Pharmacogenomics in Rare Diseases: Development Strategy for Ivacaftor as a Therapy for Cystic Fibrosis

Federico Goodsaed
Vice President
Strategic Regulatory Intelligence
Vertex Pharmaceuticals
Is there an “or” in rare diseases or personalized healthcare regarding clinical study design?

- **Rare Diseases**
  - Small number of patients
  - Genetic markers
  - Challenging clinical study design issues
    - Safety
    - Efficacy

- **Personalized Healthcare**
  - Small number of patients
  - Genetic markers
  - Challenging clinical study design issues
    - Safety
    - Efficacy
CF is a Multi-Organ Disease

Sinus problems
Nasal polyps

Salty sweat

Pancreatic dysfunction

Reduced lung function
Frequent lung infections

Malnutrition

Reproductive problems

Digestive problems
Intestinal blockages
Fatty bowel movements
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

- **CFTR Mutations**
- **Defect in CFTR Protein**
- **Loss of Chloride Transport**
- **Airway dehydration Reduced cilia beating**
Targeting the Fundamental Mechanism of CF Disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>strive</strong></td>
<td>Subjects with CF who have the G551D mutation and are aged 12 and older</td>
</tr>
<tr>
<td><strong>envision</strong></td>
<td>G551D Subjects aged 6 to 11</td>
</tr>
<tr>
<td><strong>discover</strong></td>
<td>Safety study in subjects homozygous for F508del mutation</td>
</tr>
<tr>
<td><strong>persist</strong></td>
<td>Open-label, rollover extension trial that enrolled subjects who completed STRIVE and ENVISION.</td>
</tr>
</tbody>
</table>

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

\textbf{STRIVE: Phase 3 Study Design}

- Trial sized to detect a 4.5% absolute change in percent predicted FEV$_1$ at 80% power based on Phase 2 study
- Key inclusion criteria
  - \textit{G551D} mutation on at least one CFTR allele
  - Aged $\geq 12$ years
  - FEV$_1$ 40% to 90% predicted
STRIVE: Absolute Change from Baseline in Percent Predicted FEV1

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: Results Summary

• Primary endpoint (absolute change in percent predicted FEV$_1$) achieved with a clinically meaningful magnitude of effect
  
  • 10.6% absolute improvement in percent predicted FEV$_1$ from baseline compared to placebo

• 16.7% relative improvement in FEV$_1$ % 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
Beyond G551D: Molecular and clinical phenotypes for the definition of patient populations in clinical study design
Analysis of In Vitro Data, Sweat Chloride, and Disease Severity Identified 3 Groups of CFTR Mutations

**Group 1:** *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*
Several CFTR Mutations Have Severe Defects in Channel Gating as Shown by Low Channel Open Probability

Single channel patch clamp electrophysiology in FRT cells

![Graph showing channel open probability for different CFTR mutations](image-url)
Ivacaftor Increased Channel Open Probability of Mutant CFTR Forms with Defects in Channel Gating

Single channel patch clamp electrophysiology in FRT cells

![Graph showing channel open probability with and without Ivacaftor for various CFTR mutations](image)
Baseline Chloride Transport Among Mutant CFTR Forms Tested (Non-Gating Mutations)
Ussing chamber electrophysiology in panel of FRT cells

Residual Baseline Chloride Transport

- $P < 0.05$ vs. F508del
- $P < 0.05$ vs. normal CFTR
- $P < 0.05$ vs. “0”

Mild defect/normal processing
Mild defect/normal conductance

Vertex unpublished data
Multiple Mutant CFTR Forms (Non-Gating Mutations) Responded to Ivacaftor In Vitro
Ussing chamber electrophysiology in panel of FRT cells

>10 % increase over baseline

Chloride transport (% Normal)

<table>
<thead>
<tr>
<th>CFTR Mutation</th>
<th>Without ivacaftor</th>
<th>With ivacaftor</th>
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<tbody>
<tr>
<td>S341P</td>
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<tr>
<td>R347P</td>
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<tr>
<td>L467P</td>
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<tr>
<td>S492F</td>
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<tr>
<td>A559T</td>
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<tr>
<td>A561E</td>
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<tr>
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<td>F1052V</td>
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Vertex unpublished data
Summary of Mutant CFTR Forms That Responded to Kalydeco In Vitro

<table>
<thead>
<tr>
<th>Group</th>
<th>Molecular Phenotype</th>
<th>Functional Phenotype</th>
<th>Clinical Phenotype</th>
<th>Example Mutations</th>
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</table>
Relationship Between CF Clinical Phenotype and CFTR Function

Example mutations

**Severe CF**
F508del, G551D

**Mild CF**

**Both Mild CF and CFTR-Related**

Nasal potential difference measurement
In Vitro Data Conclusions

- CFTR gating mutations are a homogeneous group
  - Same molecular defect as G551D: Defect in channel gating
  - Same functional defect as G551D: Low open probability
  - Similar in vitro response to Kalydeco as for G551D

- Molecular phenotype for CFTR gating mutations may be used to define group of patients for studies investigating clinical benefit of CFTR potentiators.

- Shared molecular and clinical phenotype of non-gating CFTR mutations that responded to Kalydeco
  - All had CFTR located at cell surface
  - All had mild defects in CFTR channel function
  - All responded to Kalydeco by >10%.
  - All associated with pancreatic sufficiency.
Complementarity of Genotypic and Phenotypic Patient Identifications

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

Genotypic Evidence
(66 of 1800 known CFTR Mutations)
~15% of CF Population

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

Pancreatic Sufficient 14%

Other Mild Phenotype ~1%

Kalydeco Monotherapy Unresponsive (F508del + others) 75%

Other Gating

A455E

G551D

R117H (5T)

2789

3849

Other Residual

Other Folding

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
Development Strategy for CF Patients other than homozygous F508del.

• Test if CF patients with other CFTR gating mutations benefit from Kalydeco

• Test if CF patients with R117H, most common residual function CFTR mutation, benefit from Kalydeco

• Test if CF patients with evidence of residual exocrine pancreatic function benefit from Kalydeco

• Pilot an “n-of-1” strategy for use in patients with less common or unknown CF mutations and/or clinical evidence of residual CFTR function.
Effect of Kalydeco in CF Patients with Non-G551D-CFTR Gating Mutations

- Phase 3, double blind, placebo-controlled, 8-week crossover with 16-week open-label period
- 20-40 subjects
- Enter subjects with as many examples of different gating mutations as practical
- Primary outcome measure: absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) through 8 weeks of treatment.
- Enrollment has started and is scheduled through H1 2013.
Effect of Kalydeco in CF Patients with R117H Residual Function CFTR Mutation

- Phase 3, randomized, double-blind, placebo-controlled, 24-week parallel group
- Up to 80 subjects
  - FEV$_1$ between 40% and 90% of predicted
- Primary outcome measure: change in % predicted FEV$_1$ in treatment group relative to placebo group
- Enrollment has started and is scheduled through H1 2013
N-of-1 Strategy

• N-of-1 trials are ultimate small sample randomized clinical trials
• First used in 1960s for behavioral research
• Essentially randomized, placebo-controlled, repeated cross-over in single individual
• Remote clinical phenotyping greatly increased practicality of N-of-1 clinical trials
• Methodology exists for aggregation of multiple N-of-1 trials to generate information similar to that of large randomized clinical trial
Pilot Study: Effect of Kalydeco in CF Patients with Molecular or Phenotypic Evidence of Residual CFTR Function

• Phase 2 exploratory, double-blind, placebo-controlled, multiple within-subject 4-week crossover ("n-of-1") with 8-wk open-label extension
• 10-20 subjects
• Evidence of
  – residual CFTR function including sweat chloride
  – 60-80mmol/L, pancreatic sufficiency (normal fecal elastase)
  – age at diagnosis ≥12 years and CFTR mutation associated with in vitro evidence of residual function
• Primary outcome measure: relative change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) after 2 weeks of treatment
• Multiple exploratory endpoints including home spirometry and lung clearance index
• Statistical analysis plan includes use of Bayesian meta-analysis of all n-of-1 data
• Enrollment has started and is scheduled through H1 2013
CF Patient Populations in Clinical Studies

- All Pancreatic Sufficient
- All Residual Function (n-of-1)
- R117H
- All Gating Defect
- G551D
- All F508del heterozygotes
Molecular Phenotype Definitions

• **Empirical**
  – Concentration distribution of genomic, proteomic or metabolomic molecules reflecting a structural or physiological condition.

• **Functional/Mechanistic**
  – Biochemical or biophysical activity of a biomolecule determined by a genomic sequence affecting either its molecular function or its number of copies.
Why Molecular Phenotypes?

- Therapeutic product development candidates often target specific patient subpopulations
  - Characterized by individual patient genotypes
  - Each patient subpopulation may be very small
  - Clinical study designs to show efficacy can be adequately powered if:
    - these subpopulations are considered as a single population
    - collectively defined by the molecular function affected by the individual genotypes

- In vitro data defining the molecular phenotype may help select patients in these clinical studies.
Applications in drug development and regulatory review
Gaucher

- **Molecular Phenotype**: β-glucocerebrosidase function
- **Enzyme Replacement Therapies**
  - Ceredase®
    - N=12, Change from baseline for hematologic and organ volume measurements
  - Cerezyme®
    - N=30, R, DB parallel group compared with Ceredase
  - Velaglucerase alfa for injection (VPRIV)
    - three clinical studies involving 82 patients with Type 1 Gaucher disease ages 4 years and older. The studies included patients who switched to VPRIV after being treated with Cerezyme.
β-glucocerebrosidase
### Selected Rare Disease Product Approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication, Year</th>
<th>Basis for Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceredase®</td>
<td>Gaucher Disease, 1991</td>
<td>N=12, Change from baseline for heme/organ volume measurements</td>
</tr>
<tr>
<td>Cerezyme®</td>
<td>Gaucher Disease, 1994</td>
<td>N=30, R, DB parallel group compared with Ceredase using similar endpoints</td>
</tr>
<tr>
<td>Aldurazyme®</td>
<td>MPS I, 2003</td>
<td>N=45, R, DB, PC; change in 6MWT and FVC (co-primary)</td>
</tr>
<tr>
<td>Elaprase®</td>
<td>MPS II, 2006</td>
<td>N=96, R, DB, PC; change in 6MWT and FVC (composite primary)</td>
</tr>
<tr>
<td>Naglazyme®</td>
<td>MPS VI, 2005</td>
<td>N=39, R, DB, PC; change in 12MWT</td>
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<tr>
<td>Fabrazyme®</td>
<td>Fabry Disease, 2003</td>
<td>N=58, R, DB, PC; clearance of GL-3 from kidney interstitial capillaries (Subpart E)</td>
</tr>
<tr>
<td>Myozyme®</td>
<td>Pompe Disease, 2006</td>
<td>N=18, Open label, Historically controlled; change in ventilator-free survival</td>
</tr>
<tr>
<td>Ammonul®</td>
<td>Hyperammonemia, 2005</td>
<td>N=316, Open label, Historically controlled; overall survival</td>
</tr>
</tbody>
</table>

Duchenne

- **Molecular Phenotype:** dystrophin function
- **Eteplirsen (AVI-4658)**
  - systemically delivered for the treatment of a substantial subgroup of patients with Duchenne muscular dystrophy (DMD)
  - clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression
- **Skips exon 51 of the dystrophin gene**
  - restores the ability to make a shorter, but still functional, form of dystrophin from mRNA
  - synthesis of a truncated dystrophin protein improves, stabilizes or significantly slows the disease process and prolongs and improves the quality of life for patients with DMD.
Dystrophin
## Biological Defect and Molecular Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Gaucher</th>
<th>Duchenne</th>
<th>Cystic Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>β-glucocerebrosidase</td>
<td>Dystrophin</td>
<td>CFTR</td>
</tr>
<tr>
<td><strong>Defect</strong></td>
<td>Over 300 mutations with minor or major effects on enzyme function</td>
<td>Multiple mutations resulting in premature truncation</td>
<td>Disease-causing mutations in the CFTR gene prevent the channel from functioning properly</td>
</tr>
<tr>
<td><strong>Molecular Phenotype</strong></td>
<td>β-glucocerebrosidase function</td>
<td>Dystrophin function</td>
<td>1) Gating Mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Residual Chloride Transport</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>enzyme replacement</td>
<td>exon-skipping</td>
<td>potentiatior corrector</td>
</tr>
<tr>
<td><strong>Regulatory Review</strong></td>
<td>approved</td>
<td>phase 3</td>
<td>approved for G551D</td>
</tr>
<tr>
<td><strong>Specific Mutations on Label</strong></td>
<td>Not referenced</td>
<td>Not referenced</td>
<td>G551D</td>
</tr>
</tbody>
</table>
Applications in drug development and regulatory review: *Summary*

- Gaucher Disease can be used as a model in which to define molecular phenotypes.
- The molecular phenotype for Gaucher Disease is found in other diseases for which enzyme replacement therapies have been developed.
- Exon-skipping therapies for Duchenne Disease represent more complex examples for molecular phenotypes.
  - Clinical study designs
  - Regulatory review
A list of core pulmonary and non-pulmonary endpoints could include

- **Lung function**
  - change in ppFEV1
  - in early disease, FEF25-75, FEF75, and/or LCI
  - pulmonary exacerbations (including use of additional antibiotics and hospitalizations)
  - PRO measures
  - imaging (chest CT score for bronchiectasis and air trapping)

- **Biometry** (weight and in children height)

- **Sweat chloride for CFTR modulators**
  - biomarker of CFTR function in the sweat gland but may not correlate with CFTR function in other organs depending on distribution and effects on CFTR biology in different tissues

**Novel trial designs should be utilized to accommodate**

- Limited population
- Increasing drug development pipeline
- Emergence of personalized medicine approaches
Can we draft a guidance on best practices in the design of clinical studies for rare diseases and personalized healthcare?

- Clinical study design issues are similar for rare diseases and personalized healthcare.
- Molecular phenotype classifications are one of several tools available to address issues with clinical study design.
- There is an urgent need for regulatory guidance in the application of alternative clinical study design strategies.