Dihydroergotamine (DHE) Plasma Concentration and Clinical Response Relationship: An In-Office PK/PD Study

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Detlef Albrecht, MD, and Shannon Strom, PhD

Satsuma Pharmaceuticals, Inc., Durham, NC, United States

Introduction

- Dihydroergotamine (DHE) mesylate exerts anti-migraine effects via a unique multi-modal mechanism of action involving interactions with both serotonergic and adrenergic receptors, has been used since 1946 for the acute treatment of migraine, and is recognized as a first-line treatment option.[1-4]
- DHE is available as a sterile injectable solution for subcutaneous (SC), intramuscular (IM), or intravenous (IV) administration, and as a liquid nasal spray (LNS).[5-7]
- Different DHE dosage forms exhibit distinct pharmacokinetic (PK) profiles, which contribute to variability in efficacy outcomes; these differences have been evaluated in randomized clinical trials.
- The DHE plasma concentration and efficacy relationship is understudied and is mostly based on indirect comparisons of PK data from healthy volunteer studies and clinical efficacy data in adults with migraine.
- STS101 (ATZUMI™) is an FDA-approved drug-device combination of a DHE mesylate powder formulation prefilled in a single-use delivery device for nasal administration.[8]
- STS101 provides rapid DHE absorption, with plasma concentrations of DHE over the 2 hours following administration ($AUC_{0\text{-}2h}$) more than two-fold greater than those following administration of either DHE LNS.[6-8]

Objective

- The objective of this study was a) to study DHE absorption during a migraine attack, and b) to evaluate the relationship of DHE plasma concentration and migraine pain response in an office setting

Methods

- This was a sub-study conducted in 31 adults aged 18–65 years at 7 sites who participated in the open-label ASCEND study (NCT04406649).
  - Participants had a history of 4–12 attacks and <15 headache days per month in each of the 3 months prior to screening.
- Participants were asked to travel to the clinical study site after recording a qualifying migraine in their e-Diary at home.
- In the clinic after recording of baseline (Time 0) assessments for pain severity, migraine symptoms, vital signs, and blood draws for PK analyses, participants were instructed to administer the study drug unsupervised.
- Additional blood draws and assessments of pain severity and migraine symptoms were done at 30 minutes, and at 1, 2, 4 & 6 hours after dosing.
- Liquid chromatography–tandem mass spectrometry was used to determine DHE plasma concentrations.
- Pain relief at 2 hours was selected as the primary efficacy endpoint for the analyses.
- Pain was assessed on a 4-point scale where 0 is no pain and 3 is severe pain.
- Pain relief was defined as a reduction of moderate or severe headache pain (2 or 3 on the scale) to mild or no headache pain (1 or 0 on the scale), with no prior use of any rescue medication.
- Descriptive statistics were used to analyze the data.

Results

- Of 31 enrolled, 27 adults were included in the analysis (3 were excluded due to missing plasma data or analytical errors and 1 due to missing pain severity data).
- STS101 was well absorbed during migraine attacks, with a mean DHE plasma C_{max} of 1591 pg/mL (range: 477–2932 pg/mL).
- Higher DHE plasma C_{max} was related to higher proportions of pain relief responders (Table 1).
- Attacks with severe baseline pain seemed to require higher DHE concentrations to achieve pain relief as compared to attacks with moderate baseline pain (Table 2).
- Attacks with moderate baseline pain seemed to achieve pain relief with lower mean DHE concentrations.
- Study participants with an "in-office" pain response at 2 hours had a higher likelihood of pain response during "at-home" use (Table 3).

Table 1. DHE Plasma Concentrations and Pain Response Data

DHE Plasma Concentration C_{max} (pg/mL)	N	Mean C_{max} pg/mL (SD)	Baseline Pain Severity Moderate/Severe	Participants With Pain Relief at 2 Hours (%)
<1000	5	633 (120)	2/3	2/5 (40%)
>1000 & <1500	8	1287 (179)	4/4	4/8 (50%)
>1500 & <2000	7	1707 (116)	5/2	4/7 (57%)
>2000	7	2622 (419)	3/4	4/7 (57%)

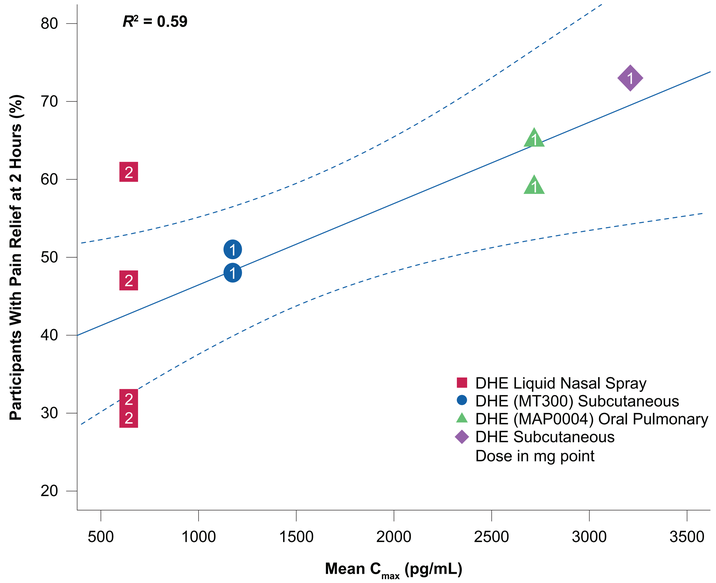
Table 2. Relationship of Baseline Pain Severity, Pain Relief at 2 Hours, and Plasma Concentration of DHE

Baseline Pain Severity	N	Participants With Pain Relief at 2 Hours (%) Mean DHE Concentration pg/mL
Moderate	14	8/14 (53%) 1498 (±710)
Severe	13	6/13 (46%) 1844 (±515)

Table 3. Predictive Value of "In-Office" Pain Relief at 2 Hours for "At-Home" Response

2-Hour Pain Relief In Office	N	Participants With 2-Hour Pain Relief at Home (%)
Yes	14	74%
No	13	51%

Figure 1. Relationship Between DHE C_{max} and Percentage of Study Participants With Pain Relief at 2 Hours in Controlled Clinical Trials[9]



Univariate linear regression analysis shows a relationship between the percentage of study participants with pain relief at 2 hours (clinical efficacy) compared to DHE C_{max} across nine randomized controlled trials of various DHE formulations, doses, and routes of administration. The dotted lines represent the 95% confidence interval boundaries. C_{max}, maximum plasma concentration; DHE, dihydroergotamine.

Conclusions

- STS101 was well absorbed during migraine attacks.
- DHE plasma C_{max} is a strong predictor for pain relief at 2 hours after dosing, with higher C_{max} resulting in higher responder proportions.
- More severe baseline pain required higher DHE plasma concentrations to induce pain relief.
- The DHE plasma C_{max} and 2-hour pain relief relationship are in line with previously reported data.
- STS101 is well absorbed during migraine attacks, and the maximum DHE plasma concentration is predictive of the pain response at 2 hours post dose.

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Disclosures

Shannon Strom and *Detlef Albrecht* are consultants to and/or stockholders of Satsuma Pharmaceuticals, Inc.

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