Phase 1 Initial Results Evaluating Safety, Tolerability, PK, and Biomarker Data Using PTI-428, A Novel CFTR Modulator


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Introduction
An HTS strategy that enriches for small molecules acting on the translated sequence of CFTR protein was used to identify a new class of modulator. This modulator has been termed a CFTR amplifier. It is mutation agnostic and ultimately leads to increased levels of immature CFTR protein, along with stabilization and increase in CFTR mRNA. Production of additional CFTR protein allows for more substrate for other CFTR modulators, such as correctors and potentiators, to act upon. In vitro data using amplifier demonstrated improvement in chloride currents across multiple CFTR mutations. PTI-428 is an amplifier entering a first-in-human trial to demonstrate safety and tolerability in CF subjects and HN.

Methods
- CF subjects (PTI-428-01): A randomized, double-blind, placebo-controlled phase 1 clinical study
  - CF subjects between ages 18-55 years
  - Not on other KALYDECO® or ORKAMBI®
  - All CFTR mutations are eligible
- HV subjects (PTI-428-02): A randomized, double-blind, placebo-controlled phase 1 and drug-drug interaction study
- Females between ages 18-55 years
- Primary objective: Assessment of safety and tolerability
- Secondary objective: Assessment of the PK of PTI-428
- Exploratory objectives: Include CFTR expressions from nasal brushings

CFTR amplifier is genotype agnostic with a distinct mechanism of action
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, leading to improved delivery of CFTR protein 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.

Mechanism of Action

Study Designs

PTI-428-01 CF Subjects

<table>
<thead>
<tr>
<th>SAD</th>
<th>MAD</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD</td>
<td>Single daily dose</td>
<td>7-day follow-up</td>
<td>Single daily dose for 7 days</td>
<td>14-day follow-up</td>
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</table>

PTI-428-02 Healthy Volunteer Subjects

<table>
<thead>
<tr>
<th>SAD</th>
<th>MAD</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAD</td>
<td>Single daily dose</td>
<td>7-day follow-up</td>
<td>Single daily dose for 7 days</td>
<td>14-day follow-up</td>
</tr>
</tbody>
</table>

Each cohort followed by SRC review of PK and safety data
Biomarker data collected pre- and post-dosing
Studies ongoing in both CF and HV subjects
Interim analysis performed on MAD, SAD, PTI-428-02

Baseline Demographics (PTI-428-02, SAD)

<table>
<thead>
<tr>
<th>Parameter/Summary</th>
<th>Placebo (N=6)</th>
<th>PTI-428 10 mg (N=6)</th>
<th>PTI-428 30 mg (N=6)</th>
<th>PTI-428 100 mg (N=6)</th>
<th>PTI-428 All Active Doses (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29.0-34.0</td>
<td>28.0-30.0</td>
<td>26.0-30.0</td>
<td>26.0-30.0</td>
<td>26.0-30.0</td>
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<tr>
<td>Weight</td>
<td>210.0-308.0</td>
<td>200.0-230.0</td>
<td>190.0-220.0</td>
<td>190.0-220.0</td>
<td>190.0-220.0</td>
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<tr>
<td>Height</td>
<td>170.0-183.0</td>
<td>170.0-183.0</td>
<td>170.0-183.0</td>
<td>170.0-183.0</td>
<td>170.0-183.0</td>
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<tr>
<td>Race/ethnicity</td>
<td>Black or African American</td>
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<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female</td>
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<td>2</td>
<td>4</td>
<td>1</td>
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</tr>
<tr>
<td>Asian</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>Hispanic/Latino</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
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<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
<td>2</td>
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</tr>
</tbody>
</table>

Results

Exposure to PTI-428 increased in an approximately dose proportional manner
PK profile is similar in HV and CF subjects
Steady state achieved by day 4
Minimal accumulation after repeat dosing with accumulation ratio for Cmax and AUC0-24 (approximately 1.4)
Preliminary data suggests PK is increased when PTI-428 is administered with and without food
PK sample collection up to 72 h post dose

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Preliminary data suggests PK is increased when PTI-428 is administered with and without food
PK sample collection up to 72 h post dose

No clinically significant changes in hemalogic parameters
No clinically significant changes in liver enzymes
No safety concerns were identified at SRC review

Figure 1: Pharmacokinetic Data – PTI-428-02 and PTI-428-01, SAD

Figure 2: Pharmacokinetic Data – PTI-428-02, MAD

Figure 3: Positive food effect in healthy volunteers

Figure 4: Safety summary – laboratory results (PTI-428-02, SAD)

Figure 5: Measurement of CFTR mRNA and protein have been developed as a clinical biomarker

Clinical Biomarker Development

Biomarker Discovery ±3.2 fold CFTR mRNA and protein increase with PTI-428 in both normal and CF patient HBE cells
Biomarker Development CFTR mRNA and protein expression measured in nasal epithelial cells of subjects with normal and CF patient
Biomarker Implementation CFTR mRNA and protein expression measured in nasal epithelial cells of subjects with normal and CF patient

Nasal brushing protocol

Figure 6: PTI-428 is biologically active in humans after a single 100 mg dose

No nasal brushing from subjects in SAD cohorts collected on multiple time points
RNA extracted and analyzed for mRNA expression of CFTR and actin

Table 1: Safety summary – adverse events (PTI-428-02, SAD)

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N=6)</th>
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<th>PTI-428 100 mg (N=6)</th>
<th>PTI-428 All Active Doses (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs Leading to Death</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>TEAEs Leading to Discontinuation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>At Least One Severe TEAE</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Related TEAE</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
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</tbody>
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Conclusions
- Amplifiers are a new class of CFTR modulators
- Exposure to PTI-428 increases in a dose proportional manner
- Steady state achieved by day 4 with repeat dosing
- PK profile similar in healthy volunteers and CF subjects
- No safety concerns identified at SRC review and AE data to date
- Two-fold increase in CFTR mRNA and protein 8 hours following a single dose of PTI-428

Abbreviations
AEB, acute exacerbation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; Cmax, maximum serum concentration; EC50, half maximal effective concentration; FEV1, forced expiratory volume in 1 second; HBE, human bronchial epithelial; HCT, hematocrit; HITS, high-throughput screen; HV, healthy volunteer; IVT, intravitreal; MAD, multiple ascending dose; N/A, not available; PK, pharmacokinetics; PLAT, plateau; PTI-428, novel amplifier; SAD, single ascending dose; SRC, scientific review committee; TEAE, treatment-emergent adverse event; WBC, white blood count.