Pharmacokinetics and safety of STS101, a novel investigational DHE powder drug-device combination in healthy subjects

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Introduction

- Migraine is the third leading cause of disability worldwide for those aged 15-49 years and is estimated to affect 40 million people in the US alone (1 in every 6 adults).[1-3]
- Dihydroergotamine mesylate (DHE) is a semi-synthetic derivative of ergotamine tartrate that has been used since 1946 for the acute treatment of migraine and is recognized as a first-line treatment option.[1,4-6]
- STS101, a novel investigational DHE nasal powder formulation delivered via an easy-to-use, easy-to-carry, pre-filled single-use device, is designed for intranasal administration for the acute treatment of migraine, with or without aura.
- A previous pharmacokinetic (PK) study demonstrated STS101 was well tolerated and achieved systemic drug exposure comparable to intramuscular (IM) DHE 1.0 mg.[7]
- This study compares the PK and safety profile of STS101 with IM DHE and liquid nasal spray (LNS) DHE.

Objective

- To evaluate safety and pharmacokinetics of STS101 5.2 mg DHE nasal powder, IM DHE, and LNS DHE in healthy subjects.

Methods

Study design

- This was a randomized, open-label, 5 period crossover study. Note that the data from two higher STS101 dose strengths is not reported here.
- Thirty-six healthy subjects were administered single doses of STS101 5.2 mg, IM DHE 1.0 mg, and LNS DHE 2.0 mg in a randomized order.
  - Subjects randomized to STS101 were able to self-administer the study drug (Figure 1)
- Blood samples to determine DHE concentrations were obtained pre-dose and up to 48 hours post-dose.
- Vital signs (i.e., respiration rate, heart rate, blood pressure), physical examinations, nasal examinations, and adverse event assessments were performed.

Results

Pharmacokinetics

- DHE plasma concentrations rose rapidly after STS101 and IM DHE, achieving mean concentrations greater than 2000 pg/mL at 20 and 5 minutes, respectively (Figure 2).
- The highest concentrations achieved (C_{max}) among STS101, IM DHE, and LNS DHE were 2230, 3730, and 673 pg/mL, respectively (Table 1).
- STS101 reached an $AUC_{0\text{-}inf}$ of 10900 hr*pg/mL, compared to 13900 and 4240 hr*pg/mL reached by IM DHE and LNS DHE, respectively.
- The PK variability (CV%) of STS101 was substantially lower than that of LNS DHE.
- The comparative bioavailability of STS101 ($AUC_{0\text{-}inf}$) was 3 times greater than that of LNS DHE.

Safety

- Treatment-emergent adverse events (TEAEs) were reported by 5 (14.3%), 10 (29.4%), and 4 (11.8%) subjects in STS101, IM DHE, and LNS DHE treatment arms, respectively.
- The most common treatment-related TEAEs were nasal congestion, nasal discomfort, and headache (Table 2).
- Most TEAEs were mild, with none reported as serious.

Figure 1. STS101 administration

Table 1. Summary of PK parameters

	Statistic	C_{max} (pg/mL)	T_{max} (hr)	$AUC_{0\text{-}0.5}$ (hr*pg/mL)	$AUC_{0\text{-}2}$ (hr*pg/mL)	$AUC_{0\text{-}inf}$ (hr*pg/mL)	$T_{1/2}$ (hr)
STS101 5.2 mg	N	35	35	35	35	35	35
	Mean	2230	NC	687	2860	10900	13.0
	SD	823	NC	271	916	4060	2.37
	CV%	36.9	NC	39.5	32.0	37.3	18.3
	Median (Min, Max)	2170 (813, 4580)	0.50 (0.25, 2.00)	691 (192, 1470)	2780 (877, 5180)	10800 (3090, 25200)	12.3 (9.51, 20.2)
IM DHE 1.0 mg	N	33	33	33	33	33	33
	Mean	3,730	NC	1420	4970	13,900	12.4
	SD	801	NC	332	811	1,990	2.65
	CV%	21.5	NC	23.4	16.3	14.3	21.4
	Median (Min, Max)	3780 (2080, 5040)	0.33 (0.08, 1.00)	1480 (757, 2050)	5190 (3340, 6660)	13900 (10100, 18100)	11.4 (8.69, 18.8)
Liquid Nasal Spray DHE 2.0 mg	N	33	33	33	33	32	33
	Mean	673	NC	109	881	4240	16.5
	SD	587	NC	113	762	2730	6.71
	CV%	87.3	NC	103	86.5	64.5	40.7
	Median (Min, Max)	531 (26.5, 1940)	1.00 (0.33, 8.00)	64.1 (0.992, 441)	720 (23.5, 2660)	3370 (918, 11200)	14.8 (7.11, 43.8)

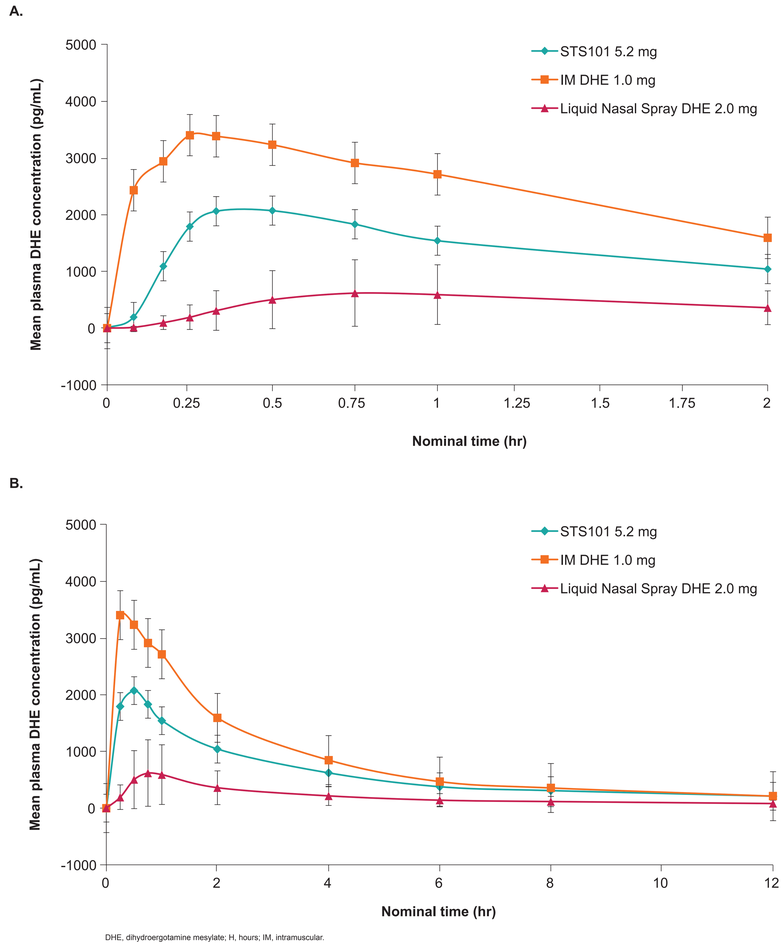
CV%, arithmetic percent coefficient of variation; DHE, dihydroergotamine mesylate; IM, intramuscular; Mean, arithmetic mean; NC, not calculated; SD, standard deviation.

Table 2. Summary of TEAEs (safety population)

	STS101 5.2 mg N=35	IM DHE 1.0 mg N=34	Liquid Nasal Spray DHE 2.0 mg N=34
Treatment-related TEAEs, n (%)	3 (8.6%)	6 (17.6%)	2 (5.9%)
Nervous system disorders, n (%)			
Dysgeusia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Headache	0 (0.0%)	2 (5.9%)	1 (2.9%)
Respiratory, thoracic and mediastinal disorders, n (%)			
Nasal congestion	2 (5.7%)	0 (0.0%)	1 (2.9%)
Nasal discomfort	1 (2.9%)	0 (0.0%)	0 (0.0%)
Nasal dryness	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rhinalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)

IM, intramuscular; TEAEs, treatment-emergent adverse events.

Figure 2. Mean DHE plasma concentrations over (A) 2 hours and (B) 12 hours



DHE, dihydroergotamine mesylate; H, hours; IM, intramuscular.

Conclusions

- STS101 (an investigational DHE nasal powder) was rapidly absorbed, and achieved mean DHE plasma concentration of 2000 pg/mL within 20 minutes.
- STS101 C_{max} and $AUC_{0\text{-}2h}$ were 3-fold greater than liquid nasal spray DHE, with much lower variability.
- STS101 was well tolerated with no serious TEAEs reported.

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Disclosures

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