NEW THERAPIES IN ONCOLOGY AND CYSTIC FIBROSIS

CFTR Modulators
A pharmacogenomic approach to treating cystic fibrosis

William Allan Prescott Jr., PharmD
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University at Buffalo School of Pharmacy and Pharmaceutical Sciences
Department of Pharmacy Practice

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Text WILLIAMPRESC537 to 22333 once to join
Limited to 50 participants

Learning Objectives - Pharmacists

1. Describe the pathophysiology of cystic fibrosis (CF) lung disease
2. Cite evidence for the safety and effectiveness of CFTR modulators in the treatment of CF lung disease

Learning Objectives – Pharmacy Technicians

1. Recall the basics of cystic fibrosis (CF) pathophysiology
2. List three CFTR modulators that are FDA approved for the treatment of CF lung disease

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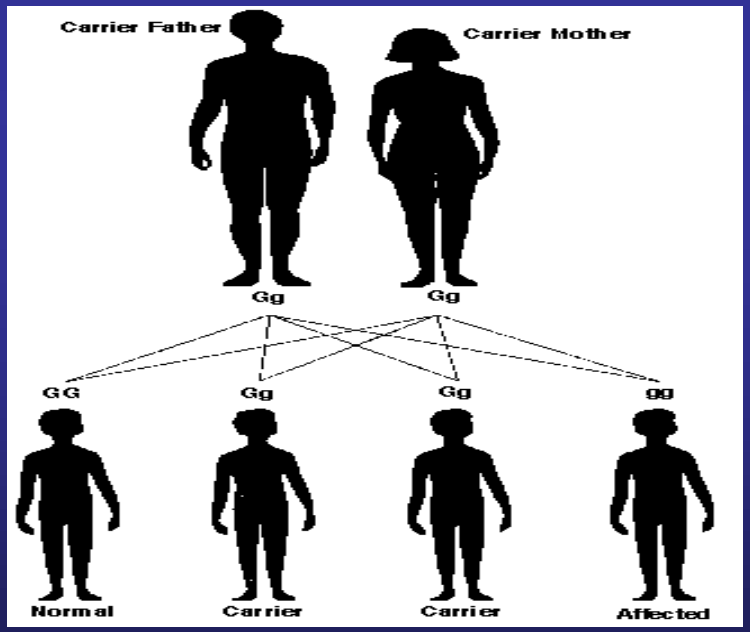
Epidemiology of CF

- CF is a genetically inherited disease that results in chloride channel dysfunction
- CF is the most common lethal genetically inherited disease affecting the Caucasian population

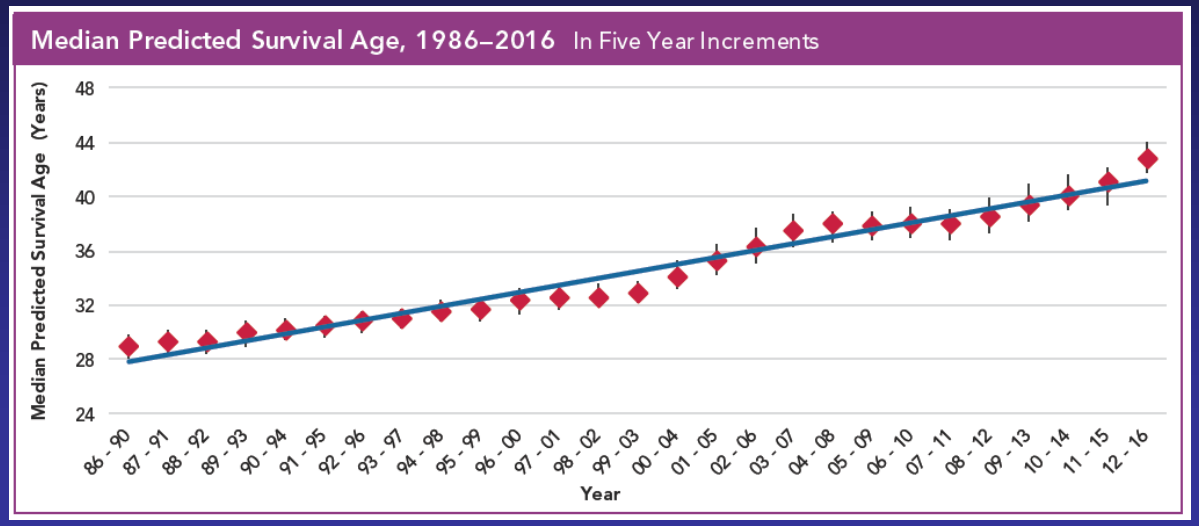


~ 30,000 persons with CF in the U.S.

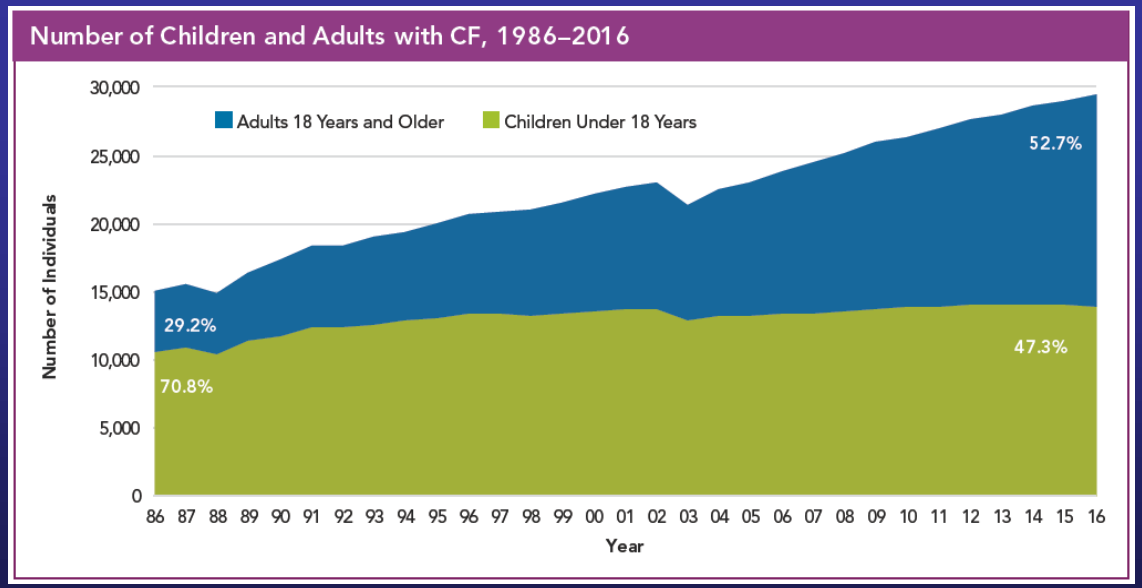
~ 1,000 children born w/ CF in the U.S. annually

CFF Patient Registry, 2016. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf

Morbidity & Mortality of CF



- Outcome dependent upon…
  - Disease genotype / severity
  - Patient management
  - Compliance with therapies



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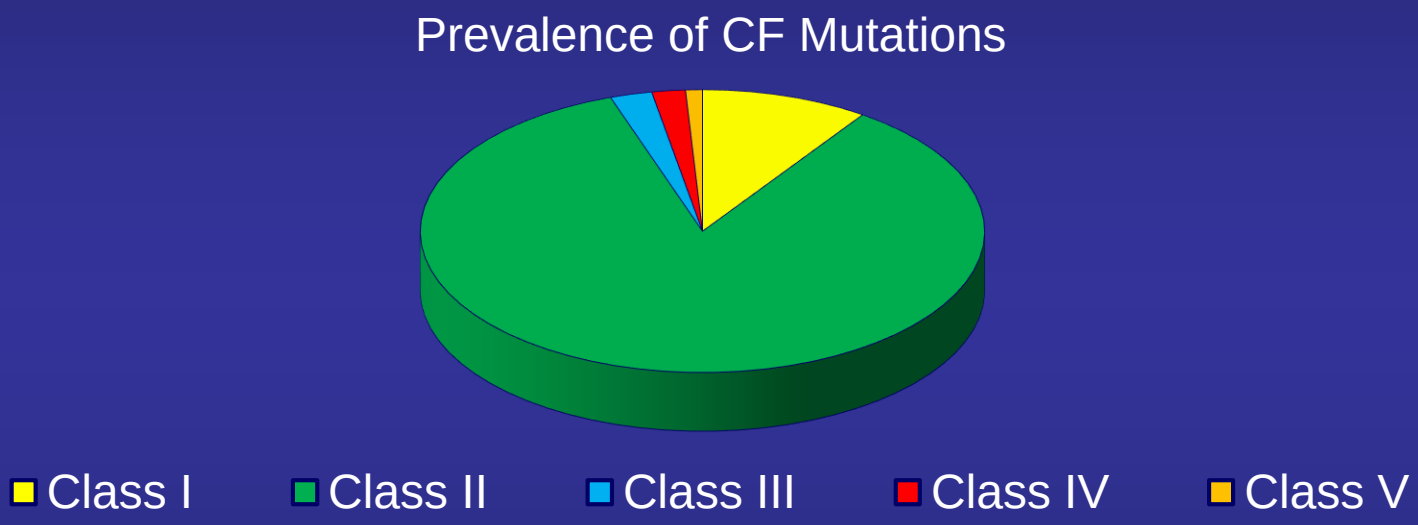
Cystic Fibrosis Pathophysiology: CFTR

- Since the CFTR gene was discovered in 1989, more than 1600 CFTR mutations have been identified



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R553X	c.1657C>T	p.Arg553X	1	527	1.8
1717-1G->A	c.1585-1G>A		1	456	1.6
3849+10kbC->T	c.3717+12191C>T		5	435	1.5
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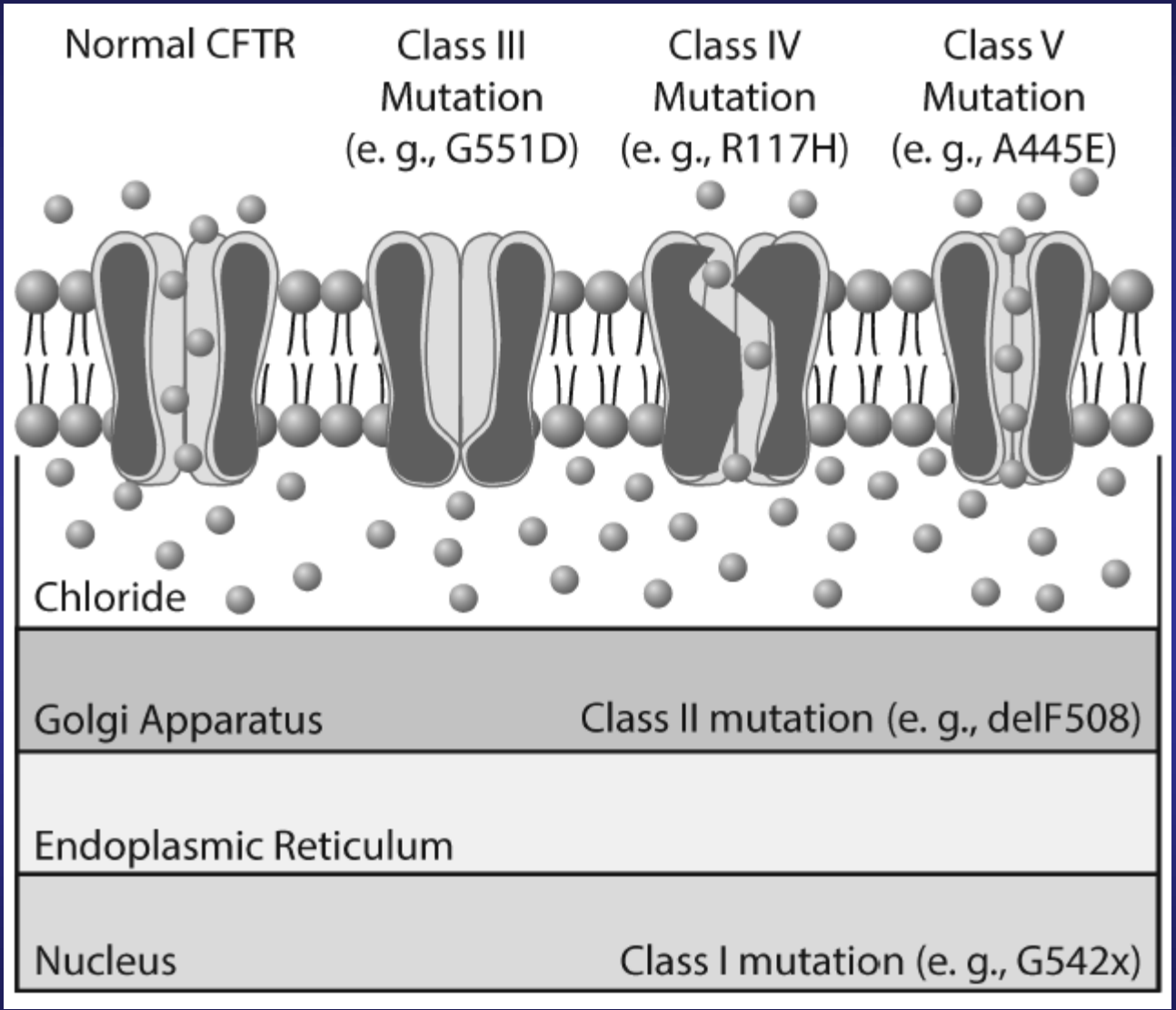
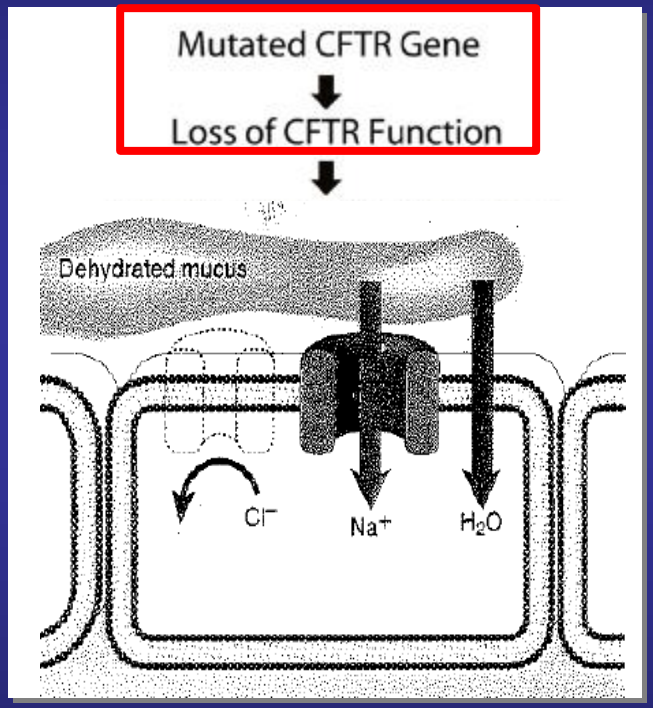
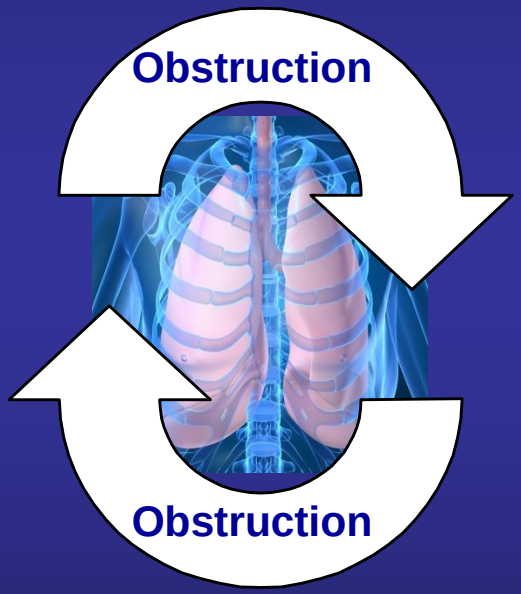


Condren ME, et al. J Pediatr Pharmacol Ther 2013;18:8-13.

CF Pulmonary Disease Pathophysiology

- Pulmonary





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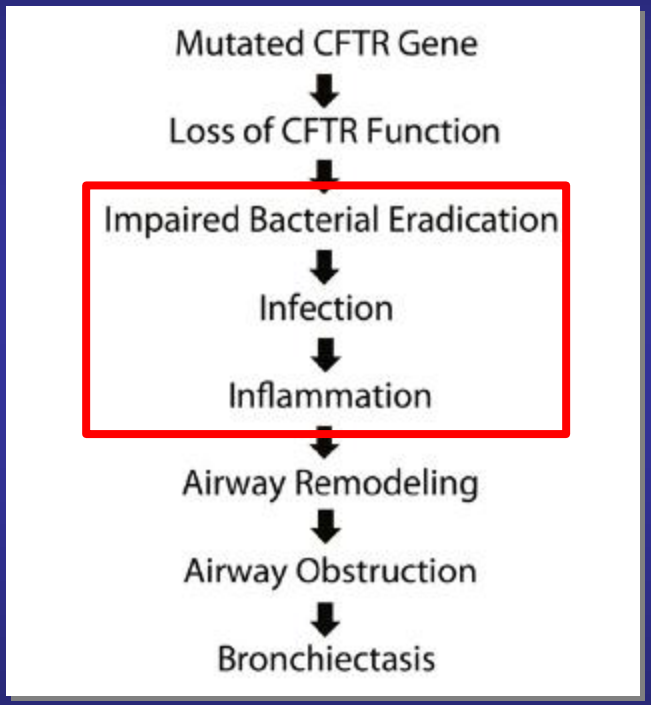

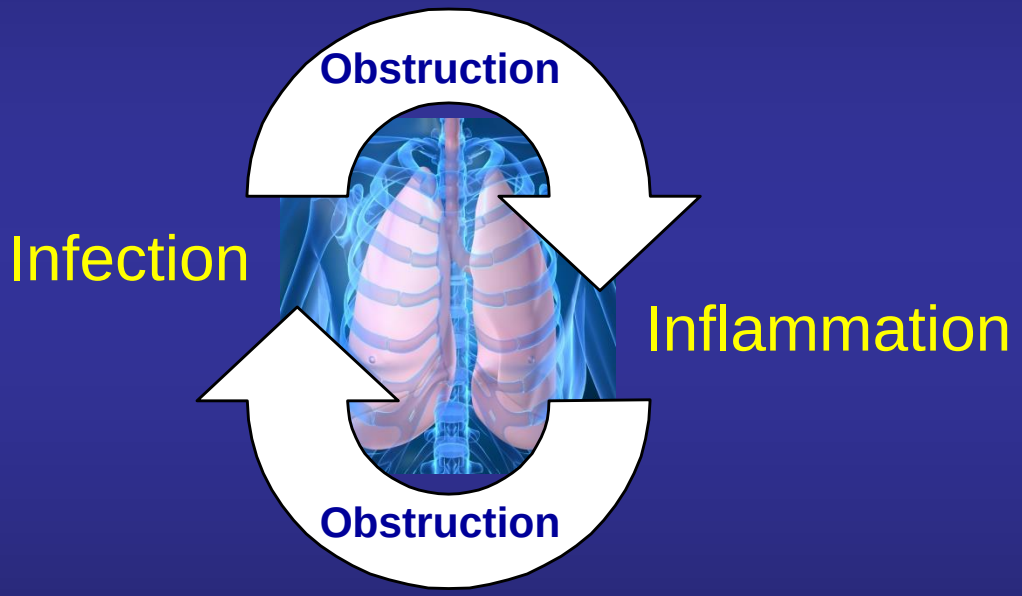

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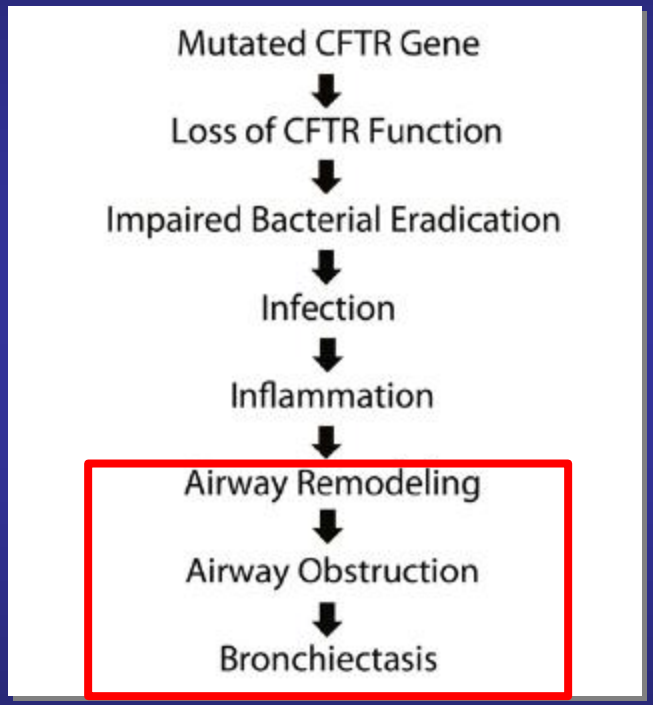
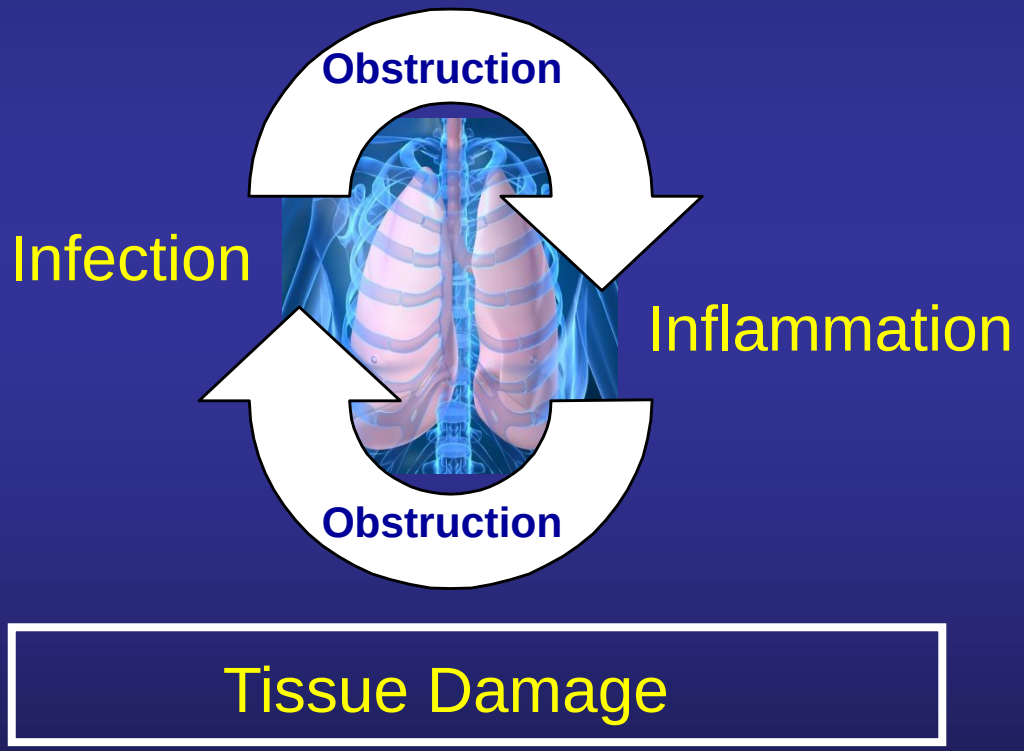
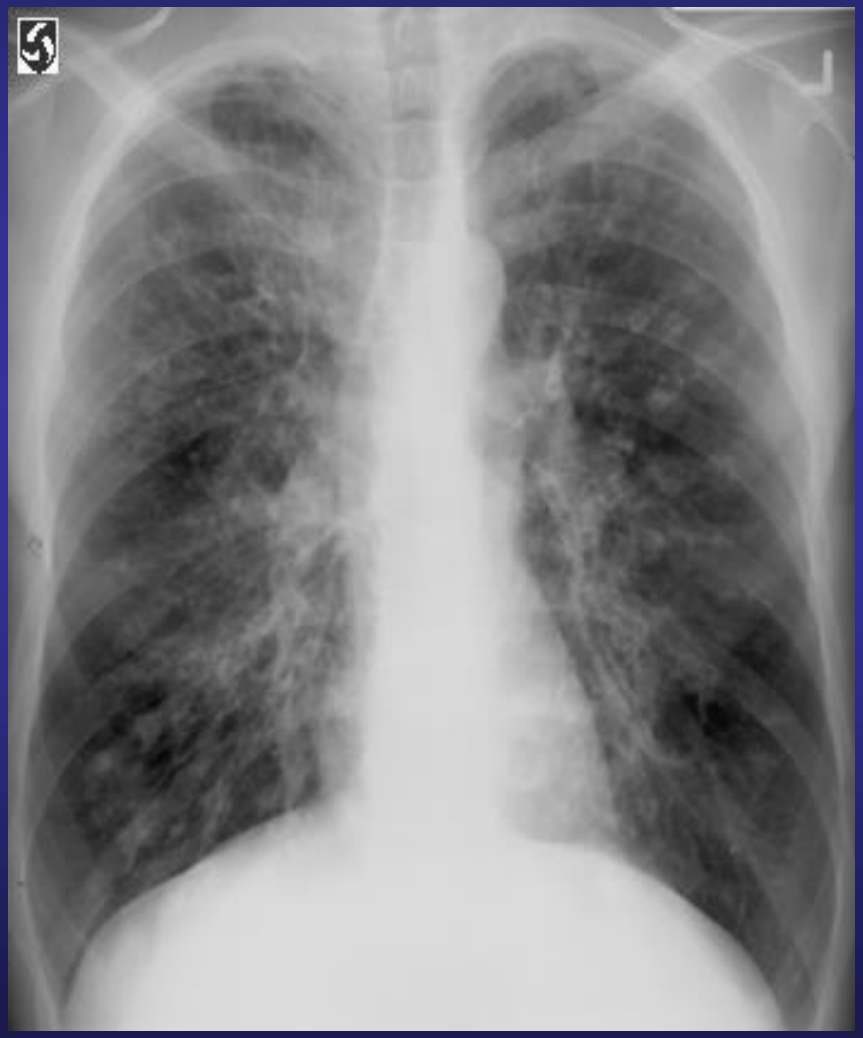


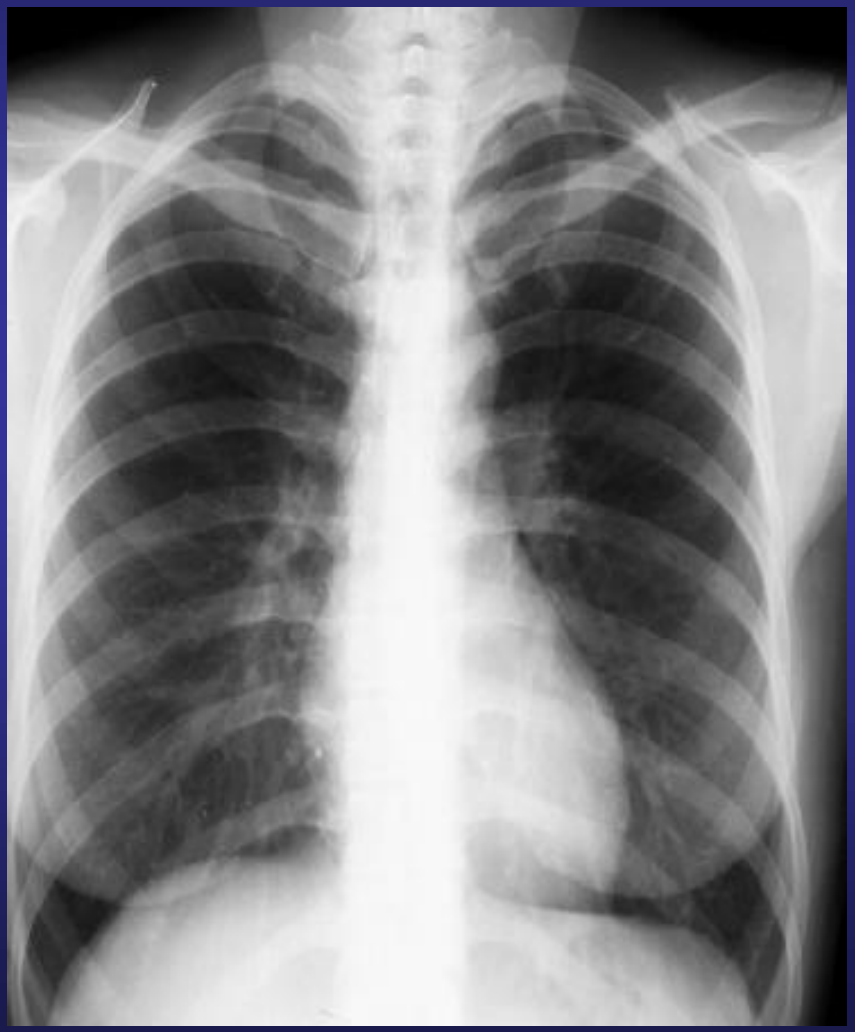


CF Pulmonary Disease – Tissue Damage

CF Lung



Healthy Lung



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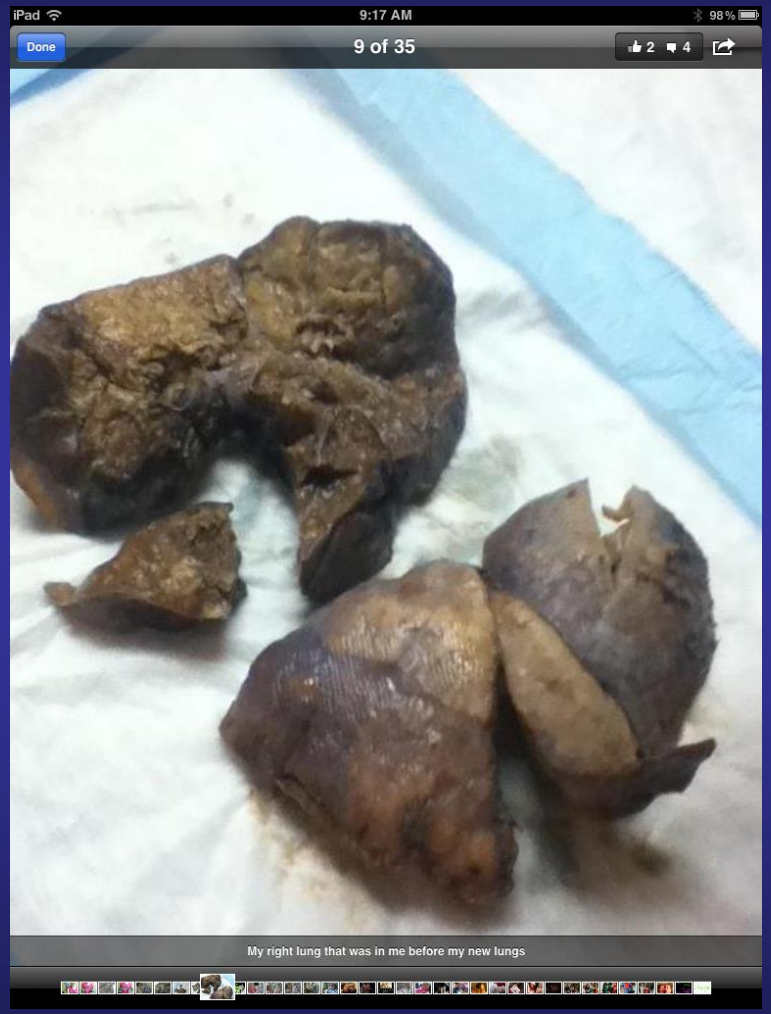
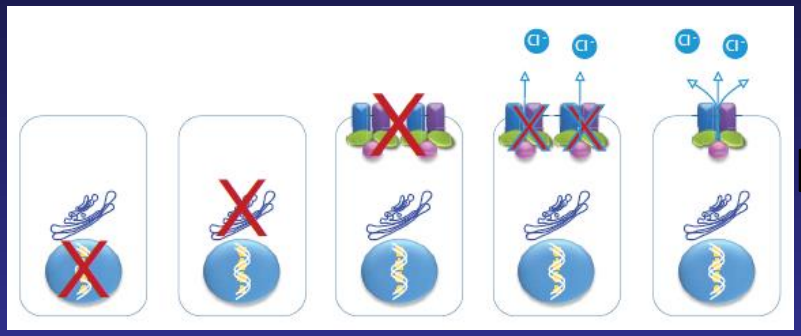
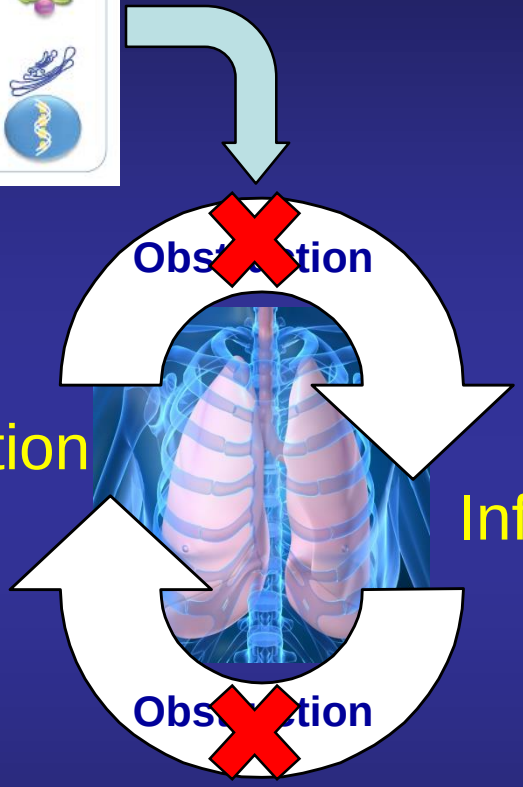


Traditional Pharmacologic Approaches to Treat CF Lung Disease



Adapted from CFF Patient Registry, 2015.



Antibiotics

- Inhaled tobramycin
- Inhaled aztreonam
- Systemic antibiotics

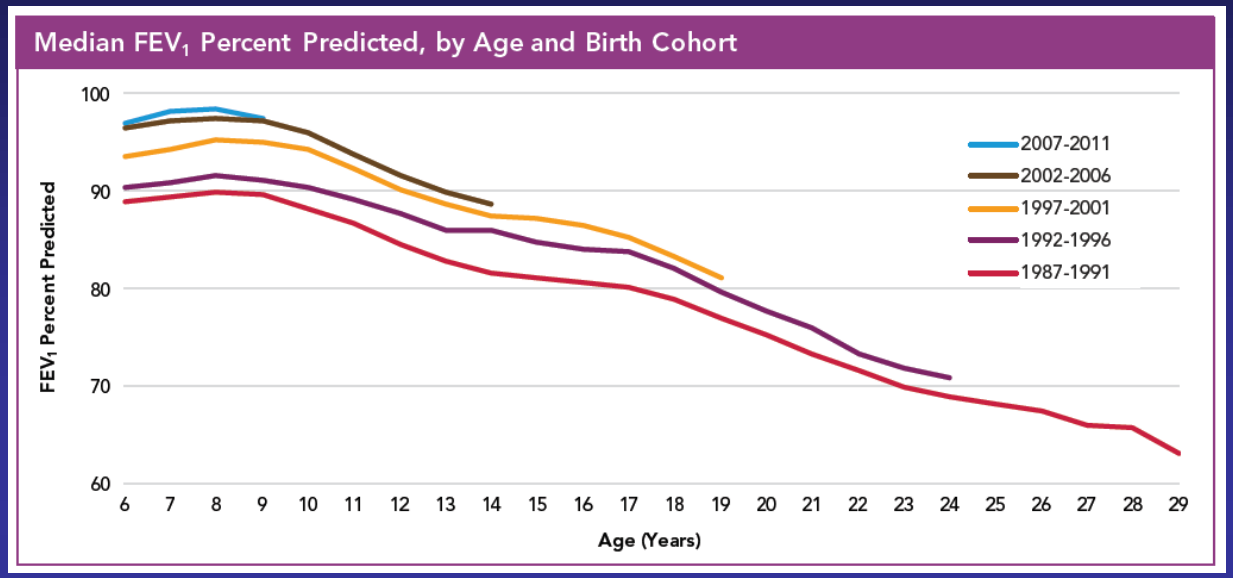
Anti-inflammatory agents

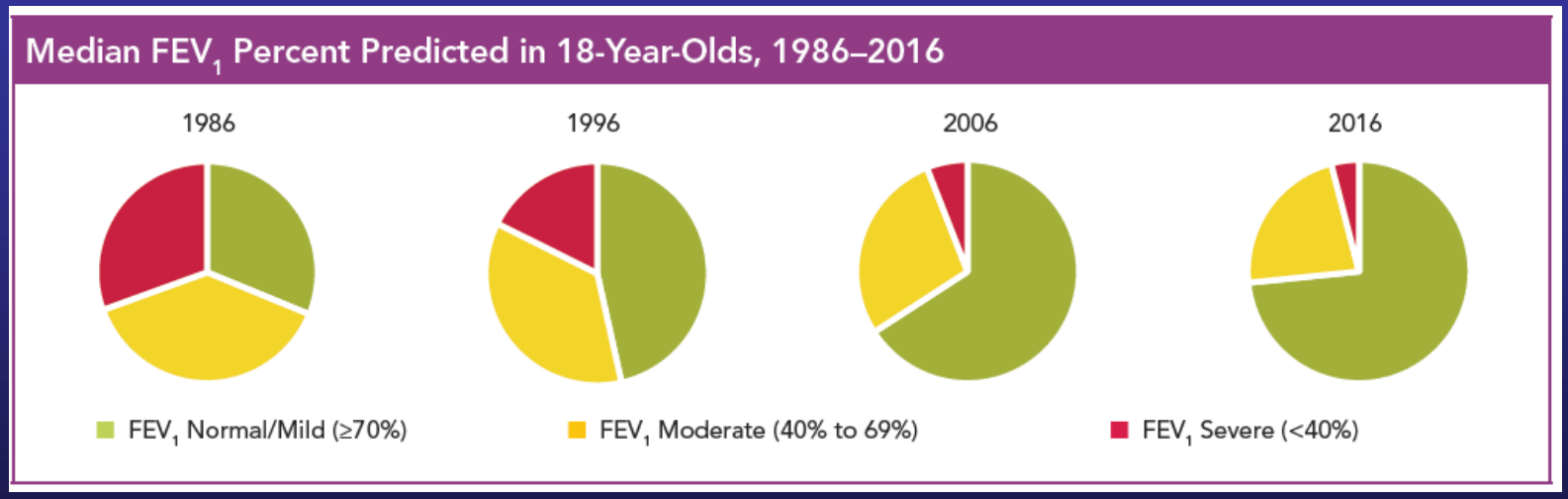
- Azithromycin
- Ibuprofen (high-dose)

Mucolytic / hydrating agents / Bronchodilators

- Dornase alfa
- Hypertonic saline
- Albuterol (if asthma present)

Treatment Impact on Pulmonary Function





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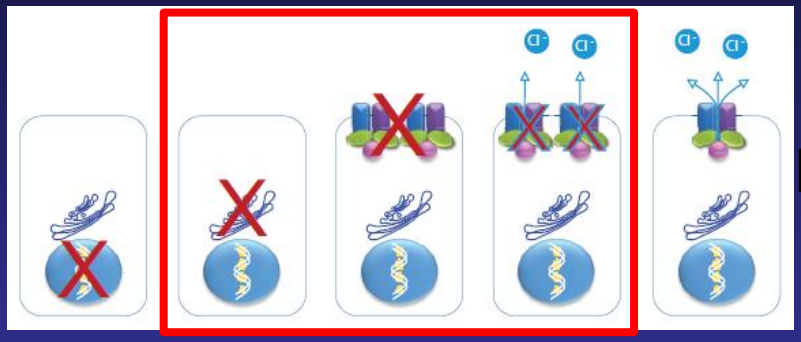
New Frontier in the Treatment of CF Lung Disease



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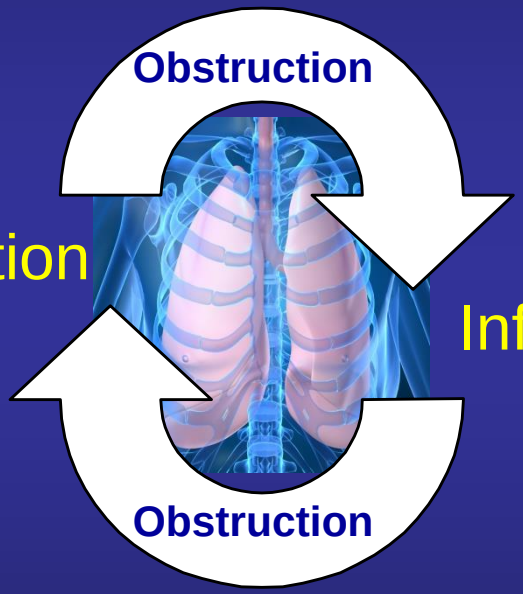
CFTR Modulators



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New Frontier in the Treatment of CF Lung Disease

FDA Clears Tezacaftor/Ivacaftor Combo for Cystic Fibrosis

Megan Brooks

February 13, 2018

The US Food and Drug Administration (FDA) has approved a third drug from Vertex Pharmaceuticals directed at an underlying cause of cystic fibrosis (CF), the company has announced.

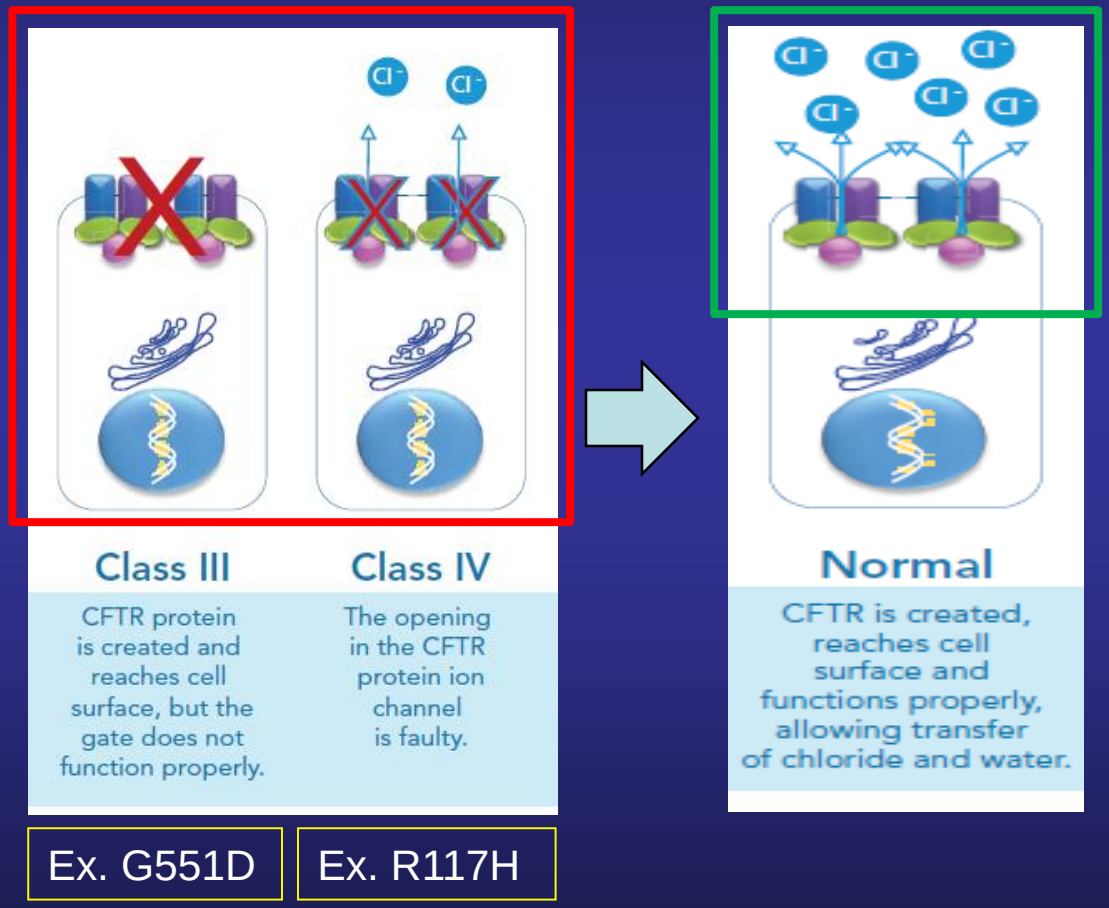
The new treatment combines ivacaftor (*Kalydeco*), approved in 2012, with tezacaftor. It will be sold under the brand name *Symdeko*. In 2015, Vertex's combination of lumacaftor and ivacaftor (*Orkambi*) became the first drug approved by the FDA to treat the underlying cause of CF.

Symdeko is indicated for the treatment of CF in people aged 12 years and older who have two copies of the F508del mutation in the CF transmembrane conductance regulator (*CFTR*) gene or who have at least one mutation that is responsive to tezacaftor/ivacaftor.

CFF Patient Registry, 2016. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf

CFTR Modulators: Ivacaftor

- Ivacaftor (Kalydeco™)
  - Facilitates opening of the chloride channel (“CFTR Potentiator”)



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Prevalence of the 10 most common CFTR mutations

CFTR Mutation			Mutation Class	Number of Individuals	Percent of All People with CF
Legacy Name	**cDNA Name**	**Protein Name**			
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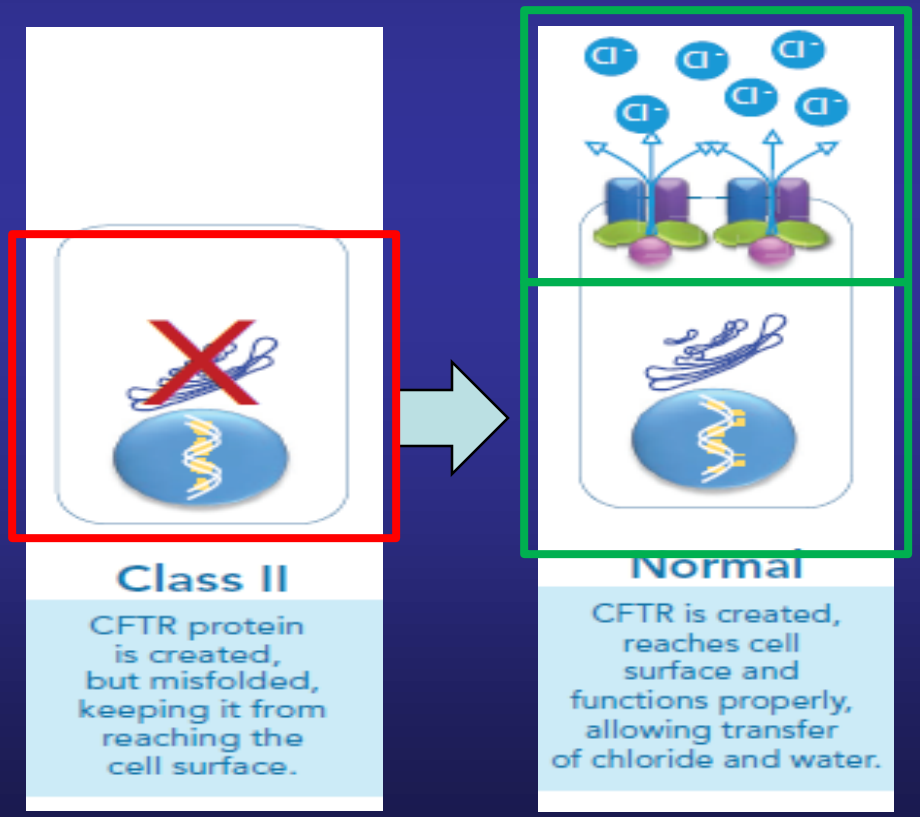
CFTR Modulators: Lumacaftor / Ivacaftor

- Lumacaftor/Ivacaftor (Orkambi™)
  - Lumacaftor component fixes the defective CFTR protein so it can move to the proper place on the airway cell surface (“CFTR corrector”)
  - Ivacaftor serves as the CFTR “potentiator”



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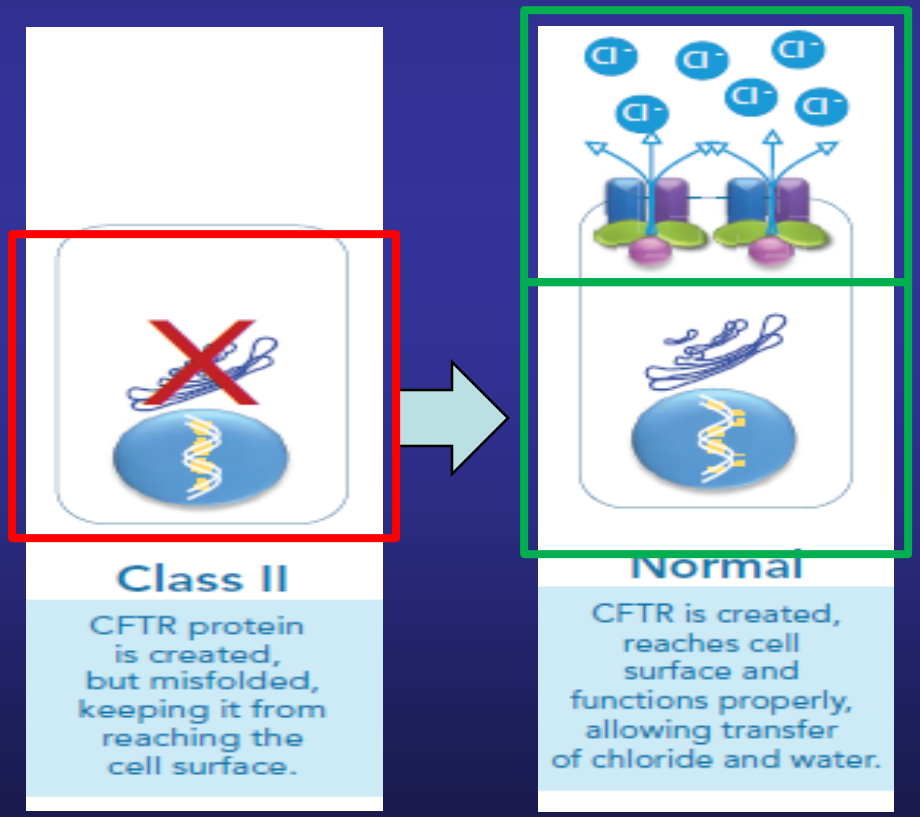

https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf

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Table 4: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO

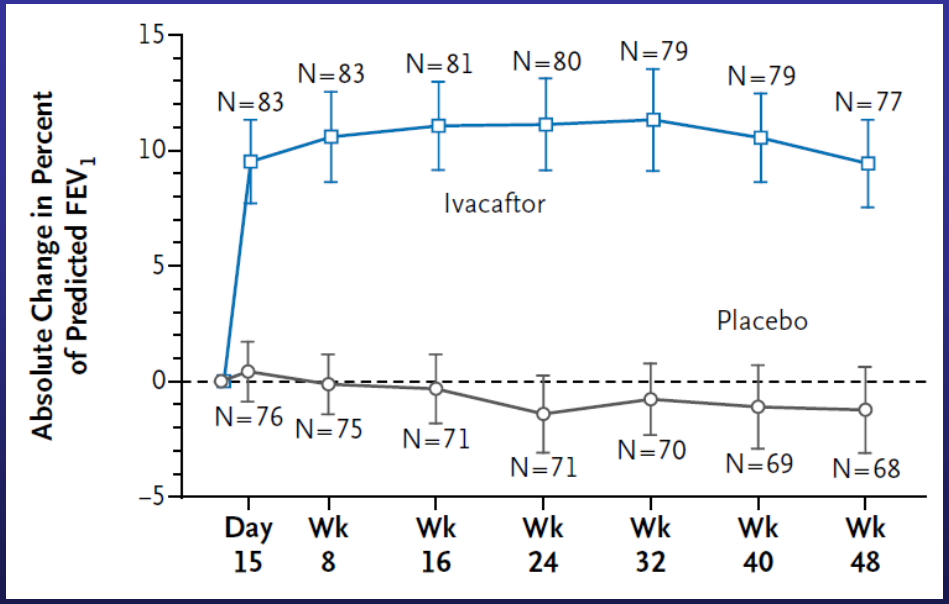
E56K	*R117C*	*A455E*	*S945L*	*R1070W*	*3272-26A→G*
P67L	*E193K*	*F508del**	*S977F*	*F1074L*	*3849+10kbC→T*
R74W	*L206W*	*D579G*	*F1052V*	*D1152H*	
D110E	*R347H*	*711+3A→G*	*K1060T*	*D1270N*	
D110H	*R352Q*	*E831X*	*A1067T*	*2789+5G→A*	

*A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 4 to be indicated.

CFF Patient Registry, 2016. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf

CFTR Modulators: Ivacaftor

- STRIVE trial - Phase 3, randomized, DB, PC study
  - Study population: CF with ≥ 1 G551D-CFTR mutation; FEV_1 40-90%
  - Demographics: Age ≥ 12 y (mean age 26 y); mean FEV_1 = 64%
  - Ivacaftor 150mg PO q12h (n=83) vs. placebo (n=78)
  - Primary outcome: Mean change in FEV_1 at 24 weeks
  - Results:
    - Improved FEV_1 at 24 / 48 w (p<0.001)
    - Similar safety profile

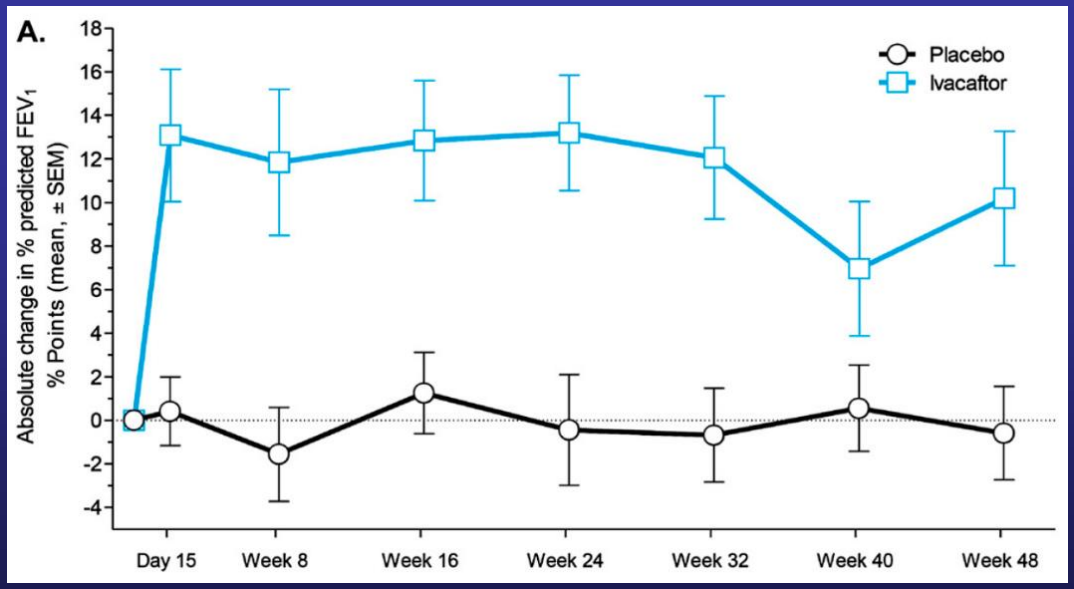


FEV_1 Normal/Mild (≥70%)
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

Ramsey BW, et al. N Engl J Med 2011;365(18):1663-72.

CFTR Modulators: Ivacaftor

- ENVISION trial - Phase 3, randomized, DB, PC study
  - Study population: CF with ≥ 1 G551D-CFTR mutation; FEV_1 40-105%
  - Demographics: Age 6-11 y (mean age 9 y); mean FEV_1 = 84%
  - Ivacaftor 150mg PO q12h (n=26) vs. placebo (n=26)
  - Primary outcome: Mean change in FEV_1 at 24 weeks
  - Results:
    - Improved FEV_1 at 24 / 48 w (p<0.001)
    - Similar safety profile



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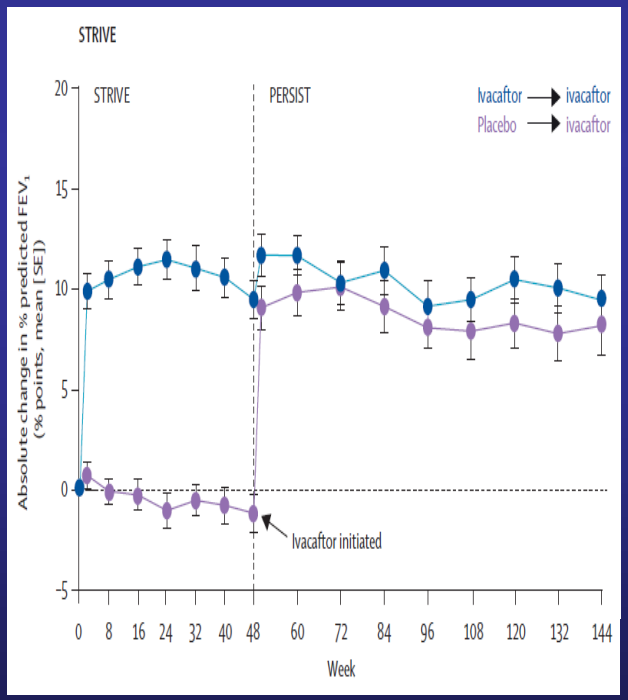
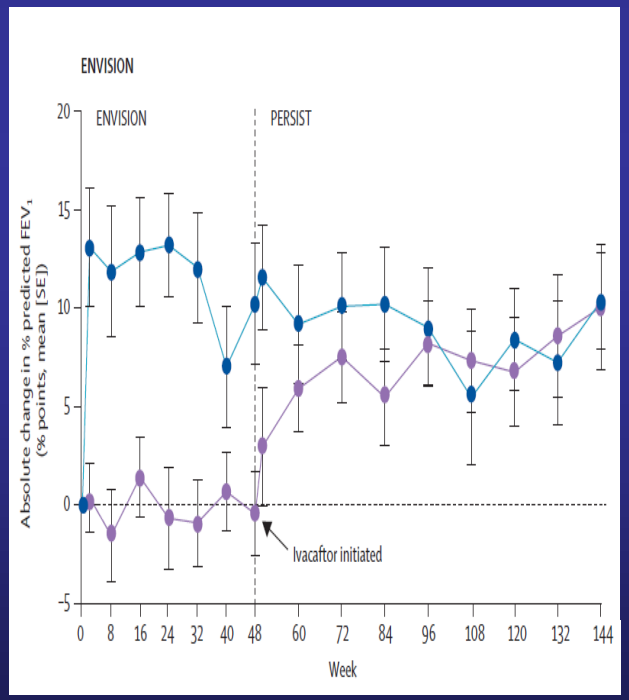
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

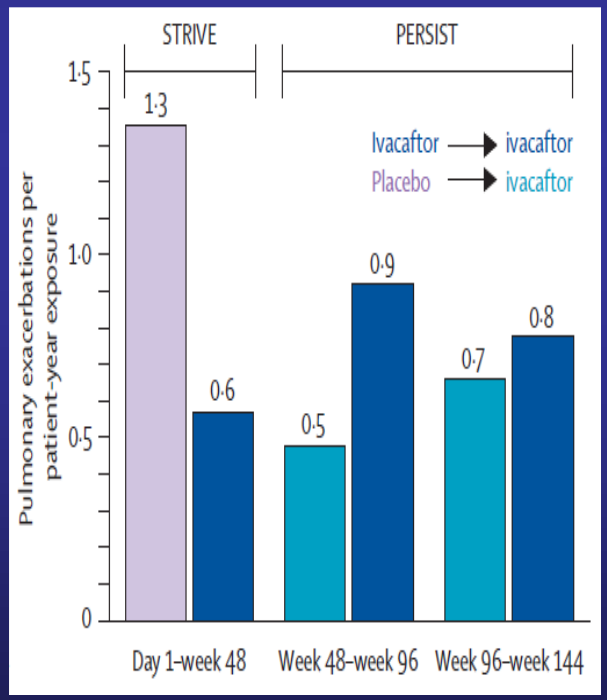
Davies JC, et al. Am J Respir Crit Care Med 2013;187(11):1219-25.

CFTR Modulators: Ivacaftor

- PERSIST study – Open-label, Extension study (of STRIVE / ENVISION)
  - Ivacaftor 150mg q12h (n=192) x 96 weeks (up to 144 weeks)
  - Results:
    - Similar safety profile (vs. previous studies)
    - Persisting efficacy…



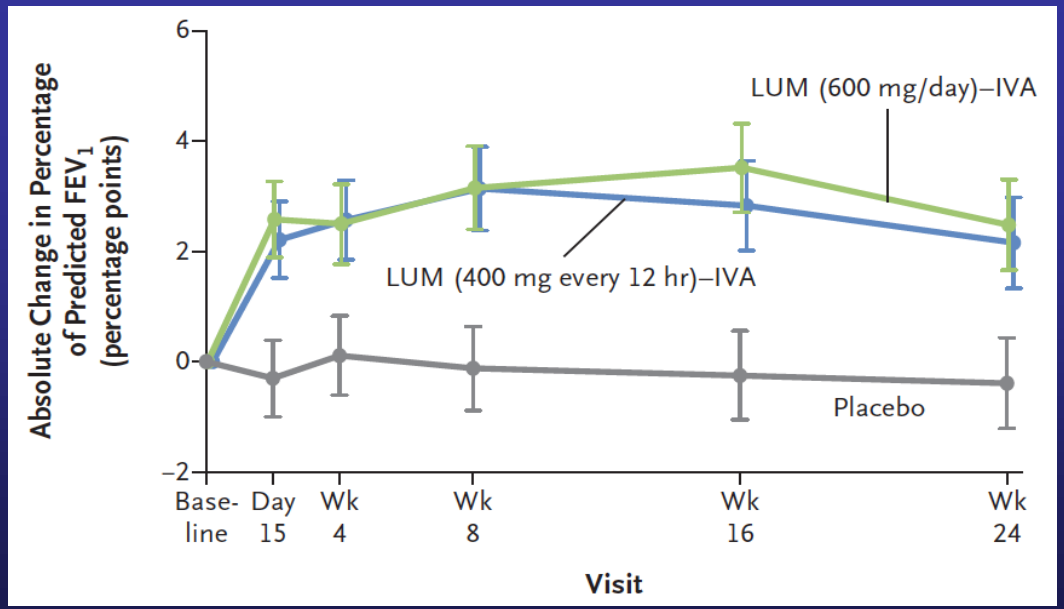




McKone EF, et al. Lancet Respir Med 2014;2:902-10.

CFTR Modulators: Lumacaftor / Ivacaftor

- TRAFFIC & TRANSPORT trials - Phase 3, randomized, DB, PC studies
  - Study population: CF; homozygous F508del-CFTR mutation; FEV_1 40-90%
  - Demographics: Age ≥ 12 y (mean age 25 y); mean FEV_1 = 60%
  - L-600mg q24h + I-250mg q12h (n=368) / L-400mg + I-250mg q12h (n=369)
  - Primary outcome: Mean change in FEV_1 at 24 weeks
  - Results – Both treatment groups demonstrated:
    - Improved FEV_1 at 24 w ($p<0.001$)
    - Similar safety profile

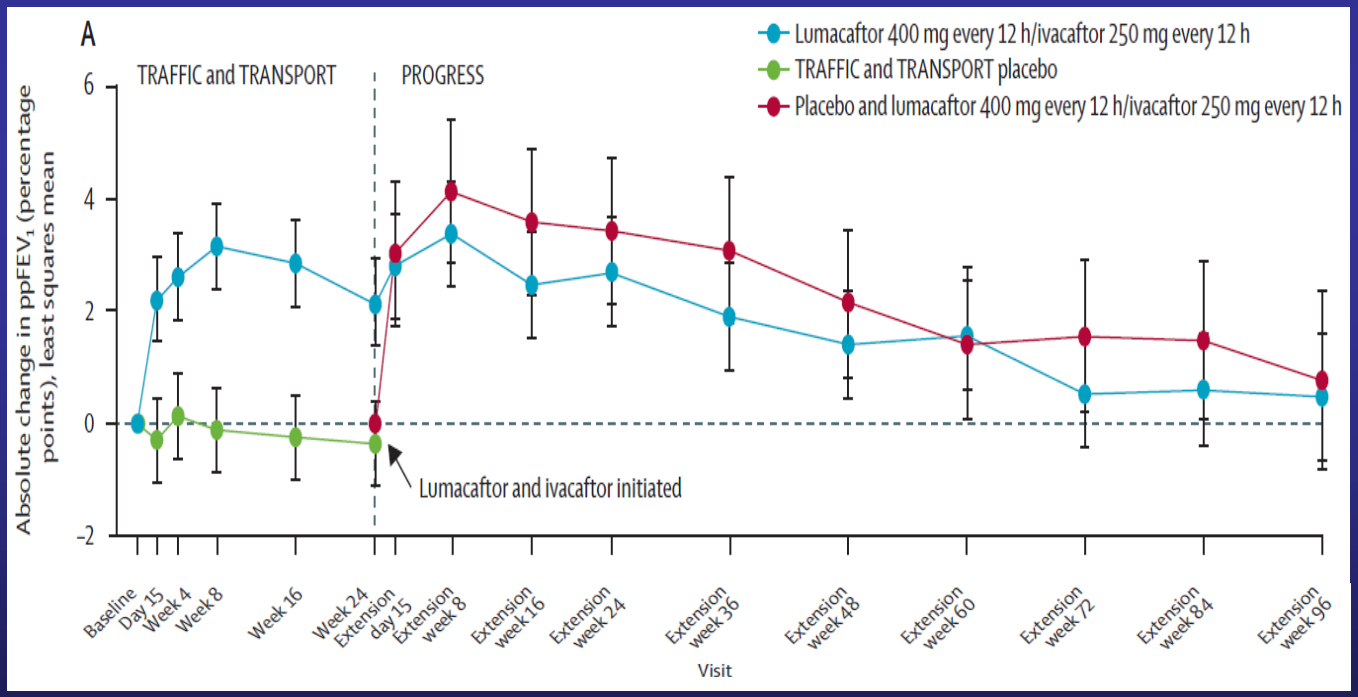


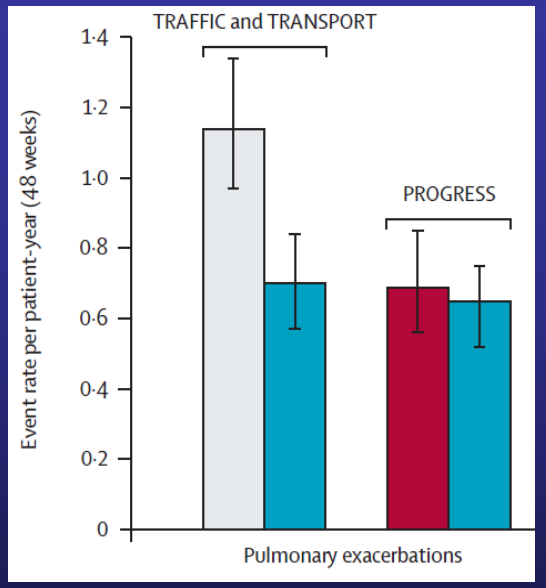
FEV_1 Normal/Mild (≥70%)
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

Wainwright CE, et al. N Eng J Med 2015;373(3):220-31.

CFTR Modulators: Lumacaftor / Ivacaftor

- PROGRESS study – DB, Extension study (of TRAFFIC / TRANSPORT)
  - L-400mg + I-250mg q12h (n=516) x 96 weeks (up to 120 weeks)
  - Results:
    - Similar safety profile (vs. previous studies)
    - Persisting efficacy…

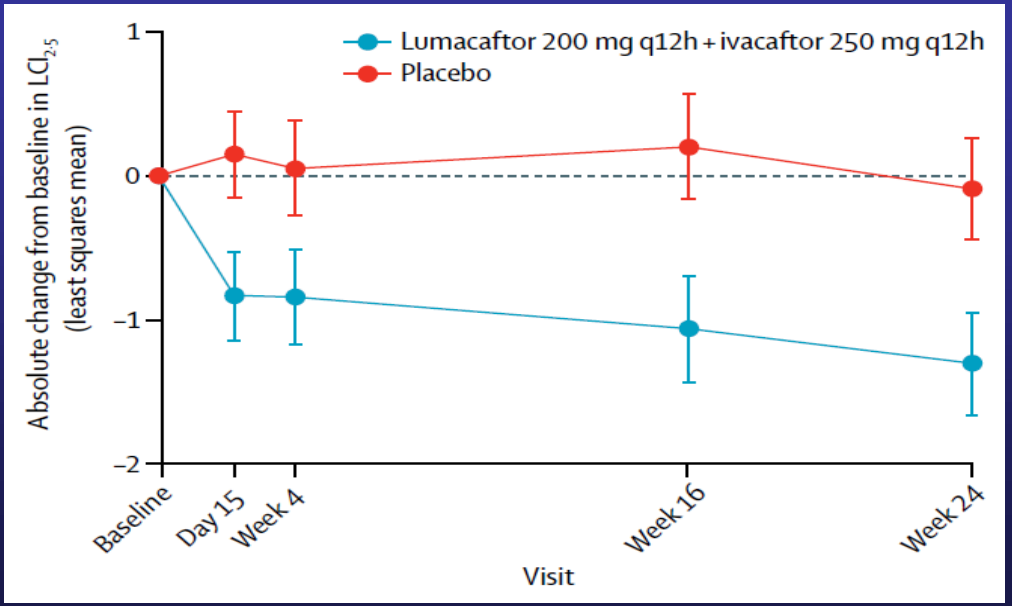




Konstan MW, et al. Lancet Respir Med 2017;5:107-18.

CFTR Modulators: Lumacaftor / Ivacaftor

- Phase 3, randomized, DB, PC study
  - Study population: CF; homozygous F508del-CFTR mutation; $FEV_1 \geq 70\%$
  - Demographics: Age $\geq$ 6-11 y (mean age 9 y); mean $FEV_1 = 90\%$
  - L-200mg + I-250 mg q12h (n=103)
  - Primary outcome: Mean change in $LCI_{2.5}$ up to end of treatment (24 weeks)
  - Results:
    - Similar safety profile
    - Improved $LCI_{2.5}$ (vs. BSL and vs. placebo) ($p<0.001$)

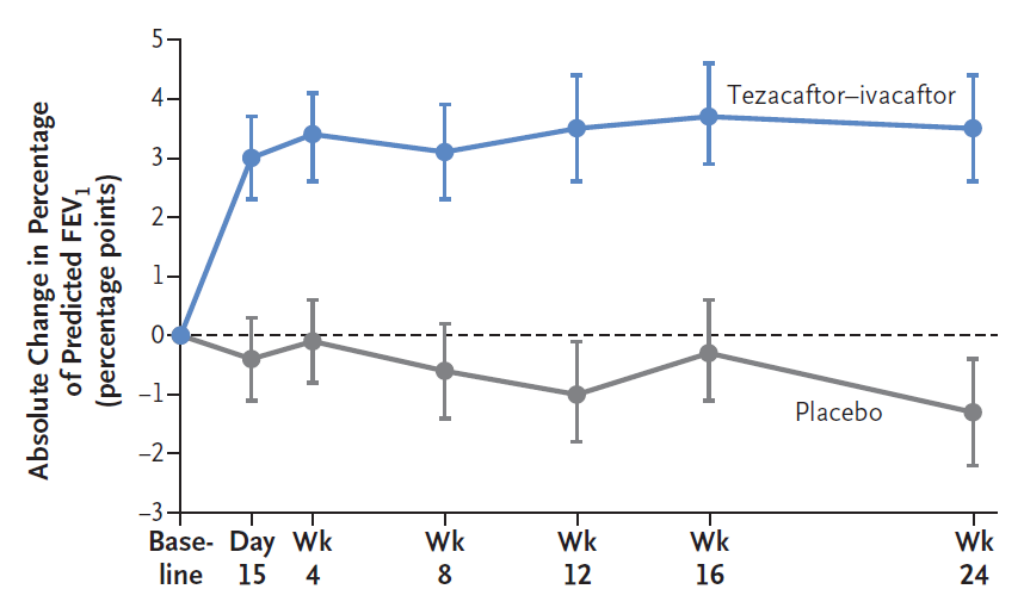


FEV_1 Normal/Mild (≥70%)
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

Ratjen, et al. Lancet Respir J 2017; 5: 557-67.

CFTR Modulators: Tezacaftor + Ivacaftor

- EVOLVE trial - Phase 3, randomized, DB, PC study
  - Study population: CF; homozygous F508del-CFTR mutation; FEV_1 40-90%
  - Demographics: Age $\geq$ 12 y (mean age ~26 y); mean FEV_1 = 60%
  - T-100mg PO Q24h + I-150mg PO Q12H (n=251) vs. placebo (n=258)
  - Primary outcome: Absolute change in FEV_1 at 24 weeks
  - Results:
    - Improved FEV_1 at 24 w ($p<0.001$)
    - Similar safety profile



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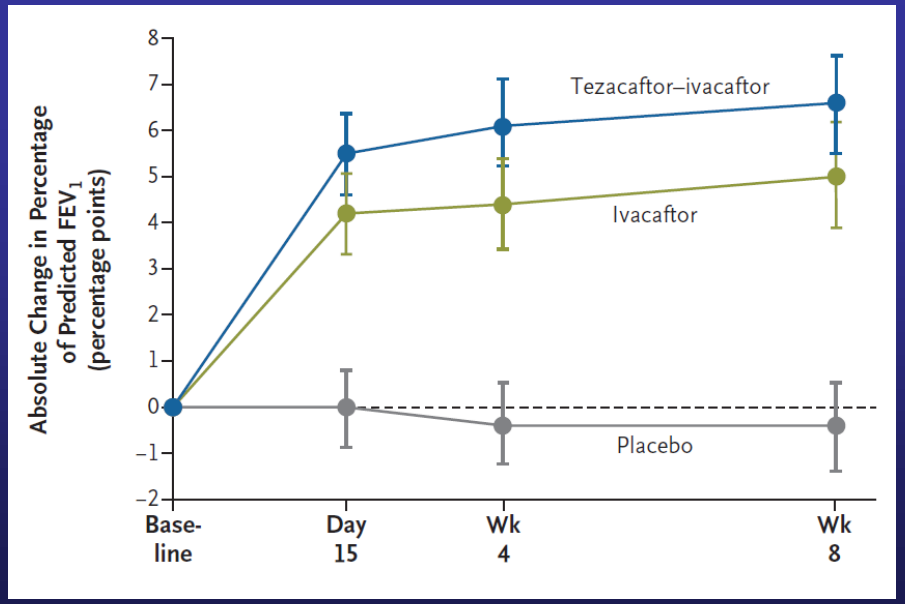
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

Taylor-Cousar JL, et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709846.

CFTR Modulators: Tezacaftor + Ivacaftor

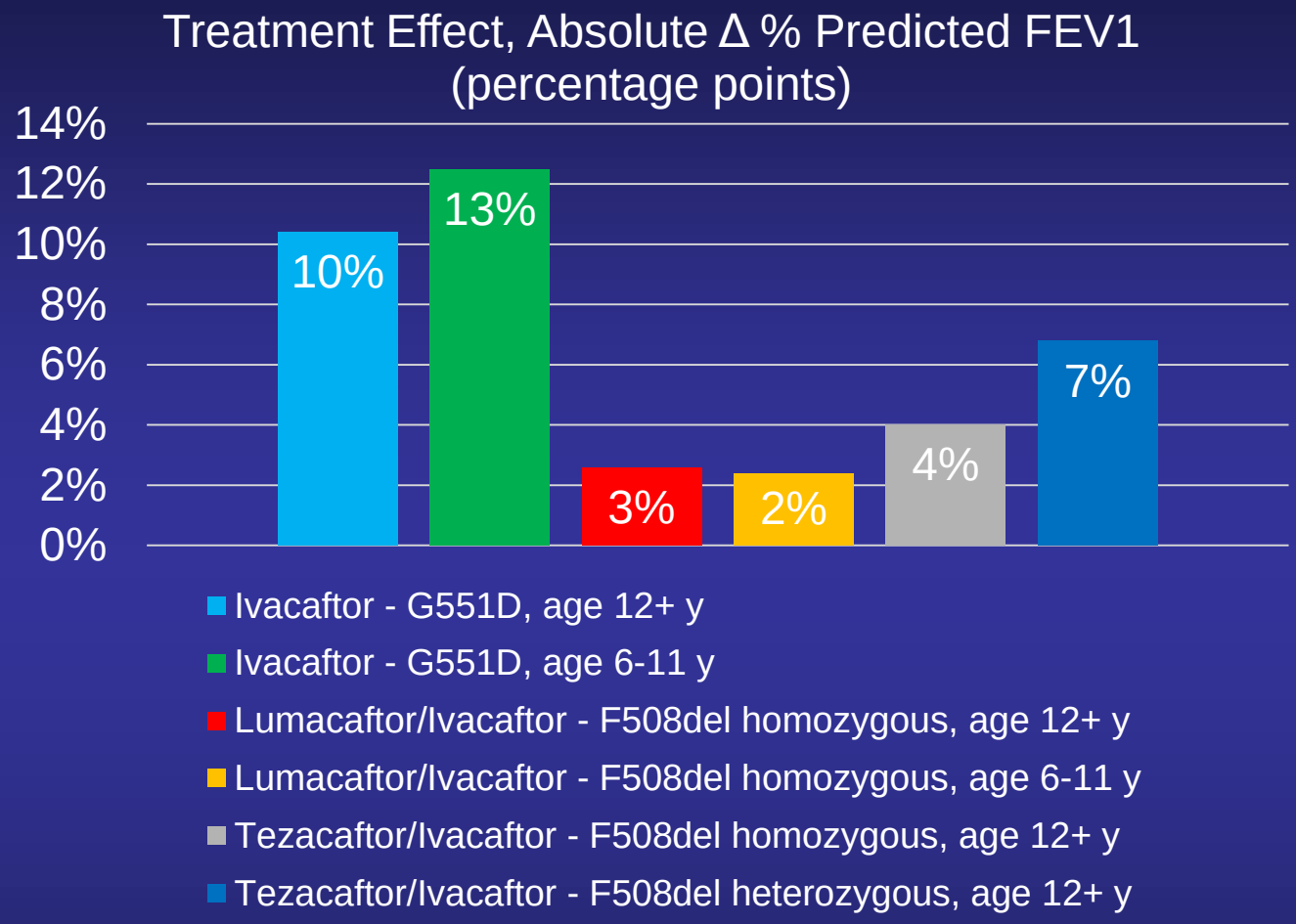
- EXPAND trial - Phase 3, randomized, DB, PC, cross-over study
  - Study population: CF; heterozygous F508del-CFTR mutation + CFTR mutation with residual function; FEV_1 40-90%
  - Demographics: Age $\geq$ 12 y (mean age 35 y); mean FEV_1 = 62%
  - T-100mg Q24H + I-150mg Q12H (n=83) vs. I-150mg Q12H (n=81) vs. placebo (n=80)
  - Primary outcome: Mean of the absolute change in FEV_1 at 4 and 8 weeks
  - Results:
    - Improved FEV_1 ($p<0.001$)
    - Similar safety profile



FEV_1 Normal/Mild (≥70%)
FEV_1 Moderate (40% to 69%)
FEV_1 Severe (<40%)

Rowe SM, et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709847.

Comparison of CFTR Modulators



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

Davies JC, et al. Am J Respir Crit Care Med 2013;187:1219-25.

Ratjen, et al. Lancet Respir J 2017; 5: 557-67.

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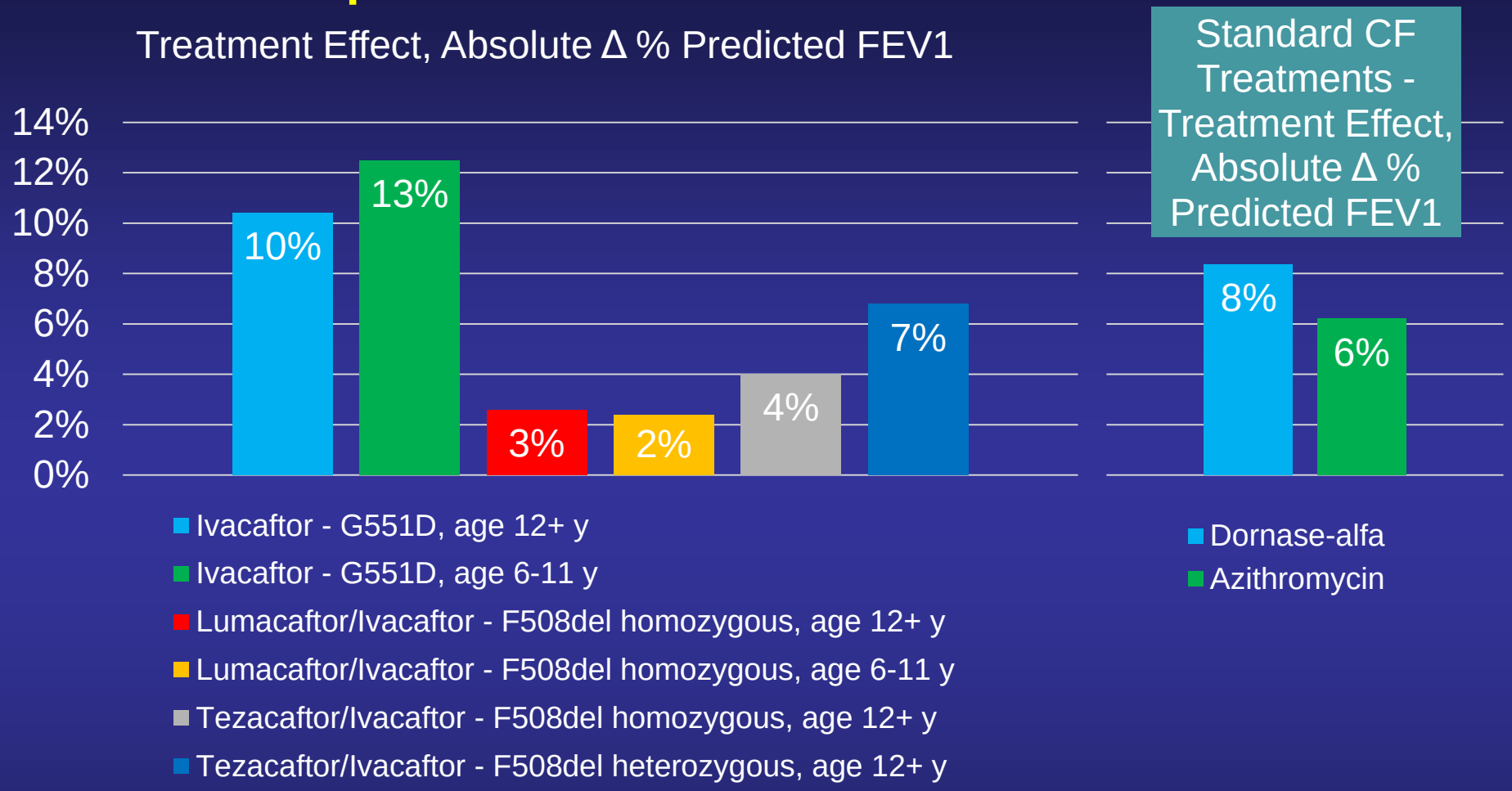
Comparison of CFTR Modulators



Yang C, et al. Cochrane Database; 2016: Issue 4. No. CD001127. DOI: 10.1002/14651858.CD001127.pub3.

Saiman L, et al. JAMA 2003; 290:1749-56.

Comparison of CFTR Modulators

Study	CFTR Modulator	CFTR	Age	APE Rate	Weight	BMI	QOL
Ramsey et al	Ivacaftor	G551D	≥ 12 y	55% ↓	↑	NR	↑
Davies et al	Ivacaftor	G551D	6-11 y	NR	↑	↑	NC
Wainwright et al	Lumacaftor + Ivacaftor	F508del homo	≥ 12 y	39% ↓	NR	↑	NC
Ratjen et al	Lumacaftor + Ivacaftor	F508del homo	6-11 y	NR	NR	NC	NC
Taylor et al	Tezacaftor + Ivacaftor	F508del homo	≥ 12 y	35% ↓	NR	NC	↑
Rowe et al	Tezacaftor + Ivacaftor	F508del homo	≥ 12 y	NC	NC	NC	↑

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

Davies JC, et al. Am J Respir Crit Care Med 2013;187:1219-25.

Wainwright CE, et al. NEJM. 2015;373(3):220-31.

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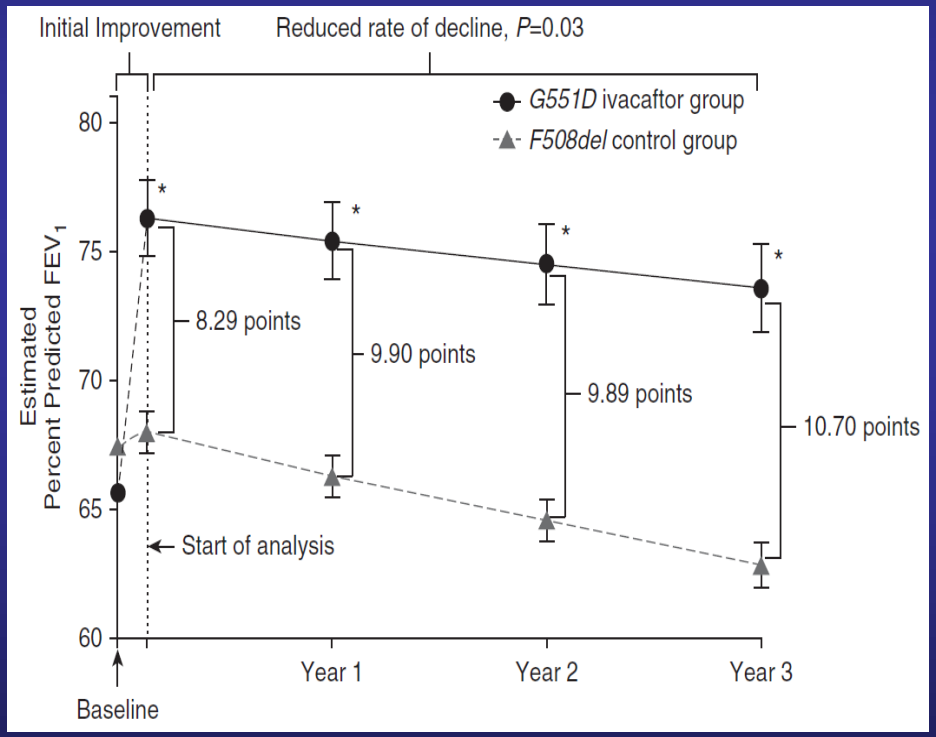
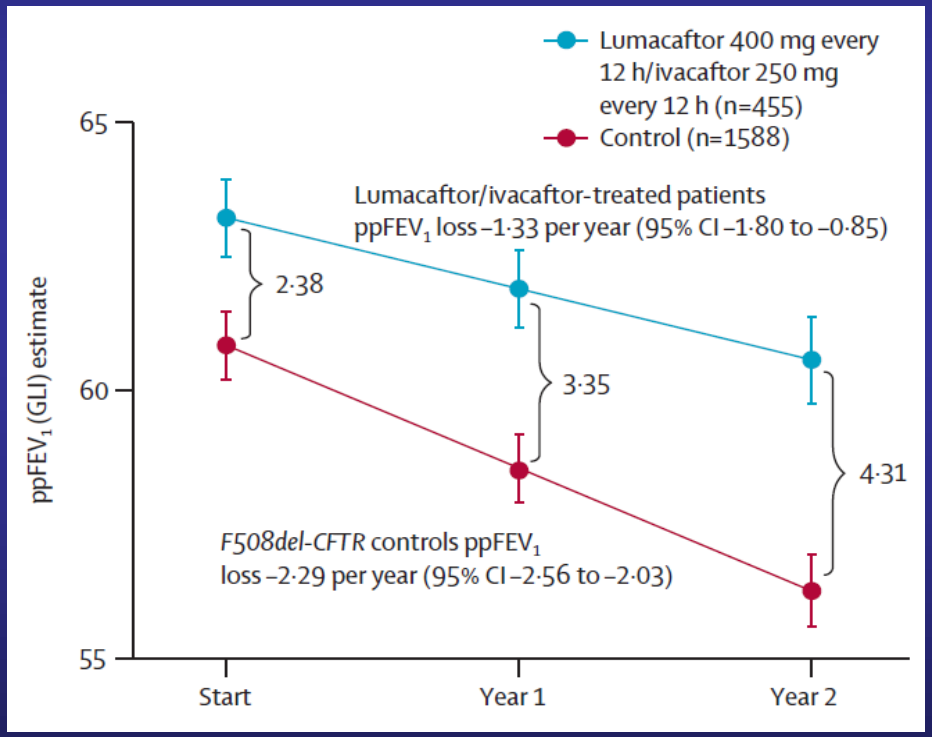
Rowe SM, et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709847.

Comparison of CFTR Modulators

- Ivacaftor: Data derived from STRIVE, ENVISION, & PERSIST vs. CFFPR cohort
  - Reduced est. annual rate of FEV1 decline: -0.91% vs. -1.72% (p=0.03)
- Lumacaftor-Ivacaftor: Data derived from TRAFFIC & TRANSPORT vs. CFFPR cohort
  - Reduced est. annual rate of FEV1 decline: -1.33% vs. -2.29% (p<0.001)



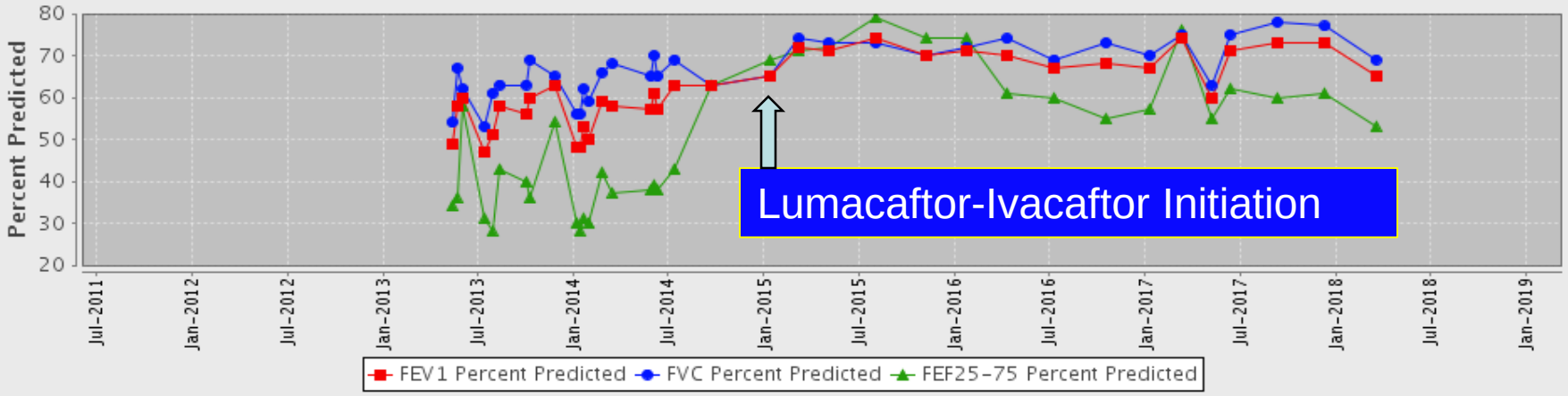


Sawicki GS, et al. Am J Respir Crit Care Med 2015;192:836-42.

Konstan MW, et al. Lancet Respir Med 2017;5:107-18.

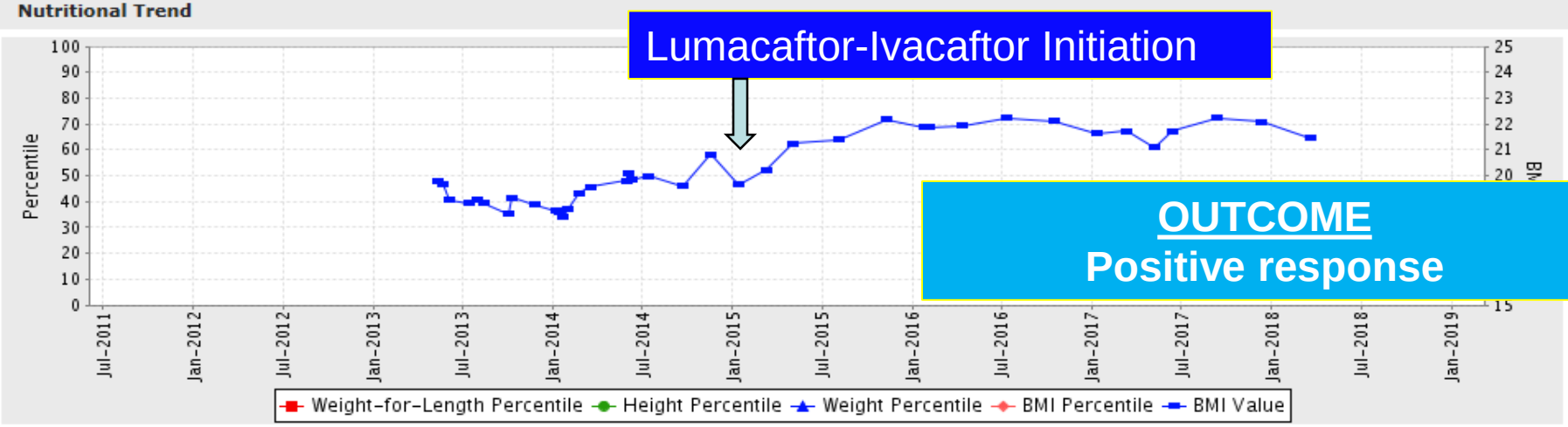
Impact of CFTR Modulators in the “Real” World

PFTs - % Predicted Homozygous F508del CFTR mutation



Last FEV1 Date:	03/19/2018	**Last FEV1 Value:**	2.76
Last FVC Date:	03/19/2018	**Last FVC Value:**	3.57
Last FEF25-75 Date:	03/19/2018	**Last FEF25-75 Value:**	2.35

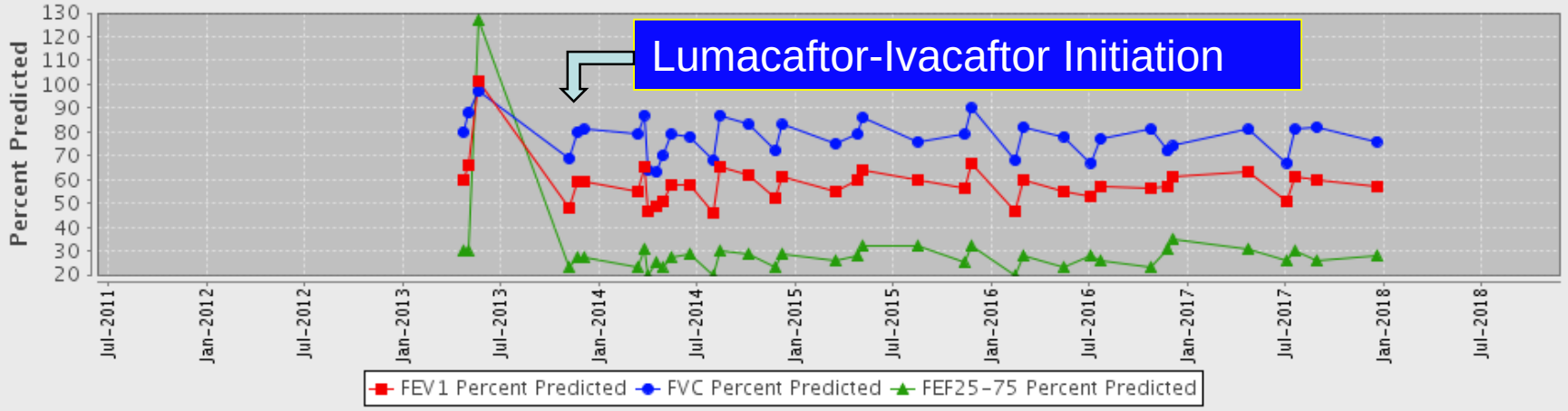
Nutritional Trend



OUTCOME
Positive response

Impact of CFTR Modulators in the “Real” World

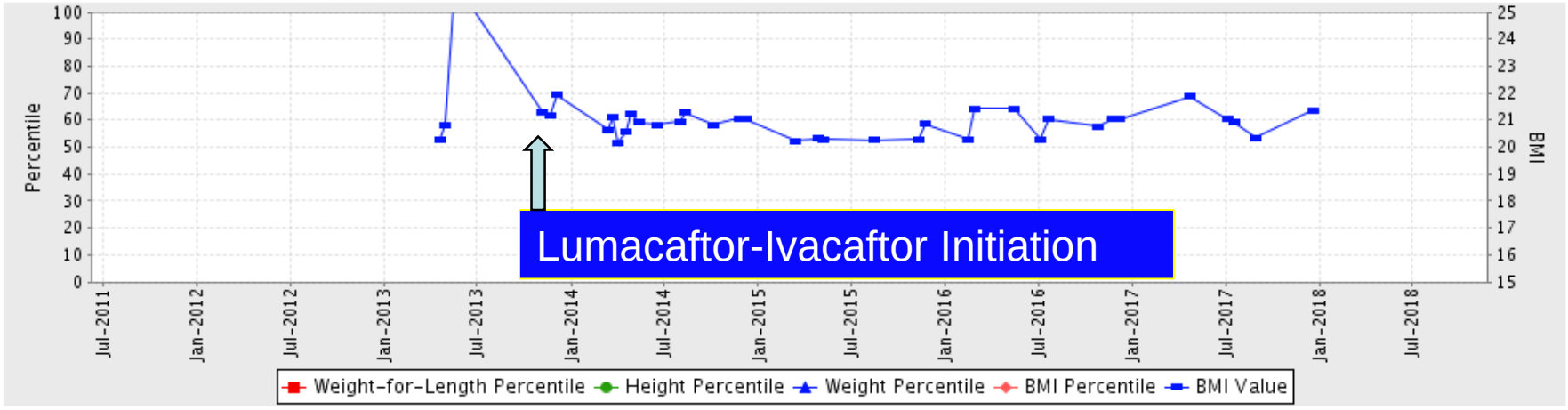
PFTs - % Predicted Homozygous F508del CFTR mutation



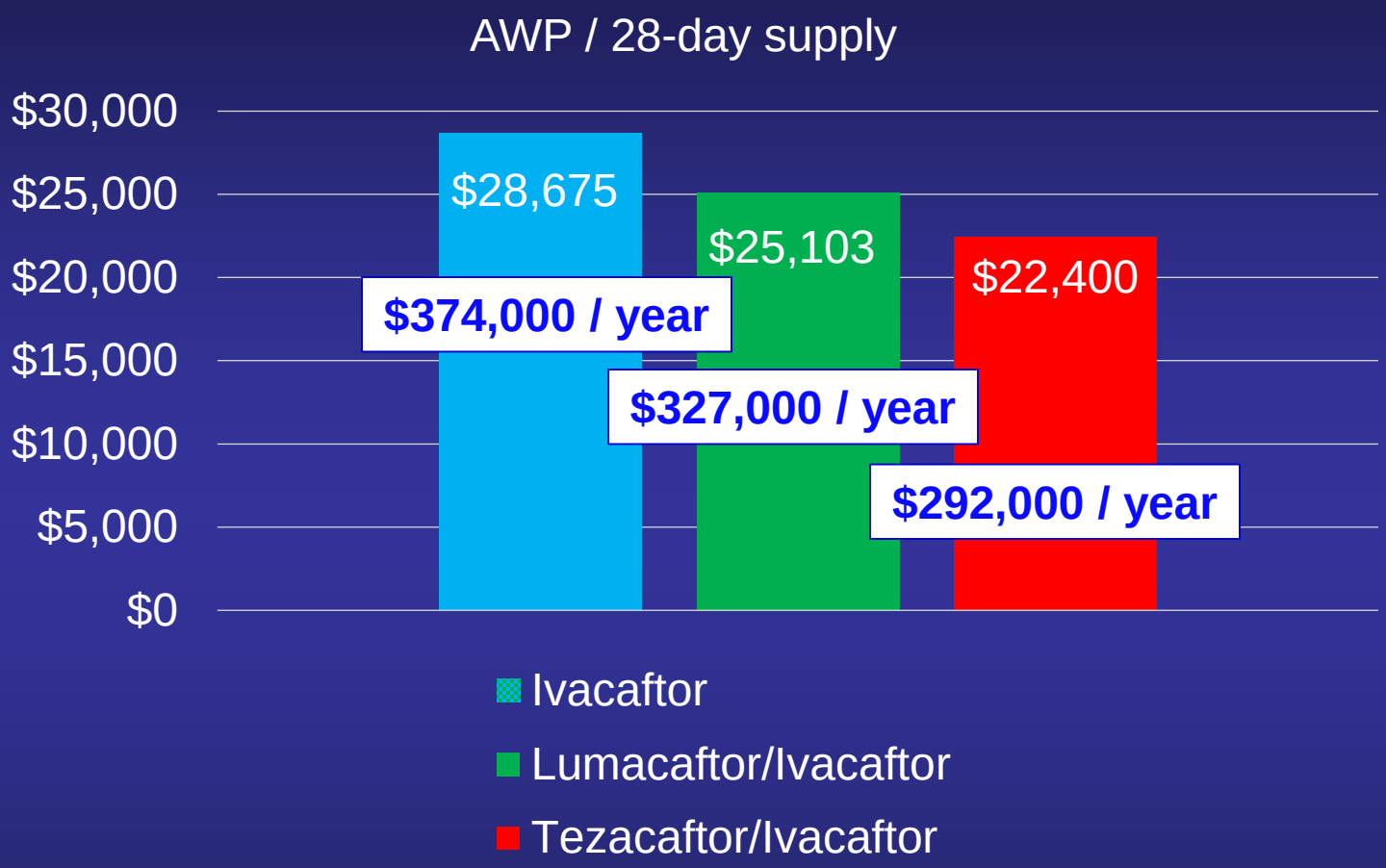
Last FEV1 Date:	12/18/2017	**Last FEV1 Value:**	1.68
Last FVC Date:	12/18/2017	**Last FVC Value:**	2.68
Last FEF25-75 Date:	12/18/2017	**Last FEF25-75 Value:**	0.9

OUTCOME
Equivocal response

Nutritional Trend



Comparison of CFTR Modulators



Lexi-comp: Ivacaftor. Accessed 2-28-18.

Lexi-comp: Lumacaftor/Ivacaftor. Accessed 2-28-18.

https://www.reuters.com/article/brief-vertex-pharma-says-established-who/brief-vertex-pharma-says-established-wholesale-acquisition-cost-of-292000-for-symdeko-in-u-s-on-annual-basis-idUSFWN1Q21HH . Accessed 2-28-18.

CFTR Modulator Dosing

CFTR Modulator	Age	Dosing	Special Directions
Ivacaftor	2-5 years (<14kg)	50mg BID	Take w/ fat-containing meal. Dose reduction required in moderate-severe hepatic dysfunction.
	2-5 years (≥14kg)	75mg BID	
	≥ 6 years	150mg BID	
Lumacaftor (L) + Ivacaftor (I)	6-11 years	L-100mg + I-125mg / tab: 2 BID	
	≥ 12 years	L-200mg + I-125mg / tab: 2 BID	
Tezacaftor (T) + Ivacaftor (I)	≥ 12 years	T-100mg + I-150mg / tab: 1 QAM AND I-150mg / tab: 1 QPM	

http://pi.vrtx.com/files/uspi_ivacaftor.pdf

CFTR Modulator DDIs

- Ivacaftor: CYP3A substrate
- Tezacaftor: CYP3A substrate, Mild CYP3A inducer
- Lumacaftor: Strong CYP3A inducer

Mechanism of DDI	Medication: Examples	CFTR Mod.	AUC	Cmax	Dose Adjustment
CYP3A inhibition (mod.)	Erythromycin Fluconazole	Ivacaftor	↑	↑	Once daily I
		Tezacaftor	?	?	QOD, alternating between T+I and I
CYP3A inhibition (strong)	Clarithromycin Itraconazole	Ivacaftor	↑↑	↑↑	Twice weekly I
		Tezacaftor	↑	↑	Twice weekly T+I
CYP3A induction	Rifampin Carbamazepine Phenobarbital Phenytoin St. John's wort	Ivacaftor	↓↓	↓↓	Avoid concomitant use
		Tezacaftor	?	?	

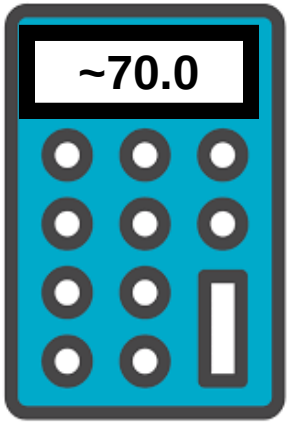
CFTR Modulator DDIs

- Ivacaftor: CYP3A substrate
- Tezacaftor: CYP3A substrate, Mild CYP3A inducer
- Lumacaftor: Strong CYP3A inducer

- Lumacaftor / Ivacaftor dose adjustment:
  - Scenario: Co-treatment with CYP3A inhibitors:
    - Lumacaftor / ivacaftor added to a regimen that includes a strong CYP3A inhibitor (e.g., itraconazole)… decrease lumacaftor / ivacaftor dose to 1 tablet daily during the first week of treatment
    - Strong CYP3A inhibitor (e.g., itraconazole) added to a regimen that includes lumacaftor / ivacaftor… no dose adjustment needed

http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf

Are we achieving our vision?



F508del Mutation Prevalence	
F508del Mutation	**Percent of All People with CF**
Homozygous F508del	45.8
Heterozygous F508del	40.7
Neither F508del or Unknown	13.5

Prevalence of the 10 most common CFTR mutations

CFTR Mutation			Mutation Class	Number of Individuals	Percent of All People with CF
Legacy Name	cDNA Name	Protein Name			
F508del	c.1521_1523delCTT	p.Phe508del	2	24,901	86.4
G542X	c.1624G>T	p.Gly542X	1	1,342	4.7
G551D	c.1652G>A	p.Gly551Asp	3	1,280	4.4
R117H	c.350G>A	p.Arg117His	4	865	3.0
N1303K	c.3909C>G	p.Asn1303Lys	2	703	2.4
W1282X	c.3846G>A	p.Trp1282X	1	658	2.3
R553X	c.1657C>T	p.Arg553X	1	527	1.8
1717-1G->A	c.1585-1G>A		1	456	1.6
3849+10kbC->T	c.3717+12191C>T		5	435	1.5
621+1G->T	c.489+1G>T		1	431	1.5

CFF Patient Registry, 2016. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2016-Patient-Registry-Annual-Data-Report.pdf

DRUG DEVELOPMENT PIPELINE

VX-659 + tezacaftor + ivacaftor

STATUS
Phase Three

THERAPEUTIC APPROACH
Restore CFTR Function

This program is testing VX-659 in combination with tezacaftor and ivacaftor. VX-659 and tezacaftor (VX-661) are new CFTR correctors. Correctors are drugs designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. Once CFTR protein reaches the cell surface, ivacaftor helps facilitate the opening of the chloride channel to allow chloride and sodium (salt) to move in and out of the cell.

Status

A phase 3 study to test the safety and effectiveness of VX-659 in people with CF age 12 years or older is underway.

VX-445 + tezacaftor + ivacaftor

STATUS
Phase Three

THERAPEUTIC APPROACH
Restore CFTR Function

This program is testing VX-445 in combination with tezacaftor and ivacaftor. VX-445 and tezacaftor (VX-661) are new CFTR correctors. Correctors are drugs designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. Once CFTR protein reaches the cell surface, ivacaftor helps facilitate the opening of the chloride channel to allow chloride and sodium (salt) to move in and out of the cell.

Status

A phase 1 and 2 study to test the safety and tolerability of VX-445 is underway. A phase 3 study will begin soon.

CFF. https://www.cff.org/Trials/Pipeline

Summary

- CF is caused by a defect in the CFTR gene, which results in defective chloride transport, culminating in a cycle of obstruction, infection, and inflammation in the CF lung.
- Chronic treatment of CF lung disease is directed toward targeting the CFTR with CFTR modulators, while continuing to treat airway obstruction, infection and inflammation.
- All approved CFTR modulators have been shown to improve pulmonary function, albeit to different degrees, and have been show to reduce the incidence of acute pulmonary exacerbations.

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Questions