HS135, a novel activin and GDF trap, is highly efficacious in preclinical models of pulmonary hypertension and obesity-associated heart failure with preserved ejection fraction

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Introduction: Activins and growth differentiation factors (GDFs) signal via the Activin Type II receptor (ActRII) and are genetically and clinically validated drivers of heart failure (HF), pulmonary hypertension (PH) and obesity. Despite initial clinical success in PH, current inhibitors of Activin mediated signalling (eg, sotatercept, an ActRIIA receptor ectodomain Fc-fusion protein) cannot be dosed to full biological activity. HS135 is a rationally designed ActRII-based fusion protein that acts as a ligand trap for pathological Activins and GDFs while sparing BMP-9 to treat PH and obesity-associated HF. We previously demonstrated that HS135 achieves best-in-class in vitro potency against Activin and GDF targets, which translated into full in vivo target engagement (not observed with ActRIIA-Fc). Here, the differentiated efficacy profile of HS135 was explored in preclinical models of PH and HF with preserved Ejection Fraction (HFpEF).

Methods: HS135 PH efficacy was assessed using the rat monocrotaline (MCT) and the mouse transaortic constriction (TAC) models, while the murine High Fat Diet (HFD) and L-NAME model was utilized to explore the potential of HS135 in obesity-associated HFpEF. In the MCT model, rats were injected twice weekly for four weeks with HS135 or ActRIIA-Fc starting the day following MCT induction. In the TAC model, mice were injected twice weekly for four weeks with HS135 or ActRIIA-Fc two weeks following surgical intervention to establish TAC. HFpEF was established by feeding mice HFD in combination with L-NAME supplied in drinking water ad libitum for 5 weeks before commencing twice weekly treatment with HS135 or empagliflozin for three weeks. In each case, tissue remodelling in the heart and lungs was assessed by IHC and RNA-seq. In addition, changes in body composition as well as markers of adiposity were evaluated.

Results: Right ventricles (RV) of MCT treated animals showed a distinct gene expression profile by RNAseq particularly related to pathways of inflammation and energy balance. This profile was only modestly improved by ActRIIA-Fc whereas RVs of HS135-treated animals were nearly indistinguishable by RNAseq from naïve mice. Similarly, in the lung, HS135 was more efficacious than ActRIIA-Fc at improving inflammation markers and rebalancing Activin and BMP signalling. In the TAC and HFD/L-NAME models, HS135 was efficacious at modulating the left ventricle phenotype. Across all models of PH and HF, HS135 led to profound increases in lean mass and a more metabolically favourable muscle gene expression profile. Furthermore, in the HFD / L-NAME model, HS135 was able to improve fat mass and markers of adiposity.

Conclusion: HS135 best-in-class target engagement profile uniquely improves PH, HF, and metabolism across in vivo models. Collectively, these data support the development of HS135 as a novel agent in cardiopulmonary and cardiometabolic disease, including PH and obesity-associated HF.