Inhalation Of IL-1 Receptor Antagonist (ALTA-2530) Achieves Stable And Prolonged Pulmonary Exposure In Nonclinical Studies Supportive Of Development For Bronchiolitis Obliterans Syndrome

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BACKGROUND

-**IL-1 overexpression in bronchiolitis obliterans syndrome (BOS)** drives chronic inflammation and fibroblast activation leading to airway remodeling and impaired oxygen transfer[1].

-**There are no approved treatments for BOS.**

-**ALTA-2530 is a novel inhaled formulation of recombinant human IL-1 receptor antagonist (rhIL-1Ra) in development for BOS.**

-Small lung airways are the target for BOS treatment[2].

-Inhaled ALTA-2530 maximizes exposure in lung while minimizing systemic exposure.

-ALTA-2530 is being optimized for convenient at-home delivery using a small handheld nebulizer.

Nebulized ALTA-2530 delivers sustained pharmacologically-relevant levels of rhIL-1Ra protein to small airways of the lung demonstrating promise for therapeutic dosing in chronic lung allograft dysfunction

ALTA-2530 Nebulization in Nonclinical Studies Delivers an Optimal Particle Size (<4μm) and Provides Sustained Lung Exposure that in Rat Were >29-fold the IC_{50} of rhIL-1Ra

Fig 1

ELF:serum exposure >2500-fold

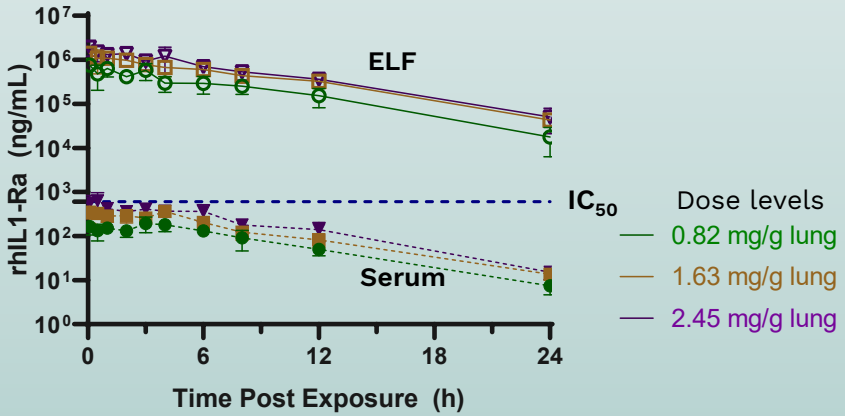

Fig 1. ALTA-2530 exposure in lung epithelial lining fluid (ELF) and serum following a single inhaled dose in rats. Epithelial lining fluid (ELF) concentrations calculated from serum-urea corrected bronchioalveolar lavage fluid concentrations. Values represent an underestimate as urea was <1mg/dL in BALF. Urea correction described in [3]Rennard et al. A commercially available IL-1Ra potency assay was used for IC50 determination.

Inhaled ALTA-2530 Delivers rhIL-1Ra to Bronchioles Deep in Monkey Lungs

Fig 2A Saline Control

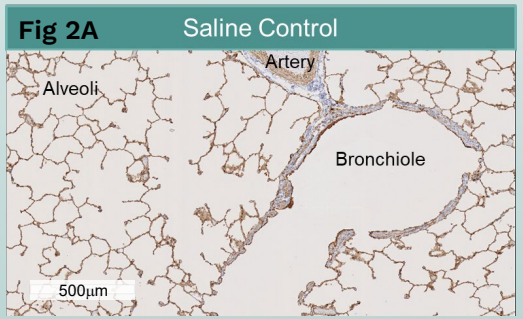

Fig 2B ALTA-2530 Treatment

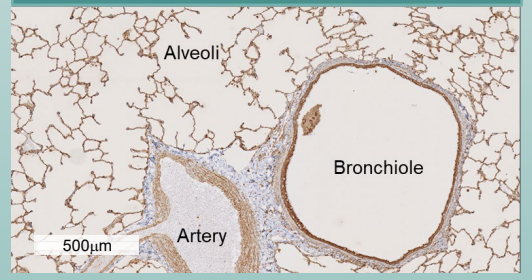

Fig 2. Healthy non-human primates (NHPs) were administered 0 (saline) or 0.86 mg/g lung of ALTA-2530 once daily for 7 days. **(A) Saline** or **(B) ALTA-2530** treated lung tissues collected 24 hours post-dose. Immunohistochemistry staining for rh-IL1Ra was conducted using a commercially available anti-IL1-Ra antibody.

ALTA-2530 was well-tolerated in acute dose and 7 day repeat dose toxicity studies in non-human primates and rats

IV delivery achieves low level, transient exposure in lung[4]

Fig 3A

Fig 3B 20 min post IV bolus dose

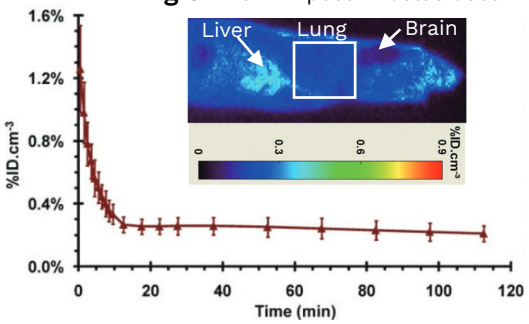

Fig 3. PET imaging and γ-counting following a bolus IV dose of [18F]IL-1Ra[4]. A. In SD rat lungs, [18F]IL-1RA uptake peaked within 1 min post-injection then decreased rapidly to reach a plateau from 10 min post-injection. **B.** Rats were injected intravenously with [18F]IL-1RA and imaged with a PET camera for 2 h.

KEY FINDINGS

- **ALTA-2530 rhIL-1Ra is stable and retains potency after nebulization**
- **rhIL-1Ra is stable in lung ELF**
- **ALTA-2530 formulation achieves extensive and prolonged exposure in ELF that at trough 24hr after dosing, is >29-fold the rhIL-1Ra IC_{50}**

  Mass Medium Aerodynamic Diameter (MMAD) from rodent study ranged from 2.18 to 3.19 μm
- **Inhaled ALTA-2530 Delivers IL-1Ra to small airways in non-human primates consistent with treatment target for BOS**

References
[1] Borthwick, et al. *Am J Transplant.* (2013); 13: 621-633.
[2] Verleden, et al. *Am J Transplant.* (2020); 00: 1-8.
[3] Rennard et al. *J Applied Physiol.* (1986); 60(2): 532-538.
[4] Cawthorne et al. *Br J Pharmacol.* (2010); 162(3): 659-672.