Pharmacokinetic comparison of STS101 (A novel investigational DHE nasal powder) with liquid nasal spray, injectable, and oral inhaled DHE formulations

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Introduction

- Migraine is a common, disabling primary headache disorder manifesting in attacks of moderate to severe pulsating, unilateral pain, with or without nausea and/or photophobia and phonophobia, generally 4-72 hours.[1]
- Dihydroergotamine mesylate (DHE), a semi-synthetic derivative of ergotamine tartrate 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]
- The currently approved LNS DHE products (Migranal® 2.0 mg and INP104 [Trudhesa®] 1.45 mg), however, have drawbacks:
  - Burdensome and/or inconvenient administration requirements;
  - Frequent adverse events/poor tolerability; and/or
  - Inconsistent efficacy, particularly at time points before 4[th] post-dose
- While DHE for injection is considered a "gold-standard" treatment for status migrainosus and other difficult-to-treat migraines, only one non-injectable DHE product, MAP0004 1.0 mg, which is administered via oral pulmonary inhalation, has demonstrated efficacy on the endpoint of freedom from pain at 2 hours in a large, randomized, and controlled clinical trial.

Objective

- To perform a literature review to compare pharmacokinetic (PK) parameters utilized for several routes of administration/formulations, including, intravenous (IV), intramuscular (IM), LNS, orally inhaled, and a novel nasal powder formulation (STS101), that were commercially available, had demonstrated anti-migraine efficacy in controlled Phase 3 studies or were in active development at the time of the literature search.

Methods

- A literature search was performed to compare PK results of several DHE routes of administration/formulations, including, IV (1.0 mg), IM (1.0 mg), LNS (2.0 and 1.45 mg), orally inhaled (1.0 mg), and a novel nasal powder formulation (STS101 5.2 mg DHE or 6.0 mg DHE mesylate).
- The study protocol designs, subject demographics, and analyses were similar across the studies; therefore, comparisons could be made.
- Extraction of DHE plasma concentration curves from the published literature was performed using WebPlotDigitizer (Automeris, Pacifica, CA).
- Variability was expressed as coefficient of variation (CV%). If a CV% was not provided in the published literature, it was calculated as the ratio of the standard deviation (SD) to the mean.
- Data for IV, orally inhaled and LNS DHE 1.45 mg are presented from cross-trial comparisons rather than head-to-head clinical studies.
- Data are presented from
  - Two STS101 Phase 1 studies in which the PK of STS101 were compared with LNS DHE 2.0 mg and IM DHE 1.0 mg injection
  - Available literature
- The first STS101 PK study (STS101-001) utilized a 1[st] generation intranasal delivery device, whereas the second study (STS101-006) utilized the device intended for commercial use that incorporated modifications to facilitate more robust delivery performance in real-world, patient-use scenarios.

Results

Pharmacokinetic profiles

- PK parameters for different DHE routes of administration/formulations are shown in Table 1.
- STS101 achieved a C_{max} greater than that of LNS products and approached that of the orally inhaled DHE product.
- STS101 AUC_{0-2hr} and AUC_{0-inf} were at least 2 times higher than LNS 2.0 mg and 1.45 mg, as well as MAP0004.

DHE plasma concentrations

- STS101 achieved a mean DHE plasma concentration of 2000 pg/mL by 20 minutes after dosing and remained above 1000 pg/mL for more than 2 hours (Figure 1).
- The PK profile achieved with the STS101 delivery device intended for commercial use was very similar to that demonstrated with the STS101 1[st] generation device.
- STS101 PK variability was lower than LNS DHE products and similar to oral inhaled DHE, with similar variability between 1[st] generation and 2[nd] generation delivery devices (Figure 2).
- Drug exposure was consistent between 1[st] and 2[nd] generation STS101 delivery devices, and approached that of IM DHE, with 2-3 times higher exposure than both LNS DHE (Figure 3).

Table 1. PK parameters for different DHE routes of administration/formulations

DHE Mesylate Formulation	Mean C_{max} ± SD (CV%), pg/mL	Median T_{max} (min, max), hours	Mean AUC_{0-2hr} ± SD (CV%), pg*mL/hr	Mean AUC_{0-inf} ± SD (CV%), pg*mL/hr
IV DHE (1.0 mg)				
Kellerman, 2013[a]	54189 ± 34970 (64.5)	0.067 (0.000, 0.100)	7331 ± 3194 (43.6)	12894 ± 3976 (30.8)
Shrewsbury, 2019	14620 ± 4906 (33.6)	0.08 (0.07, 0.10)	3019 ± 513.4 (17.0[b])	7381 ± 1139 (15.4)
IM DHE (1.0 mg)				
Humbert, 1996	4400 ± 1250 (28.0[b])	0.38 ± 0.30	Not provided	14490 ± 3780 (26.0[b])
STS101-001 Phase 1 Study	3368 ± 840 (24.9)	0.25 (0.08, 1.00)	4791 ± 907 (18.9)	13650 ± 2143 (15.7)
STS101-006 Phase 1 Study	3730 ± 801 (21.5)	0.33 (0.08, 1.00)	4970 ± 811 (16.3)	13900 ± 1990 (14.3)
LNS DHE (2.0 mg)				
Migranal SBA Study 303-022[c]	1131 ± 502[d] (44.4[b])	0.878 (not provided)	Not provided	Not provided
STS101-001 Phase 1 Study	960 ± 726 (75.7)	1.00 (0.50, 2.00)	1316 ± 989 (75.2)	6498 ± 3551 (54.7)
Shrewsbury, 2019	329 ± 261 (79.4)	0.67 (0.50, 1.8)	428.7 ± 317 (74.1[b])	2208 ± 1488 (67.4)
STS101-006 Phase 1 Study	673 ± 587 (87.3)	1.00 (0.33, 8.00)	881 ± 762 (86.5)	4240 ± 2730 (64.5)
LNS DHE (1.45 mg)				
Shrewsbury, 2019	1281 ± 682 (53.3)	0.50 (0.33, 0.78)	1595 ± 800.9 (50.2[b])	6153 ± 2721 (44.2)
Orally Inhaled DHE (1.0 mg)				
Kellerman, 2013[a]	2720 ± 1088 (40.0)	0.167 (0.067, 0.25)	1447 ± 541 (37.4)	4472 ± 1530 (34.2)
STS101 (5.2 mg)				
STS101-001 Phase 1 Study	2175 ± 884 (40.7)	0.50 (0.25, 2.00)	2979 ± 1147 (38.5)	12030 ± 4716 (39.2)
STS101-006 Phase 1 Study[e]	2230 ± 823 (36.9)	0.50 (0.25, 2.00)	2860 ± 916 (32.0)	10900 ± 4060 (37.3)

DHE, dihydroergotamine; IM, intramuscular; intravenous; LNS, liquid nasal spray; SD, standard deviation.
[a]Data is from pooled analyses of three studies.
[b]CV% was not provided in the publication, so was calculated as the SD/mean.
[c]Study 303-022 from the Migranal Summary Basis of Approval, 1997.
[d]The C_{max} data ranges from 1.13 ± 0.50 to 1.31 ± 0.27 across four PK studies in healthy volunteers presented in the Migranal Summary Basis of Approval, 1997.
[e]Final commercial delivery device.

Figure 1. Mean DHE plasma concentrations

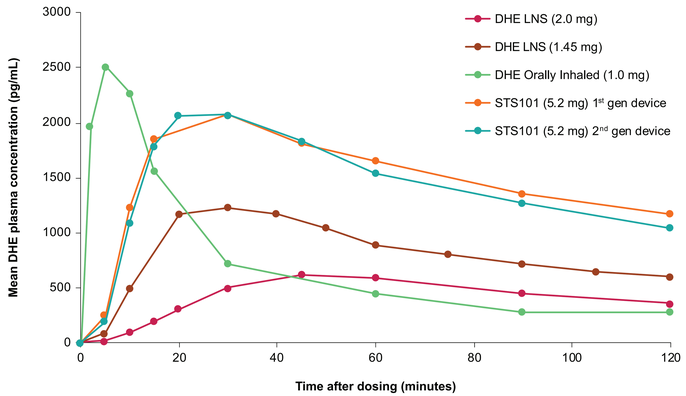


Figure 2. Variability (CV%) of C_{max} and AUC

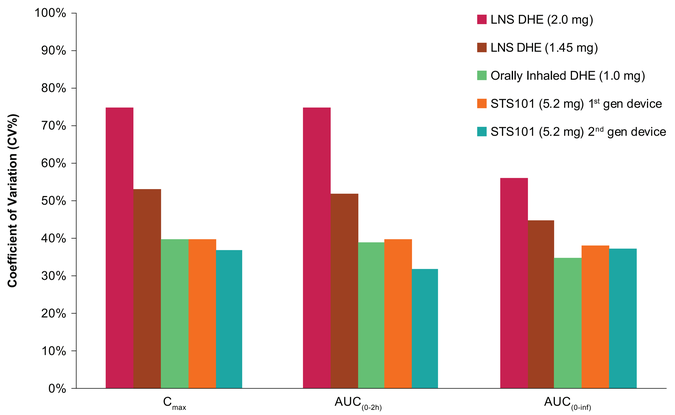
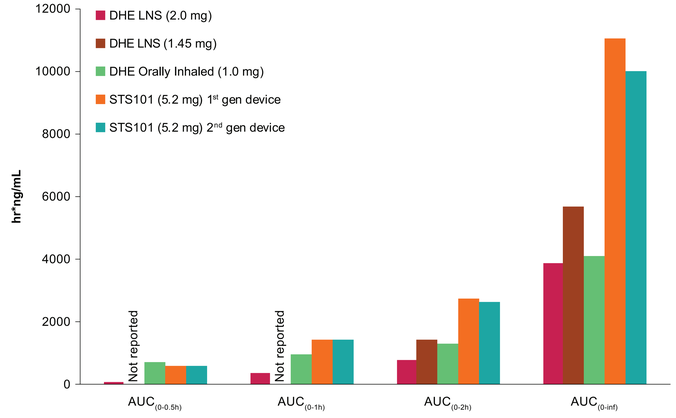


Figure 3. Drug exposure over time



Conclusions

- STS101 demonstrated greater PK values (C_{max}, AUC_{0-2hr}, and AUC_{0-24hr}) and less PK variability (CV%) compared to LNS DHE products, which may lead to more robust, consistent, and reliable clinical performance.
- Compared to the orally inhaled pulmonary DHE which demonstrated efficacy in a Phase 3 program, STS101 achieved similar C_{max}, higher AUC at all time points after 30 minutes, and similar PK variability (CV%).[9]
- STS101 showed high sustained plasma concentrations and AUC_{0-inf} comparable to the IV DHE values (but avoiding the high C_{max} of IV DHE associated with adverse events) and approaching the IM DHE values.
- Different DHE dosage forms have significantly different PK profiles, which likely influence anti-migraine effects.
- The PK profile of STS101 predicts that the acute treatment goals of rapid and consistent pain freedom and associated symptoms without recurrence should be achieved.[10]
- New development-stage products such as STS101 (an investigational DHE nasal powder) with PK profiles similar to injectable- and oral pulmonary-route DHE products have the potential to deliver robust clinical efficacy, favorable safety and tolerability, and improved ease of use.

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Disclosures

Drs. Strom and Albrecht are employees of Satsuma Pharmaceuticals. Some of these data were previously presented in poster format at the International Headache Conference 2019 and American Academy of Neurology 2020 Annual Meeting.

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