Brevenal™-- A Disease Modifying Agent for the Treatment of Pulmonary Disorders

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Brevenal-- A Novel Treatment for Lung Diseases-- Highlights

- Brevenal is a novel disease modifying candidate for the treatment of cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD)
- The Only Drug for the Treatment of Nonsense (X, W) Mutations in CF
- Brevenal is an inhalable at low doses (50-100 ug/day)
- No adverse effects are seen in doses 1,000 X the proposed clinical dose
- Designated Orphan Drug for the Treatment of CF by the FDA
The Opportunity

- Cystic Fibrosis $13.9B
- Idiopathic Pulmonary Fibrosis $3.2B
- COPD $19B
  - Very rapidly growing in China and rest of Asia due to air pollution and smoking
Company Overview

- Silurian Pharmaceuticals, Inc. develops Brevenal, a new drug candidate for Cystic Fibrosis (CF), idiopathic pulmonary disease (IPF) and Chronic Obstructive Pulmonary Disease (COPD)
- Founded 2014
- Licensed IP from University of North Carolina
- Solid IP estate of issued patents
- Strong support from CF key opinion leaders
- Currently funded by the CF Foundation
- Silurian is seeking $17M in Series A to complete Phase 1B in CF
CF- The Disease

- Cystic Fibrosis (CF) is the most common genetic disease
- Patients with CF have mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Average life expectancy is 35 years, up from 6 years in 1960
- Approximately 30,000 children and adults in the U.S., and 80,000 world wide
- The defective gene (protein) cause unusually thick, sticky mucus obstructing the lungs, pancreas and other membranes
- Mucus accumulation in the lungs leads to exacerbation and repeated infections that become resistant

Only 30% of lung symptoms are caused by the CFTR mutations
Current Therapies for CF

- CFTR modulators (potentiators and correctors) have been introduced 5 years ago
- Hydrating therapies (7% hypertonic saline), mucolytics and mechanical removal of mucus are used daily
- Antibiotics are frequently and chronically used to treat and control bacterial load
- β- agonists and corticosteroids are used to control cough and shortness of breath

Despite the introduction of CFTR modulating drugs there is no decrease in maintenance/ symptomatic therapies

CF patients spend 4-5 hours per day in treatment
IPF- The Disease and Treatment

- Idiopathic pulmonary fibrosis (IPF) is a disease in lung tissue becomes thick and stiff, or scarred, over time (fibrosis)
- IPF usually affects middle-aged and older adults
- The 5-years survival is approximately 20%
- IPF is divided to slow vs rapid progressors (absolute yearly fall in expiratory forced vital capacity (FVC) is 98 ml/year in the “slow” decliners and 480 ml/year in the “rapid” ones)

FDA approved two drugs for the treatment of patients with IPF

Both drugs have very limited efficacy (only slowing FVC decline), and with serious tolerability issues
COPD- The Disease and Treatment

• The primary causes of COPD is exposure to tobacco smoke, exposure to indoor and outdoor air pollution, occupational dusts and fumes.
• Globally, it is estimated that about 3 million deaths were caused by the disease in 2015, 5% of all deaths globally in that year.
• COPD is not curable, but treatment can relieve symptoms and improve quality of life.

Current therapies for COPD include steroids, β-agonists, bronchodilators & antibiotics.
Pulmonary Exacerbations are a Hallmark of CF, IPF and COPD

• Exacerbations are periodic flare-ups of breathing difficulties
• They are caused by accumulation of thick mucus, infections and inflammation
• Exacerbations are a major cause of morbidity in both CF, IPF and COPD

Number of pulmonary exacerbations is directly correlated to decline in lung function (FEV₁ % predicted)

Lung function decline (FEV₁ % predicted) is directly correlated to mortality
CF Market Ready for Disruption

• One dominant player, Vertex, with products with:
  1. Moderate Efficacy
     • Only 30-40% responders i.e 60% no significant benefit
     • Forced expiratory volume in one second (FEV1) improvement only 9% (Kalydeco) or (Orkambi) 2-4% in patients who have 40% of normal FEV1
     • Limited effect on exacerbations the main reason of patients lungs deteriorate
  2. Tolerability and Safety Issues As an Intended Life Long Therapy
     • High Level of side effects (Liver, Eye, shortness of Breath, diarrhea, menstrual abnormalities and fatigue)
     • Concern over long term liver toxicity in children
  3. Patient satisfaction
     • 15 % of patients discontinue treatment within three months due to side effects.
  4. Silurian’s Brevenal offers the first disease modifying therapeutic independent from CFTR for patients with all genetic backgrounds including Nonsense (‘X’) mutations
COPD Next Generation Therapeutics

• Since the launches of inhaled β agonists and inhaled corticosteroids few advances have been made to change the destiny of COPD patients

• Patients need increasing dosages of present drugs to control symptoms leading to serious, often life threatening side effects and poor quality of life

• Silurians’ Brevenal is the first in class disease modifying agent aiming to prevent exacerbations, decreasing hospitalization whilst dramatically lowering costs of treatment and improving lives of patients.
Brevenal Mechanism of Action Summary—Restoring Airways Hydration and Mucociliary Clearance (MCC)

- Brevenal binds to voltage sensitive sodium channel (VSSC, (NaV1.7)) in a novel site
- Brevenal mobilizes ATP dependent intracellular calcium
- Intracellular calcium activates the calcium activated chloride channel (CaCC) Anoctamin 1 (ANO-1) to elicit extracellular chloride release
- Brevenal increases airways surface liquid (ASL) & inhibits reabsorption of ASL, critical for mucus clearance
Brevenal Reverses CFTR + HNE MCC Inhibition for 24 hours with a Single Dose in CF Sheep Model

Human neutrophil elastase (HNE) is a critical inflammatory driver in lung diseases.

The graph shows the effect of Brevenal on CFTRinh-172 + HNE-induced slowing of TMV over time. CFTRinh is administered at time 0, followed by aerosol human neutrophil elastase (HNE). After 4hrs, when MCC is at peak inhibition (~50% of normal), sheep are treated with aerosol Brevenal (50ug/ml, 87.5ug).

Adherence to Brevenal is expected to be high with a single daily dose.
Brevenal in Combination with Orkambi™ (VX-770/VX-809) Elicits a Greater Change in airway surface liquid (ASL) Depth

Brevenal + Ivacaftor (Kalydeco™) are Additive on Reversing CFTR(inh) + HNE MCC Inhibition in Sheep

Non-Effective doses of Brevenal and Ivacaftor showed additive effect at CFTRinh + HNE induced MCC inhibition

Effect of Brevenal in combination with VX-770/VX-809 is additive/synergistic on ASL in CF patient F508del HBE donor cells.
Brevenal Substantially improves % Solids in Mucus: A Mechanistic Disease Biomarker in CF & COPD that Correlates with Clinical Outcomes

Critical Clinical Biomarker of Efficacy in CF & COPD

Normal mucus has low content of solids as opposed to COPD and CF mucus

Among CF & COPD patients, increasing mucus solids concentration is associated with lower values of FEV₁

In sheep model of CF & COPD, inhaled Brevenal has significant effect in decreasing mucus solids to values comparable to normal

Increasing mucus solids concentration dramatically decreases mucociliary transport
Seeking Series A Funding

- Silurian is seeking $17M investment in Series A to complete:
  - Preclinical Development in CF
  - Phase 1B in CF
- Line up IPF for partnering with large Bio-pharmaceutical company
- Finalize discussions with Chinese Co-development partners and investors for COPD global development
Silurian Pharmaceuticals-- Summary

• Brevenal is a disease modifying agent for the treatment of CF and COPD
  • Brevenal is used in small dose with a prolonged clinical effect when compared to current therapies- Likely high compliance from patients
  • Brevenal is superior to current therapies, while additive to CFTR modulating therapies- Likely to replace existing therapies in combination with CFTR modulators

• Funding to complete IND enabling studies and Phase 1 in CF patients

• Data from Phase 1B within 2.5- 3 years from funding
Summary of Opportunity

- Brevenal is a groundbreaking disease modifying drug harnessing CaCC chloride release in the airways, independent of the CFTR.
- Silurian will initially develop Brevenal for CF (ORPHAN DRUG DESIGNATION).
- Current sales of Kalydeco™ & Orkambi™ (Vertex) is >$2.4 Billion/ year, treating ~40% of the CF population.
- COPD market size is $11.5B and expected to grow to $19B by 2019.
- Silurian is positioned to achieve significant value inflection following each clinical development stage.

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**Vertex Pharma Loss Narrows as Cystic Fibrosis Drug Sales Grow**

Company also affirms 2016 guidance for Orkambi and Kalydeco treatments

By: TESS STYNES  
July 27, 2016 4:42 p.m. ET

Vertex Pharmaceuticals Inc. said its second-quarter loss narrowed, as sales of its cystic fibrosis drugs continued to grow.

The Boston-based biopharmaceutical company's top- and bottom-line results beat expectations.

Its drug Orkambi, which received U.S. Food and Drug Administration approval roughly a year ago, treats patients with a cystic mutation that is the leading cause of the disease.