Leukotriene Modulation Therapy  Focused on Reducing Inflammation in Orphan Lung Disease

Disease Modification in Cystic Fibrosis

Precision Approach in Pulmonary Hypertension
Experienced Management Team

- Greg Duncan, President/CEO
- Sanjeev Ahuja, MD, MBA, FACP, Chief Medical Officer
- Eric Springman, PhD, Chief Scientific Officer
- Angela Walsh, CPA, VP Financial Operations

Launch Experience

- Zoloft (sertraline HCl)
- Lipitor
- Aricept (donepezil HCl)
- Spiriva (tiotropium)
- Lyrica (pregabalin)
- Evista (raloxifene HCl)
- Celebrex
- Cialis (tadalafil)
- Viagra (sildenafil citrate)
Corporative Summary

Leukotriene modulation platform reduces inflammation
- Lead investigational candidate Acebilustat is a first-in-class, once-daily, oral medicine
- Portfolio of anti-inflammatory candidates suitable for oral, inhaled, topical formulations

Focused on rare/orphan diseases
- Acebilustat granted orphan designation in Cystic Fibrosis (CF) in US and EU

Enrolling Phase 2B CF Lung Preservation Trial
- Reduce lung clogging and damaging neutrophil elastase in CF patients
- Targets all patients, complement to background therapies

Execute Phase 2B Pulmonary Hypertension (PH) Trial
- Acebilustat and a companion diagnostic support personalized treatment approach in PH
- Advancing private capital scaling 1H 2017

Celtaxsys
Lung Inflammation Drives CF Morbidity & Mortality

Persistent inflammation leads to:
- airway obstruction
- pulmonary exacerbation
- permanently impaired lung function

Respiratory failure & premature death at 35-40 years of age

No approved treatment for CF lung inflammation
Excessive Migration of Neutrophils into Lungs Drives Chronic CF Lung Inflammation

Clear Healthy Lung

Inflamed CF Lung

- Clear, thin mucus layer

- Thickened mucus layer

- Excess Neutrophils & DNA

- Neutrophil
Neutrophil Elastase: Key to CF Pathology

- Elastase destroys the collagen matrix
- Elastase disables defense against bacteria
- Elastase inactivates CFTR
Neutrophil Overactivation: Damaging Inflammation

LTA4

LTA4H

LXA4

Neutrophil Underactivation: Uncontrolled Infection

ACEBILUSTAT

Neutrophil Overactivation: Damaging Inflammation

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ACEBILUSTAT
Acebilustat Immediately Modulates LTB4 and Sustains This Effect with Continued Administration


Acebilustat’s dose dependent inhibition of LTB4 can be customized from 50% to 90%
Acebilustat Reduces Inflammatory Biomarkers in CF Patients

**Reduced Sputum Neutrophils**
- Change from Baseline, %
  - Placebo: 50%
  - Acebilustat: -100%

**Reduced Sputum Elastase (NE)**
- Elastase, % Baseline
  - Placebo: 150%
  - Acebilustat: 8 of 12 ↓ Baseline, 4 of 12 ↓ 50% or more

**Reduced Serum CRP**
- CRP Change from Baseline after Treatment
  - Placebo: 6 mg/L
  - Acebilustat: -4 mg/L


Elastase and CRP are well documented predictors of lung function decline and future pulmonary exacerbations, respectively.
Acebilustat Tunes Down Inflammatory Response Without Immunosuppression

**Phase 1b Study Results: Bacterial Load for Each Individual Patient**

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Placebo</th>
<th>50 mg Acebilustat</th>
<th>100 mg Acebilustat</th>
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<tr>
<td>-1</td>
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<td>10^6</td>
<td>10^7</td>
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<tr>
<td>16</td>
<td>10^8</td>
<td>10^9</td>
<td>10^10</td>
</tr>
</tbody>
</table>

**Phase 1 Summary**

- No increase in bacterial load or number of species, notably during antibiotic ‘off-cycle’
- Generally well tolerated, no dose dependent AEs
- No drug-drug interaction with commonly used CF treatments, including CFTR modulators
- No food effect on PK

*Source: Elborn (2016) Clin Transl Sci PMID: 27806191*
Open to all patients, no gene specific restrictions

- 195 Patients in North America and Europe, age 18-30 years
- Baseline FEV1 percent predicted (pp) ≥ 50%, ≥ 1 exacerbation in past year
- Target patients mean annual decline of FEV1pp of 4%/annum*

Aims to demonstrate disease modification by stemming decline in lung function

- Primary endpoint: Change from baseline in FEV1pp vs placebo
- Secondary endpoint: Impact on pulmonary exacerbations vs placebo

*Source: CF Patient Registry

Fully Enrolled April, Delivers Topline Results Q2 2018
Orphan Inflammatory Disease Targets

Cystic Fibrosis
- Actively Pursuing

Pulmonary Hypertension
- Prepared to Execute
  - Orphan Inflammatory Disease
  - Lung is Target Organ
  - Focused Commercial Footprint
  - Pricing Complementarity
Elevated LTB4 Drives Pathogenesis of Pulmonary Arterial Hypertension (PAH) Associated with Connective Tissue Disorders (CTD)

**LTB4**

**Endothelial Cell Death**

**Smooth Muscle Proliferation**

**Hypertrophy**

**Fibrosis**

**Right Ventricle Strain & Dysfunction**

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*Wen Tian et al. Sci Transl Med 5, 200ra117 (2013)*

Unacceptably High Levels of Mortality in Pulmonary Hypertension Catalyzed by Inflammatory Remodeling

- PAH is a rare, fatal inflammatory disease
- Pulmonary arterial structural remodelling leads to enhanced vascular resistance
- Elevated LTB4 in 25%-50% of target patients

38,900 Target Patients

- ILD is characterized by inflammation, fibrosis, stiffening and thickening of the lung tissues
- No approved therapies for PH-ILD patients
- Elevated LTB4 in @ 50% of target patients

PAH = Idiopathic Pulmonary Arterial Hypertension, APAH = Associated Pulmonary Arterial Hypertension, CTD = Connective Tissue Disorder, ILD = Interstitial Lung Disease
Landmark Paper Establishes Key Role for LTB4 Modulator in Reversing PAH in Pre-clinical Studies

**PULMONARY HYPERTENSION**

**Blocking Macrophage Leukotriene B4 Prevents Endothelial Injury and Reverses Pulmonary Hypertension**

Wen Tian

LTB4 is Markedly Elevated in CTD-associated PAH

LTB4 Inhibition Reverses Pulmonary Hypertension in Rodent Models
Acebilustat Exhibited Dose-Dependent Efficacy in Bleomycin Induced Pulmonary Hypertension

- CT Imaging of Lung Vasculature from Bleomycin Treated Rats
  - Reduction in Fibrotic Tissue Volume & Systolic Pulmonary Artery Pressure

![Graphs showing relative fibrotic tissue volume and systolic pulmonary artery pressure.](image-url)
Celtaxsys Forward Plan

- **2017**: Acebilustat: CF P2B Trial
- **2018**: LTB4 Assay, PH IND, Acebilustat: Pulmonary HTN P2
- **2019**: Acebilustat: CF Phase 3 Trial
- **2020**: