A Genetic Approach to the Treatment of Cystic Fibrosis

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Introduction

• CFTR Modulation Approach
• Ivacaftor (VX-770) Registration Program
• Moving beyond G551D
• Lessons learned
Vertex Cystic Fibrosis Program

Hypothesis
Improving CFTR function will reduce or halt disease progression

Strategy
Develop orally bioavailable small molecule CFTR modulators to be used alone or in combination for the treatment of CF
Group I: CFTR Gating Mutations (e.g., G551D)

Group 2: Residual CFTR function (e.g., R117H, A445E)

Group 3: Minimal CFTR function
  • F508del homozygous
  • F508del/other
  • Other/other

Source: 2009 US CFF Patient Registry
CFTR Mutations Can Affect the Quantity and/or Function of CFTR Channels

- **CFTR FUNCTION**
  - at cell surface
  - Channel Opening
  - Gating
  - Little to no CFTR
  - F508del
  - Some CFTR

- **CFTR QUANTITY**
  - at cell surface
  - Channel Structure
  - Conductance
  - G551D
  - Potentiators

- **Potentiators**
  - increase channel activity of CFTR protein located at the cell surface

- **Correctors**
  - increase delivery & amount of functional CFTR protein to the cell surface
In Vitro Evidence that CFTR Modulators Restore Downstream Defects Believed to Cause Lung Disease

Cultured Airway Cells From a G551D CF Patient

Source: Van Goor et al., PNAS 2009
CF is a Multi-Organ Disease

Sinus problems
Nasal polyps

Pancreatic dysfunction

Malnutrition

Digestive problems
Intestinal blockages
Fatty bowel movements

Salty sweat

Reduced lung function
Frequent lung infections

Reproductive problems
Ivacaftor Phase 3 Registration Program
Targeting the Fundamental Mechanism of CF Disease

- Registration program focused on G551D patients
- ~340 patients across three trials

**NDA and MAA submissions in October 2011, FDA Approval January 2012**

- **strive**
  - G551D Subjects aged 12 and older

- **envision**
  - G551D Subjects aged 6 to 11

- **discover**
  - Safety study in subjects homozygous for F508del mutation

- **persist**
  - Open-label, rollover extension trial that enrolled subjects who completed STRIVE and ENVISION.
STRIVE: Phase 3 Study Design

- Trial sized to detect a 4.5% absolute change in percent predicted FEV\textsubscript{1} at 80% power based on Phase 2 study
- Key inclusion criteria
  - G551D mutation on at least one CFTR allele
  - Aged ≥ 12 years
  - FEV\textsubscript{1} 40% to 90% predicted

*B Ramsey et al, NEJM 2011;365:1663-72*
STRIVE: FEV$_1$ % Predicted Absolute Change from Baseline

Treatment effects are point estimates of VX-770 minus placebo using a mixed model for repeated measures
Values shown at each visit obtained from descriptive statistics, not model-derived measures

B Ramsey et al, NEJM 2011;365:1663-72
STRIVE: Change from Baseline in Sweat Chloride

Change in sweat chloride concentration (mmol/L (mean, 95% CI))


Placebo VX-770

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

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

B Ramsey et al, NEJM 2011;365:1663-72
Estimates are model-based. Points and 95% CI are unadjusted (raw).

Pooled data from Adolescent/Adult and Children versions
Established minimal clinically important differences (MCID) for respiratory domain is 4 (Quittner et al 2009)

B Ramsey et al, NEJM 2011;365:1663-72
Patients treated with VX-770 were 55% less likely to experience a pulmonary exacerbation through week 48.

Week 24
Hazard Ratio
0.40
P = 0.0016

Week 48
Hazard Ratio
0.46
P = 0.0012

B Ramsey et al, NEJM 2011;365:1663-72
## STRIVE: 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More common in Ivacaftor group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (16.7)</td>
<td>19 (22.9)</td>
</tr>
<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>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1.3)</td>
<td>10 (12.0)</td>
</tr>
</tbody>
</table>

*B Ramsey et al, NEJM 2011;365:1663-72*
STRIVE: Results Summary

- Primary endpoint (absolute change in percent predicted FEV₁) achieved with a clinically meaningful magnitude of effect
  - 10.6% absolute improvement in FEV₁ % predicted from baseline compared to placebo
- 16.7% relative improvement in FEV₁ % predicted from baseline compared to placebo
- Lung function improvements were rapid in onset and durable through 48 weeks
- Pattern of improvement in CFTR function mirrored improvements in lung function
- Sustained improvements through week 48 in other clinically important outcomes were observed, including risk of exacerbation, weight gain, and respiratory symptoms
- Adverse Events reported were similar between the Ivacaftor and Placebo arms
- No important safety concerns identified for administration of Ivacaftor 150 mg q12h for 48 weeks

B Ramsey et al, NEJM 2011;365:1663-72
Mean Absolute Change From STRIVE Baseline in % Pred FEV₁ by Treatment

**Mean Absolute Change From STRIVE Baseline in % Pred FEV₁**

**Final Time Point of STRIVE, PERSIST Open Label Extension begins**

Points and 95% confidence interval (CI) are unadjusted (raw).

**McKone E et al. NACFC; November 3-5, 2011; Anaheim, CA; poster 204**
Hyperpolarized $^3$He Ventilation Imaging

Healthy

Smoker

COPD

Cystic Fibrosis

Asthma

$\alpha$-1 antitrypsin def

Mitchell Albert, UMass Medical School
VX770-025002: Visit 2 (Day 15)

FEV1: 62 %pred (2.72 L)

Placebo: 2 wks
VX770-025002: Visit 4 (Day 43)

FEV1: 83 %pred (3.63 L)

VX770: 4 wks
Beyond G551D

- Other Gating and Residual function mutations
- Trafficking mutations
Approximately 5% of Patients with CF Have a **CFTR Gating Mutation**

**CFTR Gating Mutations**

- G551D
- G178R
- G551S
- G970R
- G1244E
- S1255P
- G1349D
- S549N
- S549R
- S1251N

Most are not on commonly used CFTR genotyping panels

Other CF-causing CFTR mutations (e.g., F508del)

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*Bobadilla et al. Hum Mutat. 2002 Jun;19(6):575-606; [http://genet.sickkids.on.ca](http://genet.sickkids.on.ca); European CF Society Patient Registry; 2009 US CFF Patient Registry*
VX-770 Increased the Channel Open Probability of CFTR Produced by all CFTR Gating Mutations Tested

Mutant CFTR expressed in Fischer rat thyroid cells

Van Goor F et al. NACFC; November 3-5, 2011; Anaheim, CA; abst 10
Residual CFTR function results in less severe CF

Clinical Characteristics
- Pancreatic sufficient
- Slower decline in FEV$_1$
- Live longer

Sample Mutations
- R117H
- R117C
- D110H
- R347H
- R352Q
- E56K
- P67L
- L206W
- A455E
- D579G
- S1235R
- S945L
- R1070W
- F1074L
- D110E

Sources: Davis et al., Am J Respir Crit Care Med. 1996; McKone et al., Lancet. 2003; Noone et al., Am J Respir Crit Care Med. 2000; Noone et al., Gastroenterology. 2001;Strausbaugh Clin Chest Med. 2007
VX-770 Potentiates Mutant CFTR Forms Associated with Residual CFTR Function

Mild conductance mutations
Mild processing mutations
Unknown protein defect
Conclusions

• In Vitro studies show:
  – Ivacaftor potentiated all tested mutant CFTR forms produced by CFTR gating mutations
  – Three additional CFTR gating mutations were identified which were also potentiated by ivacaftor
    • S549N, S549R, S1251N

• These data support the potential for benefit of ivacaftor in patients with CF who have CFTR gating mutations beyond G551D.
Combination Approach: CFTR Potentiator Ivacaftor (VX-770) Doubled the *In Vitro* Activity of VX-809

VX-809 and ivacaftor increased fluid transport in F508del-HBE

Van Goor et al., PNAS 2011

* p < 0.05; ** p < 0.01 (ANOVA)

Non-CF HBE + VIP = 21 ± 2 µM
Effect of Combination of VX-809 + Ivacaftor in Subjects with CF Homozygous for F508del-CFTR

Analysis of evaluable patients

- Placebo
- VX-809 alone
- VX-809 + Ivacaftor 150-mg
- VX-809 + Ivacaftor 250-mg
VX-809 Conclusions

• VX-809 is a CFTR corrector
  – Promoted the proper folding of a fraction of F508del-CFTR in the ER to increase its processing and delivery to the cell surface, resulting in enhanced chloride transport

• VX-809 and ivacaftor are additive in vitro

• VX-809 and ivacaftor are additive in subjects with CF who carry two copies of the F508del mutation

• Clinical studies are needed to determine if the improvement in F508del-CFTR function is sufficient to improve lung function
Genotypic and Phenotypic Patient Identification are Complementary

Genotypic Evidence (55 of 1700 known CFTR Mutations) ~ 15% of CF Population

- G551D
- R117H (5T)
- A455E
- 3849
- 2789
- Other Residual
- Other Gating
- Other Folding

Kalydeco monotherapy potential responders

Molecular and Phenotypic Evidence (residual function + some splice) ~ 7% of CF Population

- Typical CF phenotype with gating mutation + some splice mutations ~8% of CF population
- Atypical CF Phenotype with unknown or uncharacterized genotype ~8% of CF population

Phenotypic Evidence ~15% of CF Population (atypical or mild clinical phenotype)

- Pancreatic Sufficient 14%
- Other Mild Phenotype ~1%
- Kalydeco Monotherapy Unresponsive (F508del + others) 75%

Other

~8% of CF population

~1%
How does n-of-1 fit into the lifecycle strategy for Kalydeco? Potential to identify Kalydeco response in 10-15% of CF population not readily addressed by conventional registration trials.

- **VX770-111**
  - % All Splice Mutations: 4%
  - % All Residual Function Mutations: 4%
  - % All Residual Function Phenotype: ~15%
  - % All Gating Mutations: 4%
  - % R117H: 2.5%

- **VX770-110**
  - % G551D: 4%
  - % All Gating: +1%

N-of-1
What are N-of-1 Clinical Trials?
The ultimate small sample randomized clinical trial (SRCT) design

- First used in the 60s for behavioral research

- Essentially a randomized, placebo-controlled repeated cross-over in a single individual

- Remote clinical phenotyping has greatly increased the practicality of N-of-1 clinical trials

- Methodology exists for aggregation of multiple n-of-1 trials to generate information similar to that of a large randomized clinical trial
Efficacy Measures for Response-guided Therapy for CF

• “Gold-standard” is FEV-1

• Sweat chloride has good positive-predictive value for FEV-1 and weight improvement, but inadequate negative-predictive value

• Lung Clearance Index (LCI) shows promise with less variability than FEV1 – may be useful for mild disease

• Use of ambulatory/home monitoring can improve precision and power relative to traditional, infrequent single-time point data capture.
“Trial in a Box”
Decentralized, Response-guided Therapy

- Training eDiary
- AE logging
- Reminders
- "Smart packaging"
- Bluetooth spirometer
- Bluetooth accelerometer
- Biometric fabric
- Adherence
- Spirometry
- Actigraphy
- Cough

"Trial in a Box" is a decentralized, response-guided therapy that utilizes various technologies to monitor and manage patient data. This includes training eDiaries, adverse event (AE) logging, reminders, and "smart packaging" for medication adherence. Technologies such as Bluetooth spirometers, accelerometers, and biometric fabrics are used to collect data on respiratory function, activity levels, and symptoms like coughing. The data is then analyzed to guide therapy and improve patient outcomes.
Bayesian Adaptive Model

When n-of-1 is more than 1

- Individual n-of-1 result
- Meta-analysis of all prior Kalydeco response information
- Informative Kalydeco response subset

Response-guided Treatment Decision

**Type-I (false positive) error rate controlled by requirement for multiple, concordant individual responses**

Population Responses

Response-guided + Population-based Treatment Decision

**Type-II (false negative) error rate controlled by including results from other informative n-of-1 trials**
Lessons learned:

• Kalydeco – premier example for a personalized medicine approach
• It’s not just about genetics/genomics
• Therapeutic success is driven by both genotype and phenotype
• Biomarker situation is complex!
• New clinical development strategies (eg: n=1) could make a difference
• Complete R&D&C integration is essential
• Early involvement of regulators and payers is key
• New regulatory guidelines and global harmonization needed
Thank you

CF Foundation
Clinical Investigators and their teams
People with CF
National Patient Organizations