Silurian Pharmaceuticals

Silurian Pharmaceuticals, Inc. to present at the North American Cystic Fibrosis Conference, Phoenix, Arizona

Silurian will present recent results of its drug Brevenal for the prevention of exacerbations in Cystic Fibrosis, at the NACFC, Phoenix, Arizona, October 8-10, 2015.

Brevenal is a promising new therapy for patients with cystic fibrosis. Low doses reverse the inhibition of airway mucociliary function caused by CFTR inhibitor 172 and human neutrophil elastase (HNE). It also alleviates bronchoconstriction caused by HNE. This demonstrates that brevenal's activity is independent of CFTR, as well as it addresses the downstream pulmonary complications cause by HNE.

More so, it appears that brevenal's effect on mucociliary function is superior to currently used therapies in CF patients.

We are looking forward to advance brevenal into the clinic within the next 12-16 months.

Abstract Title: BREVENAL MODULATES SLOWED AIRWAYS MUCOCILIARY CLEARANCE INDUCED BY THE CFTR INHIBITOR 172 ALONE AND WITH HUMAN NEUTROPHIL ELASTASE

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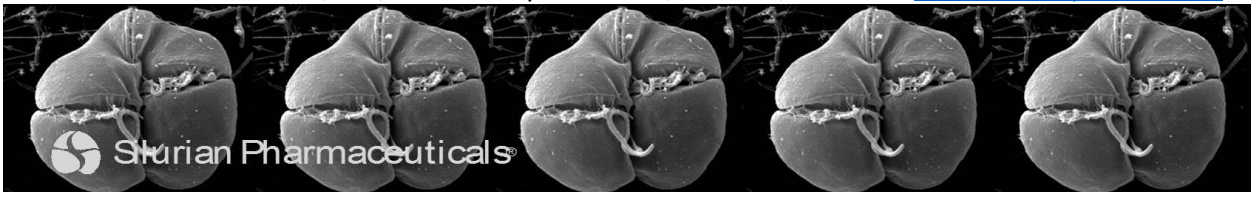
ABSTRACT BODY:

Rationale: A key pathophysiological endpoint of CFTR dysfunction is airway mucus stasis. This slowed airway mucus clearance becomes more problematic in CF exacerbations because of the additive effect of increased airway levels of free neutrophil elastase. Our previous work demonstrated that challenging sheep with aerosolized human neutrophil elastase (HNE) alone produced a slowing of mucociliary clearance (MCC) and its surrogate marker tracheal mucus velocity (TMV) and showed that agents used in the treatment of CF (i.e., glucocorticosteroids and hypertonic saline (HS) were unable to prevent this HNE-induced slowing of MCC (ARCCM,185.2012,A2773). The mechanism by which HNE slows MCC is not completely known but recent studies have suggested that HNE can directly cause CFTR degradation. Therefore, we hypothesized that if HNE was affecting CFTR function we should be able to replicate the slowing of MCC by directly interfering with CFTR. Furthermore, if inhibiting CFTR caused a slowing of



MCC we could then add in HNE to provide a more robust model to test agents that may be beneficial in the treatment of CF.

Methods: We measured TMV in conscious sheep before and for 12h after aerosol challenge with CFTR inhibitor (inh)172 (10 mg/mL) alone or in combination with HNE given 2h after aerosol challenge with CFTRinh172. We then used this model to measure the recovery of TMV after the initial challenge with CFTRinh172 alone or with the addition of HNE. Sheep were treated with aerosols of hypertonic HS (3mL 7%) 3mM amiloride, albuterol (2.5 mg/ 3mL) or brevenal (100 breaths of 50 ug/mL) a compound isolated from *K. brevis*. at 4h post CFTRinh challenge and the recovery of TMV after treatment was determined.

Results: CFTRinh172 slowed TMV by 2h and it remained low (mean ± se 61±2% of baseline, n=4) through 12h. The addition of HNE at 2h caused a slight reduction in TMV to 55±4% (n=5) of baseline at 12h post challenge. Against CFTRinh 172 alone, treatment at 4h with HS (64±4%, n=3), amiloride (66±4%, n=4), or brevenal (80 ±3, n=4) showed reversal of TMV for 3h, 6h, and 8h after treatment, respectively. Against CFTRinh172 +HNE treatment at 4h with albuterol only provided reversal of TMV until 8h (54±2%, n=4) whereas brevenal maintained TMV through 12h (81±4%, n=4). Thus, only brevenal showed significant restoration of TMV that lasted for 8 h following treatment. We then evaluated the ability of brevenal to inhibit HNE by standard enzymatic plate assay against known HNE inhibitors and found it to lack activity. This suggests that brevenal has a direct effect on MCC in vivo as its mechanism of action.

Conclusion: Brevenal showed superior and prolonged pharmacological activity against the slowing of TMV caused by CFTRinh alone or in combination with HNE. Further, the effects observed were noted at concentrations ~1000 fold lower than for the other agents tested. Thus, brevenal alone, or possibly combined with current therapies, may be beneficial for the treatment of airway diseases characterized by CFTR dysfunction and neutrophilic inflammation.

About Silurian Pharmaceuticals, Inc.

Silurian Pharmaceuticals, Inc. is dedicated to the development of new approaches for the treatment of pulmonary disorders in CF and COPD. Silurian harnesses the discovery of the novel polyketides from Marine organisms.