Interim Analysis of STS101 Nasal Safety Data From the Phase 3 Open-Label ASCEND Migraine Study

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Introduction

- Dihydroergotamine mesylate (DHE) is a recommended first-line treatment option for the acute treatment of moderate or severe migraine attacks, with or without aura.[1]
- Available via multiple routes of administration, common side effects of DHE include nausea and vomiting (regardless of the dosage form but more severe when given intravenously), which have been attributed to high peak plasma concentrations after initial administration.[2]
- While liquid nasal sprays have lower reported occurrences of nausea and vomiting, irritative nasal symptoms are common.[2,3]
- 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).

Objective

- To assess the nasal safety of STS101 5.2 mg, a novel investigational DHE nasal powder, in the acute treatment of migraine attacks in the ASCEND open-label, 12-month study.

Methods

Study design and treatment intervention

- ASCEND (NCT04406649) is a multi-center, multiple-dose, open-label, 12-month safety study of STS101 for the acute treatment of migraine in adults (18–65 years).
  - This interim analysis was conducted with a data cutoff date of December 31, 2022, and includes adverse events reported during 12 months of study drug exposure in subjects enrolled by June 30, 2022.
- After establishing eligibility, the study participants could self-administer STS101 5.2 mg as needed (PRN) for up to 2 doses within 24 hours to treat a single migraine attack and up to 12 doses/month.
- This interim analysis included participants exclusively using the STS101 incorporating the second-generation nasal delivery device planned for commercialization.

Subjects

- Study subjects must have had ≥1-year history of migraine (with or without aura) according to the ICHD-3 criteria,[4] including:
  - Migraine onset before age of 50 years
  - 4–12 migraine attacks/month in each of the 3 months prior to screening
  - <15 headache days/month in each of the 3 months prior to screening
- Those with a non-migraine headache diagnosis, history of cerebrovascular disease, and ≥2 cardiovascular risk factors were excluded.
- Subjects must have an intact nasal mucosa at baseline (i.e., no ulceration or bleeding and no or mild erythema, swelling, and rhinorrhea).

Outcomes and analyses

- Nasal safety evaluations include nasal examinations with standardized assessments of nasal findings, subjective assessments of nasal symptoms, smell identification test, and recording of treatment-emergent adverse events (TEAEs) related to nasal/administration.
- The standardized assessment of nasal findings is based on a 5-item physical examination of the nasal cavity that assesses nasal erythema, edema, rhinorrhea, bleeding, and nasal mucosa ulceration on a 4-point severity scale (0=none, 1=mild, 2=moderate, and 3=severe) completed at baseline and Month 12 (or end of study).
- The subjective assessment of nasal symptoms is an 8-item subject-completed questionnaire that uses a 100-point visual analog scale (from 0=none to 100=worst imaginable) to assess overall nasal discomfort, nasal burning, nasal itching, nasal pain, nasal blockage/obstruction, abnormal taste, runny nose, and sneezing, completed at baseline and Month 12 (or end of study).
- The Smell Identification Test™ (SIT) is a 40-item test of olfactory function completed at baseline and Month 12 (or end of study).
- Study data are summarized descriptively for the all-subjects safety population (i.e., all subjects who treated ≥1 migraine attack with study medication).

Results

Subjects

- At the time of data cut-off, 344 subjects had treated 5,571 migraine attacks with STS101.
- At baseline, the all-subjects safety population was:
  - Age 40.4 ± 10.9 years (mean ± standard deviation)
  - 85.8% female
  - 87.5% Caucasian
  - 43.6% Hispanic

Nasal/local treatment-emergent adverse events

- Of 344 subjects treated, 78 (22.7%) reported at least one nasal/local TEAE.
- The most common nasal/local TEAEs (reported by ≥2% of subjects) included nasal discomfort, dysgeusia, nasal congestion, rhinorrhea, rhinalgia, and epistaxis (Table 1).
- Fourteen (4.1%) subjects reported TEAEs leading to discontinuation of study medication (Table 2).

Nasal assessments

- Throughout the study, shifts from baseline in the objective assessment of nasal symptoms were infrequent and minimal (Table 3).
- Small, clinically irrelevant changes (generally <7 points on the 100-point visual analog scale) were observed in the subjective assessment of nasal symptom scores relative to baseline (Figure 2).
- Changes in SIT scores from baseline to Month 12/end of study were very low and clinically irrelevant (Table 4).

Figure 1. STS101 Administration

Table 1. Summary of Nasal and Local Treatment-Emergent AEs (All-Subjects Safety Population)

	All Subjects n=344	All Attacks n=5571
Any nasal TEAE, n (%)	78 (22.7)	540 (9.7)
Nasal TEAEs in ≥2% of subjects, n (%)		
Nasal discomfort	39 (11.3)	342 (6.1)
Dysgeusia [abnormal taste sensation]	26 (7.6)	154 (2.8)
Nasal congestion	17 (4.9)	201 (3.6)
Rhinorrhea [runny nose]	12 (3.5)	50 (0.9)
Rhinalgia [pain in nose]	10 (2.9)	40 (0.7)
Epistaxis [nosebleed]	8 (2.3)	10 (0.2)

TEAE, treatment-emergent adverse event.

Table 2. Nasal/Local Treatment-Emergent AEs Leading to Discontinuation of Study Medication

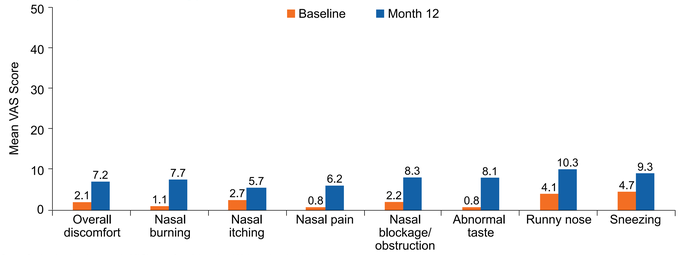
	All Subjects n=344
Rhinalgia [pain in nose], n (%)	3 (0.9)
Nasal discomfort, n (%)	2 (0.6)
Dysgeusia [abnormal taste sensation], n (%)	1 (0.3)
Epistaxis [nosebleed], n (%)	1 (0.3)
Sneezing, n (%)	1 (0.3)
Throat tightness, n (%)	1 (0.3)

*Subjects could report more than one TEAE leading to discontinuation. TEAE, treatment-emergent adverse event.

Table 3. Nasal Examination Findings at Baseline and Month 12 (or End of Study) (Safety Population: n=221)

Subjects, n (%)	Baseline	Month 12 None	Month 12 Mild	Month 12 Moderate	Month 12 Severe
Nasal Erythema	None	199 (92.1)	3 (1.4)	0 (0.0)	0 (0.0)
	Mild	10 (4.6)	4 (1.9)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Edema	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	205 (94.9)	1 (0.5)	0 (0.0)	0 (0.0)
	Moderate	6 (2.8)	4 (1.9)	0 (0.0)	0 (0.0)
Rhinorrhea	None	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	200 (92.6)	4 (1.9)	0 (0.0)	0 (0.0)
Nasal Bleeding	None	8 (3.7)	3 (1.4)	0 (0.0)	0 (0.0)
	Mild	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Ulceration	None	215 (99.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Figure 2. Mean VAS Scores for Subjective Assessment of Nasal Symptoms at Baseline and Month 12 (or End of Study)



Scores for the visual analogue scale (VAS) range from 0 (none) to 100 (worst imaginable).

Table 4. Change from Baseline in Smell Identification Test™ Scores (Safety Population)

	All Subjects n=271	
	Observed	Change from Baseline
Baseline		
n	343	
Mean (SD)	33.5 (4.40)	
Median (Min, Max)	35.0 (15.0, 40.0)	
Month 12/Early Termination		
n	210	209
Mean (SD)	33.1 (4.65)	-0.3 (3.22)
Median (Min, Max)	34.0 (7.0, 40.0)	0.0 (-8.0, 10.0)

Max, maximum; Min, minimum; SD, standard deviation.

Conclusions

- Nasal safety data from more than 5,500 attacks treated in the ongoing open-label ASCEND study indicate that STS101, a novel investigational DHE nasal powder, appears safe and well tolerated by subjects with migraine when used on a PRN basis.
- Nasal examinations, assessments of nasal symptoms and smell test data did not show clinically relevant findings and further support the nasal safety of STS101.
- Nasal AE rates are similar to or lower than rates reported in other studies with liquid DHE formulations.[5,6]

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Disclosures

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Dr. Rapoport is an advisor for AbbVie, Amgen, Biohaven, Cala Health, Satsuma, Teva Pharmaceutical Industries, Theranica, Xoc and Zosano; is on the speakers bureau of AbbVie, Amgen, Biohaven, Lundbeck, and Teva Pharmaceutical Industries; and is an Editor-in-Chief of *Neurology Reviews*.
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