Development of a CFTR Potentiator
The Perspective of a Clinical Investigator

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Cystic Fibrosis is a Lethal Orphan Disease

- Prevalence of cystic fibrosis (CF)
  - United States: ~30,000
  - Worldwide: ~70,000

- Predicted life expectancy (born 2010): 38.3 years

- Median age at death in 2010: 26.3 years

- Lung disease is the primary cause of morbidity and mortality

Cystic Fibrosis Foundation Patient Registry; 2010 Annual Data Report. Bethesda, Maryland.
CFTR Mutation Functional Defect Framework

Images depict CFTR channel expression at the cell surface

Pathophysiologic Cascade Leading From Defective CFTR Channel Function to Cystic Fibrosis Lung Disease

- CFTR gene mutation
- Reduced quantity or function of CFTR protein (channel)
- Defective ion transport
- Airway surface liquid depletion
- Defective mucociliary clearance

Mucus obstruction
Infection
Inflammation

- Scarring
- End-stage lung disease

New Therapeutic Approaches Being Developed to Target Earlier in the Pathophysiologic Cascade of Disease

Pathophysiologic Cascade of CF Lung Disease

- CFTR gene mutation
- Reduced quantity or function of CFTR protein (channel)
- Defective ion transport
- Airway surface liquid depletion
- Defective mucociliary clearance

- Mucus obstruction
  - Infection
  - Inflammation

- Scarring

- End-stage lung disease

Current approaches

Investigational approaches

- Gene therapy
- CFTR modulators
- Alternate ion channel modulators
- Osmotic therapies
- Airway clearance
  - Mucolytics
  - Bronchodilators
- Anti-infectives
- Anti-inflammatories
- Lung transplant

Cystic Fibrosis Foundation
Therapeutics Development Program

Drug Discovery
- Basic Research
- High-throughput Screening
- Combinatorial Chemistry

Drug Development
- Preclinical testing
- Clinical testing of candidate drugs Phase 1, 2, 3

Initiated by CFF in 1998
CFF Therapeutics Development Network (TDN)
Established in 1998

- Microbiology (Seattle)
- Inflammatory mediators (Cincinnati)
- Cytology interpretation (Cleveland)
- Infant PFT (Indianapolis)
- CFTR detection (Birmingham)
- Imaging (Denver)

- TDN Coordinating Center
- TDN Centers
- Resource Centers
Strengths of TDN

- 77 established clinical research sites with trained staff
  - Linked to CF care centers with base of almost 20,000 patients (67% of US CF population)
- Linked to CFF national registry for cross-sectional and longitudinal data
- National resource centers for training, interpretation and ongoing development of biomarkers and clinical outcome measures
- Coordinating center
  - Study design, statistical and data management expertise
  - Network oversight and training
  - Clinical trial conduct
- Linked to European Clinical Trials Network
Work of TDN and CFF During Pre-clinical Period

- Identification and characterization of patient population – genotype and phenotype
- Established standard operating procedures, training, baseline data, analytical approaches for key outcome measures
  - Ion transport – sweat chloride, nasal potential difference
  - Clinical efficacy – pulmonary function, respiratory exacerbations
- Assisted with clinical development plan
  - Potentiator and corrector combined or separate development pathways?
  - Study designs
  - Clinical Indications
Identification of Relevant Patient Population -- G551D

Approximate proportion of patients with each type of CFTR defect leading to CF disease

- **FUNCTION** of CFTR at the cell surface is reduced
- **QUANTITY** of CFTR at the cell surface is reduced

F508del mutation occurs in about 90% of patients with CF (including both heterozygous and homozygous); almost 50% of these patients have 2 copies.

Gating mutations occur with a prevalence of about 5%

- G551D is the most common gating mutation with a prevalence of 4-5%
- Other gating

Sweat Chloride Concentration as a Biologic Endpoint in Cystic Fibrosis

**CFTR activity as a function of sweat chloride concentration**

- **Adults, reference**
- **Children and adults**
- **Newborns**

- **CF disease diagnostic range**
- **Indeterminate range**
- **Non-CF range**


CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient; PS, pancreatic sufficient; CBAVD, congenital bilateral absence of the vas deferens.
Median FEV₁ % predicted

Patient age (years)

100
90
80
70
60
50
40
30
20
10
0

FEV₁ is the most significant predictor of survival in patients with CF

Pulmonary Exacerbation as a Clinical Endpoint

- Pulmonary exacerbations have been linked to:
  - Increased mortality\(^b,c\)
  - Faster subsequent decline in FEV\(_1\)\(^d\)
  - Reduced quality of life\(^e\)
  - Higher health care costs\(^f\)
- Frequency increases with age\(^g\)


Ivacaftor Effects at the Airway Surface in G551D/F508del-CFTR HBE

Slide showing the effects of Ivacaftor on CFTR gene defect, reduced quantity/function, defective ion transport, airway surface liquid depletion, and defective mucociliary clearance. The slide includes a diagram with tracings of cilia beat frequency and airway surface liquid.

Unpublished data provided by Vertex.

Van Goor et al. PNAS 2009;106:18825-30
VX-770 Phase 2A Study Design

Part 1
Randomized, Double-Blind, Placebo Controlled

Group A: 10 Subjects (G551D Mutation)
- N=4
- 25 mg
- 14-day
- 75 mg
- 14-day
- 7 to 28d Wash-out
- N=2
- Placebo
- 14-day
- Placebo

Group B: 10 Subjects (G551D Mutation)
- N=4
- 75 mg
- 14-day
- 25 mg
- 14-day
- 7 to 28d Wash-out
- N=2
- Placebo
- 14-day
- Placebo

Part 2

18 Subjects (G551D Mutation)
- N=7
- 150 mg
- 14-day
- 7 to 28d Wash-out
- N=7
- 250 mg
- 14-day
- 28-day
- N=4
- Placebo
Effect of VX-770 in G551D Sweat Chloride Response: Phase 2 Study Results

Response of Sweat Chloride Concentration

Ivacaftor Phase 3 Study

• Ivacaftor (also known as VX-770), an orally bioavailable, investigational CFTR potentiator for the treatment of CF in patients with the G551D-CFTR mutation

• Hypothesis:

Ivacaftor will improve FEV₁ in people with CF and a G551D mutation
Ivacaftor Study Design

- Key inclusion criteria
  - G551D mutation on at least one CFTR allele
  - Aged ≥ 12 years
  - FEV\textsubscript{1} 40% to 90% predicted
- 48-week double-blind, placebo-controlled treatment period
  - Primary analysis at Week 24
Subject Disposition

Randomized
N = 167

Placebo
N = 83

Ivacaftor
N = 84

Dosed
N = 78

Dosed
N = 83

Completed 48 wks treatment
N = 68 (87.2%)

Completed 48 wks treatment
N = 77 (92.8%)

Rolled over to PERSIST
N = 67 (85.9%)

Rolled over to PERSIST
N = 77 (92.8%)

Population for analysis

Withdrew
N = 10 (12.8%)

Adverse event 4 (5.1%)
Phys. Decision 1 (1.3%)
Prohibited med 2 (2.6%)
Withdrew consent 1 (1.3%)
Other 2 (2.6%)

Withdraw
N = 6 (7.2%)

Adverse event 1 (1.2%)
Non-compliance 2 (2.4%)
Pregnancy 1 (1.2%)
Prohibited med 1 (1.2%)
Withdraw consent 1 (1.2%)

Randomized
N = 167

Placebo
N = 83

Ivacaftor
N = 84

Dosed
N = 78

Dosed
N = 83
Change from Baseline in Sweat Chloride

- Treatment effect through Week 24
  - 47.9 mmol/L
  - P < 0.0001

- Treatment effect through Week 48
  - 48.1 mmol/L
  - P < 0.0001

Estimates are model-based. Points and 95% CI are unadjusted (raw)
FEV\textsubscript{1} % Predicted Absolute Change from Baseline

- Treatment effect through Week 24
  - + 10.6 %
  - \( P < 0.0001 \)

- Treatment effect through Week 48
  - + 10.5 %
  - \( P < 0.0001 \)

Estimates are model-based. Points and 95% CI are unadjusted (raw)
Time-to-First Pulmonary Exacerbation

Modified Fuchs’ criteria

Week 24
Hazard Ratio
0.40
P = 0.0016

Week 48
Hazard Ratio
0.46
P = 0.0012

PLACEBO VX-770
Event-Free Rate At Week 48

Proportion of event-free subjects

Study day

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 28 56 84 112 140 168 196 224 252 280 308 336 364

0.41 0.67 0.78 0.51

Seattle Children’s Hospital Research Foundation
### Safety Summary Through Week 48

**Serious adverse events occurring in > 1 subject in either group**

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (N = 78)</th>
<th>Ivacaftor (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any serious adverse event</td>
<td>33 (42.3)</td>
<td>20 (24.1)</td>
</tr>
<tr>
<td>Pulmonary exacerbation (physician determined)</td>
<td>26 (33.3)</td>
<td>11 (13.3)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>4 (5.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

**Adverse events with ≥10% incidence in either treatment group and ≥5% difference relative to placebo**

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (N = 78)</th>
<th>Ivacaftor (N = 83)</th>
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</thead>
<tbody>
<tr>
<td><strong>More common in Ivacaftor group</strong></td>
<td></td>
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</tr>
<tr>
<td>Headache</td>
<td>13 (16.7)</td>
<td>19 (22.9)</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>12 (15.4)</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>12 (15.4)</td>
<td>17 (20.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (5.1)</td>
<td>12 (14.5)</td>
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<tr>
<td>Dizziness</td>
<td>1 (1.3)</td>
<td>10 (12.0)</td>
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Summary of Phase 3 Study Findings

• Primary endpoint (absolute change in percent predicted FEV₁) was statistically significant and clinically meaningful.

• Improvements in lung function and CFTR function (sweat chloride) were noticeable at 2 weeks and sustained through 48 weeks.

• Sustained improvements through Week 48 in other clinically important outcomes were observed, including risk of exacerbation, weight gain, and respiratory symptoms.

• Adverse events were mostly respiratory in nature and led to discontinuation of 1 subject in the ivacaftor group and 4 subjects in the placebo group.

• Phase 3 data was supportive of FDA approval of Kalydeco in early 2012.
Next Steps for Other CF Mutations: Combined Corrector and Potentiator Therapy

**Corrector:** Increases cell surface density and function of F508del-CFTR

**VX-770:** Increases channel opening of corrected F508del-CFTR

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F508del-HBE

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Corrector</th>
<th>Corrector + VX-770</th>
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<tbody>
<tr>
<td>F508del-CFTR Activity</td>
<td></td>
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<tr>
<td>(% wild-type CFTR)</td>
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<td>0</td>
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Seoul Children's Hospital Research Foundation
Next Steps for Other CF Mutations (2)

- **June 2012 Vertex press release**

  “Based on data from Phase 2 study evaluating dosing of Kalydeco and VX-809, Vertex plans to initiate a pivotal program in early 2013 to evaluate a combination of Kalydeco and VX-809 in people with two copies of the F508del CFTR mutation, pending discussions with regulatory agencies.”

Lessons Learned for Successful Drug Development in an Orphan Disease

- Establish partnerships across industry, foundations, academics, federal agencies and patient/families
- Develop laboratory and clinical infrastructure in parallel and far in advance of first patient enrolled.
- Focus on deliverables and a common goal
  - Biology and mechanisms of action are secondary gains
  - Use the new drugs to further the science, e.g. GOAL study
Thank you!