Preclinical Evaluation of Cudetaxestat (BLD-0409) for Potential Drug-Drug Interactions

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Abstract

Cudetaxestat (BLD-0409) is a small-molecule, non-competitive inhibitor of autotaxin (ATX) with demonstrated direct anti-fibrotic activity in preclinical models of lung and liver fibrosis. ATX is a secreted enzyme with lysophospholipase D activity that is responsible for converting lysophosphatidylcholine ("LPC") to lysophosphatidic acid ("LPA"), a profibrotic biolipid. Increased ATX activity and excessive LPA production cause myofibroblast activation, which are cells that produce extracellular matrix proteins comprising fibrotic lesions.

Blade is developing cudetaxestat as an oral treatment for fibrosis and plans to evaluate multiple doses of cudetaxestat in idiopathic pulmonary fibrosis (IPF) patients, with or without concomitant dosing with approved therapies (pirfenidone and nintedanib). Pirfenidone and nintedanib are known to have safety and tolerability issues so understanding potential drug-drug interactions (DDI) with either medication is important. Recently, a Phase 3 IPF trial with GLPG-1690 (ziritaxestat), an investigational competitive ATX inhibitor, was halted due to its unfavorable benefit-risk profile. To better understand potential DDIs, we evaluated cudetaxestat and GLPG-1690 in preclinical *in vitro* and *in vivo* assays to assess potential interactions with nintedanib and pirfenidone.

Nintedanib is a known P-Glycoprotein (P-gp) substrate while pirfenidone is not. Standard *in vitro* assay with MDCK-II cells showed that cudetaxestat was not a substrate and was a weak inhibitor (IC_{50}=64.6 µM and 39.8 µM using quinidine and nintedanib as substrates, respectively). In contrast, GLPG-1690 was found to be a substrate and an inhibitor of P-gp (IC_{50} of 7.77 µM and 3.84 µM using quinidine and nintedanib as substrates, respectively).

In vivo studies with nintedanib, GLPG-1690 and cudetaxestat were performed in rats. Plasma exposures of drugs were quantified and compared. Cudetaxestat co-administration with nintedanib did not change nintedanib exposure. However, GLPG-1690 co-administration with nintedanib resulted in statistically significant increase of nintedanib exposures; maximum plasma concentration (C_{max}) increased ≥ 1.8-fold and area under curve (AUC) increased ≥ 2.8-fold.

Cudetaxestat was neither a substrate nor an inhibitor of P-gp at physiologically relevant concentrations. No significant change in plasma concentration of nintedanib was observed when cudetaxestat was co-administered in rats.

Standard of Care Therapies for IPF

Pirfenidone and nintedanib were approved by the US FDA to treat IPF in 2014 and remain the only approved pharmacologic SOC. While both were approved for slowing the decline in FVC by 40 – 60% vs. placebo in pivotal studies, neither drug is curative and even responsive patients continue to exhibit continued disease progression. Both agents are also associated with significant side effects. Thus, there remains a critical need for more effective and better tolerated therapies in IPF.

Autotaxin Inhibition as an IPF Therapy

The ATX inhibitor, ziritaxestat (GLPG-1690), was previously being developed in IPF by Galapagos NV. A small Phase 2a monotherapy study (FLORA) suggested potential FVC benefit after 12 weeks of treatment with no significant side effects. Subsequently, two concurrent Phase 3 studies (ISABELA 1 & 2) were initiated to assess treatment with ziritaxestat in combination with SOC (i.e., pirfenidone or nintedanib). Both studies were discontinued due to a poor risk-benefit profile. While data from those studies have not yet been published, Galapagos has stated that it did not appear to be target related.

In this context, reported here is a systematic preclinical assessment of potential for DDI of both cudetaxestat and ziritaxestat with IPF SOC therapy.

In Vitro Inhibition of P-Glycoprotein

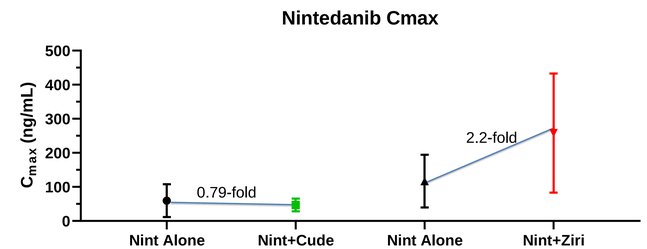
Study Design:
- Test System: MDCK-MDR1 Cells Stably Expressing P-gP
- Two probe Substrates used: Nintedanib at 10 µM or Quinidine at 100 nM
- Three compounds tested: Cudetaxestat, Ziritaxestat, and Pirfenidone
- Test Article Concentrations: 0, 0.3, 1, 3, 10, 30, and 100 µM
- Pre-incubation Time: 30 Minutes
- Incubation Time: 90 Minutes

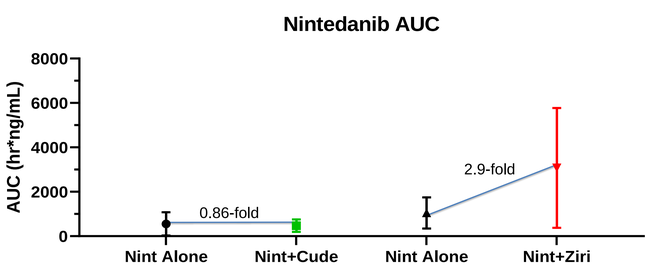
Results

P-gp Inhibition	IC_{50} µM Using Different Substrates	
	Nintedanib at 10 µM	Quinidine at 0.1 µM
Cudetaxestat (BLD-0409)	39.8	64.6
Ziritaxestat (GLPG-1690)	3.84	7.77
Pirfenidone	>100	>100

Rat Single Dose PK Study: Effect of Cudetaxestat and Ziritaxestat on Nintedanib Exposures

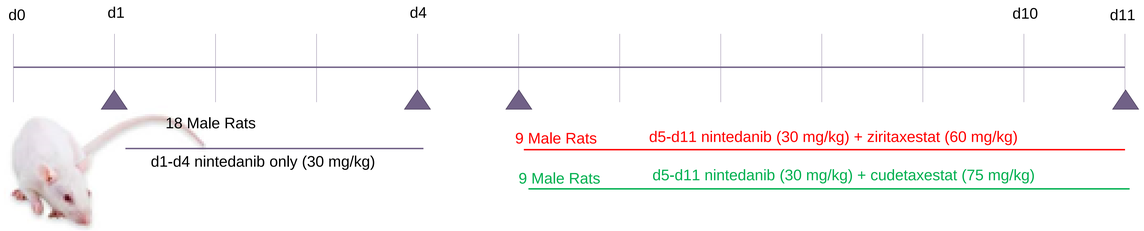
Study Design: Single oral dose of nintedanib only comparing to co-dose nintedanib (30 mg/kg) with cudetaxestat (75 mg/kg) or ziritaxestat (60 mg/kg), collecting plasma and determining drug concentrations

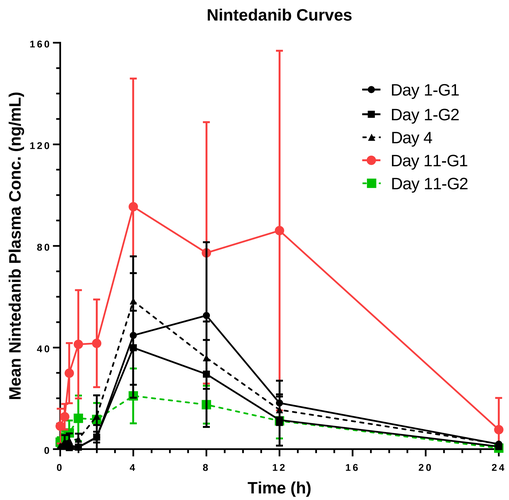


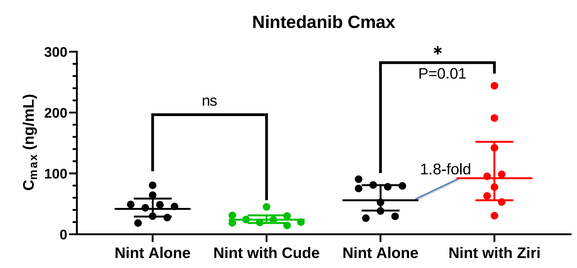


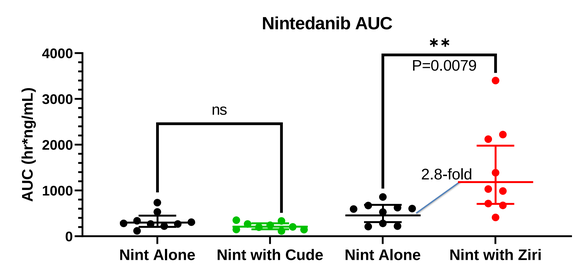
- **Nintedanib + cudetaxestat: Cmax and AUC not changed significantly**
- **Nintedanib + ziritaxestat: Cmax increased 2.2-fold and AUC increased 2.9-fold**

Multiple Day Dosing Rat PK Study: Effect of Cudetaxestat and Ziritaxestat on Nintedanib Exposures at Steady-State









Compound & Dose	Day	Compound	C_{max} (ng/mL)	AUC (h*ng/mL)
Nintedanib only at 30 mg/kg	1-G1	Nintedanib	61.3	511
	1-G2	Nintedanib	45.3	341
	4	Nintedanib	58.9	480
Nint 30 mg/kg + GLPG-1690 at 60 mg/kg	11-G1	Nintedanib	111	1439
Nint 30 mg/kg + BLD-0409 at 75 mg/kg	11-G2	Nintedanib	25.3	223

- **Co-dosing of nintedanib with either cudetaxestat or ziritaxestat did not change the exposures of cudetaxestat or ziritaxestat at steady-state**

Conclusions

- **Nintedanib (an IPF standard of care therapy) is a P-gp substrate**
- **Cudetaxestat is a weak P-gp inhibitor when either quinidine or nintedanib is used as substrate**
- **GLPG-1690 (ziritaxestat) inhibits P-gp with single digit micromolar IC_{50} values when either quinidine or nintedanib is used as substrate**
- **Cudetaxestat did not alter nintedanib exposure when co-dosed *in vivo* in rats**
- **GLPG-1690 significantly increased nintedanib exposure (Cmax ~1.8-fold and AUC ~2.8-fold) when co-dosed *in vivo* in rats**
- **~2 to 3-fold increase in nintedanib exposure may cause more adverse events**

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Walter Yu, Ravi Rajagopalan, Jack Lin, and Prabha Ibrahim are employees and shareholders of Blade Therapeutics, Inc.