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Satsuma Pharmaceuticals, Inc.

P14.008: Pharmacokinetic comparison of STS101, an intranasal dry powder formulation of dihydroergotamine, with other intranasal, injectable and oral inhaled DHE formulations.

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Disclosure Statements

- Some of these data were previously presented in poster format at the International Headache Conference 2019.

- Shannon Strom, John Kollins, and Detlef Albrecht are employees of Satsuma Pharmaceuticals.

Objective and Background

- **Objective:** To perform a literature review to compare pharmacokinetic (PK) parameters for several formulations of dihydroergotamine mesylate (DHE) including intravenous (IV), intramuscular (IM), intranasal liquid sprays, orally inhaled, and intranasal dry powder that are marketed, have demonstrated anti-migraine efficacy in controlled Phase 3 studies, or are in active development.

- **Background:** DHE has been used since 1946 for the acute treatment of migraine, but the approved DHE products, D.H.E.45® (administered IV and IM) and Migranal® (liquid nasal spray) are inconvenient or have an inconsistent response. Newer development-stage products may provide enhanced PK, improved clinical efficacy, and more patient-friendly administration.

Design and Methods

- A literature search was performed to compare PK results of several formulations of DHE including the approved products Migranal and D.H.E.45 and the development-stage products INP104 (liquid nasal spray), MAP0004 (oral pulmonary whose development has been discontinued), and STS101 (dry powder nasal formulation). The 5.2 mg DHE dose for STS101 is equivalent to 6.0 mg DHE mesylate.
- The data are presented from cross-trial comparisons, not head-to-head clinical studies. The study protocol designs, subject demographics, and analyses were similar across the studies so comparisons can be made.
- The plasma DHE analytical assay differed across studies, as more sensitive assays were developed over time. The analytical method used through 1996 was a radioimmunoassay with a limit of quantitation of 20 pg/mL. The more recent investigational development programs used high-performance liquid chromatography in conjunction with tandem mass spectrometry (LC-MS/MS) methods with a limit of quantitation of 10 pg/mL[5,8] and 8 pg/mL[7].
- Extraction of DHE plasma concentration curves from the published literature was accomplished using WebPlotDigitizer by Automeris.
- The time to effective concentration (1 ng/mL) and total time above 1 ng/mL were calculated by noncompartmental analysis within Phoenix WinNonLin v8.1 (Certara, Princeton, NJ) for the individual profiles.
- If a coefficient of variation was not provided in the published literature, it was calculated as the ratio of the standard deviation to the mean.
- The estimated minimum threshold concentration for efficacy is derived from the Migranal Summary Basis of Approval, 1997.

STS101 achieved rapid and sustained high drug exposure with low variability

Pharmacokinetic Parameters for Different Routes of Administration of DHE

- ✓ STS101 had a higher C_{max} than intranasal liquid sprays Migranal and INP104 and approached that of the orally inhaled MAP0004.
- ✓ The STS101 $AUC_{0\text{-}2hr}$ was at least 2-fold higher than Migranal, INP104, and MAP0004.
- ✓ The STS101 $AUC_{0\text{-}inf}$ was at least 2-fold higher than Migranal, INP104, and MAP0004.
- ✓ STS101 achieved 83% of the total drug exposure of IM DHE and was comparable to IV DHE.

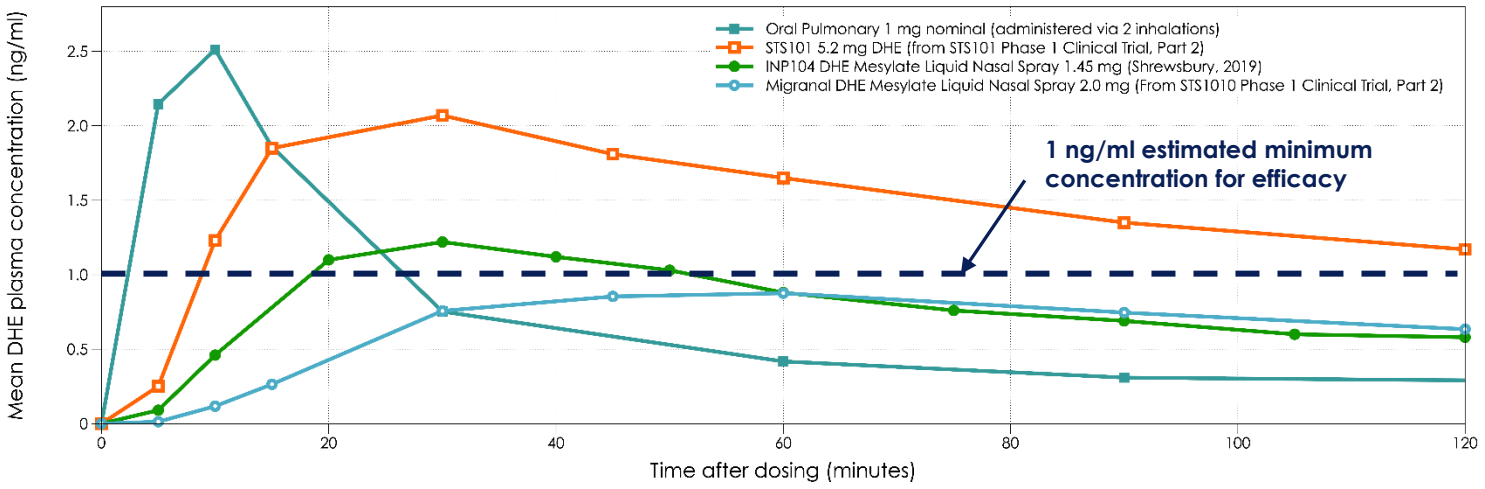
DHE Mesylate Formulation	Mean C_{max} ± SD (pg/mL) %CV	Median T_{max} [min, max] (hr)	Mean $AUC_{0\text{-}2hr}$ ± SD (pg*mL/hr) %CV	Mean $AUC_{0\text{-}inf}$ ± SD (pg*mL/hr) %CV
D.H.E. 45 IV (1 mg)				
Kellerman, 2013[1]	54,189 ± 34,970 (%CV: 64.5)	0.067 (0.000, 0.100)	7,331 ± 3,194 (%CV: 43.6)	12,894 ± 3,976 (%CV: 30.8)
Shrewsbury, 2019	14,620 ± 4,906 (%CV: 33.6)	0.08 (0.07, 0.10)	3,019 ± 513.4 (%CV: 17.0%[2])	7,381 ± 1,139 (%CV: 15.4)
D.H.E. 45 IM (1 mg)				
Humbert, 1996	4,440 ± 1,250 (%CV = 28%[2])	0.38 ± 0.30 hours	Not Provided	14,490 ± 3,780 (%CV = 26%[2])
STS101-001 Phase 1 Study	3,368 ± 840 (%CV: 24.9)	0.25 (0.08, 1.00)	4,791 ± 907 (%CV: 18.9)	13,650 ± 2,143 (%CV: 15.7)
Migranal Nasal Spray (1 mg)				
Humbert, 1996	1,020 ± 420 (%CV = 41%[2])	0.93 ± 0.63 hours	Not Provided	5,320 ± 2,300 (%CV = 43%[2])
Migranal Nasal Spray (2 mg)				
Migranal SBA Study 303-022[3]	1,131 ± 502[4] (%CV = 44.4[2])	0.878 (not provided)	Not Provided	Not Provided
STS101-001 Phase 1 Study	960 ± 726 (%CV: 75.7)	1.00 (0.50, 2.00)	1,316 ± 989 (%CV: 75.2)	6,498 ± 3,551 (%CV: 54.7)
Shrewsbury, 2019	329 ± 261 (%CV: 79.4)	0.67 (0.50, 1.8)	428.7 ± 317 (%CV: 74.1[2])	2,208 ± 1,488 (%CV: 67.4)
MAP0004 Orally Inhaled (1 mg)				
Kellerman, 2013[1]	2,720 ± 1,088 (%CV: 40.0)	0.167 (0.067, 0.25)	1,447 ± 541 (%CV: 37.4)	4,472 ± 1,530 (%CV: 34.2%)
INP104 Intranasal Spray (1.45 mg)	1,281 ± 682 (%CV: 53.3)	0.50 (0.33, 0.78)	1,595 ± 800.9 (%CV: 50.2[2])	6,153 ± 2,721 (%CV: 44.2)
Shrewsbury, 2019				
STS101 Intranasal Powder (5.2 mg)				
STS101-001 Phase 1 Study	2,175 ± 884 (%CV: 40.7)	0.50 (0.25, 2.00)	2,979 ± 1,147 (%CV: 38.5)	12,030 ± 4,716 (%CV: 39.2)

[1] Data is from pooled analyses of 3 studies.
[2] %CV was not provided in the publication, so was calculated as the SD/mean.
[3] Study 303-022 from the Migranal Summary Basis of Approval, 1997
[4] The C_{max} data ranges from 1.13 ± 0.50 to 1.31 ± 0.27 across 4 PK studies in healthy volunteers presented in the Migranal Summary Basis of Approval, 1997.

STS101 achieved the minimum effective concentration within 10 minutes and remained above the threshold for >2 hours

Mean DHE plasma concentration of STS101 vs. other non-injectable DHE products

- ✓ MAP0004 achieves a rapid rise in DHE blood levels, but within 30 minutes falls below the estimated minimum effective concentration of 1 ng/mL.
- ✓ STS101 results in DHE levels remaining above the minimum effective concentration for more than 2 hours.

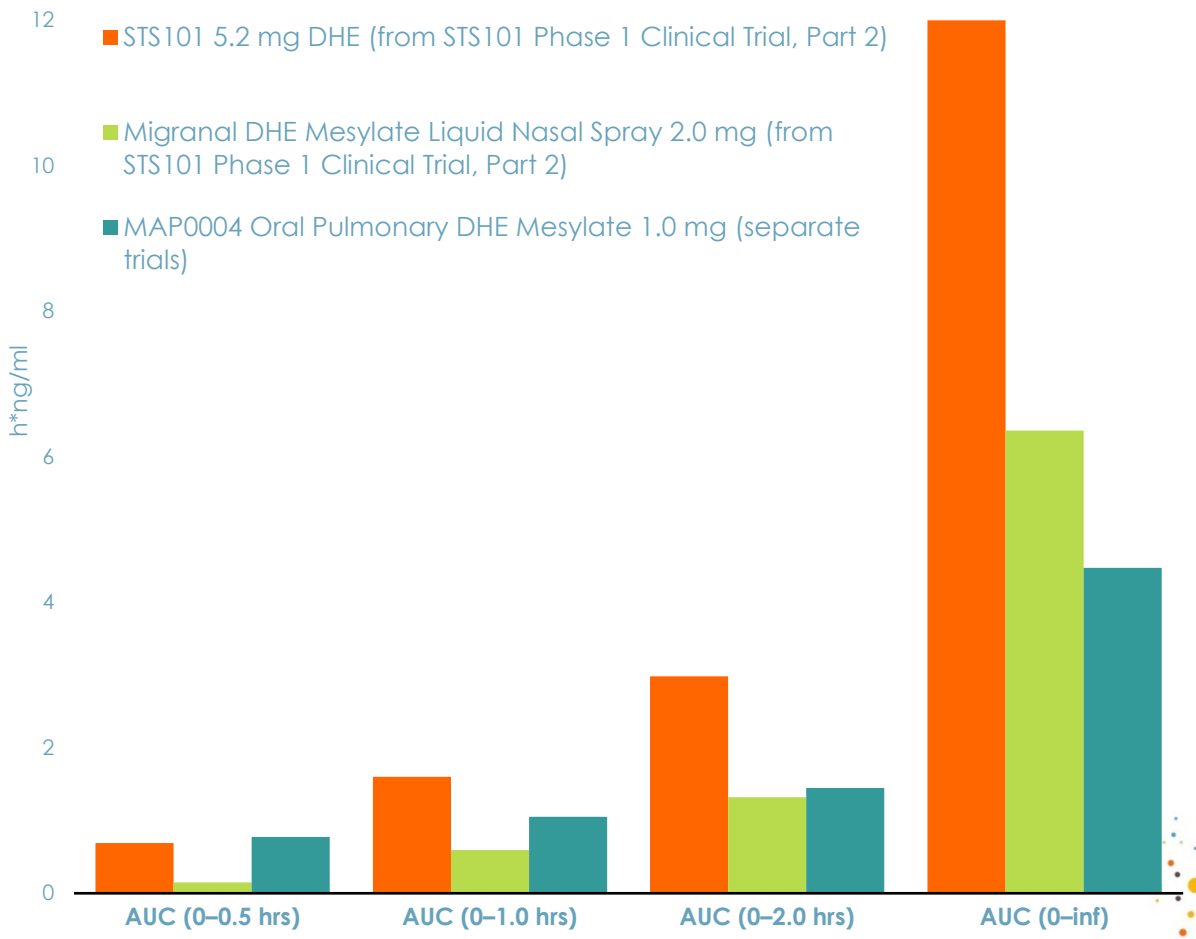


The minimum effective concentration of 1 ng/mL was estimated based on data from the PK and dose-ranging efficacy studies with the approved Migranal liquid nasal spray.

STS101 achieved higher cumulative drug exposure than other non-injectable DHE products by ~30 minutes and all timepoints thereafter

Drug exposure over time of STS101 vs. other non-injectable DHE products

- ✓ STS101 achieved approximately 2.5-3.0x total drug exposure ($AUC_{0\text{-}inf}$) vs MAP0004.
- ✓ STS101 achieved higher drug exposure than Migranal liquid nasal spray at all times post-dose
- ✓ STS101 achieved comparable drug exposure to MAP0004 by ~30 minutes and was greater than MAP0004 at all times thereafter.



The oral pulmonary DHE product reached the estimated minimum effective concentration first, but STS101 had a longer total time above the threshold

Time to achieve and total time above the estimated minimum effective concentration

- ✓ MAP0004 achieves a rapid rise in blood levels, but falls below the estimated minimum effective concentration quickly of 1 ng/mL.
- ✓ STS101 maintains an effective blood level past 2 hours.

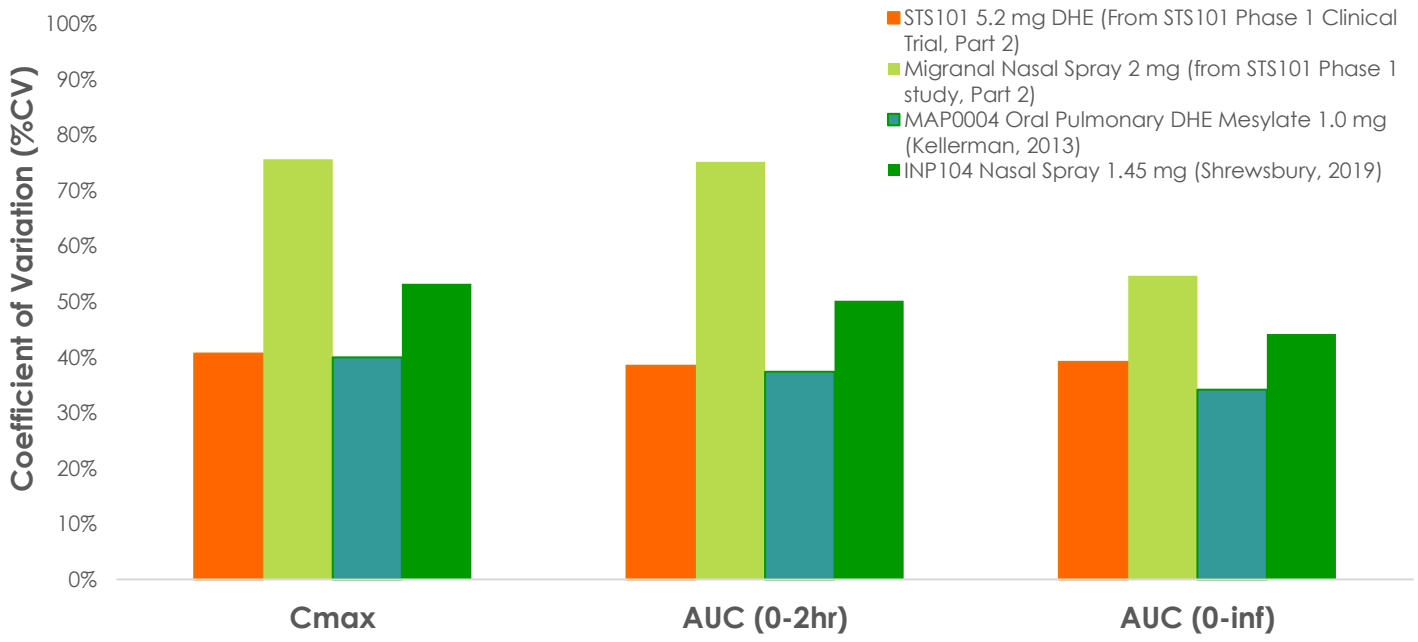
Treatment	Time to achieve 1 ng/mL (minutes)	Total time above 1 ng/mL (minutes)
STS101 5.2 mg (From STS101 Phase 1 Clinical Trial, Part 2)	8.8	147.8
MAP0004 1 mg (from Kellerman, 2013)	2.3	23.0
INP104 1.45 mg (from Shrewsbury, 2019)	18.4	33.4
Migranal 2 mg (historical, Study 303-022 from SBA)	Not achieved	Not achieved

The minimum effective concentration of 1 ng/mL was estimated based on data from the PK and dose-ranging efficacy studies with the approved Migranal liquid nasal spray.

STS101 plasma concentrations had low variability compared to other non-injectable DHE products

C_{max} and AUC Coefficient of Variation of STS101 vs. other non-injectable DHE products

- ✓STS101 had low variability similar to oral pulmonary DHE (MAP0004).
- ✓STS101 had lower variability than the DHE liquid nasal sprays (Migranal and INP104).



Conclusions

- STS101 demonstrated higher PK (C_{max}, $AUC_{0\text{-}2hr}$, and $AUC_{0\text{-}24hr}$) and less PK variability (%CV) as compared to the DHE liquid nasal spray products (Migranal and INP104).
- As compared with orally inhaled pulmonary DHE (MAP0004) that demonstrated efficacy in a Phase 3 program, STS101 achieved similar C_{max} and higher AUC at all time points after ~30 minutes as well as similar PK variability (%CV).
- STS101 showed high sustained plasma concentrations and $AUC_{0\text{-}inf}$ 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.
- Lower PK variability may lead to more consistent and reliable clinical performance.
- 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[1].
- A Phase 3 efficacy study (EMERGE) with STS101 is ongoing to evaluate the product as an acute treatment for migraine (NCT 03901482).

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