pregnancy exists.

3. Cardiovascular Risk Factors

Study Protocol Exclusion Criteria # 7

"Presence of two or more of the following cardiovascular risk factors:
a. Receiving antihypertensive medication for treatment of hypertension
b. Hypercholesteremia (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"

Interpretation

Criterion 7b, is considered **present** if:

a) a subject is taking any kind of cholesterol lowering medications
b) a subject has an LDL >159 mg/dL in the screening or randomization visit labs
c) a subject has the diagnosis of hypercholesteremia in the medical history, regardless if the subject is currently taking drug or other cholesterol lowering treatments, or has no LDL >159 mg/dL. The presence of the diagnosis constitutes the risk factor.

4. Nicotine Use & Beta-blockers

Study Protocol Exclusion Criteria # 19

"Concomitant use of peripheral and central vasoconstrictors including propranolol and nicotine (from smoking, vaping or smokeless products)"

Interpretation

If subjects have been using nicotine products in the past, they must have discontinued those for at least one year before screening to be enrolled in the study. The rationale is resumption of nicotine is common and a long enough period of abstinence must be achieved before the subject can be allowed into the study.

Additional note: beta-blockers other than propranolol such as metoprolol are allowed.

5. Serum HCG tests

a) **All females** are required to have serum HCG tests at Visits 1, 2, and 3 regardless of results.
b) Females who are surgically sterile (bilateral tubal ligation, hysterectomy, or total hysterectomy) and who have serum HCG results of "Inconclusive" at Visit 1, **DO NOT** need to repeat the test; however, serum HCG tests at Visits 2 and 3 must still be done.

c) All other “Inconclusive” HCG test results except as noted in “b” need to be repeated at least one week after the first HCG test and the results need to be sent to the Medical Monitor for confirmation.
d) Surgical sterilization must be documented in medical records/medical history/source documents and eCRFs.

Detlef Albrecht

Digitally signed
by Detlef Albrecht
Date: 2019.10.10
12:55:09 -07'00'

20 Feb 2020

To: **EMERGE Study Investigators**

From: **Detlef Albrecht, MD**
Satsuma Chief Medical Officer

Reg.: **STS101-002 – Administrative Change Letter #3 (20 Feb 2020)**
Protocol Section 5.1 – PBO Filled Devices

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

Protocol Section 5.1.1 – Description of Investigational Product and Packaging (P. 39)

The non-investigational product used for subject training during the Screening and Randomization Visits currently are STS1010 devices filled with microcrystalline cellulose (MCC).

Clarification

In addition to the MCC filled STS101 Training Devices, Satsuma will utilize Placebo filled STS101 Training Devices. Additional information regarding this change:

1. In the Study STS101-002 currently devices filled with microcrystalline cellulose (MCC) are used for training and demonstration of the study drug administration.
2. Due to a shortage of MCC filled devices, Satsuma needs to use placebo filled devices for training and demonstration. These placebo-filled devices contain mannitol and hydroxypropyl methylcellulose (HPMC) in addition to the MCC.
3. Please note that these training devices are used for demonstration only and no administration of powder into the nose occurs during training with the subject.

Detlef Albrecht
Digitally signed by Detlef Albrecht
Date: 2020.02.18 15:24:47 -08'00'

Satsuma Pharmaceuticals

400 Oyster Point Boulevard, Suite 221, South San Francisco, CA 94080