A Phase 1B, Multi-Center, Randomized, Placebo-Controlled Trial of Inhaled Seralutinib in Subjects With WHO Group 1 Pulmonary Arterial Hypertension (PAH)

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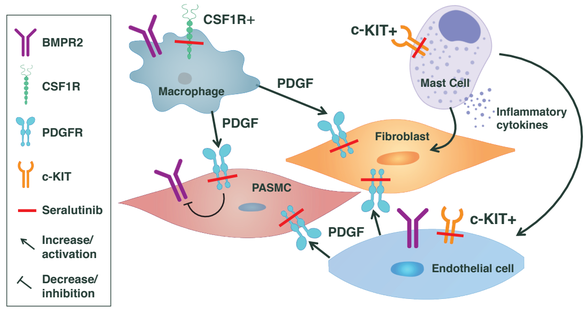
BACKGROUND

- Abnormal signaling of PDGFα/β, CSF1R, and c-KIT as well as BMPR2 deficiency drive cellular overgrowth in the lung vasculature and play key roles in the development of PAH[1,2,3]
- Seralutinib (formerly GB002) is a new chemical entity delivered via dry powder inhalation that inhibits PDGFRα/β, CSF1R, and c-KIT, and modulates BMPR2 (**Figure 1**)
- Studies of inhaled seralutinib in animal models showed
  - Higher lung exposure than that of plasma by 30×
  - Reversal of pulmonary vascular remodeling, improved hemodynamic parameters, increased lung BMPR2 and reduced circulating NT-proBNP[4,5]
- Phase 1 studies in healthy volunteers demonstrated that seralutinib was well tolerated at doses up to 90 mg BID[6]
- This study is the first clinical experience reported with inhaled seralutinib in subjects with PAH at dose levels expected to have biologic and clinical activity

Dry Powder Inhaler

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



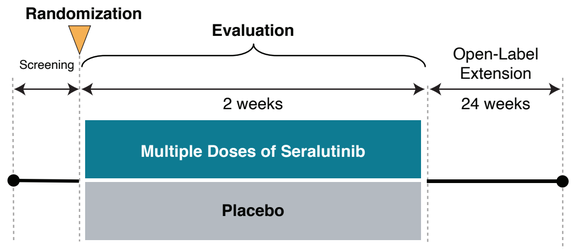
OBJECTIVES

- **Primary:** Determine the safety and tolerability of seralutinib when administered via dry powder inhalation for 14 days in subjects with WHO Group 1 PAH
- **Secondary:** Assess pharmacokinetic parameters of inhaled seralutinib

METHODS

- Phase 1b, multi-center, double-blind, randomized, placebo-controlled study (**NCT03926793**)
- Selected inclusion criteria
  - Diagnosis of WHO Group 1 PAH, Functional Class II-IV
  - Prior cardiac catheterization data consistent with PAH
  - Baseline 6MWT > 100 m
  - On PAH background medication
- Subjects 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 (**Figure 2**)
  - Doses were selected based on preclinical efficacy studies and extensive pharmacokinetic/pharmacodynamic modeling
- Endpoints
  - **Primary:** Adverse event (AE) incidence, changes from baseline in pulmonary function, laboratory parameters, and vital signs
  - **Secondary:** Pharmacokinetic parameters
  - **Exploratory:** Target engagement CSF1R whole blood assay
- Subjects who completed the 2-week treatment period were eligible to participate in a 24-week open-label extension study

Figure 2. Study Schema



RESULTS

- 8 subjects enrolled and completed the 2-week study
  - N=6, seralutinib; N=2, placebo
  - 4 seralutinib-treated subjects received an escalated dose (90 mg BID) starting at day 8

RESULTS (CONTINUED)

Table 1. Demographics and Baseline Characteristics (N=8)

Demographics	
Age (Range)	30 - 63 years
Female / Male, n	7 / 1
Functional Class at Baseline, n	
Class II	6
Class III	2
PAH Etiology, n	
Idiopathic	4
Heritable	2
Scleroderma/Systemic Sclerosis	2
Background PAH Medications*, n	
Double Therapy	3
Triple Therapy	5
PGI or IP Receptor Agonist**	5

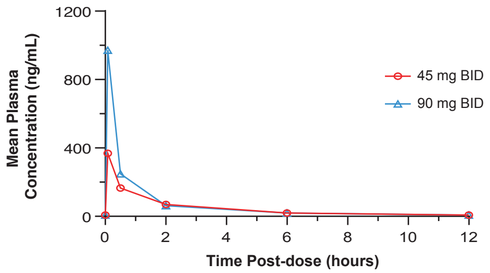
*Single or combination therapy with phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, endothelin receptor antagonists, and prostanoids (with the exception of inhaled prostanoids) was allowed **PGI, prostaglandin; IP, prostaglandin I2 receptor

Safety

- No serious adverse events were reported
- Most frequently reported AEs were mild-moderate cough and mild headache
- No AEs resulted in dose reduction, interruption, or discontinuation of seralutinib
- No clinically significant changes in laboratory parameters, electrocardiograms, pulmonary function tests, or vital signs occurred

Pharmacokinetics (PK)

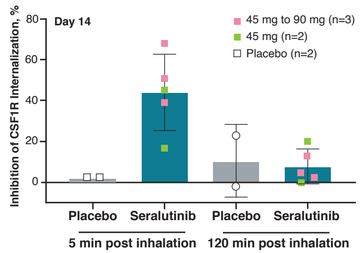
Figure 3. The PK profile of inhaled seralutinib was dose-proportional and characterized by low systemic exposure and rapid clearance (N=5, evaluable)



Target Engagement

- Seralutinib blocked CSF1R internalization at 5 min post inhalation demonstrating successful target engagement (**Figure 4**)
- Fast clearance from circulation was associated with reduced inhibition 120 min post inhalation

Figure 4. CSF1R Stabilization Assay (N=7, evaluable)



CSF1R activity in systemic circulation indicates seralutinib target engagement.

SUMMARY

- Seralutinib is a new inhaled therapy that targets novel biological pathways in PAH pathophysiology, including inhibition of PDGFR, CSF1R, c-KIT, and modulation of BMPR2
- This is the first clinical experience in PAH subjects with seralutinib; seralutinib at doses up to 90 mg BID was well tolerated with mild-moderate AEs
- The PK profile was consistent with that seen in healthy volunteers[6]; exposure was dose-proportional, with low systemic exposure characteristic of an inhaled product
- A target engagement assay in whole blood showed that seralutinib blocked CSF1R activation with a time-course that was consistent with the systemic PK profile
- 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 PAH is currently recruiting subjects

REFERENCES

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