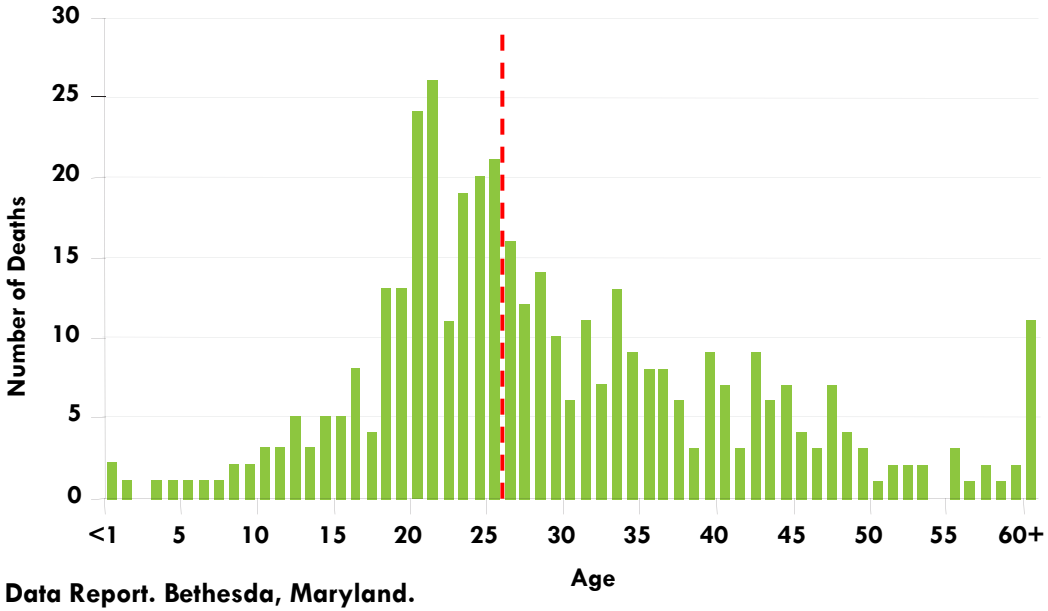
Development of a CFTR Potentiator
The Perspective of a Clinical Investigator

Bonnie W. Ramsey, M.D.

Endowed Professor of Pediatrics, UW School of Medicine
Director, Center for Clinical and Translational Research,
Seattle Children's Research Institute

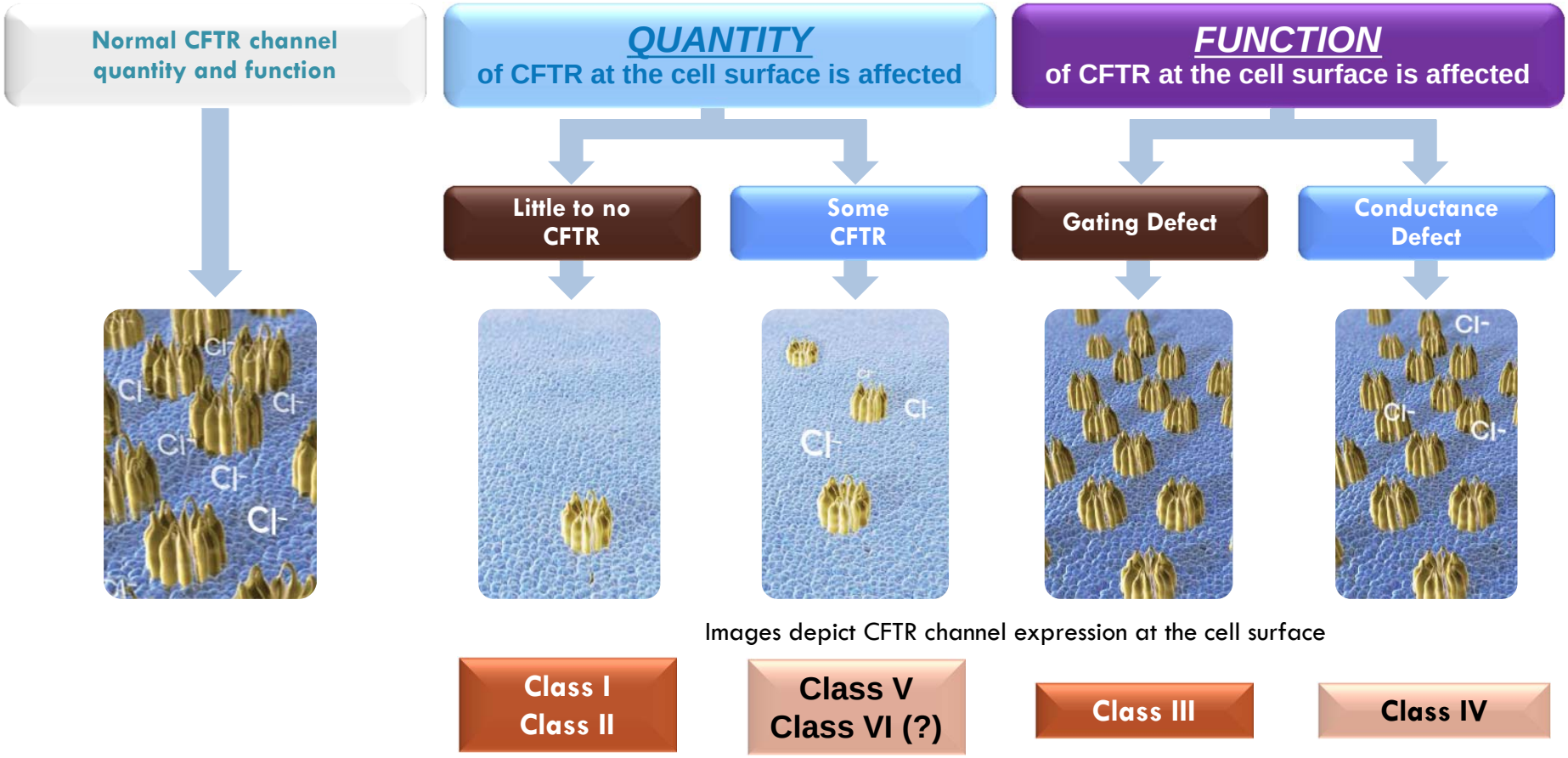
Cystic Fibrosis is a Lethal Orphan Disease

- Prevalence of cystic fibrosis (CF)
  - United States: ~30,000
  - Worldwide: ~70,000
- Predicted life expectancy (born 2010): 38.3 years
- Median age at death in 2010: 26.3 years
- Lung disease is the primary cause of morbidity and mortality



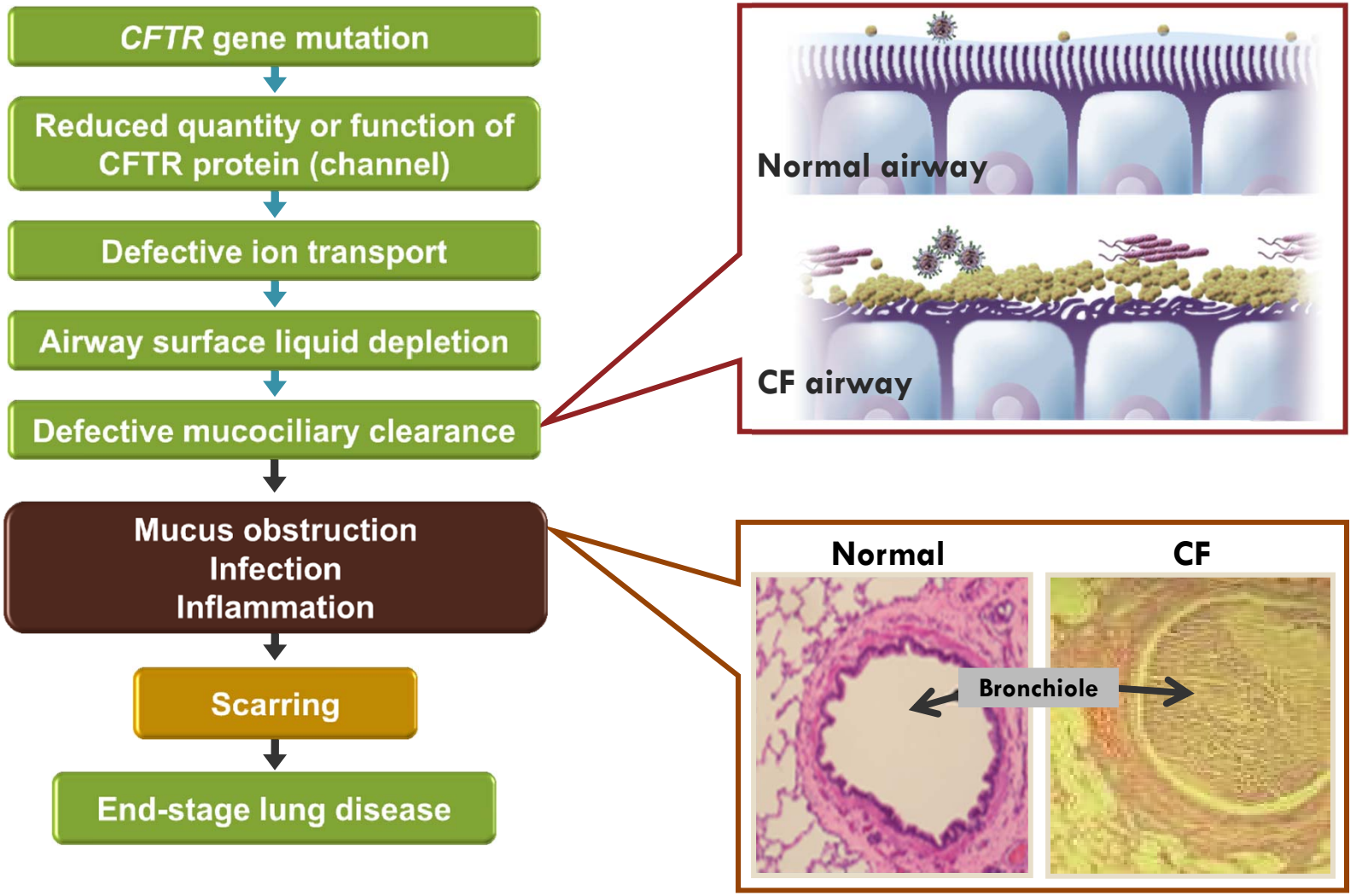
Cystic Fibrosis Foundation Patient Registry; 2010 Annual Data Report. Bethesda, Maryland.

CFTR Mutation Functional Defect Framework



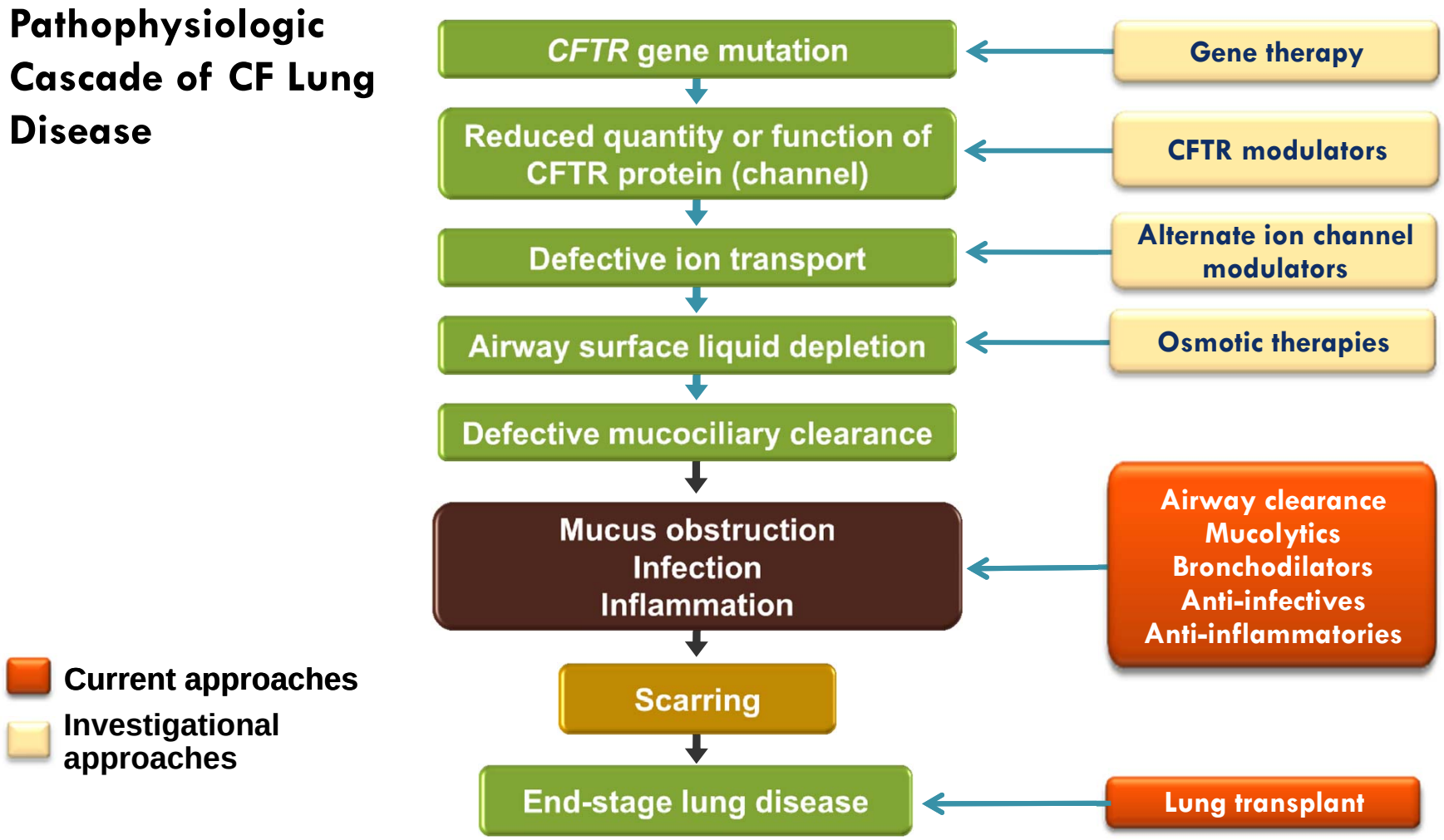
1. MacDonald KD et al. *Pediatr Drugs*. 2007;9:1-10; 2. Zielenski J. *Respiration*. 2000;67:117-133;
3. Welsh MJ et al. Cystic fibrosis. In: Valle D et al, eds. *OMMBID*. The McGraw-Hill Companies Inc; 2004:part 21, chap 201;
4. O' Sullivan et al. *Lancet*. 2009;373:1891-1904.

Pathophysiologic Cascade Leading From Defective CFTR Channel Function to Cystic Fibrosis Lung Disease



Ratjen. *Respir Care*. 2009;54:595-605.

New Therapeutic Approaches Being Developed to Target Earlier in the Pathophysiologic Cascade of Disease



Ratjen. *Respir Care*. 2009;54:595-605; Jones et al. *Drugs*. 2009;69:1903-1910; Proesmans et al. *Eur J Pediatr*. 2008;167:839-498.

Cystic Fibrosis Foundation Therapeutics Development Program

Drug Discovery

- Basic Research
- High-throughput Screening
- Combinatorial Chemistry

Drug Development

- Preclinical testing
- Clinical testing of candidate drugs Phase 1, 2, 3

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Initiated by CFF in 1998

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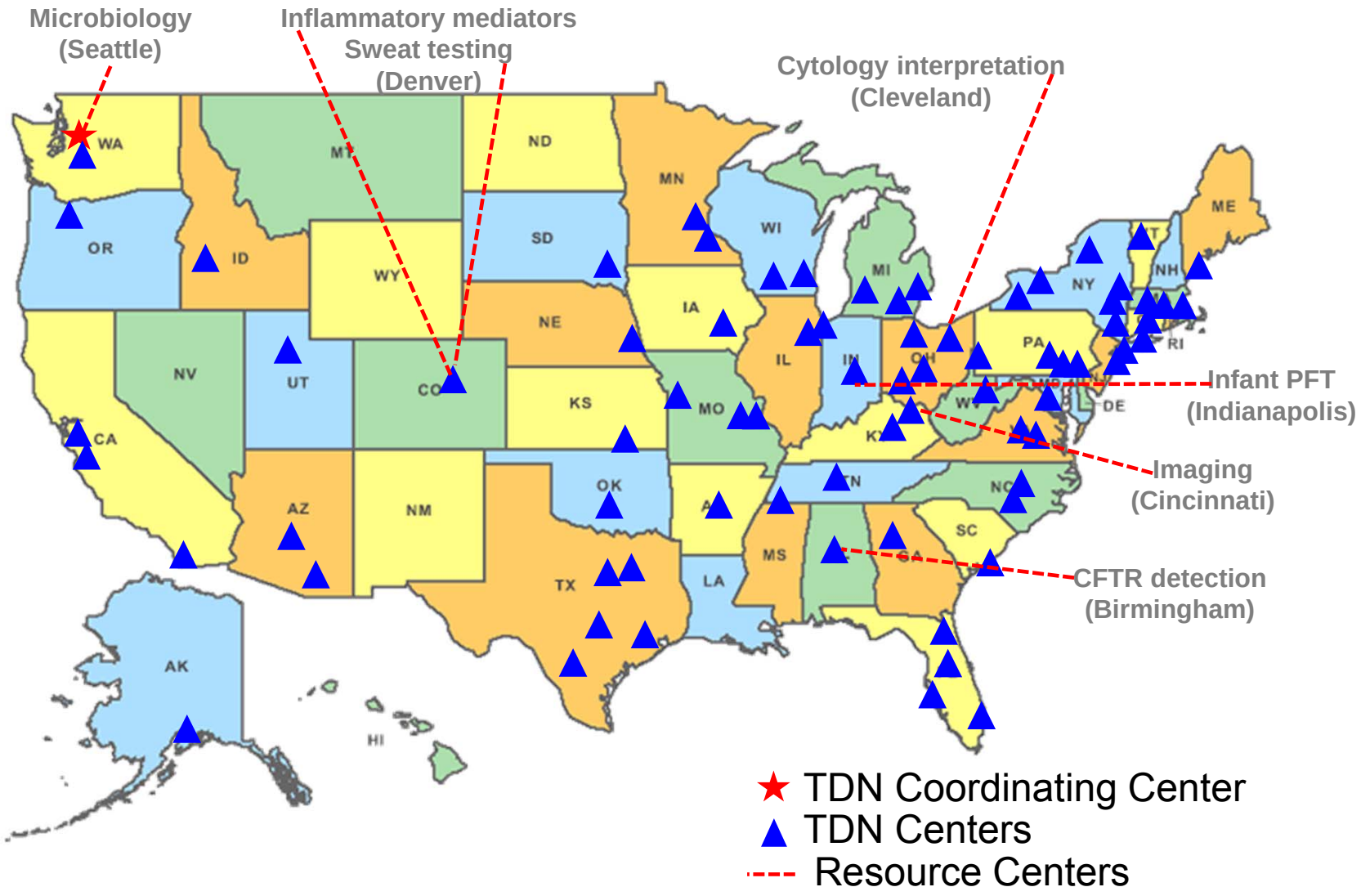
CFF Therapeutics Development Network (TDN)

Established in 1998



Strengths of TDN

- 77 established clinical research sites with trained staff
  - Linked to CF care centers with base of almost 20,000 patients (67% of US CF population)
- Linked to CFF national registry for cross-sectional and longitudinal data
- National resource centers for training, interpretation and ongoing development of biomarkers and clinical outcome measures
- Coordinating center
  - Study design, statistical and data management expertise
  - Network oversight and training
  - Clinical trial conduct
- Linked to European Clinical Trials Network

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Work of TDN and CFF During Pre-clinical Period

- Identification and characterization of patient population – genotype and phenotype
- Established standard operating procedures, training, baseline data, analytical approaches for key outcome measures
  - Ion transport – sweat chloride, nasal potential difference
  - Clinical efficacy – pulmonary function, respiratory exacerbations
- Assisted with clinical development plan
  - Potentiator and corrector combined or separate development pathways?
  - Study designs
  - Clinical Indications

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Identification of Relevant Patient Population -- G551D

Approximate proportion of patients with each type of CFTR defect leading to CF disease

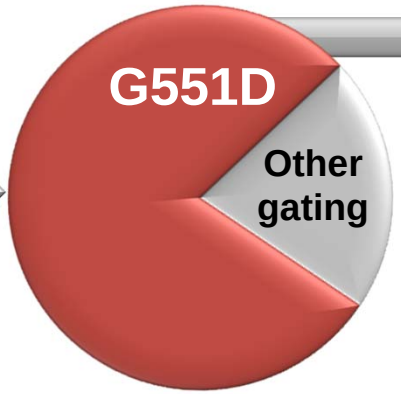
FUNCTION
of CFTR at the cell surface is reduced[1]

QUANTITY
of CFTR at the cell surface is reduced[1]

F508del mutation occurs in about 90% of patients with CF (including both heterozygous and homozygous); almost 50% of these patients have 2 copies[2,3]

Gating mutations occur with a prevalence of about 5%

Gating Mutations (eg, G551D)



G551D is the most common gating mutation with a prevalence of 4-5%[4]

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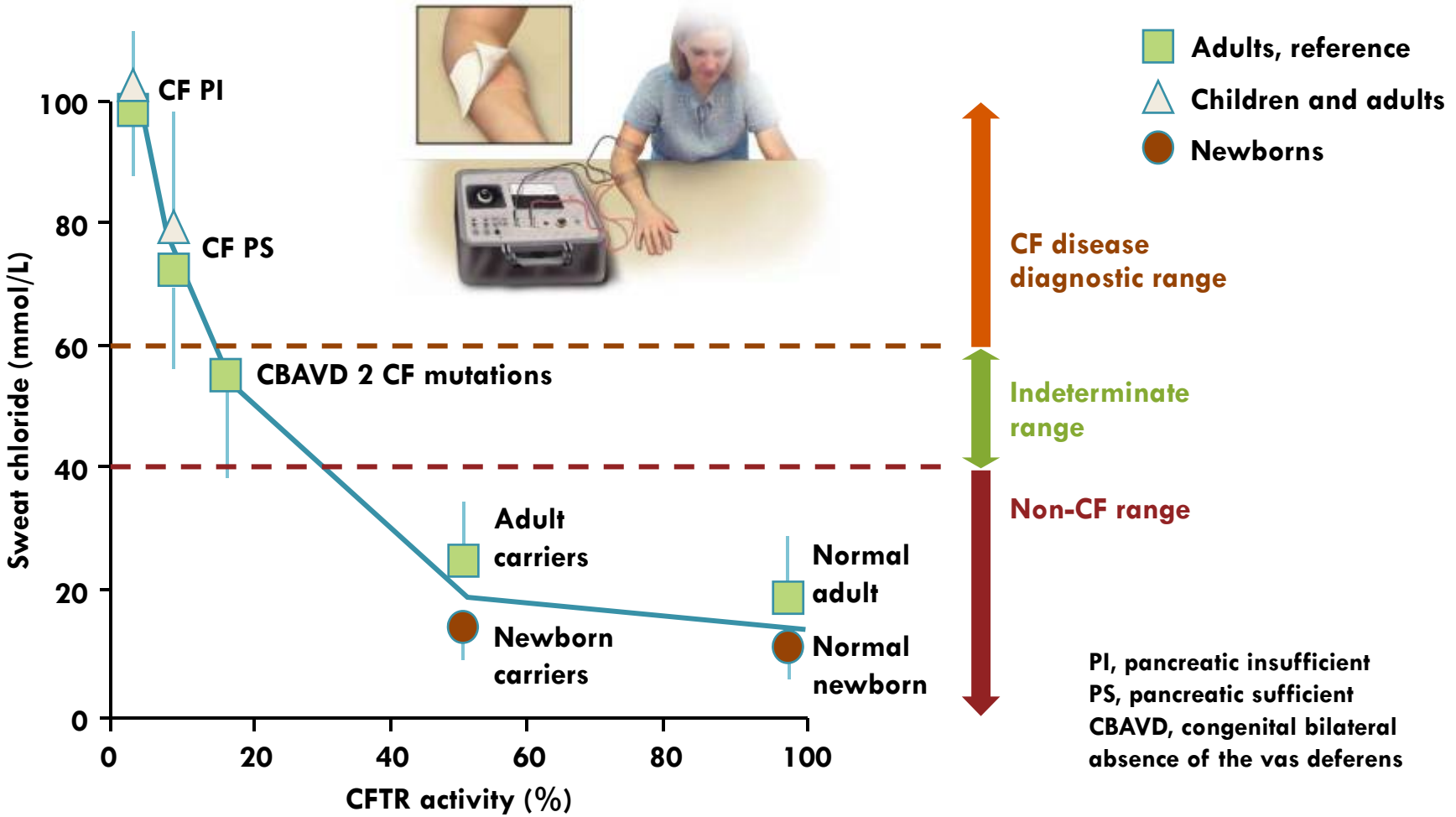
1.Zielenski J. *Respiration*. 2000;67:117-133; 2. Rowe SM et al. *N Engl J Med*. 2005 ;352:1992-2001;
3. Flume PA. 34th Annual European Cystic Fibrosis Conference. 2011; 4. Ramsey BW et al. *N Engl J Med*. 2011;365:1663-1672.

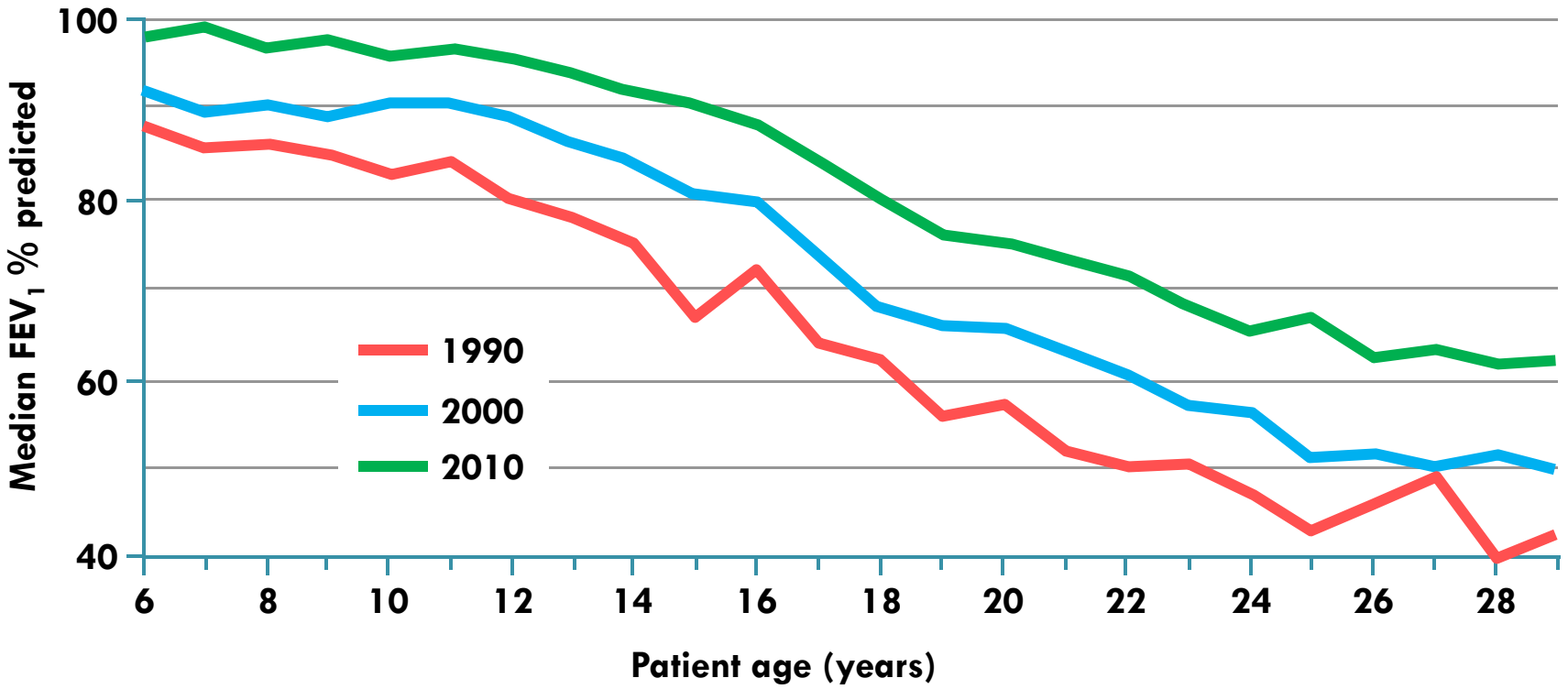
Sweat Chloride Concentration as a Biologic Endpoint in Cystic Fibrosis

CFTR activity as a function of sweat chloride concentration



Farrell et al. *J Pediatr.* 2008;153:S4-S14. Graph adapted from Rowe et al. *Proc Am Thorac Soc.* 2007;4:387-398.

Pulmonary Function as a Clinical Endpoint



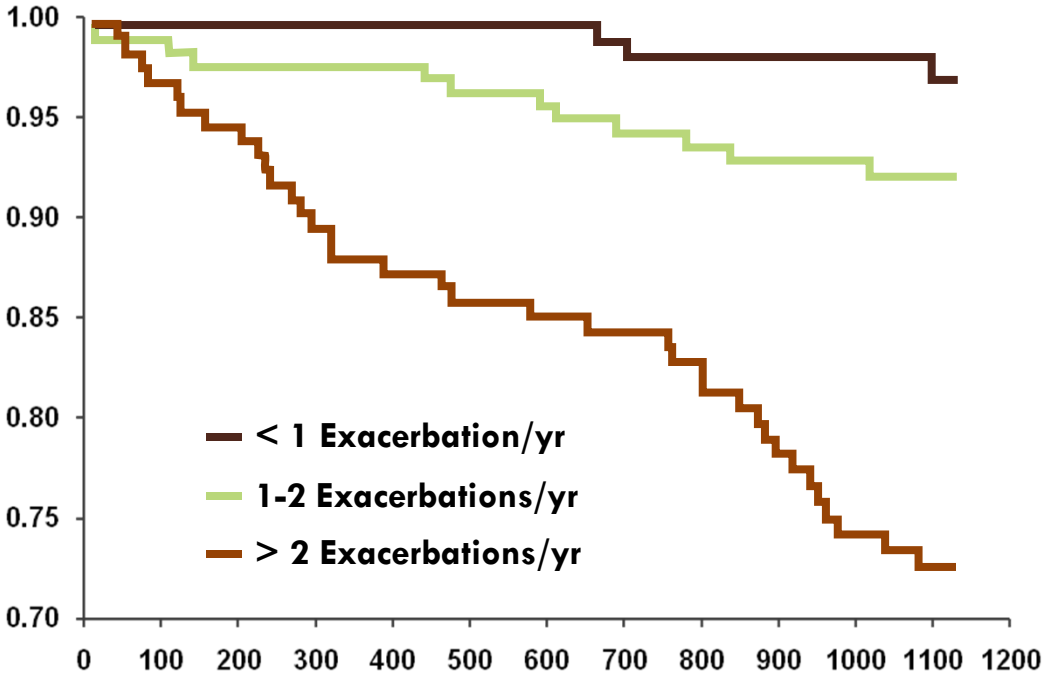
FEV_1 is the most significant predictor of survival in patents with CF

CFF Patient Registry Annual Data Report 2009. Bethesda, MD. Cystic Fibrosis Foundation. 2011; Pellegrino et al. *Eur Respir J.* 2005;26:48-968; Davies et al. *Respir Care.* 2009;54:606-615; Kerem E, et al. *N Engl J Med.* 1992;326:1187-1891.

Pulmonary Exacerbation as a Clinical Endpoint

- Pulmonary exacerbations have been linked to[a]
  - Increased mortality[b,c]
  - Faster subsequent decline in FEV_1[d]
  - Reduced quality of life[e]
  - Higher health care costs[f]
- Frequency increases with age[g]

Survival: Death or Transplant[h]



[a] Sanders DB, et al. *Am J Respir Crit Care Med* 2010;182:627–632; [c] Mayer-Hamblett N, et al. *Am J Respir Crit Care Med* 2002;166:1550–1555; [c] Liou T, et al. *Am J Epidemiol* 2001;153:345–352; [d] Konstan M, et al. *J Pediatr* 2007;151:134–139;
[e] Britto M, et al. *Chest* 2002;121:64–72; [f] Lieu T, et al. *Pediatrics* 1999;103:e72; [g] Goss CH et al. *Thorax*. 2007;62:360-367;
[h] deBoer K et al. *Thorax*. 2011;66:680-685.

Ivacaftor Effects at the Airway Surface in G551D/F508del-CFTR HBE

CFTR gene defect

↓

Reduced quantity o function of CFTR protein

Ivacaftor

↓

Defective ion transport ☑

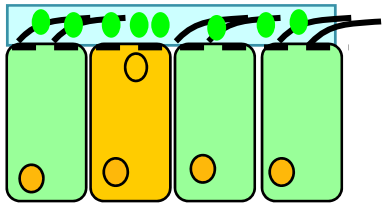
↓

Airway surface liquid depletion ☑

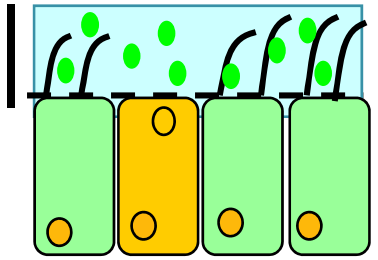
↓

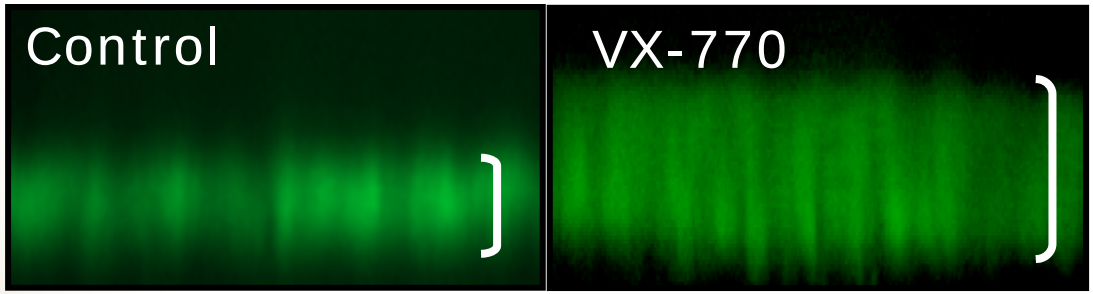
Defective mucociliary clearance

Airway surface liquid*



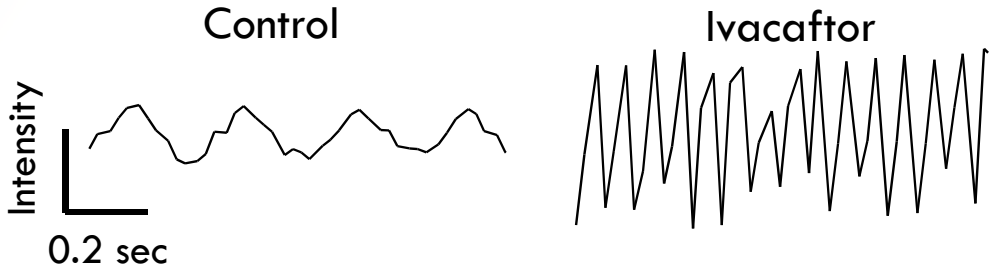
ASL





Unpublished data provided by Vertex

Cilia beat frequency (representative tracings)



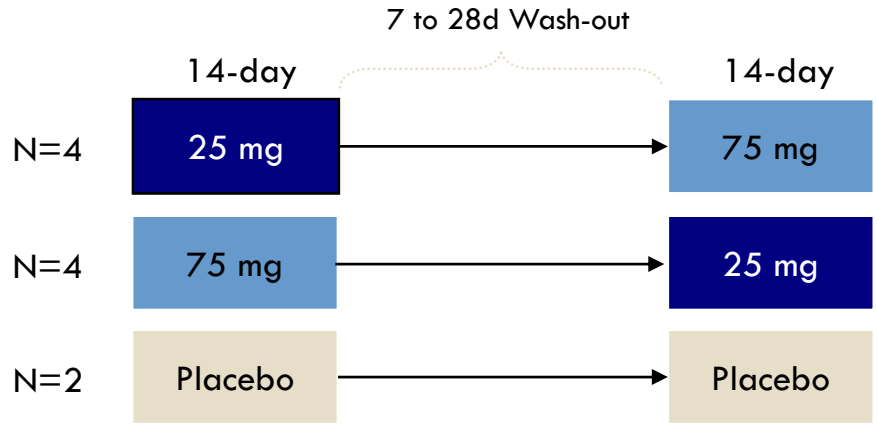
Van Goor et al. PNAS 2009;106:18825-30

VX-770 Phase 2A Study Design

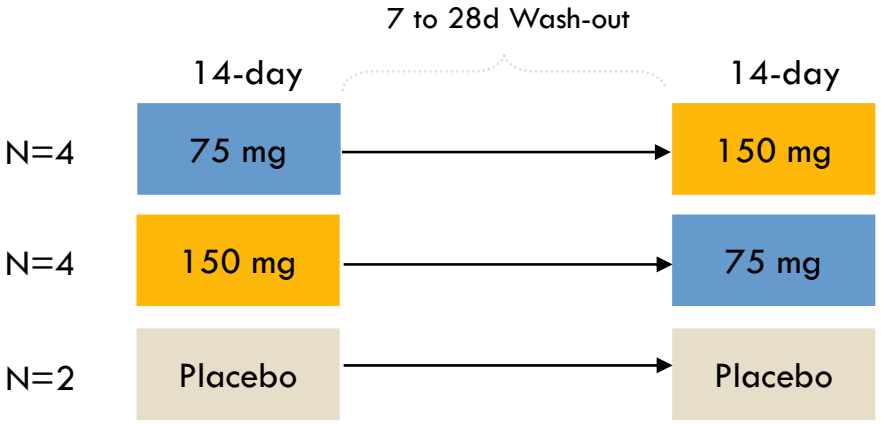
Part 1

Randomized,
Double-Blind,
Placebo Controlled

Group A:
10 Subjects
(G551D Mutation)

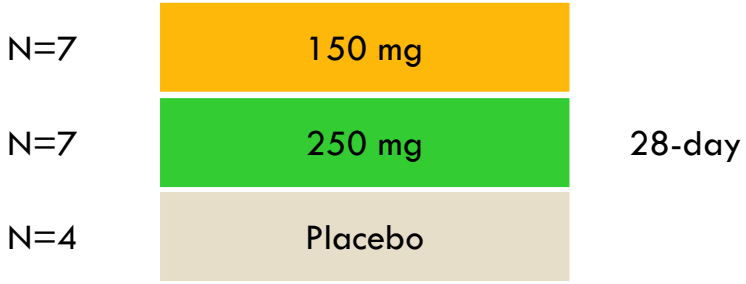


Group B:
10 Subjects
(G551D Mutation)



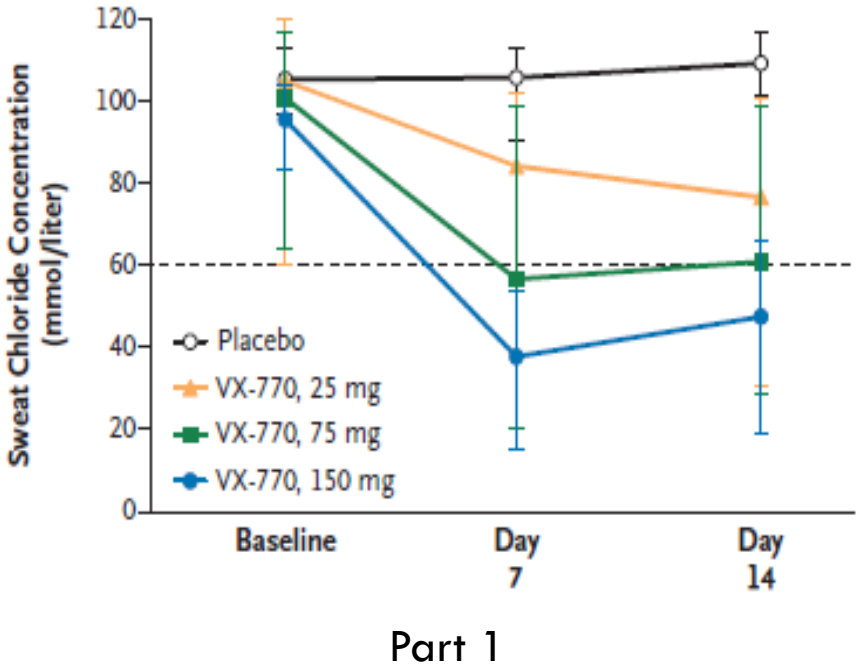
Part 2

18 Subjects
(G551D Mutation)

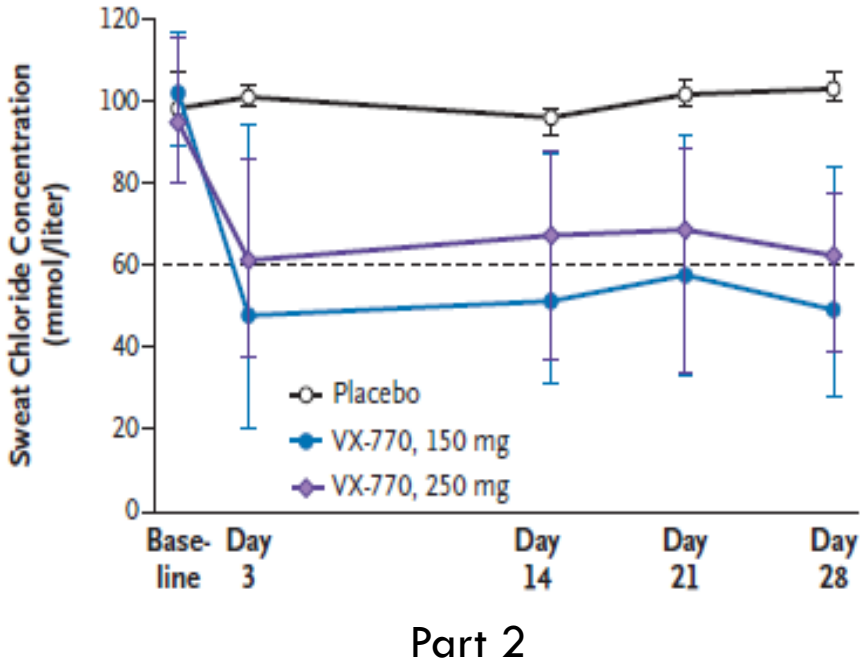


Effect of VX-770 in G55ID Sweat Chloride Response: Phase 2 Study Results

Response of Sweat Chloride Concentration



Part 1



Part 2

Accurso, FJ et al, *N Engl J Med* 2010 Nov 18;363:1991-2003

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Ivacaftor Phase 3 Study

- Ivacaftor (also known as VX-770), an orally bioavailable, investigational CFTR potentiator for the treatment of CF in patients with the *G551D-CFTR* mutation
- Hypothesis:

  Ivacaftor will improve FEV_1 in people with CF and a G551D mutation

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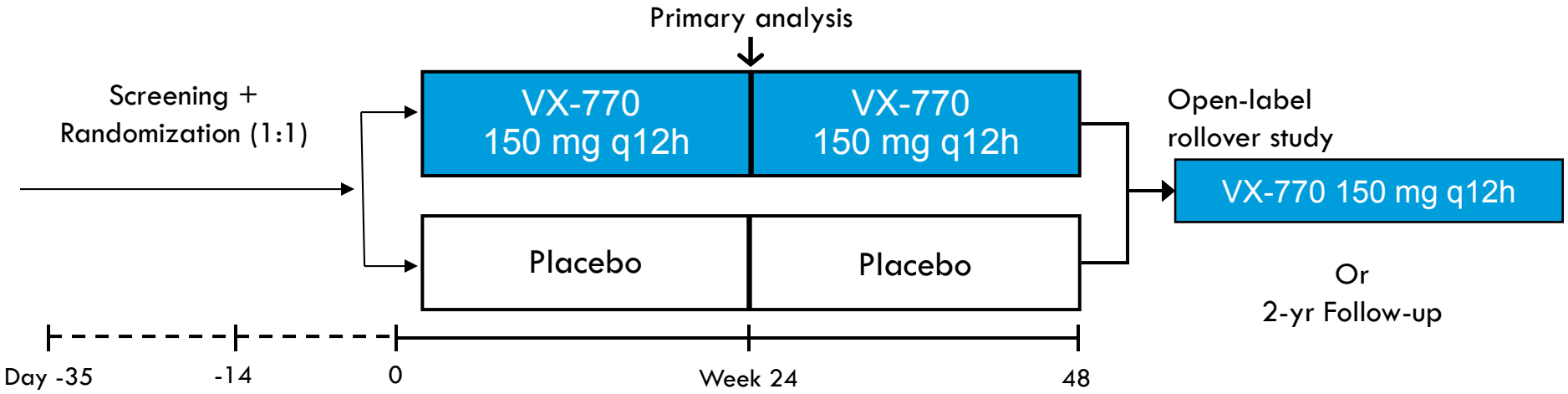
Ivacaftor Study Design



- Key inclusion criteria
  - G551D mutation on at least one *CFTR* allele
  - Aged ≥ 12 years
  - FEV_1 40% to 90% predicted
- 48-week double-blind, placebo-controlled treatment period
  - Primary analysis at Week 24

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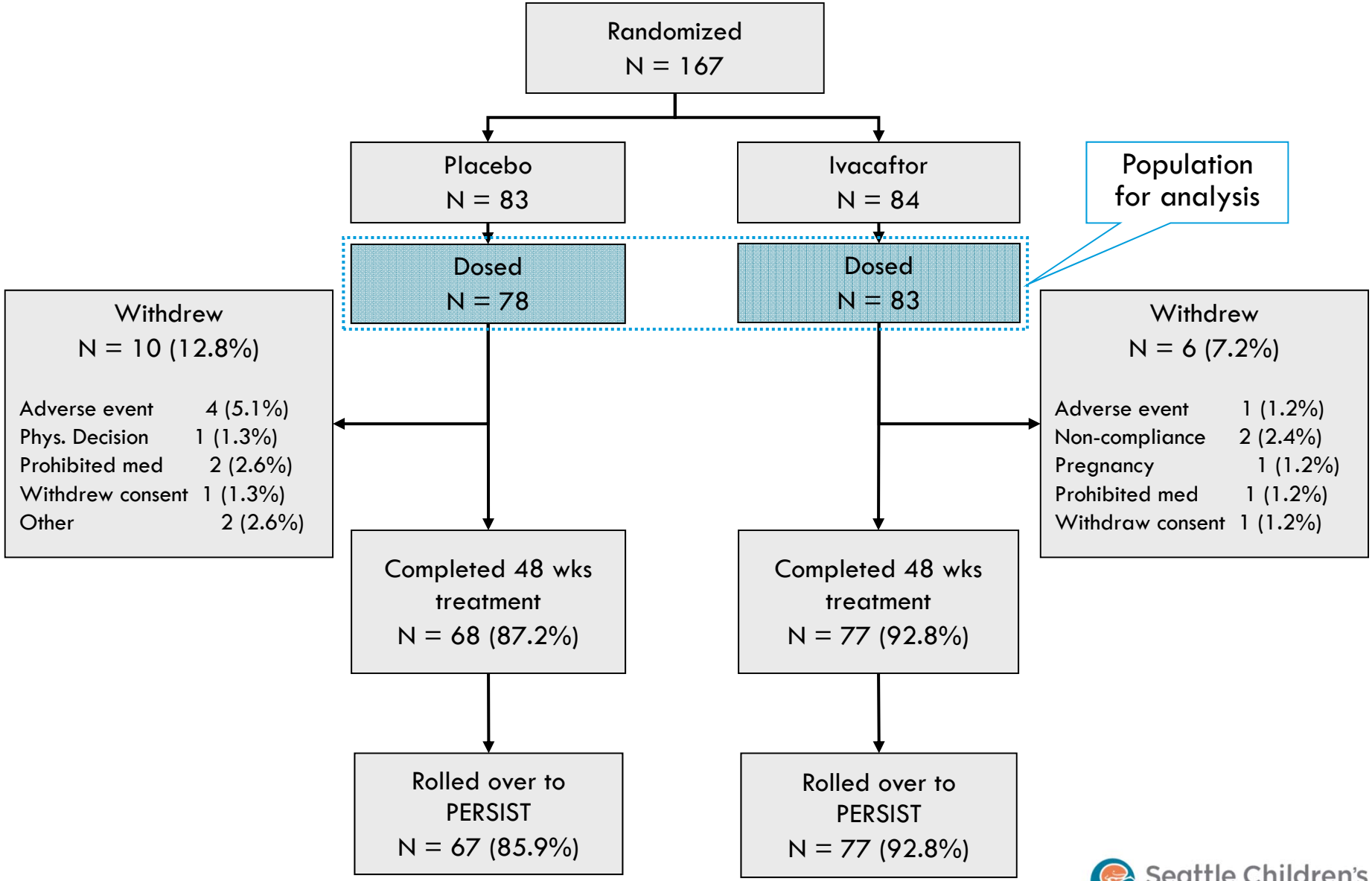
Subject Disposition



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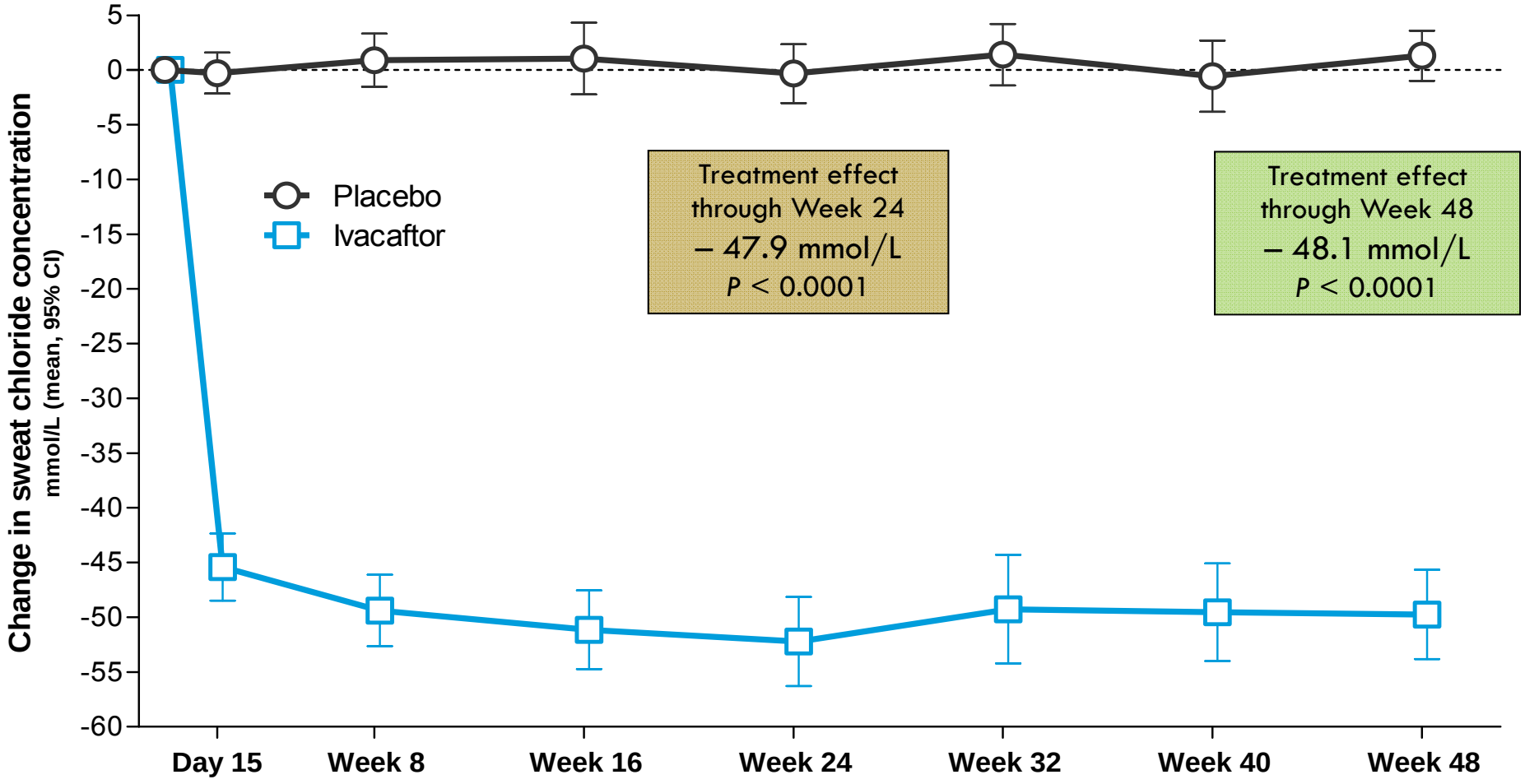
Change from Baseline in Sweat Chloride



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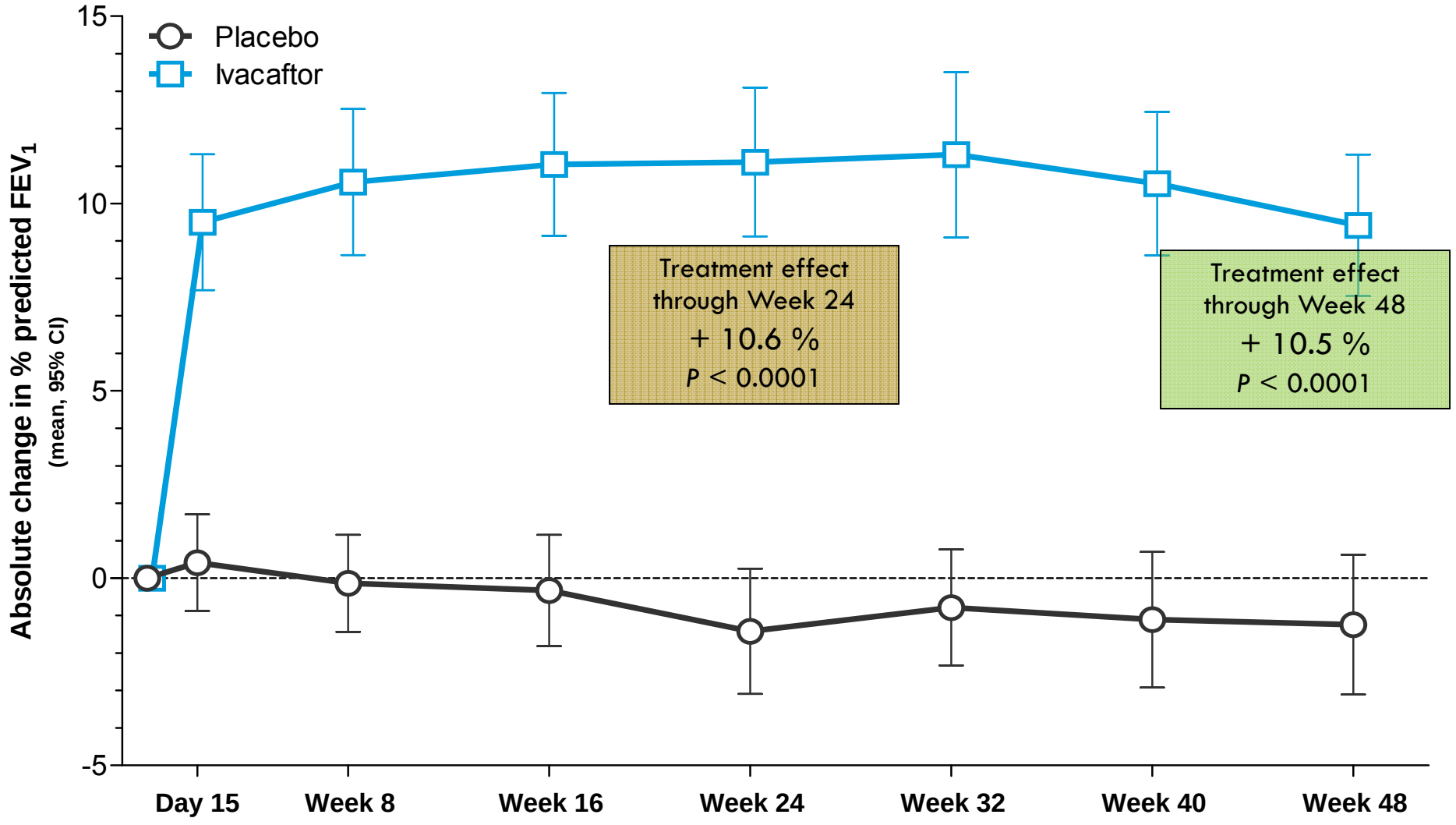
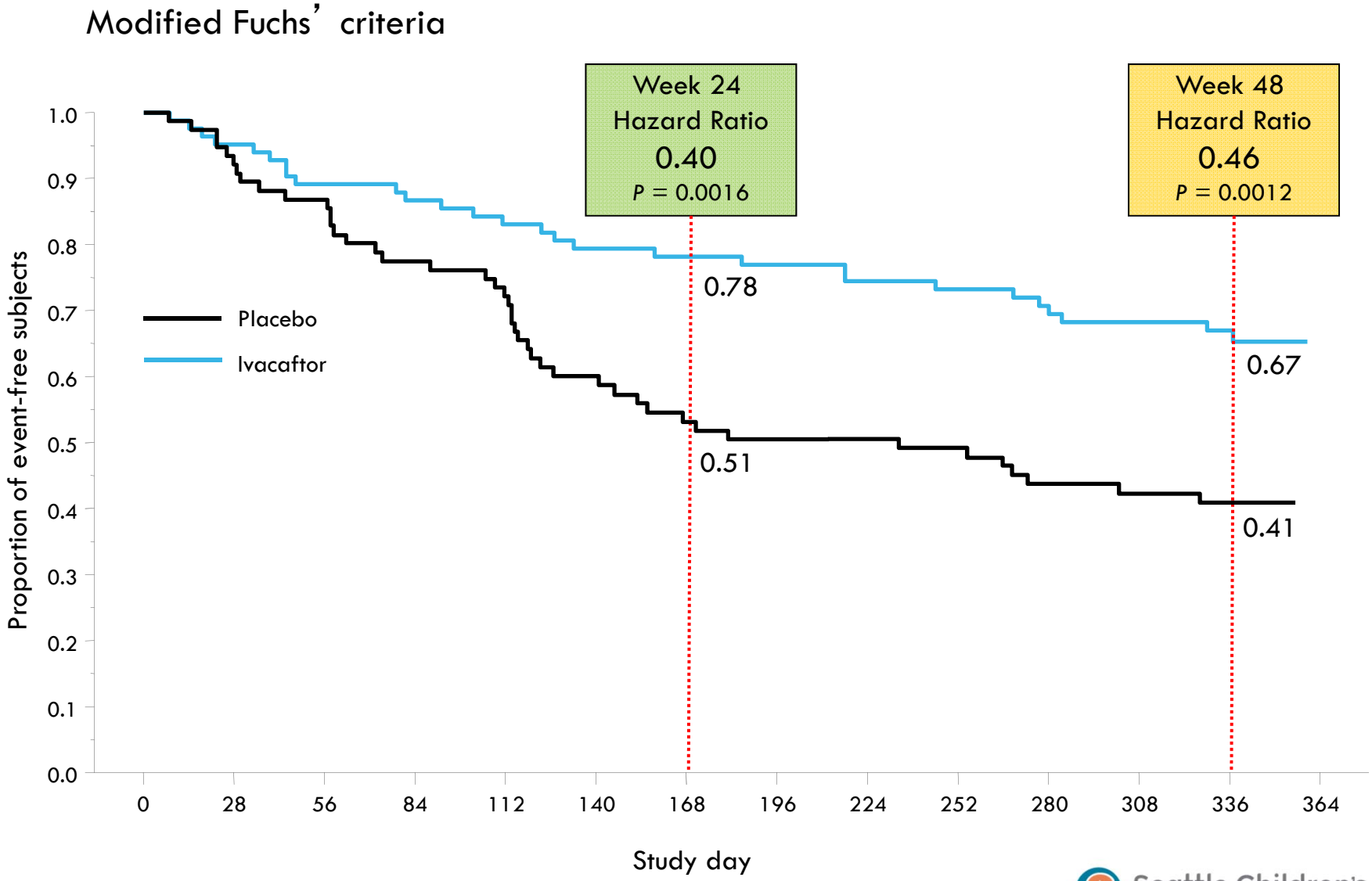
Estimates are model-based. Points and 95% CI are unadjusted (raw)

FEV_1 % Predicted Absolute Change from Baseline



Estimates are model-based. Points and 95% CI are unadjusted (raw)

Time-to-First Pulmonary Exacerbation



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Safety Summary Through Week 48

Serious adverse events occurring in > 1 subject in either group

Adverse event, n (%)	**Placebo** (N = 78)	**Ivacaftor** (N = 83)
Subjects with any serious adverse event	33 (42.3)	20 (24.1)
Pulmonary exacerbation (physician determined)	26 (33.3)	11 (13.3)
Hemoptysis	4 (5.1)	1 (1.2)
Hypoglycemia	0	2 (2.4)

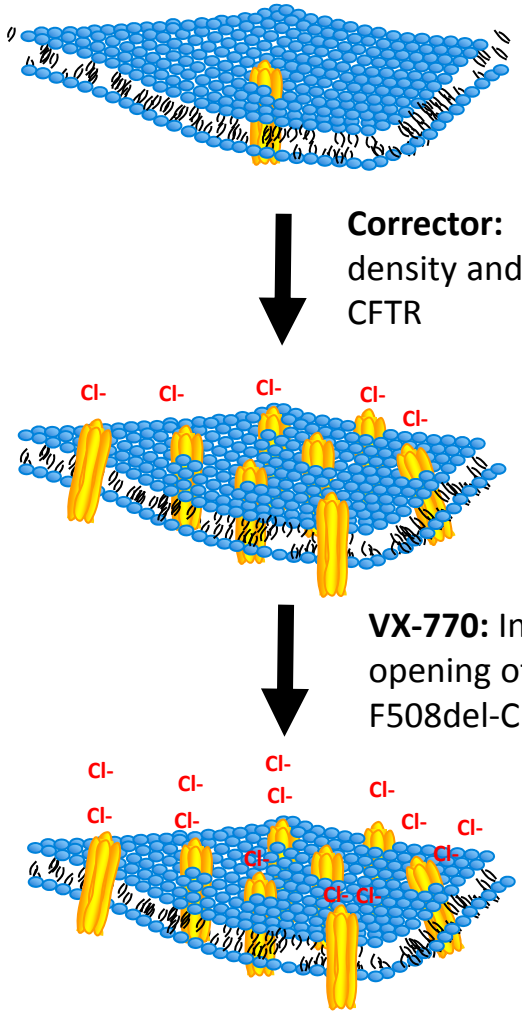
Adverse events with ≥10% incidence in either treatment group and ≥5% difference relative to placebo

Adverse event, n (%)	**Placebo** (N = 78)	**Ivacaftor** (N = 83)
More common in Ivacaftor group		
Headache	13 (16.7)	19 (22.9)
Upper respiratory tract infection	12 (15.4)	19 (22.9)
Nasal congestion	12 (15.4)	17 (20.5)
Rash	4 (5.1)	12 (14.5)
Dizziness	1 (1.3)	10 (12.0)

Summary of Phase 3 Study Findings

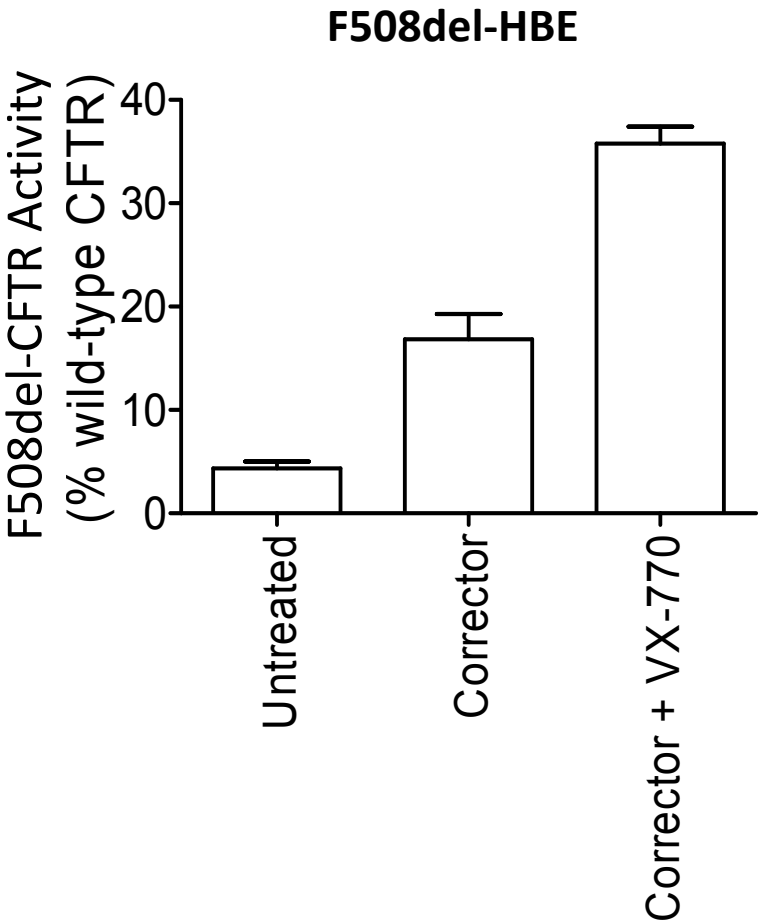
- Primary endpoint (absolute change in percent predicted FEV_1) was statistically significant and clinically meaningful.
- Improvements in lung function and CFTR function (sweat chloride) were noticeable at 2 weeks and sustained through 48 weeks.
- Sustained improvements through Week 48 in other clinically important outcomes were observed, including risk of exacerbation, weight gain, and respiratory symptoms.
- Adverse events were mostly respiratory in nature and led to discontinuation of 1 subject in the ivacaftor group and 4 subjects in the placebo group.
- Phase 3 data was supportive of FDA approval of Kalydeco in early 2012.

Next Steps for Other CF Mutations: Combined Corrector and Potentiator Therapy



Corrector: Increases cell surface density and function of F508del-CFTR

VX-770: Increases channel opening of corrected F508del-CFTR



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Next Steps for Other CF Mutations (2)

- June 2012 Vertex press release

"Based on data from Phase 2 study evaluating dosing of Kalydeco and VX-809, Vertex plans to initiate a pivotal program in early 2013 to evaluate a combination of Kalydeco and VX-809 in people with two copies of the F508del *CFTR* mutation, pending discussions with regulatory agencies."

(http://www.vrtx.com/current-projects/drug-candidates/VX-809.html)

Lessons Learned for Successful Drug Development in an Orphan Disease

- Establish partnerships across industry, foundations, academics, federal agencies and patient/families
- Develop laboratory and clinical infrastructure in parallel and far in advance of first patient enrolled.
- Focus on deliverables and a common goal
  - Biology and mechanisms of action are secondary gains
  - Use the new drugs to further the science, e.g. GOAL study

Thank you!