Title: GB002, a Novel Inhaled PDGFR Kinase Inhibitor, Demonstrates Efficacy in the SU5416 Hypoxia Rat Model of PAH

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Introduction: Pulmonary arterial hypertension (PAH) is a progressive disorder characterized by excessive smooth muscle cell proliferation, vascular remodeling, increased pulmonary arterial pressure, and right ventricular hypertrophy. The platelet-derived growth factor (PDGF) signaling pathway is activated in human PAH and plays an important role in BMPR2 regulation. A nonselective PDGFR inhibitor imatinib demonstrated improved exercise capacity and hemodynamics in patients with advanced PAH; however, serious adverse events occurred due to systemic administration.

Hypothesis: We hypothesized that localized lung delivery of GB002, a novel potent PDGFRα/β inhibitor, would lead to beneficial vascular reverse remodeling and improved cardiopulmonary hemodynamics, while limiting systemic exposure.

Materials and Methods: We evaluated a dry powder formulation of GB002, delivered by inhalation, on disease progression in the SU5416 Hypoxia rat (SU5416/H) model of PAH. GB002 treatment was initiated after established PAH was confirmed by echocardiography post a single 20 mg/kg SUGEN injection, followed by 3-weeks of hypoxia and 2-weeks of normoxia. Statistical analysis was performed with one-way ANOVA. Significance was set at $p<0.05$. Data presented are mean +/- SEM.

Results: Two-week treatment with GB002 significantly reduced right ventricular systolic pressure (Control PAH 85.2 ± 11 mmHg (n=7) vs GB002 46.7±3.9 mmHg (n=9), $p<0.005$) and mean pulmonary artery pressure (Control PAH 50.4 ± 5.4 mmHg (n=7) vs GB002 31.9±2.6 mmHg (n=9), $p<0.005$). Hemodynamic changes were accompanied by reduced pulmonary arteriole muscularization and restoration of BMPR2 protein expression in the lung lobes in GB002-treated animals. In parallel, decreased plasma levels of NT-proBNP and PDGF-B were observed, along with modulation of pro-inflammatory cytokines. GB002 was well tolerated.

Conclusions: These data demonstrate that localized delivery of GB002 is efficacious on multiple measures of disease activity in the SU5416/H model. GB002 treatment is associated with disease remodeling including improved cardiopulmonary hemodynamics, reduced pulmonary arteriolar muscularization, restoration of BMPR2 signaling, reduced NT-proBNP and improved cytokines