Clinical Translational Research in Cystic Fibrosis – “Where are we in 2011 and where will we be in 5 years?"

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Disclosure Statement

In my capacity as Director of the Cystic Fibrosis Foundation (CFF) Therapeutics Development Network Coordinating Center, I have received grants from the following companies in the past 3 years:

AlgiPharma AS
Amgen, Inc.
Aradigm Corporation
Axcan Pharma, Inc.
Bayer Healthcare AG
Chiesi Pharmaceuticals Inc.
CSL Behring L.L.C.
Gilead Sciences
GlaxoSmithKine
Inspire Pharmaceuticals, Inc.
KaloBios

MerLion Pharmaceuticals GmbH
Mpex Pharmaceuticals, Inc.
MPM Asset Management LLC
N30 Pharmaceuticals, LLC
Novartis Pharmaceuticals Corp.
Pharmaxis Ltd.
PTC Therapeutics, Inc.
Solvay Pharmaceuticals, Inc.
Transave, Inc.
Vectura Ltd.
Vertex Pharmaceuticals Incorporated

I also receive grant funding from CFF and the National Institutes of Health.
Today’s Presentation

- Examples of success in CF translational research
- What resources does the CF community already have?
- What are our challenges?
- What are the next steps for clinical translational research as we focus on early lung disease and young children?
Pathogenesis

Defective CF Gene

Defective/Deficient CFTR

Decreased Chloride Secretion
Increased Sodium Absorption

Bronchial Obstruction

Infection

Inflammation

Bronchiectasis
Therapeutic Approaches by Class

Class III

Class IV

Class VI

Cystic fibrosis transmembrane conductance regulator

Accelerated turnover

Class II

Proteosome

Golgi complex

Class I

Endoplasmic reticulum

Nucleus

Class V

Translational Readthrough

CFTR Potentiator

CFTR Processing Corrector

Drug Discovery Process Leading to VX-770

High Throughput Screening → Medicinal Chemistry → Biology Activity in Cell Cultures* → Animal Studies → Human Studies

100,000’s of molecules
1000’s
100’s
10’s
7-10

*Human bronchial epithelial cells

Supported by CFF and Vertex
VX-770, A Potentiator, Increases G551D/F508del-CFTR Activity

Ussing chamber studies using G551D/ΔF508-HBE cultures

VX-770, A Potentiator, Increases G551D/F508del-CFTR Activity

VX-770 Phase 2A Study Design

Part 1
Randomized, Double-Blind, Placebo Controlled

Group A: 10 Subjects (G551D Mutation)
- N=4
  - 25 mg
  - 75 mg

Group B: 10 Subjects (G551D Mutation)
- N=4
  - 75 mg
  - 150 mg

Part 2
18 Subjects (G551D Mutation)
- N=7
  - 150 mg
  - 250 mg

- N=4
  - Placebo

7 to 28d Wash-out
Sweat Chloride Change from Baseline

Combined Part 1 and 2 data through Day 14 - Mean (95% CI)

- Placebo (n = 10)
  - Sweat chloride concentration (mmol/L): -2.0

- VX-770 25 mg (n = 7)
  - Sweat chloride concentration (mmol/L): -33.8 *

- VX-770 75 mg (n = 14)
  - Sweat chloride concentration (mmol/L): -42.0 *

- VX-770 150 mg (n = 16)
  - Sweat chloride concentration (mmol/L): -46.0 *

- VX-770 250 mg (n = 7)
  - Sweat chloride concentration (mmol/L): -27.1 *

* p < 0.01 within-group and vs. placebo
Linear trend for dose groups p < 0.001

Relative Change in FEV$_1$ % Predicted

VX-770 improvements in lung function were statistically significant

Combined Part 1 and Part 2 to Day 14 - Mean (95% CI)

![Graph showing relative change in FEV$_1$ % predicted for different treatments]

VX-770 Registration Program in CF

Orphan Drug and Fast Track Designation

Three separate registration studies:

- Primary trial to enroll ages 12+ with G551D mutation
- Patients aged 6 to 11 with G551D mutation
- Phase 2 study of CF patients homozygous for the F508del mutation
Vertex News Release (1)  
February 23, 2011

“Phase 3 study of VX-770 (Strive) showed profound and sustained improvements in lung function (FEV₁) in patients with cystic fibrosis and G551D mutation”

- Strive enrolled 161 patients worldwide with CF and at least one G551D mutation
- Patients received VX-770 (n=83) 150mg pill or placebo pill (n=78) twice daily for 48 weeks
# Vertex News Release (2)
February 23, 2011

## Results (VX-770 compared with placebo)

<table>
<thead>
<tr>
<th></th>
<th>24 weeks</th>
<th>48 weeks</th>
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<tbody>
<tr>
<td><strong>FEV₁</strong></td>
<td></td>
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<tr>
<td>Mean absolute change</td>
<td>10.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Relative change</td>
<td>16.7%</td>
<td>16.9%</td>
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<tr>
<td><strong>Pulmonary exacerbation requiring antibiotics</strong></td>
<td></td>
<td>↓ 55%</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td>↑ 3.1kg (6.8 lbs)</td>
</tr>
<tr>
<td><strong>Sweat chloride (baseline 100 mmol/L)</strong></td>
<td></td>
<td>↓ &lt; 60 mmol/L</td>
</tr>
</tbody>
</table>
Strategies to Rescue F508del-CFTR: Restore Both Trafficking and Gating

Additivity of Corrector and Potentiator in F508del-HBE Cells

\[ I_{CFTR} = n \times P \times g \]

F508del-CFTR Activity (% of wild-type CFTR)

- Untreated
- Corrector VX-809
- Corrector + VX-770
Two Phase 2a Clinical Trials in $\Delta$F508/$\Delta$F508 Patients

- VX-770 (Discover Trial)
  - 140 patients with CF and $\Delta$F508 mutations to test safety
  - Drug was safe except some cough and rash
  - Results
    - $\text{FEV}_1 \uparrow \ 1.6\%$ at 16 weeks
    - Sweat chloride $\downarrow \ 2.6 \text{ mmol/L}$ at 16 weeks
Phase 2a VX-809 Trial Study Findings
(2/5/2010)
(n=89)

- Safety – well-tolerated; one patient per arm discontinued for adverse events
- CFTR activity measured by sweat chloride

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Mean Change in Sweat Cl-*</th>
<th>P-value</th>
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<tbody>
<tr>
<td>25 mg</td>
<td>0.10 mmol/L</td>
<td>N/S</td>
</tr>
<tr>
<td>50 mg</td>
<td>-4.61 mmol/L</td>
<td>N/S</td>
</tr>
<tr>
<td>100 mg</td>
<td>-6.13 mmol/L</td>
<td>0.0498</td>
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<tr>
<td>200 mg</td>
<td>-8.21 mmol/L</td>
<td>0.0092</td>
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</tbody>
</table>

* compared with placebo arm

- Vertex has moved forward with combined VX-770 and VX-809 clinical trials
CFF Infrastructure that Supports Successful Clinical Research

- Therapeutics Development Network
- National Registry
- Continuous Quality Improvement Program
- CFF Care Centers
Cystic Fibrosis Foundation (CFF) Care Centers

116 Care Centers
51 Affiliate Centers
Key Features of CFF Care Centers that Support Clinical Research

- Multi-disciplinary teams supported by an annual CFF grant
  - MDs, RNs, dietary, social work, respiratory therapy, genetics, etc.
- **Commitment to** teaching and **research**
- Accreditation process with peer review site visits every three years
- **Standardized treatment plans** (inpatient and outpatient) to reduce variability
- **Ongoing collection of clinical data** for patient registry
- Foundation for 77 Therapeutics Development Network (TDN) centers
CFF Continuous Quality Improvement (CQI) Program

- Inspired by 2001 Institute of Medicine (IOM) report, CFF initiated CQI programs at all CF Care Centers

- Key priorities of this program:
  - Understanding the relationship between process and outcome in clinical care
  - The use of guidelines, data registries and front line data support
  - Involving patients in the care process
  - Understanding the impact of new therapies in ongoing clinical practices
How CFF CQI Supports Research

- Further decreases variability in care standards
- Helps to understand confounding factors leading to variability
- Creates culture of inquiry
- Promotes transparency and close partnership with families (parent advisory committee)
What is CFF Doing to Reduce Barriers to Participation in Research Studies?

- Changing the culture:
  - “Learn, Ask, Join”
  - “I Am The Key”

www.cff.org
Enrollment Success in the CF Population

- Well trained research staff
- Patients easily identified and screened through registry
- Low screen failures (< 10%)
- Families very knowledgeable and committed
- Low attrition rate (< 10%)
A Powerful Research Tool

Patient Registry
Annual Data Report to the Center Directors
2008

Cystic Fibrosis Foundation
| Adding tomorrows every day.
Patient Registry – A Powerful Research Tool
Example 1: Natural History Studies

Of patients born between 1985 and 1989 (the earliest cohort shown here in green), 88% survived to age 19. For patients born between 1990 and 1994, 92% survived to age 15.
Patient Registry – A Powerful Research Tool

Example 2: Identifying Optimal Patient Populations

Methicillin-Resistant S. aureus Infection Rate, by CF Center

The national rate is 22.6 percent (green bar). The range is 0 to 45.2 percent.
CFF Infrastructure that Supports Successful Clinical Research

- Therapeutics Development Network
- National Registry
- Continuous Quality Improvement Program
- CFF Care Centers
CFF Therapeutics Development Network (TDN)

Established in 1998
CFF TDN Accomplishments

- Over 100 therapeutic and observational trials successfully completed utilizing network sites and resources
- Over 30 investigational new drugs reached Phase 1 and 2
- Approximately 12 therapies have reached Phase 3 trials
- Four therapeutic pathways have been completed with FDA approval
  - Inhaled Aztreonam (Cayston®)
  - Three Pancreatic Enzyme Preparations (Zenpep®, Creon®, Pancreaze®)
Challenges We Face in the Next 5 Years (1)

- Disease progression is slowing
  - Magnitude of change in outcome measures reduced and prolonged
  - Sample size and study durations increase

- More approved therapies are available
  - Safety considerations (e.g., drug – drug interactions)
  - Comparative effectiveness studies will be necessary

- Baseline population characteristics are changing
  - Example – Patient population in inhaled aztreonam studies (2007-2009) had the same FEV\(_1\) range as inhaled tobramycin studies (1995-1997) but were 10 years older!
  - Importance of concurrent placebo group rather than historical controls
Challenges We Face in the Next 5 Years (2)

- Moving to younger, milder patients
  - Developing age appropriate clinical endpoints
  - Safety monitoring in young, vulnerable population — short-term and lifetime follow-up

- Finite patient population and funding
  - Setting priorities across the world community
  - Using resources wisely and efficiently
Key Priorities for the CF Research Community in the Next 5 Years

- Ensure patient safety and family trust
- Ensure responsible use of shared resources
- Better understand natural history of early lung disease
- Facilitate outcome measure development
- Develop new approaches to study designs
Priority #1: Continue to Ensure Patient Safety

- Established CFFT Data Safety Monitoring Board (Wayne Morgan, Director)
- Established centralized medical monitoring program (Chris Goss, Medical Director)
- Accumulating safety laboratory data and adverse event profiles (CFF TDN virtual data bank)
- Needs for the next 5 years
  - Expand safety database and sharing of safety data across studies (CFF, NIH, industry) – at a minimum include placebo populations
  - Continue to collect normative and natural history data – especially in infancy
Priority #2: Responsible Utilization of Clinical Resources

- Joint European (ECFS CTN) and US (CFF TDN) review of large multi-center clinical trials through TDN Protocol Review Committee
- Central database (CCSM) tracking all US multi-center trials at 77 TDN sites, enabling accurate enrollment projections
- Percent of patient population at TDN sites newly enrolled in studies during previous 12 months
  - Interventional
    - Range across sites = 0.5 - 27%
    - Median = 9%
  - Observational
    - Range across sites = 0 - 56%
    - Median = 10%
## Responsible Utilization of Shared Resources: Current Repositories

<table>
<thead>
<tr>
<th>Resource</th>
<th>Data</th>
<th>Specimens</th>
<th>Oversight</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDN virtual data repository</td>
<td>Placebo data for RCT’s</td>
<td>-----------------</td>
<td>NRCC (Sam Moskowitz, Chair)</td>
</tr>
</tbody>
</table>
| TDN NRC banked specimens                      | Variable data linked to TDN studies | • Bacterial pathogens (UW)  
• Sera  
• BAL                              | NRCC                                    |
| CFFT Specimen Bank (ProMedx)                  | Standard template of identifying data | • Sera  
• Microbiology                      | CFFT Biomarkers Committee (S. Sagel, Chair) |
| Wisconsin NBS study (2012)                    | Identifying data for specimens | • Sera (ProMedx)  
• Micro (UW)                           | CFFT Biomarkers Committee              |
| International CF Modifier Consortium          | DNA Sequencing data           | DNA                                     | Consortium Steering Committee (currently not open to non-investigators) |
Priorities for Shared Resources

- Proactive consenting of patients/families for banking
- Central database with “search engine” to track specimens and linked data
- Transparency and open access to large repositories
- Partnership of CFF, NIH and industry to support effort
Priority #3
Better Understand Natural History of Early Disease

Priorities from NHLBI Workshop Sept. 20-21, 2010:

- Leverage Newborn Screening to elucidate the natural history and clinical manifestations of early lung disease
- Develop a spectrum of biomarkers of early CF lung disease, measures of structural lung disease in connection with physiologic functions
- Explore the role of CF modifier genes and their associated variants in early lung disease
- Develop enabling technologies/tools/animal models of early lung disease (e.g. better imaging technologies)
Baby Observational and Nutritional Supplement Study (BONUS)

- To define and describe weight gain and growth in first year of life in CF newborns
- Explore nutritional, microbiologic and inflammatory characteristics that may be associated with optimal or poor growth
- Enzyme sub-study
  - Evaluate effect of the doses of pancreatic enzyme replacement on fat and protein malabsorption
- Establish a data and specimen repository for future studies
- Starting in late 2011
- 125 infants at 30 sites
Incredible Opportunity from Cross-Species Investigations
Newborn CF Piglets Fail To Eradicate Bacteria

David A. Stoltz, “Cystic Fibrosis Pigs Develop Lung Disease & Exhibit Defecetive Bacterial Eradication at Birth” (2010) Science Translational Medicine Vol 2 Issue 29: pg. 5, Fig . 7.
Priority #4: Facilitate Outcome Measures Development

Level 1: Clinical Efficacy Measures

Level 2: Validated Surrogate Endpoints

Level 3: Non-Validated Surrogate Endpoints

Level 4: Biomarkers

Kindly provided by Nicole Hamblett
Purpose of the open forum was for the FDA to gain perspective about clinical management of CF lung disease and outcome measures being used for both clinical care and research studies.

Three key clinical outcomes of interest to the Anti-microbial Division were discussed:

- Patient related outcome measures
- Pulmonary exacerbation definition
- \( FEV_1 \)
FDA Workshop
Take Away Messages

- FDA is keenly interested in completing the validation of at least one patient related outcome (PRO) measure of respiratory symptoms
  - Two leading candidates:
    - CF Questionnaire – Revised (CFQ-R)
      Quittner AL et al., *Chest* 2009;135(6):1610-8
    - CF Research Symptom Diary
      Goss, CH et al., *JCF* 2009;8(4):245-52
- FDA and European Medicines Agency (EMeA) would like an international effort to develop a universally-accepted definition of a pulmonary exacerbation
- FEV$_1$ and other pulmonary functions are not accepted by all FDA divisions as a primary endpoint; important secondary endpoint
- FDA encourages the CF community to lead the effort to validate outcome measures
Biomarkers

Biomarkers serve an important role in drug development

- As measures of biologic activity:
  - Identifying therapeutic targets
  - Screening candidate drugs

- As correlates for clinical efficacy:
  - Providing proof of concept in early stage trials
  - Understanding mechanism of action
  - Identifying responders to treatment
Candidate Biomarkers for Early Disease

- Measures of CFTR function
  - Sweat Chloride
  - Nasal Potential Difference

- Measures of airway hydration and Mucociliary Clearance (MCC)

- Measures of early lung disease
  - HRCT Imaging
  - Infection
  - Inflammation
HRCT Reveals Early Structural Damage

- HRCT detects regional structural damage prior to ↓ PFTs
- Emerging measure of early lung disease in CF

Long FR, PATS 2007; de Jong PA, Eur Respir J 2004; Davis SD, AJRCCM 2007
Incredible Opportunity from Cross-Species Investigations
CF Pigs Develop Pulmonary Disease

Non-CF

CF

CF

David A. Stoltz, "Cystic Fibrosis Pigs Develop Lung Disease & Exhibit Defecetive Bacterial Eradication at Birth" (2010) Science Translational Medicine Vol 2 Issue 29: pg. 5, Fig. 7.
Priority #5
New Approaches to Study Designs

- With multiple approved CF therapies available, we can no longer rely on randomized placebo-controlled clinical trials
- Next generation will look at comparisons of approved agents
- Unlikely that industry will conduct these trials
- The CF community will need to move towards comparative effectiveness research
Comparative Effectiveness Research (CER)

- IOM Report:
  - Defines CER as the “generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care.”

Types of CER Studies

- **Prospective observational studies**
  - Cohort and case control
  - Before/after

- **Retrospective observational studies**
  - Cohort and case control
  - Before/after

- **Cost benefit analyses**

- **Practical clinical trials**
Examples of Observational Studies of Therapeutic Interventions in CF

- Observational assessment of Ibuprofen in US CFF Patient Registry
  - Difference, 0.48% pred./year (95% CI, 0.19 to 0.78)

- 2 Randomized, controlled trials:
  - 4 year study (N=85)
    - $\text{FEV}_1$ % of predicted rate of decline slower in ibuprofen group
    - -1.48% compared to -3.57% per year
  - Canadian Ibuprofen 2 year study DB RCT (N=142)
    - Sign. reduction in the rate of decline of FVC % pred. (0.07 +/- 0.51 vs -1.62 +/- 0.52; P = .03)

Konstan, MW et al. AJRCCM. 2007;176:1084
Konstan, MW et al. NEJM, 1995; 332:848
Lands, LC et al. J. Peds. 2007;151:249
Practical Clinical Trials (PCTs)

- Distinct from classic randomized clinical trials which explain the “how” and “why” a treatment works:
  - Highly defined population to maximize effect
  - Well defined primary efficacy outcome
  - Required for development of new therapies

- PCT are designed to assist decision makers on optimal clinical approaches
  - Based on diverse “real world” populations
  - Most helpful for comparing approved therapies

- Outcomes are much broader with longer follow-up
  - Quality of life
  - Patient /family satisfaction
  - Cost analysis
An Example of CF PCT

Early Pseudomonas Infection Control Clinical Trial

337 Screened

- 29 Screen Failures
- 4 Eligible but not randomized

304 Randomized

- CYCLED (n=152)
- CULTURE-BASED (n=152)

**Tobramycin & Oral Ciprofloxacin** (n=76)
- 8 Withdraw

**Tobramycin & Oral Placebo** (n=76)
- 8 Withdraw

**Tobramycin & Oral Ciprofloxacin** (n=76)
- 8 Withdraw

**Tobramycin & Oral Placebo** (n=76)
- 3 Withdraw

304 included in the intent to treat population used for all analyses
EPIC Results:
Percent of Pa Positive Patients

- Cycled TSI-Cipro N=76
- Cycled TSI-Placebo N=76
- Culture Based TSI-Cipro N=76
- Culture Based TSI-Placebo N=76

Week: 10, 22, 34, 46, 58, 70

p=0.69
Primary objectives:
- Evaluate the microbiologic effect and safety of a 2 week MRSA eradication protocol

Selection criteria:
- 90 individuals with CF, 4 to 45 years of age, with recent MRSA respiratory tract infection
- Patients randomized to either treatment or observation

Treatment arms:
- Oral antibiotics for 14 days
  - Trimethoprim sulfa (Bactrim®)
  - Rifampin
- Topical antibiotics daily for 5 days
- Environmental decontamination for 21 days

Observation arm:
- Only receive treatment if symptomatic

Follow-up: 6 months

Outcome measures:
- Frequency of eradication of MRSA from oropharyngeal cultures
- Frequency of pulmonary exacerbations
- Safety and adherence to protocol

Sponsor: CFFT
Future CER Studies in CF

- Careful retrospective and prospective cohort studies will be an integral component of CER in CF
  - Limitations of cohort data need to be addressed with new methodologies
- CF is ideally positioned to implement expanded CER research because of the CFF Patient Registry and other ongoing prospective cohorts (EPIC Observational Study)
- Immediate opportunities
  - Newborn screening
  - Impact of quality improvement projects
  - Comparison of newly approved therapies such as inhaled antibiotics
Where Will the CF Community Be in 2015? (1)

- At least one FDA approved therapy targeting the underlying defect in CF is available to patients
  - Corrects CFTR function
  - Improves airway hydration and mucociliary clearance

- Key biomarkers to characterize and elucidate the primary pathophysiology of CF lung disease have been developed through natural history and animal model studies
Where Will the CF Community Be in 2015? (2)

Through comparative trials, the international CF community better understands treatment combinations to maintain pulmonary gastrointestinal health in CF patients:

- Antibiotic combinations
- Treatment of exacerbations
- Airway clearance
<table>
<thead>
<tr>
<th>Title</th>
<th>Sponsor</th>
<th>Study Type</th>
<th>Patients</th>
<th>Status</th>
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<tbody>
<tr>
<td><strong>CFTR Modulators/Correctors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) VX-770-105</td>
<td>Vertex</td>
<td>Open Label Extension</td>
<td>110</td>
<td>Enrolling</td>
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<tr>
<td>2) VX-770-106</td>
<td>Vertex</td>
<td>Phase 2 FEV1 &gt;90% LCI</td>
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<td>MPEX 209 (inhaled levofloxacin)</td>
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<td>3) STAR-TOO (Early MRSA treatment)</td>
<td>CFFT</td>
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<td>Insmed</td>
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<td><strong>Anti-Inflammatory</strong></td>
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<tr>
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<td>Boeringer-Ingellheim</td>
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<td>2) Pharma NAC</td>
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<td>3) GSK-SB-656-933</td>
<td>GlaxoSmithKline</td>
<td>Phase 2</td>
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<td>Enrollment Complete</td>
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<tr>
<td><strong>Restore Airway Surface Liquid</strong></td>
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<td>1) Hypertonic Saline in Infants</td>
<td>CFFT/NIH</td>
<td>Phase 2</td>
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<td>Pharmaxis</td>
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Thank You

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Cystic Fibrosis Foundation