Effects of GBT1118, A Potent Allosteric Modifier of Hemoglobin Oxygen Affinity, on Bleomycin-Induced Murine Model of Hypoxemia and Lung Fibrosis

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**Introduction**

Hypoxic pulmonary fibrosis (HPF) is a deadly lung disease that causes chronic, progressive, and irreversible fibrosis. HPF is characterized by alveolar damage and exaggerated fibrotic tissue production that results in obliteration of lung parenchyma and subsequent lung dysfunction(1). Currently, around 5 million people worldwide are affected by HPF with over 126,000 patients in the United States with a median survival time of approximately 2.5 years from the time of diagnosis(2). Although various therapeutic drugs, including corticosteroids and pirfenidone, have been approved for the treatment of HPF, treatment options are still limited for this deadly disease(3). Therefore, there continues to be a significant need for novel and effective therapeutic drugs for HPF.

A prominent clinical feature of HPF is hypoxia, and any data are available to treat exertional breathlessness, a debilitating clinical manifestation of hypoxia(4). GBT1118 is an analog of GB440, a novel orally bioavailable small molecule that binds covalently and reversibly via Schiff base to theϝ1ε1ε3ε6ε4ε2ε alpha chain and allosterically modulates the Hb-oxygen (Hb-O2) affinity. It elicits a concentration-dependent left shift in the oxygen equilibrium curve with subsequent increase in Hb-O2 affinity and arterial oxygen loading. We have previously reported increased Hb oxygen affinity by GBT1118, which resulted in improved tissue oxygenation and enhanced survival during severe hypoxic challenge (5)(6) inspired here. We investigated whether GBT1118 could ameliorate hypoxia associated with lung fibrosis induced by bleomycin in mice(6, 7).

**Experimental Design**

**Methods**

GBT1118 was evaluated in the bleomycin-induced lung fibrosis model. Bleomycin (3 units/kg) or saline control was administered to C57BL/6 mice via intraperitoneal injection on day 2. After pulmonary fibrosis and hypoxia were induced by day 7, mice were then treated with vehicle control or two different dose levels of GBT1118 via oral administration from day 8 to day 15. Mice were weighed daily. Arterial blood gases and oxygen saturation were measured on day 7 and day 14. Bronchoalveolar lavage fluid (BALF) was analyzed for leukocyte cell count and collagen quantification. Lung tissues were analyzed for fibrosis by histopathology(6).

**PK/PD Analysis**

**Results**

**GBT1118 fully rescues bleomycin-induced hypoxemia**

**GBT1118 improves bleomycin-induced body weight loss**

**Conclusion**

GBT1118, an allosteric hemoglobin modifier, has been shown to:
- have strong anti-hypoxic effects with improved arterial oxygen saturation to near normal level.
- ameliorate the loss of body weight associated with bleomycin exposure.
- inhibit the increase in numbers of inflammatory cell infiltrates.
- result in an approximately 50% reduction in BALF collagen levels, and lung weight normalization.

Exertional breathlessness and worsening hypoxia are prominent clinical features of HPF progression. The data from this study support the concept that a hemoglobin modifier such as GBT1118 that enhances Hb-O2 affinity and improves arterial oxygenation could potentially be used to treat hypoxemia associated with pulmonary fibrosis.

**References**


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