# CYP3A4 Inhibitor Itraconazole Does Not Cause Clinically Relevant Interactions With STS101 (Dihydroergotamine Nasal Powder)

P-307

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## Introduction

- Dihydroergotamine (DHE) mesylate—a semi-synthetic derivative of ergotamine tartrate—has a long history of use for the treatment of migraine.[1,2]
- Currently available formulations of DHE (solution for subcutaneous, intramuscular, or intravenous administration, and liquid nasal sprays) contain the mesylate salt of DHE (1.0 mg, 1.45 mg, and 2.0 mg DHE mesylate/mL, respectively) and are recommended as first-line treatment options for the acute treatment of moderate to severe migraine attacks, with or without aura.[3-5]
- STS101 (ATZUMI™) is a recently FDA-approved drug–device combination consisting of 5.2 mg of DHE powder (6.0 mg DHE mesylate) in a single-use nasal delivery device for the acute treatment of migraine.[6,7]
- The approved US prescribing information for DHE mesylate contains a boxed warning regarding the possibility of serious and/or life-threatening peripheral ischemia with coadministration of strong CYP3A4 inhibitors.[3-5]
- This Phase 1 drug-drug interaction study was conducted to describe the pharmacokinetics and safety of DHE following administration of single doses of STS101 5.2 mg with and without concomitant itraconazole.

## Objective

- To describe the pharmacokinetics and safety of DHE following the administration of single doses of 5.2 mg of STS101 with and without concomitant itraconazole

## Methods

### Study Design and Treatment Intervention

- This was a single-center (Quotient Sciences, Miami FL), single-dose (in each period), open-label, 1-sequence, 2-period, crossover, pharmacokinetic and safety study in healthy, non-fasted adults aged 18–50 years (Figure 1).
- After establishing eligibility, participants were admitted to a research clinic to undergo scheduled baseline assessments and reconfirm their eligibility.
- On Day 1 of Period 1, participants received a single dose of STS101.
- Itraconazole was administered on Day 3 of Period 1 and continued through Day 3 of Period 2.
- Concomitant administration of STS101 occurred 1 hour after the 13th daily dose of itraconazole on Day 1 of Period 2.

### Laboratory Values & Safety

- Serial blood samples for determination of plasma DHE concentrations were collected before STS101 dosing (0 hour) and at 5, 10, 15, 20, 30, 45, 60, and 90 minutes, and 2, 4, 6, 8, 12, 24, 36, and 48 hours after STS101 dosing.
- Safety was monitored through an assessment of treatment-emergent adverse events (TEAEs), and through review of laboratory, vital sign, 12-lead electrocardiogram (ECG), and nasal cavity and physical examination data.

### Statistical Analysis

- The DHE and total 8'-OH-DHE pharmacokinetic parameters ($C_{max}$, $AUC_{0-48}$, and $AUC_{inf}$) for STS101 with (test) and without (reference) co-administration of itraconazole were assessed using a linear, repeated-measures, mixed-effect model.
- The least-squares geometric mean ratios and 90% confidence intervals (CIs) were reported.

## Results

### Participants

- A total of 31 participants were enrolled and included 17 men and 14 women (mean [SD] age: 38 [7.9] years).
- The population was primarily White (n=26/31, 83.9%) and entirely Hispanic/Latino
  - Hispanic Black/African American, n=5
  - Hispanic White, n=26

### Plasma Concentration

- Plasma concentrations of DHE were slightly higher following the administration of STS101 + itraconazole (Figure 2, Table 1).
- $C_{max}$ (geometric mean [CV%])
  - 2440 (41.3%) pg/mL for STS101 alone
  - 2770 (32.3%) pg/mL for STS101 + itraconazole
- $AUC_{last}$ (geometric mean [CV%])
  - 10900 (33.3%) h*pg/mL for STS101 alone
  - 12900 (24.8%) h*pg/mL for STS101 + itraconazole
- The metabolite (8'-OH-DHE) to parent ratio was higher for STS101 + itraconazole than for STS101 alone (Table 2).
- Plasma DHE concentrations were quantifiable at 5 minutes post-dose and remained quantifiable through the 48-hour sampling window for both treatments.
- Mean peak plasma concentrations of DHE occurred at 0.33 hours post-dose.
- Overall, mean concentrations were slightly higher following administration of STS101 + itraconazole (Table 1 and 2).

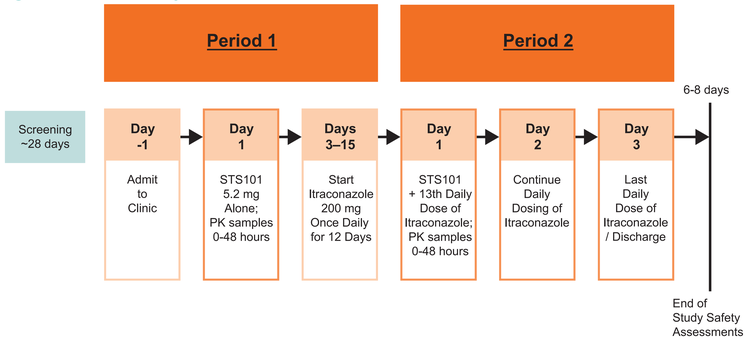
### Safety

- The co-administration of STS101 + itraconazole was not associated with an increase in the frequency of TEAEs compared with STS101 alone (Table 3).

### Laboratory Values

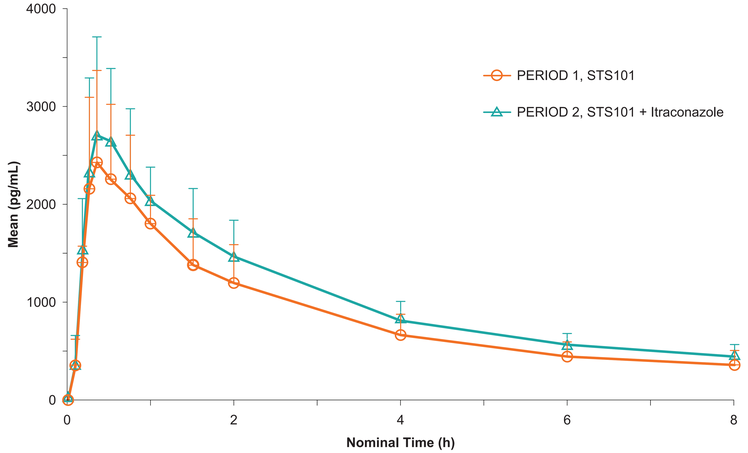
- No clinically significant adverse effects of a single dose of STS101 alone or with itraconazole were observed in nasal examinations, laboratory values (hematology, serum chemistry, urinalysis), blood pressure, pulse rate, or safety ECGs.

### Figure 1. Overall Study Schedule




PK, pharmacokinetic.

### Figure 2. Comparison of DHE Pharmacokinetic Parameters of STS101 + Itraconazole Versus STS101 Alone




### Table 1. Summary of Plasma DHE Pharmacokinetic Parameters

| | | $C_{max}$ (pg/mL) | $T_{max}$ (h) | $AUC_{0-48}$ (h*pg/mL) | $AUC_{last}$ (h*pg/mL) | $AUC_{inf}$ (h*pg/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|---|
| STS101 | N | 31 | 31 | 31 | 31 | 31 | 31 |
| | Mean (SD) | 2600 (863) | NC | 11400 (3180) | 11400 (3180) | 11900 (3320) | 11.8 (2.15) |
| | CV% | 33.1 | NC | 27.9 | 27.9 | 27.9 | 18.3 |
| | Geometric Mean | 2440 | NC | 10900 | 10900 | 11400 | 11.6 |
| | Geometric CV% | 41.3 | NC | 33.3 | 33.3 | 33.1 | 17.7 |
| | Min | 756 | 0.25 | 4570 | 4570 | 4910 | 8.05 |
| | Median | 2750 | 0.33 | 11900 | 11900 | 12600 | 11.1 |
| | Max | 4080 | 1.00 | 16900 | 16900 | 17600 | 17.6 |
| STS101 + Itraconazole | N | 30 | 30 | 30 | 30 | 30 | 30 |
| | Mean (SD) | 2600 (870) | NC | 13200 (3130) | 13200 (3130) | 13900 (3280) | 12.5 (2.60) |
| | CV% | 30 | NC | 23.6 | 23.6 | 23.7 | 20.8 |
| | Geometric Mean | 2770 | NC | 12900 | 12900 | 13500 | 12.3 |
| | Geometric CV% | 32.3 | NC | 24.8 | 24.8 | 25.0 | 20.6 |
| | Min | 1260 | 0.25 | 7830 | 7830 | 8150 | 8.64 |
| | Median | 2700 | 0.42 | 13100 | 13100 | 13700 | 12.4 |
| | Max | 4800 | 1.50 | 19200 | 19200 | 20100 | 19.6 |

CV, coefficient of variability; NC, not calculated; SD, standard deviation.

### Table 2. Summary of Plasma Total 8'-OH-DHE Pharmacokinetic Parameters

| | | $C_{max}$ (pg/mL) | $T_{max}$ (h) | $AUC_{0-48}$ (h*pg/mL) | $AUC_{last}$ (h*pg/mL) | $AUC_{inf}$ (h*pg/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|---|
| STS101 | N | 31 | 31 | 31 | 31 | 31 | 31 |
| | Mean (SD) | 121 (61.7) | NC | 1310 (518) | 1230 (565) | 1510 (560) | 15.3 (3.50) |
| | CV% | 50.9 | NC | 39.5 | 46.0 | 37.1 | 22.9 |
| | Geometric Mean | 106 | NC | 1210 | 1090 | 1410 | 14.9 |
| | Geometric CV% | 60.1 | NC | 44.1 | 56.7 | 38.7 | 23.5 |
| | Min | 28.9 | 0.75 | 400 | 234 | 655 | 10.0 |
| | Median | 111 | 2.00 | 1290 | 1220 | 1490 | 15.6 |
| | Max | 278 | 8.00 | 2530 | 2530 | 2830 | 22.5 |
| STS101 + Itraconazole | N | 30 | 30 | 30 | 30 | 30 | 30 |
| | Mean (SD) | 560 (409) | NC | 3540 (1490) | 3530 (1520) | 3940 (1470) | 15.5 (4.06) |
| | CV% | 72.9 | NC | 42.4 | 43.2 | 37.2 | 26.2 |
| | Geometric Mean | 451 | NC | 3190 | 3120 | 3670 | 14.9 |
| | Geometric CV% | 78.1 | NC | 54.9 | 63.0 | 41.1 | 28.9 |
| | Min | 60.0 | 0.75 | 587 | 364 | 1380 | 7.54 |
| | Median | 502 | 2.00 | 3530 | 3530 | 3850 | 16.0 |
| | Max | 2070 | 4.00 | 6880 | 6880 | 7240 | 23.2 |

CV, coefficient of variability; NC, not calculated; SD, standard deviation.

### Table 3. Summary of Treatment Emergent Adverse Events

| | STS101 (N=31) | STS101 + Itraconazole (N=30) |
|---|---|---|
| **Participants with ≥1 event,** n (%) | 10 (32.3) | 1 (3.3) |
| Ocular hyperemia | 2 (6.5) | 0 |
| Headache | 2 (6.5) | 0 |
| Skin irritation | 2 (6.5) | 0 |
| Nausea | 1 (3.2) | 0 |
| Facial pain | 0 | 1 (3.3) |
| Nasal congestion | 1 (3.2) | 0 |
| Nasal discomfort | 1 (3.2) | 0 |

## Conclusions

- The co-administration of STS101 and itraconazole did not lead to clinically relevant changes in DHE exposure or tolerability and safety.
- DHE plasma $C_{max}$ and AUC were increased by approximately 14% and 19% (with CIs of 101–129% for $C_{max}$ and 108–130% for AUC), respectively, when co-administered with itraconazole and had no associated clinical sequelae, with STS101 well tolerated in both conditions.

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### Disclosures

*Dr. Albrecht* was an employee and stockholder of Satsuma Pharmaceuticals at the time of study conduct and is now a consultant and stockholder for Satsuma Pharmaceuticals.
*Dr. Lipton* has been a consultant, advisory board member, and/or has received honoraria from Allergan\AbbVie, American Academy of Neurology, American Headache Society, Amgen, Biohaven Pharmaceuticals, BioVision, Boston Scientific, Dr. Reddy's Laboratories, electroCore, EON, Eli Lilly, eNeura Therapeutics, GlaxoSmithKline, Impel Neuropharma, Lundbeck Seattle BioPharmaceuticals, Merck, Pernix, Pfizer, Satsuma, Teva, Vector, and Vedanta. In addition, he has stock or stock options in Axon, Cooltech, and Manistee, and has received research support from Amgen, FDA, National Headache Foundation, and the NIH.
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