Headache
ISSN 0017-8748
doi: 10.1111/head.13737
Published by Wiley Periodicals, Inc.

Research Submission

A Phase 1, Randomized, Open-Label, Safety, Tolerability, and Comparative Bioavailability Study of Intranasal Dihydroergotamine Powder (STS101), Intramuscular Dihydroergotamine Mesylate, and Intranasal DHE Mesylate Spray in Healthy Adult Subjects

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Objective.—To investigate and compare the safety and the pharmacokinetics of dihydroergotamine (DHE) after administration of intranasal DHE powder (STS101), intranasal DHE spray (Migranal®), and intramuscular (IM) DHE injection in healthy subjects.

Methods.—This was a 2-part, active-controlled, 3-period crossover study over 3 weeks, separated by 1-week washout periods. In part 1, 3 ascending dosage strengths of STS101 (1.3, 2.6, and 5.2 mg) were administered to 15 healthy subjects with no history of migraine. In part 2, 27 healthy subjects were administered 1 dose each of STS101 5.2 mg, Migranal DHE Mesylate Liquid Nasal Spray 2.0 mg, and IM DHE Mesylate 1.0 mg in a randomized order. Liquid chromatography, tandem mass spectrometry was used to determine plasma levels of DHE and its major metabolite, 8′OH-DHE. Pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{0\text{-}2\ h}$, $AUC_{0\text{-}48\ h}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$) for DHE and metabolite were calculated. Geometric means and 90% confidence intervals of log-transformed data were calculated and the ratio of means compared. Safety was evaluated by monitoring adverse events, vital signs, electrocardiograms, subjective and objective assessments of nasal signs and symptoms, and changes in laboratory parameters. The study is registered as NCT03874832.

Results.—Forty-three subjects were enrolled and received study medication. Forty completed all study activities, 14 in part 1 and 26 in part 2. In part 1, DHE plasma levels showed a dose-dependent increase, with STS101 5.2 mg reaching a mean C_{max} of 1870 pg/mL with a T_{max} of 23 minutes. In part 2, STS101 5.2 mg showed rapid absorption, achieving mean DHE plasma concentrations of 1230 and 1850 pg/mL at 10 and 15 minutes after administration, respectively. In comparison to Migranal, STS101 5.2 mg showed approximately 2-fold higher C_{max} (2175 vs 961 pg/mL), $AUC_{0\text{-}2\ h}$ (2979 vs 1316 h × pg/mL), and $AUC_{0\text{-}inf}$ (12,030 vs 6498 h × pg/mL), respectively. The mean $AUC_{0\text{-}inf}$ of STS101 5.2 mg was comparable to IM DHE (12,030 vs 13,650 h × pg/mL). STS101 5.2 mg showed substantially lower variability compared to Migranal for C_{max} (41% vs 76%), $AUC_{0\text{-}2\ h}$ (39% vs 75%), and $AUC_{0\text{-}inf}$ (39% vs 55%). The incidence of treatment emergent AEs (TEAEs), all mild and transient, reported in parts 1 and 2 combined was 9/15 (60%), 5/15 (33%), and 16/41 (39%) of the subjects after 1.3, 2.6, and 5.2 mg STS101, respectively, and 4/26 (15%) and 5/27 (19%) of the subjects after IM DHE and Migranal, respectively.

Conclusion.—STS101 showed rapid absorption, achieving effective DHE plasma concentrations within 10 minutes. It achieved substantially higher C_{max}, $AUC_{0\text{-}2\ h}$ and $AUC_{0\text{-}inf}$, compared to Migranal suggesting potentially better efficacy than Migranal. Its variability was better than Migranal, thus offering improved consistency of response. $AUC_{0\text{-}inf}$ was comparable to IM DHE, suggesting prolonged action and low recurrence. Additionally, the C_{max} was sufficiently low to avoid any significant nausea reported

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Accepted for publication December 7, 2019.

with IV DHE. Thus, STS101 is an easy to administer, non-injected, acute treatment for migraine, with a favorable tolerability profile and is expected to provide rapid and consistent freedom from pain and associated migraine symptoms without recurrence.

Key words: dihydroergotamine mesylate, dihydroergotamine, migraine, pharmacokinetics, intranasal

Abbreviations: CYP cytochrome, DHE dihydroergotamine, ECG electrocardiogram, IM intramuscular, IV intravenous, LC-MS/MS liquid chromatography, tandem mass spectrometry, PK pharmacokinetic, VAS visual analog scale

(*Headache* 2020;60:701-712)

INTRODUCTION

Dihydroergotamine (DHE), especially after intravenous (IV), or intramuscular (IM) administration, is an effective acute treatment for migraine, and could potentially have a broader role in the management of migraine given its unique advantages over triptans.[1-3] However, there is currently no patient-friendly, rapidly absorbed, reliably and consistently effective, easy-to-administer DHE dosage form. The only approved non-injectable DHE product, Migranal® liquid nasal spray, suffers from cumbersome preparation, requires more than 15 minutes to administer a full dose, and has highly variable and unpredictable pharmacokinetic (PK) properties that lead to inconsistent and unreliable clinical response.[1,2,4,5] STS101 (Satsuma Pharmaceuticals, Inc, South San Francisco, CA; Figs. 1 and 2) is a discreet, single-use, drug-device combination product designed to facilitate quick, simple, and intuitive intranasal administration of a novel DHE powder formulation that provides favorable PK properties; in particular, it results in rapid and sustained absorption via the nasal mucosa to achieve DHE plasma concentrations that have been demonstrated to be effective.[6-13] By improving upon ease and speed of administration and providing favorable PK properties, STS101 may facilitate broader utilization of DHE and realization of the unique benefits of DHE by people with migraine. The objective of this Phase 1 study was to evaluate and compare the safety and the pharmacokinetics of DHE after administration of intranasal DHE powder (STS101), intranasal DHE spray (Migranal), and IM DHE injection in healthy subjects.

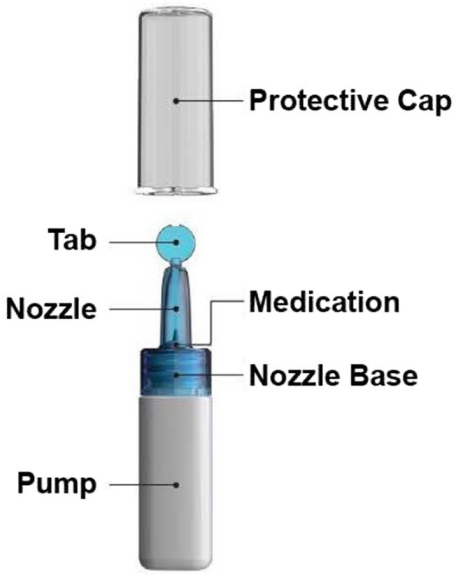

Fig. 1.—STS101.

METHODS

Study Design.—This was a 2-part, active-controlled, 3-period crossover study over 3 weeks, separated by 1-week washout periods (Fig. 3). In part 1, 3 ascending dosage strengths of STS101 were administered in 15 healthy subjects. In part 2, 27 healthy subjects were administered 1 dose each of STS101 5.2 mg, Migranal DHE Mesylate Liquid Nasal Spray 2.0 mg, and IM DHE Mesylate 1.0 mg in a randomized order.

The study was conducted at the Seaview (Quotient) Phase 1 Clinic in Miami, FL in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and in compliance with United States Food and Drug Administration regulations for informed consent and protection of subject rights. The study was approved and monitored by Advarra IRB, Columbia, MD and written informed consent was obtained from each subject before study enrollment. The study is registered as NCT03874832.

Conflict of Interest: DA, MI and DD are employees of Satsuma Pharmaceuticals, Inc. SH and JL are employees of Seaview/Quotient.
Funding: The study was funded by Satsuma Pharmaceuticals, Inc.

Fig. 2.—STS101 administration.

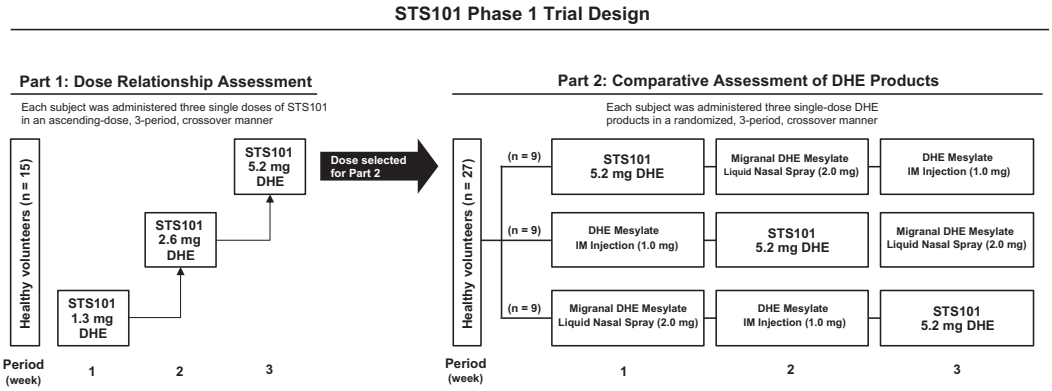

Fig. 3.—Study design.

Study Subjects.—Participants were 18-50 year old healthy subjects of any race and either gender, with no clinically significant abnormality identified in the medical or laboratory evaluations, including a 12-lead electrocardiogram (ECG). Exclusion criteria included any clinically significant central nervous system, cardiac, pulmonary, metabolic, renal, hepatic, or gastrointestinal conditions, and smoking within 12 months before the study. Use of drugs or foods known to interfere with metabolization of DHE via the cytochrome (CYP) 3A4 P450 pathway or peripheral vasoconstrictors, for example triptans, was not permitted. Use of nonprescription medications, including vitamins and natural, herbal, and dietary supplements, had to be discontinued 7 days prior to the screening visit.

Treatments.—In part 1, eligible subjects received 1.3, 2.6, and 5.2 mg (equivalent to 1.5, 3.0, and 6.0 mg DHE mesylate, respectively) of STS101 (Satsuma Pharmaceuticals, Inc, South San Francisco, CA) in an ascending dose order. In part 2, eligible subjects received STS101 5.2 mg, Migranal 2.0 mg (Valeant Pharmaceuticals, Bridgewater, NJ) and IM DHE 1.0 mg (Perrigo, Minneapolis, MN) in a randomized order based on a randomization list with 9 blocks containing all 3 sequences. The randomization list was generated by the study statistician using "Proc Plan" in SAS. The randomization at the study site was done by a study nurse after subjects had completed screening and were determined to be eligible to participate. All subjects remained in the Phase 1 unit for 48 hours after drug administration. Prior to dosing, they refrained from consuming alcohol for 48 hours and caffeinated beverages for 12 hours.

Study Assessments.—Vital signs (respiration rate, heart rate, blood pressure) were recorded before dosing and post dose at 30 and 60 minutes and 2, 4, and 24 hours. Physical examinations were performed pre-dose and post dose at 24 hours. Adverse events were elicited pre-dose and post-dose at 5, 10, 15, 30, 45, 60, and 90 minutes and at 2, 4, 6, 8, 12, 24, 36, and 48 hours. An ECG was performed at screening, pre-dose and post dose at

15, 30, 60, and 90 minutes, and at 2, 4, 8, and 24 hours. Blood samples were taken for eligibility at screening and for routine clinical laboratory evaluations pre-dose and post-dose at 24 hours. An 8-item instrument was used to assess the severity of nasal signs and symptoms (discomfort, burning, itching, sneezing, pain, runny nose, obstruction, and abnormal taste) on a 0-100 mm visual analog scale (VAS), where 0 represents absence of symptom and 100 represents the worst severity of symptom. Subjects completed the VAS pre-dose and post dose at 5, 15, and 60 minutes, and at 4 and 24 hours. Nasal examinations were completed by the same trained and qualified nurse practitioner using a 5-item instrument evaluating the presence and severity of erythema, edema, rhinorrhea, bleeding, and ulceration pre-dose and post dose at 5, 15, and 60 minutes, and at 4 and 24 hours. Blood samples to determine concentrations of DHE and the metabolite were obtained pre-dose and at 5, 10, 15, 30, 45, 60, and 90 minutes and at 2, 4, 6, 8, 12, 24, 36, and 48 hours post-dose.

Bioanalytical and PK Methods.—Quantitative liquid chromatography, tandem mass spectrometry (LC-MS/MS) was used to determine plasma levels of parent DHE and its primary metabolite, 8′OH-DHE. Following extraction, samples were subjected to LC-MS/MS analysis in electrospray positive ion mode using a Sciex API 5000 machine. The method was linear over the standard concentration ranges studied (8-8000 pg/mL for DHE and 19-1900 pg/mL for 8′OH-DHE); imprecision (coefficient of variation) did not exceed 5.6% (CV on CS: DHE: 3.7%/β: 5.6%/α: 5.1%). Replicate analyses of intra- and inter batch DHE quality control samples showed accuracy of 98.2%-108.5% and assay imprecision <5.2%. Replicate 8′OH-DHE analyses of intra- and inter batch quality control samples showed accuracy of 100.7%-107.9% and 94.5%-107.8% and assay imprecision <3.6% and <18.4% for β-8′OH-DHE and α-8′OH-DHE, respectively. Mean (standard deviation) Recovery from human plasma at low, medium, and high levels were of 98.2, 96.5, and 92.3% for DHE, 97.6, 96.9, and 92.5% for β-8′OH-DHE and 90.7, 88.7, and 84.2% for α-8′OH-DHE. All bioanalytical analyses were performed by Syneos/Inventive Health, Quebec City, Canada.

Statistical Methods.—No formal calculation of sample size was performed. Based on similar previous studies, the number of subjects enrolled in this study was considered sufficient to generate meaningful safety and pharmacokinetic data.[5-7]

DHE and 8′OH-DHE concentrations through 48 hours after dosing were used to calculate summary statistics (n, arithmetic mean, SD, %CV, minimum, median, maximum, geometric mean [converting back to the original units], and %CV for the geometric mean) of these pharmacokinetic parameters: C_{max}, T_{max}, $AUC_{0\text{-}30\ min}$, $AUC_{0\text{-}2\ h}$, $AUC_{0\text{-}24\ h}$, $AUC_{0\text{-}48\ h}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$.

The comparative bioavailability of STS101 to IM DHE and Migranal was assessed using a linear mixed model on the natural log-transformed, unadjusted values for AUC_{last}, $AUC_{0\text{-}inf}$, and C_{max}. The model included sequence, period, and treatment as fixed factors, and subject within sequence as a random effect. For each comparison, estimates of the mean difference and corresponding 90% confidence interval (CI) were obtained from the model and exponentiated to provide an estimate of the ratio of geometric means and the 90% CI for the ratio. WinNonlin (Pharsight Corporation, Mountain View, CA, USA) and SAS (SAS Institute, Cary, NC, USA) were used for analyses.

RESULTS

Baseline demographics showed a mean age of 41.1 years (range: 29-50) in part 1 participants and a mean age of 36.8 years (range: 18-49) in part 2 participants (Table 1). In part 1, 14 subjects completed all 3 administrations. One subject was discontinued due

Table 1.—Baseline Characteristics of Study Population

Parameter	Part 1	Part 2
Number of subjects	15	28
Gender (F/M)	8/7	12/16
Age, years†	41.1 (7.0)	36.8 (7.9)
Range	29-50	18-49
Race		
White	13	25
Black or African American	2	3
Weight, kg†	77.6 (13.6)	77.5 (14.5)
Range	58.8-113.5	52.5-108.6
Body mass index, kg/m^2†	27.2 (2.3)	26.7 (2.5)
Range	23.6-31.3	21.3-30.9

†Mean ± standard deviation.

to a positive drug screen before receiving the STS101 5.2 mg dose strength. In part 2, 1 subject withdrew for personal reasons after receiving STS101 and did not receive IM DHE and Migranal. Twenty-seven subjects were dosed with STS101 and are included in the PK and safety analyses. Twenty-seven subjects were dosed with Migranal and are included in the safety analysis because 1 subject, in whom no post dosing blood samples were drawn due to poor venous access, was replaced with an additional subject. Twenty-six subjects who received Migranal are included in the PK analysis. Twenty-six subjects were dosed with IM DHE and are included in the PK and safety analyses.

PK Evaluation.—*DHEPart 1*.—Following administration of ascending doses of STS101 dose-dependent DHE plasma concentrations and pharmacokinetics were shown (Table 2; Fig. 4). The mean C_{max} was 645, 1244, and 1870 pg/mL for the 1.3, 2.6, and 5.2 mg dose strengths, respectively. Mean $AUC_{0\text{-}2\ h}$ was 956, 1683, and 2549 h × pg/mL, and mean $AUC_{0\text{-}inf}$ was 4172, 7022, and 10,150 h × pg/mL, for the 1.3, 2.6, and 5.2 mg dose strengths, respectively.

Part 2.—DHE plasma concentrations rose rapidly after STS101 5.2 mg and IM DHE injection, with mean concentrations exceeding 1000 pg/mL at 10 minutes and 5 minutes after dosing, respectively (Table 3). STS101

Table 2.—Summary of Pharmacokinetic Parameters for DHE; Part 1

	Mean ± Standard Deviation		
PK Parameter	STS101 1.3 mg (n = 15)	STS101 2.6 mg (n = 15)	STS101 5.2 mg (n = 14)
C_{max}, (pg/mL)	645 (418)	1243 (576)	1870 (823)
C_{max}, CV (%)	65	46	44
$AUC_{0\text{-}2\ h}$, h × pg/mL	956 (592)	1683 (719)	2549 (1132)
$AUC_{0\text{-}last}$, h × pg/mL	3931 (1800)	6653 (2411)	9696 (3717)
$AUC_{0\text{-}inf}$, h × pg/mL	4172 (1860)	7022 (2557)	10,150 (3814)
$AUC_{0\text{-}inf}$, CV (%)	45	36	38
T_{max}, h (median [min, max])	0.75	0.50	0.50
	0.50, 1.50	0.25, 2.00	0.25, 0.50
$t_{1/2}$ (h)	12.9 (2.12)	12.6 (1.28)	12.0 (1.61)
CL/F, L/h	423 (176)	476 (158)	673 (265)
Vz/F, L	8074 (4493)	8529 (2413)	11,650 (4680)

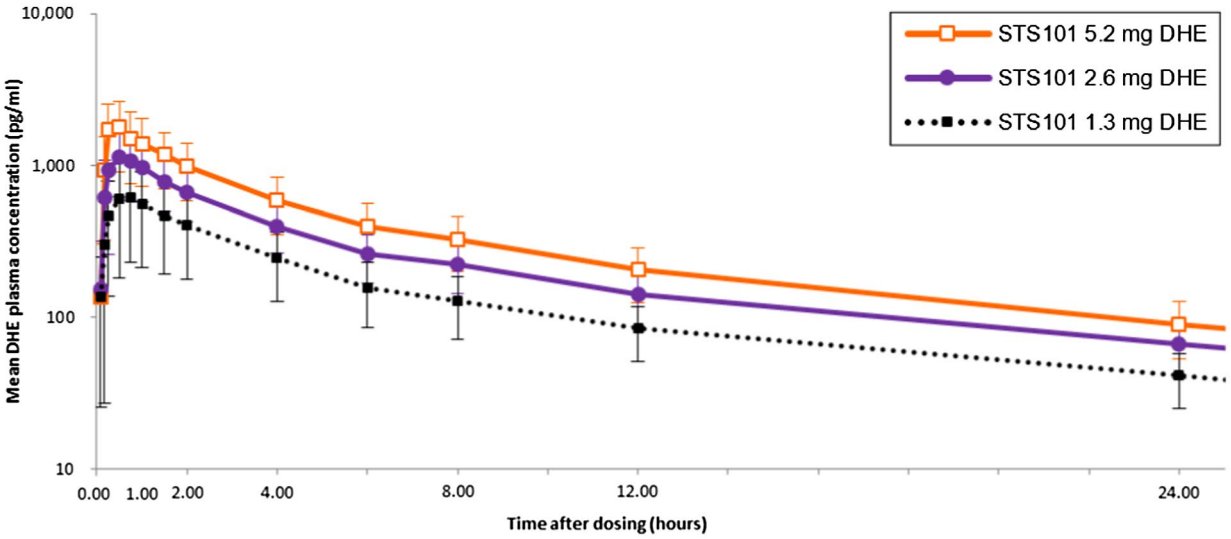

Fig. 4.—Mean DHE plasma concentrations in healthy subjects after administration of a single dose of STS101 (1.3, 2.6 and 5.2 mg DHE; 0-24 hours; Part 1).

5.2 mg showed DHE plasma concentrations and pharmacokinetics comparable to IM DHE and 2-3-fold higher values compared to Migranal (Table 4 and Fig. 5). The mean C_{max} was 2175, 3368 and 961 pg/mL for the STS101 5.2 mg, IM DHE and Migranal, respectively. The median T_{max} was 30, 15 and 60 minutes for STS101 5.2 mg, IM DHE and Migranal, respectively. The mean $AUC_{0\text{-}2\ h}$ was 2979, 4791 and 1316 h × pg/mL, and the mean $AUC_{0\text{-}inf}$ was 12,030, 12,650 and 6498 h × pg/mL for STS101 5.2 mg, IM DHE and Migranal, respectively. The elimination half-life was 11.8, 11.2 and 12.7 hours for STS101 5.2 mg, IM DHE and Migranal, respectively. The variability (coefficient of variation) for C_{max}, $AUC_{0\text{-}2\ h}$, and $AUC_{0\text{-}inf}$ with STS101 was 41%, 39% and 39%, respectively (Table 4). This was substantially lower than for Migranal, which had %CV of 76%, 75% and 55%, for C_{max}, $AUC_{0\text{-}2\ h}$, and $AUC_{0\text{-}inf}$, respectively.

The comparative bioavailability showed ratios of geometric means (and associated 90% confidence intervals; CI) for STS101 5.2 mg and IM DHE of 83% (68, 100), 81% (66, 99) and 61% (48, 77) for AUC_{inf}, AUC_{last}, and C_{max}, respectively (Table 5). The ratios of the geometric means for the comparison of STS101 5.2 mg to Migranal were 205% (169, 250), 217% (178, 266), and 283% (222, 359) for AUC_{inf}, AUC_{last}, and C_{max}, respectively (Table 5).

8′OH-DHE.—Dose dependent 8′OH-DHE plasma concentrations and pharmacokinetics were shown in part 1. In part 2, STS101 5.2 mg showed a higher AUC_{last} as compared to IM DHE and Migranal (Table 6).

Adverse Events.—The incidence of treatment emergent AEs (TEAEs) reported in parts 1 and 2 combined was 9/15 (60%), 5/15 (33%), and 16/41 (39%) of the subjects after 1.3, 2.6, and 5.2 mg STS101, respectively, and 4/26 (15%) and 5/27 (19%) of the subjects after IM DHE and Migranal, respectively (Table 7). All adverse events were mild and transient. No subject was withdrawn from the study for an adverse event. No deaths or serious adverse events occurred. Subjects treated with STS101 reported a higher frequency of nasal adverse events than those treated with IM DHE or Migranal. The most frequent adverse event reported after STS101 was mild nasal discomfort/burning. Subjects reporting dysgeusia noted a mild bitter or sour taste.

Table 3.—Mean DHE Plasma Concentrations 0-120 Minutes (pg/mL; ±SD); Part 2

Time Point (Minutes)	STS101 5.2 mg	IM DHE	Migranal
5	251 (221)	2672 (978)	13 (12)
10	1229 (814)	3008 (1009)	116 (122)
15	1849 (917)	3020 (905)	264 (225)
30	2074 (872)	3039 (828)	757 (633)
60	1654 (648)	2576 (459)	876 (689)
120	1171 (442)	1659 (255)	634 (432)

Table 4.—Summary of Pharmacokinetic Parameters for DHE; Part 2

	Mean ± Standard Deviation		
PK Parameter	STS101 5.2 mg (n = 27)	IM DHE (n = 26)	Migranal (n = 26)
C_{max}, (pg/mL)	2175 (884)	3368 (840)	961 (727)
C_{max}, CV (%)	41	25	76
$AUC_{0\text{-}30\ min}$	686 (326)	1357 (389)	152 (131)
$AUC_{0\text{-}2\ h}$	2979 (1147)	4791 (908)	1316 (990)
$AUC_{0\text{-}2\ h}$, CV (%)	39	19	75
$AUC_{0\text{-}last}$, h × pg/mL	11,440 (4357)	13,240 (2022)	5973 (3409)
$AUC_{0\text{-}inf}$, h × pg/mL	12,030 (4716)	13,650 (2143)	6498 (3551)
$AUC_{0\text{-}inf}$, CV (%)	39	16	55
T_{max}, h (median [min, max])	0.50 0.25, 2.00	0.25 0.08, 1.00	1.00 0.50, 2.00
$t_{1/2}$ (h)	12 (2)	11 (2)	13 (2)
CL/F, L/h	594 (284)	75 (13)	478 (442)
Vz/F, L	10,030 (5030)	1204 (239)	8393 (6628)

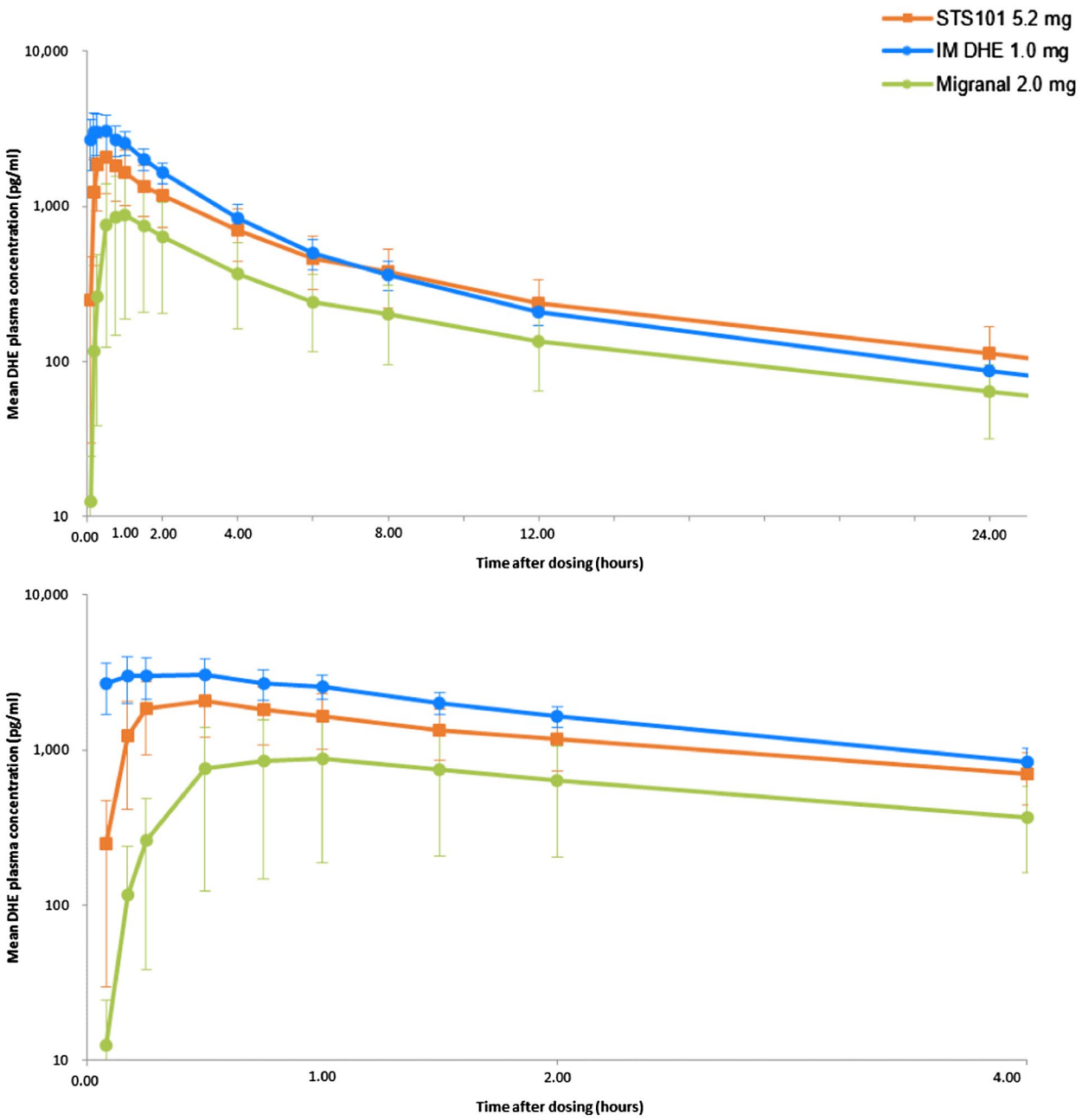

Fig. 5.—Mean DHE plasma concentration in healthy subjects after administration of a single dose of STS101 5.2 mg, IM DHE, and migranal (Top, 0-24 hours; Bottom, 0-4 hours Part 2).

The subjective evaluation of nasal signs and symptoms showed minimal average scores (Fig. 6) indicating the mild nature of the nasal adverse events. The nasal examinations did not show any clinically relevant findings. None of the ECGs, physical examinations, and laboratory tests showed any relevant clinical findings. No device malfunctions were reported.

DISCUSSION

Migraine continues to be an area of high unmet medical need with considerable burden and disability for patients that results in substantial direct and indirect costs.[14-16] Consensus goals for acute migraine treatment include rapid and consistent freedom from pain and associated symptoms without recurrence,

Table 5.—Plasma DHE Comparative Bioavailability Assessment (STS101 5.2 mg vs Migranal and STS101 5.2 mg vs IM DHE)

PK Parameter	STS101 5.2 mg (Geometric Mean)	IM DHE (Geometric Mean)	Ratio of Geometric Means (%)	One-sided 90% CI for Ratio of Geometric Means (%) (Lower, Upper)
$AUC_{0\text{-last}}$ (h × pg/mL)	10,580	13,030	81	66, 99
$AUC_{0\text{-inf}}$ (h × pg/mL)	11,090	13,410	83	68, 100
C_{max} (pg/mL)	1974	3253	61	48, 77

PK Parameter	STS101 5.2 mg (Geometric Mean)	Migranal (Geometric Mean)	Ratio of Geometric Means (%)	One-sided 90% CI for Ratio of Geometric Means (%) (Lower, Upper)
$AUC_{0\text{-last}}$ (h × pg/mL)	10,580	4873	217	178, 265
$AUC_{0\text{-inf}}$ (h × pg/mL)	11,090	5402	205	169, 250
C_{max} (pg/mL)	1974	699	283	222, 359

Table 6.—Summary of Pharmacokinetic Parameters for 8′OH-DHE; Part 2 (All Subjects)

	Mean ± Standard Deviation		
PK Parameter	STS101 5.2 mg (n = 27)	IM DHE (n = 26)	Migranal (n = 26)
C_{max} (pg/mL)	126 (56)	69 (26)	35 (22)
C_{max} CV (%)	45	37	64
$AUC_{0\text{-last}}$, h × pg/mL	1382 (566)	726 (328)	546 (463)
$AUC_{0\text{-inf}}$, h × pg/mL	1923 (512)	NC	NC
T_{max}, h (median [min, max])	2.00 0.5, 4.00	1.00 0.75, 2.00	2.00 1.47, 6.00
$t_{1/2}$ (h)	19 (6)	17 (5)	21 (7)

NC = not calculated.

restored ability to function, minimal need for repeat dosing or rescue medications and minimal or no AEs.[14]

Although oral triptans are commonly prescribed for the acute treatment of migraine attacks, a large meta-analysis of 24,089 patients treated with oral triptans in double-blind, controlled studies found that only approximately 30% on average achieved freedom from pain and approximately 40% did not experience relief by 2 hours following treatment.[17] In addition triptans suffer from inconsistency of response, high rate of recurrence, and high potential for medication overuse headaches.[1,10,17] These results suggest that the current treatment approach for many people with migraine is suboptimal and may explain the low treatment adherence and persistence with oral triptans that has been reported.[18]

DHE has been a staple in migraine therapy for over 70 years and is recognized in migraine treatment guidelines as being a safe and effective initial treatment option for moderate and severe migraine attacks.[1,2] The broad receptor activity profile of DHE may contribute to the benefits of DHE treatment given that migraine pathophysiology involves multiple transmitter systems.[1,3,17] DHE's unique anti-migraine activity includes effectiveness even when administered long after the onset of an attack, effectiveness despite the presence of cutaneous allodynia/ central sensitization, low migraine recurrence rates producing a long refractory period after treatment, and a low risk of causing medication overuse headache, that is believed to be lower than that of triptans.[1-3] However, the need for an injection (intravenous, intramuscular, or subcutaneous) to administer DHE solution and the highly variable pharmacokinetic and consequent inconsistent

Table 7.—Incidence of AEs Occurring in at least 2 Participants in Any Treatment Group

	STS101				
Treatment Emergent AE	1.3 mg (n = 15)	2.6 mg (n = 15)	5.2 mg (n = 41)	Migranal (n = 27)	IM DHE (n = 26)
Any treatment emergent AEs	9 (60.0%)	5 (33.3%)	16 (39.0%)	5 (18.5%)	4 (15.4%)
Eye disorders					
Lacrimation increased			3 (7.3%)		
Gastrointestinal disorders					
Abdominal pain			2 (4.9%)		
General disorders and administration site conditions					
Vessel puncture/injection site reactions	3 (20.0%)	3 (20.0%)			1 (3.8%)
Nervous system disorders					
Dysgeusia	1 (6.7%)	1 (6.7%)	9 (22.0%)	2 (7.4%)	
Headache	2 (13.3%)	1 (3.8%)		1 (3.7%)	1 (3.8%)
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	2 (13.3%)		5 (12.2%)		
Nasal discomfort	4 (26.7%)	3 (20.0%)	14 (34.1%)	2 (7.4%)	
Nasal pruritus			3 (7.3%)		
Rhinalgia			5 (12.2%)	1 (3.7%)	
Rhinorrhea	1 (6.7%)	1 (6.7%)	6 (14.6%)		
Sneezing			2 (4.9%)		

clinical performance of Migranal, as well as burdensome and time-consuming administration procedure, have limited use of DHE in the acute management of migraine.[1,2] MAP0004, an orally inhaled, pulmonary-route dosage form of DHE was developed and demonstrated favorable efficacy and safety in Phase 2 and 3 clinical studies.[13] However, due to manufacturing issues, MAP0004 failed to receive approval from the US Food and Drug Administration, and its development was subsequently discontinued.[5] Thus, there continues to be a significant unmet clinical need for a non-injected DHE dosage form that can be quickly and easily self-administered by migraine patients and results in rapid, consistent, and robust efficacy without significant adverse events.

This healthy subject study was designed to evaluate the tolerability, safety, and PK profile of STS101, a novel drug-device combination product containing a powder formulation of DHE that is self-administered into a single nostril by an air-driven, single-use, disposable nasal delivery device.

In part 1 of the study, dose dependent DHE plasma concentrations were demonstrated over a range of 1.3-5.2 mg STS101. In part 2, the DHE plasma concentrations for 5.2 mg STS101 exceeded concentrations previously reported for Migranal and were comparable to IM DHE.[6,7]

Rapid absorption of any drug for acute treatment of migraine is assumed to be critical for the onset of pain relief.[18,19] The study data suggest that STS101 5.2 mg provides rapid DHE absorption achieving plasma concentrations and an $AUC_{0\text{-}30\ min}$ that have been previously shown to result in an onset of clinical efficacy within about 30 minutes.[8,13]

The plasma concentration over 2 hours ($AUC_{0\text{-}2\ h}$) is important for the 2-hour efficacy endpoints of freedom from pain and most bothersome symptom (photophobia, phonophobia, nausea) in clinical efficacy studies.[18] The reported $AUC_{0\text{-}2\ h}$ values showed more than 2-fold higher DHE concentrations with STS101 compared to Migranal. The $AUC_{0\text{-}2\ h}$ values also exceed previously reported data for the oral inhaled DHE product (MAP0004) and INP104, a liquid DHE formulation administered by a novel, propellant-driven nasal delivery device, by about 2-fold.[5,8]

DHE has been reported to have a long pharmacodynamic half-life and a prolonged receptor residence time due to tight binding.[19] Sustained high plasma

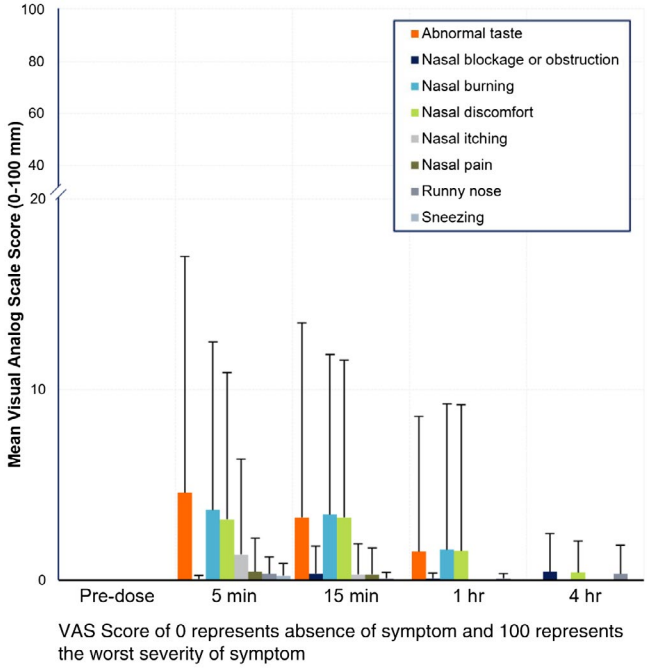

Fig. 6.—Subjective nasal symptoms visual analog scale data (STS101 5.2 mg; Part 2). VAS score of 0 represents absence of symptom and 100 represents the worst severity of symptom.

concentrations beyond 2 hours ($AUC_{0\text{-inf}}$) may also contribute to the sustained efficacy and lower recurrence rates seen with DHE in general and especially with the IM and SC administration which provide the highest $AUC_{0\text{-inf}}$.[6,8-10,15] In this study the $AUC_{0\text{-inf}}$ for STS101 5.2 mg achieved 83% of the values of the IM DHE and 205% of the values for Migranal. Moreover, the $AUC_{0\text{-inf}}$ of STS101 was about 2-fold and 2.5-fold larger in comparison to MAP0004 and INP104, respectively.[5,8]

Migranal use has been hampered by high plasma concentration variability leading to inconsistent and unreliable clinical performance.[17,20] In this study the variability for C_{max} and AUC were substantially lower with STS101 as compared to Migranal, suggesting STS101 may have more predictable, reliable, and robust clinical performance. Plasma concentrations observed following Migranal administration were similar to those reported in historical studies, despite the fact that the current study utilized different bioanalytical methods (LC-MS/MS) than in historical studies (radioimmunoassay).[6,7]

The major metabolite, 8′OH-DHE showed higher C_{max} and AUC after STS101 compared to IM DHE and Migranal. However, in a pharmacological receptor binding study no receptor activity of 8′OH-DHE was demonstrated at values 3 times higher than the C_{max} value reported here, establishing the metabolite as inactive at such low concentrations.[21]

All treatment emergent adverse events were mild in nature, transient and related to the nasal route of administration or known effects of DHE mesylate, for example, taste sensations. No clear dose response relationship for adverse events was seen for STS101. The reported frequency of nasal adverse events may have been impacted by the use of the 8-item instrument visual analog scale for the assessment of subjective nasal irritation. The overall frequency of nasal adverse events was comparable to those of other nasal migraine products.[4,22-24] There was a notable absence of nausea and vomiting with STS101, which is a major limitation of IV DHE. A lower C_{max} compared to the C_{max} reported for IV administration of DHE may be a possible explanation.[25]

In conclusion, STS101 showed a favorable tolerability profile in healthy subjects and resulted in DHE plasma concentrations comparable to IM DHE and higher than Migranal. Based on this data, STS101 is expected to provide rapid pain relief, improvement in functionality and excellent 2-hour and sustained pain

freedom rates. To further evaluate the therapeutic utility of STS101 in the acute treatment of migraine, a large, double-blind, placebo-controlled Phase 3 efficacy study is planned (NCT03901482).

Acknowledgments: The authors would like to thank John Kollins, Rob Schultz and Shannon Strom for their support, Marie-Eve Coulombe for managing the bioanalytical activities, Elisabeth Victor, Isis Fonseca, Maria Cuartas, Suhaills Perez-Castillo, Beverlyn Campbell, Olga Acosta, and Michelle Suarez for performing all study activities with the subjects, Antonio Regueira and Nadege Noel for pharmacy support, Ann Weltervreden Penix for statistical analysis, Deb Koons for clinical monitoring and Cina Salas for writing assistance.

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REFERENCES

1. Saper JR, Silberstein S, Dodick D, Rapoport A. DHE in the pharmacotherapy of migraine: Potential for a larger role. *Headache*. 2006;46(Suppl. 4):S212-S220.
2. Baron EP, Tepper SJ. Revisiting the role of ergots in the treatment of migraine and headache. *Headache*. 2010;50:1353-1361.
3. Silberstein SD, Kori SH. Dihydroergotamine: A review of formulation approaches for the acute treatment of migraine. *CNS Drugs*. 2013;27:385-394.
4. *Migranal® Prescribing Information*. Aliso Viejo, CA: Valeant Pharmaceuticals; 2017.
5. Shrewsbury SB, Jeleva M, Satterly KH, Lickliter J, Hoekman J. STOP 101: A phase 1, randomized, open-label, comparative bioavailability study of INP104, dihydroergotamine mesylate (DHE) administered intranasally by a I123 precision olfactory delivery (POD®) device, in healthy adult subjects. *Headache*. 2019;59:394-409.
6. Schran HF, Tse FLS, Chang C-T, et al. Bioequivalence and safety of subcutaneously and intramuscularly administrred dihydroergotamine in healthy volunteers. *Curr Ther Res*. 1994;55:1501-1508.
7. Humbert H, Cabiac MD, Dubray C, Lavene D. Human pharmacokinetics of dihydroergotamine administered by nasal spray. *Clin Pharmacol Ther*. 1996;60:265-275.
8. Kellerman DJ, Forst A, Combs DL, Borland S, Kori S. Assessment of the consistency of absorption of dihydroergotamine following oral inhalation: Pooled results from four clinical studies. *J Aerosol Med Pulm Drug Deliv*. 2013;26:297-306.
9. Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. Dihydroergotamine Working Group. *Arch Neurol*. 1996;53:1285-1291.
10. 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;53:180-184.
11. Carleton SC, Shesser RF, Pietrzak MP, et al. 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;32:129-138.
12. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache*. 2001;41:976-980.
13. Aurora SK, Silberstein SD, Kori SH, et al. MAP0004, orally inhaled DHE: A randomized, controlled study in the acute treatment of migraine. *Headache*. 2011;51:507-517.
14. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1-18.

15. Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache*. 2018;58:700-714.
16. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: Will health politicians now take notice? *J Headache Pain*. 2018;19:19-27.
17. Dahlöf C, Maassen Van Den Brink A. Dihydroergotamine, ergotamine, methysergide and sumatriptan – Basic science in relation to migraine treatment. *Headache*. 2012;52:707-714.
18. Thomsen LL, Dixon R, Lassen LH, et al. 311C90 (Zolmitriptan), a novel centrally and peripheral acting oral 5hydroxytryptamine1D agonist: A comparison of its absorption during a migraine attack and in a migraine-free period. *Cephalalgia*. 1996;16:270-275.
19. Ferrari A, Pinetti D, Bertolini A, Coccia C, Sternieri E. Interindividual variability of oral sumatriptan pharmacokinetics and of clinical response in migraine patients. *Eur J Clin Pharmacol*. 2008;64:489-495.
20. 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;33:1122-1131.
21. Cook RO, Shrewsbury SB, Ramadan NM. Reduced adverse event profile of orally inhaled DHE (MAP0004) vs IV DHE: Potential mechanism. *Headache*. 2009;49:1423-1434.
22. *IMITREX (Sumatriptan) Nasal Spray Prescribing Information*. Research Triangle Park, NC: GlaxoSmithKline; 2017.
23. Munjal S, Brand-Schieber E, Allenby K, Spierings ELH, Cady RK, Rapoport AM. A multicenter, open-label, long-term safety and tolerability study of DFN-02, an intranasal spray of sumatriptan 10 mg plus permeation enhancer DDM, for the acute treatment of episodic migraine. *J Headache Pain*. 2017;18:31.
24. *ONZETRA™ Xsail™ (Sumatriptan Nasal Powder) Prescribing Information*. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; 2016.
25. Kellerman D, Kori S, Forst A. Nausea associated with dihydroergotamine is a function of maximum concentration and not route of administration (P03.238). *Neurology*. 2012;78:P03.238.