STS101 Demonstrates Rapid, Consistent Absorption and Sustained Target Plasma Concentrations of Dihydroergotamine (DHE) With Low Variability

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Introduction

- The main goal for the acute treatment of migraine is rapid and consistent freedom from pain and associated symptoms, without recurrence.[1]
- Dihydroergotamine mesylate (DHE) has been used since 1946 for the acute treatment of migraine and is recommended as a first-line treatment option in injectable and liquid nasal spray (LNS) formulations.[2-4]
- STS101, a novel investigational DHE nasal powder formulation delivered via an easy-to-use, easy-to-carry, pre-filled, single-use, intranasal device, achieves systemic drug exposures comparable to the intramuscular (IM) DHE formulation and is well-tolerated.[5]
- For DHE, high early exposure (i.e., $AUC_{0\text{-}0.5h}$) and rapid achievement of peak drug plasma concentrations (C_{max}) in the range of approximately 2000 to 2500 pg/mL may maximize therapeutic response at 2 hours post-dose while avoiding the signature DHE side effects of nausea and vomiting; however, the currently approved DHE LNS (Migranal® 2.0 mg) has slow absorption, low C_{max}, and high pharmacokinetic (PK) variability, which may explain the inconsistent efficacy at 2 hours post-dose reported across randomized, double-blind, placebo-controlled clinical trials.[6]
- Here we present data comparing STS101 5.2 mg, delivered via both 1st and 2nd generation intranasal delivery devices, to DHE LNS 2.0 mg.

Objective

- To evaluate the ability of STS101 and DHE LNS to consistently achieve PK profiles that predict robust early efficacy, maintenance of therapeutic response over time, and minimal side effects in two Phase 1 PK studies.

Methods

Study design

- Studies STS101-001 and STS101-006 were randomized, open-label, crossover studies in which healthy subjects self-administered single doses of study medication, including STS101 5.2 mg and DHE LNS 2.0 mg (2 times 2 administrations of 0.5 mg, 15 minutes apart), under supervision of the study site staff.
- Blood samples to determine DHE concentrations were obtained pre-dose and up to 48 hours post-dose.
  - Liquid chromatography–tandem mass spectrometry was used to determine plasma levels of DHE
- The first STS101 PK study (STS101-001) utilized a 1st generation intranasal delivery device, whereas the second study (STS101-006) utilized a 2nd generation device intended for commercial use (Figure 1).

Results

DHE plasma concentrations (arithmetic means)

- In both studies, STS101 achieved a mean concentration of greater than 2000 pg/mL within approximately 15–20 minutes after dosing and remained above 1000 pg/mL for ≥2 hours (Figure 2).
- The STS101 PK profile achieved with the 2nd generation delivery device intended for commercial use was very similar to the 1st generation device.

Comparison of DHE plasma pharmacokinetic parameters (geometric means)

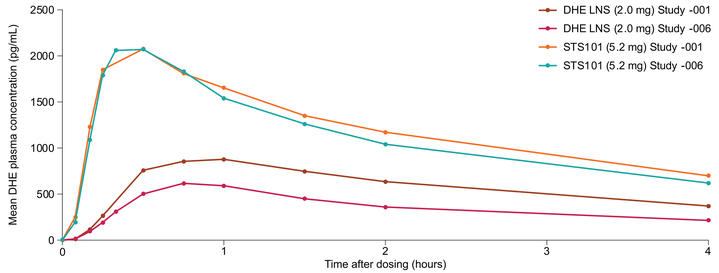
- As reflected by the ratios of the geometric means for C_{max} and AUC parameters of STS101 and DHE LNS, the bioavailability of STS101 was 2–6-fold greater than DHE LNS (Table 1).
- STS101 median T_{max} values were at 0.5 hours, while the median T_{max} for DHE LNS was at 1.0 hour.
- STS101 PK variability between the 1st and 2nd generation devices was similar, and was much lower than that of DHE LNS, as indicated by %CV for both C_{max} and AUC (Figure 3).
- Drug exposure (AUC) with STS101 was consistent between 1st and 2nd generation delivery devices and was significantly greater than DHE LNS at all time points (Figure 4).

Safety

- The most common treatment-related TEAEs reported with STS101 were dysgeusia, nasal discomfort, nasal congestion, and rhinalgia.
- Most TEAEs reported with STS101 were mild, with none reported as serious.

Figure 1. STS101 Administration

Figure 2. Mean DHE Plasma Concentrations (Arithmetic Means)



DHE, dihydroergotamine; LNS, liquid nasal spray.

Table 1. Summary of PK Parameters (Geometric Means)

DHE PK Parameter	STS101-001		STS101-006	
	STS101 5.2 mg (n=27)	DHE LNS 2.0 mg (n=26)	STS101 5.2 mg (n=35)	DHE LNS 2.0 mg (n=33)
C_{max} (pg/mL) (%CV)	1974 (50.8)	706 (103)	2090 (37.8)	417 (155)
T_{max} (h) (range)	0.50 (0.25 – 2.00)	1.00 (0.50 – 2.00)	0.50 (0.25 – 2.00)	1.00 (0.33 – 8.00)
$AUC_{0\text{-}0.5}$ (h·pg/mL) (%CV)	602 (59.8)	96.1 (151)	636 (42.9)	57.0 (232)
$AUC_{0\text{-}2}$ (h·pg/mL) (%CV)	2730 (47.7)	971 (102)	2710 (37.1)	550 (157)
AUC_{last} (h·pg/mL) (%CV)	10580 (44.2)	4908 (79.3)	9550 (40.9)	2920 (88.2)
AUC_{inf} (h·pg/mL) (%CV)	11090 (44.6)	5418 (76.0)[a]	10100 (41.0)	3450 (74.7)[b]

[a]n=25; [b]n=32.

Figure 3. Variability (CV%) of C_{max} and AUC

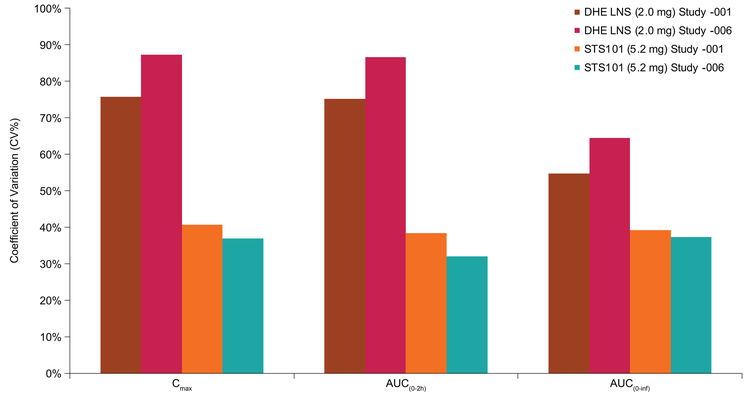


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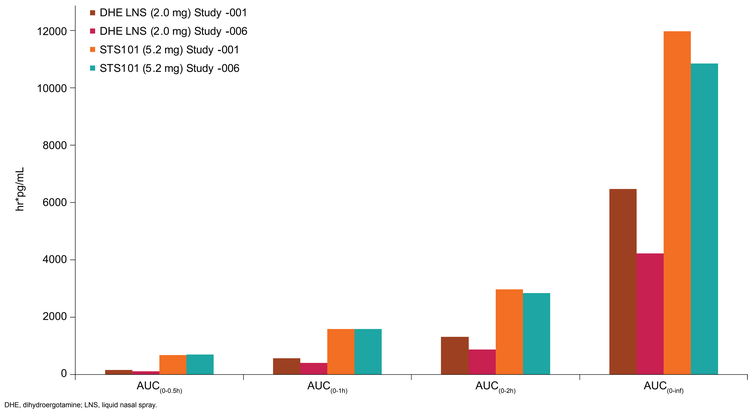
Figure 4. Drug Exposure Over Time



DHE, dihydroergotamine; LNS, liquid nasal spray.

Conclusions

- Across the two studies, STS101 achieved rapid and consistent DHE absorption while sustaining target plasma concentrations with low variability.
- The STS101 PK profile may translate to a DHE product with faster onset and more robust, sustained anti-migraine activity as compared to the marketed DHE LNS.

References

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Disclosures

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