Pharmacogenomics in Rare Diseases: Development Strategy for Ivacaftor as a Therapy for Cystic Fibrosis

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VERTEX

Is there an “or” in rare diseases or personalized healthcare regarding clinical study design?

- Rare Diseases
  - Small number of patients
  - Genetic markers
  - Challenging clinical study design issues
    - Safety
    - Efficacy
- Personalized Healthcare
  - Small number of patients
  - Genetic markers
  - Challenging clinical study design issues
    - Safety
    - Efficacy

VERTEX

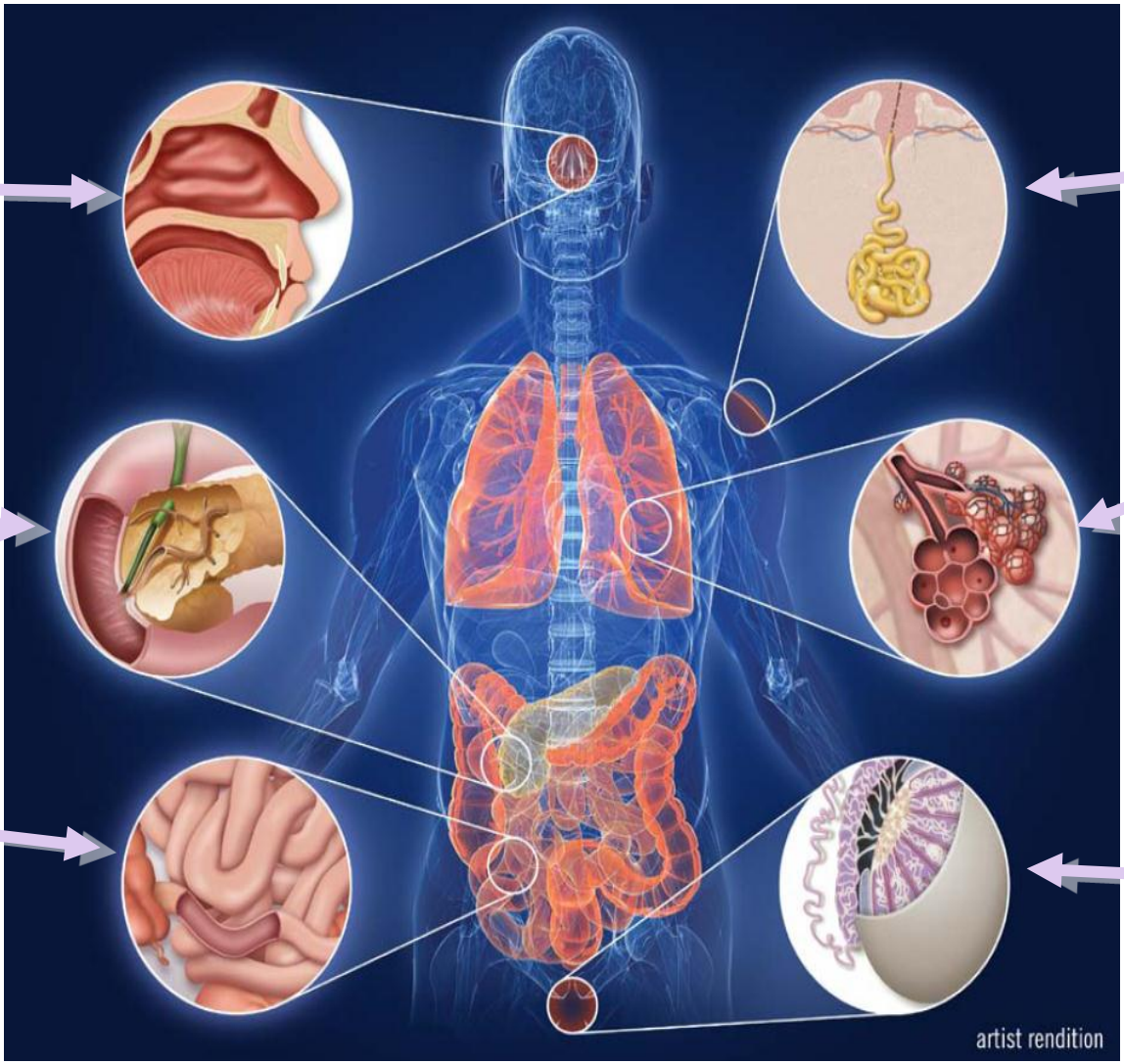
CF is a Multi-Organ Disease

Sinus problems
Nasal polyps

Pancreatic dysfunction

Malnutrition

Digestive problems
Intestinal blockages
Fatty bowel movements



Salty sweat

Reduced lung function
Frequent lung infections

Reproductive problems

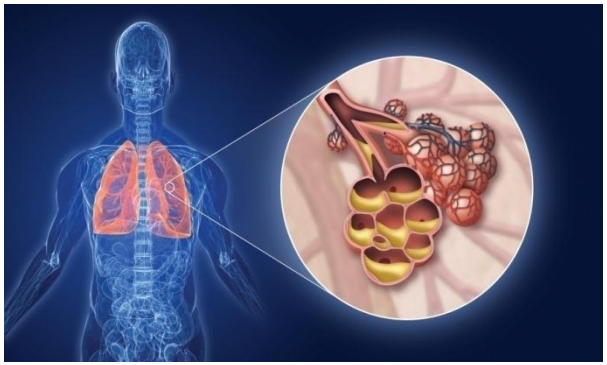
Vertex Cystic Fibrosis Program

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

Targeting the Fundamental Mechanism of CF Disease

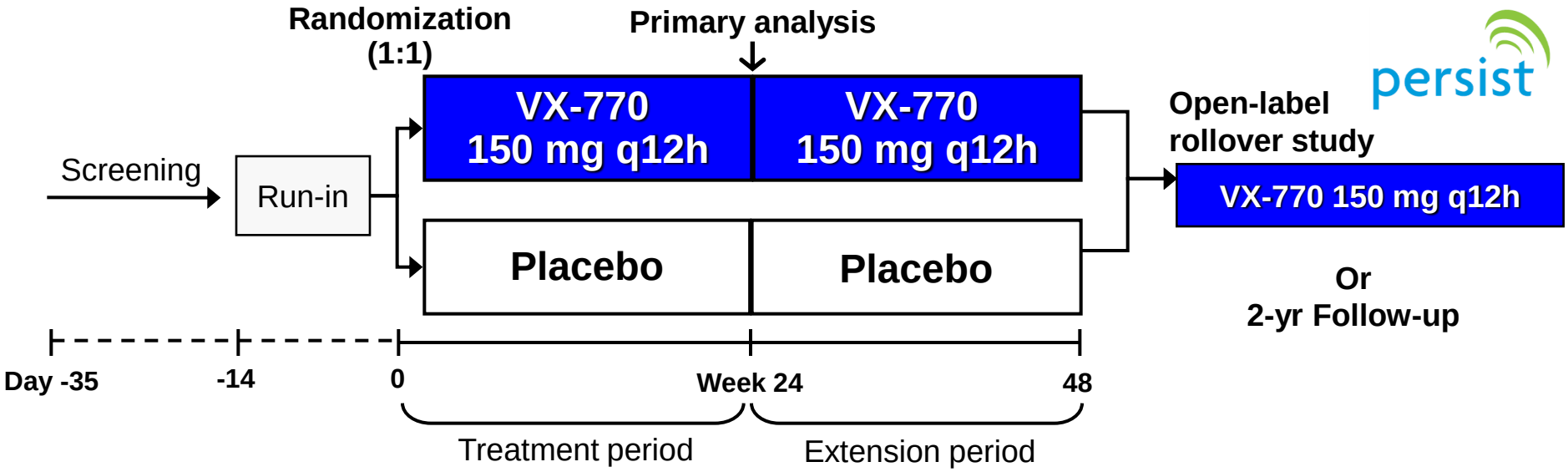
Registration program focused on G551D patients ~340 patients across three trials

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

- ☑ strive — Subjects with CF who have the G551D mutation and are 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

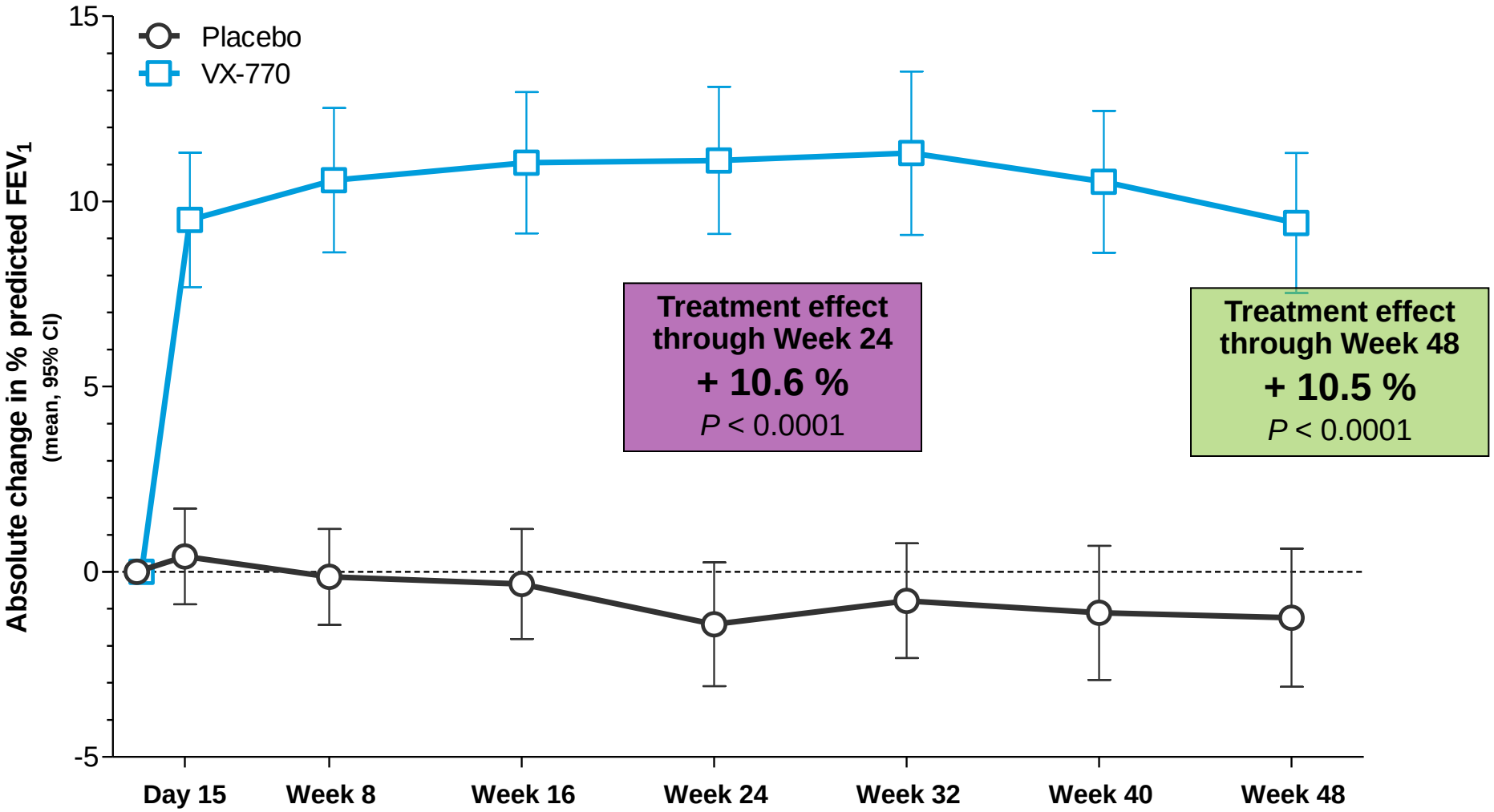
STRIVE: Phase 3 Study Design



- 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

VERTEX

STRIVE: Absolute Change from Baseline in Percent Predicted FEV1



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

VERTEX

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 percent predicted FEV_1 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

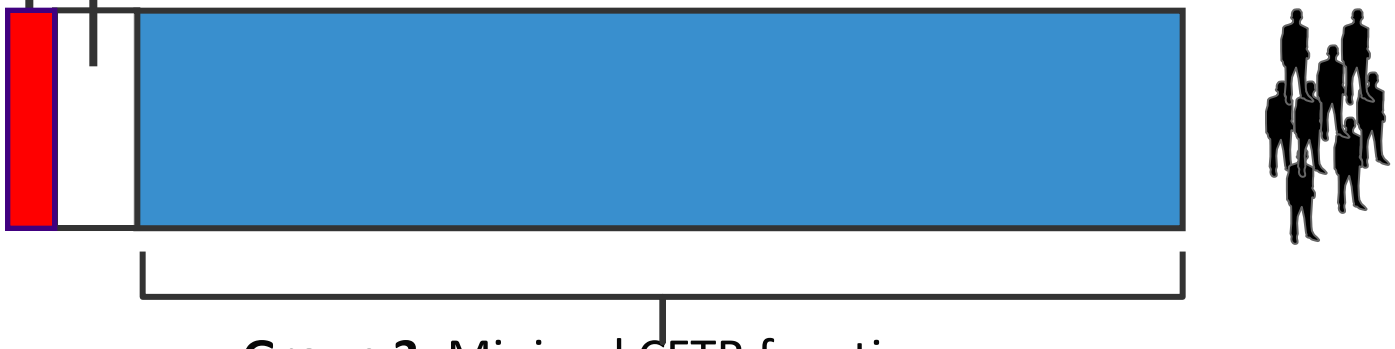
Beyond G551D: Molecular and clinical phenotypes for the definition of patient populations in clinical study design

VERTEX

Analysis of In Vitro Data, Sweat Chloride, and Disease Severity Identified 3 Groups of CFTR Mutations

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

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



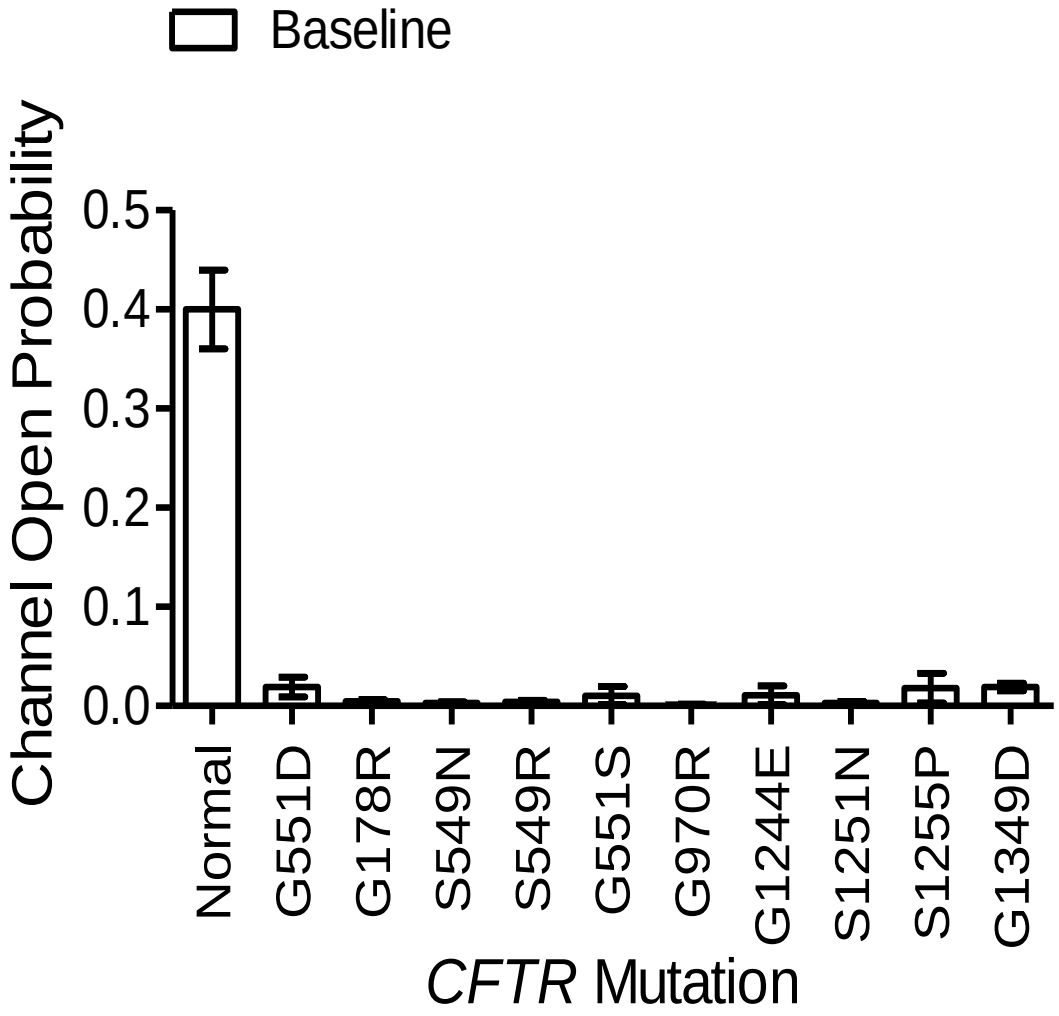
Group 3: Minimal CFTR function

- F508del homozygous
- F508del/other
- Other/other

Source: 2009 US CFF Patient Registry

VERTEX

Several CFTR Mutations Have Severe Defects in Channel Gating as Shown by Low Channel Open Probability
Single channel patch clamp electrophysiology in FRT cells

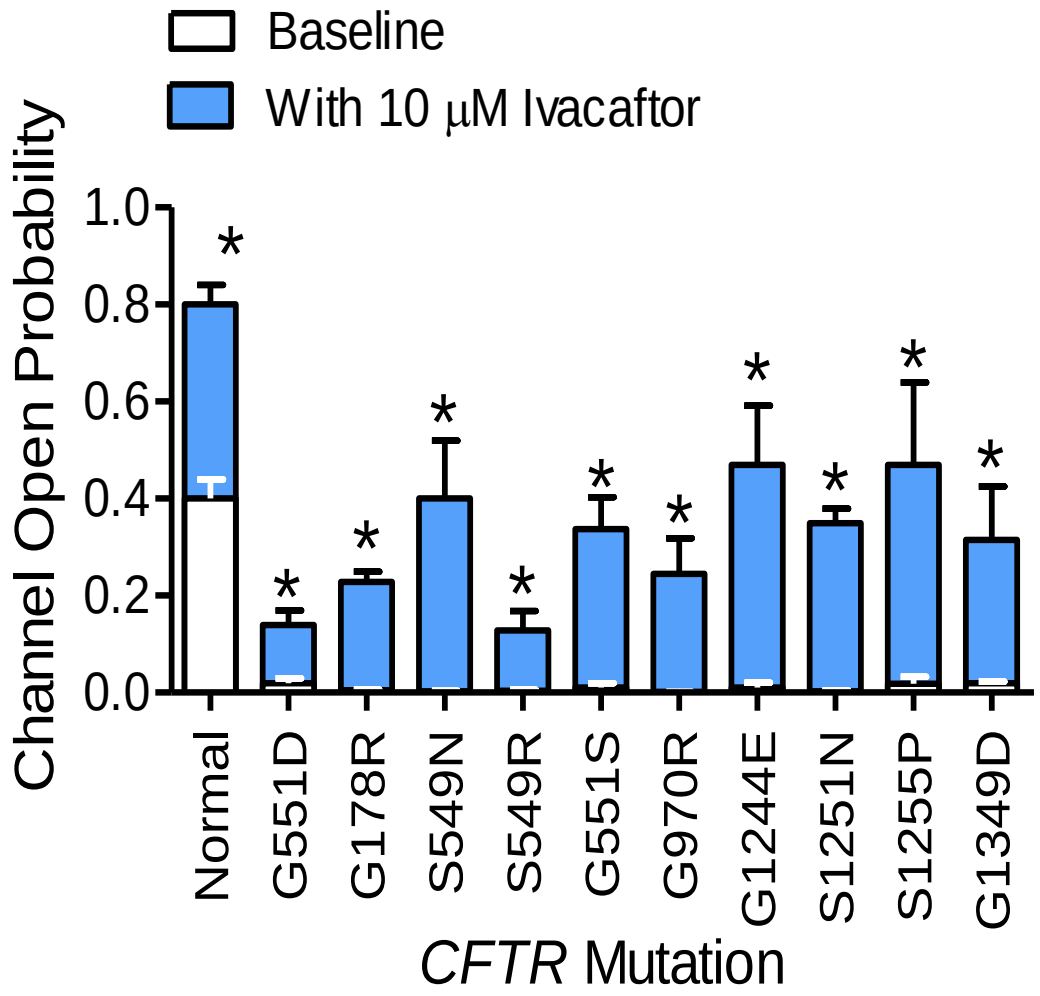


J Cyst Fibros. 2012 May;**11(3)**:237-45.

VERTEX

Ivacaftor Increased Channel Open Probability of Mutant CFTR Forms with Defects in Channel Gating

Single channel patch clamp electrophysiology in FRT cells



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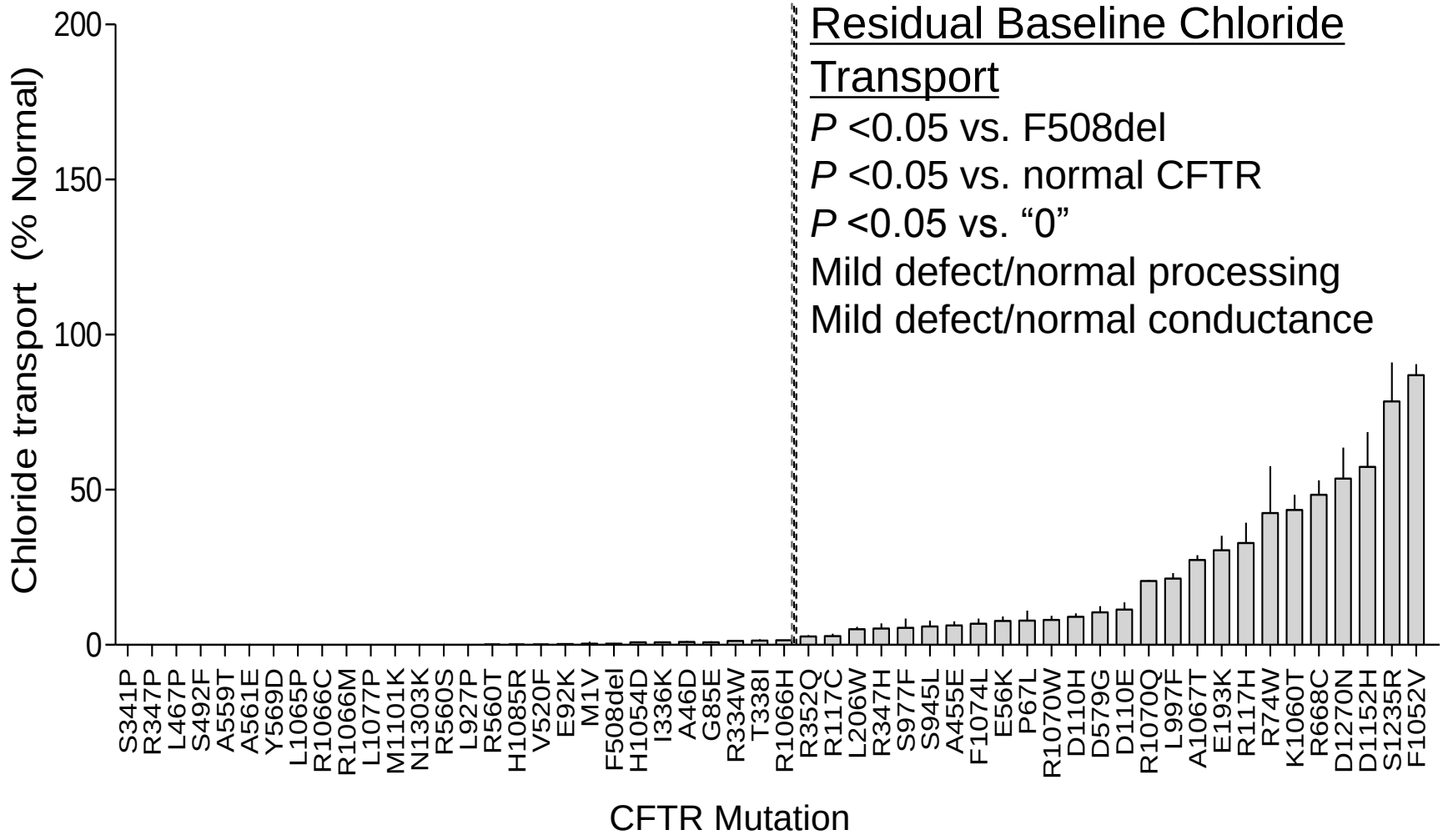
VERTEX

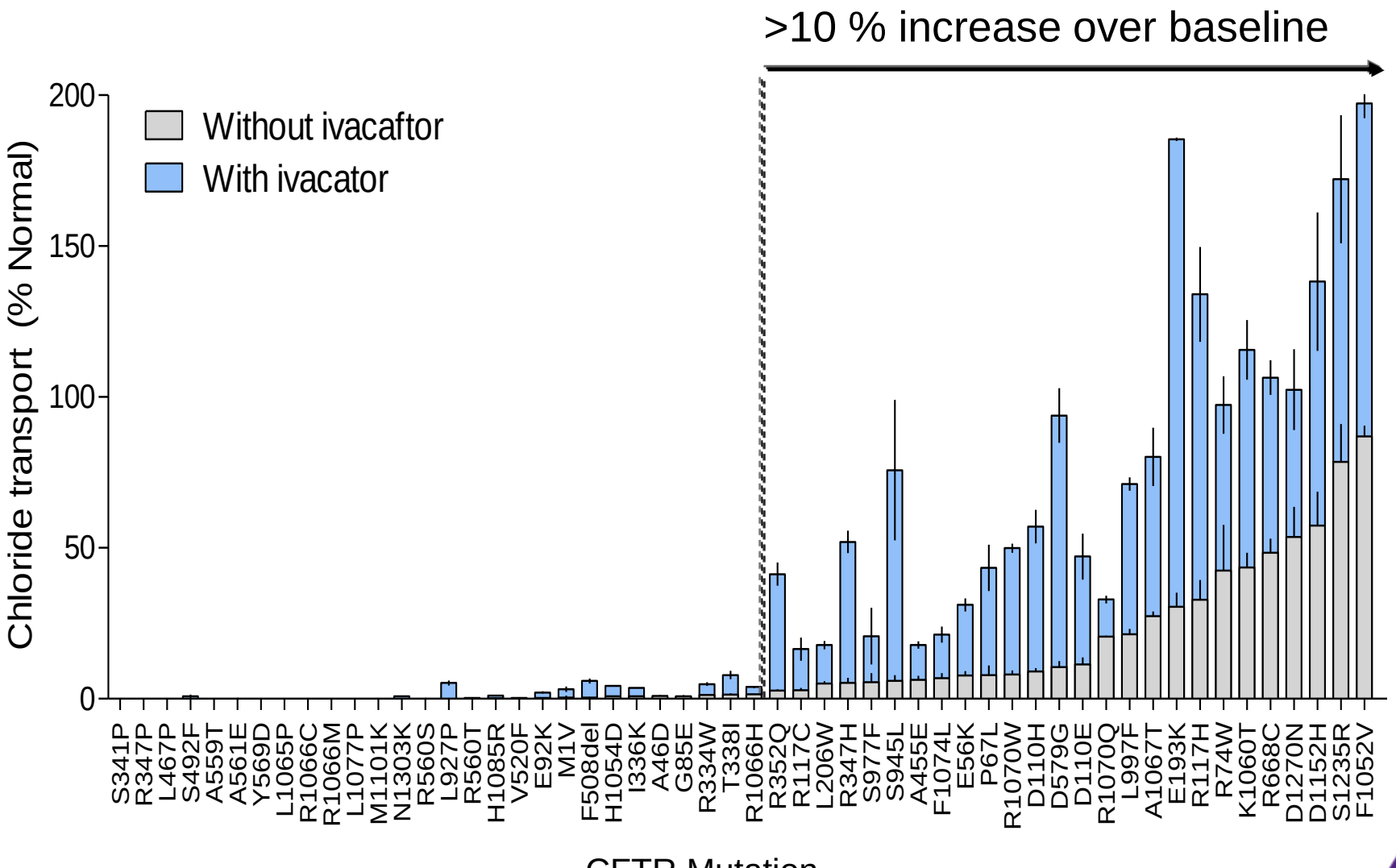
Baseline Chloride Transport Among Mutant CFTR Forms Tested (Non-Gating Mutations)
Ussing chamber electrophysiology in panel of FRT cells



Vertex unpublished data

VERTEX

Multiple Mutant CFTR Forms (Non-Gating Mutations) Responded to Ivacaftor In Vitro Ussing chamber electrophysiology in panel of FRT cells



Vertex unpublished data

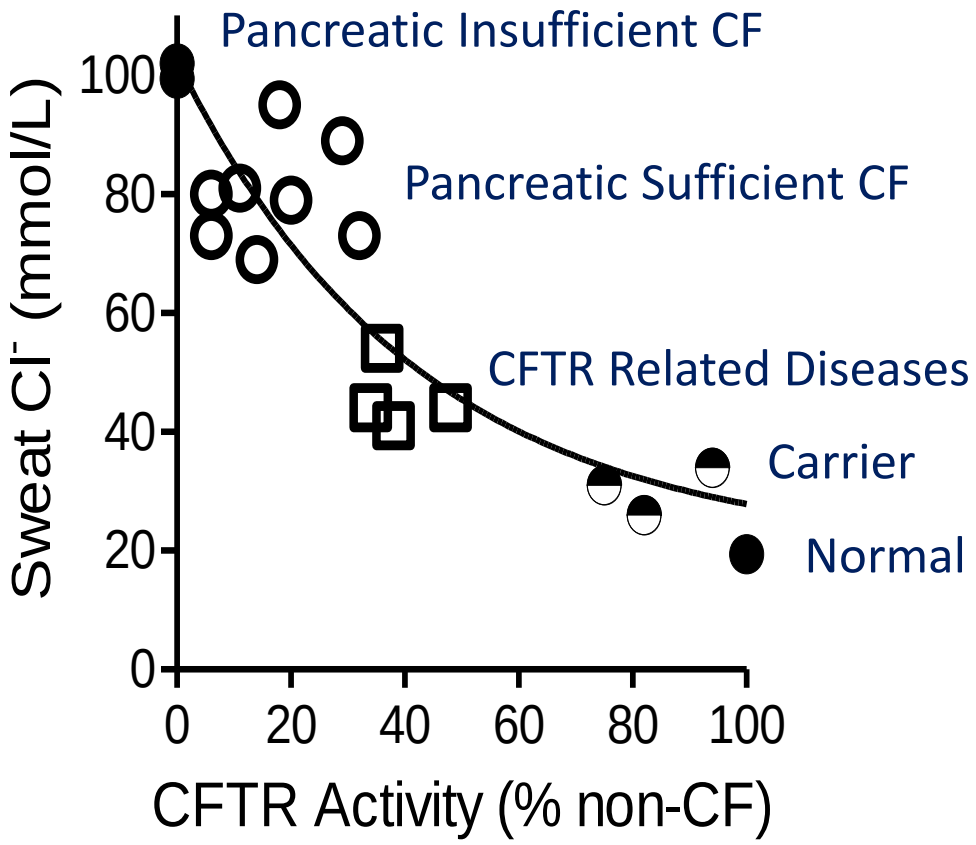
VERTEX

Summary of Mutant CFTR Forms That Responded to Kalydeco In Vitro

Group	Molecular Phenotype	Functional Phenotype	Clinical Phenotype	Example Mutations
Severe gating defects	Severe gating defect	Minimal baseline function	High sweat chloride High incidence of pancreatic insufficiency	G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D
Residual baseline chloride transport	Mild gating defect Mild processing defect Mild conductance defect	Residual baseline function	Lower sweat chloride Lower incidence of pancreatic insufficiency	E56K, P67L, R74W, D110E, D110H, R117C, R117H, L206W, R347H, R352Q, A455E, D579G, R668C, S945L, S997F, L997F, R1070Q, R1070W, F1074L, D1152H, S1235R, D1270N, 2789+5G->A, 3272-26A->G, 3849+10kbC->T

VERTEX

Relationship Between CF Clinical Phenotype and CFTR Function



Nasal potential difference measurement

Example mutations

Severe CF

F508del, G551D

Mild CF

R117H-5T, P67L, A455E, R352Q, R117C, D110H, L206W, V232D

Both Mild CF and CFTR-Related

D1152H, S997F, R117H-7T, L997F, R74W, R668C, S1235R, and D1270N

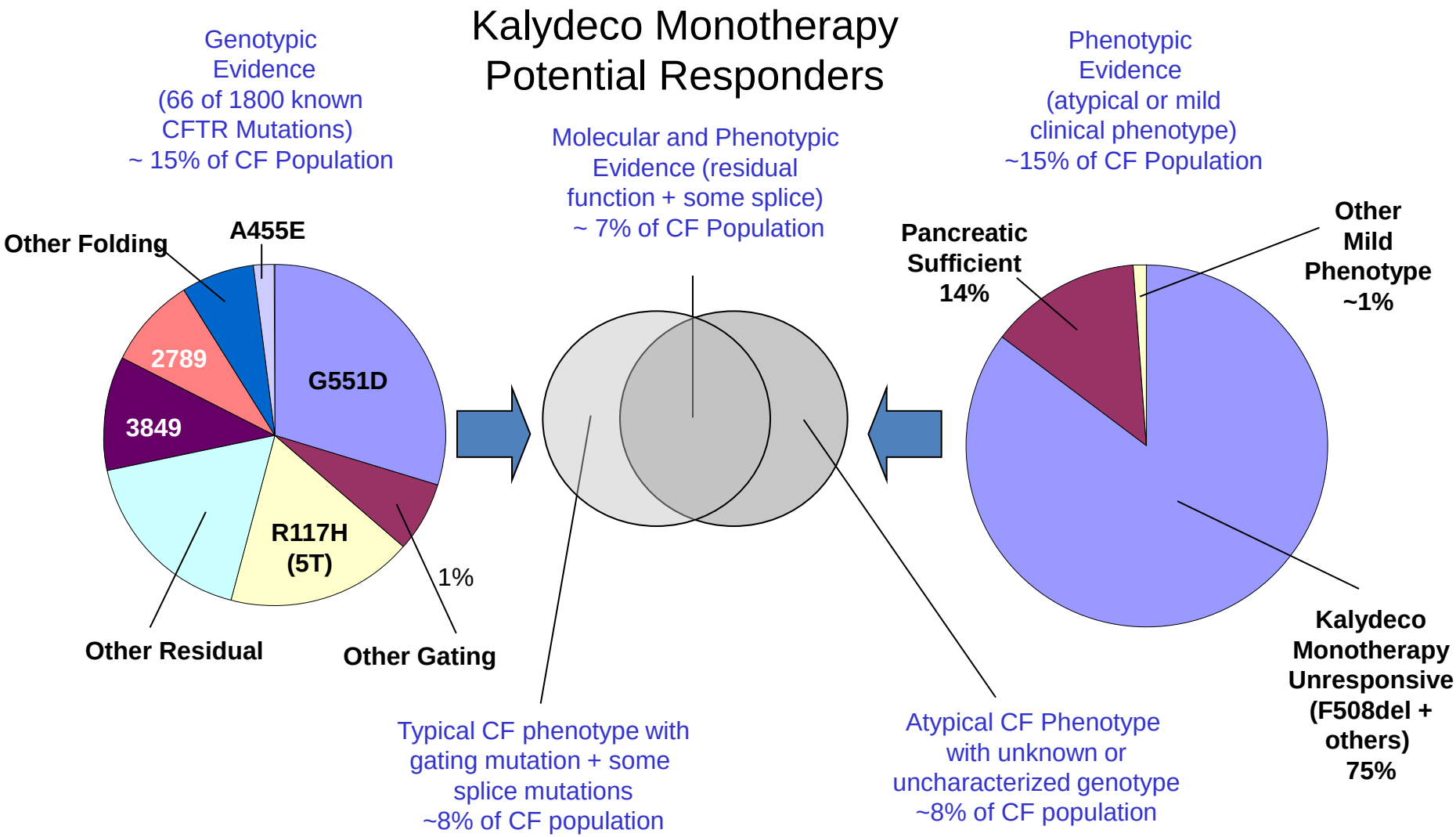
VERTEX

In Vitro Data Conclusions

- CFTR gating mutations are a homogeneous group
  - Same molecular defect as G551D: Defect in channel gating
  - Same functional defect as G551D: Low open probability
  - Similar in vitro response to Kalydeco as for G551D
- Molecular phenotype for CFTR gating mutations may be used to define group of patients for studies investigating clinical benefit of CFTR potentiators.
- Shared molecular and clinical phenotype of non-gating CFTR mutations that responded to Kalydeco
  - All had CFTR located at cell surface
  - All had mild defects in CFTR channel function
  - All responded to Kalydeco by >10%.
  - All associated with pancreatic sufficiency.

VERTEX

Complementarity of Genotypic and Phenotypic Patient Identifications



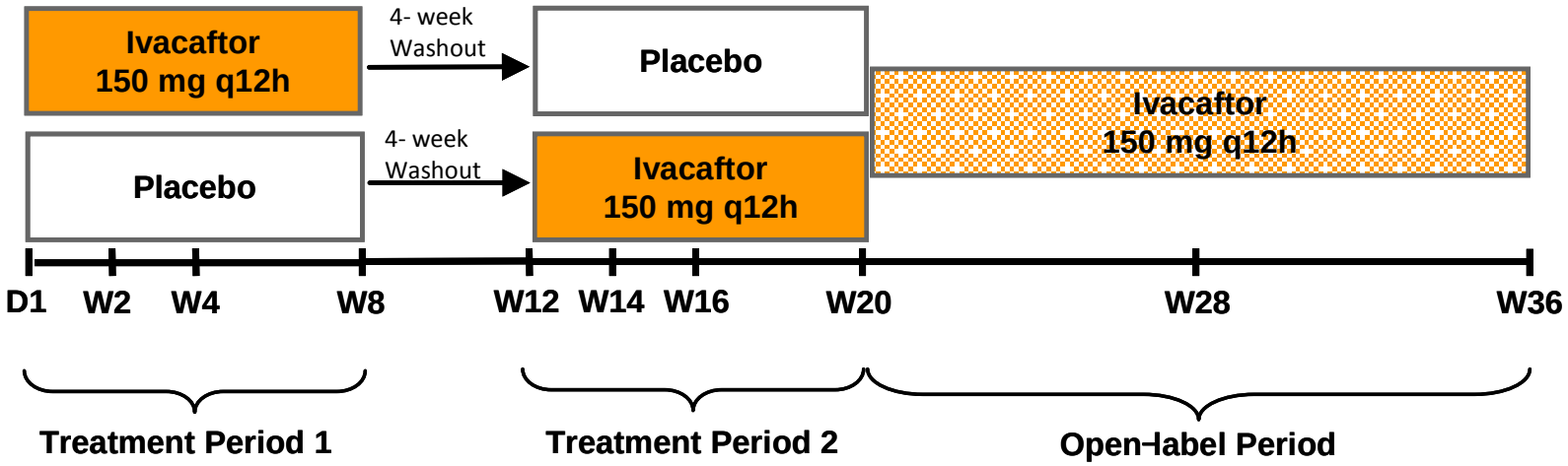
VERTEX

Development Strategy for CF Patients other than homozygous F508del.

- Test if CF patients with other CFTR gating mutations benefit from Kalydeco
- Test if CF patients with R117H, most common residual function CFTR mutation, benefit from Kalydeco
- Test if CF patients with evidence of residual exocrine pancreatic function benefit from Kalydeco
- Pilot an “n-of-1” strategy for use in patients with less common or unknown CF mutations and/or clinical evidence of residual CFTR function.

VERTEX

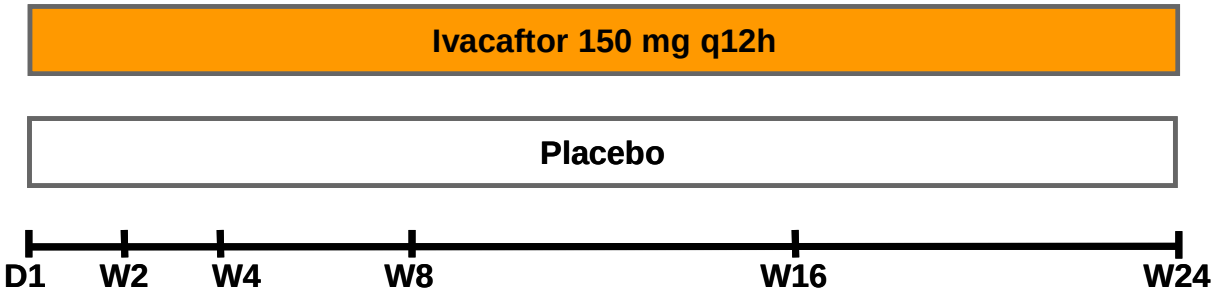
Effect of Kalydeco in CF Patients with Non-*G551D-CFTR* Gating Mutations



- Phase 3, double blind, placebo-controlled, 8-week crossover with 16-week open-label period
- 20-40 subjects
- Enter subjects with as many examples of different gating mutations as practical
- Primary outcome measure: absolute change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) through 8 weeks of treatment.
- Enrollment has started and is scheduled through H1 2013.

VERTEX

Effect of Kalydeco in CF Patients with R117H Residual Function CFTR Mutation



- Phase 3, randomized, double-blind, placebo-controlled, 24-week parallel group
- Up to 80 subjects
  - FEV_1 between 40% and 90% of predicted
- Primary outcome measure: change in % predicted FEV_1 in treatment group relative to placebo group
- Enrollment has started and is scheduled through H1 2013

VERTEX

N-of-1 Strategy

- N-of-1 trials are ultimate small sample randomized clinical trials
- First used in 1960s for behavioral research
- Essentially randomized, placebo-controlled, repeated cross-over in single individual
- Remote clinical phenotyping greatly increased practicality of N-of-1 clinical trials
- Methodology exists for aggregation of multiple N-of-1 trials to generate information similar to that of large randomized clinical trial

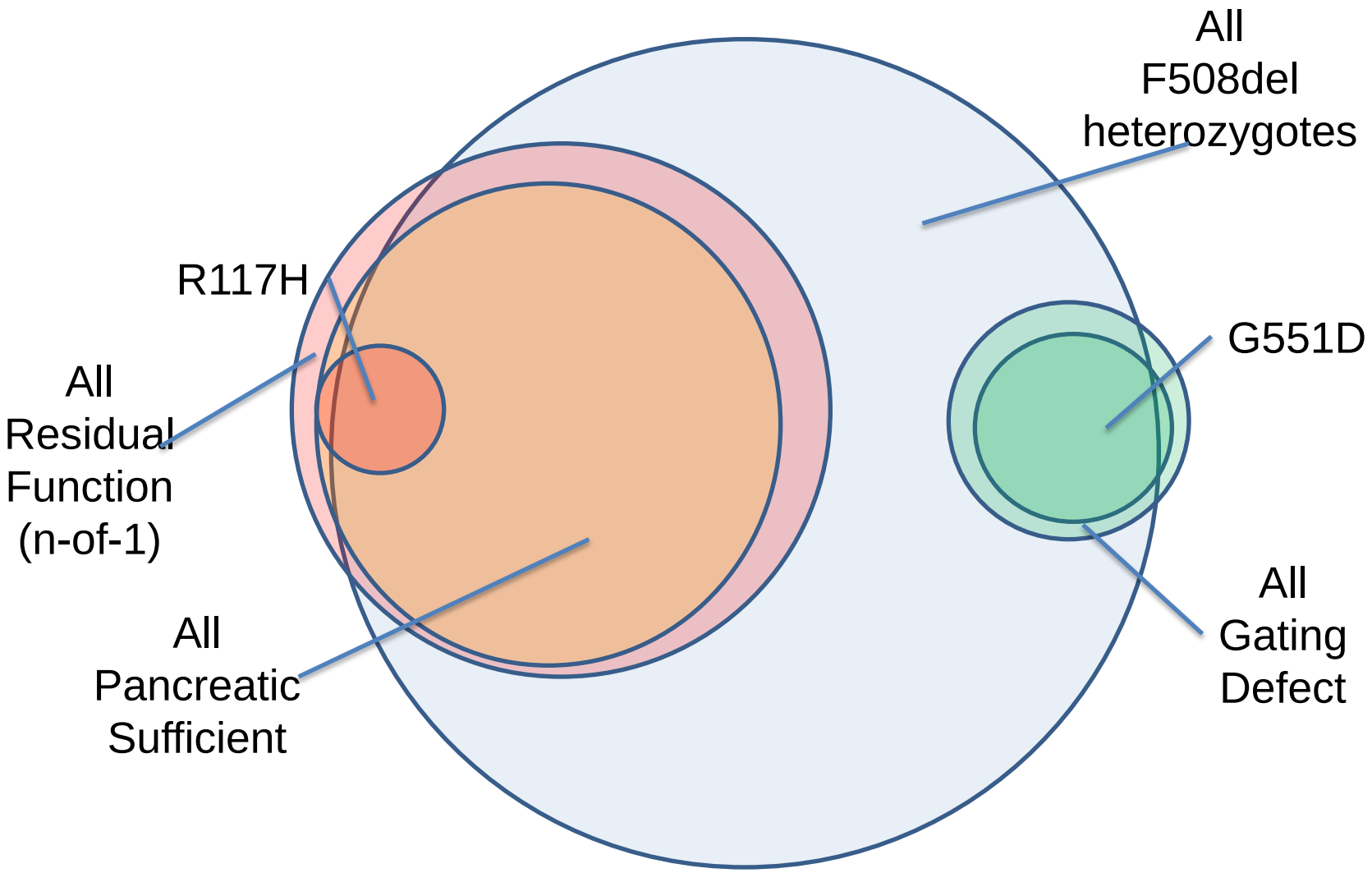
VERTEX

Pilot Study: Effect of Kalydeco in CF Patients with Molecular or Phenotypic Evidence of Residual CFTR Function

- Phase 2 exploratory, double-blind, placebo-controlled, multiple within-subject 4-week crossover ("n-of-1") with 8-wk open-label extension
- 10-20 subjects
- Evidence of
  - residual CFTR function including sweat chloride
  - 60-80mmol/L, pancreatic sufficiency (normal fecal elastase)
  - age at diagnosis ≥12 years and *CFTR* mutation associated with in vitro evidence of residual function
- Primary outcome measure: relative change from baseline in percent predicted forced expiratory volume in 1 second (FEV1) after 2 weeks of treatment
- Multiple exploratory endpoints including home spirometry and lung clearance index
- Statistical analysis plan includes use of Bayesian meta-analysis of all n-of-1 data
- Enrollment has started and is scheduled through H1 2013

VERTEX

CF Patient Populations in Clinical Studies



VERTEX

Molecular Phenotype Definitions

- **Empirical**
  - Concentration distribution of genomic, proteomic or metabolomic molecules reflecting a structural or physiological condition.

- **Functional/Mechanistic**
  - Biochemical or biophysical activity of a biomolecule determined by a genomic sequence affecting either its molecular function or its number of copies.

VERTEX

Why Molecular Phenotypes?

- **Therapeutic product development candidates often target specific patient subpopulations**
  - Characterized by individual patient genotypes
  - Each patient subpopulation may be very small
  - Clinical study designs to show efficacy can be adequately powered if:
    - these subpopulations are considered as a single population
    - collectively defined by the molecular function affected by the individual genotypes
- **In vitro data defining the molecular phenotype may help select patients in these clinical studies**.

VERTEX

Applications in drug development and regulatory review

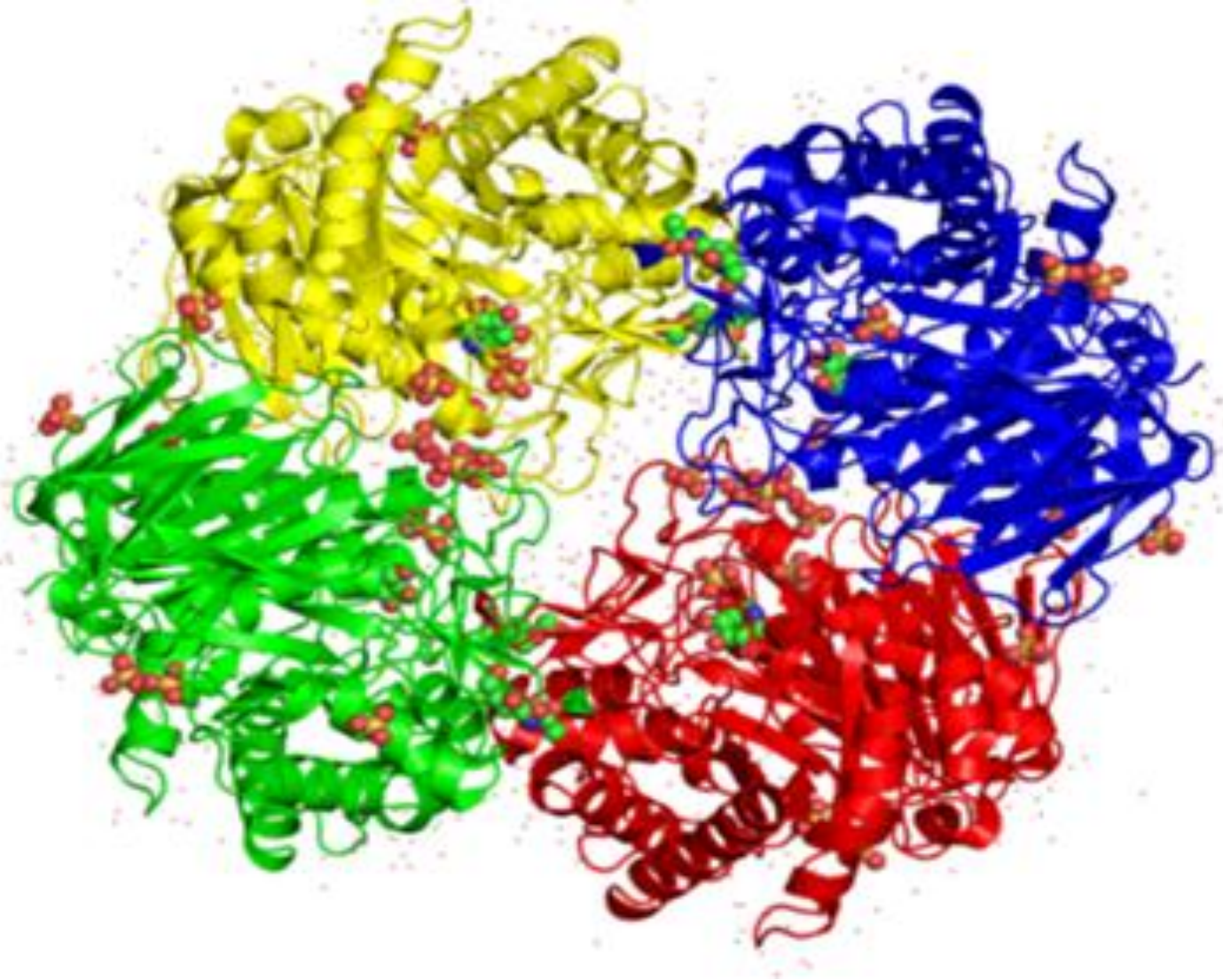
VERTEX

Gaucher

- *Molecular Phenotype*: ß-glucocerebrosidase function
- Enzyme Replacement Therapies
  - Ceredase®
    - N=12, Change from baseline for hematologic and organ volume measurements
  - Cerezyme®
    - N=30, R, DB parallel group compared with Ceredase
  - Velaglucerase alfa for injection (VPRIV)
    - three clinical studies involving 82 patients with Type 1 Gaucher disease ages 4 years and older. The studies included patients who switched to VPRIV after being treated with Cerezyme.

VERTEX

ß-glucocerebrosidase



VERTEX

Selected Rare Disease Product Approvals

Drug	Indication, Year	Basis for Approval
Ceredase®	Gaucher Disease, 1991	N=12, Change from baseline for heme/organ volume measurements
Cerezyme®	Gaucher Disease, 1994	N=30, R, DB parallel group compared with Ceredase using similar endpoints
Aldurazyme®	MPS I, 2003	N=45, R, DB, PC; change in 6MWT and FVC (co-primary)
Elaprase®	MPS II, 2006	N=96, R, DB, PC; change in 6MWT and FVC (composite primary)
Naglazyme®	MPS VI, 2005	N=39, R, DB, PC; change in 12MWT
Fabrazyme®	Fabry Disease, 2003	N=58, R, DB, PC; clearance of GL-3 from kidney interstitial capillaries (Subpart E)
Myozyme®	Pompe Disease, 2006	N=18, Open label, Historically controlled; change in ventilator-free survival
Ammonul®	Hyperammonemia, 2005	N=316, Open label, Historically controlled; overall survival

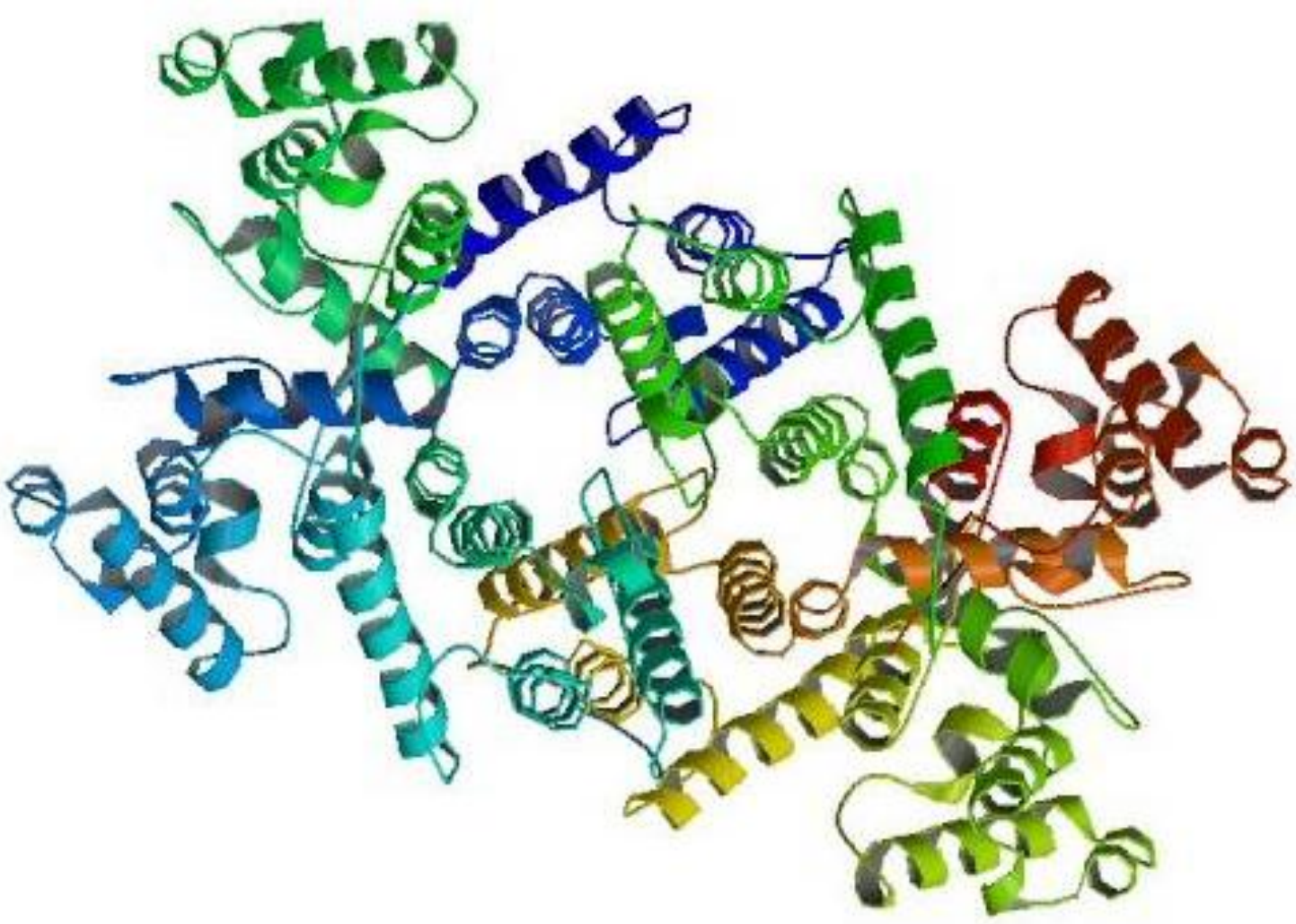
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM248672.pdf

Duchenne

- *Molecular Phenotype:* dystrophin function
- Eteplirsen (AVI-4658)
  - systemically delivered for the treatment of a substantial subgroup of patients with Duchenne muscular dystrophy (DMD)
  - clinical studies of eteplirsen in DMD patients have demonstrated a broadly favorable safety and tolerability profile and restoration of dystrophin protein expression
  - Skips exon 51 of the dystrophin gene
    - restores the ability to make a shorter, but still functional, form of dystrophin from mRNA
    - synthesis of a truncated dystrophin protein improves, stabilizes or significantly slows the disease process and prolongs and improves the quality of life for patients with DMD.

VERTEX

Dystrophin



VERTEX

Biological Defect and Molecular Phenotype

	Gaucher	Duchenne	Cystic Fibrosis
Gene	ß-glucocerebrosidase	Dystrophin	CFTR
Defect	Over 300 mutations with minor or major effects on enzyme function	Multiple mutations resulting in premature truncation	Disease-causing mutations in the CFTR gene prevent the channel from functioning properly
Molecular Phenotype	ß-glucocerebrosidase function	Dystrophin function	1) Gating Mutations 2) Residual Chloride Transport
Therapy	enzyme replacement	exon-skipping	potentiator corrector
Regulatory Review	approved	phase 3	approved for G551D
Specific Mutations on Label	Not referenced	Not referenced	G551D

VERTEX

Applications in drug development and regulatory review: *Summary*

- Gaucher Disease can be used as a model in which to define molecular phenotypes.
- The molecular phenotype for Gaucher Disease is found in other diseases for which enzyme replacement therapies have been developed.
- Exon-skipping therapies for Duchenne Disease represent more complex examples for molecular phenotypes.
  - Clinical study designs
  - Regulatory review

VERTEX

EMA Cystic Fibrosis Workshop: *September 2012*

- A list of core pulmonary and non-pulmonary endpoints could include
  - Lung function
    - change in ppFEV1
    - in early disease, FEF25-75, FEF75, and/or LCI
    - pulmonary exacerbations (including use of additional antibiotics and hospitalizations)
    - PRO measures
    - imaging (chest CT score for bronchiectasis and air trapping)
  - Biometry (weight and in children height)
  - Sweat chloride for CFTR modulators
    - biomarker of CFTR function in the sweat gland but may not correlate with CFTR function in other organs depending on distribution and effects on CFTR biology in different tissues
- Novel trial designs should be utilized to accommodate
  - Limited population
  - Increasing drug development pipeline
  - Emergence of personalized medicine approaches

VERTEX

Can we draft a guidance on best practices in the design of clinical studies for rare diseases and personalized healthcare?

- Clinical study design issues are similar for rare diseases and personalized healthcare.
- Molecular phenotype classifications are one of several tools available to address issues with clinical study design.
- There is an urgent need for regulatory guidance in the application of alternative clinical study design strategies.

VERTEX