Translational Pharmacology of GB0139, an Inhaled Small Molecule Galectin-3 Inhibitor for the Treatment of Idiopathic Pulmonary Fibrosis

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Introduction

Galectin-3 (Gal-3) is a pro-fibrotic β-galactoside-binding lectin highly expressed in the fibrotic lung & macrophages from idiopathic pulmonary fibrosis (IPF) patients[1] & GB0139 (formerly TD139) is a novel, inhaled, small molecule Gal-3 inhibitor being developed for the treatment of this disease[2]. In this study the translational pharmacology of GB0139 from pre-clinical to clinical studies are presented.

Methods

GB0139 was evaluated in pre-clinical studies investigating Gal-3 *in vitro* affinity & potency, *in vivo* PK/PD in naïve & bleomycin-treated mice (male C57/Bl6 mice)[1,2]. A randomized, double-blind, multi-centre, placebo-controlled, phase IIa study was completed to assess safety, tolerability, & PK/PD of GB0139 in 24 patients with IPF. Three dose cohorts of 8 patients with IPF were evaluated using a 5:3 ratio (active:placebo). Inhaled GB0139 was delivered at 0.3 mg, 3 mg or 10 mg QD for 14 days. Patients underwent bronchoalveolar lavage (BAL) prior to dosing and after 14 days. GB0139 drug concentration was measured in the BAL fluid, BAL macrophages & plasma. Gal-3 expression on BAL macrophages was measured by flow cytometry & systemic biomarkers of Gal-3 inhibition & fibrosis measured in plasma.

Conclusions

GB0139 is safe & well tolerated in man & demonstrates low systemic exposure coupled with high lung concentrations that result in suppression of Gal-3 expression on BAL macrophages & decreases in plasma biomarkers associated with IPF progression. Pre-clinical *in vitro* & *in vivo* studies have been shown to be clinically translatable. This study supported the progression of GB0139 into a phase IIb study in IPF patients[3].

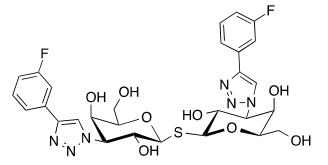
References

1. MacKinnon AC, Gibbons MA, Farnworth SL, *et al. Am. J. Respir. Crit. Care Med.* 2012;185(5):537-546.
2. Delaine T, Collins P, MacKinnon A, *et al.*, *ChemBioChem* 2016;17(18):1759-1770.
3. NCT03832946 - A Study to Test the Efficacy & Safety of Inhaled GB0139 in Subjects with Idiopathic Pulmonary Fibrosis (IPF) https://clinicaltrials.gov/

Results

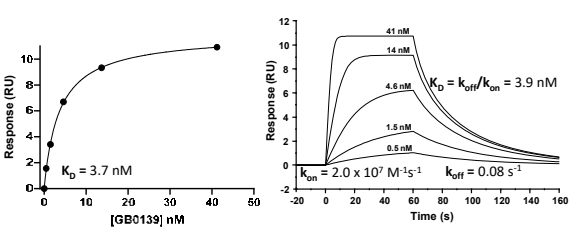
In vitro pharmacodynamics

GB0139

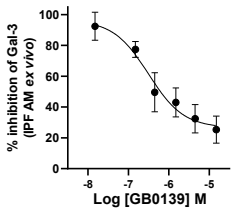


	Human ±SD (n)	Mouse ±SD (n)
FP K_D (nM)	2.1 ± 0.1 (4)	54 ± 17 (3)

GB0139 Gal-3 Affinity & Kinetics (SPR)



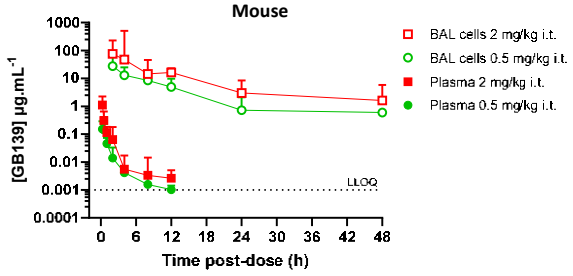
***Ex vivo* IPF BAL cells**



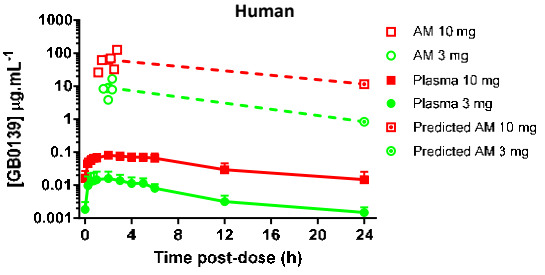
GB0139 demonstrates high affinity for Gal-3 & inhibits Gal-3 expression *ex vivo* on IPF BAL cells (IC_{50} = 361 ± 108 nM (mean ± SD, n=3 patients)).

In vivo & clinical pharmacokinetics

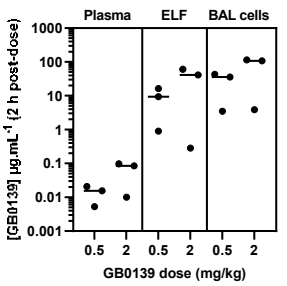
Mouse



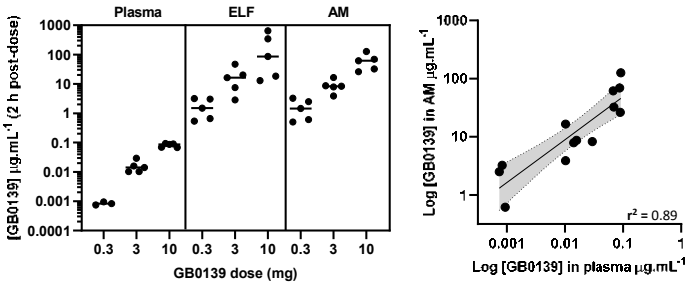
Human



Mouse



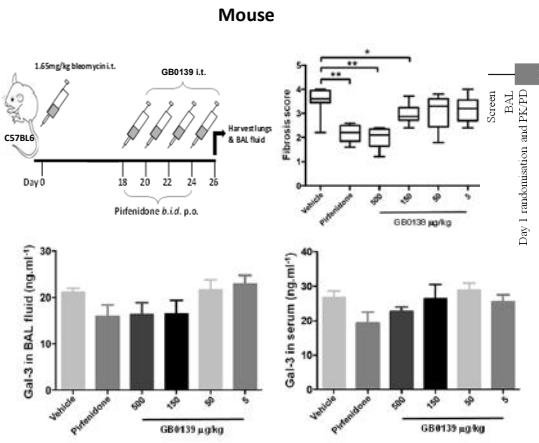
Human



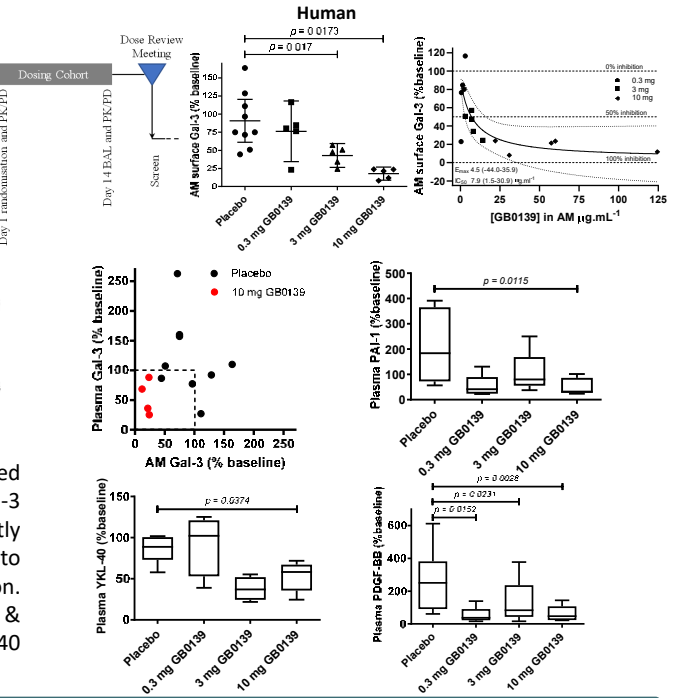
In naïve C57BL6 mice, GB0139 delivered via i.t. administration was quickly absorbed & cleared from the plasma with high levels retained in the lung over 48 h. In the clinic, inhaled GB0139 was well tolerated at all doses & rapidly absorbed with concentrations in alveolar macrophages (AM) between 567- & 1,930-fold higher than systemic exposure at 2 h. AM levels correlated with plasma levels across the dosing range.

In vivo & clinical pharmacodynamics

Mouse



Human



GB0139 in a bleomycin lung fibrosis model attenuated mechanistic & fibrotic endpoints. In humans, Gal-3 expression on BAL macrophages was significantly lower in the 3 mg & 10 mg dose groups compared to placebo, with a concentration-dependent inhibition. This was associated with reductions in plasma Gal-3 & biomarkers relevant to IPF pathobiology (PAI-1, YKL-40 & PDGF-BB).

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