Presented at the American Academy of Neurology 2020 Annual Meeting

Water-insoluble Mucoadhesive Formulation Enables Consistent and Rapid Intranasal Absorption of Drugs, including Granisetron, Zolmitriptan and Dihydroergotamine

Author: Mic Iwashima

P14.006 Headache Science 2

Disclosure Statements

- Some of these data were previously published in ONdrugDelivery, November 2012.
- Mic Iwashima is an employee of Satsuma Pharmaceuticals, Inc.

Objective and Background

- **Objective:** To conduct a review of the pharmacokinetic profiles achieved in human subjects with a water-insoluble, mucoadhesive powder formulation technology used to deliver granisetron, zolmitriptan and dihydroergotamine (DHE) by the nasal route.

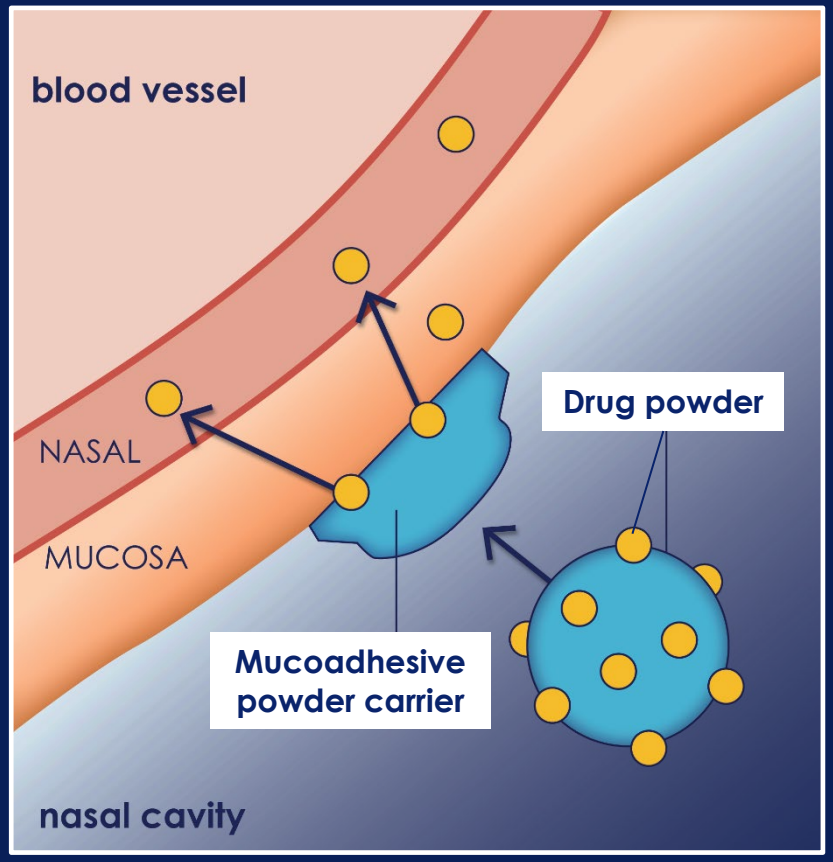
- **Background:** The nasal route is an attractive route for drug delivery, as the nasal cavity is lined with blood vessels that provide direct access to the systemic circulation. However, absorption of drug compounds formulated as traditional liquid nasal sprays can be poor and highly variable. For example, the commercially available liquid nasal DHE product* has slow and variable absorption, resulting in inconsistent achievement of the blood concentration of ~1 ng/ml thought to be minimally necessary for clinical efficacy, despite administration via four individual sprays over 15 minutes. Application of the mucoadhesive powder formulation technology described herein to DHE and other drugs could enable the development of new nasal-route therapeutic products with superior pharmacokinetic and clinical performance as compared to traditional liquid nasal spray formulation products.

*Migranal DHE liquid nasal spray

Design and Methods

- The characteristics of the water-insoluble, mucoadhesive nasal powder formulation technology are reviewed, including historical results from human pharmacokinetic studies with granisetron and zolmitriptan nasal formulations utilizing the technology. Then, the applicability of the technology for DHE is assessed based on the results of a human pharmacokinetic study.

Novel water-insoluble, mucoadhesive nasal powder formulation technology maximizes absorption



Novel nasal powder technology overcomes limitations of traditional liquid nasal sprays in the following ways:

1. Maximizes formulation deposition on surface of vascularized nasal mucosa
2. Creates steep drug concentration gradient across nasal membrane without dilutive liquid solvents
3. Sustains contact with the nasal membrane by utilizing a water-insoluble mucoadhesive carrier

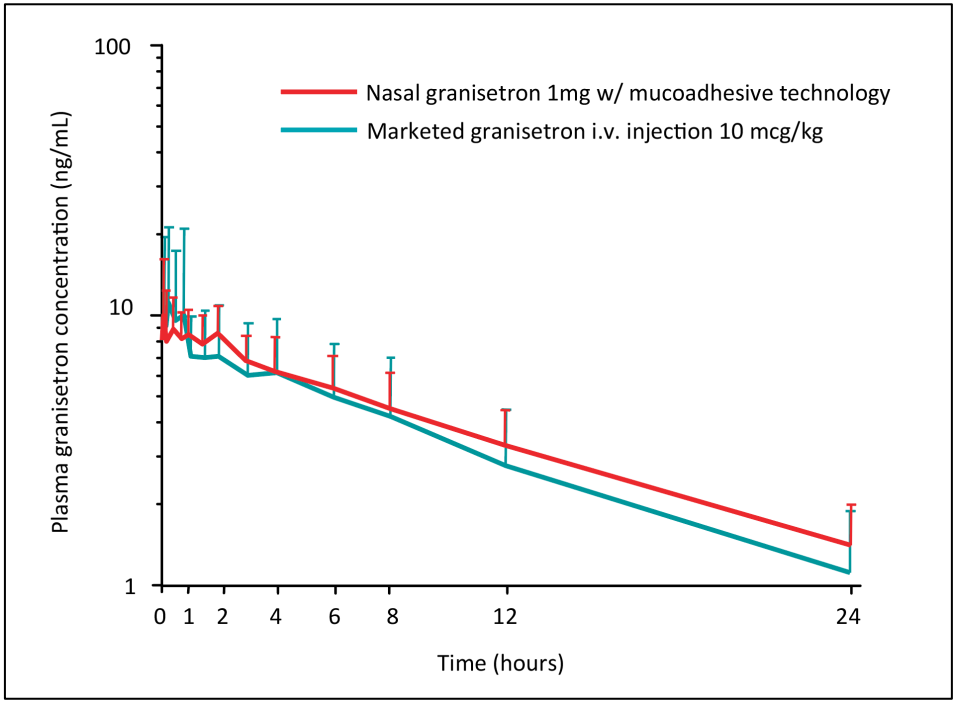
Novel nasal powder technology vs IV injection
Granisetron PK comparison in humans

Novel nasal powder technology achieves:

- 100% absolute bioavailability versus IV injection, suggesting 100% of the dose was absorbed via nasal mucosa and none was absorbed by GI tract*
- Rapid absorption with C_{max} achieved by 20 minutes
- Low inter-patient PK variability

*Oral bioavailability of granisetron is 60%.

Plasma granisetron concentration in human subjects



Novel nasal powder technology vs marketed liquid nasal spray

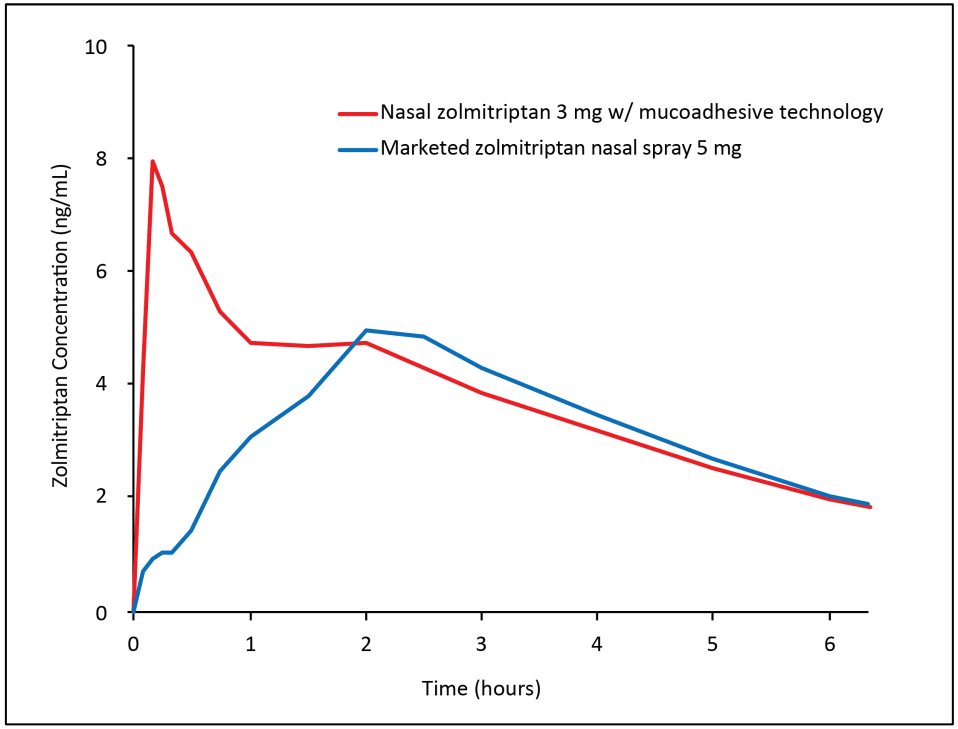
Zolmitriptan PK comparison in humans

Compared to marketed nasal liquid spray product*, novel nasal powder technology achieves:

- Greater absorption (1.8x higher bioavailability)
- Significantly faster absorption:
  - 3.3x higher bioavailability in the first 2 hours
  - C_{max} within 20 minutes versus 120 minutes (for liquid nasal spray)

* Zomig® Nasal Spray

Plasma zolmitriptan concentration in human subjects



STS101 vs **Liquid Nasal Spray** & **IM injection**

DHE PK comparison in humans

STS101 (DHE nasal powder)

DHE formulation with the novel water-insoluble, mucoadhesive nasal powder formulation technology

Delivery method

- Proprietary single-use, prefilled device
- Convenient and patient-friendly; no assembly or priming required
- Provides for administration of a full-dose within seconds
- Pocket-sized, smaller than delivery devices for liquid nasal sprays; discreet and disposable

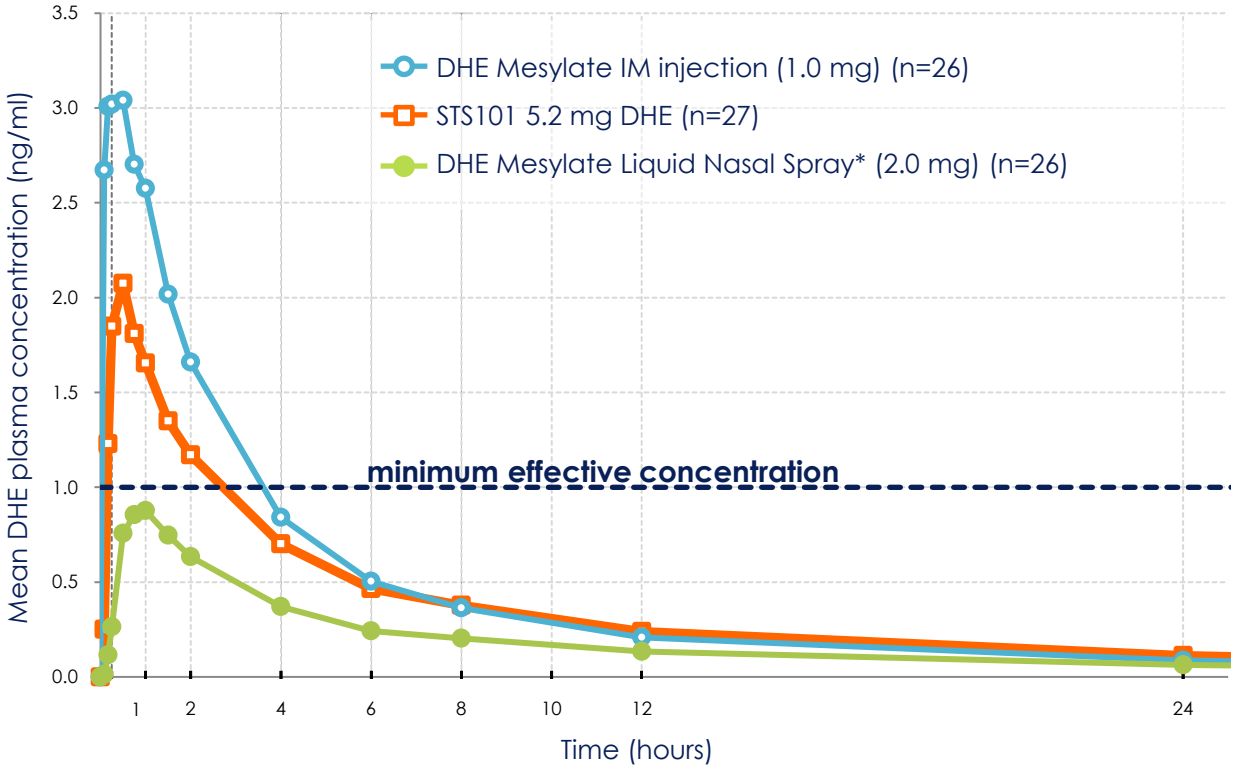
STS101 vs **Liquid Nasal Spray** & **IM injection**
DHE PK comparison in humans

STS101 achieved and sustained PK comparable to intramuscular (IM) DHE and better than DHE liquid nasal spray

- 83% of total drug exposure ($AUC_{0\text{-}inf}$) of IM DHE
- 2.0x total drug exposure ($AUC_{0\text{-}inf}$) vs. DHE liquid nasal spray

*Migranal®

Plasma DHE concentration in human subjects (over 24 hours)



STS101 vs Liquid Nasal Spray & IM injection

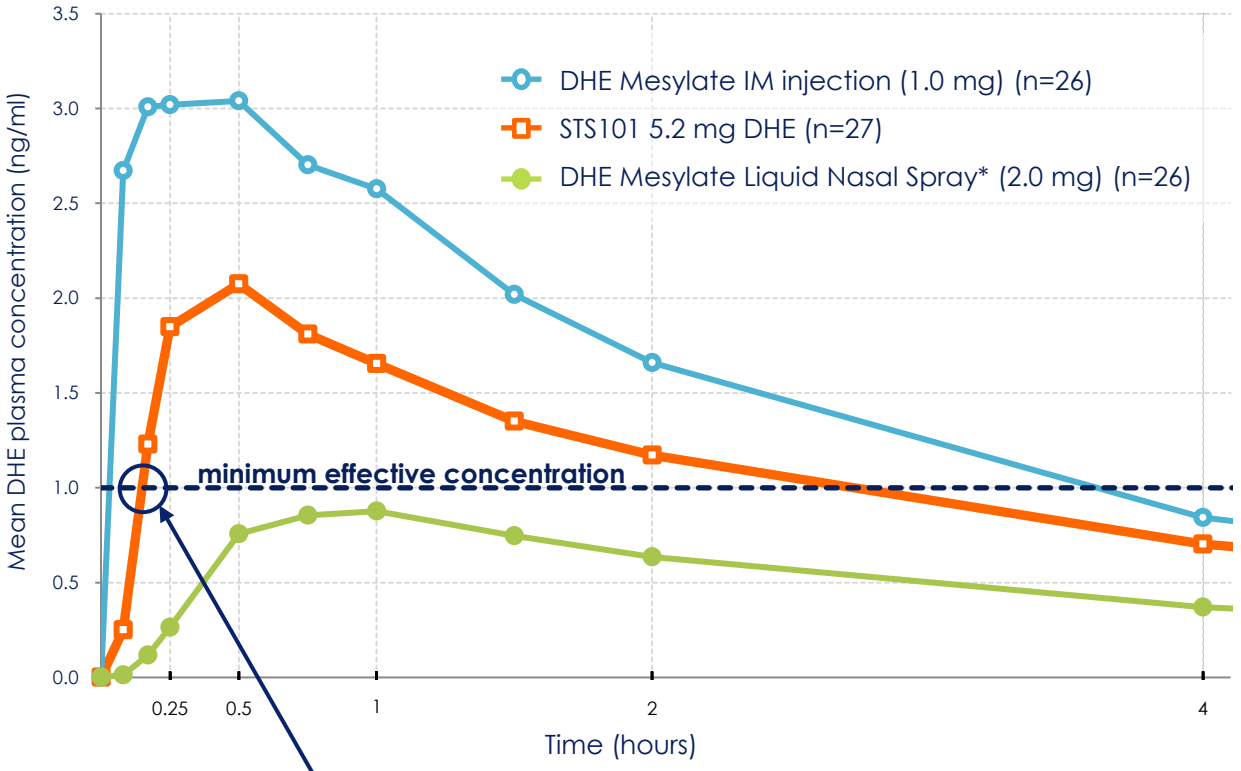
DHE PK comparison in humans

STS101 rapidly achieved clinically relevant plasma concentrations

- Minimum effective concentration (1 ng/ml) achieved within 10 minutes
- Approximately 2.0x total drug exposure in the first 2 hours vs. DHE liquid nasal spray

*Migranal®

Plasma DHE concentration in human subjects (over 4 hours)



Minimum effective concentration achieved within 10 min

Conclusions

- The water-insoluble mucoadhesive nasal powder formulation technology enables consistent and rapid absorption of multiple drugs, including granisetron, zolmitriptan and DHE
- Application of the mucoadhesive nasal formulation technology could enable the development of new nasal-route therapeutic products with superior pharmacokinetic and clinical performance as compared with traditional liquid nasal spray formulation products
- A mucoadhesive nasal powder formulation of DHE demonstrates faster absorption and greater systemic exposure versus DHE liquid nasal spray and a PK profile similar to DHE administered by IM injection
- STS101 may enable the well-established anti-migraine benefits of DHE administered via IM injection to be achieved with a much easier-to-administer and non-injectable dosage form

References

1. Haruta, S. Achieving the Potential of Nasal Drug Delivery. ONdrugDelivery Pulmonary. 31:4-7, April 2012.

2. European Medicines Agency. (2011, December 9) Kytril - Article 30 referral - Annex III. *European Medicines Agency*. Retrieved from https://www.ema.europa.eu/documents/referral/kytril-article-30-referral-annex-iii_en.pdf