Cardiovascular safety of STS101, a novel investigational DHE nasal powder product: initial data from the ASCEND study

Alan Rapoport, MD[1], Shannon Strom, PhD[2], Detlef Albrecht, MD[2]

[1]David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [2]Satsuma Pharmaceuticals, Inc., South San Francisco, CA, USA

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).
- As a first-line therapy for the acute treatment of migraine, the effectiveness of DHE has been demonstrated with several administration methods (i.e., intravenous, intramuscular, subcutaneous, intranasal, and oral inhalation).[1-6]
- DHE, a semi-synthetic ergotamine tartrate derivative, likely elicits antimigraine response via agonist activity at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors and can cause vasoconstriction.[2,3]
- DHE package inserts carry warnings regarding use in subjects with cardiovascular (CV) disease or risk factors.[7]
  - CV risk factors include hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of coronary artery disease, females who are surgically or physiologically postmenopausal, or males who are over 40 years of age
- However, these warnings are based on single case reports associated with excessive dosage, other risk factors, or use of concomitant medications.[8]
- No formal evaluation of the risks of DHE in subjects with CV risk factors has been conducted.

Objective

- This analysis aims to assess the cardiovascular safety of STS101, a novel investigational DHE nasal powder, in the acute treatment of migraine attacks in an open-label, 12-month study.

Methods

Study design and treatment intervention

- ASCEND (NCT04406649) is an ongoing, multi-center, multiple-dose, open-label, 12 month safety study of STS101 (DHE nasal powder drug-device combination) in the acute treatment of migraine in adults aged 18–65 years with migraine.
  - The data cutoff date for this preliminary analysis was June 30, 2021 and includes adverse events reported up to 9 months of study drug exposure in some subjects
- After establishing eligibility, subjects could self-administer STS101 as needed (PRN) for up to 2 doses of 5.2 mg within 24 hours to treat a single migraine attack and up to 12 doses per month for the 12-month study (Figure 1).

Patients

- Study subjects must have ≥1-year history of migraines (with or without aura) according to the International Classification of Headache Disorder, 3rd edition, including[9]:
  - Migraine onset before age of 50 years
  - 4–12 attacks/month in each of the 3 months prior to screening
  - <15 headache days/month in each of the 3 months prior to screening
- Subjects were allowed to have one CV risk factor (e.g., hypertension, hypercholesteremia, obesity, diabetes mellitus, family history of premature coronary heart disease, or be a postmenopausal female, or male over age 45).

Outcomes and analyses

- CV safety evaluations include adverse event assessments, blood pressure, and electrocardiogram (ECG).
  - Adverse event assessment will be performed at every study visit (months 1–6, 8, 10, and 12)
  - Blood pressure will be evaluated at every visit (screening, baseline, 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
- Due to the ongoing nature of the study, preliminary results (baseline, month 3, and month 6) are reported for blood pressure and ECG outcomes.

Results

Patients

- The safety population included 273 subjects who treated 4247 migraine attacks, of those, 143 completed 6 months of treatment while treating 3653 migraine attacks (average of 4.3 treated attacks per month).
  - Mean age: 39 ± 11 years
  - 89% female
  - 84% Caucasian (36% Hispanic)

Adverse event assessment

- A total of 6 CV TEAEs were reported in 5 (1.8%) subjects, with 5 deemed as treatment-related.
- Of the 5 treatment-related CV TEAEs reported in 4 subjects, 3 (increased blood pressure, flushing/hot flashes) were assessed as mild and 2 (tachycardia, flushing/hot flashes) were assessed as moderate in severity (Table 1).
- An incident of postural orthostatic tachycardia syndrome in 1 subject was reported as a serious adverse event (SAE) due to hospitalization, however, was not treatment-related.
- All TEAEs were transient and resolved without treatment or sequelae, with no treatment-related SAEs.

Blood pressure assessment

- Analyses of blood pressure at every study visit did not show clinically meaningful changes in mean systolic or diastolic blood pressure (Figure 2A-B).
- No blood pressure outliers were reported at baseline and screening; minimal cases were observed during monthly visits (Table 2).

ECG assessment

- Analyses of ECGs at months 3 and 6 did not show clinically meaningful changes from baseline in mean heart rate, QRS, and QTcF (Figures 3A-C).

Figure 1. STS101 administration

Table 1. Summary of related cardiovascular TEAEs

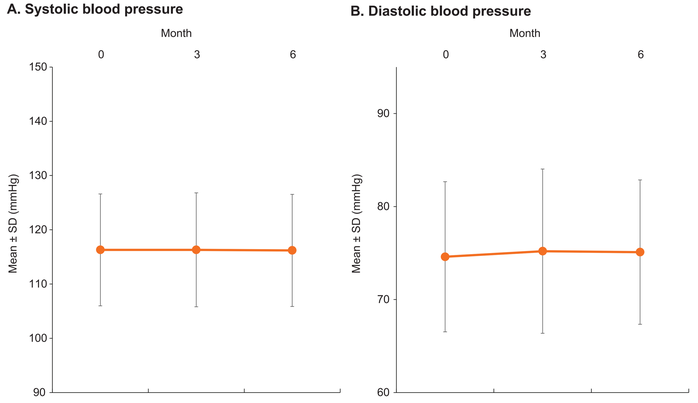
Treatment-related TEAEs, n (%)	Total Subjects N=273	Total Attacks N=4247
Tachycardia	1 (0.4)	1 (0.0)
Blood pressure increased	1 (0.4)	1 (0.0)
Flushing/hot flash	2 (0.7)	3 (0.0)

TEAE, treatment-emergent adverse event.

Table 2. Blood pressure outliers by visit

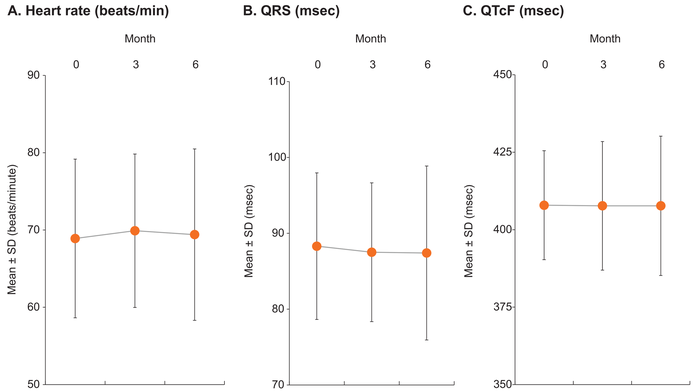
	Baseline n (%)	Month 3 n (%)	Month 6 n (%)
	N=272	N=203	N=142
Diastolic blood pressure >90 mmHg	0	7 (3.4)	2 (1.4)
Systolic blood pressure >140 mmHg	0	1 (0.5)	0

Figure 2. Mean (A) systolic and (B) diastolic blood pressure by visit



SD, standard deviation.

Figure 3. ECG findings by visit: A) heart rate, B) QRS, and C) QTcF



ECG, electrocardiogram; SD, standard deviation.

Conclusions

- Cardiovascular safety of STS101 (an investigational DHE nasal powder) was assessed in ASCEND, an ongoing long-term safety study in the acute treatment of migraine.
- When used long-term on a PRN basis, STS101 was well tolerated with no clinically relevant cardiovascular concerns.
- CV adverse events were rare and, if present, were mild to moderate in severity.
- No clinically relevant changes in systolic or diastolic blood pressure were observed during the treatment period.
- Similarly, ECG findings showed consistent results for heart rate, QRS, and QTcF throughout the study duration.

References

1. Marmura MJ, et al. *Headache*. 2015;55(1).
2. Silberstein SD, et al. *Headache*. 2003;43(2).
3. González-Hernández A, et al. *J Headache and Pain*. 2018;19(1).
4. Burstein R, et al. *Annals of Neurol*. 2004;55(1).
5. Dahlöf C, et al. *Headache*. 2012;52(4).
6. Hoskin KL, et al. *Brain*. 1996;119(1).
7. Novartis. *DHE 45 US Prescribing Information November 2017*.
8. Silberstein SD, et al. *Neurology*. 1995;45(3):577-584.
9. Headache Classification Committee of the International Headache Society (IHS). ICHD, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.

Disclosures

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. *Drs. Strom* and *Albrecht* are employees of Satsuma Pharmaceuticals.

Acknowledgements

The authors thank the patients, their families, and the study sites that participated in this study. The authors also thank The Medicine Group, LLC (New Hope, PA, USA) for providing medical writing support, which was funded by Satsuma Pharmaceuticals, Inc. (South San Francisco, CA, USA) in accordance with Good Publication Practice guidelines.

Presented at the American Academy of Neurology (AAN) 74th Annual Meeting; April 2–7, 2022 (Seattle, WA), April 24-26, 2022 (Virtual)