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A Phase 1, Open-Label Study of Inhaled Seralutinib to Assess Potential Effects on the Pharmacokinetics of Cytochrome P450 and Transporter Substrates in Healthy Subjects

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BACKGROUND

- Seralutinib is a potent, clinical stage kinase inhibitor that targets key pathways involved in the progression of PAH, namely PDGFRα/β, CSF1R, c-KIT, and BMPR2 deficiency[1-3] (**Figure 1**)
- Seralutinib is administered by dry power inhalation and maximizes the therapeutic index by directly targeting diseased pulmonary arterioles, minimizing systemic exposure, and decreasing the potential for off-target adverse effects (**Figure 2**)
- Some medications, including PAH disease-specific medications, are metabolized by certain CYP enzymes and/or cleared by drug transporters
- Seralutinib was shown *in vitro* to potentially impact CYP enzymes and drug transporters
- This study examined the potential effect of inhaled seralutinib on the PK of CYP450 and transporter probe substrates to support use of concomitant medications in the clinical development program

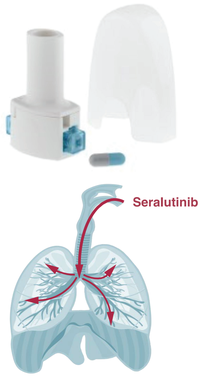
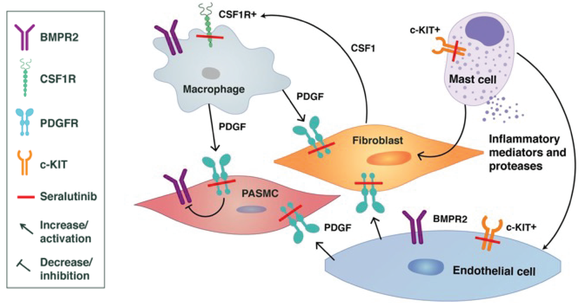


Figure 2. Seralutinib dry powder inhaler and route of administration

Figure 1. Mode of action of seralutinib in reversing pathologic remodeling in PAH



METHODS

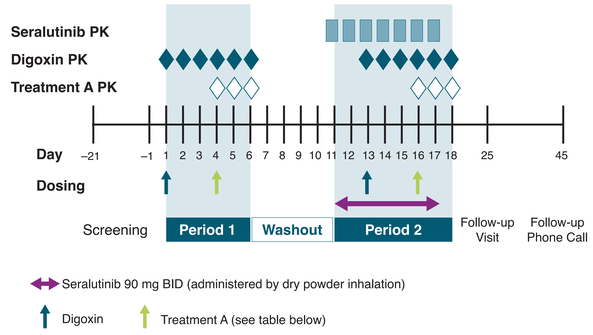
Study Design

- Open-label, single-group, single sequence, DDI study to simultaneously assess 6 different potential interactions (**Figure 3**)
- 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

Objectives

- **Primary:** Evaluate the potential effect of seralutinib on the PK of probe substrates
- **Secondary:** Assess the safety and tolerability of seralutinib co-administered with probe substrates

Figure 3. Study 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

RESULTS

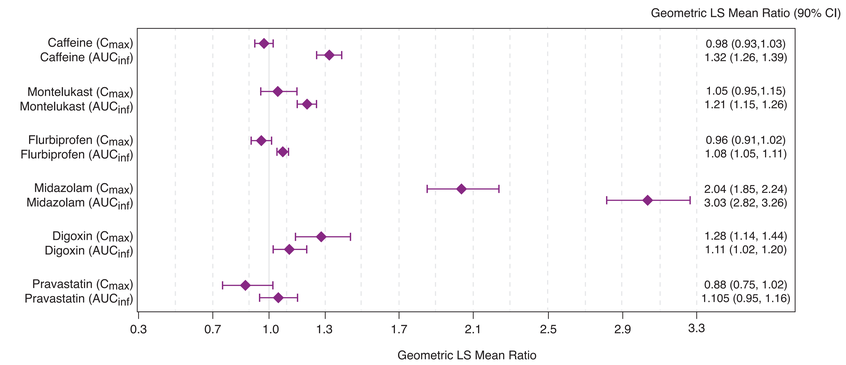
Pharmacokinetics (Figure 4)

- 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 inhibited P-gp (increased digoxin C_{max} by 28%)

Safety

- No SAEs or AEs leading to drug withdrawal or early termination from the study were reported

Figure 4. Forest Plot of Geometric LS Mean Ratios of Plasma Pharmacokinetic Parameters of Probe Substrates (PK Population)



Notes: AUC_t was used for pravastatin due to 15 occurrences of missing AUC_{inf} results.
Comparisons of probe substrates (with vs without seralutinib) for C_{max}, AUC_{inf}, and AUCt were based on a linear mixed effects model on log-transformed values which included treatment as a fixed effect and measurements within each subject as repeated measures
Geometric LS Mean Ratios were converted to the original scale by back exponentiation of the log mean differences.

SUMMARY & CONCLUSIONS

- **Seralutinib administered alone or with various probe substrates was well tolerated**
- **Seralutinib demonstrated a favorable DDI profile**
  - **Not an inhibitor or inducer of CYP2C8, CYP2C9, CYP2C19 and OATP1B1/1B3**
  - **A moderate inhibitor of CYP3A and a weak inhibitor of CYP1A2**
  - **Slightly inhibited P-gp; increase in digoxin exposure was observed**
- **Seralutinib is not expected to have clinically relevant DDIs with PAH medications except possibly for sildenafil (CYP3A substrate)**
  - **An increase in the exposure of sildenafil could occur**
- **These results support use of concomitant medications in the ongoing Phase 2 study [TORREY, NCT04456998; evaluating the efficacy and safety of inhaled seralutinib in patients with WHO Group 1 PH (FC II or III)]**

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.

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; c-KIT, stem cell factor receptor; C_{max}, maximum observed plasma concentration; CSF1R, colony stimulating factor 1 receptor; CYP, cytochrome P450; DDI, drug-drug interaction; LS, least-squares; OATP, organic anion transporting polypeptide; PAH, pulmonary arterial hypertension; PDGF, platelet-derived growth factor; P-gp, P-glycoprotein; PK, pharmacokinetic; (S)AE, (serious) adverse event

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