**EVIDENCE OF TARGET ENGAGEMENT AND MODULATION: BIOMARKER ANALYSIS OF THE PHASE 1b INHALED SERALUTINIB STUDY**


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**BACKGROUND**

- **Abnormal signaling of PDGFα/β, CSF1R, and c-KIT as well as BMPR2**
- Seralutinib is an inhibited small-molecule kinase inhibitor which selectively targets PDGFα/β, CSF1R, and c-KIT signaling, and modulates BMPR2.
- Studies of inhibited seralutinib in animal models support pharmacodynamic activity in the human lung at dose levels expected to have biologic and clinical activity:
  - 30-fold higher lung/plasma exposure (Figure 1)
  - Extended lung target engagement
  - Reversal of pulmonary vascular remodeling, improved hemodynamics, increased lung BMPR2 and reduced circulating NT-proBNP.
- **Phase 1 studies in healthy volunteers and PAH subjects demonstrated** that seralutinib was well tolerated at doses up to 90 mg BID.
- Here we use peripheral markers to measure target engagement and pharmacodynamic activity in circulation in PAH subjects.

**RESULTS**

**Target Engagement**

- Seralutinib inhibits CSF1R receptor internalization in PAH subjects at 5 min post inhalation demonstrating successful target engagement at the dose levels studied (Figure 2)
- Consistent with rapid systemic clearance, CSF1R internalization is no longer inhibited at 120 minutes

**Pharmacodynamics: Gene Expression**

- **Gene expression profiles at day 14 relative to baseline are supportive of biological activity** by seralutinib (Figure 3):
  - Differentially expressed treatment-associated shifts in 779 genes, after adjusting for false discovery
  - The seralutinib-associated pharmacodynamic signature was most prominent in subjects receiving the higher seralutinib dose in week 2 of the study
  - Seralutinib signature will be measured and related to efficacy in an ongoing phase 2 study

**SUMMARY**

- Preliminary biomarker findings suggest seralutinib demonstrates biological activity in PAH patients after 2 weeks of treatment:
  - Target engagement and modulation of gene expression in the periphery suggest pharmacodynamic activity
  - FOXP3/CXCR4 7:1 ratio may represent a biomarker of therapeutic effect; requires further validation
  - A randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical study (TORREY; NCT04456998) to evaluate efficacy and safety of seralutinib for the treatment of WHO Group 1 PH is currently recruiting patients.
- Candidate biomarkers will be measured in the phase 2 study to identify predictive and pharmacodynamic markers of treatment response, with the aim of advancing personalized medicine in PAH.

**REFERENCES**


**ACKNOWLEDGEMENTS**

The authors would like to thank the study investigators, study coordinators, and especially the patients and families who participated in this study at all the sites in the USA (California, Colorado, Connecticut, Florida, Kentucky, Massachusetts, Minnesota, North Carolina, Ohio, Pennsylvania, South Carolina, Texas, and the United Kingdom (Glasgow, London, Newcastle).