Case Study of Long-Term Safety, Tolerability, And Hemodynamic Response of PB1046, A Sustained-Release Analogue for Vasoactive Intestinal Peptide (VIP), in an Adult Subject With Pulmonary Arterial Hypertension (PAH)

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Background:
- PB1046 is a first-in-class vasoactive intestinal peptide (VIP) analogue under development for the treatment of PAH (Figure 1a):
  - VIP’s biologic effects are mediated by two G-protein-coupled receptors - VPAC1 and VPAC2 receptors.
  - VPAC2 in the pulmonary vasculature may play a role in PAH pathogenesis.
  - PB1046 is 100x more selective for VPAC2 compared to VPAC1 (Figure 1b).
- Molecular Structure of PB1046:
  - PB1046 is a 634 amino acid recombinant fusion protein expressed in Escherichia coli.
  - Human VIP is at the N-terminus with a physiologically inert polymeric elastin-like polypeptide (ELP) sequence at the C-terminus, resulting in a >60 hr half-life of the VIP analogue (Figure 1).
  - The VIP moiety comprises the first 28 amino acids of mature human VIP with a single additional methionine at the N-terminus to confer VPAC2 selectivity.
- CardioMEMS™ HF System:
  The safety and accuracy of the CardioMEMS™ HF System, which monitors pulmonary artery (PA) pressure from a sensor implanted into the PA, has been previously documented, along with correlations with Swan-Ganz measurements and echocardiography.

Methods:
- The multi-dose safety, PK, and VIP-based pharmacodynamic effects of PB1046 were evaluated in an open-label, multi-dose Phase 1 pilot study in PAH patients who have a permanently implanted CardioMEMS™.
- PB1046 was administered subcutaneously once-weekly for 8 weeks (extended due to subjective improvements) at dose levels previously tested and shown to be safe.

Results:
- Three patients presented previously (PVRI 2018) completed the study with no related serious adverse events, symptomatic hypotension, or syncope. PB1046 was well tolerated with only mild injection site erythema.
- In 2 patients, hemodynamic monitoring showed reduced mean PA pressure and total pulmonary resistance with increased stroke volume and cardiac output and stable heart rate. One patient elected long-term maintenance therapy and remained on PB1046 for >18 months total.
- Long-term PB1046 therapy demonstrated clinically meaningful improvement in all hemodynamic parameters assessed, which remained stable throughout the treatment period (Figure 2).
- After completing approximately 1 year of therapy, the patient’s dose was tapered gradually prior to discontinuation. After each incremental dose reduction, hemodynamic perturbation was observed followed by stabilization (Figure 3, red boxes).
- Withdrawal of therapy led to marked reversion of hemodynamic parameters to pretreatment levels approximately 3 months post-final dose of PB1046 (Figure 3a and b).

Mechanism of PB1046– Slow Release and Prolonged Half-Life:

**Figure 1a. PB1046: Long-lasting VIP analogue**

**Figure 1b. PB1046: VPAC2 selective**

**Figure 3a. Long-term hemodynamic response of PB1046**

**Figure 3b. Reversal of PB1046 effect after study drug discontinuation**

Conclusions:
- In a case study of a PAH patient treated for >18 months with PB1046, long-term, sustained improvements in pulmonary hemodynamics that gradually reversed post-discontinuation of study drug suggest possible disease modifying effects of PB1046 and support ongoing investigation of PB1046 as a novel VIP-based therapy for PAH patients.
- A randomized, double-blind, parallel-group Phase 2b PAH study is ongoing to assess 16 weeks of PB1046 treatment added to standard of care therapy for NYHA/WHO functional class II and III PAH patients.

Acknowledgements:
We thank the patients who participated in this study and the research teams and investigators who made this study possible.