

IOA-289 - a Novel, Clinical Stage Autotaxin Inhibitor for the Treatment of Fibrotic Lung Disease



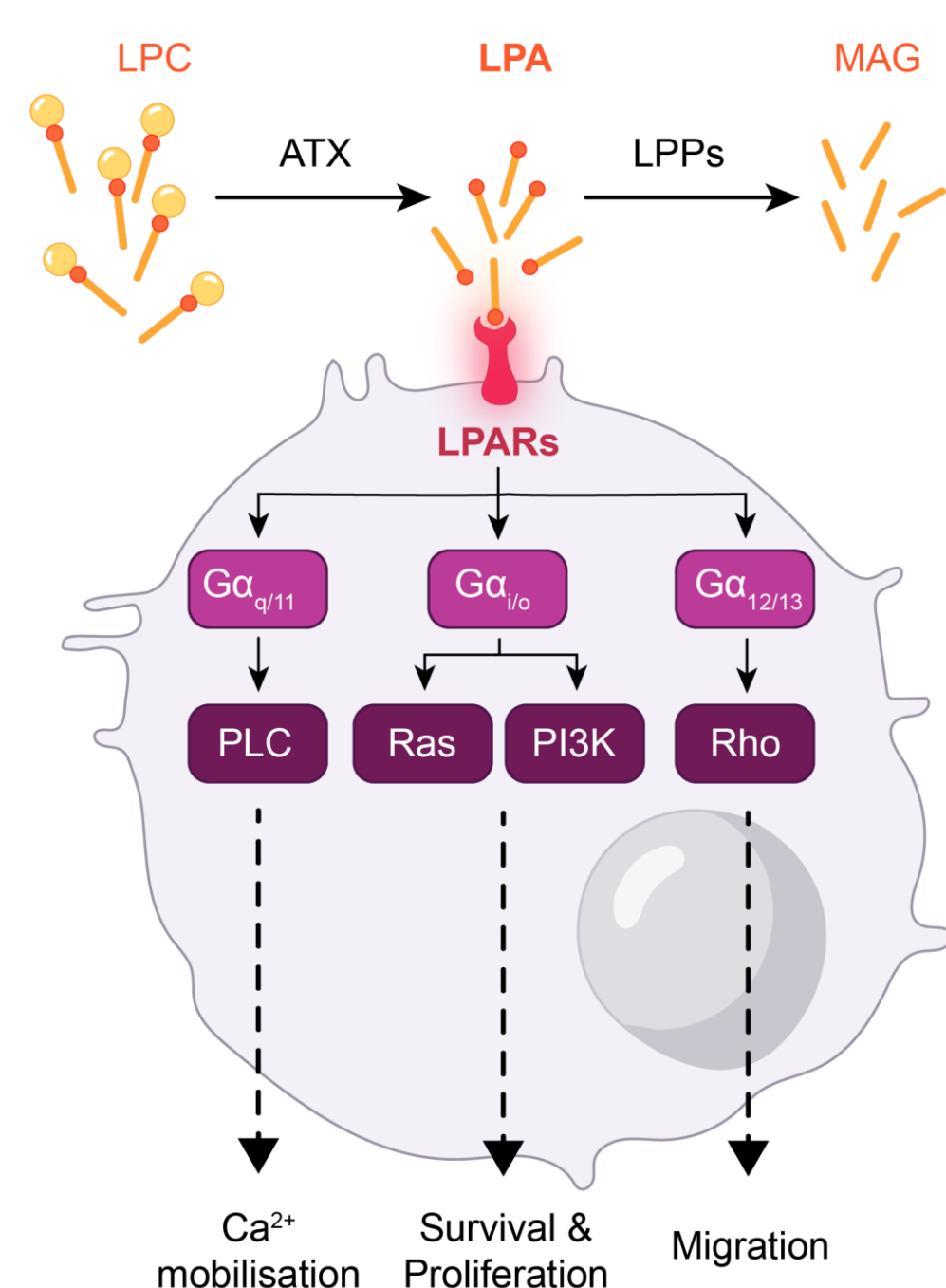
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Background

Autotaxin (ATX) is a secreted glycoprotein with lysophospholipase D activity that hydrolyzes lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA). LPA signaling through LPA receptors is implicated in controlling cellular activities including migration, proliferation and survival in fibrotic pathologies, including idiopathic pulmonary fibrosis (IPF) and cancer (Figure 1). Several inhibitors of the ATX/LPA pathway have been developed for treatment of IPF. IOA-289 is a novel, highly potent autotaxin inhibitor with a unique chemical structure that is in clinical development for the treatment of fibrotic pathologies including cancer. IOA-289 does not bind to the catalytic zinc region of ATX but binds to both the substrate pocket as well as to the LPA carrier channel thereby blocking both functions of ATX. This results in a more favorable safety profile compared to first generation inhibitors. A second ATX inhibitor from a different chemical series is in preclinical development.

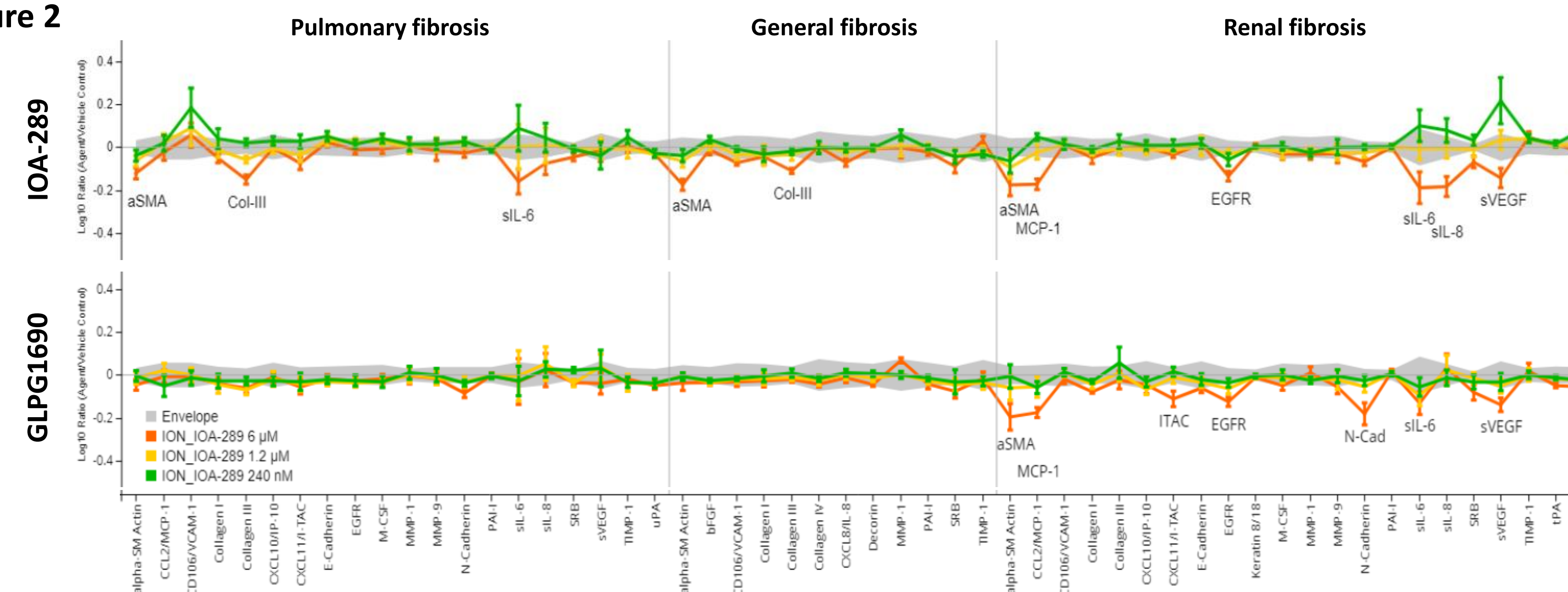
Figure 1



IOA-289 is a potent modulator of fibrosis

The BioMAP® Fibrosis panel consists of systems that models fibrotic tissues and disease by co-culturing stimulated human primary cells; lung epithelial cells and fibroblasts, lung fibroblasts only or renal epithelial cells with lung fibroblasts. IOA-289 and GLPG1690 were tested at concentrations of 6, 1.2 and 0.24 μM. At 6 μM IOA-289 decreased the activity of fibrosis relevant factors, including sIL-6, MCP-1, αSMA, collagen-III, and sVEGF. In contrast to IOA-289, GLPG1690 did not show any significant effect in this assay in the pulmonary and general fibrosis system (Figure 2).

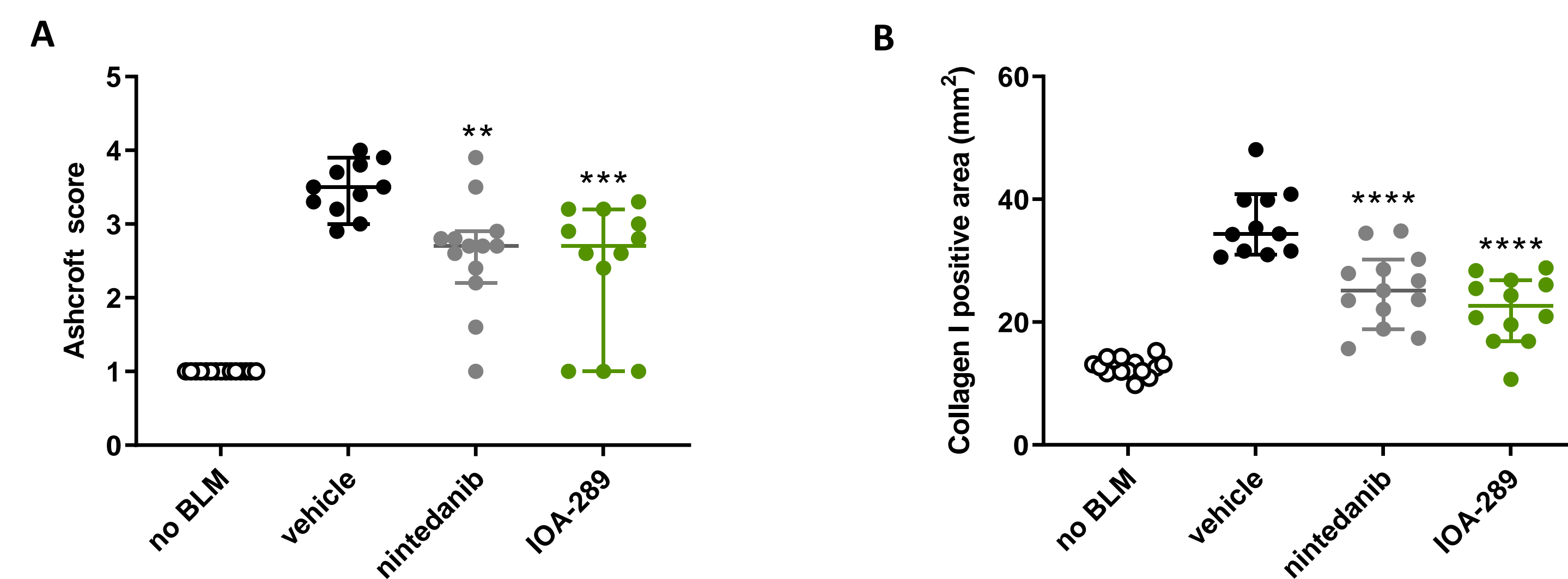
Figure 2



IOA-289 is efficacious in bleomycin lung fibrosis mouse model

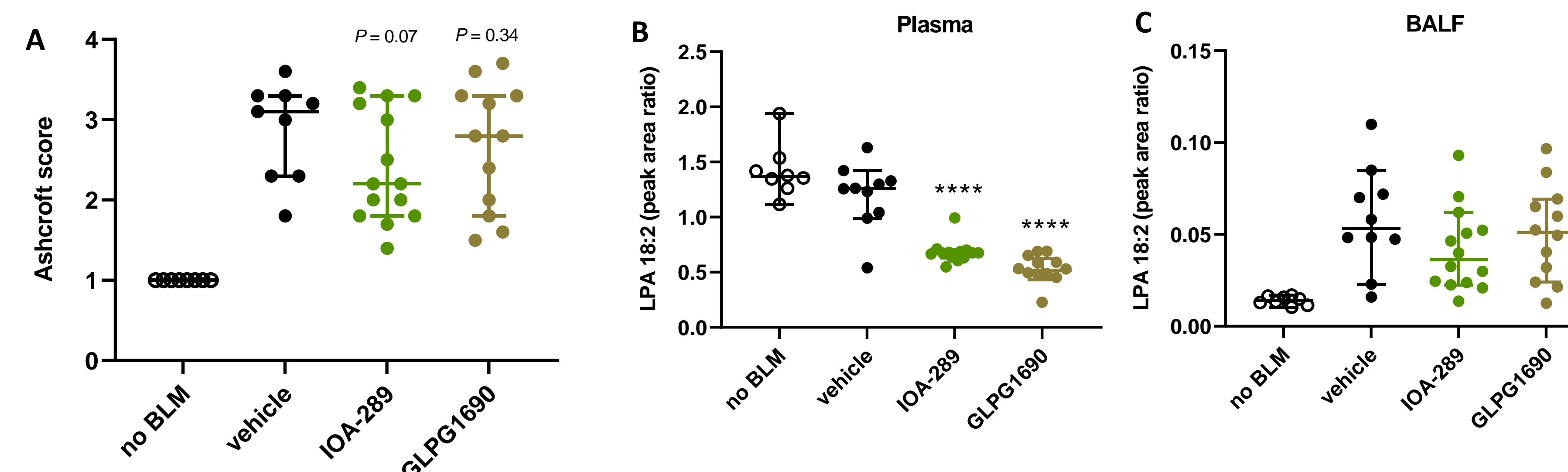
In vivo efficacy testing of IOA-289 at 10 mg/kg p.o. BID in the intranasal bleomycin (BLM) induced lung fibrosis model showed marked reduction of efficacy read-outs by Ashcroft score (Figure 3A) and collagen content (Figure 3B), equal or better than standard-of-care nintedanib dosed at 60 mg/kg BID p.o.

Figure 3



In an independent experiment, IOA-289 was tested head-to-head with GLPG1690 both at 10 mg/kg p.o. BID. IOA-289 showed a greater reduction in fibrosis score compared with GLPG1690 (Figure 4A). LPA levels in plasma were significantly reduced by both treatments and IOA-289 also markedly reduced LPA levels in BALF (Figure 4B and C).

Figure 4



Methods

- In vitro* activity on biomarkers of fibrosis was assessed using the BioMAP® screen, profiling with 3 different human primary cell systems.
- In vivo* efficacy was studied in the bleomycin-induced pulmonary fibrosis (BLM) model in C57BL/6 mice with prophylactic treatment of compounds for the study duration. For histopathological evaluation, lung tissue was stained according to Crossman's Trichrome and assessed using the Ashcroft score for fibrosis.
- LPA levels in plasma and bronchoalveolar lavage fluid (BALF) were quantified by LC-MS/MS.

IOA-289 is a potent ATX inhibitor

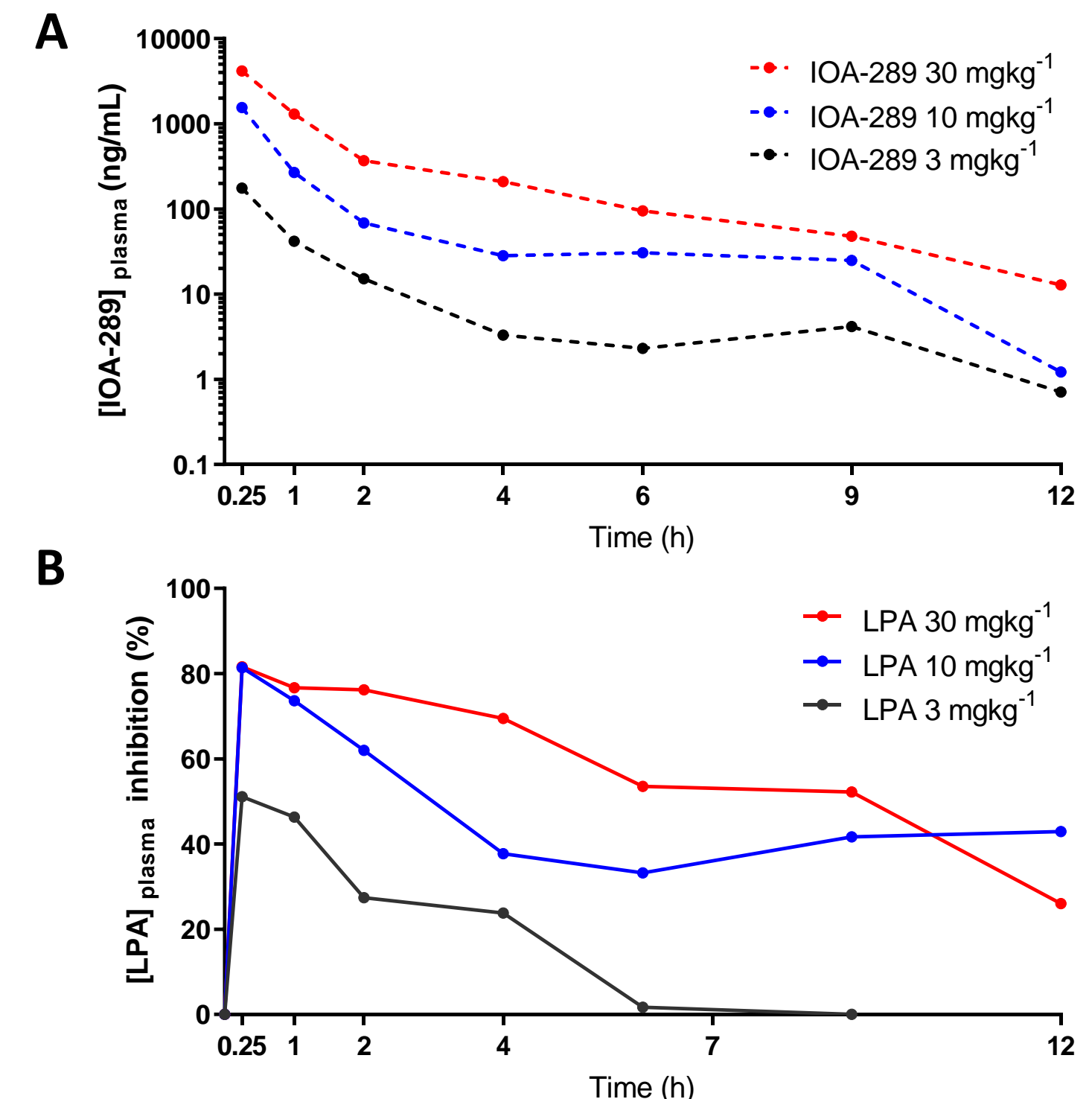
Characteristics of IOA-289.

Parameter	IOA-289	GLPG1690
IC ₅₀ ATX	10 nM	39 nM
IC ₅₀ LPA 18:2 (human plasma)	34 nM	98 nM
MW (Da)	502	588
Caco2 permeability / efflux ratio	25·10 ⁻⁶ cms ⁻¹ / 1.5	6.7·10 ⁻⁶ cms ⁻¹ / 4.1
Oral bioavailability (m/r)	41% / 37%	29% / 37%
CEREP safety screen (safety factor for 44 off-targets)	> 100	

IOA-289 PK and PD

Male CD1 mice dosed with 3, 10 or 30 mg/kg of IOA-289 p.o. showed dose-dependent reduction of circulating LPA C18:2 with an ED₅₀ value at 1 h post-dose of around 3 mg/kg (Figure 5A and B).

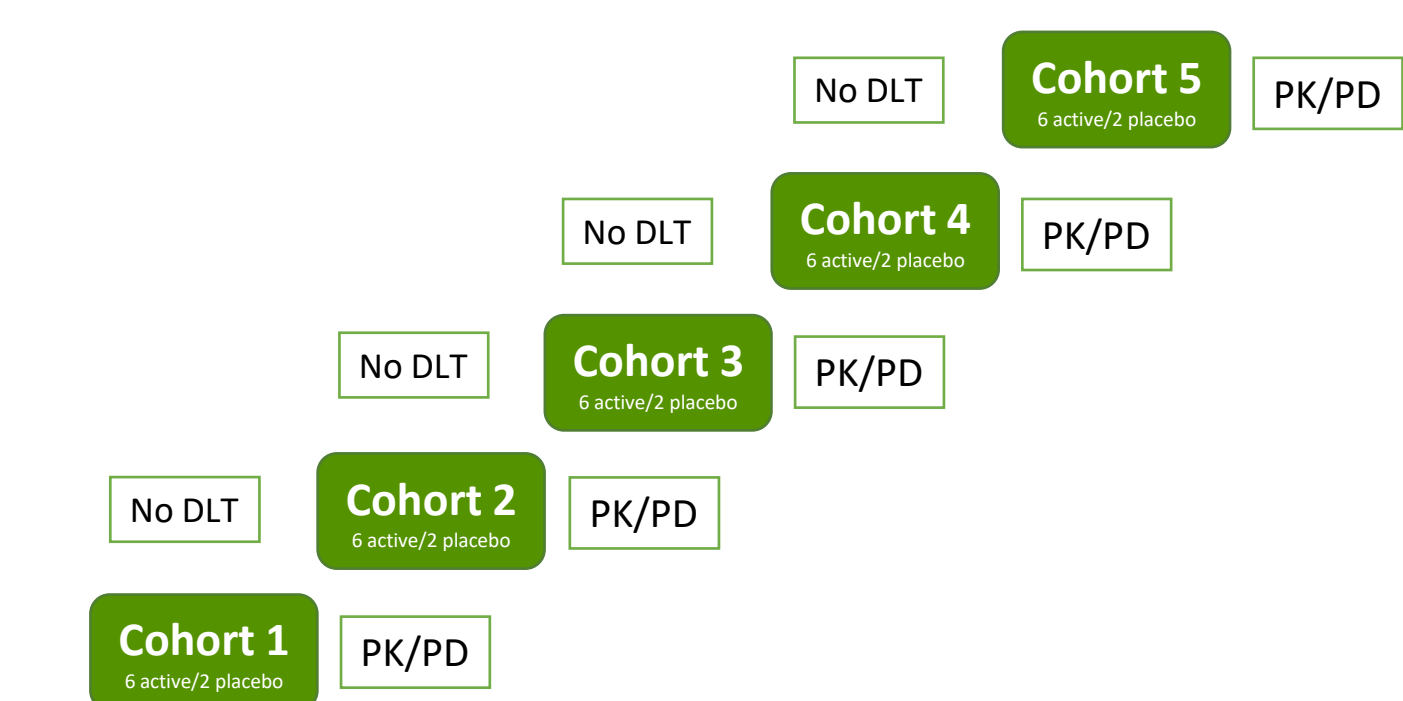
Figure 5



Status: Phase I clinical trial

Following successful completion of GLP toxicology studies, IOA-289 has entered a first-in-human clinical trial for safety and tolerability in healthy volunteers. The study consists of a randomized, double-blind, placebo-controlled, single ascending oral dose administration of IOA-289 to healthy male subjects in a fasted state. Subjects will be randomized to a single oral dose of IOA-289 or matching placebo capsules (Figure 6). Pharmacokinetic parameters and reduction of LPA levels will be determined.

Figure 6



Conclusion

- IOA-289 is a highly potent and selective inhibitor of ATX.
- Inhibition of ATX by IOA-289 showed superior efficacy to standard-of-care and GLPG1690 in the BLM model.
- IOA-289 has an acceptable safety and PK profile and non-clinical safety studies did not raise any safety issues.
- Based on an extensive preclinical package supporting proof of concept in oncology, IOA-289 is entering into clinical trials in the first half of 2021 for fibrotic cancer indications.
- IOA-289 has great potential to be further developed for fibrotic pathologies, including idiopathic pulmonary fibrosis (IPF) and other organ specific fibrosis indications.

Conflict of interest statement:

MD, KNS, ML, LvdV and ZJ are employees and shareholders of ionctura