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

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BACKGROUND

• Abnormal signaling of PDGFα, CSFIR, and c-KIT, as well as BMPR2 deficiency drive cellular overgrowth in the lung vasculature and play key roles in the development of PAH.

• Seralutinib is an inhaled small-molecule kinase inhibitor which selectively targets PDGFα, CSFIR, and c-KIT signaling, and modulates BMPR2.

• Studies of inhaled seralutinib in animal models support pharmacodynamic activity in the human lung at doses levels expected to have biological and clinical activity:

  – 30-fold higher lung:plasma exposure
  – 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 patients demonstrated that seralutinib was well tolerated at doses up to 90 mg BID.

• Phase 2b multi-center, double-blind, randomized, placebo-controlled study (NCT03207868): Eight subjects (PAH, PC-III, on 2-3 background therapies) were randomized 3:1 to receive inhaled seralutinib 45 mg BID (escalating to 90 mg BID on day 8 at PI discretion) or placebo for 2 weeks.

• Following informed consent, peripheral blood was collected for exploratory biomarker assessment at baseline and day 14 of three transportaes relative to inhalation (pre-dose, 5 min and 120 min).

• Percent inhibition of CSFIR receptor internalization was measured using a novel whole blood M-CSF induced CSFIR internalization FACs assay developed in-house and run at Primity Bio.

• Whole blood gene expression mRNA profiling was performed using NovaSeq.

METHODS

• Phase 1b, multi-center, double-blind, randomized, placebo-controlled study (NCT03207868): Eight subjects (PAH, PC-III, on 2-3 background therapies) were randomized 3:1 to receive inhaled seralutinib 45 mg BID (escalating to 90 mg BID on day 8 at PI discretion) or placebo for 2 weeks.

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RESULTS

TARGET ENGAGEMENT

• Seralutinib inhibits CSFIR receptor internalization in PAH subjects at 5 min post inhalation demonstrating successful target engagement at the doses levels studied (Figure 2).

• Consistent with rapid systemic clearance, CSFIR internalization is no longer inhibited at 120 minutes.

PHARMACODYNAMICS: EPIDEMIOLOGICAL IMMUNOPROFILING

• Preliminary studies implicate FOXP3/C4D-Treg deficiency in development and severity of PAH.

• FOXP3/C4D ratio is elevated in all patients treated with seralutinib (median 17% increase).

• FOXP3/C4D is a novel candidate diagnostic marker for disease-modifying activity.

Figure 3. Seralutinib transiently inhibits CSFIR internalization. A. CSFIR assay schema; B. CSFIR activity in systemic circulation indicates target engagement at 5 minutes post-treatment (bars show mean and standard deviation).

Figure 4. Epigenetic immunoprofiling assay shows percent change from baseline in FOXP3/C4D ratio (% baseline).

SUMMARY & CONCLUSIONS

• 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/C4D T-cell ratio may represent a biomarker of therapeutic effect; requires further validation.

• A randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical study (TORNADYHO15459898) to evaluate efficacy and safety of seralutinib for the treatment of WHO Group 1 PH is currently recruiting subjects.

• 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


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