Seralutinib is a potent, clinical stage kinase inhibitor that targets key pathways involved in the progression of PAH, namely FGFR1/2, c-KIT, PDGF, and BMPR2 deficiency.1–4 (Figure 1) 

Seralutinib is administered by dry powder inhalation and maximizes the therapeutic index by directly targeting diseased pulmonary arterioles, decreasing the potential for off-target adverse effects.2 (Figure 2) 

Some medications, including PAH disease-specific medications, are metabolized by certain CYP enzymes and/or cleared by drug transporters.4 Seralutinib was shown in vitro to potentially impact CYP enzymes and drug transporters.1 This study examined the potential effect of inhaled seralutinib on the PK of CYP450 and transporter substrates to support use of concomitant medications in the clinical development program.1

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

**RESULTS**

Pharmacokinetics (Figure 4) 
- Seralutinib co-administration increased midazolam Cmax by 3-fold and AUC by 3.03-fold, indicating that seralutinib is a weak inhibitor of CYP3A4
- Seralutinib is neither an inhibitor nor an inducer of CYP2C8, CYP2C9 and CYP2C19
- Slightly inhibited P-gp (increased digoxin Cmax by 2.04-fold)
- Not an inhibitor or inducer of CYP1A2

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

**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 CYP3A4, CYP2C9, CYP2C19 and OATP1B1/1B3
- A moderate inhibitor of CYP3A4 and a weak inhibitor of CYP2C8
- 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. Yamamoto et al. JASPE. 2019;33(3).

**ABBREVIATIONS**

CYP, cytochrome P450; DDI, drug-drug interaction; LS, least-squares; OATP, organic anion transporting polypeptide; PAH, pulmonary arterial hypertension; P-gp, P-glycoprotein; PAH, pulmonary arterial hypertension; P-gp, P-glycoprotein; PAH, pulmonary arterial hypertension; P-gp, P-glycoprotein; (S)AE, (serious) adverse event