A Genetic Approach to the Treatment of Cystic Fibrosis

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VERTEX

Introduction

- CFTR Modulation Approach
- Ivacaftor (VX-770) Registration Program
- Moving beyond G551D
- Lessons learned

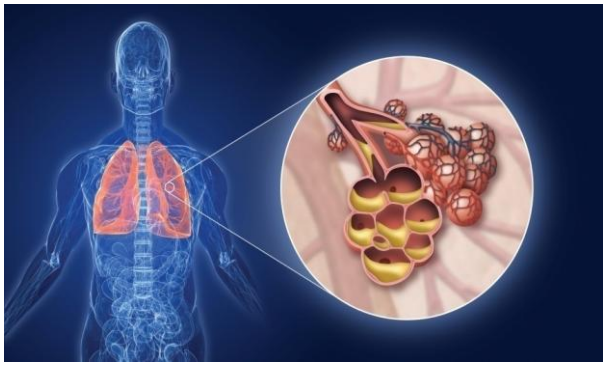
Vertex Cystic Fibrosis Program

CFTR Mutations

Defect in CFTR Protein

Loss of Chloride Transport

Airway dehydration
Reduced cilia beating



Hypothesis

Improving CFTR function will reduce or halt disease progression

Strategy

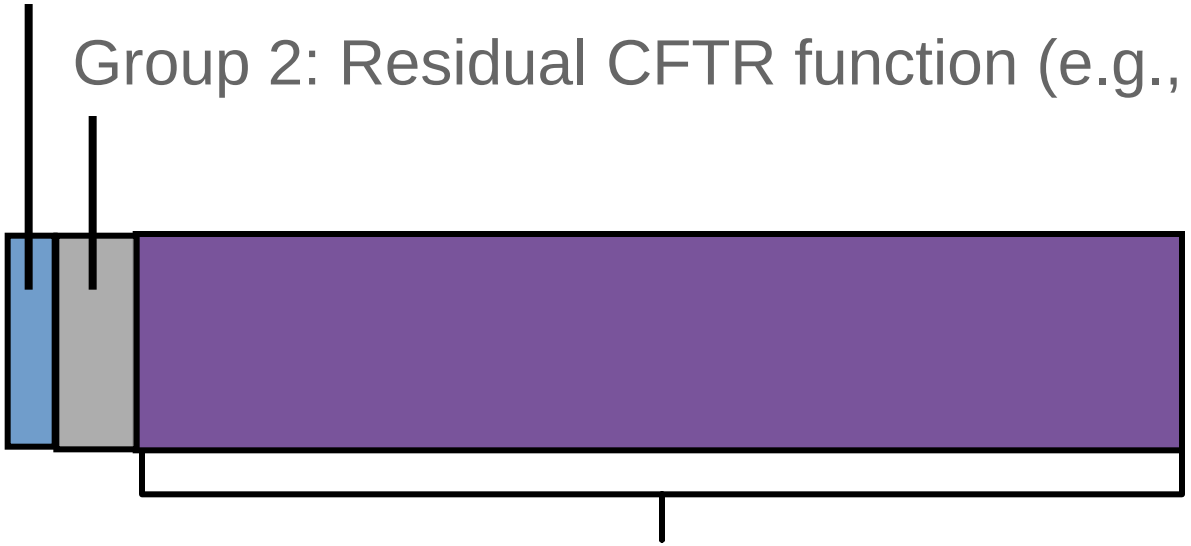
Develop orally bioavailable small molecule CFTR modulators to be used alone or in combination for the treatment of CF

VERTEX

1700+ Mutations: Analysis of the *In Vitro* Data, Sweat Chloride, and Disease Severity Led Us to Identify 3 Groups of CFTR Mutations

Group I: *CFTR* Gating Mutations (e.g., G551D)

Group 2: Residual CFTR function (e.g., R117H, A445E)



Group 3: Minimal CFTR function

- F508del homozygous
- F508del/other
- Other/other

Source: 2009 US CFF Patient Registry

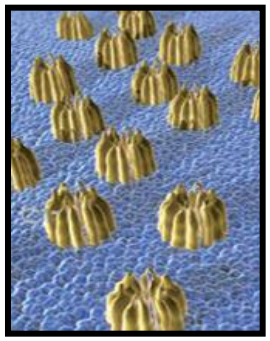
CFTR Mutations Can Affect the Quantity and/or Function of CFTR Channels

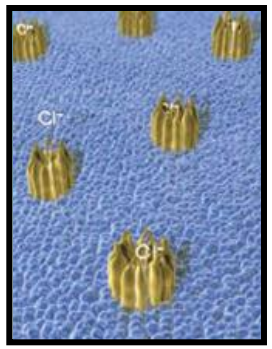
CFTR FUNCTION
at cell surface

- **Gating**
  Channel Opening
- **Conductance**
  Channel Structure

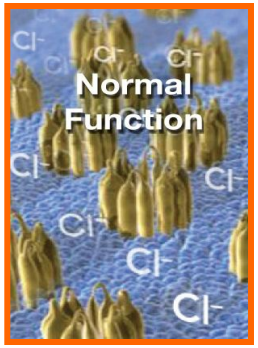
CFTR QUANTITY
at cell surface

- **Little to no CFTR**
- **Some CFTR**





Potentiators
increase channel activity of CFTR protein located at the cell surface



Correctors
increase delivery & amount of functional CFTR protein to the cell surface

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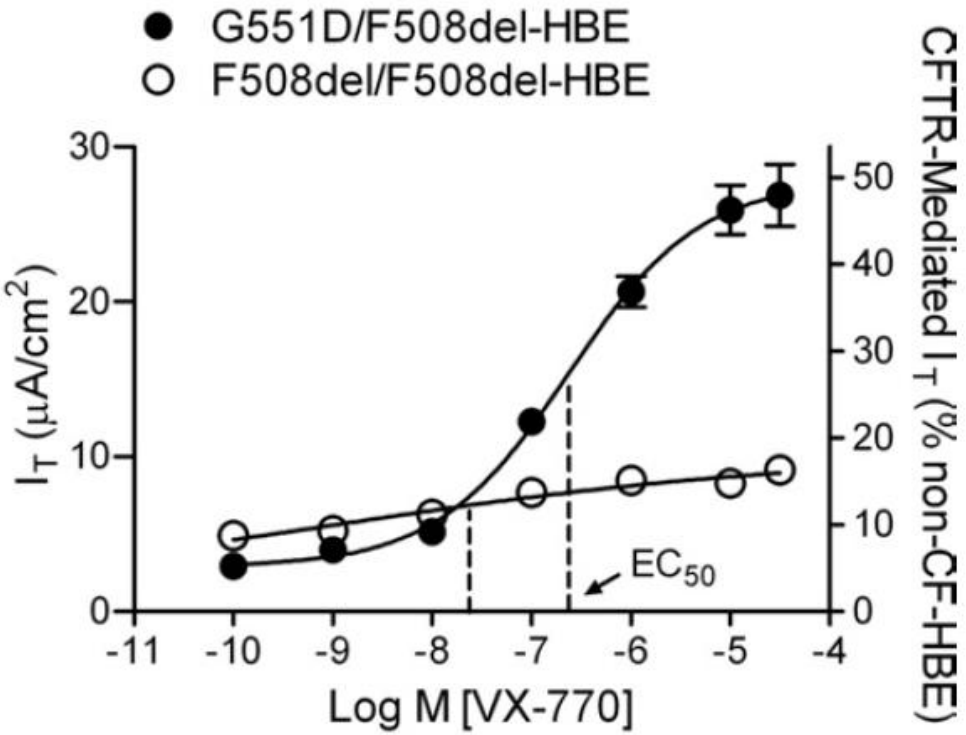
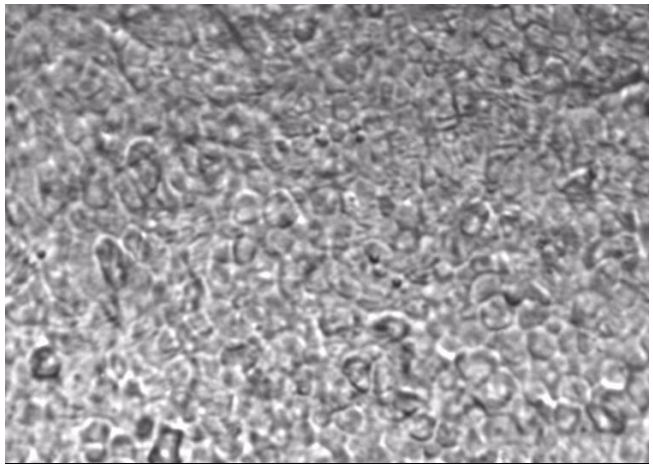
In Vitro Evidence that CFTR Modulators Restore Downstream Defects Believed to Cause Lung Disease

Cultured Airway Cells From a G551D CF Patient

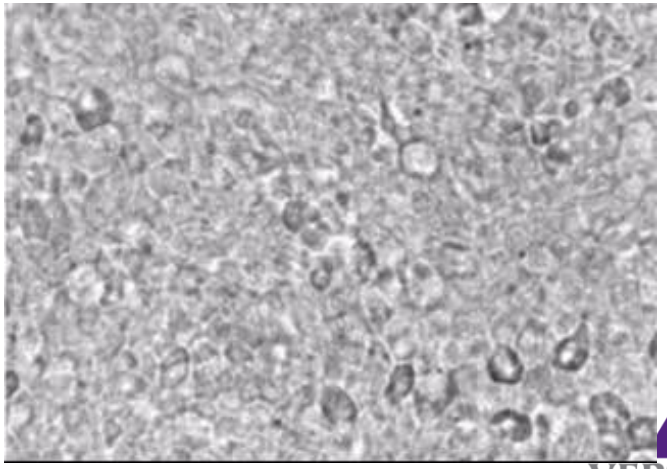


Source: Van Goor et al., PNAS 2009

No Ivacaftor



With Ivacaftor



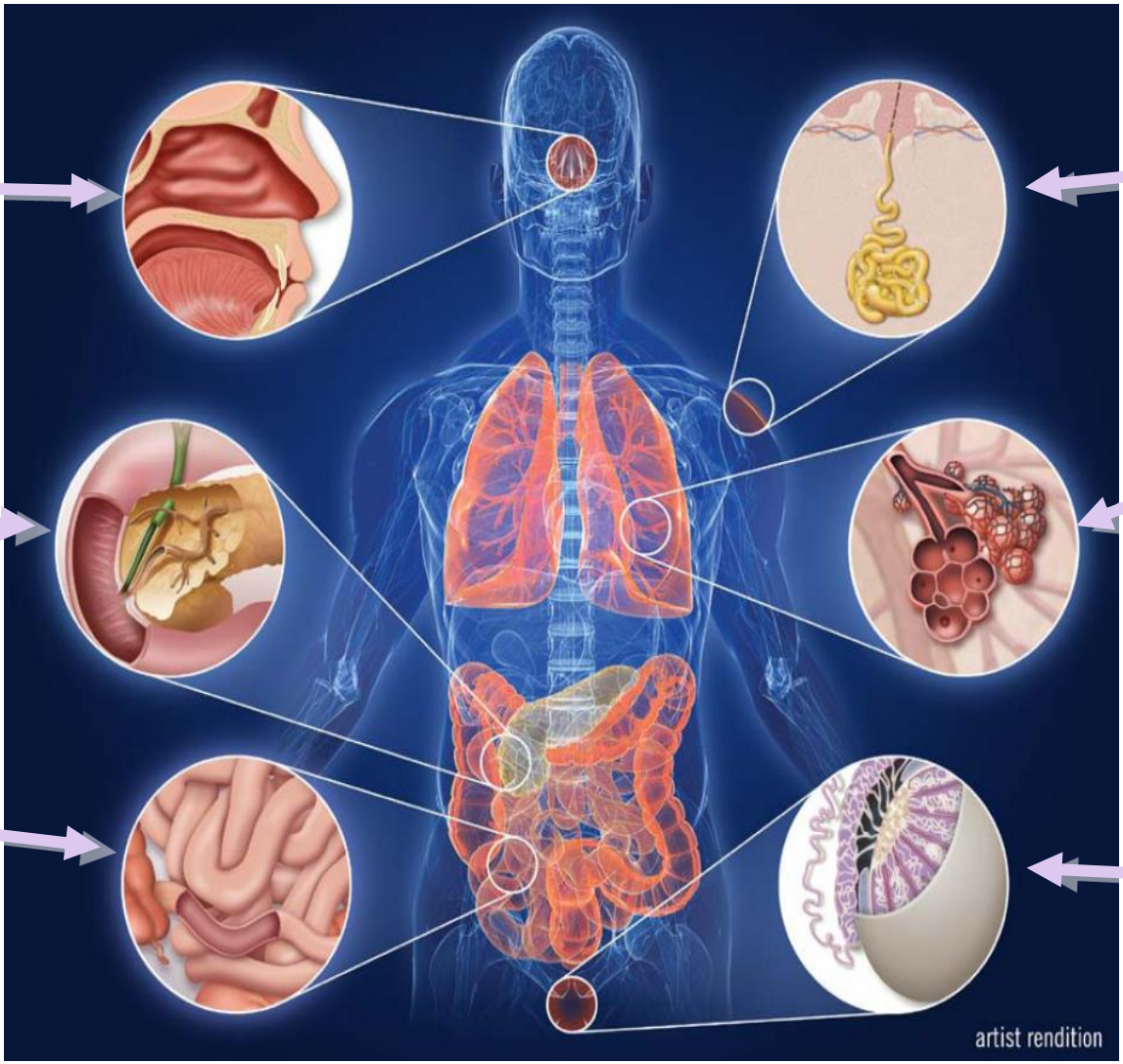
CF is a Multi-Organ Disease

Sinus problems
Nasal polyps

Pancreatic dysfunction

Malnutrition

Digestive problems
Intestinal blockages
Fatty bowel movements



Salty sweat

Reduced lung function
Frequent lung infections

Reproductive problems

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Ivacaftor Phase 3 Registration Program

Targeting the Fundamental Mechanism of CF Disease

Registration program focused on G551D patients

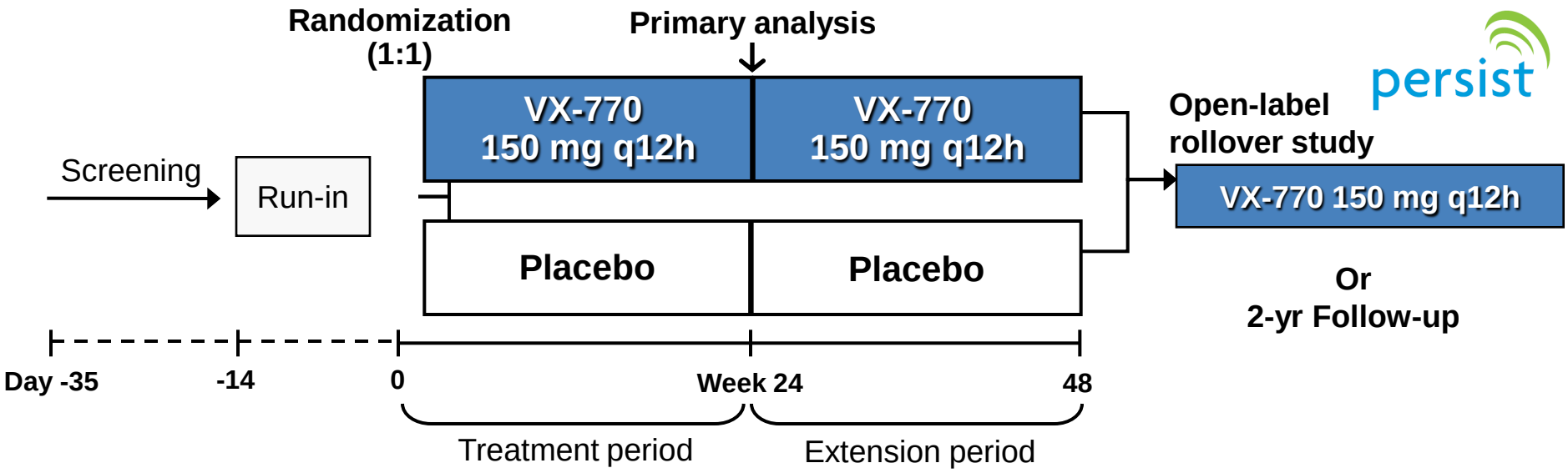
~340 patients across three trials

NDA and MAA submissions in October 2011,
FDA Approval January 2012

- strive — G551D Subjects aged 12 and older
- envision — G551D Subjects aged 6 to 11
- discover — Safety study in subjects homozygous for F508del mutation
- persist — Open-label, rollover extension trial that enrolled subjects who completed STRIVE and ENVISION.

VERTEX

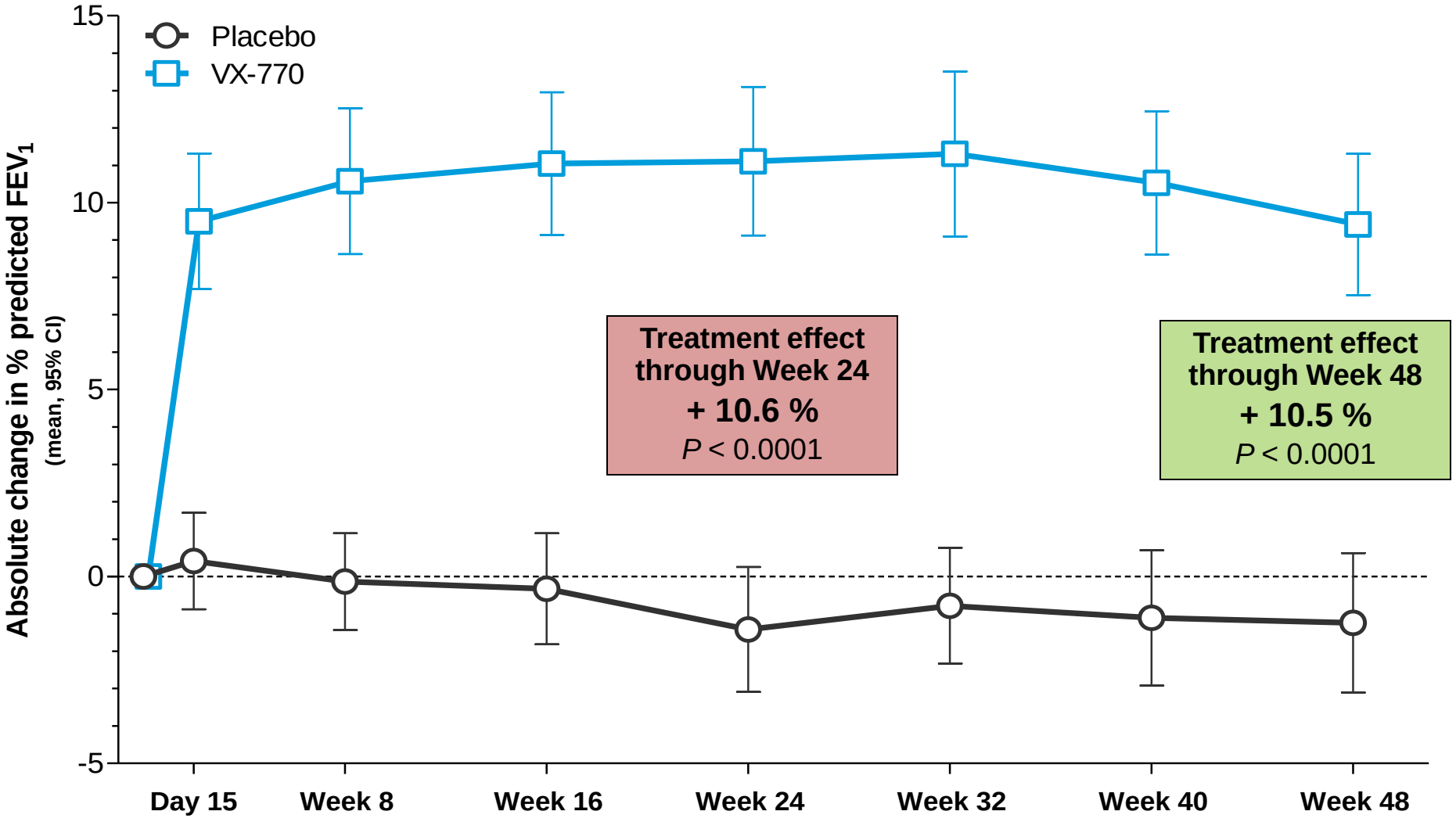
STRIVE: Phase 3 Study Design



- Trial sized to detect a 4.5% absolute change in percent predicted FEV_1 at 80% power based on Phase 2 study
- Key inclusion criteria
  - G551D mutation on at least one CFTR allele
  - Aged ≥ 12 years
  - FEV_1 40% to 90% predicted

B Ramsey et al, NEJM 2011;365:1663-72

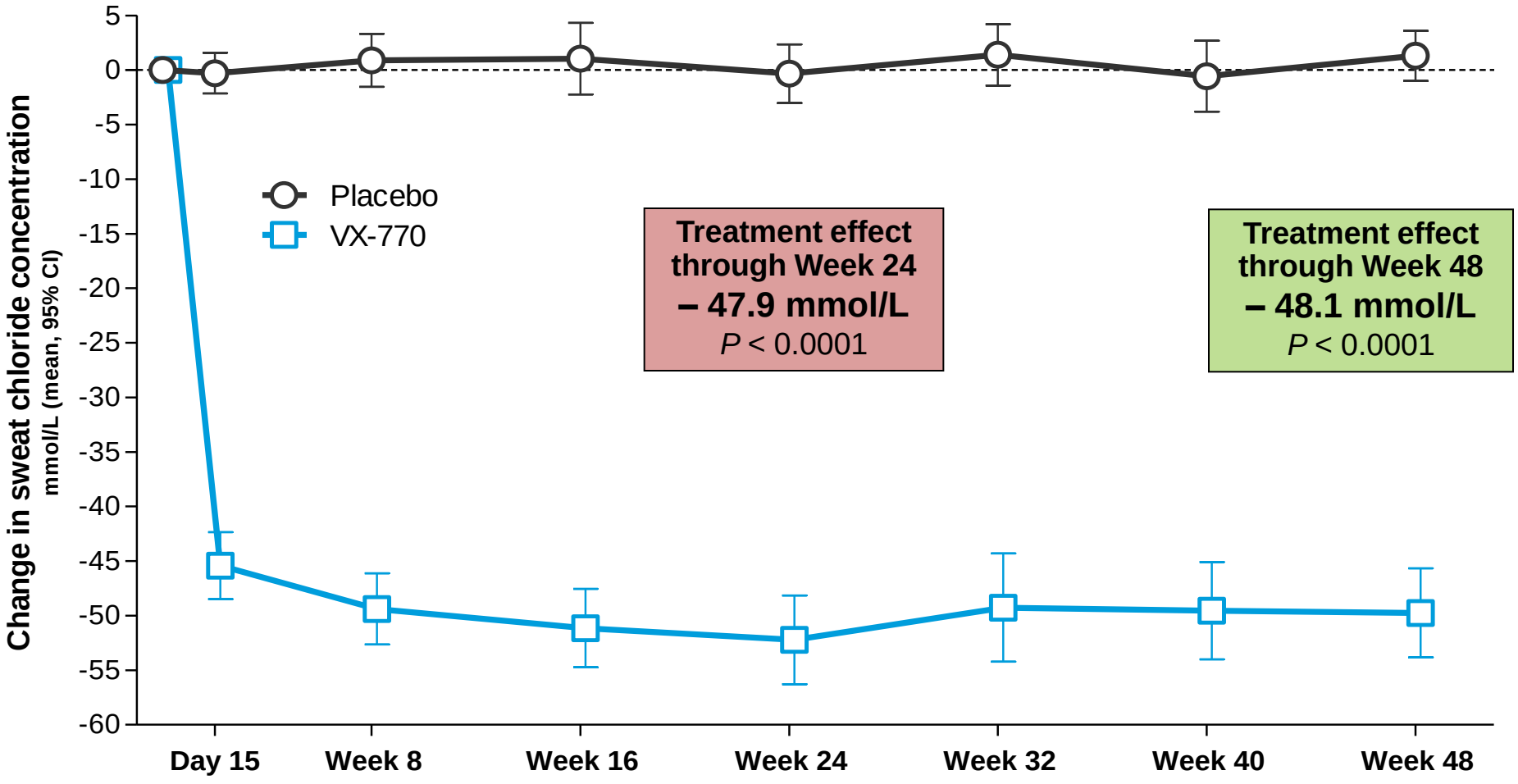
STRIVE: FEV_1 % Predicted Absolute Change from Baseline



Treatment effects are point estimates of VX-770 minus placebo using a mixed model for repeated measures
Values shown at each visit obtained from descriptive statistics, not model-derived measures

B Ramsey et al, NEJM 2011;365:1663-72

STRIVE: Change from Baseline in Sweat Chloride



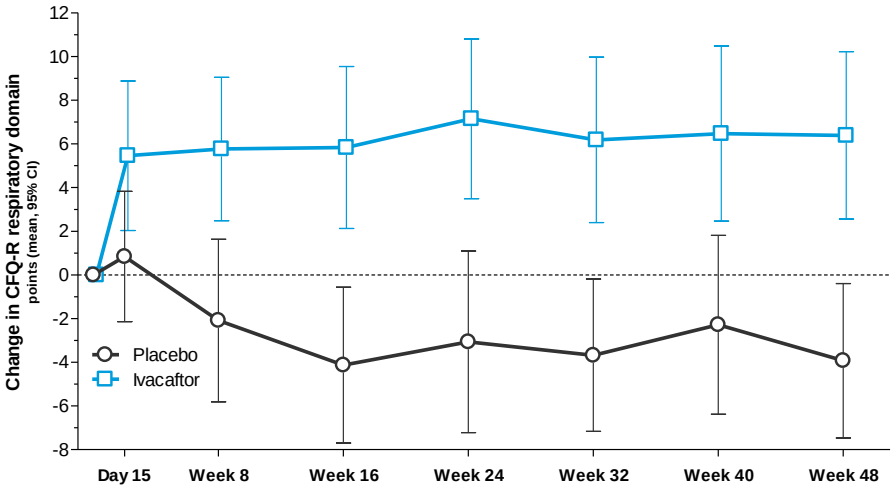
B Ramsey et al, NEJM 2011;365:1663-72

STRIVE: Changes from Baseline in CFQ-R Respiratory Domain and Weight

Change from Baseline in CFQ-R Respiratory Domain

Treatment effect through Week 24 + 8.1 *P* < 0.0001

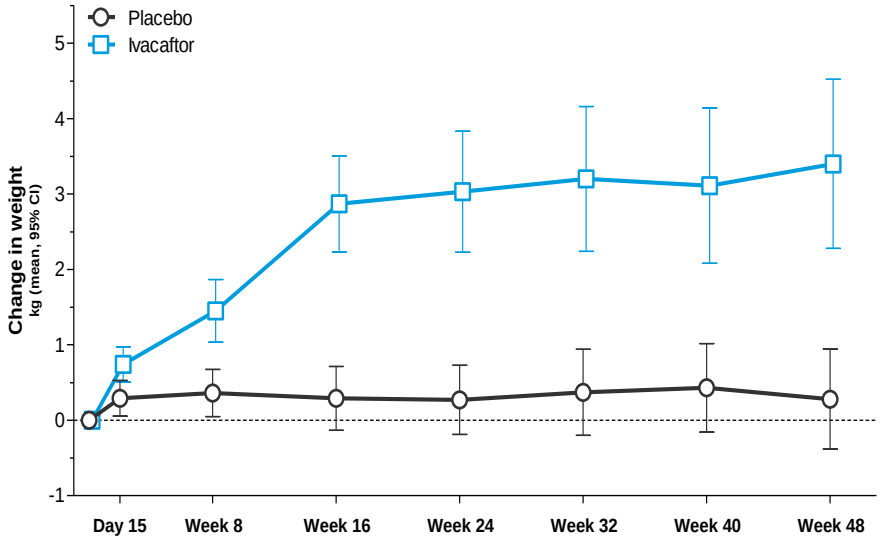
Treatment effect through Week 48 + 8.6 *P* < 0.0001



Change from Baseline in Weight

Treatment effect at Week 24 + 2.8 kg *P* < 0.0001

Treatment effect at Week 48 + 2.7 kg *P* = 0.0001



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

Pooled data from Adolescent/Adult and Children versions
Established minimal clinically important differences (MCID) for respiratory domain is 4 (Quittner et al 2009)

B Ramsey et al, NEJM 2011;365:1663-72

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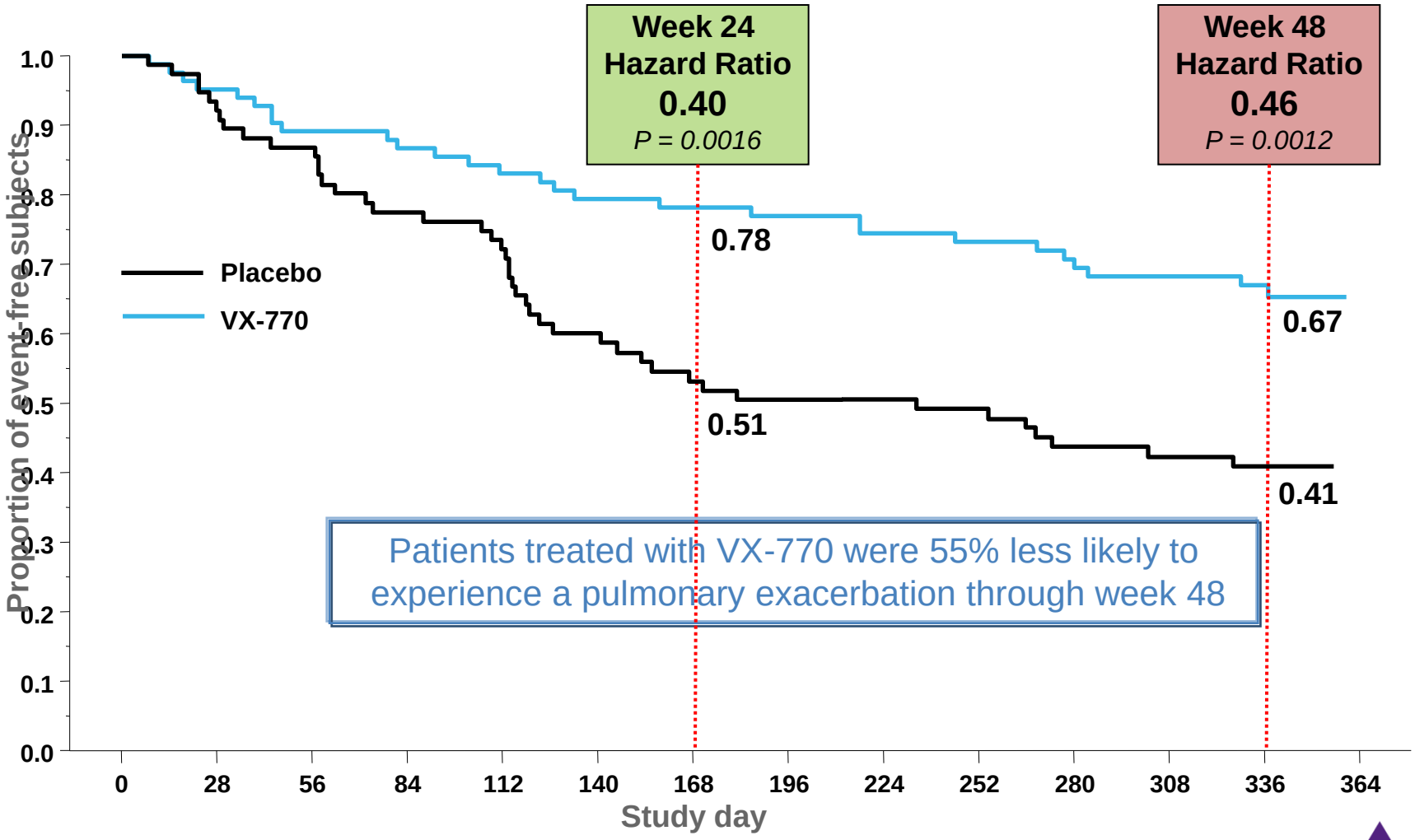
STRIVE: Time-to-First Pulmonary Exacerbation

Modified Fuchs' criteria



B Ramsey et al, NEJM 2011;365:1663-72

STRIVE: 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)

B Ramsey et al, NEJM 2011;365:1663-72

STRIVE: Results Summary

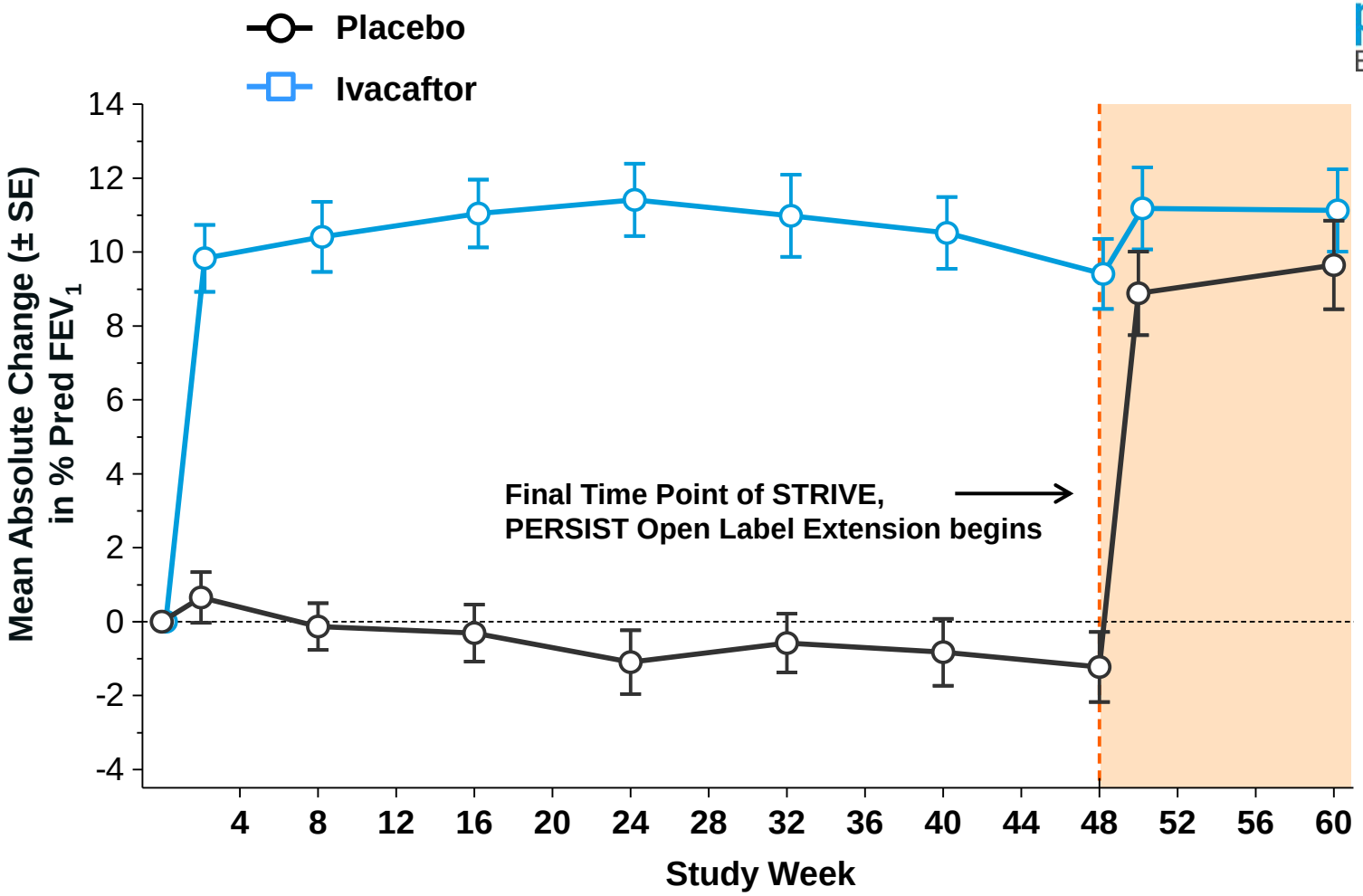
- Primary endpoint (absolute change in percent predicted FEV_1) achieved with a clinically meaningful magnitude of effect
  - **10.6%** absolute improvement in FEV_1 % predicted from baseline compared to placebo
- 16.7% relative improvement in FEV_1 % predicted from baseline compared to placebo
- Lung function improvements were rapid in onset and durable through 48 weeks
- Pattern of improvement in CFTR function mirrored improvements in lung function
- Sustained improvements through week 48 in other clinically important outcomes were observed, including risk of exacerbation, weight gain, and respiratory symptoms
- Adverse Events reported were similar between the Ivacaftor and Placebo arms
- No important safety concerns identified for administration of Ivacaftor 150 mg q12h for 48 weeks

B Ramsey et al, NEJM 2011;365:1663-72

VERTEX

Mean Absolute Change From STRIVE Baseline in % Pred FEV_1 by Treatment

persist
Extension trial



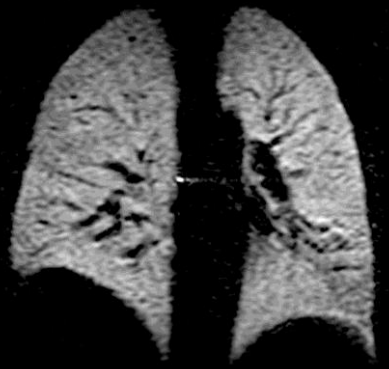
Points and 95% confidence interval (CI) are unadjusted (raw).

McKone E et al. NACFC; November 3-5, 2011; Anaheim, CA; poster 204

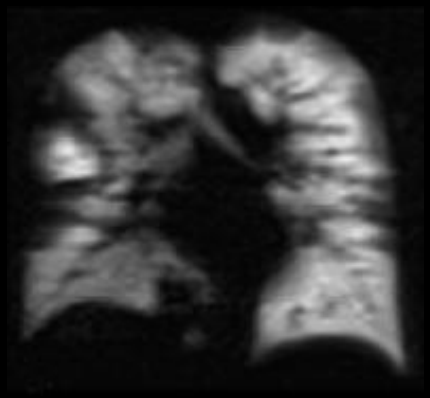
VERTEX

Hyperpolarized ^{3}He Ventilation Imaging

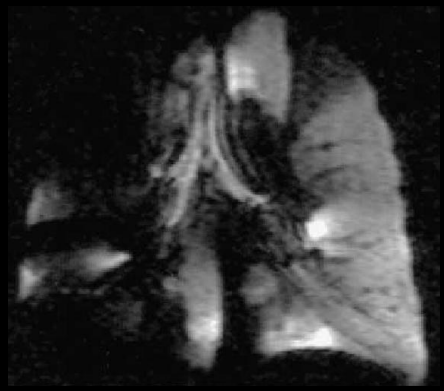
Healthy

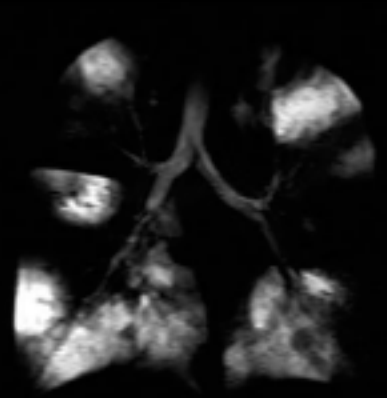


Smoker

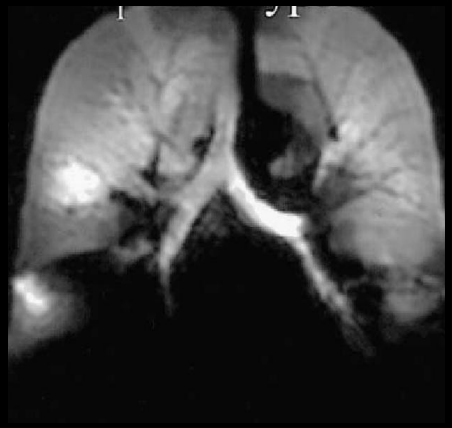


COPD

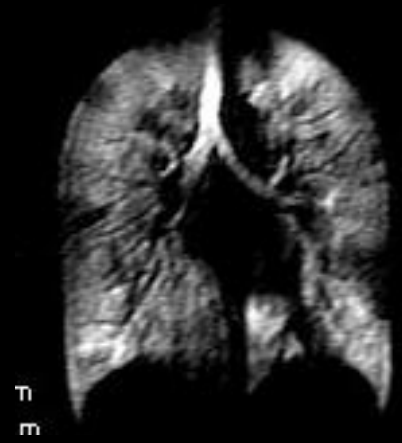




Cystic Fibrosis



Asthma

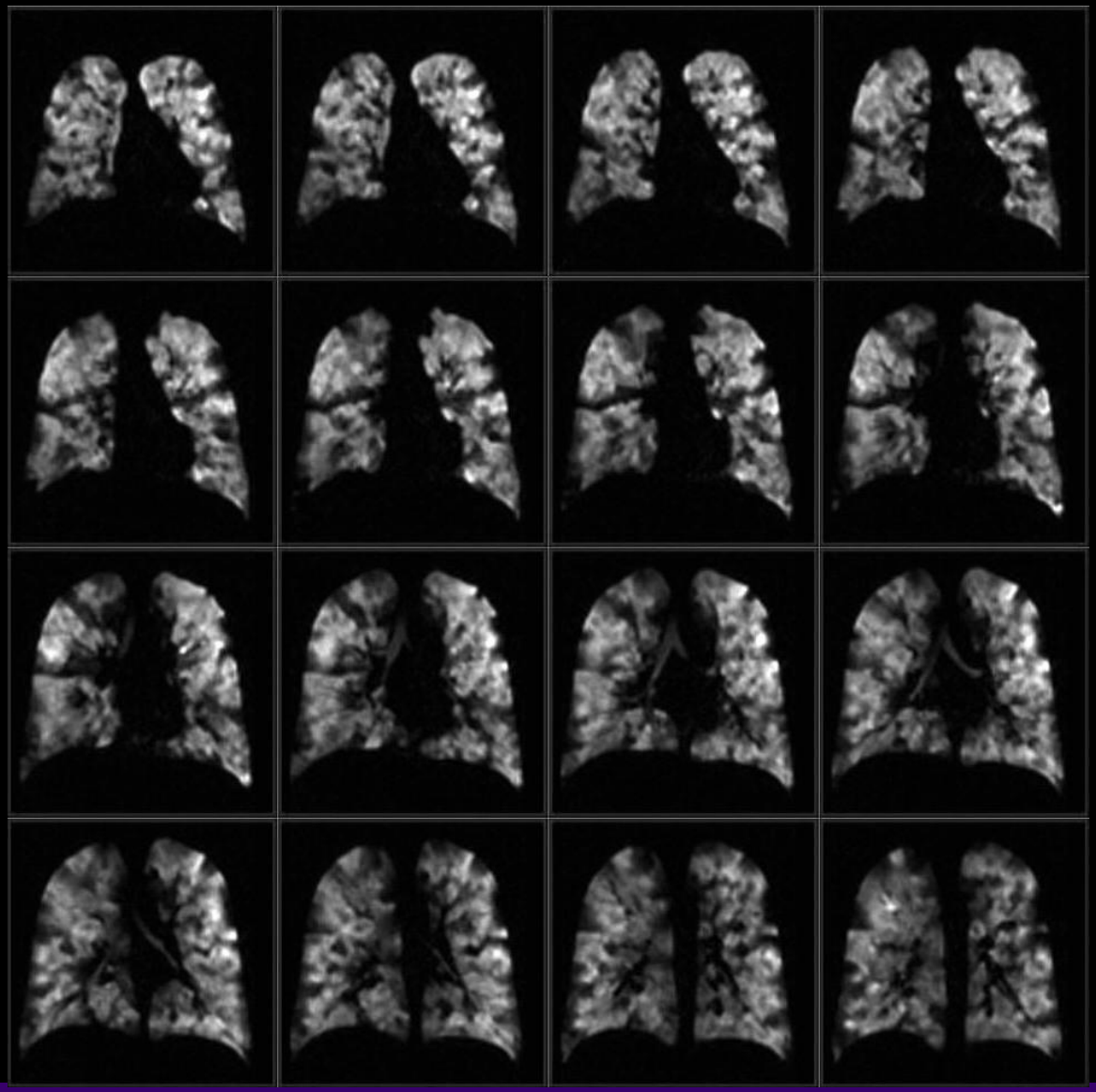


α-1 antitrypsin def

Mitchell Albert, UMass Medical School

VX770-025002: Visit 2 (Day 15)

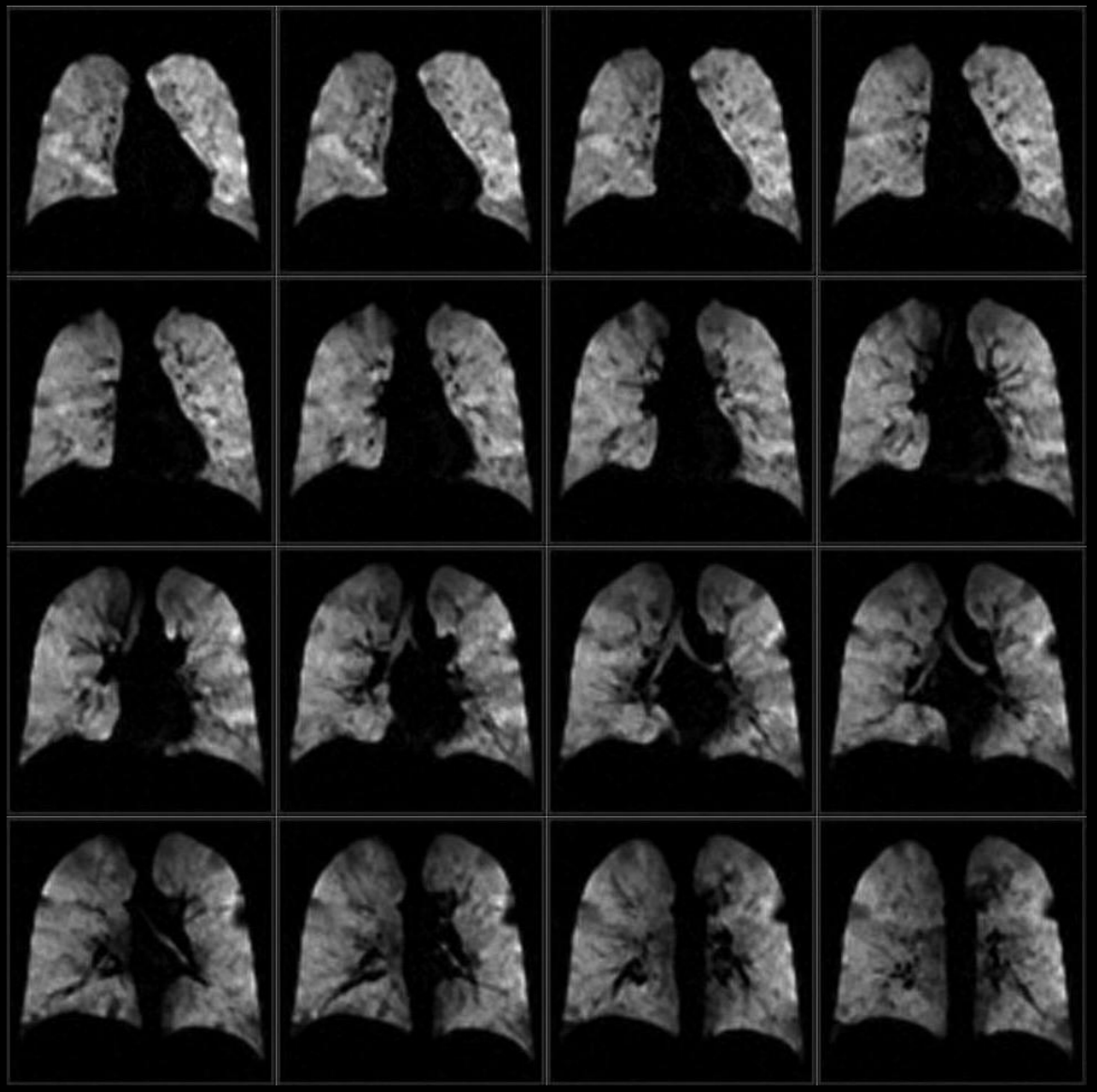
FEV1: 62 %pred (2.72 L)



Placebo: 2 wks

VX770-025002: Visit 4 (Day 43)

FEV1:
83 %pred
(3.63 L)

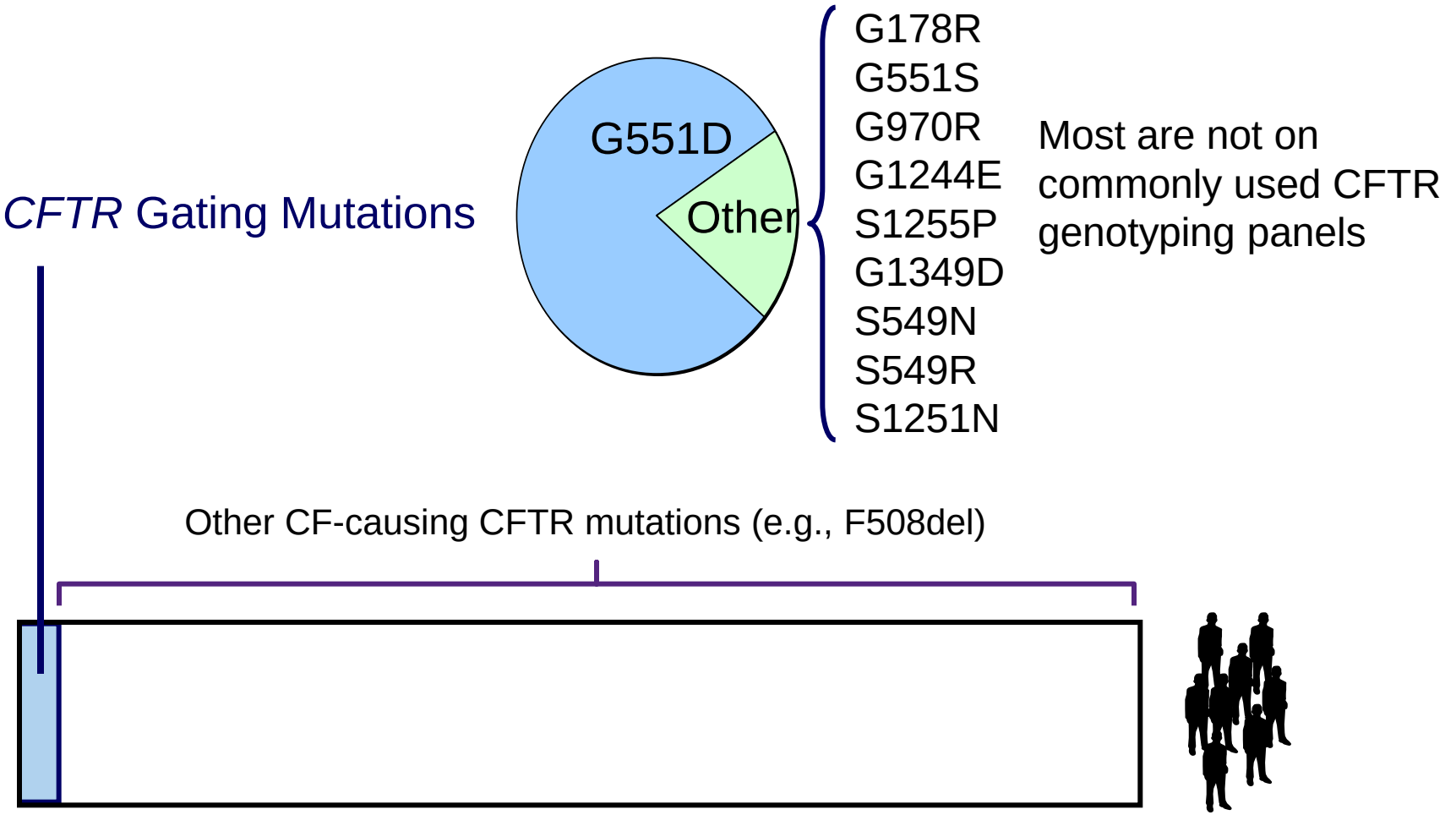


VX770:
4 wks

Beyond G551D

- Other Gating and Residual function mutations
- Trafficking mutations

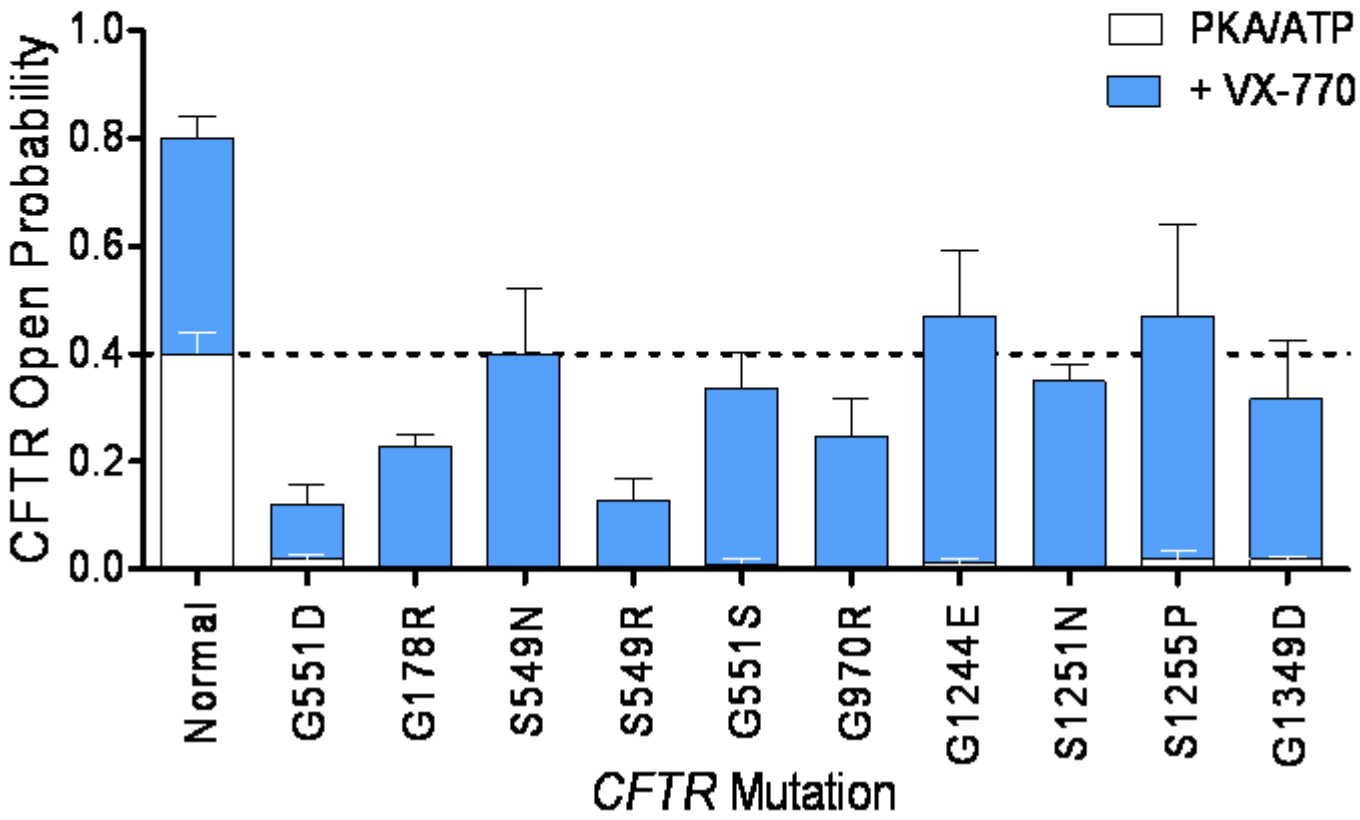
Approximately 5% of Patients with CF Have a *CFTR* Gating Mutation



Bobadilla et al. Hum Mutat. 2002 Jun;19(6):575-606; http://genet.sickkids.on.ca; European CF Society Patient Registry; 2009 US CFF Patient Registry

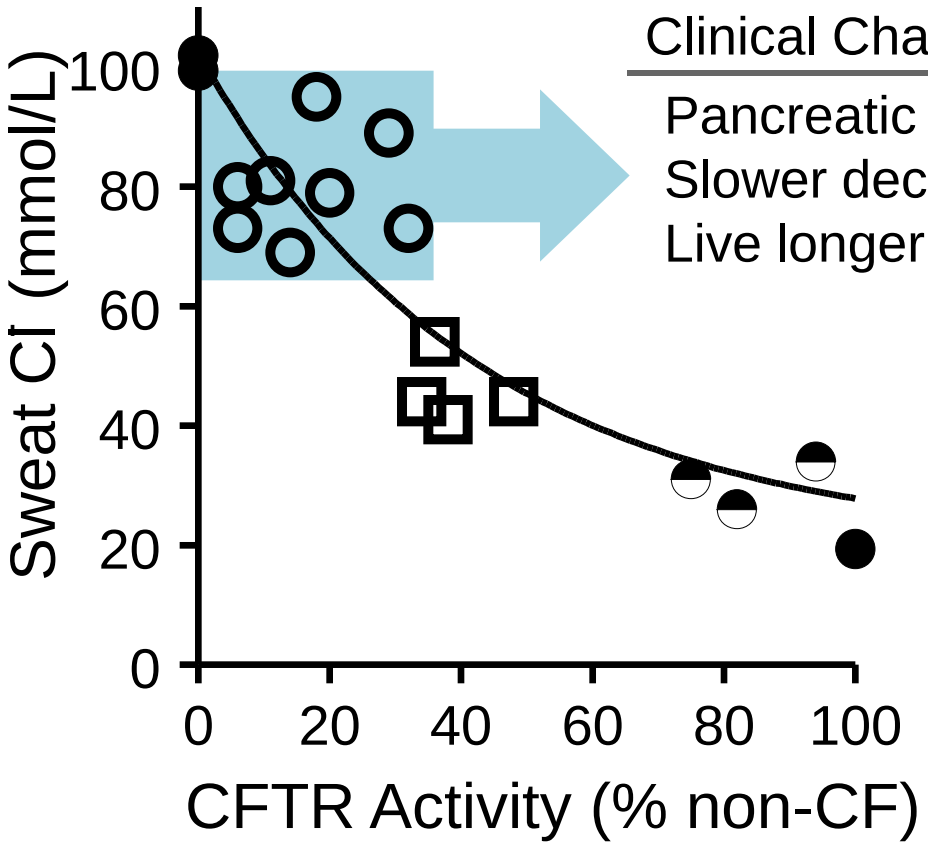
VX-770 Increased the Channel Open Probability of CFTR Produced by all *CFTR* Gating Mutations Tested

Mutant CFTR expressed in Fischer rat thyroid cells



Van Goor F et al. NACFC; November 3-5, 2011; Anaheim, CA; abst 10

Residual CFTR function results in less severe CF



Clinical Characteristics

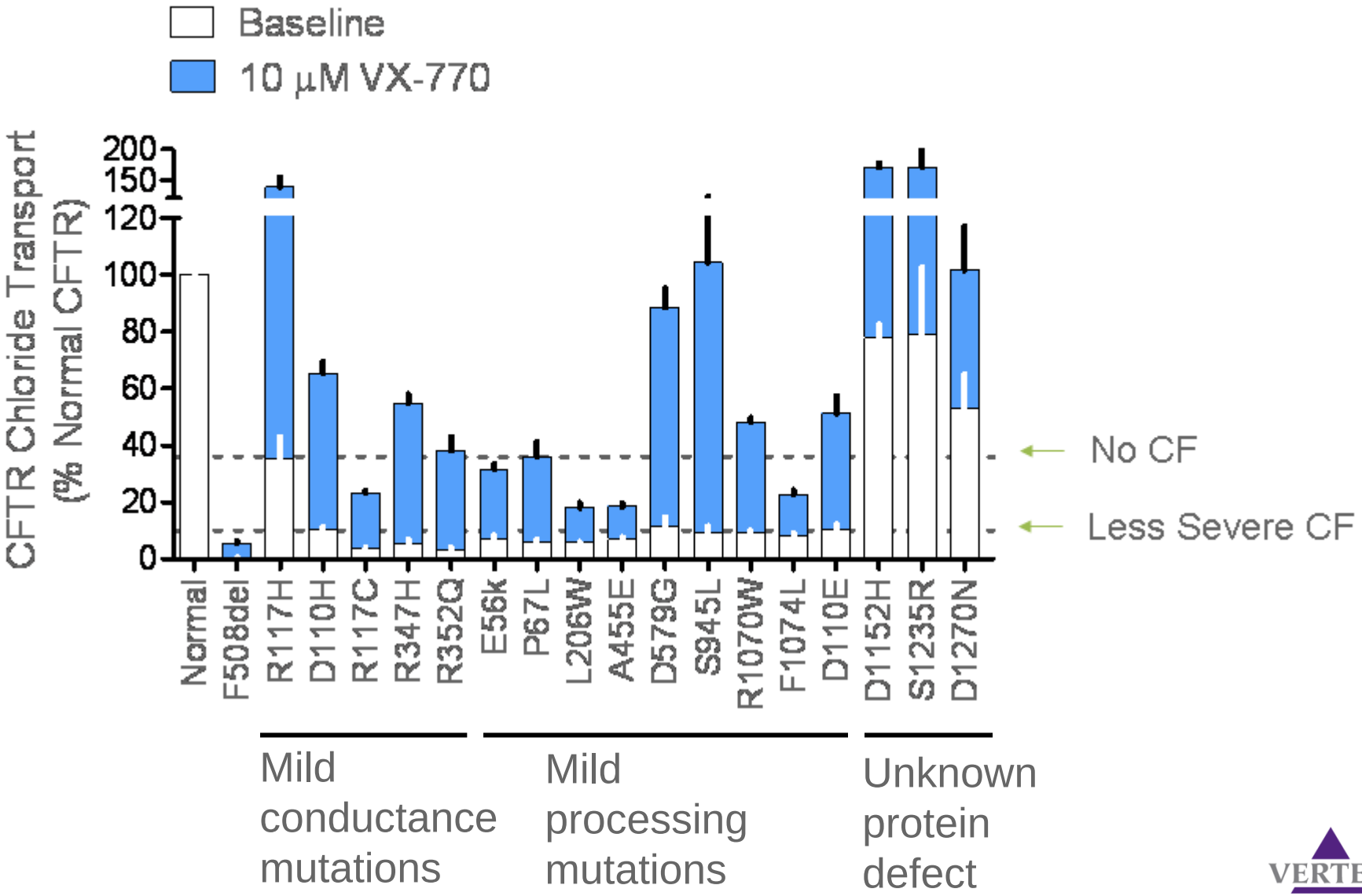
Pancreatic sufficient
Slower decline in FEV_1
Live longer

Sample Mutations

R117H
R117C
D110H
R347H
R352Q
E56K
P67L
L206W
A455E
D579G
S1235R
S945L
R1070W
F1074L
D110E

Sources: Davis et al., Am J Respir Crit Care Med. 1996; McKone et al., Lancet. 2003; Noone et al., Am J Respir Crit Care Med. 2000; Noone et al., Gastroenterology. 2001; Strausbaugh Clin Chest Med. 2007

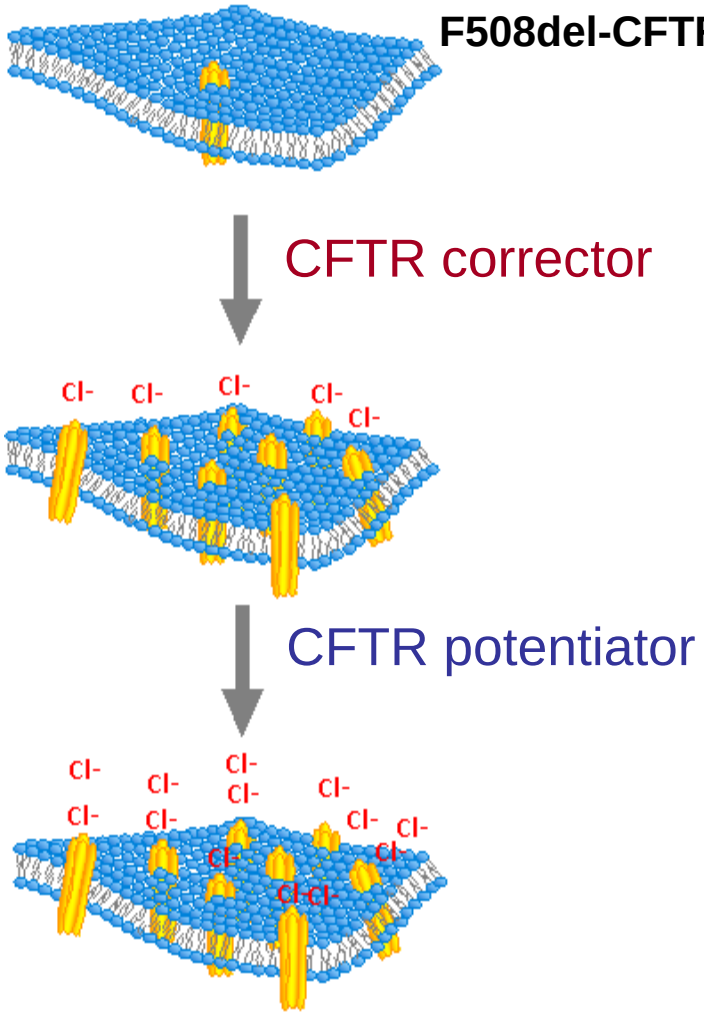
VX-770 Potentiates Mutant CFTR Forms Associated with Residual CFTR Function

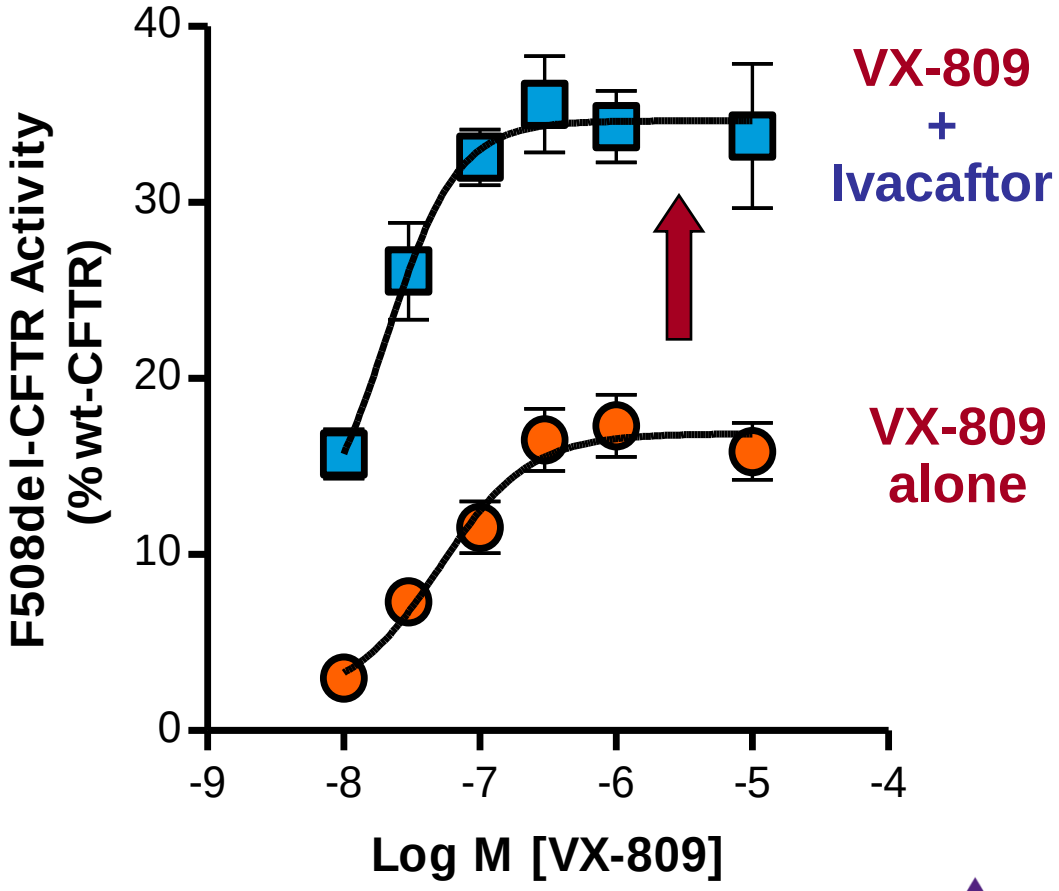


Conclusions

- In Vitro studies show:
  - Ivacaftor potentiated all tested mutant CFTR forms produced by *CFTR* gating mutations
    - G551D, G178R, G551S, G970R, G1244E, S1255P, G1349D
  - Three additional *CFTR* gating mutations were identified which were also potentiated by ivacaftor
    - S549N, S549R, S1251N
- These data support the potential for benefit of ivacaftor in patients with CF who have *CFTR* gating mutations beyond G551D.

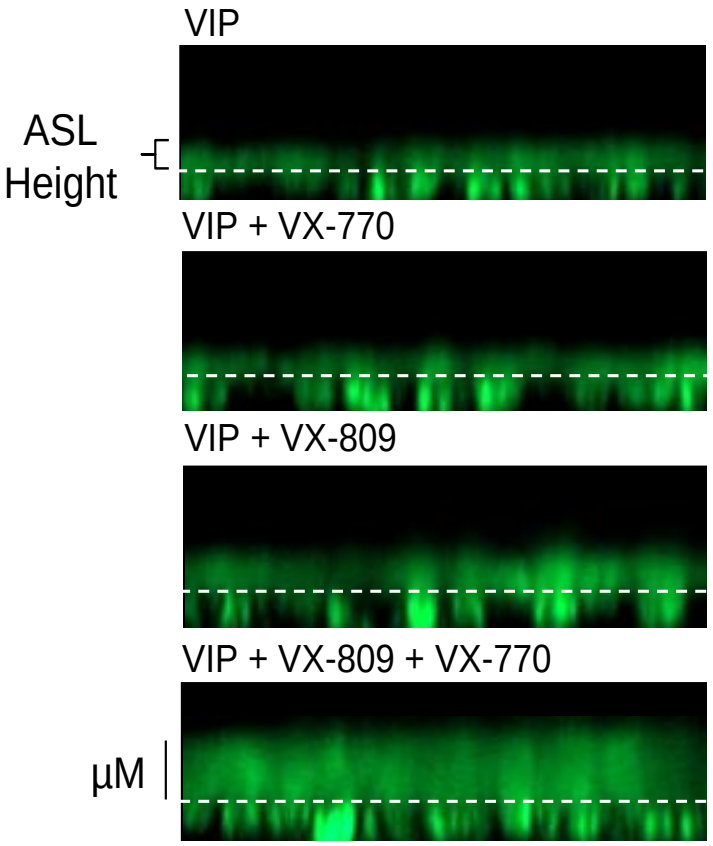
Combination Approach: CFTR Potentiator Ivacaftor (VX-770) Doubled the *In Vitro* Activity of VX-809

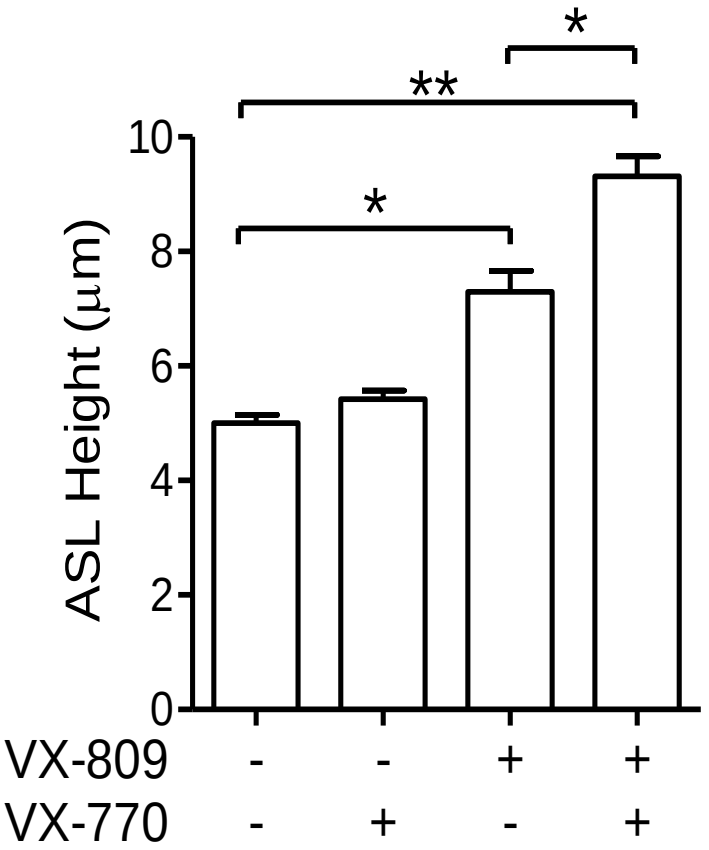




Van Goor et al. Pediatr Pulmonol 2009;44(S32):154absS9.4

VX-809 and ivacaftor increased fluid transport in F508del-HBE

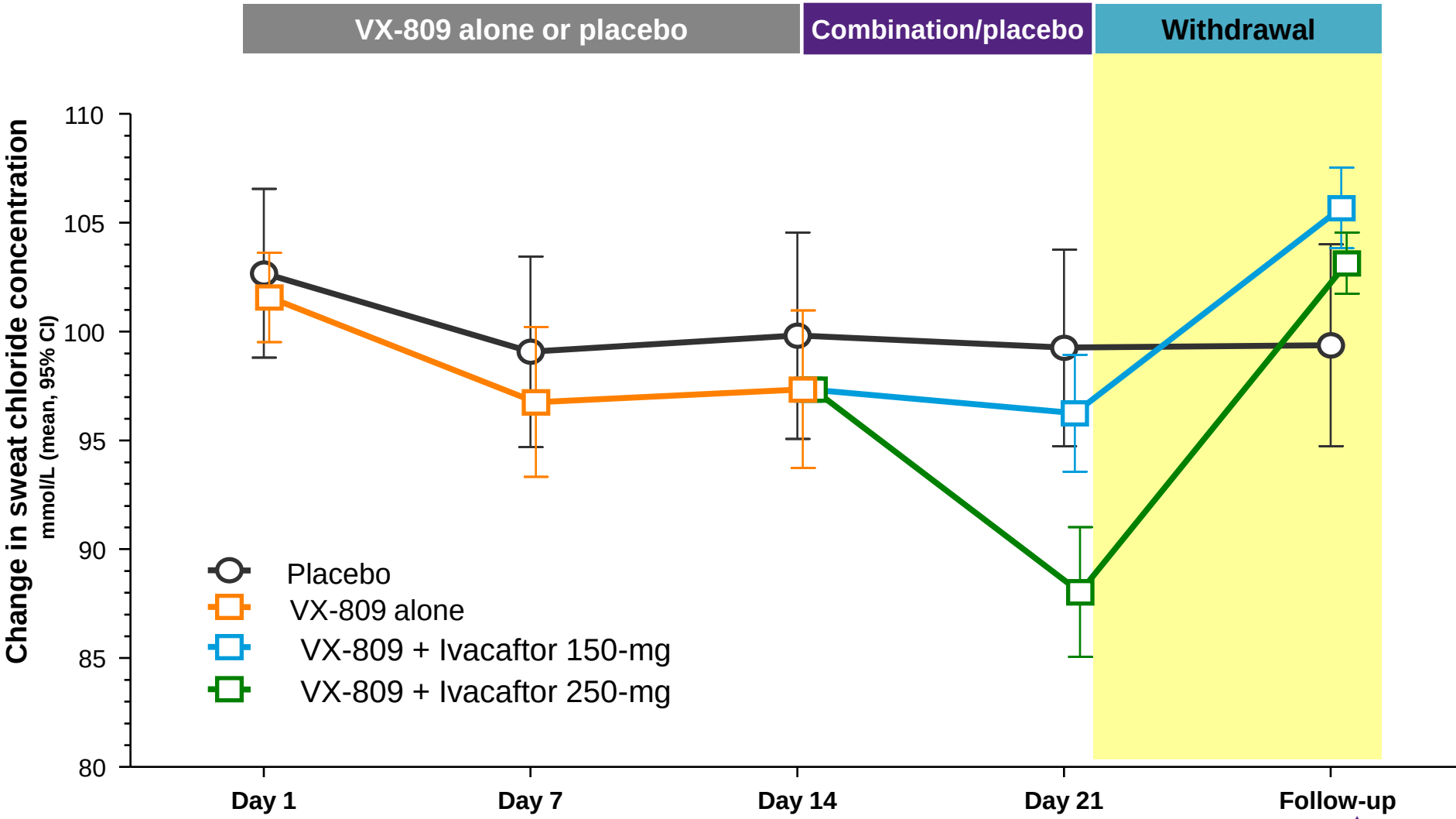




* $p < 0.05$; ** $p < 0.01$ (ANOVA)
Non-CF HBE + VIP = 21 ± 2 µM

Van Goor et al., PNAS 2011

Effect of Combination of VX-809 + Ivacaftor in Subjects with CF Homozygous for *F508del-CFTR*



Analysis of evaluable patients

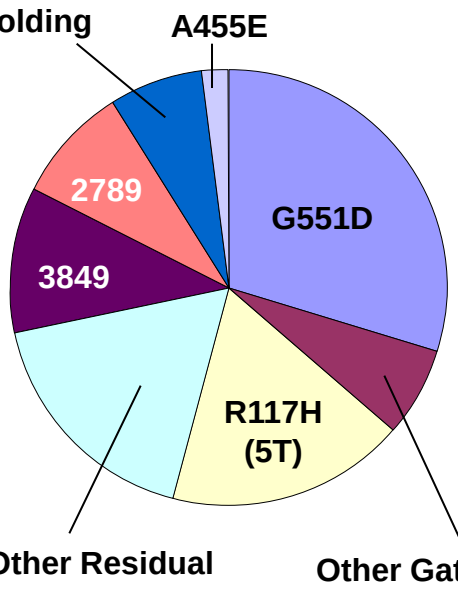
VX-809 Conclusions

- VX-809 is a CFTR corrector
  - Promoted the proper folding of a fraction of F508del-CFTR in the ER to increase its processing and delivery to the cell surface, resulting in enhanced chloride transport
- VX-809 and ivacaftor are additive in vitro
- VX-809 and ivacaftor are additive in subjects with CF who carry two copies of the F508del mutation
- Clinical studies are needed to determine if the improvement in F508del-CFTR function is sufficient to improve lung function

VERTEX

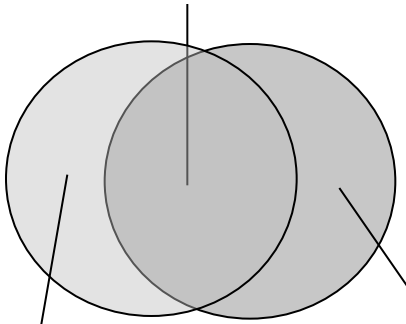
Genotypic and Phenotypic Patient Identification are Complementary

Genotypic Evidence (55 of 1700 known CFTR Mutations) ~ 15% of CF Population

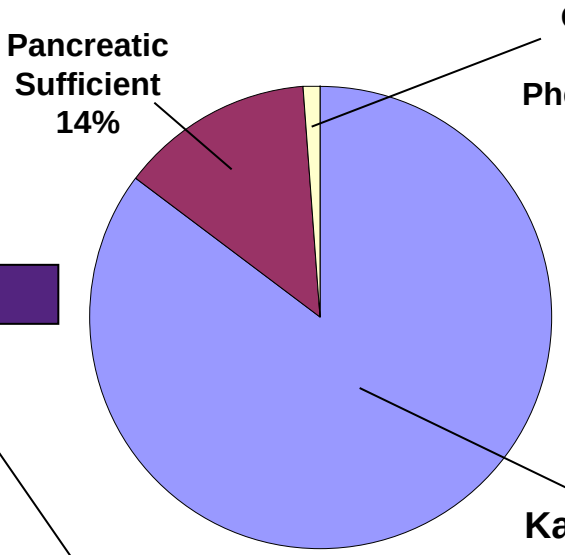


Kalydeco monotherapy potential responders

Molecular and Phenotypic Evidence (residual function + some splice) ~ 7% of CF Population



Phenotypic Evidence ~15% of CF Population (atypical or mild clinical phenotype)



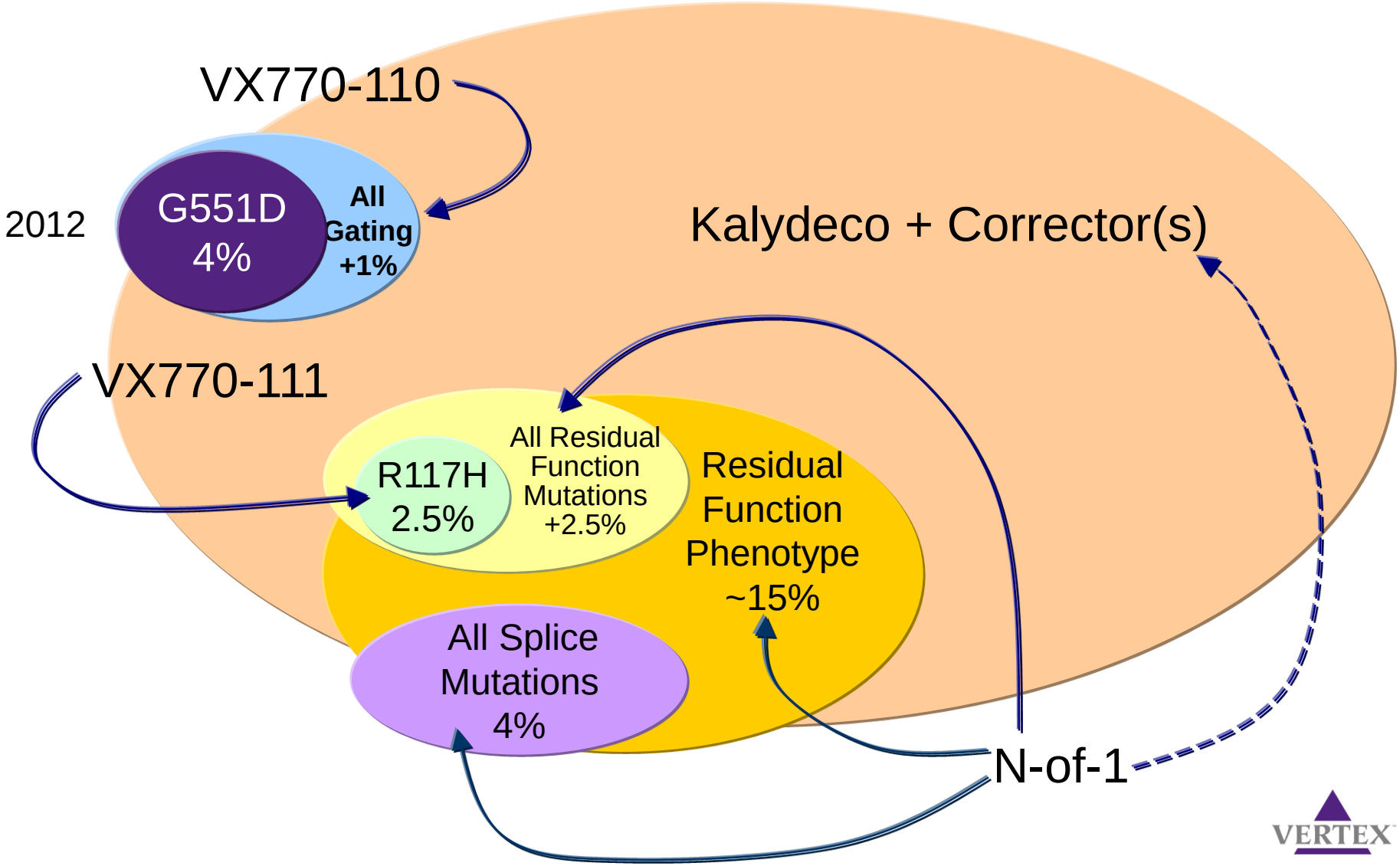
Typical CF phenotype with gating mutation + some splice mutations ~8% of CF population

Atypical CF Phenotype with unknown or uncharacterized genotype ~8% of CF population

VERTEX

How does n-of-1 fit into the lifecycle strategy for Kalydeco?

Potential to identify Kalydeco response in 10-15% of CF population not readily addressed by conventional registration trials.



What are N-of-1 Clinical Trials?

The ultimate small sample randomized clinical trial (SRCT) design

- First used in the 60s for behavioral research
- Essentially a randomized, placebo-controlled repeated cross-over in a single individual
- Remote clinical phenotyping has greatly increased the practicality of N-of-1 clinical trials
- Methodology exists for aggregation of multiple n-of-1 trials to generate information similar to that of a large randomized clinical trial

VERTEX

Efficacy Measures for Response-guided Therapy for CF

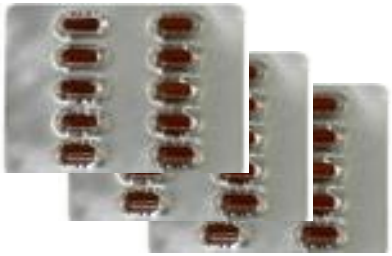
- "Gold-standard" is FEV-1
- Sweat chloride has good positive-predictive value for FEV-1 and weight improvement, but inadequate negative-predictive value
- Lung Clearance Index (LCI) shows promise with less variability than FEV1 – may be useful for mild disease
- Use of ambulatory/home monitoring can improve precision and power relative to traditional, infrequent single-time point data capture.

VERTEX

“Trial in a Box”

Decentralized, Response-guided Therapy

Adherence



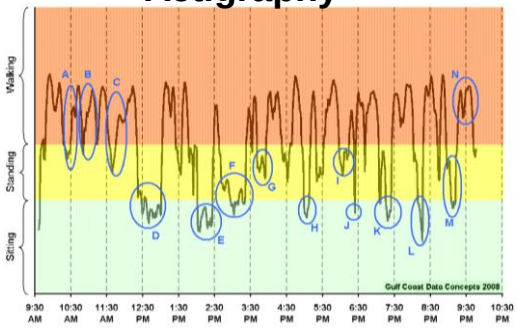
“Smart packaging”

Bluetooth spirometer

Spirometry

Bluetooth accelerometer

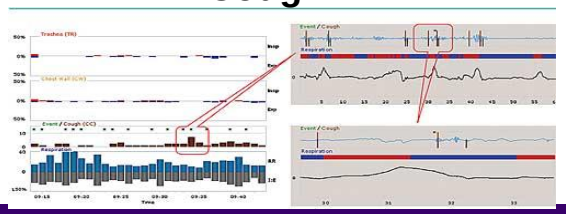
Actigraphy



Training
eDiary
AE logging
Reminders

Biometric fabric

Cough



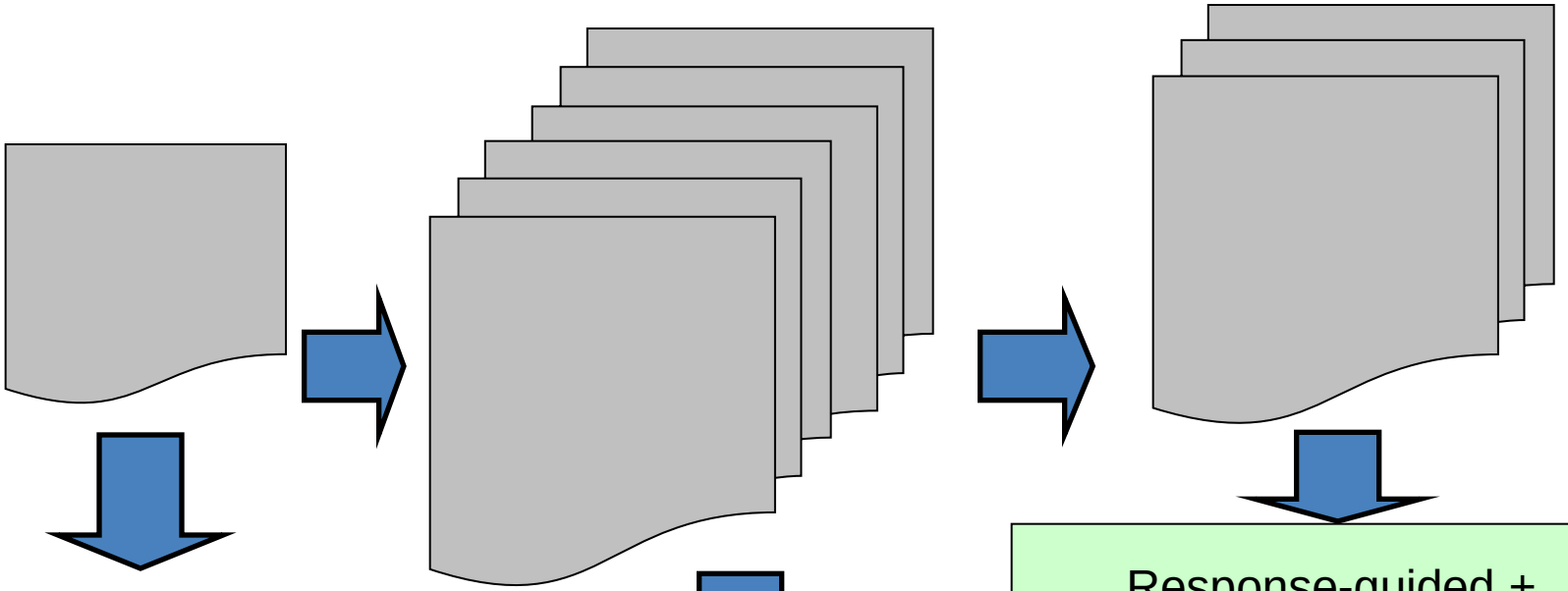
Bayesian Adaptive Model

When n-of-1 is more than 1

Individual n-of-1 result

Meta-analysis of all prior Kalydeco response Information

Informative Kalydeco response subset



Response-guided Treatment Decision

Type-I (false positive) error rate controlled by requirement for multiple, concordant individual responses*

Population Responses

Response-guided + Population-based Treatment Decision

Type-II (false negative) error rate controlled by including results from other informative n-of-1 trials*

Lessons learned:

- Kalydeco – premier example for a personalized medicine approach
- It's not just about genetics/genomics
- Therapeutic success is driven by both genotype and phenotype
- Biomarker situation is complex!
- New clinical development strategies (eg: n=1) could make a difference
- Complete R&D&C integration is essential
- Early involvement of regulators and payers is key
- New regulatory guidelines and global harmonization needed

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CF Foundation

Clinical Investigators and their teams

People with CF

National Patient Organizations

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