Assessment of the Potential for Drug-Drug Interactions Between INP104 and Gepants for Migraine Management Using a Model-based Approach

Sutapa Ray, PhD[1]; Bradley Torphy, MD[2]; Shivang Joshi, MD, MPH, RPh[3]; Robert E. Vann, PhD[1]; Brett Downing, M.Eng[1]; Daniella Fonseca, DNP, ARNP, AGACNP-BC[1]; Judie Gutierrez, PhD, MBA[1]; Stephen B. Shrewsbury, MB ChB[4]; Sheena K. Aurora, MD[1]

[1]Impel Pharmaceuticals, Seattle, WA, USA; [2]Chicago Headache Center and Research Institute, Chicago, IL, USA; [3]Community Neuroscience Services, Westborough, MA, USA; [4]Formerly Impel Pharmaceuticals, Seattle, WA, USA

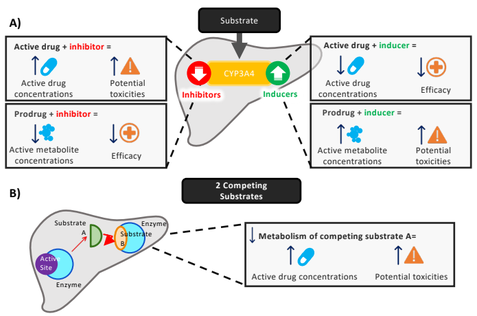
Introduction

- Nasally administered dihydroergotamine mesylate (DHE; INP104) and orally administered gepants are approved migraine therapies[1-4]
- Mechanistically, DHE exhibits broad receptor coverage (serotonergic, adrenergic, and dopaminergic), while gepants are calcitonin gene-related peptide (CGRP) receptor antagonists[1-5]
- It is likely that INP104 and gepants will be coadministered in clinical practice; however, no clinical studies investigating possible drug-drug interactions (DDIs) between these agents exist[6]
- Cytochrome P450 3A4 (CYP3A4) is one of the most clinically relevant P450 enzymes in the liver, metabolizing over half of CYP450-metabolized drugs[7-9]
- When drug interactions with CYP3A4 occur, they are generally classified as enzyme induction or inhibition—the consequences of which can contribute to alterations to drug metabolism and potential toxicities (Figure 1)[7,10-12]
- Previous studies using an investigational, orally inhaled DHE mesylate product coadministered with ketoconazole (a known potent CYP3A4 inhibitor) demonstrated minimal clinical risk, but an investigation of potential DDIs between INP104 and agents such as gepants is warranted[13,14]

Objective

- This study was a critical pharmacokinetic and pharmacodynamic evaluation aimed to predict whether coadministration of INP104 and gepants for migraine management could result in potential DDIs based on available publications and reports

Figure 1. Clinical relevance of potential drug-drug interactions (A) and substrate-substrate competition (B) with CYP3A4[12,15,16]



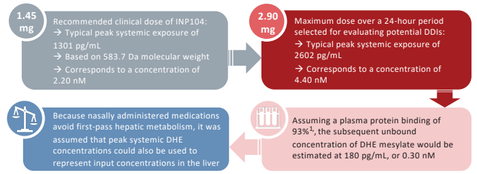
(A) Schematic of the potential metabolic and subsequent therapeutic consequences following CYP3A4 inhibition or induction, from a parent drug (direct inhibition/induction) or a drug metabolite (metabolism-dependent inhibition/induction). (B) General depiction of what may occur following substrate-substrate competition for CYP3A4, depending on the relative affinity of the substrate for CYP3A4 and its characteristics.

Methods

Study Design

- Any potential DDIs between INP104 and atogepant, rimegepant, or ubrogepant were evaluated according to methods and criteria detailed in the latest Food and Drug Administration (FDA)[17], European Medicines Agency (EMA)[18], Ministry of Health, Labour and Welfare (MHLW)[19], and International Council For Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[20] guidelines
- Predictions were made based on available data for INP104 and gepants via publications, source documents, and public resources such as prescribing information or databases, and the available data were assessed to determine if predictions can sufficiently rule out clinically relevant interactions
  - An in vitro pharmacokinetic study was conducted assessing the inhibitory potency (IC_{50}) of DHE mesylate toward CYP3A4/5 by measuring the activity of CYP3A4/5 in the presence and absence of DHE mesylate (from 0.1-100 nM) in human liver microsomes[6]
  - Direct inhibition as well as time- and metabolism-dependent inhibition of each enzyme was measured by probe substrate activity, analyzed by liquid chromatography with tandem mass spectrometry
- Whether DHE is an inhibitor/inducer of both drug metabolizing enzymes or drug transporter proteins in the intestines and liver, or if the metabolism of DHE itself is inhibited/induced due to DDIs, was assessed
- Potential interactions have been evaluated using basic approaches, and static or dynamic mechanistic models were not considered in this study (Figure 2)

Figure 2. Input parameters



Results

Potential CYP3A4 inhibition/induction from or on gepants[2-4]

- All 3 available gepants are principally metabolized in the liver and are sensitive substrates of CYP3A4, which suggests gepant pharmacokinetics could potentially be influenced by inhibitors/inducers of CYP3A4 (Table 1)

Table 1. Potential impact of CYP3A4 inhibition/induction on gepants

Effect of CYP3A4 inhibition or induction on gepants[2-4]		
	Effect of CYP3A4 inhibitor on drug exposure	Dose considerations for coadministration of gepants with CYP3A4 inhibitors or inducers
Atogepant	5.45-fold increase[a]	• Dose should be reduced if given along with potent inhibitor • No adjustment needed if given with moderate/weak inhibitor • Dose should be increased if given with potent/moderate inducer
Rimegepant	4.03-fold increase[a]	• Coadministration with potent inhibitors should be avoided • No adjustment needed if given with moderate/weak inhibitor • Coadministration with potent/moderate inducers should be avoided
Ubrogepant	9.65-fold increase[b]	• Coadministration with potent inhibitors or inducers should be avoided • Dose should be adjusted with moderate inhibitors • Dose should be increased if given with moderate inducer

Note: Inhibitors of CYP3A4 included. [a]itraconazole; [b]ketoconazole.

- None of the 3 gepants is a potent inhibitor/inducer of CYP3A4 (Table 2)

Table 2. Potential impact of gepants on CYP3A4 activity

Effect of gepants on CYP3A4[2-4]	
	Summary
Atogepant	• Weak inhibitor of CYP3A4 (41% at 100 µM) • Weak inducer of CYP3A4 (>2-fold expression at 5-20 µM)
Rimegepant	• Time-dependent inhibitor of CYP3A4 (IC_{50} 5µM) • Not an inducer of CYP3A4
Ubrogepant	• Not an inhibitor or inducer of CYP3A4 in vitro

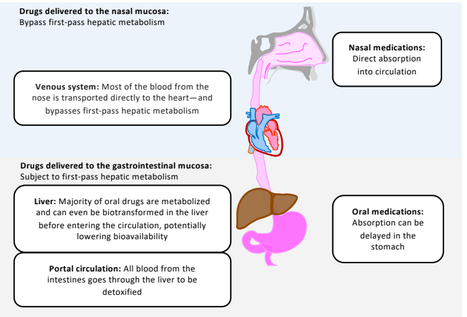
Potential inhibition/induction from or on DHE mesylate

- DHE is primarily metabolized in the liver (with 1 active metabolite, 8'-beta-hydroxydihydroergotamine), and believed to be a substrate of CYP3A4[1,21,22]
  - Coadministration of INP104 with potent CYP3A4 inhibitors is contraindicated[1]
- DHE was not found to be an inhibitor of CYP3A4 activity in vitro using current methods (under any investigated concentration; IC_{50} >100 µM)
  - There was no evidence of direct or metabolism-dependent inhibition of CYP3A4/5 by DHE mesylate at the concentrations measured
- Although there are no data on the inhibitory potential of 8'-beta-hydroxydihydroergotamine, no clinically relevant DDIs are predicted based on its average total exposure of <20% and peak exposure <5% compared to parent DHE

Anatomic and mechanistic considerations for INP104 in relation to potential DDIs

- While first-pass metabolism may limit the bioavailability of orally administered drugs, since INP104 is nasally administered, it bypasses gastrointestinal (GI) and hepatic first-pass metabolism. This may also limit the potential for local DDIs in the gut to occur (Figure 3)[23-26]
  - Metabolic capacity in the nasal cavity is generally considered to be lower than in the liver
  - Oral administration of DHE mesylate exhibits <1.5% bioavailability, compared with 58.9% bioavailability achieved with intranasally administered DHE mesylate in a phase 1 study[5]
  - Inhibition of CYP3A4 by DHE in the GI tract can be ruled out given any maximal intestinal luminal concentrations reached with INP104 would be well below the IC_{50} seen in vitro
- The pharmacodynamic profiles of DHE and the gepants are not anticipated to overlap significantly given their differing mechanisms of action, though potential pharmacodynamic DDIs cannot be completely excluded

Figure 3. General considerations regarding the impact of first-pass hepatic metabolism on therapeutic drug levels and onset of effect[23-26]



Potential inhibition of transporter proteins by gepants or DHE

- No clinically relevant DDIs from inhibition of, or being a substrate for, transporter proteins by gepants or DHE are anticipated, but they cannot be formally excluded due to limited data (Table 3)

Table 3. Effect of gepants or DHE on transporter proteins

Interactions with transporter proteins	
	Considerations for coadministration of gepants or DHE in regard to transporter proteins
Gepants	• Atogepant is a substrate of P-gp, OATP1B1, and OATP1B3 • Rimegepant and ubrogepant are substrates of P-gp and BCRP – Dose adjustments recommended if gepants administered with potent transporter protein inhibitors[2-4] • **Each gepant weakly inhibits transporter proteins such as OAT1B1 and OAT1B3, among others**
DHE	• There are no data demonstrating that DHE is a potential substrate of transporter proteins, though clinically relevant interactions are theoretically unlikely when administered nasally • **Data are lacking on the potential for DHE-mediated inhibition of drug transporter proteins, but it is reportedly a weak inhibitor of P-gp, OCT2, MATE1, and MATE2 in vitro** • Any relevant DDIs can be excluded based on current guidelines: – Hypothetical maximum DHE concentration in the GI tract (20 µM) is <10x higher than the in vitro IC_{50} for GI transporters, and the maximum unbound concentration (0.30 nM) is <1/10 the in vitro IC_{50}

Conclusions

- All evaluations reported here were made based on a critical assessment of available data, and have not been demonstrated in a controlled clinical study at the time of this review
- All 3 gepants are sensitive substrates of CYP3A4 and can therefore be influenced by inhibitors/inducers of CYP3A4, though none of the 3 gepants is a potent inhibitor/inducer of CYP3A4
- In vitro data suggest that DHE is not an inhibitor of CYP3A4 activity
- Data exclude clinically relevant DDIs from hepatic/gastrointestinal metabolic inhibition by gepants or from nasal metabolic inhibition of DHE
- Based on available data, no DDIs of clinical concern are theoretically predicted if DHE and gepants are coadministered within recommended clinical doses

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B Torphy is a speaker for Abbvie, Amgen, Impel Pharmaceuticals, Eli Lilly, Lundbeck, Pfizer, and Teva. He consults for Abbvie, Amgen, Eli Lilly, Neurolief, Teva, and Theranica. He has served as a principal investigator for Abbvie, Amgen, Eli Lilly, Pfizer, Teva, and Theranica. S Ray, RE Vann, B Downing, D Fonseca, and SK Aurora are full-time employees of Impel Pharmaceuticals and are stockholders in Impel Pharmaceuticals. SB Shrewsbury was formerly a full-time employee of and an officer of Impel Pharmaceuticals. He remains a stockholder. Editorial support was provided by IMPRINT Science and funded by Impel Pharmaceuticals Inc. IMPEL and POD are registered trademarks of Impel Pharmaceuticals Inc.