Clinical Evaluation of Cudetaxestat for Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Potential Drug-Drug Interactions

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ABSTRACT

INTRODUCTION: Cudetaxestat (BLD-0409) is an oral small molecule targeting the enzyme autotaxin (ATX) by noncompetitve 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. Cudetaxestat was evaluated in four Phase 1 studies, with >200 healthy volunteers enrolled.

METHODS: A single ascending dose SAD) and multiple ascending dose (MAD) dose-ranging study (NCT04146805) evaluated safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of cudetaxestat oral solution formulation at multiple dose exposures up to 1000mg.

A relative bioavailability study (NCT04814472) compared single oral 750 mg dose of cudetaxestat tablet and solution formulations. Food effect on plasma PK and PD parameters following a high-fat meal and single-dose dose proportionality were assessed.

A standard CYP450 drug-drug interaction (DDI) study (NCT04814498) determined the effect of cudetaxestat on the PK of probe substrates for CYP450 enzymes and evaluated its safety and tolerability when administered alone and with a cocktail of CYP450 probe substrates (Geneva cocktail less fexofenadine).

An open-label, randomized, fixed-sequence, DDI study (NCT04814498) was conducted to evaluate the steady-state pharmacokinetics of Standard of Care (SoC) therapies, nintedanib or pirfenidone, when dosed in conjunction with cudetaxestat.

RESULTS: Results from the SAD/MAD study demonstrated that cudetaxestat oral solution was generally well-tolerated with only transient, mild, gastrointestinal (GI) treatment-emergent adverse events (TEAE) across multiple doses. Peak plasma levels occurred within 4 hours in all doses evaluated. Daily (QD) administration resulted in < 1.2-fold accumulation between 1 and 14 days for all doses except 500 mg where 1.5-fold accumulation was observed. PD effects were observed at all doses evaluated; duration of inhibition was stronger and more sustained at higher doses.

Results from the relative bioavailability study demonstrated that the tablet under fed and fasted conditions was better tolerated overall. No GI TEAE were observed. There was no evidence of dose-related toxicity at higher doses of tablet administration with standard meal. Exposure was lower with tablet administration under fasted conditions. Tablet administration with food resulted in increased exposure. The maximal plasma LPA C18:2 (PD marker) percentage reduction from baseline was at ~4 hours, irrespective of formulation, dose, or fed conditions.

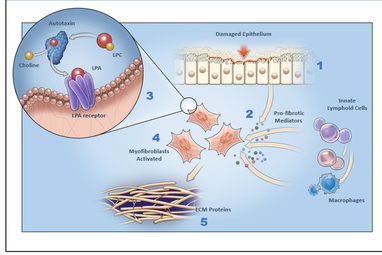
Results from the CYP450 DDI study demonstrated that cudetaxestat does not appear to inhibit CYP2B6, CYP1A2, CYP2C9, or CYP3A4 but possibly induces CYPC19. No new TEAE, laboratory vital signs, ECG and physical examinations were observed.

Results from the DDI study with SoC therapy demonstrated that cudetaxestat in combination with nintedanib or pirfenidone was well-tolerated and without treatment-related serious adverse events. Neither Nintedanib nor pirfenidone significantly alter the exposure of cudetaxestat

While cudetaxestat produced a modest increase in C_{max} of nintedanib, there was no significant change in AUC and no significant change in either C_{max} or AUC of pirfenidone.

Overall, the results indicate that cudetaxestat was well-tolerated with no safety concerns in any of the Phase 1 studies performed and supports the conduct of the Phase 2 study (B-0409-201) in patients with IPF.

Autotaxin / Lysophosphatidic Acid (LPA) Drives Fibrosis



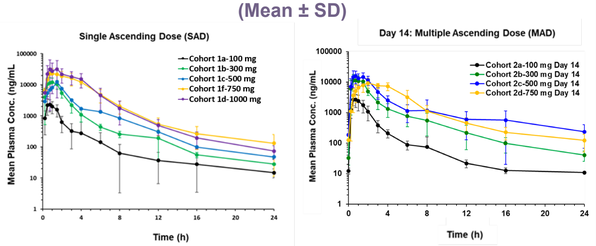
1. **Dysregulated Damage Response** Fibrosis is triggered by dysregulated cell / tissue damage response following epithelial injury.
2. **Release of Pro-fibrotic Mediators** Pro-fibrotic mediators, cytokines and the enzyme autotaxin are released. Increased autotaxin levels produce excessive lysophosphatidic acid (LPA).
3. **Autotaxin Production of LPA** LPA binds to LPAR1 (receptor on myofibroblasts) and triggers signaling cascade resulting in migration, activation and release of additional mediators.
4. **Myofibroblast Activation** Excessive LPA activates myofibroblasts.
5. **Secretion of ECM Proteins** Activated myofibroblasts secrete ECM proteins (scarring) that disrupt normal organ architecture and function.

Phase 1 SAD and MAD Study (NCT04146805)

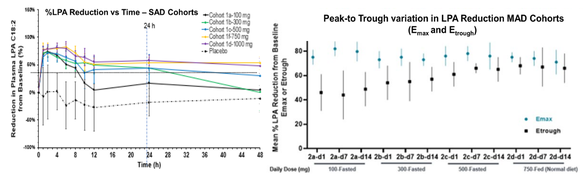
STUDY DESIGN (n-80)

- Administered QD as liquid suspension vs. matching placebo suspension
- 6 SAD cohorts completed; 100, 300, 500, 750, and 1000mg
- 4 MAD cohorts completed; 100, 300, 500, and 750mg (fed)

Representative SAD and MAD Time vs Plasma Concentration (Mean ± SD)



Target Engagement: LPA C18:2 Reduction from Baseline



STUDY FINDINGS

- Cudetaxestat was well tolerated
- No serious adverse events (SAEs); most common AEs were mild, transient GI upset (nausea, abdominal discomfort)
- Demonstrated PK/PD correlation; sustained reduction in plasma LPA with higher doses; minimal peak to trough level variation of LPA at doses 500 mg/day and above
- Data support clinical once-daily dose up to 750 mg or 500 mg BID (fed)

Phase 1 Relative Bioavailability Oral Solution vs. Oral Tablet (NCT04814472)

STUDY DESIGN (n-34)

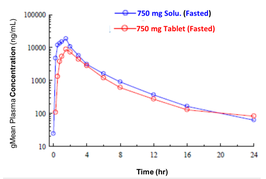
Part 1 (n=18)

- Compare PK of single oral solution formulation vs. single oral tablet formulation under fed and fasted conditions

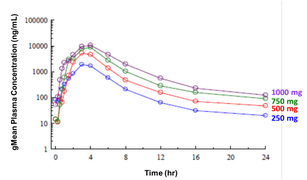
Part 2 (n=16)

- Evaluate dose proportionality of oral tablet formulation at 250, 500, 750, and 1000 mg
- Single dose with 3-day wash out

Part 1: Time vs Plasma Conc. Solution & Tablet Formulations



Part 2: Single Dose: Time vs Plasma Conc. Tablet Dose Proportionality

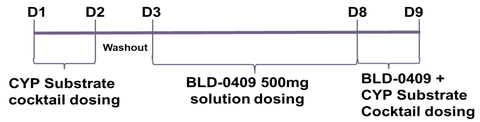


STUDY FINDINGS

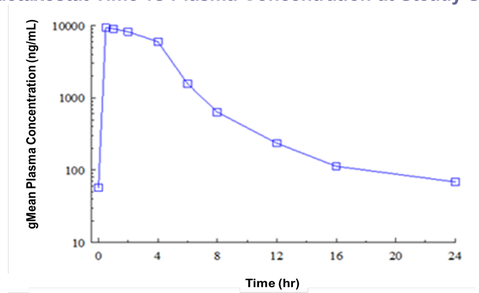
- Comparable PK and PD profile for the two formulations
- Fed condition increases the tablet C_{max} ~1.5X and AUC by ~2X compared to fasted condition
- Increase in C_{max} and $AUC_{(0-t)}$ more than dose proportional in all doses
- Tablet formulation improved GI tolerability over solution formulation, with no severe adverse events or drop-outs due to adverse events for either formulation

Phase 1 Standard CYP450 DDI Study (NCT04814498)

STUDY DESIGN (n=16)



Cudetaxestat Time vs Plasma Concentration at Steady State



STUDY FINDINGS

Cudetaxestat:

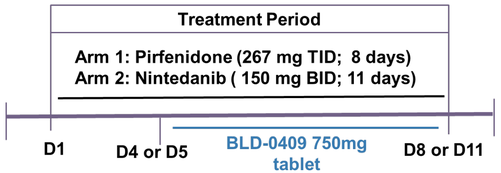
- Does not appear to inhibit CYP2B6, CYP1A2, CYP2C9, or CYP3A4
- Is a weak inhibitor of CYP2D6
- Appears to be an inducer of CYP2C19
- CYP cocktail administration had no impact on cudetaxestat exposure profile

Phase 1 DDI Study with IPF Standard of Care (SoC) Therapy (NCT04814498)

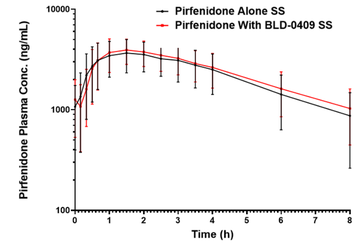
OBJECTIVE

To assess the safety and effect of cudetaxestat on the PK of IPF standard of care therapy (pirfenidone or nintedanib)

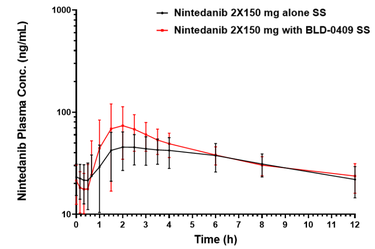
STUDY DESIGN (n-83)



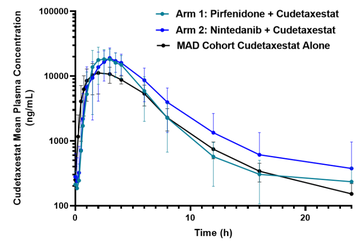
Pirfenidone Plasma Concentrations vs Time with & without Cudetaxestat (Mean ± SD)



Nintedanib Plasma Concentration vs Time with & without Cudetaxestat (Mean ± SD)



Cudetaxestat Plasma Concentration vs Time with Pirfenidone or Nintedanib (Mean ± SD)



STUDY FINDINGS

- Neither Nintedanib nor pirfenidone significantly alter the exposure of cudetaxestat
- Cudetaxestat does not affect the PK of pirfenidone.
- Cudetaxestat does not significantly increase the exposure of nintedanib ($AUC_{(0-12)}$)
- Most common TEAEs were mild GI upset (diarrhea and nausea)
- There were no treatment-related SAEs

CONCLUSIONS

Results from the four Phase 1 studies indicate cudetaxestat

- Exhibited minimal potential for DDI with IPF SoC therapy (pirfenidone or nintedanib)
- Demonstrated sustained target engagement (LPA reduction) over a 24-hour period
- Exhibited minimal potential for CYP450 substrate interactions
- Was well-tolerated across all Phase 1 studies in healthy volunteer with no treatment-related SAEs
- Oral tablet formulation showed improved GI tolerability profile over solution formulation

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