European Cystic Fibrosis Society
Basic Science Conference
Update Call

March 30, 2016
4:00 p.m. ET
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Cystic Fibrosis is One of the Most Common Life-Limiting Genetic Diseases with No Known Cure

- **70,000 to 100,000**: affected globally - majority in the U.S., Canada, Europe and Australia
- **29 years**: median age of death in U.S.
- **Progressive disease**: caused by gene mutations that encode CFTR, a protein that regulates ion flow to and from cell surface
- **Results**: buildup of mucus in lungs, pancreas and gastrointestinal tract
- **Vast majority of patients die of respiratory failure**
- **Therapeutic approach**: revolutionized with the advent of CFTR modulators such as correctors and potentiators

Hospitalized cystic fibrosis patient recovering from an exacerbation getting ready to be discharged with his chronic palliative treatment. Today, modulators offer a new treatment paradigm to slow disease progression.
Amplifiers Help Other Modulators Overcome Substrate Limitations

Potentiators, such as ivacaftor, act by increasing the opening time of the CFTR channel resulting in higher ion flow.

Correctors, such as lumacaftor, are thought to facilitate the processing of mutated CFTR protein substrate leading to improved delivery to the cell membrane.

Amplifiers selectively increase the amount of immature CFTR protein in the cell providing additional substrate for correctors and potentiators to act upon.
IND filed, and effective PTI-428 Phase 1 data in cystic fibrosis patients expected Q2 2016

GLP toxicology data expected in Q4 2016

Cystic fibrosis and COPD programs are wholly owned

Eligible to receive up to $200M in milestones via Biogen collaboration

Eligible to receive up to $1.2B in milestones via Astellas collaboration

*Cystic Fibrosis: PTI-428, PTI Corrector, PTI Potentiator
**Usp14: Ubiquitin specific protease 14
***UPR: Unfolded Protein Response
PTI-428 and PTI-NC-733 May Provide the Best Potential Efficacy for the Majority of Cystic Fibrosis Population

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>% Population</th>
<th>Target for PTI-NC-733</th>
<th>Predicted PTI-428 + Orkambi or Kalydeco</th>
<th>Kalydeco</th>
<th>Orkambi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gating Mutation</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conductance &amp; Synthesis Mutations</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing Mutation</td>
<td>47%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stop Codon Mutation</td>
<td>39%</td>
<td></td>
<td></td>
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</tbody>
</table>

Approximate % Cystic Fibrosis Population (U.S. & Canada)

- **F508del Heterozygotes**: 39%
- **F508del Homozygotes**: 47%
- **Approximate % Population (U.S. & Canada)**: 10% (includes Gating Mutation, Conductance & Synthesis Mutations)
- **Stop Codon Mutation**: 12%

Approximate % Cystic Fibrosis Population (U.S. & Canada)
ABSTRACT: “Characterization of CFTR amplifiers, mutation-agnostic modulators that increase protein levels and complement other cystic fibrosis therapeutic modalities”

- Amplifiers increase CFTR protein and stabilize CFTR mRNA
- Amplifiers increase substrate for additional modulators
- Amplifiers work across CFTR genotypes
- Amplifiers are also active in non-lung tissues and in vivo
• *In vitro*, amplifiers nearly double the functional rescue conferred by marketed modulators:

- Ussing chamber current measurements of F508del homozygous HBE cells treated with PTI-CH for 24h show enhanced chloride transport relative to conditions without the drug
- PTI-CH confers approximately two-fold increase in F508del CFTR function as a stand-alone agent or in combination to lumacaftor and ivacaftor

### Table

<table>
<thead>
<tr>
<th>Condition</th>
<th>ivacaftor</th>
<th>lumacaftor</th>
<th>PTI-CH</th>
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</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>lumacaftor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PTI-CH</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
• *In vitro*, amplifiers increase the amount of CFTR mRNA
  - Steady-state analysis shows PTI-CH increases CFTR mRNA by two-fold without affecting total mRNA
  - In the absence of mRNA transcription, amplifiers stabilize F508del-CFTR (data not shown)
Amplifiers Can Exceed Ivacaftor *in vitro* and Double It When Used in Combination

- PTI-CH works in genotypes other than F508del/F508del
  - PTI-CH enhances R117H/F508del CFTR function to levels greater than or equal to ivacaftor alone
  - PTI-CH enhances ivacaftor activity in R117H/F508del HBE
- By acting on the early steps of CFTR biogenesis, amplifiers provide more substrate for known modulators, suggesting combined use can offer a greater clinical benefit

<table>
<thead>
<tr>
<th></th>
<th>DMSO</th>
<th>lumacaftor</th>
<th>ivacaftor</th>
<th>PTI-CH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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R117H/F508del CFTR Chloride Transport Activity (% of ivacaftor)

Combined with a potentiatior and amplifier, PTI-C1811 provides in vitro efficacy superior to lumacaftor.

On its own, PTI-C1811 provides in vitro F508del-CFTR maturation superior to lumacaftor.

PTI-C1811 adds to lumacaftor.

PTI-C1811-mediated correction and functional rescue are maintained under conditions where lumacaftor correction is attenuated by ivacaftor destabilization.
PTI-C1811 Has Superior *in vitro* Efficacy to Lumacaftor in F508del/F508del Donor HBE Cells

- HBE cells derived from F508-del CFTR homozygous donors show robust increase in F508del-CFTR activity in response to treatment with PTI-C1811 corrector.
- The maximum *in vitro* efficacy of PTI-C1811 is approximately 1.4X that of lumacaftor in the same triple combination with an amplifier (PTI-CH) and a potentiator (ivacaftor).

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>F508del-CFTR activity chloride ion flow (%)</th>
<th>Efficacy to Lumacaftor + Ivacaftor + PTI-CH</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTI-C1811</td>
<td>+</td>
<td><em>144%</em></td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>+</td>
<td>100%</td>
</tr>
<tr>
<td>PTI-CH (Amplifier)</td>
<td>+</td>
<td>100%</td>
</tr>
</tbody>
</table>

Legend:
- '+' indicates the presence of the respective compound in the treatment combination.
PTI-C1811 Prevents Destabilization of F508del-CFTR Caused by Chronic Incubation with Ivacaftor

- PTI-C1811 causes a functional increase in F508del-CFTR activity which remains stable under chronic (24h) ivacaftor conditions.

<table>
<thead>
<tr>
<th></th>
<th>Lumacaftor</th>
<th>Acute Ivacaftor</th>
<th>Ivacaftor 24h</th>
<th>PTI-C1811</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride Activity (corrector + acute addition ivacaftor)</td>
<td>100%</td>
<td>48%</td>
<td>100%</td>
<td>86%</td>
</tr>
</tbody>
</table>
PTI-C1811: Additive to Lumacaftor and Key Component of Proprietary Triple Combination

- Triple combination containing PTI-C1811 corrector, PTI-CH amplifier and PTI-P271 potentiator has superior effect on F508del-CFTR activity compared to lumacaftor and ivacaftor (left panel)
- PTI-C1811 is additive to lumacaftor (right panel and third bar, left panel)
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