CORRELATED CHANGES IN INFLAMMATION BIOMARKERS FROM A PHASE 1 STUDY OF ACEBILUSTAT IN ADULT CYSTIC FIBROSIS PATIENTS

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Introduction

In cystic fibrosis (CF) patients, the interplay between inflammation and infection plays a central role in the progression of lung disease, characterized by increased pulmonary exacerbations and rapid decline of lung function. The need for safe and effective anti-inflammatory treatments for patients with CF remains high. Acebilustat is an anti-inflammatory treatment in development for CF which acts by reducing production of the potent inflammatory mediator leukotriene B4 (LTB4) and shifting the balance of immune modulation in favor of the pro-resolution mediator lipoxin A4 (LXA4). A previous Phase 1b study showed that once-daily oral acebilustat reduced markers of lung and systemic inflammation over the course of two weeks of treatment in adult CF patients (Elborn 2016). Long-term treatment with acebilustat is hypothesized to reduce the excessive burden of neutrophils and neutrophil elastase in the lungs of CF patients, thereby reducing pulmonary exacerbations and preserving lung function over time. Here, further analysis of the Phase 1b data demonstrates highly correlated reductions in markers of inflammation in CF patients treated with acebilustat. These results provide evidence for proof of mechanism and added support for the therapeutic hypothesis underpinning the ongoing Phase 2 study testing preservation of lung function over 48 weeks of acebilustat treatment in CF patients (NCT02443688).

Overview of Trial Design

• 4 clinical sites in the UK
• 17 enrolled, 16 completed
  – 5 on placebo, 4 completed
  – 6 on 50 mg, all completed
  – 6 on 100 mg, all completed
• 15 days treatment

Changes in Sputum WBC and PMN Are Highly Correlated

- All 6 patients treated with 100 mg acebilustat showed reductions from baseline sputum WBC
- No PMN data was reported for the one of the patients (WBC reduced by 17%)
- 4 of 6 patients treated with 50 mg acebilustat showed reductions in sputum WBC and PMN.
- Based on the high degree of correlation and because of the missing PMN data, further analyses utilize WBC to represent PMN.

Changes in Sputum NE Are Highly Correlated with Sputum LTB4

- Four of 12 patients exhibited at least a 50% reduction from baseline in both elastase and LTB4 after two weeks of acebilustat treatment
- Eleven of 12 treated patients exhibit some reduction in either LTB4 or elastase
- The high degree of correlation observed between LTB4 and NE in acebilustat treated CF patients substantiates the mechanistic relationship between treatment and effect

Changes in Sputum DNA Are Highly Correlated With Sputum Elastase

- Changes in sputum DNA are highly correlated with elastase in acebilustat treated CF patients
- Elastase can serve as a surrogate for DNA in assessing treatment effects

Conclusions

- Changes in elastase provide an adequate and sufficient representation of changes in WBC, PMN and DNA in sputum from acebilustat treated CF patients.
- Correlated changes in inflammation biomarker measures indicate that CF patients treated with once-daily oral acebilustat who achieve significant reduction in sputum LTB4 will likely also exhibit reductions in most or all inflammation biomarkers.
- Furthermore, the high degree of correlation between changes in sputum LTB4 with changes in sputum PMN, NE and DNA provides evidence linking acebilustat mechanism of action (modulating LTB4 production) to observed treatment effects (reduced markers of neutrophil-driven inflammation and lung injury).
- A trend toward reduction in serum CRP was observed in acebilustat treated CF patients showing reductions in sputum markers of inflammation.
- Correlation of changes in sputum elastase and serum CRP with clinical outcomes will be assessed in the ongoing Phase 2 trial testing 68 weeks of treatment with once-daily oral acebilustat in adult CF patients.

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References