Symptom-based CF Therapies
Median Predicted Survival Age of US Patients with Cystic Fibrosis

Source: Cystic Fibrosis Foundation, National Patient Registry
Finding CFTR Modulators

• **CFF Therapeutic Development Program (TDP) started in 1998**

  – Created to encourage industry and academia to focus on CF and CFTR as drug target

  – **Components of TDP**
    – Financial assistance
    – Research tools and scientific advice
    – Well organized clinical trial network
• Orally bioavailable drugs
• Two CFTR targets:

**Potentiators:**
Increase opening (gating) of CFTR channels

**Correctors:**
Increase number and function of CFTR channels at the cell surface
Phase 3 Results (G551D)

Phase 3 Results of CF Therapies

Relative Change in FEV$_1$ % Predicted from Baseline (with 95% CI)

- **ivacaftor**
- Inhaled tobramycin
- Dornase alfa
- Azithromycin

Time (weeks): 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
2012 - FDA Approves Ivacaftor
What else can we learn from G551D patients who will be treated with ivacaftor?
Mucociliary Clearance: *The Movie*

Baseline

Ivacaftor - 3 months

Trachea

Stomach

Courtesy of Dr. Tim Corcoran, U. Pittsburgh
**Effect of Ivacaftor on Small Bowel pH**

Clinical Implications:
- Improved exogenous pancreatic enzyme efficacy
- Reduced GI symptoms and improved nutrition
- Early use: preserve endogenous exocrine function?

Data courtesy of Dr. Daniel Gelfond and the GOAL pH Pill Sub-study Team
P. aeruginosa Culture Rate

Data courtesy of Dr. Steve Rowe and the GOAL Study Team
Ivacaftor Lung Function Benefit Persists

See: McKone et al. NACFC 2013
Effect of Decreased Rate of Decline in FEV\textsubscript{1}

- Blue line: G551D With Ivacaftor
- Red line: F508del/F508del

Lung Transplant
<table>
<thead>
<tr>
<th>Year</th>
<th>Mutation</th>
<th>% Population (cumulative)</th>
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<tbody>
<tr>
<td>2012</td>
<td>G551D</td>
<td>4%</td>
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<tr>
<td>2013</td>
<td>other gating mutants</td>
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</table>

**Predicted:**

- 2014- R117h: 8%
- 2015-2016 – residual function: 15%
What About the Most Common Mutation - F508del?

50% of US patients have F508del mutations on both alleles

90% of US patients have at least one F508del mutation
• Orally bioavailable drugs
• Two CFTR targets:

**Potentiators:**
Increase opening (gating) of CFTR channels

**Correctors:**
Increase number and function of CFTR channels at the cell surface
Phase 3 Study Design

Screen Day -28 to Day -1
N=167

Randomize 1:1:1 on Day 1
N=167
N=167
N=167

24-Week Dosing Period

SAFETY FOLLOW UP
At Week 28
OR
BLINDED (ACTIVE) ROLLOVER
Up to 96 Weeks

Study VX12-809-105

Homozygous F508 subjects

- Lumacaftor 400 mg Q12H + Ivacaftor 250 mg Q12H
- Lumacaftor 600 mg QD + Ivacaftor 250 mg Q12H
- Placebo + Placebo
Lumacaftor/Ivacaftor Improved FEV<sub>1</sub>

Absolute Change from Baseline in Percent Predicted FEV<sub>1</sub>

- Placebo
- LUM 600 mg qd / IVA 250 mg q12h
- LUM 400 mg q12h / IVA 250 mg q12h

* P<0.025
Lumacaftor/Ivacaftor Decreased Hospitalizations and IV Antibiotics

-39% $P=0.0028$

-61% $P<0.0001$

-45% $P<0.0001$

-56% $P<0.0001$

Ramsey, Boyle, Elborn…Wainwright et al. Poster #250 NACFC 2014
• FEV1 absolute improvement- 3%
• Pulmonary exacerbations reduced by 30-40%
• Weight gain

• FDA advisory committee recommended approval on May 12, 2015.
• Decision by July 2, 2015
What about patients that only have one copy of F508del?

Their F508del response should be approximately one half that of homozygous patients.
Lumacaftor/Ivacaftor does not improve FEV$_1$ in $F508del$ Heterozygotes
Effect of 28 days of VX-661/ Ivacaftor on FEV$_1$ in F508del Homozygotes

Donaldson, Pilewski....Rodman, et al. ECFS 2014

**CFTR Corrector: VX-661**

- Works with similar mechanism to lumacaftor to traffick F508del-CFTR to cell surface
- Longer Half-life; Less drug-drug interactions than lumacaftor; No evidence of early chest tightness

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Donaldson, Pilewski....Rodman, et al. ECFS 2014
All patients with one or two copies of F508del

• Study 106  -  F508del / F08del  (Homozygotes)
• Study 107  -  F508del / Null  (Heterozygotes)
• Study 108  -  F508del / Residual  (Heterozygotes)
• Study 109  -  F508del / Gating  (Heterozygotes)
Ongoing Efforts to Identify the Next Generation F508del CFTR Correctors
• A large diversified chemical space is being screened
  – Strategically diverse chemical libraries
  – Millions of compounds screened last year

• Novel screens are being performed
  – Primary screens in human bronchial epithelial cells
  – Screens with CFTR domains (NBD1 stability)
  – Airway surface liquid maintenance

• Goal is to have efficacy greater than that seen with Kalydeco in G551D patients

• Timeline
  – Clinical trials could start next year
  – Projected approvals: 2019-2023
Goal of Second Generation Program on CFTR Activity

**Goal**

Un-treated

Kalydeco

VX-809

VX-809 + Kalydeco

VX-809 + Kalydeco + 2cd Corrector

**CFTR Activity (in vitro)**

G551D

F508del/F508del

Normal

Goal
Predicted:
2015- Lumacaftor/Ivacaftor for F508del/F508del (50% of population)

2017- VX661 could possibly replace lumacaftor and patients with one F508del are added (30% of population)

2021- Second Gen correctors begin to improve benefit for all F508 del patients
CFTR Modulators and US CFTR Genotype Distribution

- Corrector and Kalydeco responsive mutations
- Remaining patients with nonsense mutations (3%)
- Remaining patients w/o nonsense mutations (2%)

Our Goal is CFTR Modulation for 100% Patients!
Potential Pulmonary Treatments For The Last 5% of Patients

- Nonsense mutations
  - Represents 3% of the remaining because most have another mutation that already responds to treatment
  - New novel and robust screening programs underway
  - Ataluren in phase 3 testing

- Mutations unlikely to respond to small molecules (2%)
  - DNA transfer (gene therapy)
  - mRNA transfer (bypasses gene to make CFTR)
  - Restore airway surface liquid
    - ENaC inhibition
    - Alternative chloride channel activation
    - Novel delivery of hypertonic saline solutions
  - Mucus rheology altering agents
Personalized CF Regimens

• Maximize CFTR function
  – Initially based on the patient’s CFTR mutations
  – Ultimately a personalized response may be used

• Symptomatic therapies will be utilized as needed
  – Infants and young children with excellent CFTR restoration may not need other therapies
  – Understanding impact of various levels of CFTR restoration will help us determine what additional therapies are needed to maintain health
  – Older patients with established disease will probably continue to need other therapies
Long-term Issues

• Cost of therapies
• Burden of therapies
• Access to therapies
• Adherence to therapies

• Is there a better way?
Moving Toward a Better Way

Gene (DNA) → RNA → Protein → Symptoms

- CF Mutation
- Replication
- Transcription
- Translation
- CFTR

Permanent Repair
- Gene delivery
- Stem cell biology
- Gene editing

RNA Therapy
- Readthrough
- RNA replacement
- RNA editing

CFTR Modulation
- Potentiators
- Correctors

Standard Therapy
- Infection
- Mucus
- Inflammation
- Nutrition