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Phase 1 Drug-Drug Interaction Studies of Inhaled Seralutinib in Healthy Subjects

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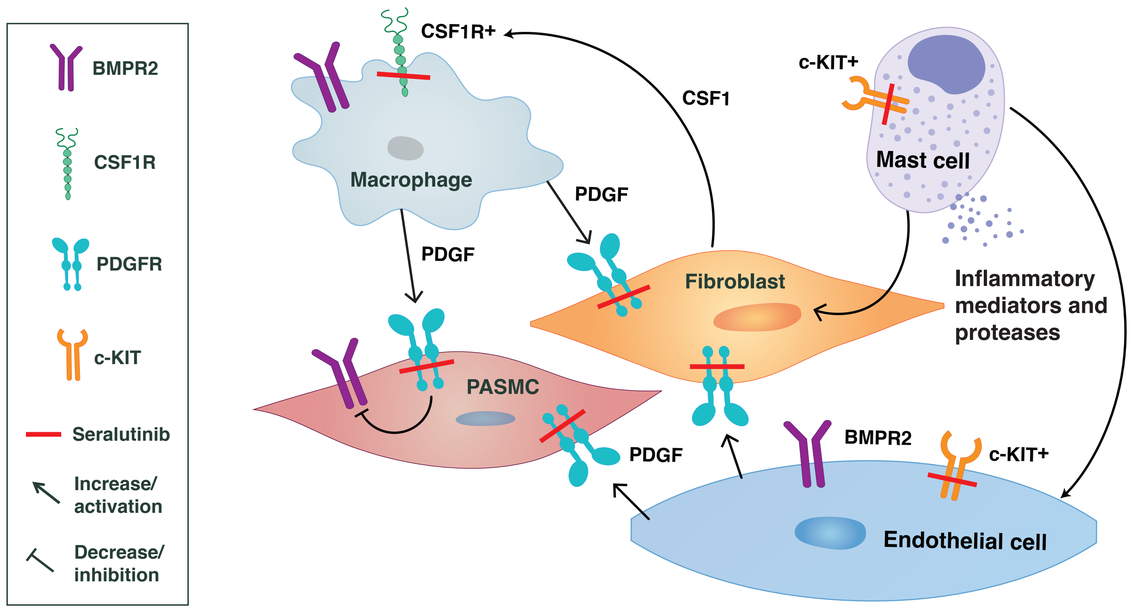
BACKGROUND

- Pulmonary arterial hypertension (PAH) treatment requires co-administration of multiple therapies, some of which are metabolized by cytochrome P450 (CYP) enzymes and/or cleared by drug transporters
- Seralutinib is a potent, small molecule kinase inhibitor currently being examined in a Phase 2 trial in patients with PAH (TORREY; NCT04456998)
- Seralutinib targets key pathways involved in PAH pathogenesis, namely PDGFR α/β, CSF1R, c-KIT, and BMPR2 deficiency (**Figure 1**)[1-3]
- Seralutinib is administered by dry power inhalation and was specifically designed to maximize the therapeutic index by directly targeting diseased pulmonary arterioles and reducing systemic exposure
- *In vitro* experiments suggest that seralutinib may impact CYP enzymes and drug transporters and is primarily metabolized by CYP3A; however, the clinical impact on co-administration with CYP substrates and inhibitors is unclear
- We conducted two studies in healthy volunteers to assess for potential drug-drug interactions with seralutinib

Dry powder inhaler

Figure 1. Seralutinib mechanism of action



OBJECTIVE

- **Study 1:** Evaluate potential effects of inhaled seralutinib on the PK of a cocktail of CYP enzyme and transporter substrates[4]
- **Study 2:** Examine the effect of CYP3A inhibition on the PK of seralutinib
- Evaluate the safety and tolerability of seralutinib alone and with co-administered drugs utilized in both studies

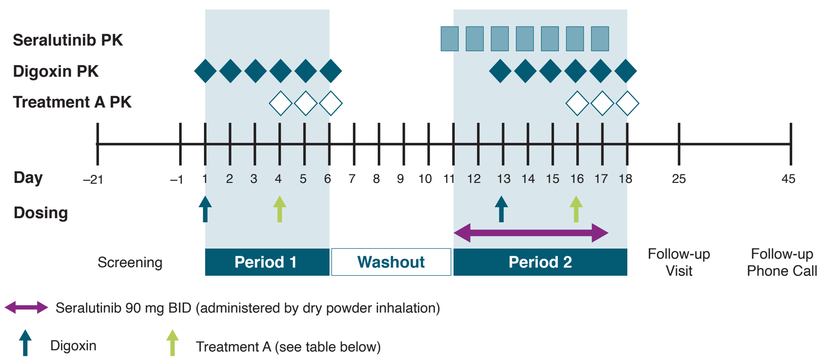
METHODS

- The potential drug interaction liability of seralutinib was evaluated in two healthy volunteer studies

STUDY 1 – Seralutinib as a precipitant (perpetrator of drug interaction)

- Open-label, single-group, single-sequence, DDI study to simultaneously assess 6 different potential interactions (**Figure 2**)
- 24 healthy adult subjects received a cocktail of 6 probe substrates (digoxin + Treatment A), with or without seralutinib
- Two dosing periods (P) with washout in between
  - P1: digoxin + Treatment A
  - P2: seralutinib + digoxin + Treatment A

Figure 2. Study 1 Schema

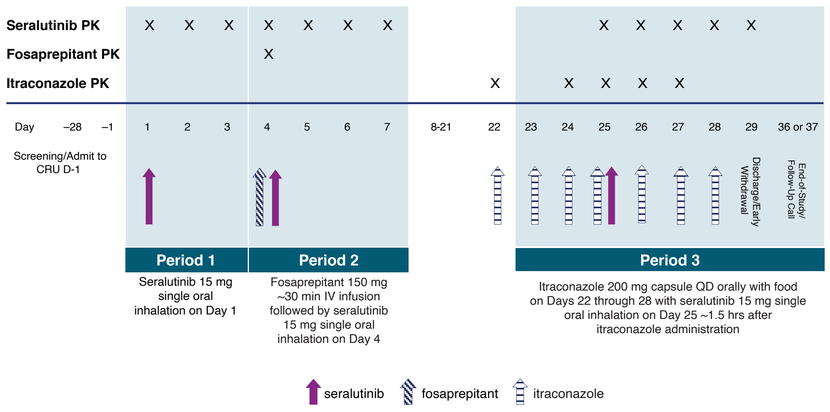


Probe Substrates		Dose Form	Dose (mg)	Route of Administration
	Digoxin (P-gp)	Tablet	0.25	Oral
Treatment A	Caffeine (CYP1A2)	Tablet	200	Oral
	Montelukast (CYP2C8)	Tablet	10	Oral
	Flurbiprofen (CYP2C9)	Tablet	50	Oral
	Midazolam (CYP3A)	Oral Syrup	5	Oral
	Pravastatin (OATP1B1/1B3)	Tablet	40	Oral

STUDY 2 – Seralutinib as an object (victim of drug interaction)

- Open-label, single-group, single-sequence, DDI study of inhaled seralutinib plus fosaprepitant (weak CYP3A inhibitor) or itraconazole (strong CYP3A inhibitor) (**Figure 3**)
- 19 healthy adult subjects received seralutinib, with or without fosaprepitant or itraconazole
- Three dosing periods (P) with washout in between
  - P1: seralutinib
  - P2: seralutinib + fosaprepitant
  - P3: seralutinib + itraconazole
- The effect of the moderate CYP3A inhibitor erythromycin on the PK of seralutinib was assessed with static mechanistic modeling and leveraging itraconazole DDI data

Figure 3. Study 2 Schema



METHODS (continued)

- Plasma concentrations were determined using validated assays; PK parameters were estimated using noncompartmental methods
- Point estimates of geometric mean ratios (GMRs) and associated 2-sided 90% CIs for C_{max}, AUC_t, and AUC_{inf} with versus without seralutinib (**Study 1**) or with versus without fosaprepitant or itraconazole (**Study 2**) were derived from the log transformed data with a linear mixed effects model and back-exponentiated. The GMRs and corresponding 90% CIs of C_{max}, AUC_t, and AUC_{inf} are presented in forest plots (**Figure 4** and **Figure 5**)
- Safety was assessed throughout the study (clinical laboratory tests, vital signs, electrocardiograms, and adverse events)

RESULTS

Demographics and Baseline Characteristics

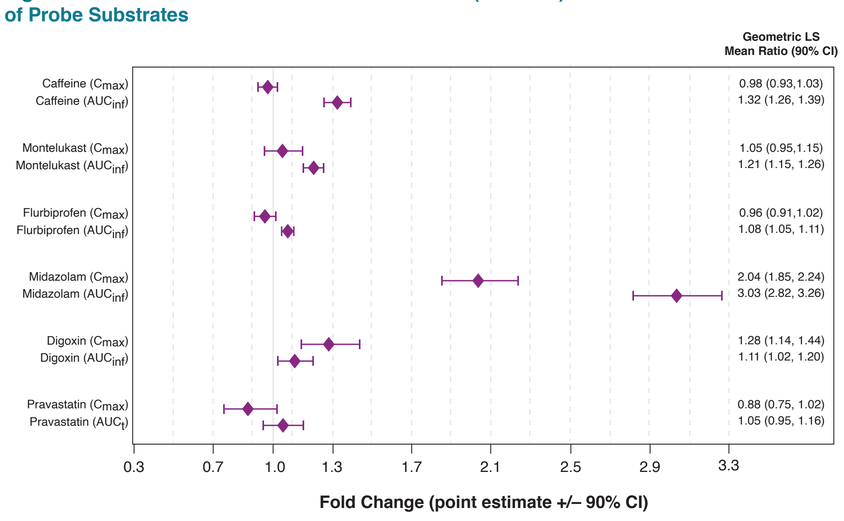
Baseline Characteristics	Study 1 (N=24)	Study 2 (N=19)
Age (years), Mean (SD)	44.5 (7.37)	41.6 (8.32)
Sex, n (%) Female	22 (91.7)	2 (10.5)
Race, n (%) Black White Other	4 (16.7) 20 (83.3) 0 (0)	6 (31.6) 11 (57.9) 2 (10.6)
Body Mass Index (kg/m²), Mean (SD)	26.30 (2.85)	27.91 (2.98)

Pharmacokinetics

STUDY 1 (Figure 4)

- Seralutinib co-administration increased
  - midazolam C_{max} 2-fold and AUC 3-fold, indicating that seralutinib is a moderate inhibitor of CYP3A
  - caffeine AUC by 33%, indicating that seralutinib is a weak inhibitor of CYP1A2
- Seralutinib
  - is neither an inhibitor nor an inducer of CYP2C8, CYP2C9 and OATP1B1/1B3
  - slightly inhibits P-gp (digoxin is a NTI drug; its prescribing information provides guidance on co-dosing with P-gp inhibitors)

Figure 4. Forest Plot of Geometric LS Mean Ratios (± 90% CI) of Plasma PK Parameters of Probe Substrates

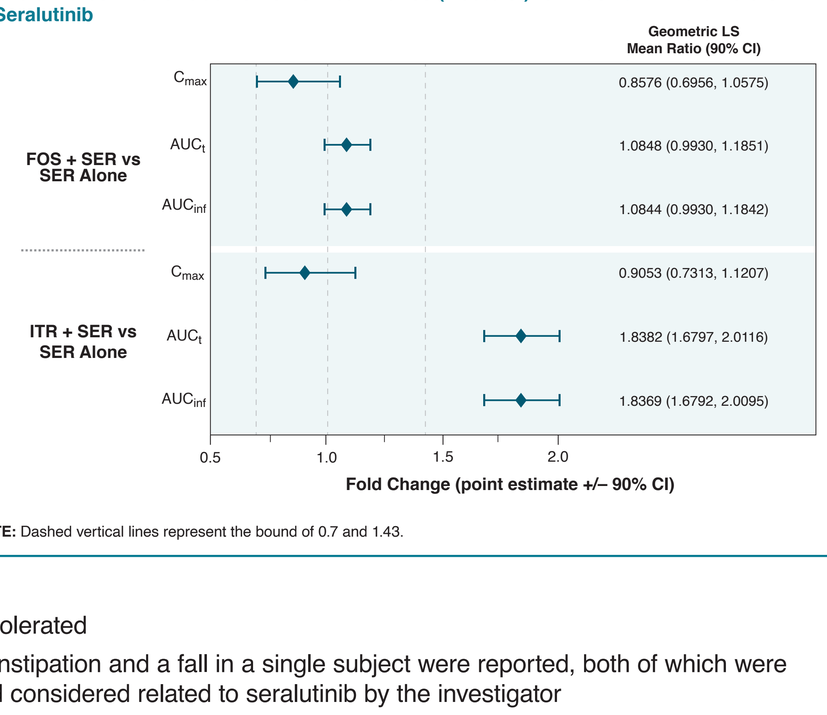


NOTE: AUC_t was used for pravastatin due to 15 occurrences of missing AUC_{inf} results.

STUDY 2 (Figure 5)

- Fosaprepitant and itraconazole increased seralutinib AUC by 8% and 84%, respectively
- Erythromycin was predicted to increase seralutinib AUC by 25-39%
- No effect on C_{max} was observed or predicted for these CYP3A inhibitors

Figure 5. Forest Plot of Geometric LS Mean Ratios (± 90% CI) for Plasma PK Parameters of Seralutinib



NOTE: Dashed vertical lines represent the bound of 0.7 and 1.43.

Safety (both studies)

- Seralutinib was generally well tolerated
- Treatment emergent AEs of constipation and a fall in a single subject were reported, both of which were considered mild in severity and considered related to seralutinib by the investigator
- No SAEs or AEs leading to drug withdrawal or early termination from the studies were reported

SUMMARY AND CONCLUSIONS

- Inhaled seralutinib demonstrated a favorable DDI profile and can be co-administered with most medications, including PAH background therapies
- Inhaled seralutinib was generally well tolerated when given alone or with various probe substrates (**Study 1**) and fosaprepitant (weak CYP3A inhibitor) or itraconazole (strong CYP3A inhibitor) (**Study 2**)
- These results support use of concomitant medications in the ongoing Phase 2 TORREY study and any future trials evaluating inhaled seralutinib in PAH

REFERENCES

1. Yamamura et al. *FASEB J.* 2019;33:7363; **2.** Chen et al. *BMC Genomics.* 2016;17:781; **3.** Perros et al. *Am J Respir Crit Care Med.* 2008;178:81; **4.** Li et al. *Pulm Circ* 2021; 11(4) 1–24.

ABBREVIATIONS

AUC_{inf}, area under the plasma concentration time curve from time 0 extrapolated to infinity; AUC_t, area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration; BID, twice daily; BMPR2, bone morphogenetic protein receptor type 2; CI, confidence interval; c-KIT, stem cell factor receptor; C_{max}, maximum observed plasma concentration; CRU, clinical research unit; CSF1R, colony stimulating factor 1 receptor; CYP, cytochrome P450; DDI, drug-drug interaction; FOS, fosaprepitant; ITR, itraconazole; IV, intravenous; LS, least-squares; NTI, narrow therapeutic index; OATP, organic anion transporting polypeptide; PAH, pulmonary arterial hypertension; PDGFR, platelet-derived growth factor receptor; P-gp, P-glycoprotein; PK, pharmacokinetic(s); QD, once daily; (S)AE, (serious) adverse event; SER, seralutinib.

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