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

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Cystic Fibrosis Foundation

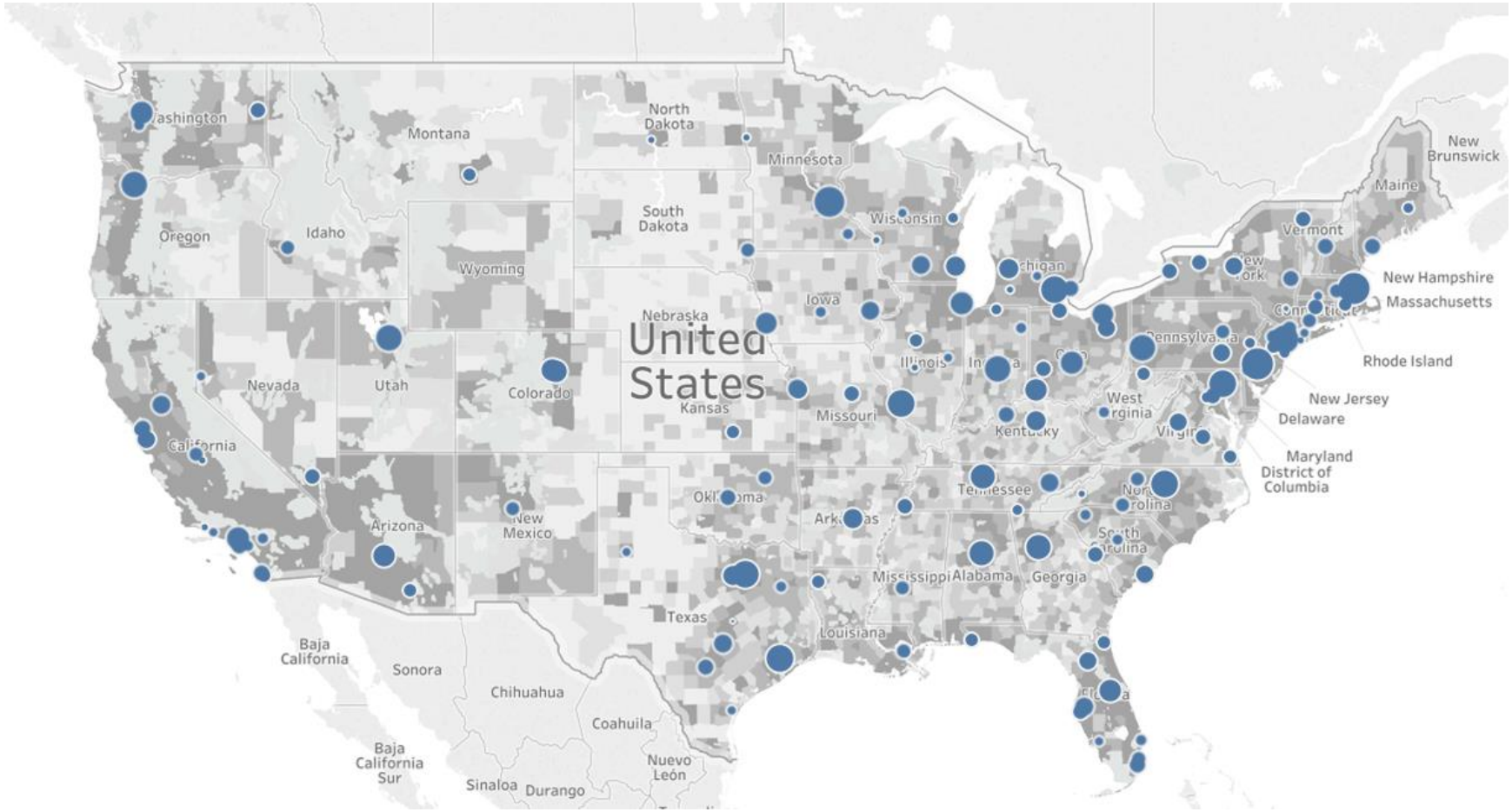
Disclosure

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



Size related to total # patients by center US population density

133 Centers:

Pediatric Programs	126
Adult Programs	118
Affiliate Programs	43

CF Foundation Patient Registry

ANNALSATS Articles in Press. Published -2016 as 10.1513/AnnalsATS.201511-781OC

CF Foundation Patient Registry

POST-MARKETING SURVEILLANCE STUDIES

Ensure safety and effectiveness of approved products

CF SmartReports

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

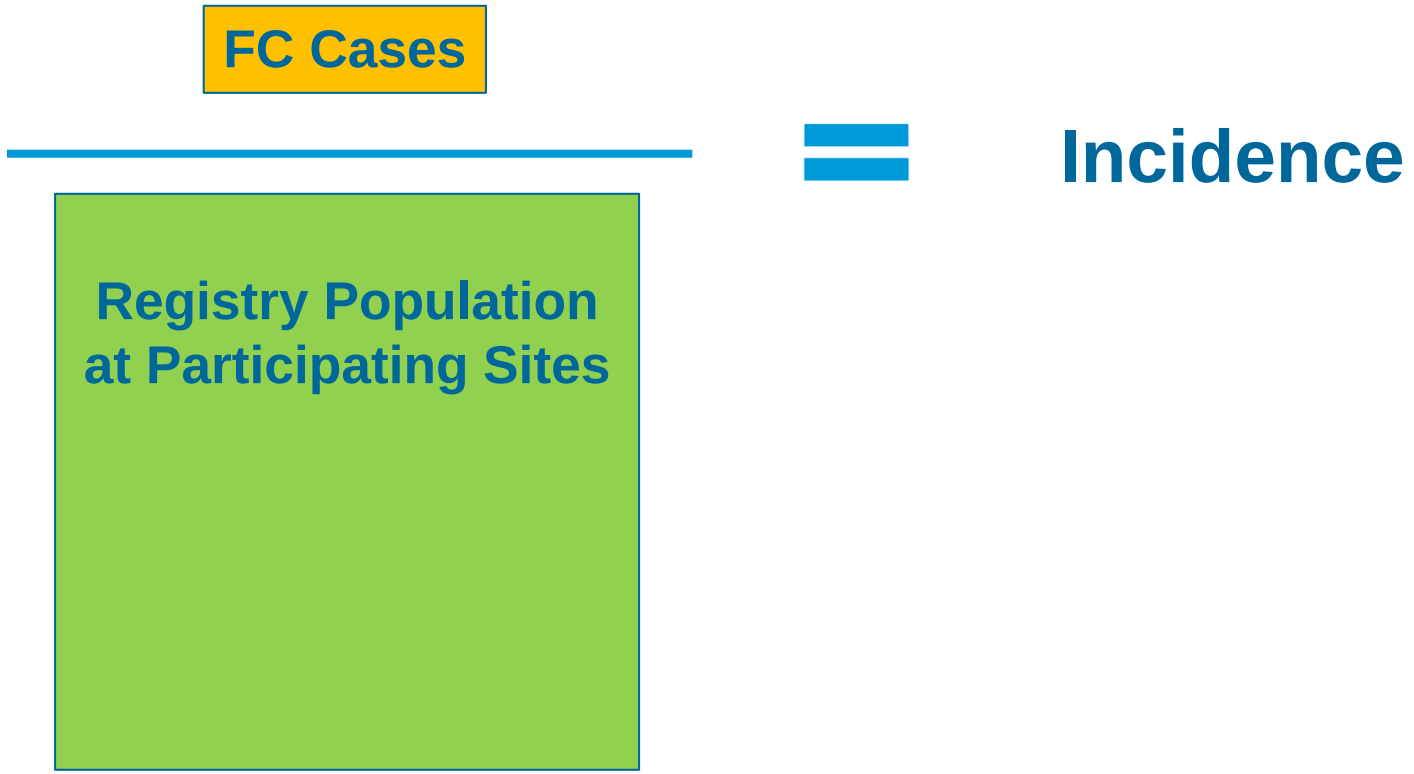
- Reformulated pancreatic enzymes - *A Long-Term Prospective Observational Safety Study of the Incidence of and Risk Factors for **Fibrosing Colonopathy** in CF Patients Treated with Pancreatic Enzyme Replacement Therapy: A Harmonized Protocol Across Sponsors*

- 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

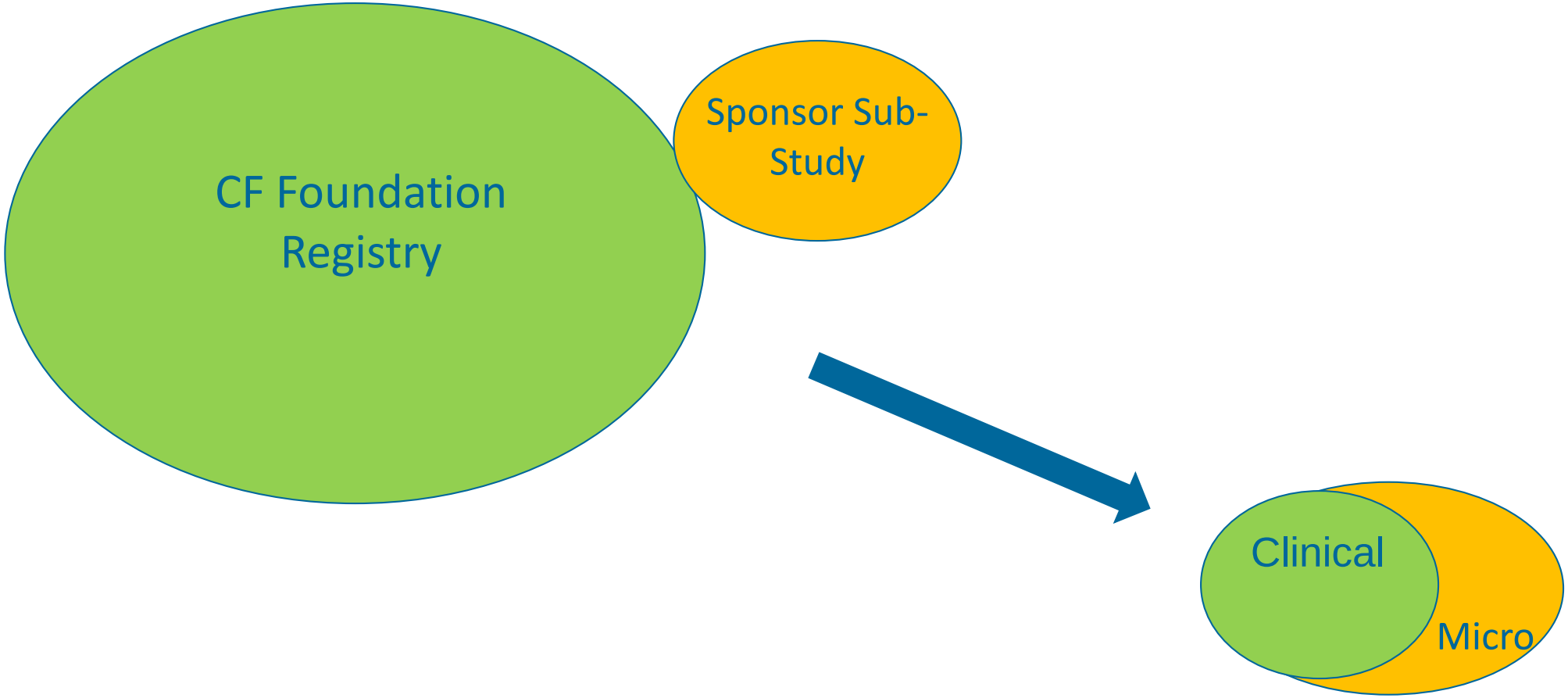
Fibrosing Colonopathy Study



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



Assess changes in antibiotic susceptibility
AND the impact on key clinical outcomes

Phase 4 Studies Designed to Meet Post-Approval Requirements/Commitments

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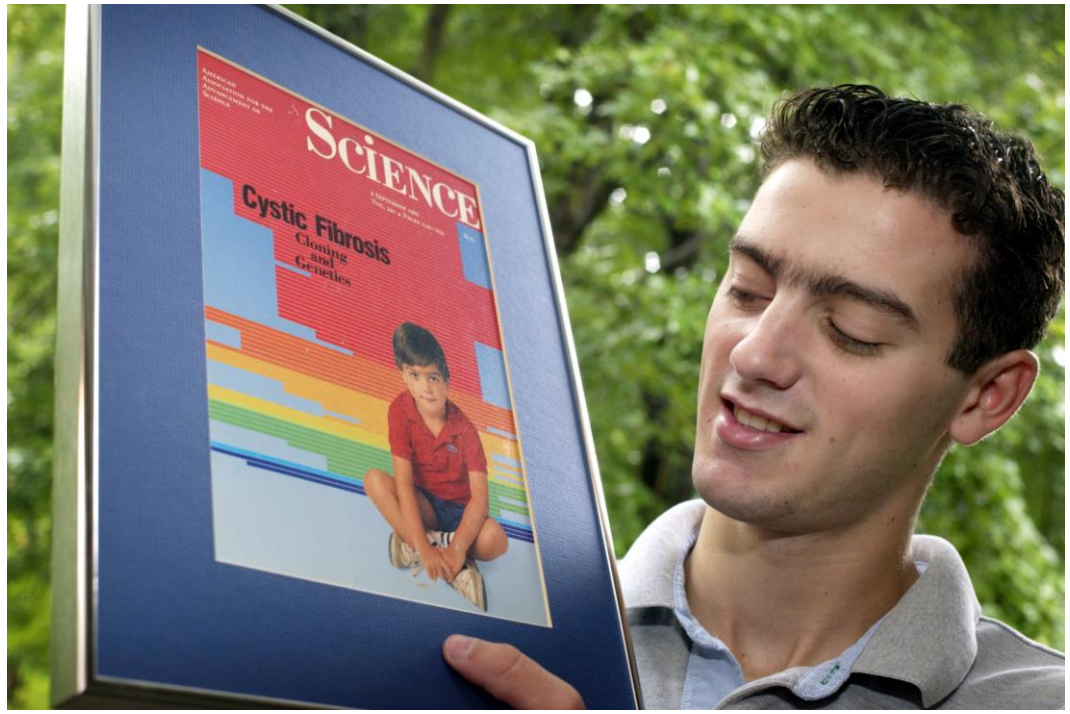
- CFTR modulator - *1) An Observational Study to Evaluate the Long-term Safety of Ivacaftor in Patients with Cystic Fibrosis (PASS)*

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.

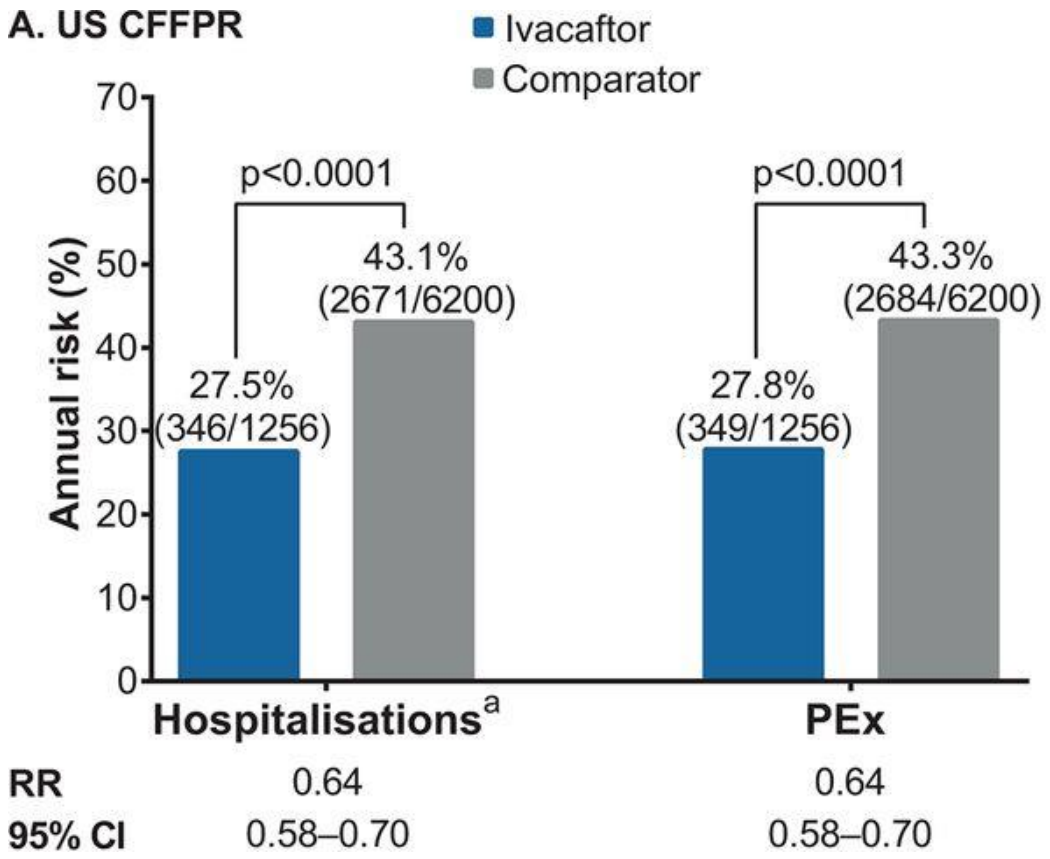
ORIGINAL ARTICLE

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 Bilton[6,8]

Thorax 2018;73:731-740

Hospitalizations and pulmonary exacerbations for ivacaftor and comparator cohorts



Bessonova et al. Thorax 2018;73:731-740

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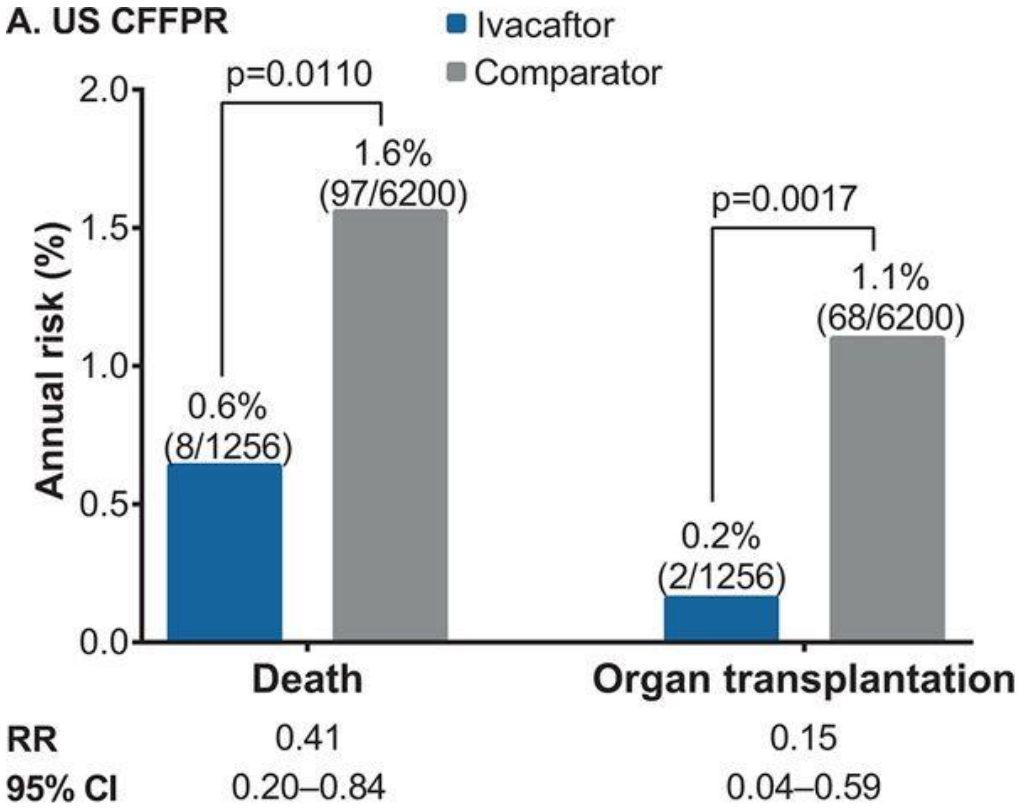
THORAX

Death and organ transplantation for ivacaftor and comparator cohorts



Bessonova et al. Thorax 2018;73:731-740

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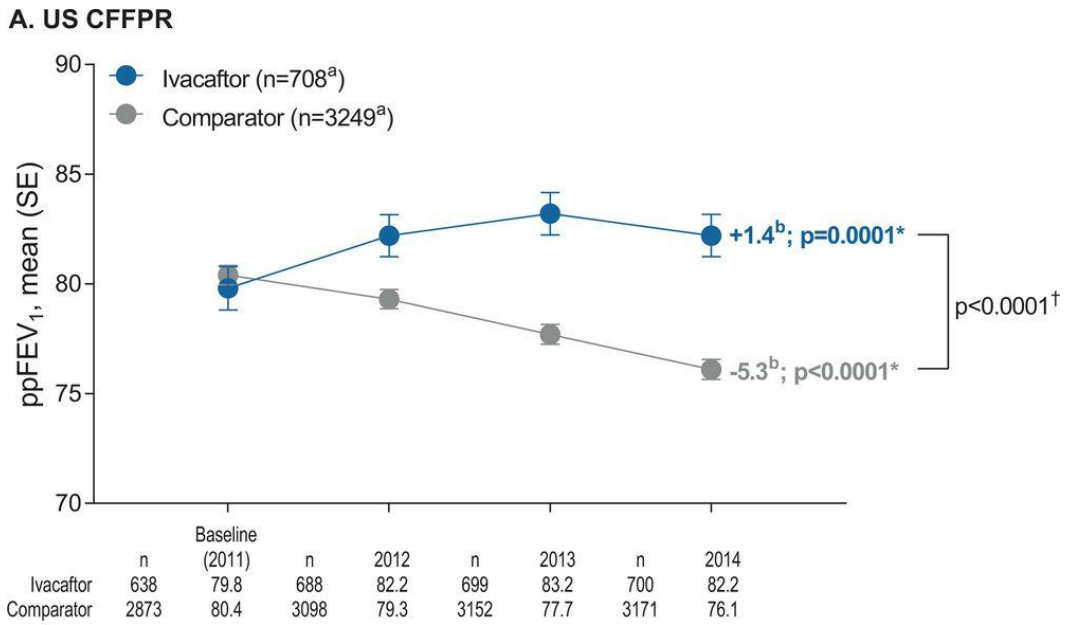
THORAX

Lung function changes over time for ivacaftor and comparator cohorts



Bessonova et al. Thorax 2018;73:731-740

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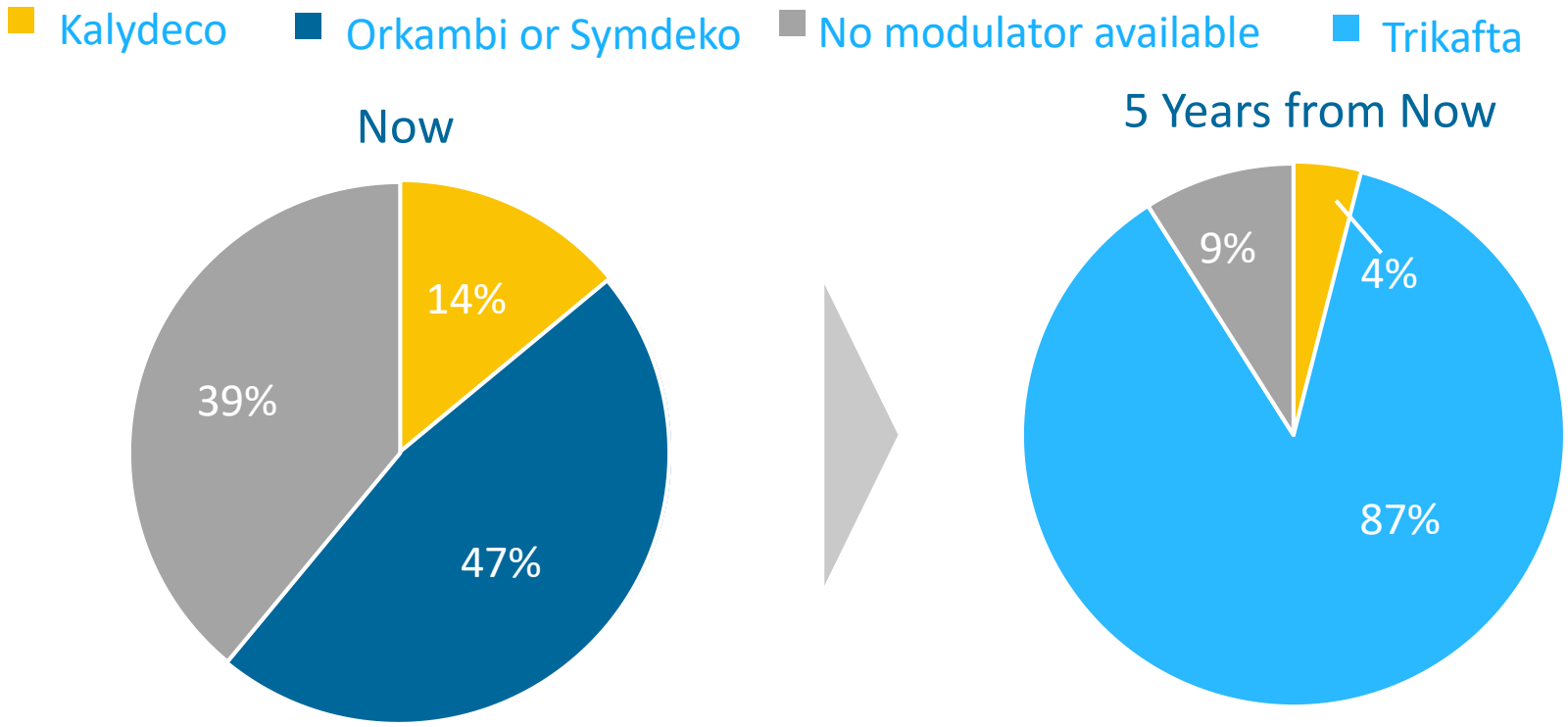
THORAX

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