Pharmacokinetics and Safety of Intranasal Dihydroergotamine Powder (STS101)

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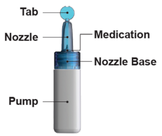
Introduction

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 and other treatments.[1-3] However, there is currently no non-injected DHE dosage form that is easily and quickly self-administered and rapidly achieves and sustains drug plasma concentrations necessary for consistent, reliable and robust efficacy. STS101 is a compact, single-use, drug-device combination product (Fig. 1) designed to facilitate quick and easy intranasal self-administration of a novel DHE powder formulation. By improving upon speed and ease of administration and providing favorable PK properties, STS101 may facilitate broader utilization of DHE and realization of the unique benefits of DHE in migraine. We herein report the results of a Phase 1 clinical pharmacology and safety study of STS101 in healthy adult subjects without a history of migraine.

Figure 1. STS101

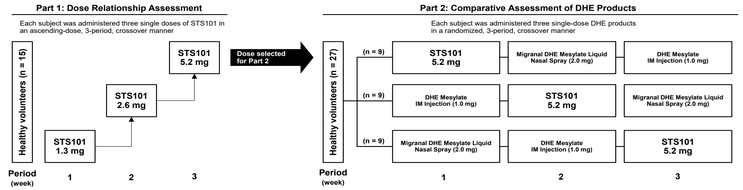


Methods

Study Design

- 2-part, active-controlled, 3-period crossover study over 3 weeks, separated by 1-week washout periods.
- Part 1: 15 healthy subjects received 1.3, 2.6 & 5.2 mg STS101 in ascending order.
- Part 2: 27 healthy subjects received one dose each of STS101 5.2 mg (equivalent to 6.0 mg DHE mesylate), Migranal DHE Mesylate Liquid Nasal Spray 2.0 mg and IM DHE Mesylate 1.0 mg in a randomized order.

Figure 2. Study Design



Study Subjects

- 18 to 50 year-old healthy subjects, with no clinically significant abnormality identified in medical or laboratory evaluations, including a 12-lead electrocardiogram (ECG).
- Use of drugs or foods known to interfere with metabolization of DHE via the cytochrome CYP450 3A4 pathway was not permitted.

Study Assessments

Safety

- Vital signs (respiration rate, heart rate, blood pressure), physical examinations, ECGs, and routine clinical laboratory evaluations
- Adverse events (AEs) elicited 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.
- Nasal examinations & evaluations of subjective nasal irritation with a 0-100 mm visual analogue scale (VAS) pre-dose and at 5, 15, 60 minutes and 4 hours post dose.

Pharmacokinetics

- Blood samples to determine DHE concentrations 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.
- Quantitative liquid chromatography, tandem mass spectrometry (LC-MS/MS) was used to determine plasma levels of DHE.
- PK parameters including C_{max}, T_{max}, $AUC_{0\text{-}30min}$, $AUC_{0\text{-}2h}$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}inf}$, and $t_{1/2}$ for DHE were calculated for all treatment groups. Geometric means and 90% confidence intervals of log-transformed data were calculated, and the ratio of means was compared.

Results

- **STS101 5.2 mg achieved DHE plasma concentrations estimated to be necessary for efficacy (>1 ng/mL) within 10 minutes**
- **STS101 5.2 mg achieved approximately 2-fold higher systemic drug exposure compared to Migranal DHE Mesylate Liquid Nasal Spray 2.0 mg**
- **STS101 5.2 mg showed significantly lower plasma concentration variability than Migranal DHE Mesylate Liquid Nasal Spray 2.0 mg**
- **STS101 5.2 mg achieved systemic drug exposure ($AUC_{0\text{-}inf}$) comparable to IM DHE Mesylate 1.0 mg**
- **STS101 showed dose dependent DHE plasma concentrations**
- **STS101 was well tolerated (all AEs were mild; no AEs lead to discontinuation; no SAEs)**

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

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
$AUC_{0\text{-last}}$, h*pg/mL	3931 (1800)	6653 (2411)	9696 (3717)
$AUC_{0\text{-inf}}$, h*pg/mL	4172 (1860)	7022 (2557)	10150 (3814)
$AUC_{0\text{-inf}}$, CV (%)	45	36	38
T_{max}, h (median [min, max])	0.75 0.50, 1.50	0.50 0.25, 2.00	0.50 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)	11650 (4680)

Table 3. 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
$AUC_{0\text{-}30min}$	686 (326)	1357 (389)	152 (131)
$AUC_{0\text{-}2h}$	2979 (1147)	4791 (908)	1316 (990)
$AUC_{0\text{-last}}$, h*pg/mL	11440 (4357)	13240 (2022)	5973 (3409)
$AUC_{0\text{-inf}}$, h*pg/mL	12030 (4716)	13650 (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	10030 (5030)	1204 (239)	8393 (6628)

Table 4. 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)	10580	13030	81	66, 99
$AUC_{0\text{-inf}}$ (h*pg/mL)	11090	13410	83	68, 100
C_{max} (pg/mL)	1974	3253	61	48, 77

PK Parameter	STS101 (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)	10580	4873	217	178, 265
$AUC_{0\text{-inf}}$ (h*pg/mL)	11090	5402	205	169, 250
C_{max} (pg/mL)	1974	699	283	222, 359

Figure 3. Mean DHE Plasma Concentrations in Healthy Subjects after Administration of a Single Dose of STS101 (1.3, 2.6 and 5.2 mg DHE)

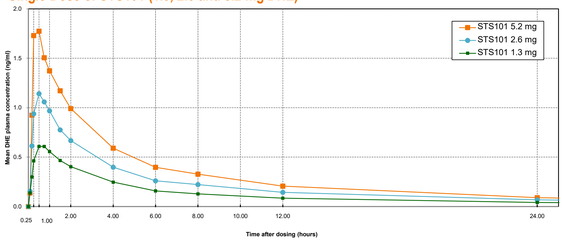


Figure 4. Mean DHE Plasma Concentration in Healthy Subjects after Administration of a Single Dose of STS101 5.2 mg, IM DHE, and Migranal

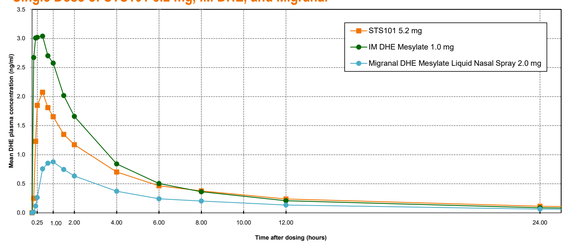


Figure 5. Mean DHE Plasma Concentration in Healthy Subjects after Administration of a Single Dose of STS101 5.2 mg, IM DHE, and Migranal (0-4 hrs)

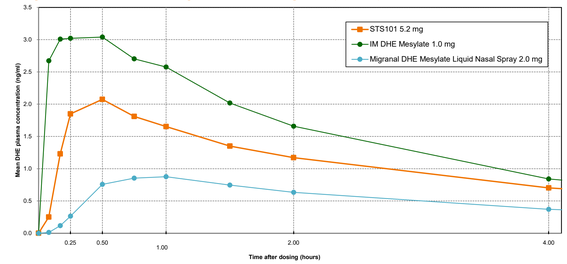
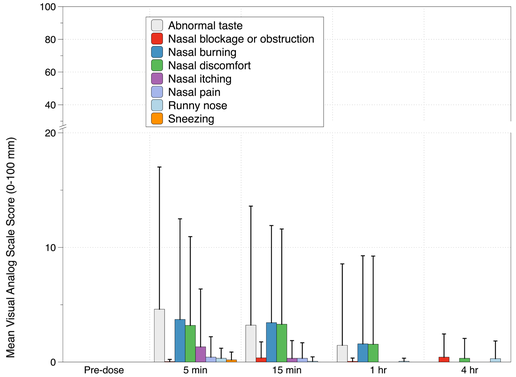


Table 6. Incidence of AEs occurring in at least 2 Participants in Any Treatment Group

Treatment Emergent AE	STS101 1.3 mg (n=15)	STS101 2.6 mg (n=15)	STS101 5.2 mg (n=41)	Migranal Nasal spray (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%)		

STS101 was well tolerated. Nasal exams showed no clinically relevant findings. Minimal average scores in the subjective nasal irritation assessments further underscore the mild nature of adverse events (Fig. 6).

Figure 6. Subjective Nasal Irritation Visual Analogue Scale Data (Part 2; STS101 5.2 mg only)



Conclusions

STS101 5.2 mg was well tolerated and showed DHE plasma concentrations that are expected to provide rapid and consistent freedom from pain and associated migraine symptoms without recurrence. A Phase 3 efficacy study (EMERGE) has recently been initiated.

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:S212-20. doi: 10.1111/j.1526-4610.2006.00605.x.
2. Baron EP, Tepper SJ. Revisiting the role of ergots in the treatment of migraine and headache. Headache. 2010;50(8):1353-61. doi: 10.1111/j.1526-4610.2010.01662.x.
3. Silberstein SD, Kori SH. Dihydroergotamine: a review of formulation approaches for the acute treatment of migraine. CNS Drugs. 2013;27(5):385-94. doi: 10.1007/s40263-013-0061-2.