Challenges in Cystic Fibrosis Drug Development

A Presentation by:
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Cystic Fibrosis Facts

• A genetic life-shortening orphan disease
• Median predicted survival age 37.4 years (2008)
• About 30,000 patients in the US
• Gene defect: CFTR chloride transport protein found in apical membrane of epithelial cells
• Key disease manifestations: pancreatic insufficiency, fat and nutrient malabsorption, lung disease

...adding tomorrows every day.
Drug Development for Cystic Fibrosis: Measuring Progress

1. Development pipeline

2. Survival data
<table>
<thead>
<tr>
<th>Category</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Therapy</td>
<td>COMPACTED DNA</td>
</tr>
<tr>
<td>CFTR Modulation</td>
<td>POTENTIATOR VX-770 ATALUREN</td>
</tr>
<tr>
<td></td>
<td>CORRECTOR VX-809</td>
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<tr>
<td>Restore Airway</td>
<td>DENIFUSOL HYPERTONIC SALINE</td>
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<tr>
<td>Surface Liquid</td>
<td>BRONCHITOL SPL-8811 MOL1 1901</td>
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<tr>
<td>Mucus Alteration</td>
<td>GS9431</td>
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<td></td>
<td>PELMOZYMINE PENTAMETHYLTHYMINE</td>
</tr>
<tr>
<td>Anti-Inflammatory</td>
<td>ORAL N-ACETYLCysteine DHA SILDENAFIL</td>
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<td>SULFADIAZEIN INHALED GLUTATHIONINE GSK 856 933</td>
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<tr>
<td></td>
<td>PIOGLITAZONE HYDROXYCHLOROQUINE SIMVASTATIN</td>
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<td>IIE-3286</td>
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<td>Anti-Infective</td>
<td>TIP (TOBRAMYCIN INHALED POWDER) AZLI TOBI AZITHROMYCIN</td>
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<td>ARIKACE BAY Q3939 MP-376 GS-9310/11</td>
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<td>KB801</td>
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<td>Transplantation</td>
<td>INHALED CYCLOSPORINE</td>
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<tr>
<td>Nutrition</td>
<td>PANCRELIPEASE PRODUCTS LIPROTMASE</td>
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<td>AquaADEKs</td>
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<td>PRE-CLINICAL</td>
<td>Initial Testing in Laboratory</td>
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<tr>
<td>PHASE 1</td>
<td>Human Safety Trial</td>
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<tr>
<td>PHASE 2</td>
<td>Human Safety &amp; Efficacy Trial</td>
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<td>PHASE 3</td>
<td>Definitive Trial</td>
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<tr>
<td>AVAILABLE TO PATIENTS</td>
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</tbody>
</table>

September 1, 2009
Median Predicted Survival Age, 1985-2006
Overcoming CF Drug Discovery Barriers

• Drug discovery awards and contracts
• Drug discovery tools
• Model systems
• Academic discovery awards

...adding tomorrows every day.
Overcoming Discovery Barriers: Drug discovery awards and contracts

- CFFT helps reduce the risk for our partners in CF indications

\[
\text{Risk} = \text{Uncertainty} \times \text{Cost} \times \text{Timing}
\]

- Validation of Underlying Science
- Funding Vehicles
- Understanding Path to Proof-of-Concept

...adding tomorrows every day.
Overcoming Discovery Barriers: Drug discovery tools

- Antibody distribution program
- Tool compound distribution program (controls)
- Primary human epithelial cells harvested from lung transplants
- Purified CFTR protein supply
- Validated assay services
  - CFTR activity: Chantest, academic labs
  - Mechanism of action: academic labs
  - Specificity: Chantest, academic labs
Overcoming Discovery Barriers: Model systems

• Primary human lung epithelial cells are the current pre-clinical model system for CFTR modulators
  – Early VX-770 clinical data supports model
  – Correlation with cell lines must be validated for every chemical series and every cell line

• Inadequate animal model systems
  – Mouse model does not have lung disease
  – Pig model currently being evaluated
  – Ferret model in process
Overcoming Discovery Barriers: Academic discovery awards

• Technology Access Program experiment
  – Some success in validating discovery assays
  – Gaps in hit-to-lead progression
    • Medicinal chemistry
    • Drug-like properties
    • Liability characterization
  – As of late 2009, no academic series has progressed to early clinical candidacy

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Overcoming Clinical Development Barriers

- Therapeutic Development Network (TDN)
- CREC and protocol review process
- Clinical trial enrollment
- Outcome measures & Biomarker validation
Overcoming Clinical Development Barriers: CREC & PRC

• Clinical Research Executive Ctte
  – Define and implement policies for TDN
  – Assign priority scores to proposed protocols for centers’ consideration (not a veto)

• *Independent* CF Data Safety Monitoring Board (DSMB)
  – Ensures specific safety issues for CF subjects are monitored closely

• Protocol Review Committee
  – All protocols that come through the network undergo the same review process
  – Typically protocols are improved by incorporating feedback

...adding tomorrows every day.
Overcoming Clinical Development Barriers

• Clinical trial enrollment is often the rate limiting step for CF studies
  – Small patient base
  – Inclusion/exclusion criteria narrows population
  – Complex trial design issues

• Solution “I am the Key” campaign
  – Create a culture of clinical trial participation
  – Communication and information
    • internet, brochures, webcasts, u-tube

...adding tomorrows every day.
Estimate Patient Enrollment

<table>
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<tr>
<th>Year</th>
<th># Subjects</th>
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<tr>
<td>2003</td>
<td>1000</td>
</tr>
<tr>
<td>2006</td>
<td>3000</td>
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<td>2009</td>
<td>6000</td>
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Overcoming Clinical Development Barriers to be overcome

• Contract negotiations
  – Indemnification and IP at academic clinical centers
  – Need a clear path forward to centralized IRBs

• Outcome measures
  – Need harmonization between US and EU
  – How to measure *maintenance of health*?
  – Extrapolations from large population diseases (COPD, infection) not always “do-able” for orphan diseases because of low patient numbers