Interim Analysis of Long-Term Safety and Tolerability Data of STS101 From the Phase 3 Open-Label ASCEND Study

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Introduction

- STS101, a novel investigational dihydroergotamine mesylate (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).
- Common side effects of DHE include nausea and vomiting (regardless of dosage form), which have been attributed to high peak plasma concentrations after initial administration.[1,2]
- While liquid nasal sprays have lower reported occurrences of nausea and vomiting, irritative nasal symptoms are common.[1,2]
- Two previous Phase 1 studies of STS101 showed that a dose level of 5.2 mg rapidly achieved plasma concentrations in the target therapeutic range (approaching those of intramuscular DHE and 2-3-fold higher than liquid nasal sprays) with a favorable tolerability profile in healthy subjects.[3,4]

Objective

- To report preliminary safety and tolerability data from an ongoing, long-term (12 month), open-label Phase 3 study for STS101 5.2 mg for the acute treatment of migraine attacks.

Methods

Study design and treatment intervention

- ASCEND (NCT04406649) is an ongoing, open-label, 12 month study of STS101 (DHE nasal powder) in adults aged 18–65 years with migraine.
  - The data cutoff date for this preliminary analysis was June 30, 2022
- After establishing eligibility, subjects could self-administer STS101 5.2 mg up to 2 doses within 24 hours to treat a single migraine attack, and up to 12 doses per month (Figure 1).

Subjects

- Study subjects must have ≥1-year history of migraine (with or without aura) according to the International Classification of Headache Disorders, 3rd edition, including[5]:
  - 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
- Exclusion criteria included subjects with a diagnosis of non-migraine headache, history of cerebrovascular disease, and those with ≥2 cardiovascular risk factors.
- Subjects must have an intact nasal mucosa at baseline (i.e., no ulceration or bleeding; no or mild erythema, swelling, and rhinorrhea).

Outcomes and Analyses

- Safety evaluations include physical and nasal examinations, vital signs, ECGs, laboratory tests, and treatment emergent adverse event (TEAE) assessments.
- TEAE assessment will be performed at every study visit (months 1–6, 8, 10, and 12).
- Blood pressure and assessment of nasal symptoms will be evaluated at every visit (screening, baseline, and months 1–6, 8, 10, and 12).
- A 12-lead ECG will be performed in triplicate at screening, baseline, and months 3, 6, 8, 10, and 12.
- This interim safety analysis included those participants who used the STS101 incorporating the second-generation nasal delivery device planned for commercialization.

Results

Subjects

- The safety population included 344 subjects who treated 5571 migraine attacks, with 143 completing 6 months of treatment while treating 3653 migraine attacks (average of 4.3 treated attacks per month).
  - Mean age: 40 ± 11 years
  - 86% female
  - 89% Caucasian (44% Hispanic)
- Of the total migraine attacks, 1095 (19.7%) were treated with a second dose for a total of 6666 STS101 doses used.

Discontinuation due to adverse events

- A total of 14 (4.1%) subjects discontinued the study due to TEAEs, which were deemed treatment-related in 14 subjects (Table 1).

Adverse events

- In total, at least one treatment-related TEAE was observed in 26% (n=88) of subjects, with most frequent being nasal discomfort (11.0%), dysgeusia (7.6%), and nasal congestion (4.4%) (Table 2).
- Treatment-related TEAEs were observed in 13.7% of migraine attacks (n=763/5571).
- TEAEs were generally mild and transient, with no treatment-related SAEs.
- Among nasal TEAEs observed, 95% were assessed as mild.
- A 45-year-old Caucasian male experienced a serious TEAE of non-ST elevation myocardial infarction (NSTEMI). Follow up investigations revealed that the subject had a prior undisclosed history of cardiovascular ischemic disease and bipolar disorder, which should have excluded him from study participation.

Nasal examinations

- No instances of nasal bleeding or nasal ulceration were observed at baseline and 6 months of treatment, and instances of edema, erythema, and rhinorrhea were of mild severity (Table 3).
- No clinically relevant changes in ECGs or blood pressure evaluations were observed from baseline to 6 months (Table 4).

Figure 1. STS101 administration

Table 1. Treatment discontinuations due to TEAEs

	All Subjects n=344
Any TEAE leading to discontinuation, n (%)	14 (4.1)
Nasal AEs	7 (2.0)
Rhinalgia	3 (0.9)
Nasal discomfort	2 (0.6)
Epistaxis	1 (0.3)
Sneezing	1 (0.3)
Throat tightness	1 (0.3)
Vomiting	1 (0.3)
Dysgeusia	1 (0.3)
Rhinitis	1 (0.3)

TEAE, treatment-emergent adverse event.

Table 2. Summary of reported TEAEs

	Total Subjects n=344	Total Migraine Attacks n=5571
	n (%) with ≥1 TEAE	**n (%) with ≥1 TEAE**
Any TEAE, n (%)	157 (45.6)	763 (13.7)
Treatment-related TEAE	88 (25.6)	616 (11.1)
Most frequent treatment-related TEAE	**n (%) reporting TEAE at least once**	**n (%) attacks with TEAE**
Nasal discomfort	38 (11.0)	338 (6.1)
Dysgeusia [abnormal taste sensation]	26 (7.6)	154 (2.8)
Nasal congestion	15 (4.4)	198 (3.6)
Nausea	6 (1.7)	9 (0.2)
Rhinorrhea	8 (2.3)	45 (0.8)
Vomiting	4 (1.2)	6 (0.1)
Epistaxis	6 (1.7)	8 (0.1)
Lacrimation increased	3 (0.9)	13 (0.2)

TEAE, treatment-emergent adverse event.

Table 3. Summary of objective nasal assessment of symptoms in 6-month completers (N=166)

Subjects, n (%)	Month 6	Baseline None	Baseline Mild	Baseline Moderate	Baseline Severe
Nasal Erythema	None	158 (96.3)	2 (1.2)	0 (0.0)	0 (0.0)
	Mild	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal Edema	None	161 (98.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhea	None	158 (96.3)	2 (1.2)	0 (0.0)	0 (0.0)
	Mild	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Nasal Bleeding	None	162 (98.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	2 (1.2)	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	164 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 4. Summary of ECG and blood pressure evaluations

	Baseline mean ± SD	Month 6 mean ± SD
Heart rate (beats/min)	69.6 ± 9.93	69.1 ± 9.86
RR (msec)	874.8 ± 125.57	881.2 ± 127.75
QRS (msec)	88.2 ± 9.79	87.4 ± 10.19
QTcF (msec)	409.8 ± 17.82	410.4 ± 19.64
Diastolic blood pressure	74.9 ± 7.87	74.8 ± 7.97
Systolic blood pressure	116.4 ± 10.61	116.3 ± 10.87

Conclusions

- STS101 (an investigational DHE nasal powder) was well tolerated by subjects with migraine when used long-term and on a PRN (as needed) basis during the ASCEND study.
- TEAEs were mostly local, mild, and transient.
- Incidence of discontinuations due to TEAEs was low (4.1%).
- Nasal evaluations, ECGs, and blood pressure assessments showed no clinically relevant changes.

References

1. Ziegler DK, et al. *Neurology*. 1994;44(3).
2. Silberstein SD, et al. *Headache*. 2020;60(1):40-57.
3. Albrecht D, et al. *Headache*. 2020;60(4):701-712.
4. Safety and tolerability results based on November 9, 2021 STS101-006 Study.
5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.

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