Prediction of Pharmacokinetics of Repeat Dosing of Dihydroergotamine Mesylate via Precision Olfactory Delivery (INP104) for the Acute Treatment of Migraine

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Introduction

- Dihydroergotamine mesylate (DHE) is a well-recognized, long-established, effective acute therapy for migraine and status migrainosus, which is a debilitating migraine attack lasting >72 hours and often refractory to most oral acute treatments[1-4]
- Historically, DHE is delivered intravenously, but is often associated with nausea and vomiting, requiring co-administration of an antiemetic. Furthermore, IV DHE must be administered in a clinic or hospital setting, which can limit its use[1,5,6]
- INP104 is a drug-device combination product that delivers DHE to the upper nasal space using Precision Olfactory Delivery (POD®) and has been approved by the US Food and Drug Administration for the acute treatment of migraine with or without aura in adults[4,6]
- INP104 has demonstrated long-term safety and exploratory efficacy in an open-label phase 3 safety study (STOP 301)[5]
- In a phase 1 trial (STOP 101), observed plasma DHE concentrations from a single dose of INP104 matched that of a single dose of intravenous (IV) DHE from 30 minutes up to 48 hours, but with less nausea and vomiting observed.[6] However, treatment with IV DHE, but not INP104, resulted in statistically significant increases in blood pressure from baseline[7]
- The approved dose of INP104 is 1.45 mg, which can be repeated if needed at least 1 hour after the first dose, with no more than 2 doses administered within 24 hours or 3 doses within 1 week[8]
- For treatment of status migrainosus in the inpatient clinic/infusion center setting, the Raskin protocol is often used for IV DHE administration, which involves repetitive dosing of IV DHE every 8 hours for up to 3 days[3]
- Repeat dosing studies are warranted to better understand the pharmacokinetics (PK) of different INP104 dosing regimens to help guide clinical decision making

Objective

- To predict the PK of repeat dosing of INP104 and compare it with the predicted PK of repeat dosing of IV DHE

Methods

Study Design of STOP 101[6]

- STOP 101 was a phase 1, open-label, randomized, crossover study in healthy participants that investigated the PK of a single dose of INP104 (N=31) compared with that of IV DHE (N=32)
  - Eligible participants were adults aged 18-55 years in general good health and with no significant medical history (including recent migraine attacks: those with ≥1 attack in the past 6 months or those receiving prophylactic antimigraine medication were excluded)

Study Analysis

- 31 and 32 participants received INP104 and IV DHE, respectively, and had complete plasma concentration vs time profiles that were included in the analysis
- Nonparametric superposition using the Phoenix WinNonlin non-parametric superposition tool was used to predict repeat-dose PK for different dosing regimens of INP104 compared with IV DHE
- Dosing regimens for 1.45 mg INP104 were based on the US prescribing information for INP104[8] and on the Raskin protocol[3]
  - Three INP104 doses daily for 5 days (based on the Raskin protocol[3])
  - Two INP104 doses 1 hour apart[8]
  - One INP104 dose daily for 3 days[8]
  - One INP104 dose every 2 days for 5 days[8]
- Dosing regimens for 1.0 mg IV DHE (bolus) were based on the Raskin protocol[3]
  - Three IV DHE doses daily for 5 days
- Individual profiles for plasma concentration vs time were simulated. Noncompartmental methods were used to derive secondary exposure parameters including maximum concentration (C_{max}) and area under the curve over one dosing interval (AUC_{tau})
- Descriptive statistics were used to summarize derived exposure parameters

Conclusion

- This analysis of STOP 101 study participants used a nonparametric superposition tool to predict and compare the PK of repeat dosing of INP104
- The total DHE exposure from INP104 administered three times daily based on the Raskin protocol is predicted to be generally similar to the established IV DHE dosing regimen. However, peak concentrations of DHE from INP104 dosing were substantially lower than from IV DHE administration, suggesting that INP104 might offer the potential to minimize systemic side effects associated with high peak plasma concentrations, as was demonstrated in previous INP104 studies
- Simulations of repeat dosing of INP104 indicate that administering two INP104 doses 1 hour apart will produce higher DHE exposure compared with a single dose, with limited accumulations observed with the other INP104 repeat-dosing regimens
- The data provide valuable information on INP104 dosing protocols that may help guide physicians in utilizing INP104 in the clinic, although further clinical investigation is warranted

Results

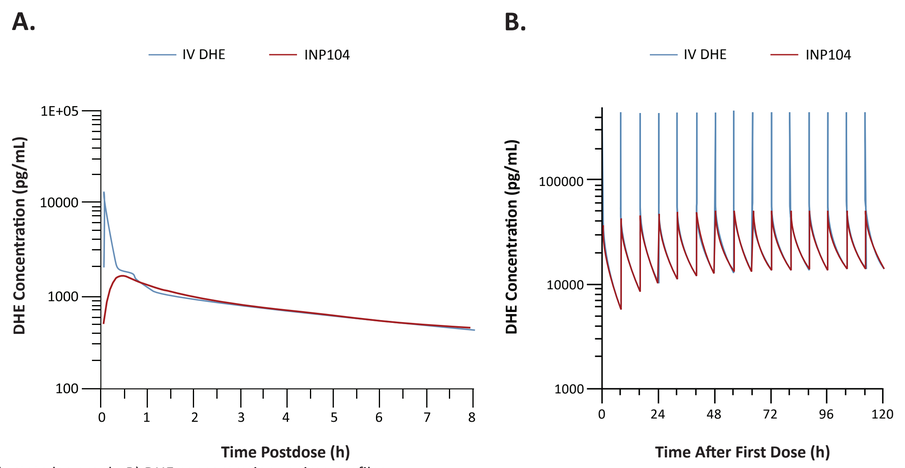
- There was limited accumulation of DHE exposure with any of the repeat-dosing regimens simulated. Exposure parameters are detailed in the Table

Table. Exposure Parameters of INP104 and IV DHE Dosing Regimens

	C_{max} (pg/mL)				AUC (h*pg/mL)			
	First Dose		Last Dose		First Dose		Last Dose	
	Geometric Mean	CV%	Geometric Mean	CV%	Geometric Mean	CV%	Geometric Mean	CV%
IV DHE 1.0 mg								
Three doses daily for 5 days	12,508	56	12,912	48	4990	21	7493[a]	19
INP104 1.45 mg								
Three doses daily for 5 days (based on the Raskin protocol[3])	1098	65	1510	61	3174	60	55,901[a]	60
Two doses 1 hour apart[8]	1098	65	1740	63	5597	60	11,195[b]	60
One dose daily for 3 days[8]	1098	65	1181	64	4639	58	5519[c]	59
One dose every 2 days for 5 days[8]	1098	65	1127	65	5321	59	5596[d]	60

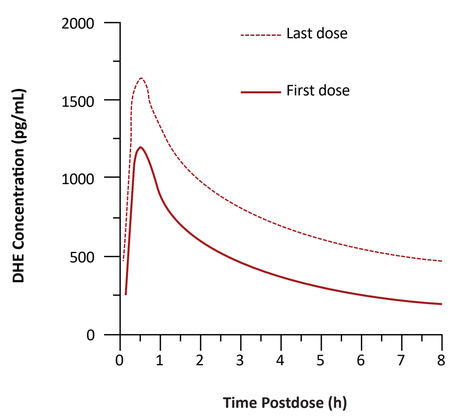
- **Three INP104 doses daily for 5 days vs Three IV DHE doses daily for 5 days (Figure 1)**
  - Total DHE exposures were similar between INP104 and IV DHE dosing regimens
  - Peak exposures were ~10x lower from INP104 vs IV DHE dosing regimen
  - **Three IV DHE doses daily for 5 days**
    - C_{max}: 3% higher vs a single dose
    - $AUC_{0\text{-}8h}$: 50% higher vs a single dose
  - **Three INP104 doses daily for 5 days (Figure 2)**
    - C_{max}: 38% higher vs a single dose
    - $AUC_{0\text{-}8h}$: 77% higher vs a single dose
    - Steady state was reached within the first 2 days of INP104 dosing

Figure 1. INP104 vs IV DHE Three Doses Daily for 5 Days - DHE Concentration



A) Steady state log graph. B) DHE concentration vs time profiles.
DHE = dihydroergotamine; IV = intravenous.

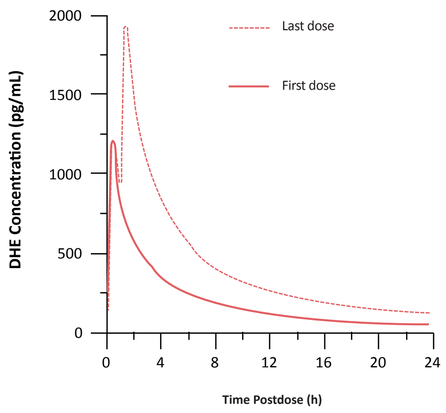
Figure 2. Three INP104 Doses Daily for 5 Days - DHE Concentration



DHE = dihydroergotamine.

- Other INP104 dosing regimens
  - **Two INP104 doses 1 hour apart (Figure 3)**
    - C_{max}: 59% higher vs a single dose
    - $AUC_{0\text{-}inf}$: ~100% higher vs a single dose
  - **One INP104 dose daily for 3 days (Figure 4)**
    - C_{max}: 8% higher vs a single dose
    - $AUC_{0\text{-}24h}$: 19% higher vs a single dose
  - **One INP104 dose daily every 2 days for 5 days (Figure 5)**
    - C_{max}: 3% higher vs a single dose
    - $AUC_{0\text{-}48h}$: 5% higher vs a single dose

Figure 3. Two INP104 Doses 1 Hour Apart - DHE Concentration



DHE = dihydroergotamine.

Figure 4. One INP104 Dose Daily for 3 Days - DHE Concentration

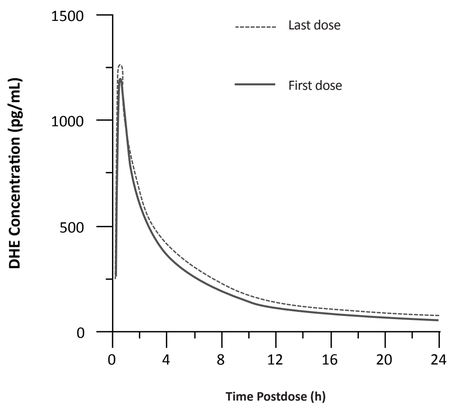
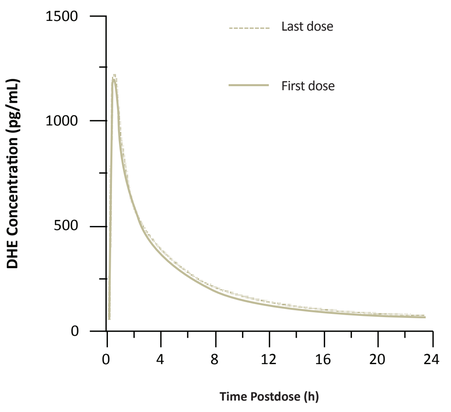


Figure 5. One INP104 Dose Every 2 Days for 5 Days - DHE Concentration



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