Role of the CF Foundation in Addressing Post-Approval Regulatory Obligations

Bruce C. Marshall, MD
Cystic Fibrosis Foundation
Disclosure

The Cystic Fibrosis Foundation has entered into therapeutic development award agreements to develop CFTR modulators that may result in intellectual property and royalty rights from various pharmaceutical companies.
Cystic Fibrosis

- Autosomal recessive disease
  - 1,000 new cases/year in USA
  - 35,000 US patients (100,000 worldwide)
- Most common life-shortening inherited disease of Caucasians
- Complex, multisystem chronic disease
  - Majority of deaths due to lung disease
Care Center Network

133 Centers:

- Pediatric Programs 126
- Adult Programs 118
- Affiliate Programs 43

Size related to total # patients by center | US population density
CF Foundation Patient Registry

- 1969: CF Registry started by Dr. Warren Warwick at the University of Minnesota
- 1980s: CFF begins to expand and update Registry under leadership of Dr. Bob Beall
- 2006: Metrics on center outcomes made publicly available online
- 2010: Enhanced web-based platform

**Detailed medication collection**
- Mucolytics
- Inhaled Antibiotics
- Bronchodilators
- Corticosteroids

**Encounter based**
- Ability to embed studies in registry
- CRMS and CFTR-related diagnoses added
- Expanded data collection in microbiology, genotype results, and infants under 2
CF Foundation Patient Registry

POST-MARKETING SURVEILLANCE STUDIES

2018 PATIENT REGISTRY ANNUAL DATA REPORT

CF SmartReports

Ensure safety and effectiveness of approved products

Lung Function Status

Patient ID: D456
Patient Name: John Doe
Date of Birth: 01/01/1990
Status: Active

Recent Clinical Dates and Values

- Diagnosis Information
  - Cystic Fibrosis
  - Diagnosis Date: 01/01/1990
  - Recent Clinical Dates:
    - Jan 2019

- Hospitalizations
  - Hospital Name: Johns Hopkins Hospital
  - Date of Admission: 01/01/2019

- Medications
  - Current Medications (01/01/2019)
    - Azithromycin 500mg, Clarithromycin 500mg, Amoxicillin 500mg
  - Current Conditions (01/01/2019)
    - Pulmonary Fibrosis

- Nutritional Status
  - Height: 120cm
  - Weight: 50kg

- FEV1 % Predicted
  - Jan 2019: 60%
  - Feb 2019: 58%

- FEV1 % Predicted
  - Jan 2019: 60%
  - Feb 2019: 58%

DFC Foundation

2018 PATIENT REGISTRY ANNUAL DATA REPORT
FDA Drug Approvals with Post-Approval Requirements/Commitments

- 10-year prospective observational study to assess the risk of fibrosing colonopathy for reformulated pancreatic enzymes
- 5-year prospective observational study to assess the risk of antibiotic resistance to a new inhaled antibiotic
- 5-year prospective observational study to assess the safety of a new CFTR modulator
Phase 4 Studies Designed to Meet Post-Approval Requirements/Commitments

• **Reformulated pancreatic enzymes** - A Long-Term Prospective Observational Safety Study of the Incidence of and Risk Factors for **Fibrosing Colonopathy** in CF Patients Treated with Pancreatic Enzyme Replacement Therapy: A Harmonized Protocol Across Sponsors

• **Inhaled antibiotic** - A Prospective, 5-year Registry Study to Monitor the Susceptibility to Aztreonam of Pseudomonal Isolates from Patients with CF
Fibrosing Colonopathy Study

• Specific safety concern – rare complication
• Calculation of incidence requires numerator and denominator
• Anonymized registry patients at participating sites serve as the denominator (no separate consent required)
• Separate “study” developed to collect additional data on suspected FC cases
  • IRB-approved, patient consented study
  • Suspected cases adjudicated by expert panel
  • Positive FC cases serve as the numerator
Fibrosing Colonopathy Study

Registry Population at Participating Sites

FC Cases

= Incidence
Inhaled Antibiotic Study

- IRB-approved, patient consented study
- Subset of centers selected
- Patient selection criteria to enrich for treatment with inhaled antibiotics
- Collect annual respiratory cultures
- Standardize microbiology methods by using a central lab
- Link to clinical outcomes in the registry
Inhaled Antibiotic Study

CF Foundation Registry

Sponsor Sub-Study

Clinical Micro

Assess changes in antibiotic susceptibility AND the impact on key clinical outcomes
Phase 4 Studies Designed to Meet Post-Approval Requirements/Commitments


- **Inhaled antibiotic** - A Prospective, 5-year Registry Study to Monitor the Susceptibility to Aztreonam of Pseudomonal Isolates from Patients with CF

- **CFTR modulator** - 1) An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients with Cystic Fibrosis (PASS)
Scientific Breakthroughs Lead to Transformational Therapies
CFTR Modulator Study

- Use existing anonymized registry data to compare those on ivacaftor to a propensity matched comparator group:
  - Outcomes include lung function (FEV1), pulmonary exacerbation and hospitalization rates, mortality, number of lung transplants, etc.
ORIGINAL ARTICLE

Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor

Leona Bessonova,¹ Nataliya Volkova,¹ Mark Higgins,² Leif Bengtsson,¹ Simon Tian,¹ Christopher Simard,¹ Michael W Konstan,³ Gregory S Sawicki,⁴ Ase Sewall,⁵ Stephen Nyangoma,⁶ Alexander Elbert,⁷ Bruce C Marshall,⁷ Diana Bilton⁶,⁸

*Thorax 2018;73:731-740*
Hospitalizations and pulmonary exacerbations for ivacaftor and comparator cohorts

Bessonova et al. Thorax 2018;73:731-740
Death and organ transplantation for ivacaftor and comparator cohorts

Bessonova et al. Thorax 2018;73:731-740
Lung function changes over time for ivacaftor and comparator cohorts

Bessonova et al. Thorax 2018;73:731-740
CFTR Modulators: Now and 5 Year Projection

About 6% “Highly Effective” (i.e., Kalydeco for G551D or better)

91% “Highly Effective”
Key Success Factors

- Strong infrastructure in place
  - Care Center Network
  - Patient registry
- Experienced partners
- Ongoing relationship with pharmaceutical sponsors
- Credibility with FDA