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

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Abstract

Cudetaxestat (BLD-0409) is an oral small molecule targeting the enzyme autotaxin (ATX) by noncompetitive inhibition. ATX is a secreted enzyme that produces most of the lysophosphatidic acid (LPA). Increased ATX activity and excessive LPA production cause multiple adverse pathophysiologic phenomenon including myofibroblast activation. Activated myofibroblasts secrete extracellular matrix proteins which aggregate into fibrotic lesions. In preclinical studies, cudetaxestat demonstrated direct anti-fibrotic activity and differentiating biochemical characteristics.

Blade is developing cudetaxestat as an oral treatment for fibrosis. Cudetaxestat will be studied as an oral therapeutic for patients with idiopathic pulmonary fibrosis (IPF). Cudetaxestat is intended to be dosed with or without concomitant administration with approved therapies (pirfenidone and nintedanib). Pirfenidone and nintedanib are known to have safety and tolerability issues so understanding potential drug-drug interactions with either medication is important. Recently, Phase 3 IPF trials with ziritaxestat (GLPG-1690), an investigational competitive ATX inhibitor, was halted due to its unfavorable benefit-risk profile. To better understand potential DDIs, we evaluated cudetaxestat and ziritaxestat 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, ziritaxestat 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, ziritaxestat 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, ziritaxestat 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.

Current 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 therapies. While both were approved for slowing the decline in FVC by 40 – 60% vs. placebo in pivotal studies, 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 competitive ATX inhibitor, ziritaxestat, 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 in a peer-reviewed medical journal, Galapagos has stated that it did not appear to be target related.

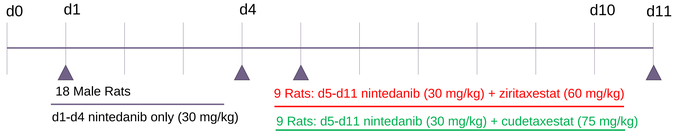
In this context, reported here is a systematic preclinical assessment of potential for DDI of both cudetaxestat and ziritaxestat with IPF SOC therapy.

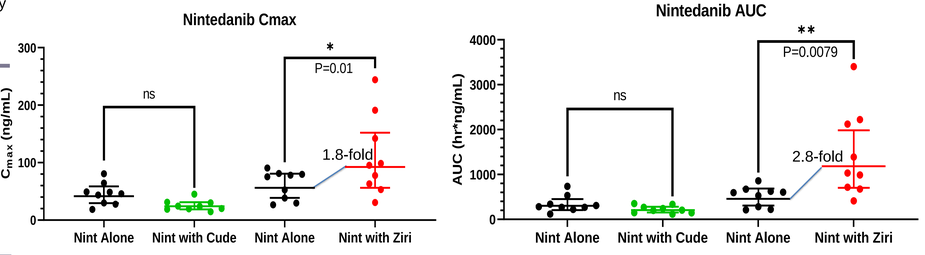
In Vitro Inhibition of P-Glycoprotein

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

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

Rat Study 1: Multiple Day Dosing Rat PK Study: Effect of Cudetaxestat and Ziritaxestat on Nintedanib Exposures at Steady-State. Determining Exposures

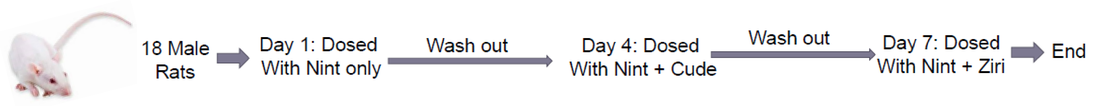


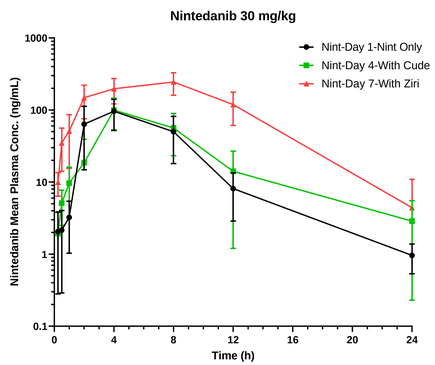


Compound & Dose	Day	Compound	C_{max} (ng/mL)	AUC (h*ng/mL)
Nintedanib only at 30 mg/kg	1-G1	Nintedanib	61.3	511
	1-G2	Nintedanib	45.3	341
	4	Nintedanib	58.9	480
Nint 30 mg/kg + ziritaxestat at 60 mg/kg	11-G1	Nintedanib	111	1439
Nint 30 mg/kg + Cudetaxestat at 75 mg/kg	11-G2	Nintedanib	25.3	223

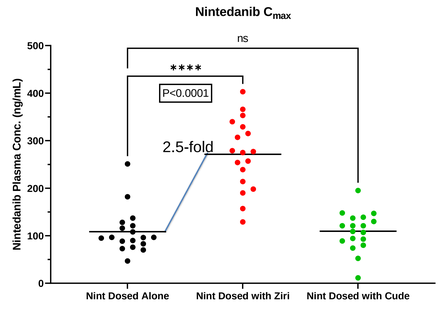
Rat Study 1 Results:
1. Co-dosing of nintedanib with cudetaxestat did not change nintedanib exposures at steady state.
2. Co-dosing of nintedanib with ziritaxestat changed nintedanib exposures significantly at steady state.

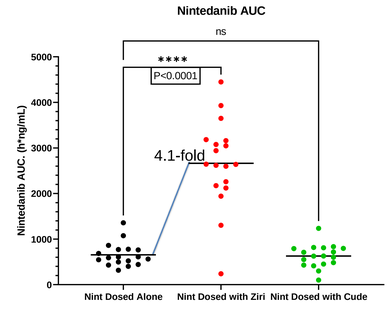
Rat Study 2: Single Dose PK Study using 18 Rats for statistical Analysis





Compound	Description	C_{max} (ng/mL)		AUC_{last} (h*ng/mL)	
		Mean	%CV	Mean	%CV
Nintedanib	Day 1: Dosed alone	109	43	656	39
	Day 4: Dosed with Cude	109	38	628	40
	Day 7: Dosed with Ziri	271	27	2670	36
Cudetaxestat	Day 4: Co-dosed with Nint	111000	16	1630000	15
Ziritaxestat	Day 7: Co-dosed with Nint	19200	18	182000	37





Rat Study 2 Results:
1. **Co-dose of nintedanib with cudetaxestat did not change nintedanib exposures.**
2. **Co-dose of nintedanib with ziritaxestat changed the exposures of nintedanib statistically.**

Conclusions

- **Nintedanib is a P-gp substrate.**
- **Cudetaxestat is a weak P-gp inhibitor when either quinidine or nintedanib is used as substrate.**
- **Ziritaxestat inhibits P-gp with single digit micromolar IC_{50} values when either quinidine or nintedanib is used as substrate.**
- **Cudetaxestat does not significantly alter nintedanib exposure when co-dosed *in vivo* in rats.**
- **Ziritaxestat significantly increased nintedanib exposure when co-dosed *in vivo* in rats.**

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