CFTR and a Path to a Cure

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Disclosures

- Our CF Center has been involved in some of the Vertex CFTR modulator clinical trials

Objectives

- Establish that defective Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein is the underlying cause of cystic fibrosis (CF)
- Review current CFTR modulator therapies and supporting data
- Consider the impact a novel viral pathogen (SARS-CoV-2) may have on individuals with Cystic Fibrosis

CF is a Life-Shortening Disease With Clinical Manifestations Throughout the Body

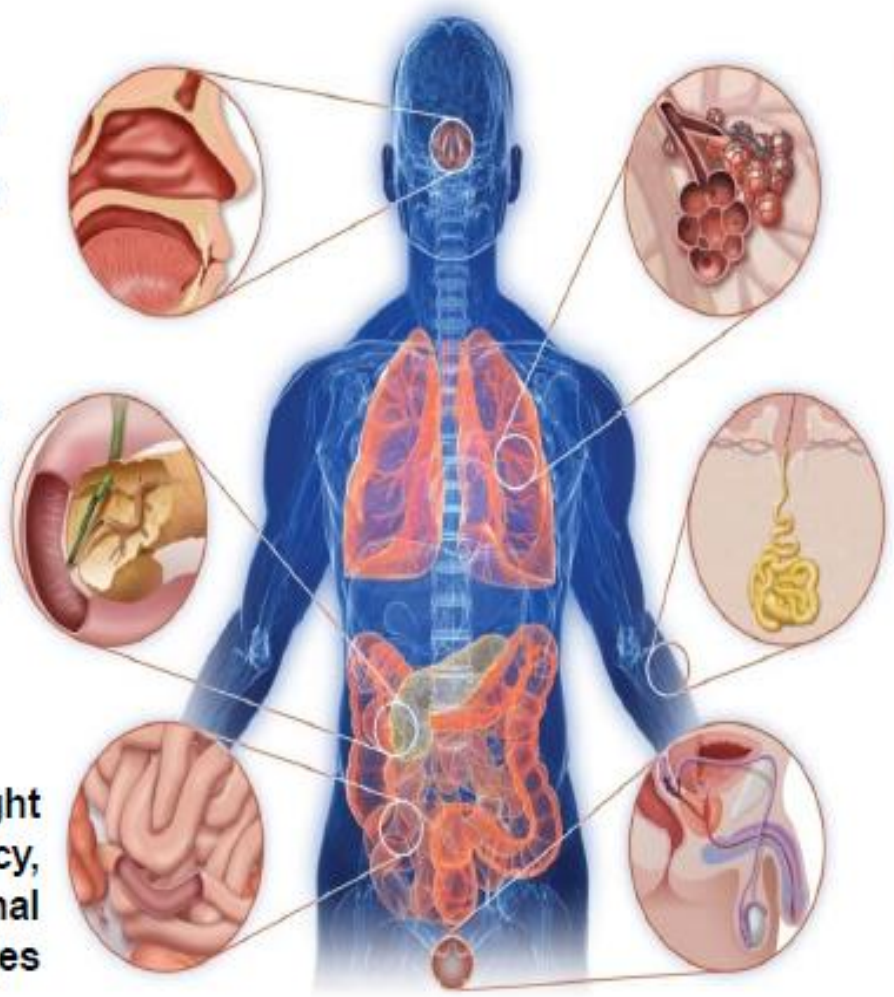
Sinus infections

Nasal polyps

Exocrine pancreatic insufficiency and resulting malnutrition

Endocrine pancreatic insufficiency and resulting CF-related diabetes

Failure to thrive/gain weight due to pancreatic insufficiency, digestive problems, and intestinal blockages



Reduced lung function

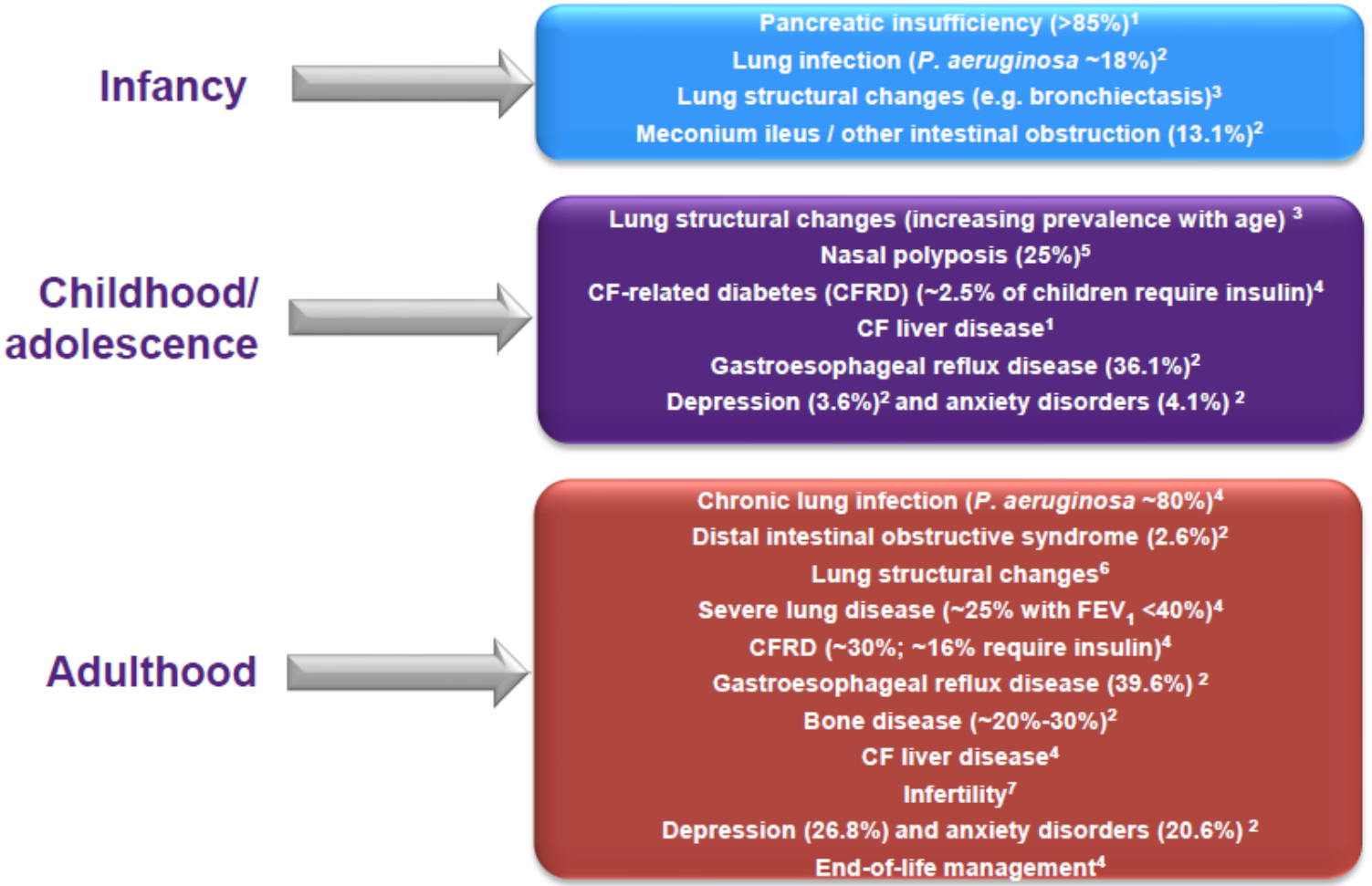
Frequent lung infections, inflammation, and progressive lung disease

Elevated Sweat Chloride

Reproductive Tract

- Infertility
- Congenital bilateral absence of the vas deferens (CBAVD) in men

Symptoms of CF Begin at an Early Age

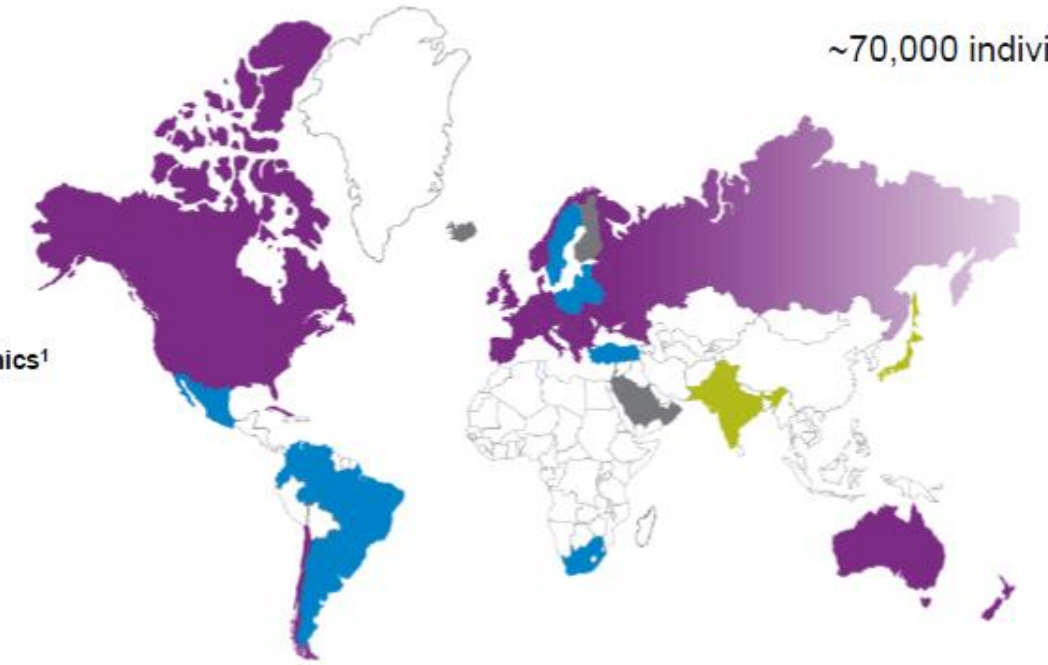


1. Wilschanski M, Durie PR. Gut. 2007;56(8):1153-1163. 2. Cystic Fibrosis Foundation (CFF) Patient Registry. 2017 Annual Data Report. Bethesda, MD: CFF; 2018.
3. Stick SM et al. J Pediatr. 2009; 155(5):623-628. 4.Yankaskas JR et al. Chest. 2004;125(1 suppl):1S-39S. 5. Davis PB et al. Am J Resp Crit Care Med.
1996;154(5):1229-1256. 6.de Jong et al. Thorax.2006;61:80-85. 7. O'Sullivan BP, Freedman SD. Lancet. 2009;373(9678):1891-1904.

CF Is a Rare Genetic Disease Primarily Affecting Caucasians

Worldwide Incidence Trends[1]

~70,000 individuals worldwide[1]



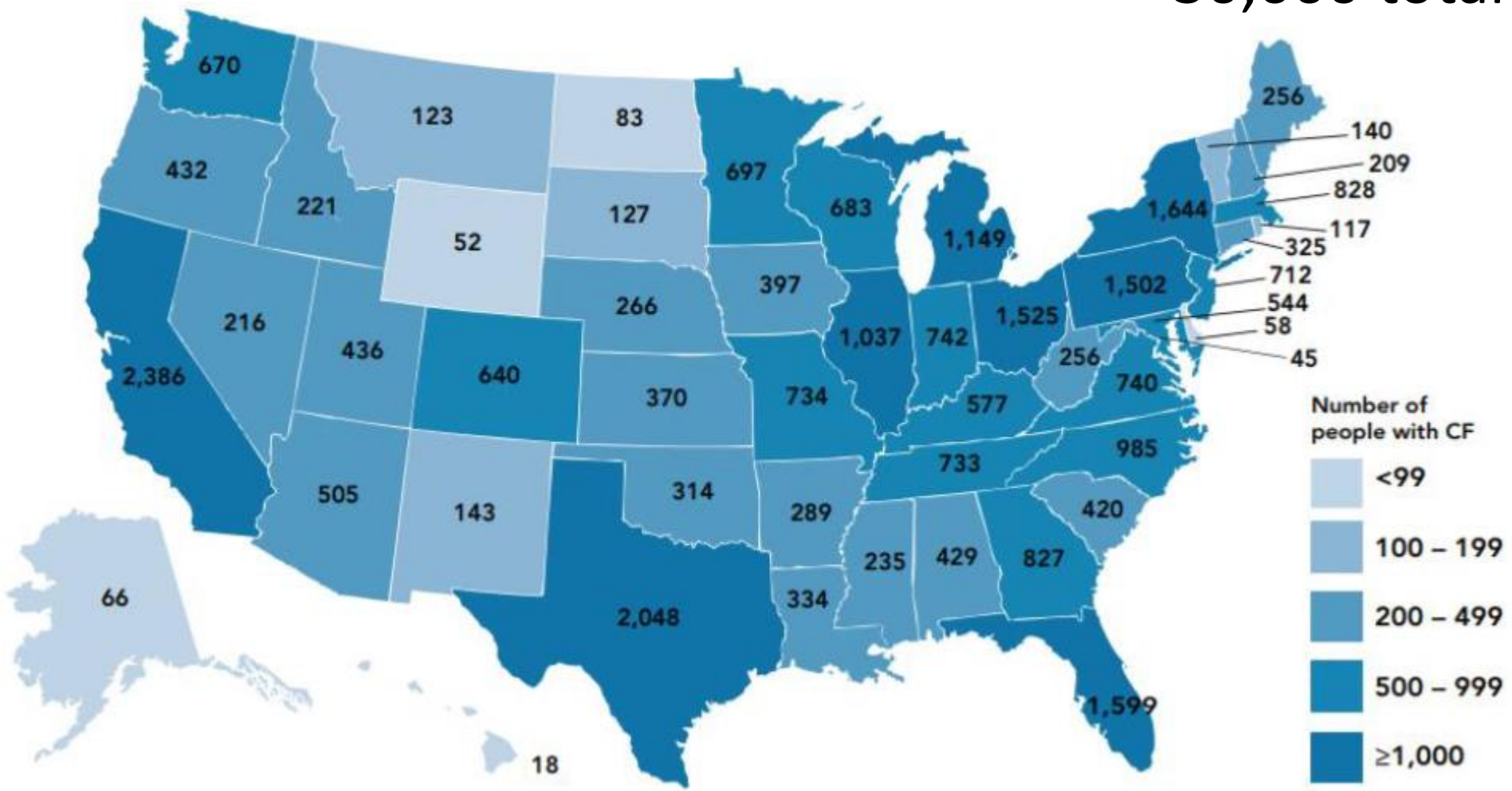
US CF 2016 Racial Demographics[1]

People with CF in US N=29,887	
Race (not mutually exclusive)	
White	93.6%
African American	4.6%
Other race	3.6%
Hispanic (any race)	8.7%

1. Graphic adapted from World Health Organization. The molecular genetic epidemiology of cystic fibrosis. Report of a joint meeting of WHO/ECFTN/ICF(M)A/ECFS, June 2002
2. Cystic Fibrosis Foundation (CFF) Patient Registry. 2017 Annual Data Report. Bethesda, MD: CFF; 2018.

Number of Individuals with CF Residing in Each State in 2017

~ 30,000 total in US

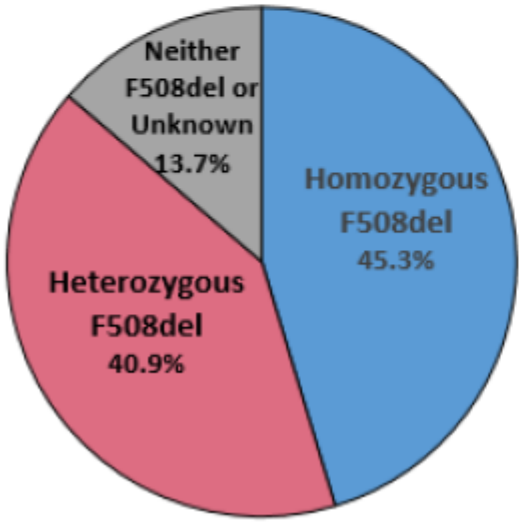


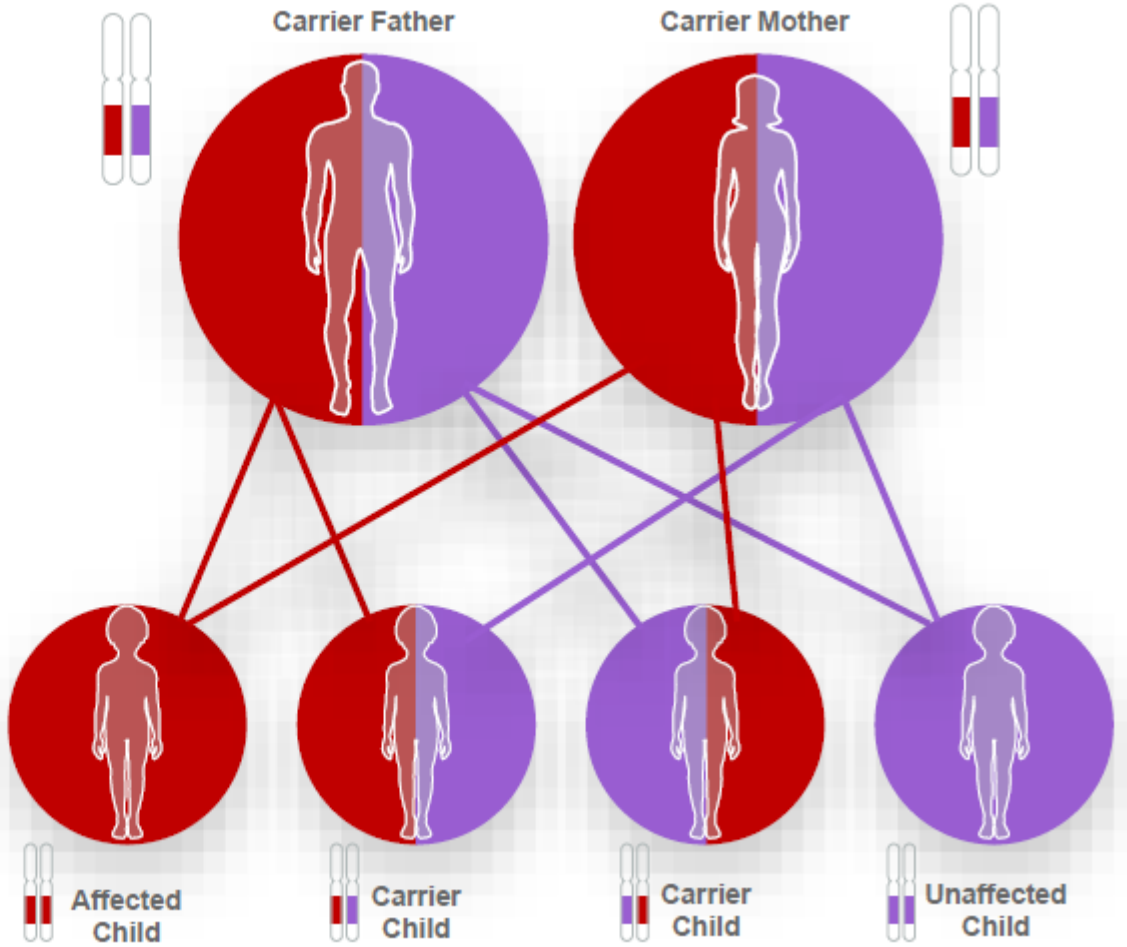
Cystic Fibrosis Foundation; 2017 Cystic Fibrosis Foundation Patient Highlights; https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Cystic-Fibrosis-Foundation-Patient-Registry-Highlights.pdf accessed January 8, 2019

CF Inheritance Pattern: Autosomal Recessive

- Each copy of the *CFTR* gene must carry a disease-causing mutation for CF to develop[1]

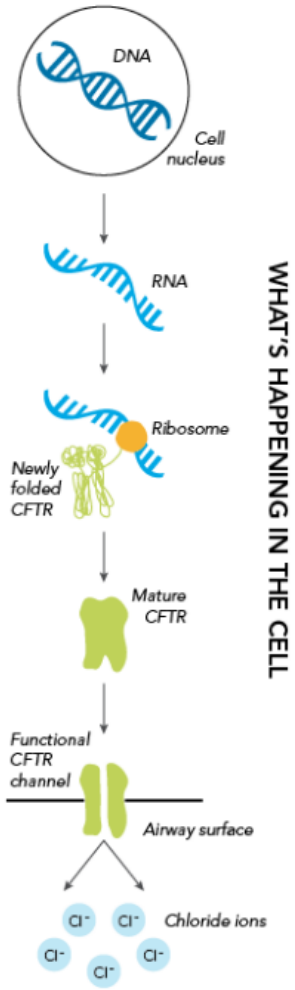
F508del Mutation Prevalence[2]

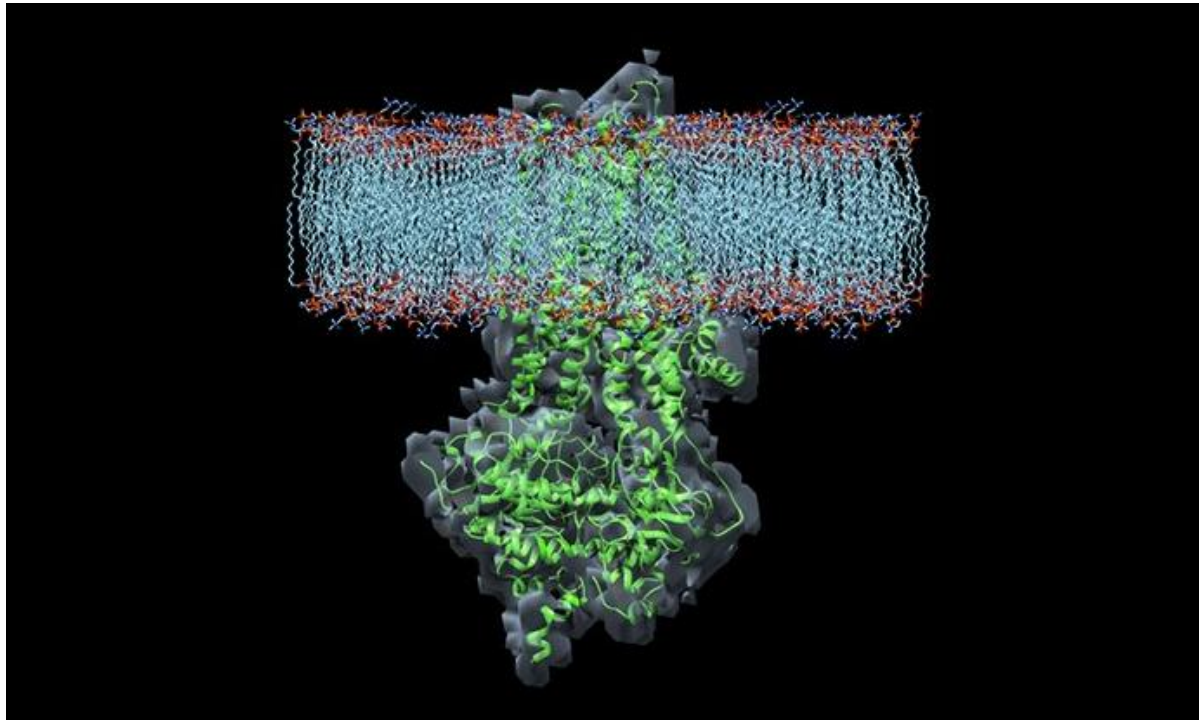




1. National Institutes of Health. Genetics Home Reference Handbook. http://ghr.nlm.nih.gov/handbook/inheritance.pdf. Published November 9, 2015
2. Cystic Fibrosis Foundation (CFF) Patient Registry. 2017 Annual Data Report. Bethesda, MD: CFF; 2018.

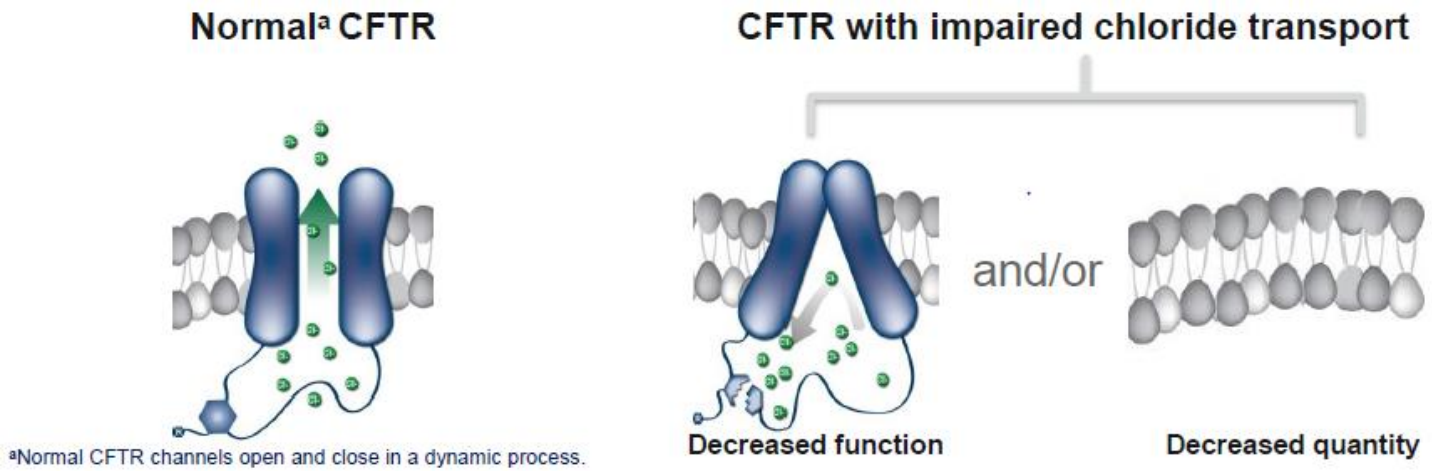
What’s happening in the cell?



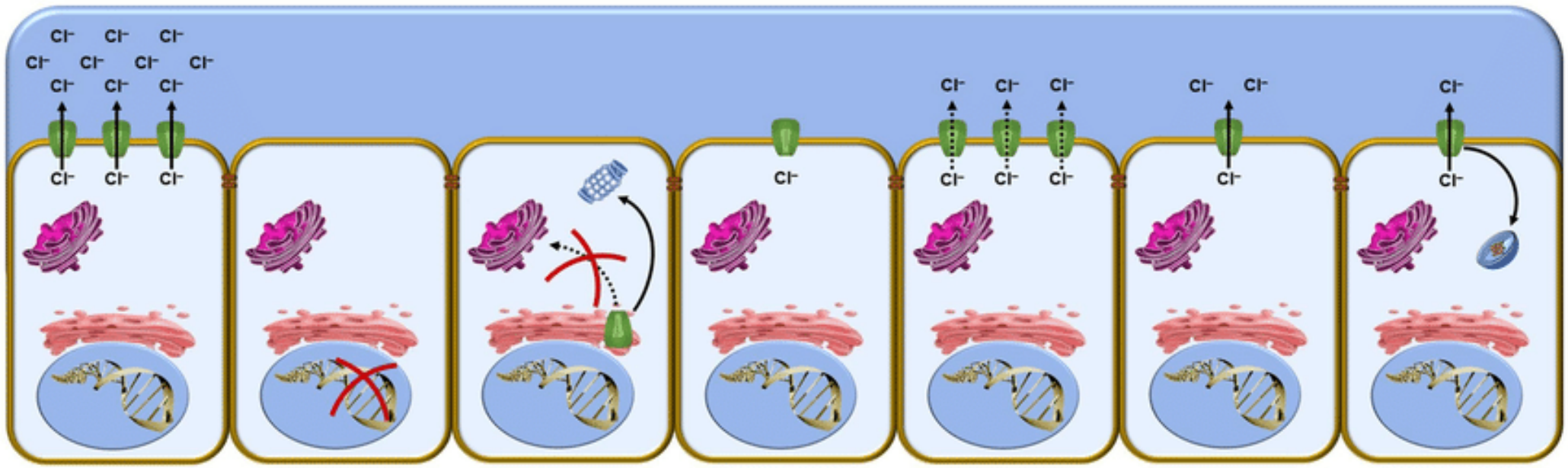


Loss of CFTR Protein Activity: the Underlying Cause of CF Disease

- ***Cystic fibrosis transmembrane conductance regulator*** **(CFTR)** gene encodes CFTR protein that functions at the cell surface of epithelial cells as a **channel to transport chloride** and bicarbonate
- CF caused by a **reduction in quantity and/or function of CFTR channels**
- **Impaired chloride ion transport** leads to fluid and electrolyte imbalances in epithelial tissues resulting in **thickened mucosal secretions**: lungs, pancreas, GI system and reproductive organs

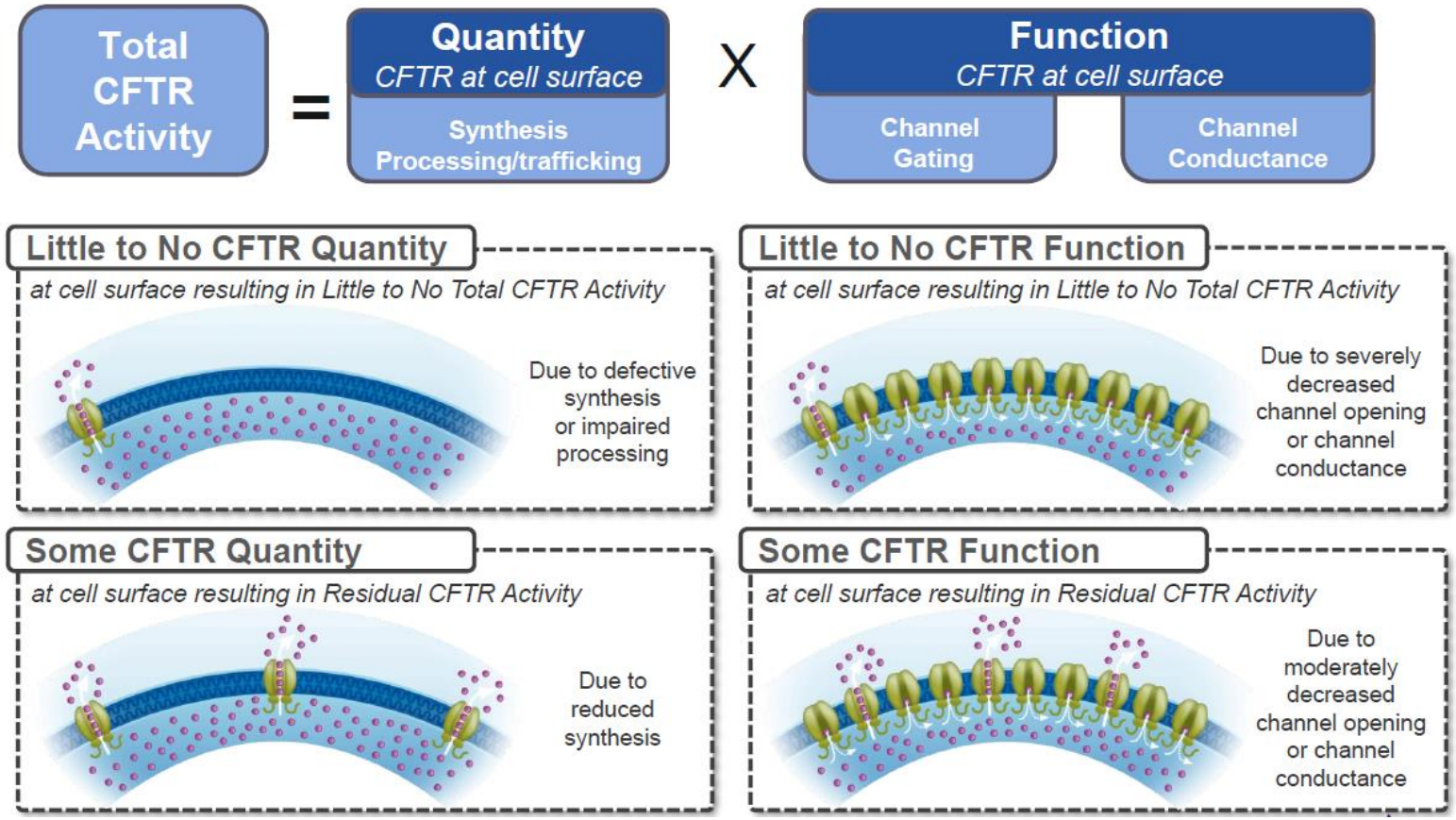


[a]Normal CFTR channels open and close in a dynamic process.



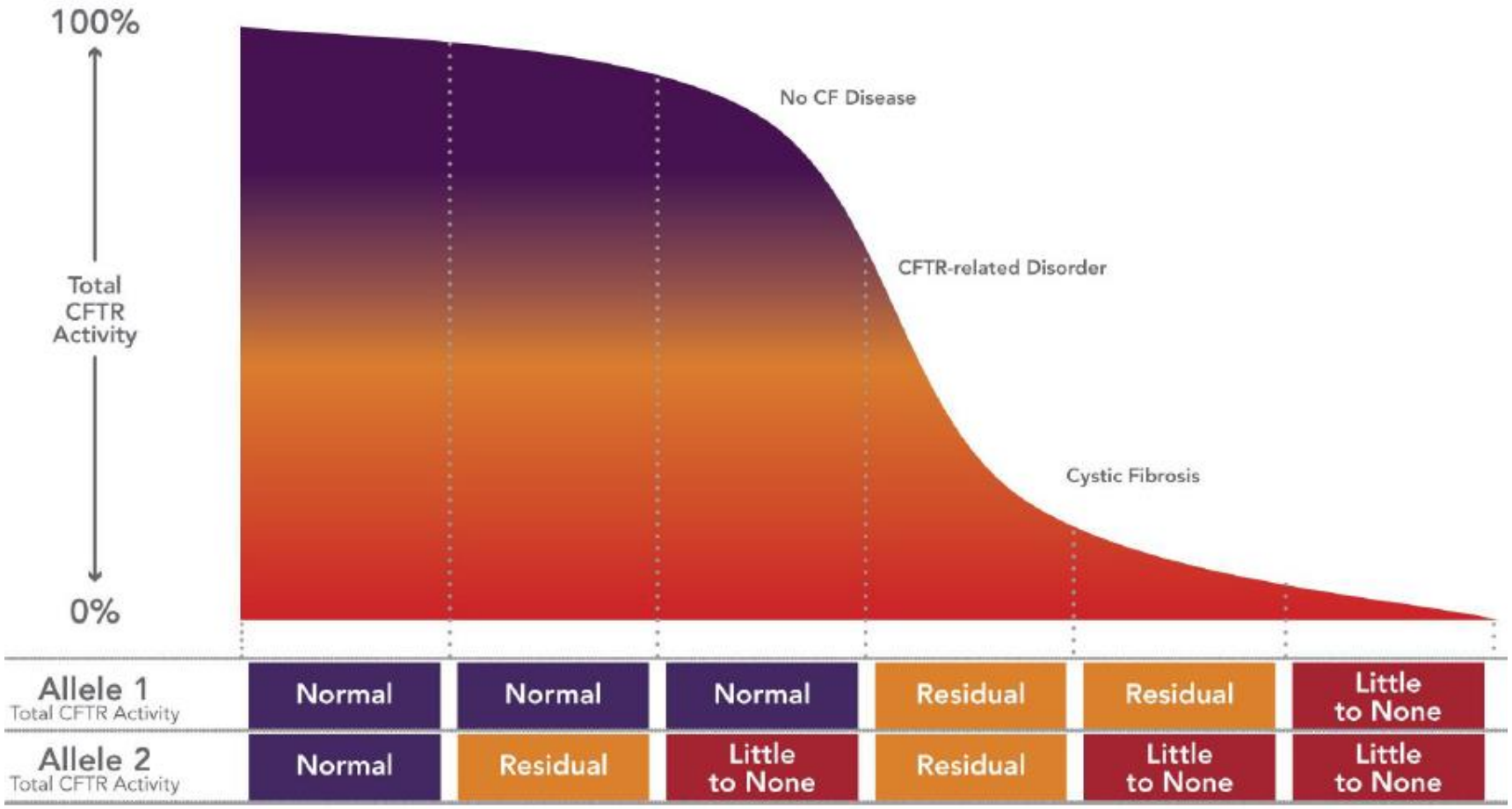
	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

Effect of CFTR Mutations on Total CFTR Activity

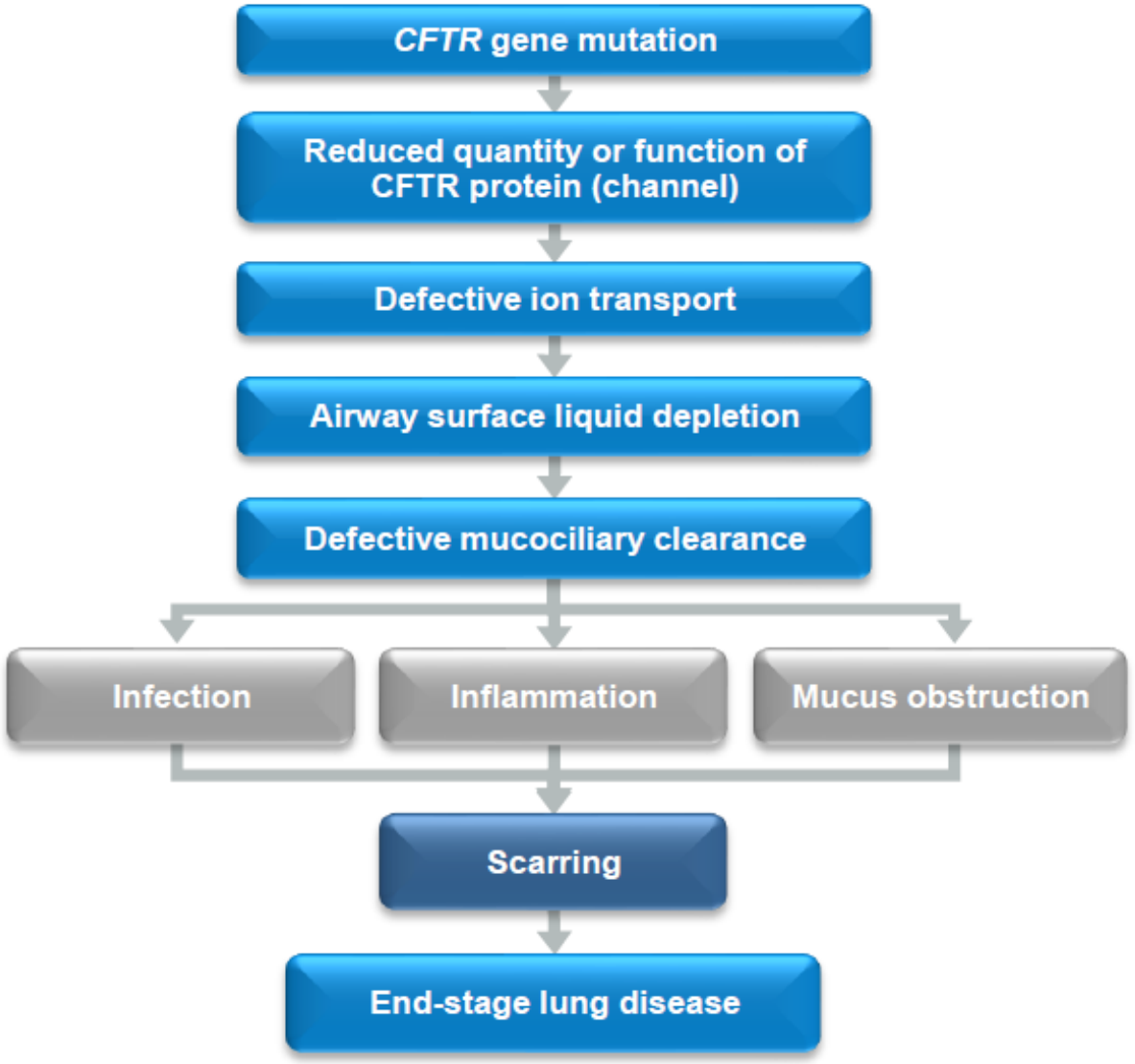


Zielenski J. Respiration 2000;67:117–33; Castellani C et al. J Cyst Fibros 2008;7:179–96

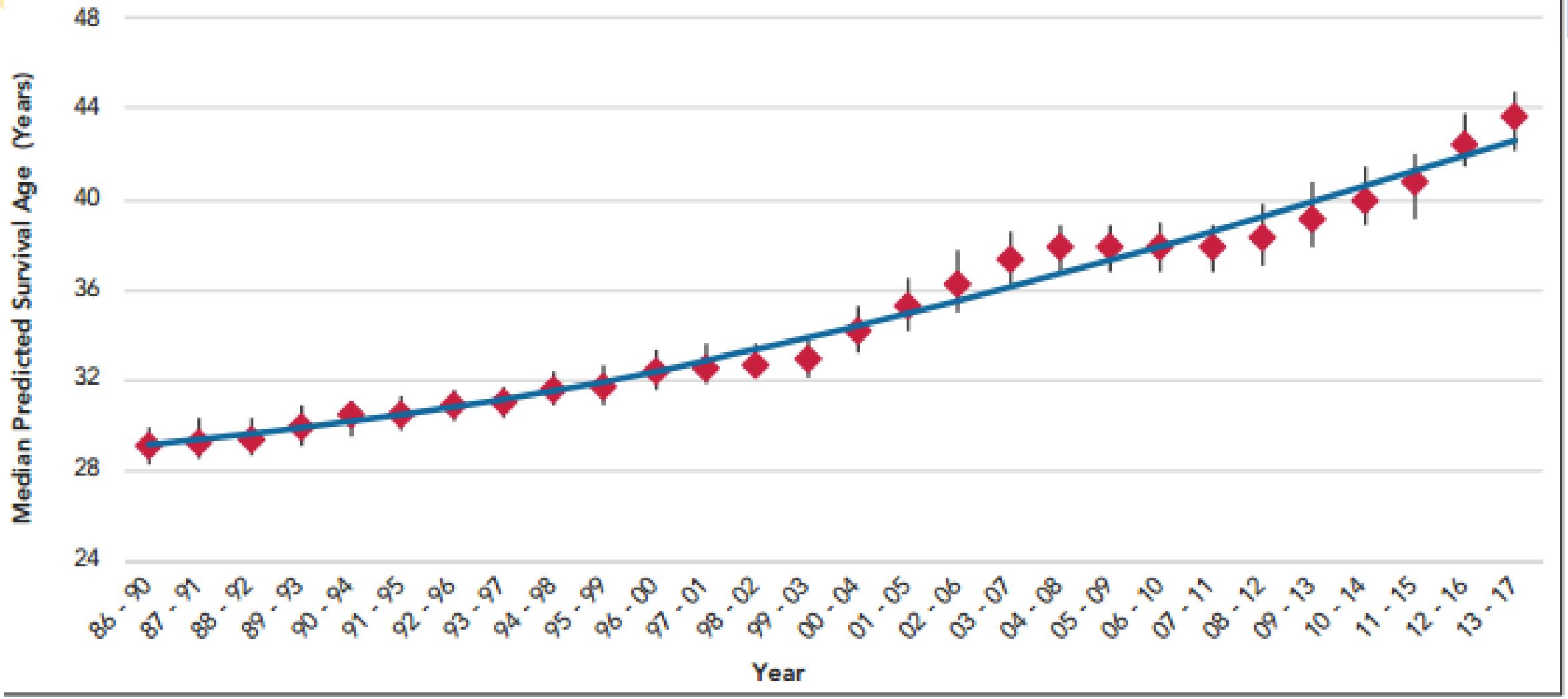
CFTR Genotype of Both Alleles determines Total CFTR Activity: CF Phenotype



Pathophysiology of CF Lung Disease



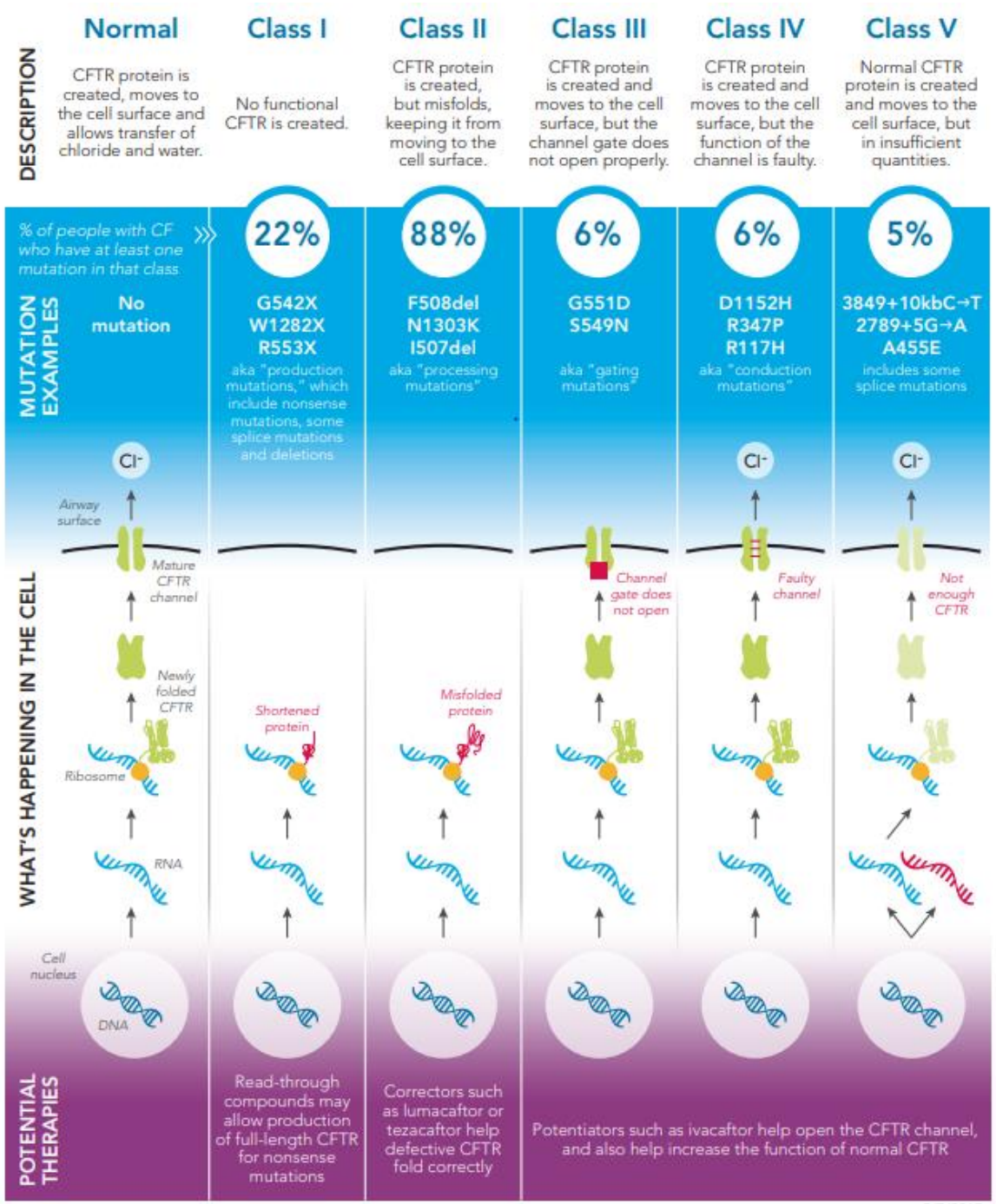
Median Predicted Survival Age, 1986–2017 In Five Year Increments



CFTR Modulators

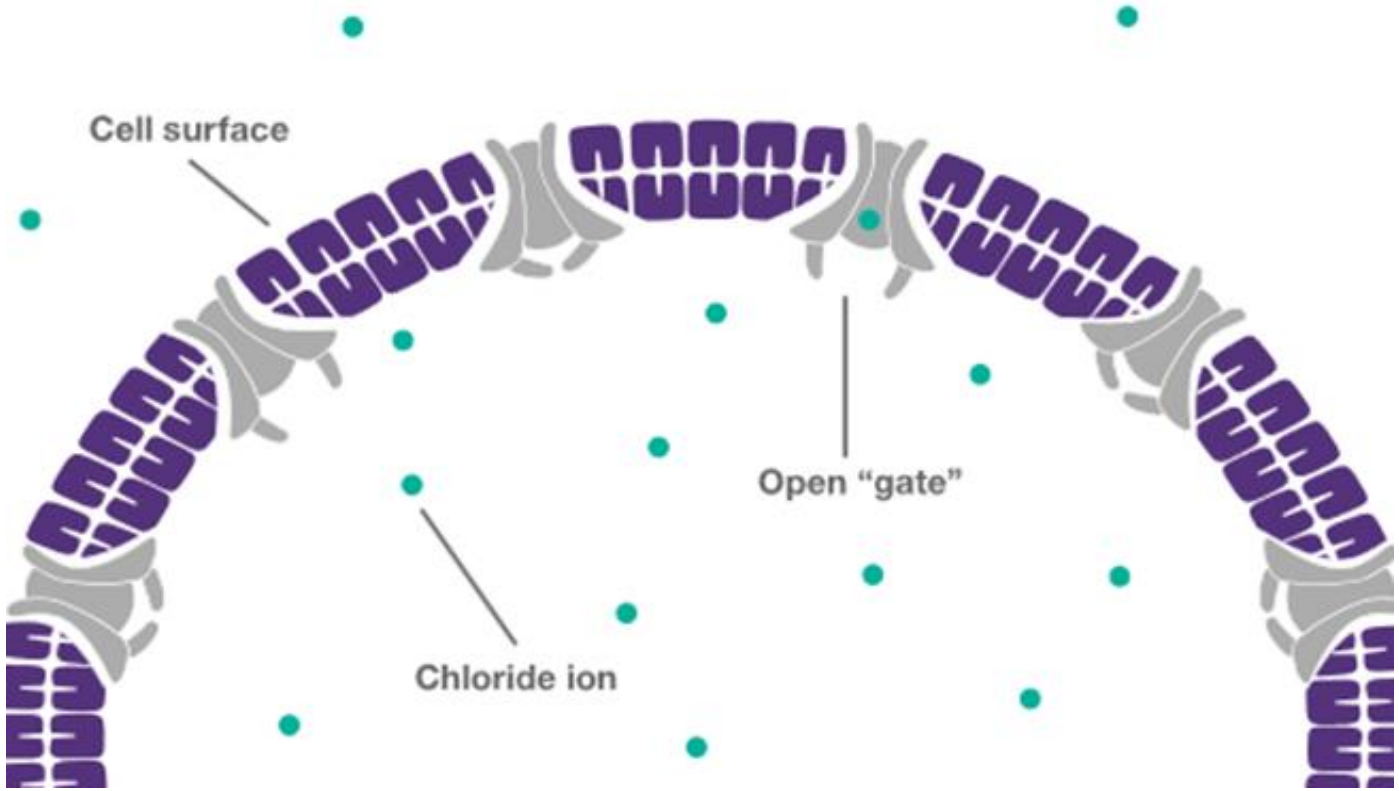
- High-throughput assays
- Screen small molecules
- Repair mutant CFTR (cell assays)

- Potentiators
- Correctors
- Amplifiers



Potentiators

- CFTR gets to the cell surface and potentiators open the gates!



Potentiators

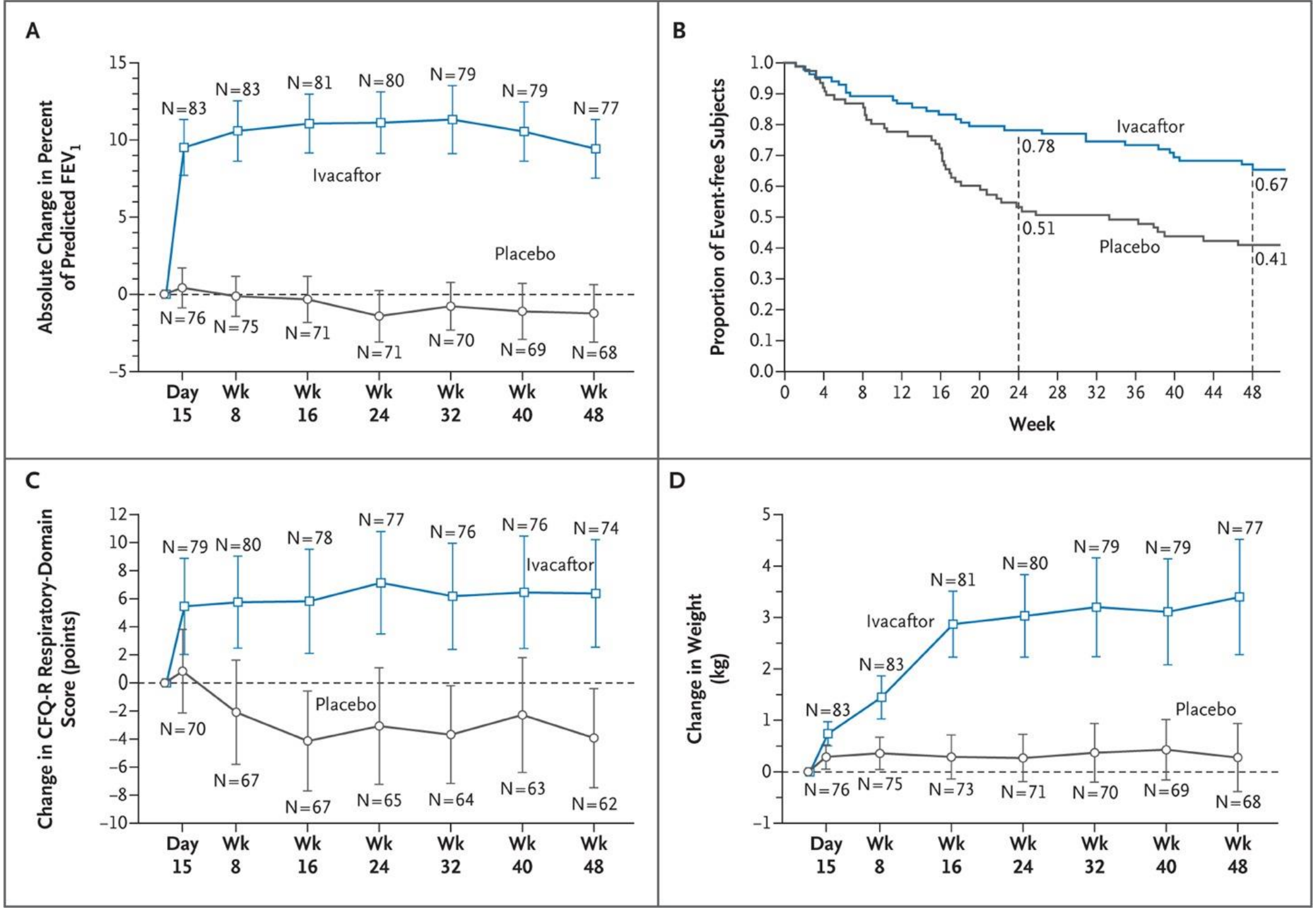
- Ivacaftor, VX-770 (Kalydeco®) FDA approved in 2012
- Target - G551D (Class 3 mutation)
- Recently approved down to the age of 6 months
- 38 CFTR gene mutations

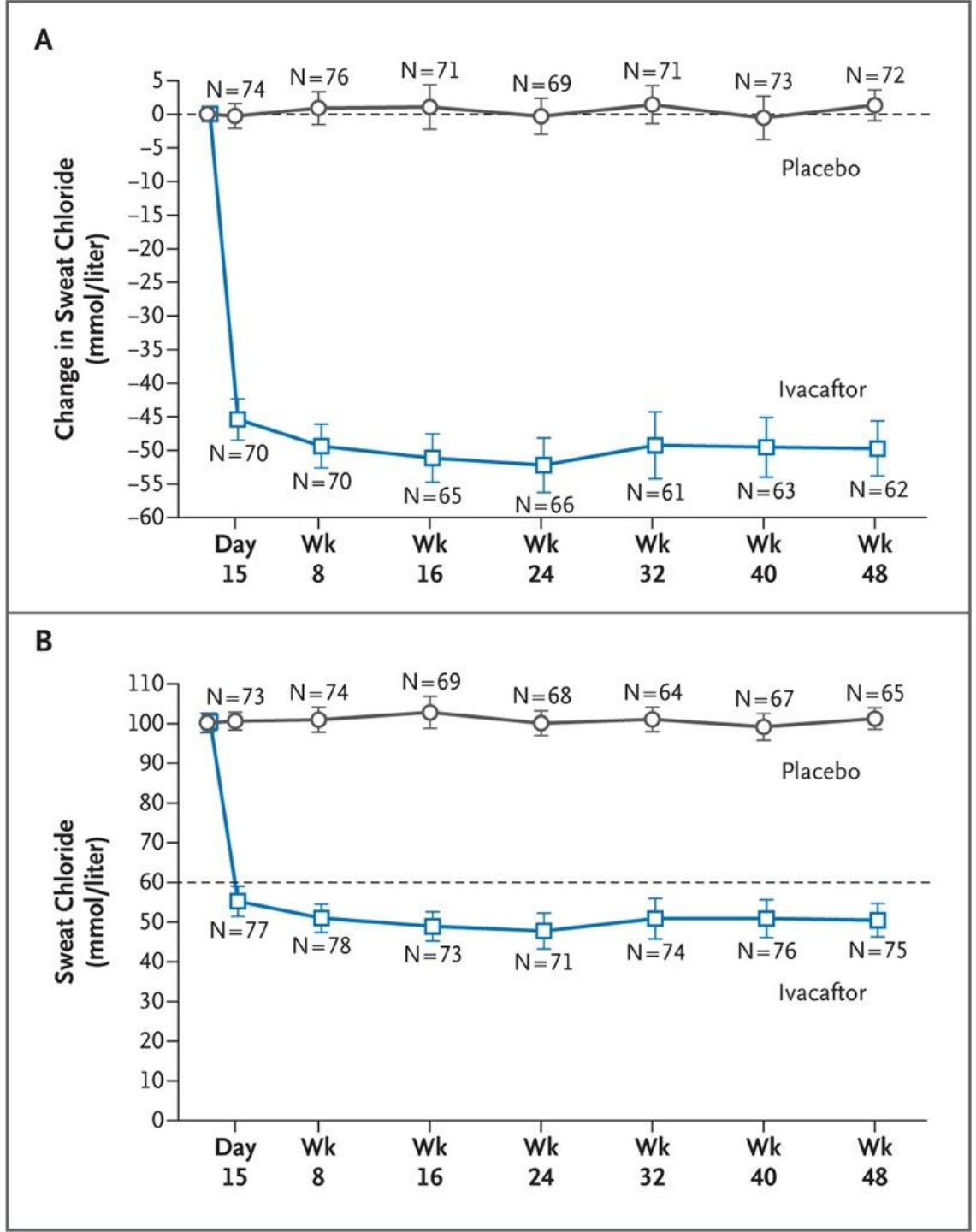
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*


A
Absolute Change in Percent of Predicted FEV_1
15
10
5
0
−5
N=83
N=83
N=81
N=80
N=79
N=79
N=77
Ivacaftor
Placebo
N=76
N=75
N=71
N=71
N=70
N=69
N=68
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48
B
Proportion of Event-free Subjects
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Ivacaftor
0.78
0.67
0.51
Placebo
0.41
0
4
8
12
16
20
24
28
32
36
40
44
48
Week
C
Change in CFQ-R Respiratory-Domain Score (points)
12
10
8
6
4
2
0
−2
−4
−6
−8
−10
N=79
N=80
N=78
N=77
N=76
N=76
N=74
Ivacaftor
Placebo
N=70
N=67
N=67
N=65
N=64
N=63
N=62
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48
D
Change in Weight (kg)
5
4
3
2
1
0
−1
N=77
N=79
N=79
N=80
N=81
Ivacaftor
N=83
N=83
Placebo
N=76
N=75
N=73
N=71
N=70
N=69
N=68
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48


A
Change in Sweat Chloride (mmol/liter)
5
0
−5
−10
−15
−20
−25
−30
−35
−40
−45
−50
−55
−60
N=74
N=76
N=71
N=69
N=71
N=73
N=72
Placebo
Ivacaftor
N=70
N=70
N=65
N=66
N=61
N=63
N=62
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48
B
Sweat Chloride (mmol/liter)
110
100
90
80
70
60
50
40
30
20
10
0
N=73
N=74
N=69
N=68
N=64
N=67
N=65
Placebo
Ivacaftor
N=77
N=78
N=73
N=71
N=74
N=76
N=75
Day 15
Wk 8
Wk 16
Wk 24
Wk 32
Wk 40
Wk 48

Correctors

- CFTR is misfolded and cannot reach cell surface
- Correctors assist in protein folding and processing to help reach the cell surface
- Used for the most common type of *CFTR* mutation; F508del

Correctors

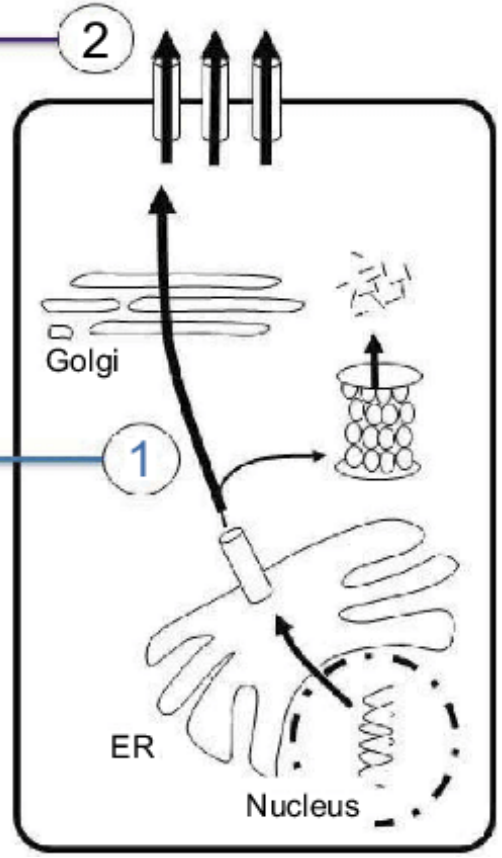
- Lumacaftor (VX-809) and Tezacaftor (VX-661)
- Help CFTR protein fold correctly and reach the cell surface
- Not approved as monotherapy for CF
- Combining a potentiator with a corrector can improve CFTR activity

CFTR Potentiator:Ivacaftor

Potentiates the channel-open probability (channel gating) of CFTR at the cell surface

CFTR Corrector:Lumacaftor

Facilitates the processing and trafficking of CFTR to increase the amount of CFTR at the cell surface



1st Corrector + Potentiator

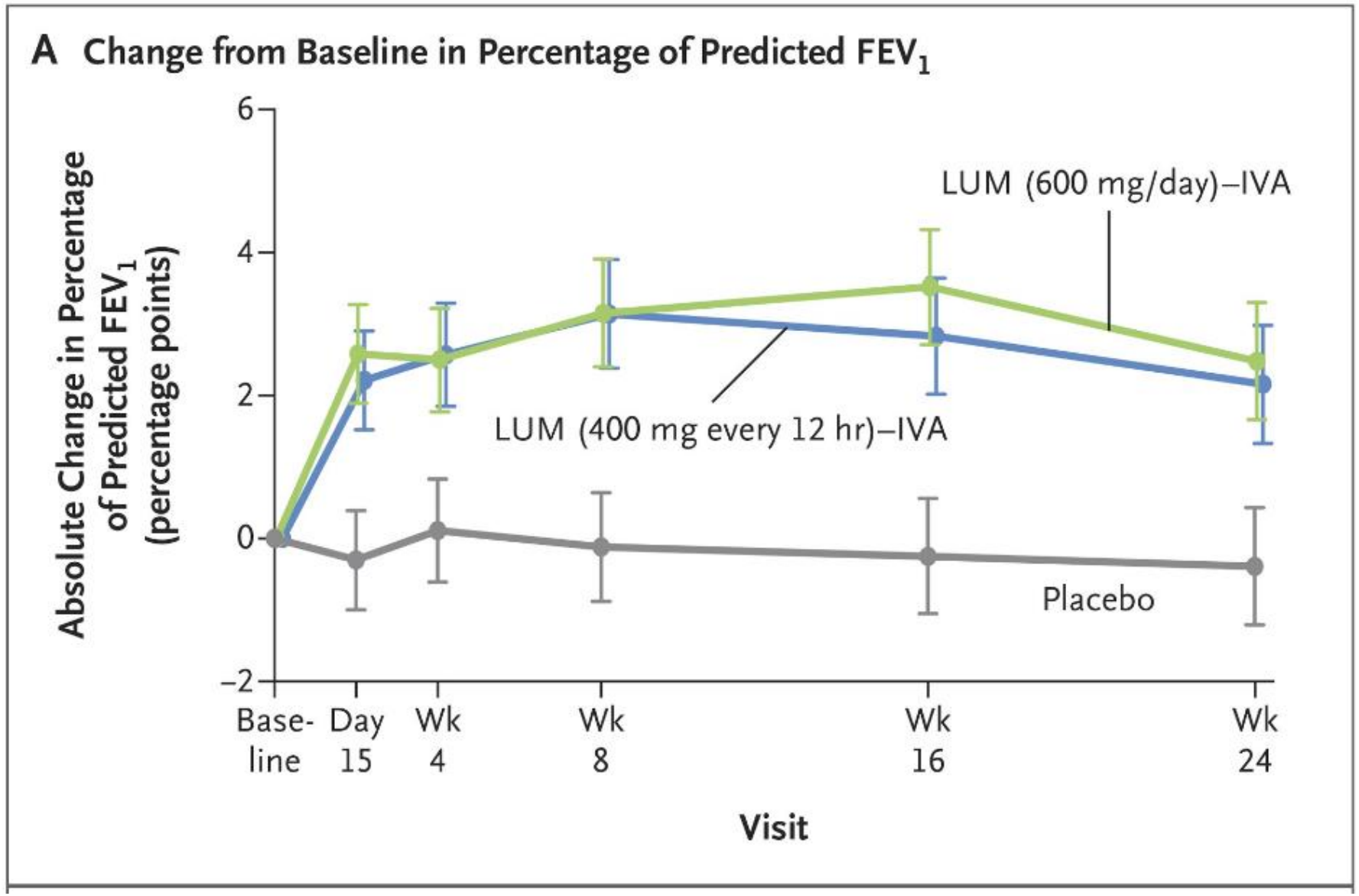
- Lumacaftor + Ivacaftor combination — Orkambi®
  - -F508del/F508del mutations
  - -CF patients as young as 2 years
  - -Improved clinical outcomes
    - -improved FEV1
    - -reduced symptoms

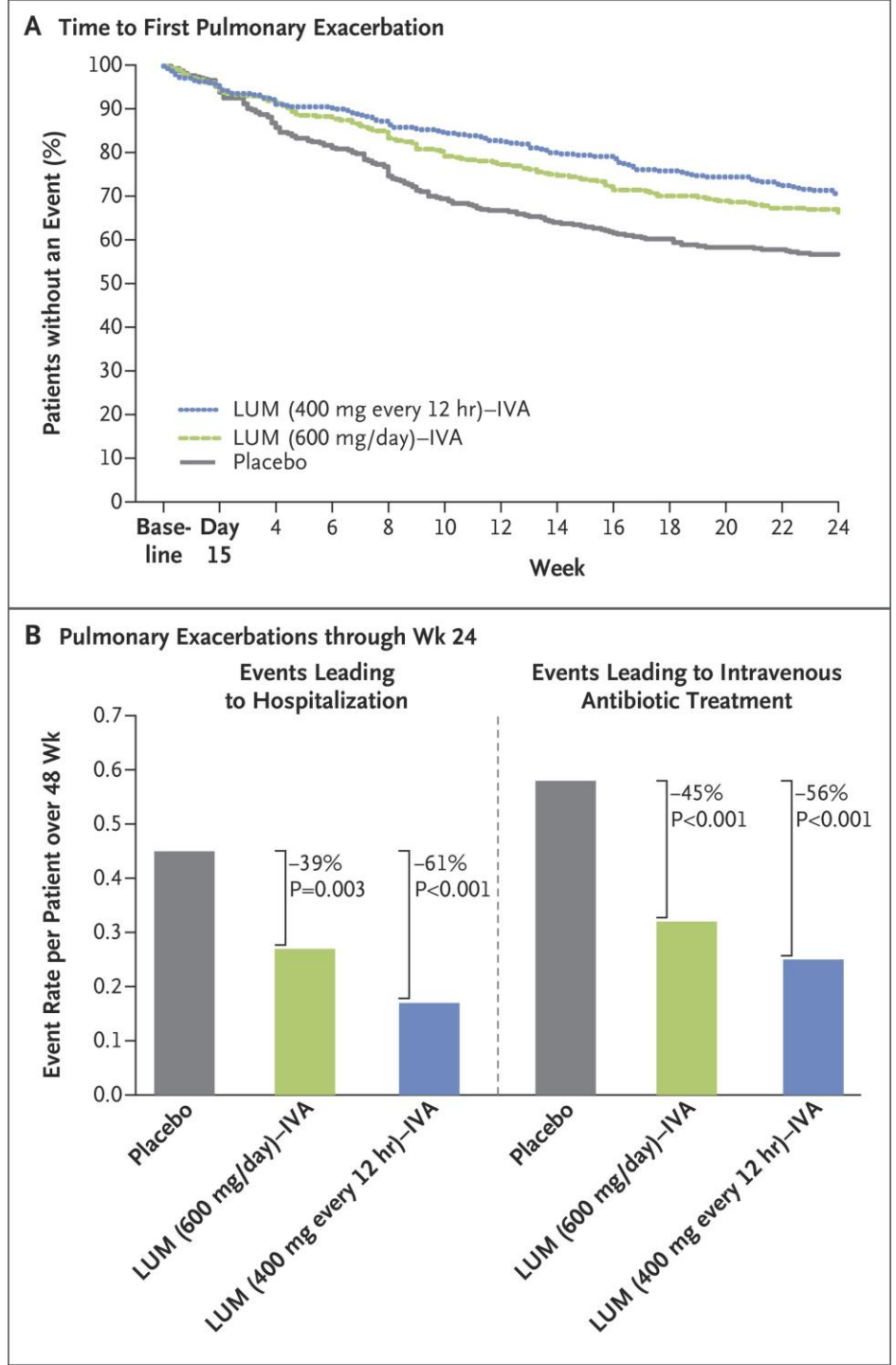
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

C.E. Wainwright, J.S. Elborn, B.W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J.C. Davies, K. De Boeck, P.A. Flume, M.W. Konstan, S.A. McColley, K. McCoy, E.F. McKone, A. Munck, F. Ratjen, S.M. Rowe, D. Waltz, and M.P. Boyle, for the TRAFFIC and TRANSPORT Study Groups*

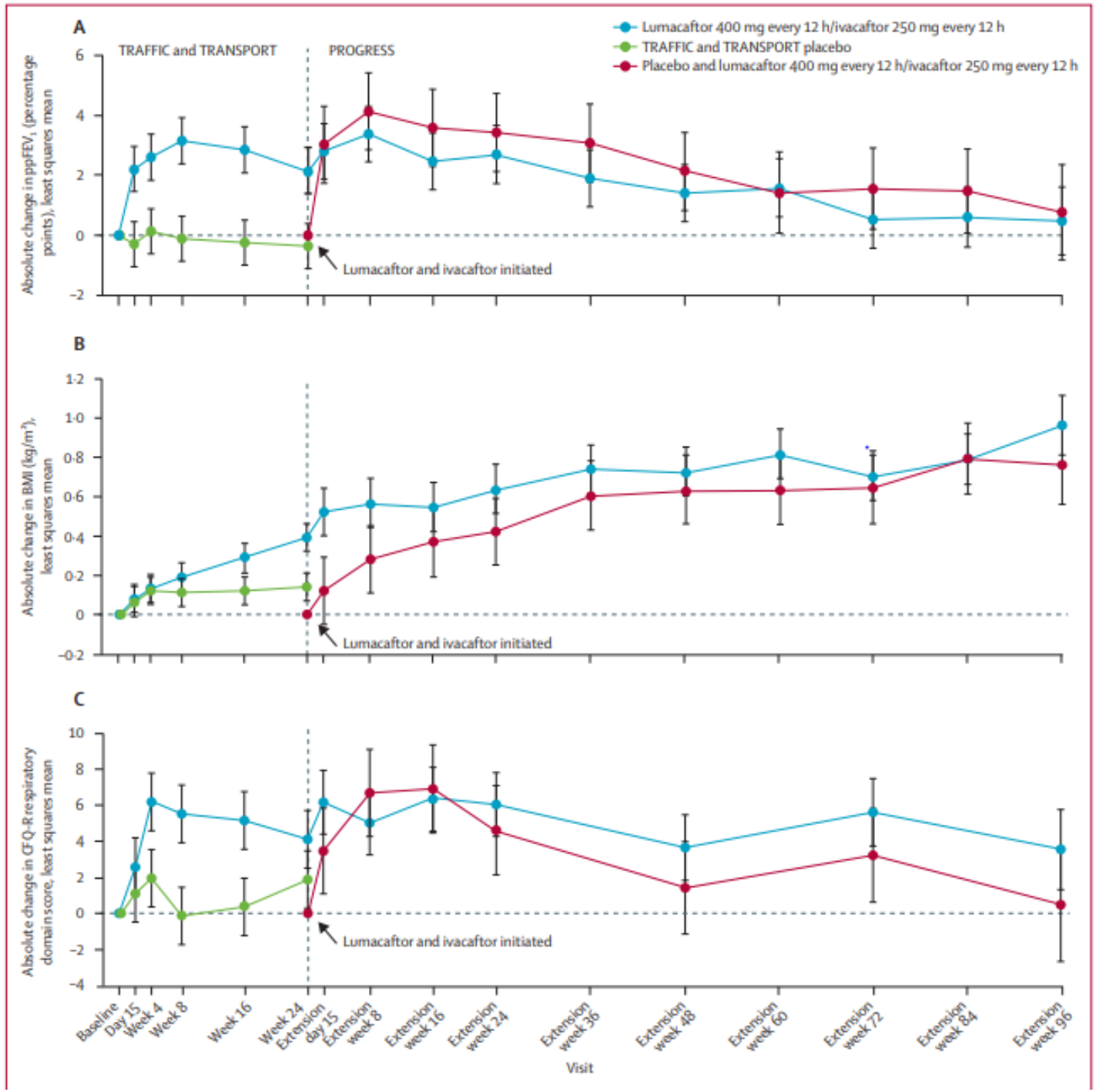

A Change from Baseline in Percentage of Predicted FEV1
Absolute Change in Percentage of Predicted FEV1 (percentage points)
6
4
2
0
−2
LUM (600 mg/day)–IVA
LUM (400 mg every 12 hr)–IVA
Placebo
Base-line
Day 15
Wk 4
Wk 8
Wk 16
Wk 24
Visit

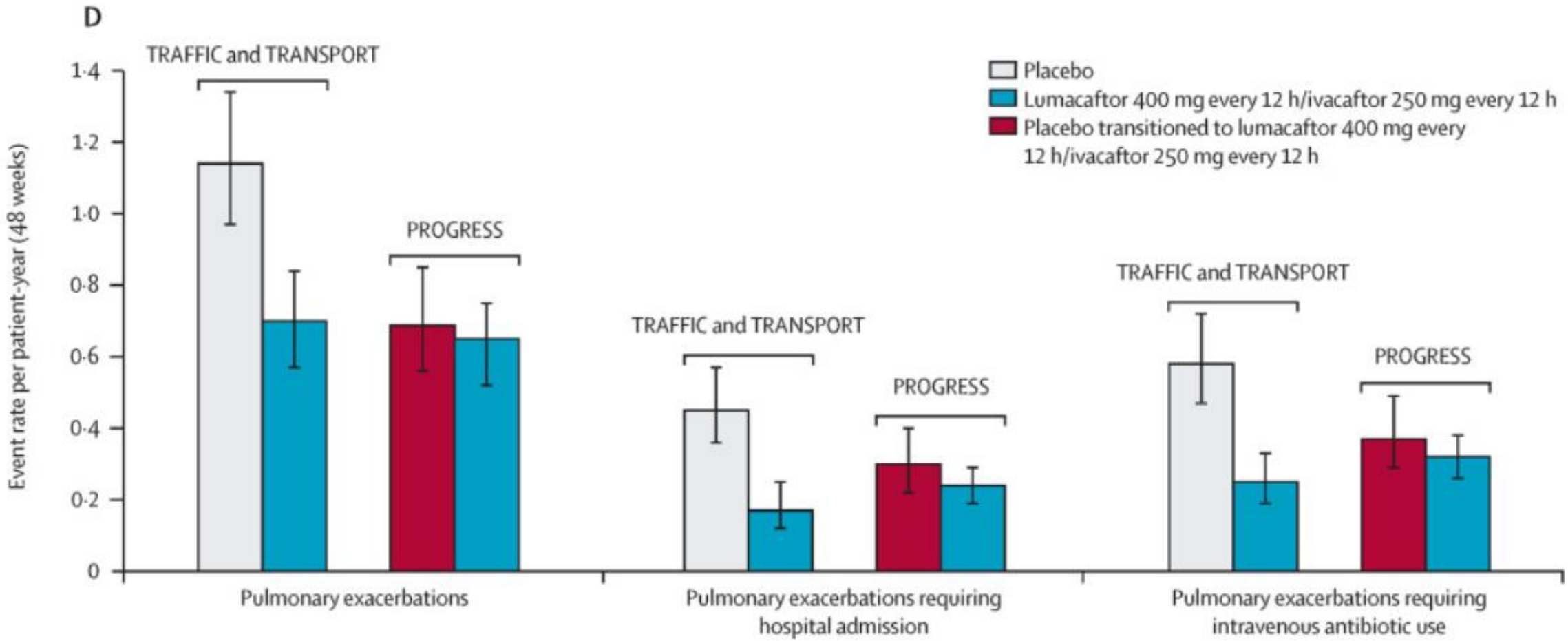

A Time to First Pulmonary Exacerbation
Patients without an Event (%)
100
90
80
70
60
50
40
30
20
10
0
LUM (400 mg every 12 hr)–IVA
LUM (600 mg/day)–IVA
Placebo
Base-line
Day 15
4
6
8
10
12
14
16
18
20
22
24
Week
B Pulmonary Exacerbations through Wk 24
Events Leading to Hospitalization
Events Leading to Intravenous Antibiotic Treatment
Event Rate per Patient over 48 Wk
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
–39%
P=0.003
–61%
P<0.001
–45%
P<0.001
–56%
P<0.001
Placebo
LUM (600 mg/day)–IVA
LUM (400 mg every 12 hr)–IVA
Placebo
LUM (600 mg/day)–IVA
LUM (400 mg every 12 hr)–IVA

Lancet Respir Med 2017;
5: 107–18

Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the *F508del-CFTR* mutation (PROGRESS): a phase 3, extension study

Michael W Konstan, Edward F McKone, Richard B Moss, Gautham Marigowda, Simon Tian, David Waltz, Xiaohong Huang, Barry Lubarsky, Jaime Rubin, Stefanie J Millar, David J Pasta, Nicole Mayer-Hamblett, Christopher H Goss, Wayne Morgan, Gregory S Sawicki


A
TRAFFIC and TRANSPORT
PROGRESS
Lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h
TRAFFIC and TRANSPORT placebo
Placebo and lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h
Absolute change in ppFEV1 (percentage points), least squares mean
6
4
2
0
−2
Lumacaftor and ivacaftor initiated
B
Absolute change in BMI (kg/m²), least squares mean
1·2
1·0
0·8
0·6
0·4
0·2
0
−0·2
Lumacaftor and ivacaftor initiated
C
Absolute change in CFQ-R respiratory domain score, least squares mean
10
8
6
4
2
0
−2
−4
Lumacaftor and ivacaftor initiated
Baseline
Day 15
Week 4
Week 8
Week 16
Week 24
Extension day 15
Extension week 8
Extension week 16
Extension week 24
Extension week 36
Extension week 48
Extension week 60
Extension week 72
Extension week 84
Extension week 96
Visit


D
TRAFFIC and TRANSPORT
PROGRESS
TRAFFIC and TRANSPORT
PROGRESS
TRAFFIC and TRANSPORT
PROGRESS
Placebo
Lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h
Placebo transitioned to lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h
Event rate per patient-year (48 weeks)
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0
Pulmonary exacerbations
Pulmonary exacerbations requiring hospital admission
Pulmonary exacerbations requiring intravenous antibiotic use

2nd Corrector + Potentiator

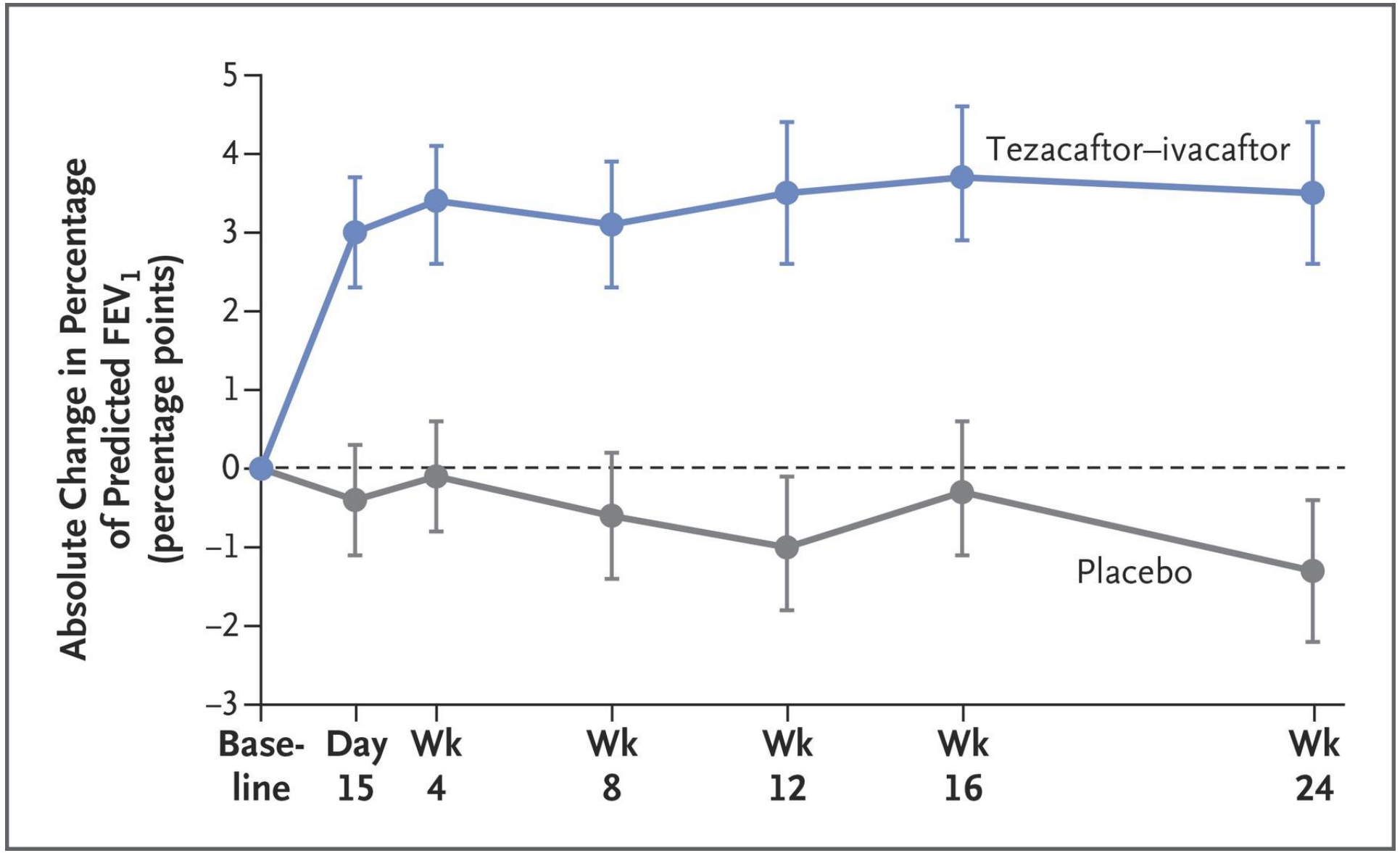
- Tezacaftor/Ivacaftor– Symdeko®
  - -F508del/F508del mutations
  - -CF patients 6 years and older

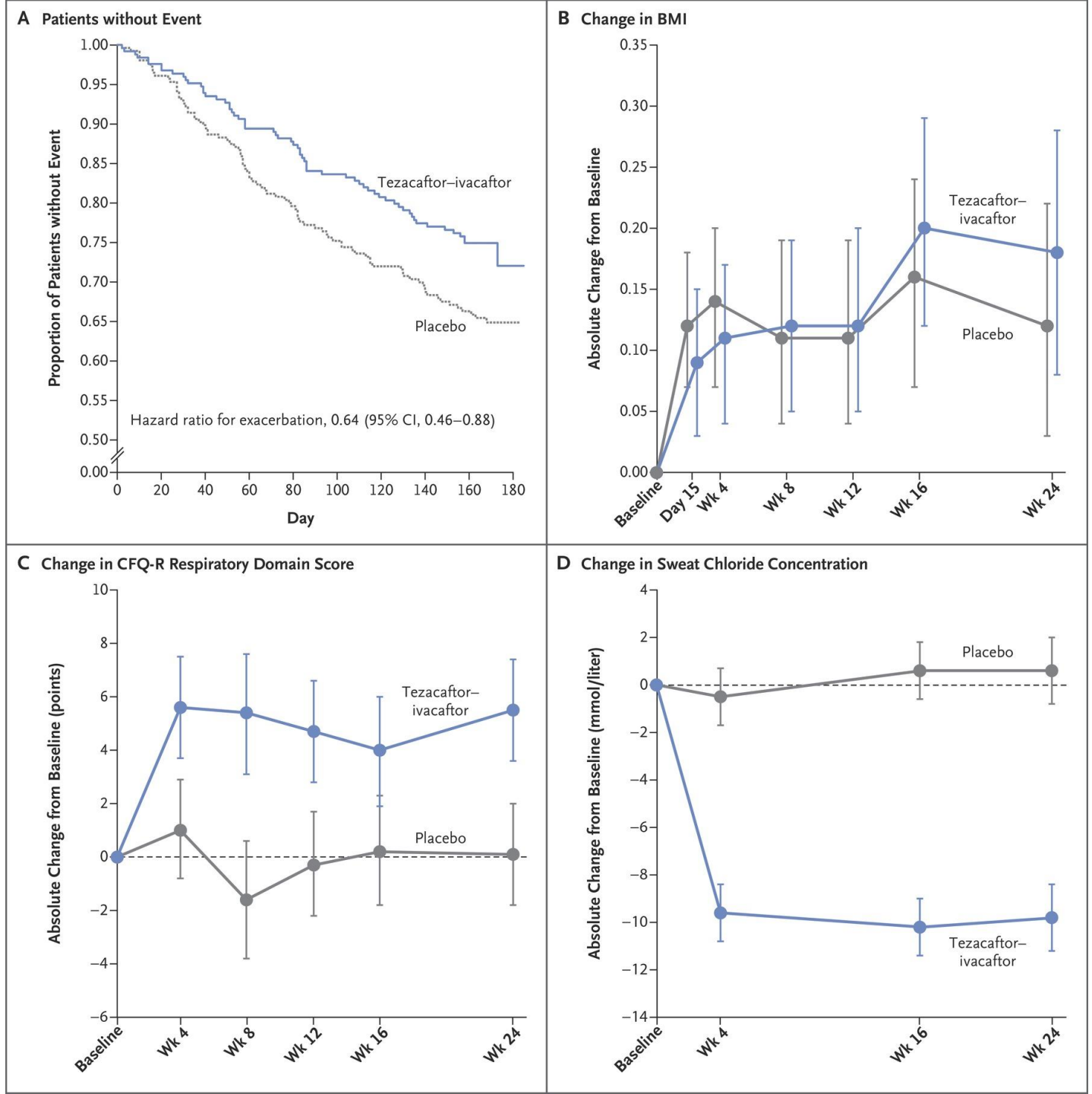
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 23, 2017 VOL. 377 NO. 21

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del

Jennifer L. Taylor-Cousar, M.D., Anne Munck, M.D., Edward F. McKone, M.D., Cornelis K. van der Ent, M.D., Ph.D., Alexander Moeller, M.D., Christopher Simard, M.D., Linda T. Wang, M.D., Edward P. Ingenito, M.D., Ph.D., Charlotte McKee, M.D., Yimeng Lu, Ph.D., Julie Lekstrom-Himes, M.D., and J. Stuart Elborn, M.D.


Absolute Change in Percentage of Predicted FEV1 (percentage points)
5
4
3
2
1
0
−1
−2
−3
Tezacaftor–ivacaftor
Placebo
Base-line
Day 15
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24


A Patients without Event
Proportion of Patients without Event
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.00
Tezacaftor–ivacaftor
Placebo
Hazard ratio for exacerbation, 0.64 (95% CI, 0.46–0.88)
0
20
40
60
80
100
120
140
160
180
Day
B Change in BMI
Absolute Change from Baseline
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Tezacaftor–ivacaftor
Placebo
Baseline
Day 15
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24
C Change in CFQ-R Respiratory Domain Score
Absolute Change from Baseline (points)
10
8
6
4
2
0
−2
−4
−6
Tezacaftor–ivacaftor
Placebo
Baseline
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24
D Change in Sweat Chloride Concentration
Absolute Change from Baseline (mmol/liter)
4
2
0
−2
−4
−6
−8
−10
−12
−14
Placebo
Tezacaftor–ivacaftor
Baseline
Wk 4
Wk 16
Wk 24

Theratyping

- Process of matching medications with mutations (Personalized Medicine)
- Testing CFTR modulators on cells affected by **rare** CFTR mutations
- Application to FDA to expand drug to new mutation without clinical trials

Ivacaftor

38 mutations

Gating Mutations

G178R	G1244E	S549R
G551D	G1349D	S1251N
G551S	S549N	S1255P

Residual Function Mutations

A455E	E193K	R117C
A1067T	F1052V	R347H
D110E	F1074L	R352Q
D110H	G1069R	R1070Q
D579G	K1060T	R1070W
D1152H	L206W	S945L
D1270N	P67L	S977F
E56K	R74W	

Splice Mutations

711+3A→G	3272-26A→G	E831X
2789+5G→A	3849+10kbC→T	

Conduction Mutation

R117H

Tezacaftor + Ivacaftor

26 mutations

Protein Processing Mutations

F508del + F508del		

Residual Function Mutations

A455E	E56K	R74W
A1067T	E193K	R117C
D110E	F1052V	R347H
D110H	F1074L	R352Q
D579G	K1060T	R1070W
D1152H	L206W	S945L
D1270N	P67L	S977F

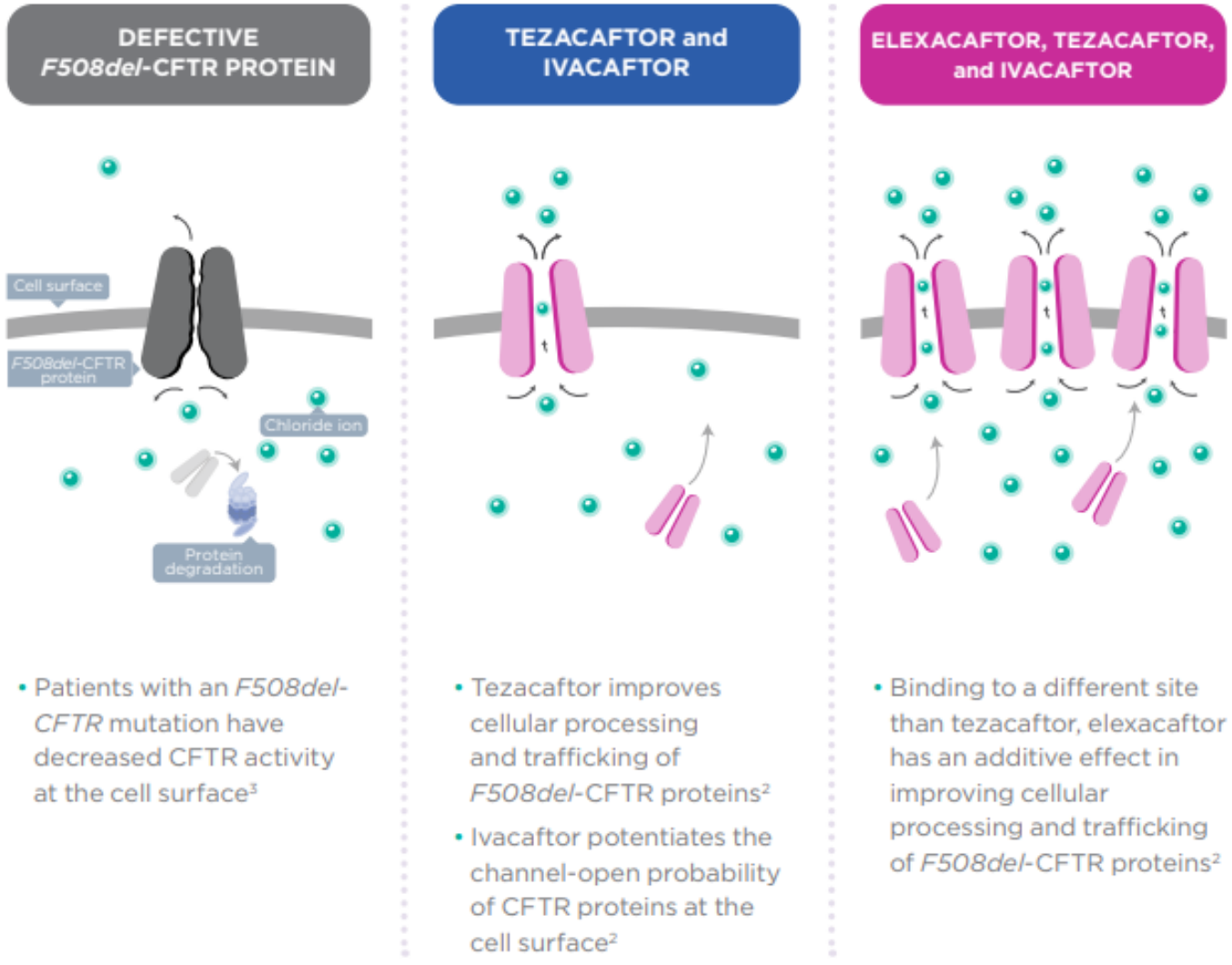
Splice Mutations

711+3A→G	3272-26A→G	E831X
2789+5G→A	3849+10kbC→T	

Triple Combination Modulator

- Elexacaftor + Tezacaftor + Ivacaftor
  - 2 correctors + potentiator
- FDA approved October 2019
- 12 years and older

Targeting *F508del*-CFTR brings more active CFTR proteins to the cell surface[2]

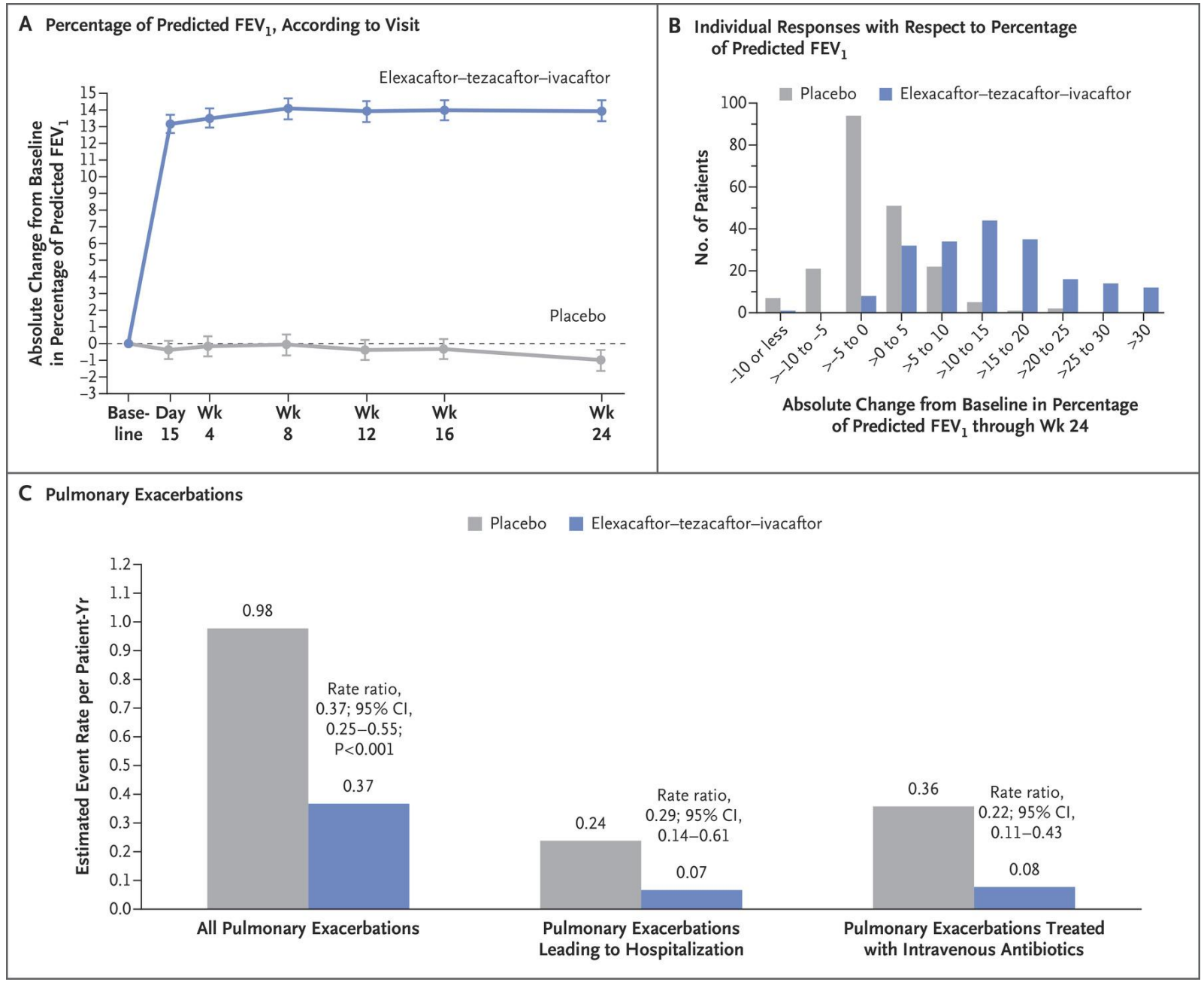


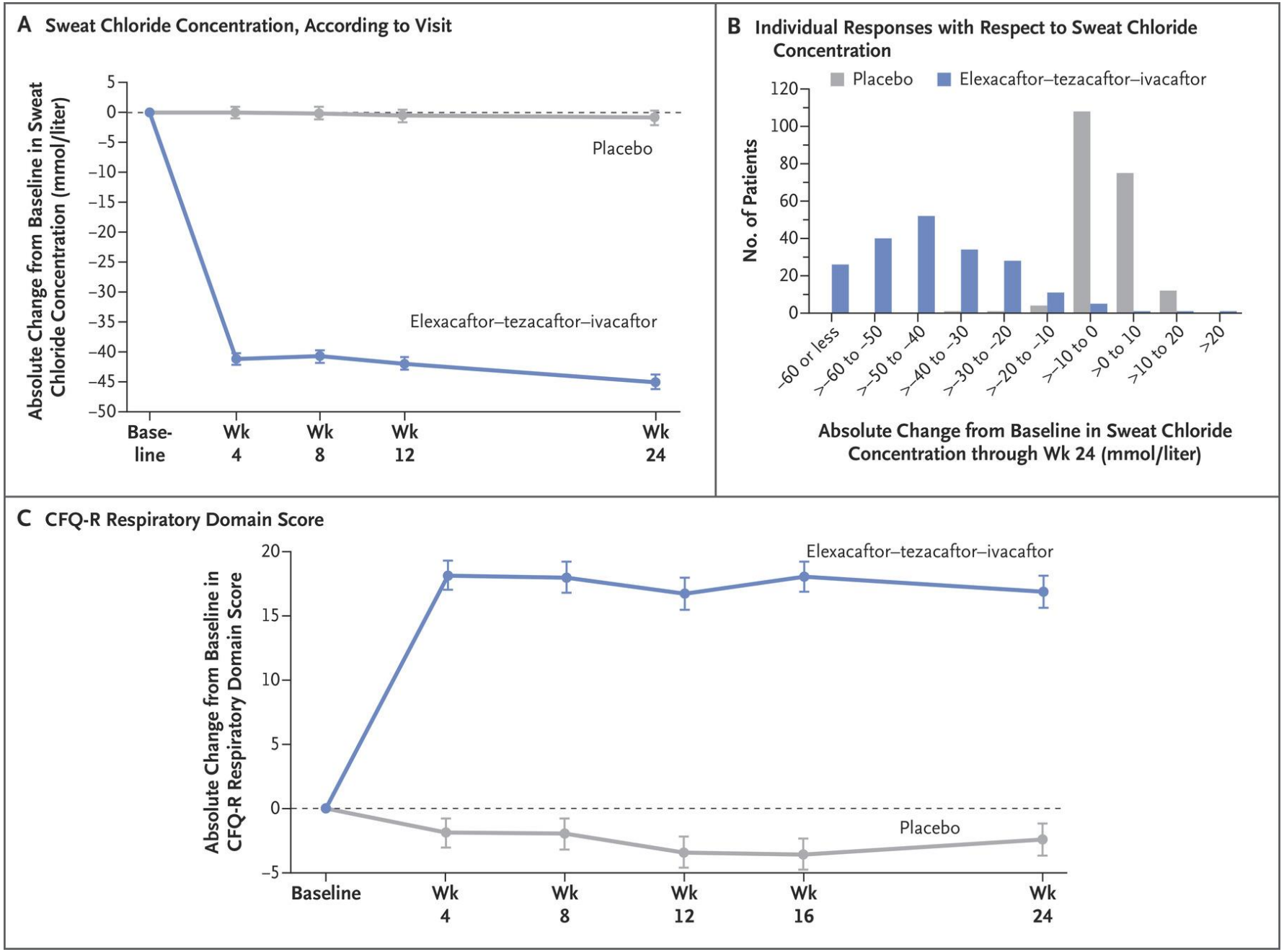
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele

P.G. Middleton, M.A. Mall, P. Dřevínek, L.C. Lands, E.F. McKone, D. Polineni, B.W. Ramsey, J.L. Taylor-Cousar, E. Tullis, F. Vermeulen, G. Marigowda, C.M. McKee, S.M. Moskowitz, N. Nair, J. Savage, C. Simard, S. Tian, D. Waltz, F. Xuan, S.M. Rowe, and R. Jain, for the VX17-445-102 Study Group*


A Percentage of Predicted FEV1, According to Visit
Elexacaftor–tezacaftor–ivacaftor
Placebo
Absolute Change from Baseline in Percentage of Predicted FEV1
Base-line
Day 15
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24
B Individual Responses with Respect to Percentage of Predicted FEV1
Placebo
Elexacaftor–tezacaftor–ivacaftor
No. of Patients
–10 or less
>–10 to –5
>–5 to 0
>0 to 5
>5 to 10
>10 to 15
>15 to 20
>20 to 25
>25 to 30
>30
Absolute Change from Baseline in Percentage of Predicted FEV1 through Wk 24
C Pulmonary Exacerbations
Placebo
Elexacaftor–tezacaftor–ivacaftor
Estimated Event Rate per Patient-Yr
0.98
Rate ratio, 0.37; 95% CI, 0.25–0.55; P<0.001
0.37
0.24
Rate ratio, 0.29; 95% CI, 0.14–0.61
0.07
0.36
Rate ratio, 0.22; 95% CI, 0.11–0.43
0.08
All Pulmonary Exacerbations
Pulmonary Exacerbations Leading to Hospitalization
Pulmonary Exacerbations Treated with Intravenous Antibiotics


A Sweat Chloride Concentration, According to Visit
Absolute Change from Baseline in Sweat Chloride Concentration (mmol/liter)
5
0
−5
−10
−15
−20
−25
−30
−35
−40
−45
−50
Placebo
Elexacaftor–tezacaftor–ivacaftor
Base-line
Wk 4
Wk 8
Wk 12
Wk 24
B Individual Responses with Respect to Sweat Chloride Concentration
Placebo
Elexacaftor–tezacaftor–ivacaftor
No. of Patients
120
100
80
60
40
20
0
−60 or less
>−60 to −50
>−50 to −40
>−40 to −30
>−30 to −20
>−20 to −10
>−10 to 0
>0 to 10
>10 to 20
>20
Absolute Change from Baseline in Sweat Chloride Concentration through Wk 24 (mmol/liter)
C CFQ-R Respiratory Domain Score
Absolute Change from Baseline in CFQ-R Respiratory Domain Score
20
15
10
5
0
−5
Elexacaftor–tezacaftor–ivacaftor
Placebo
Baseline
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24

Elexacaftor + Tezacaftor + Ivacaftor

Protein Processing Mutations
F508del + F508del
F508del + any other mutation

Adverse Reactions

- Elevated liver enzymes
- GI manifestations (transient)
- Increased cough (transient)
- Rash (transient)
- Cataract
- Medication interactions: antifungals, antibiotics

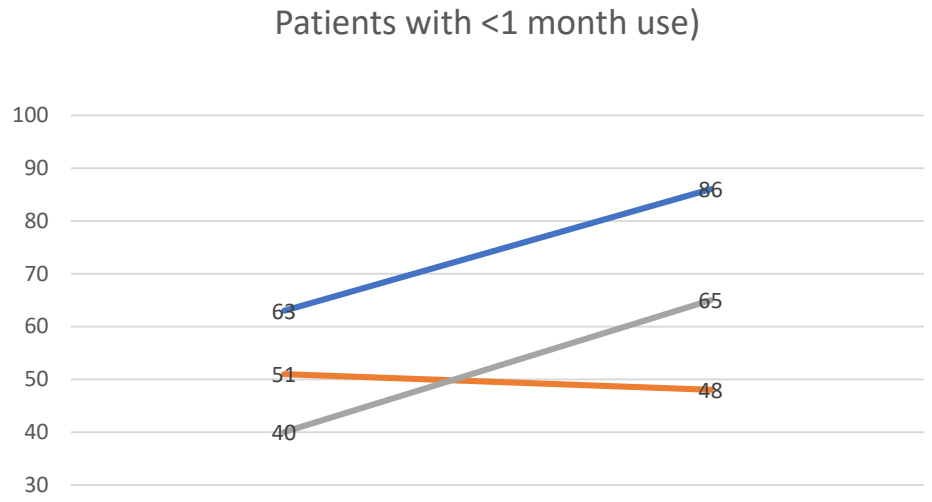
CF patients at UMass

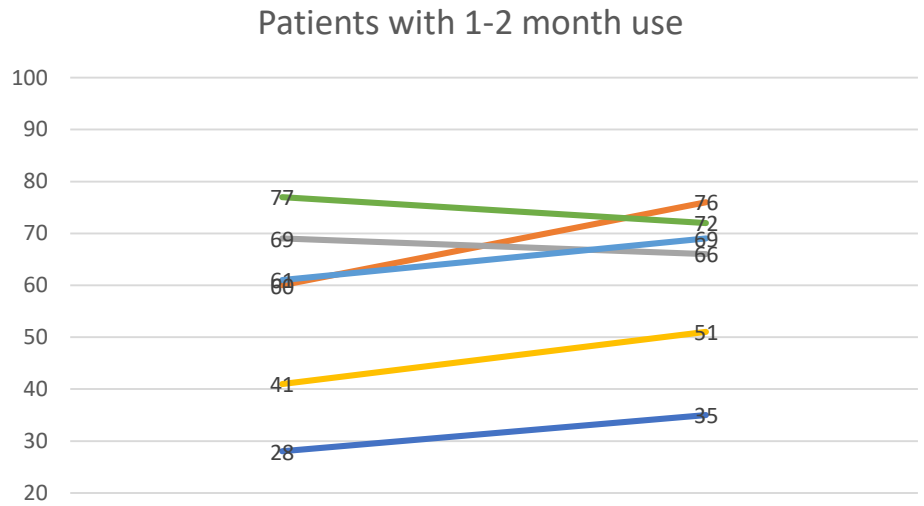
- 43 patients started on Trikafta between November 2019 and March 2020
- Follow-up available for 21 patients (aged 13 to 54)
  - Decreased cough
  - Decreased sputum production
  - Improved energy
  - Improved exercise tolerance
  - Less nasal congestion
  - Better tolerance of respiratory infections

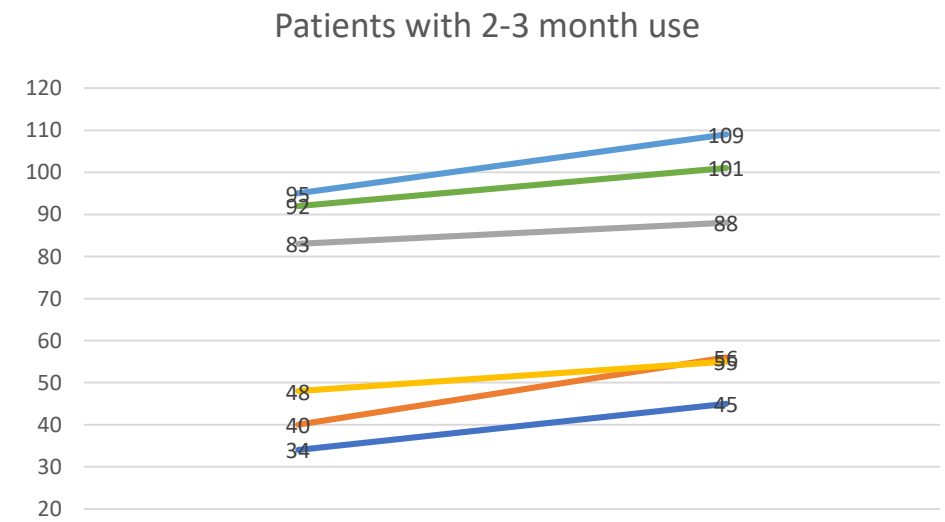
Thank you Diane Waitkevich and Fei Jamie Dy!!!

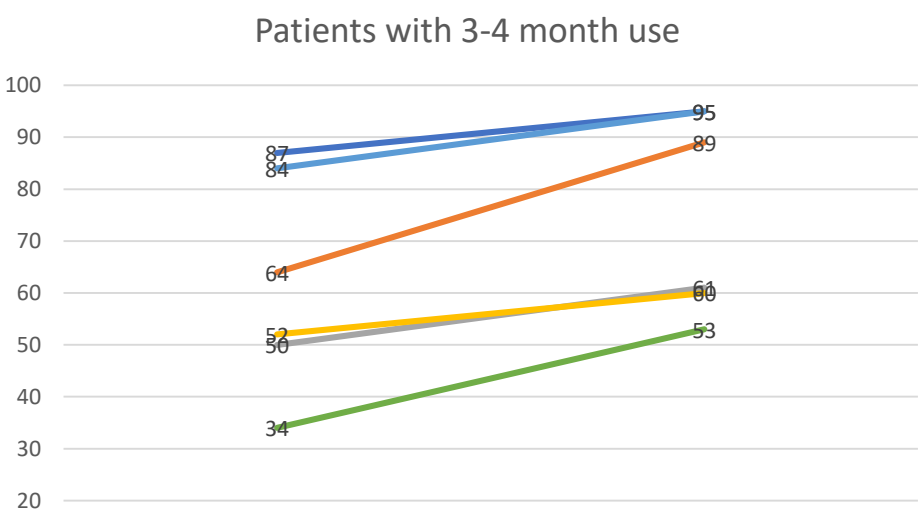
PFT data

- FEV1 values 0-3 months before starting Trikafta and 0-4 months after starting Trikafta



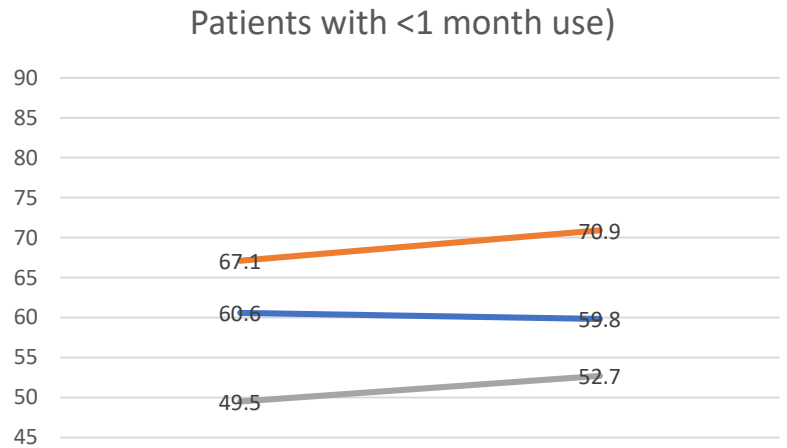


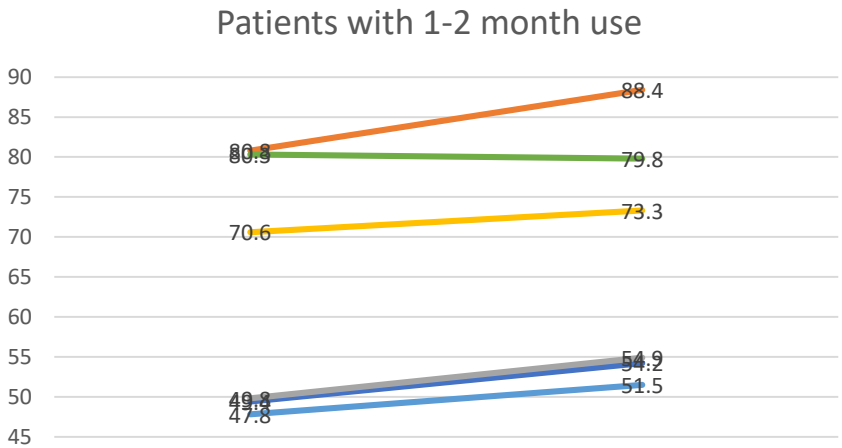


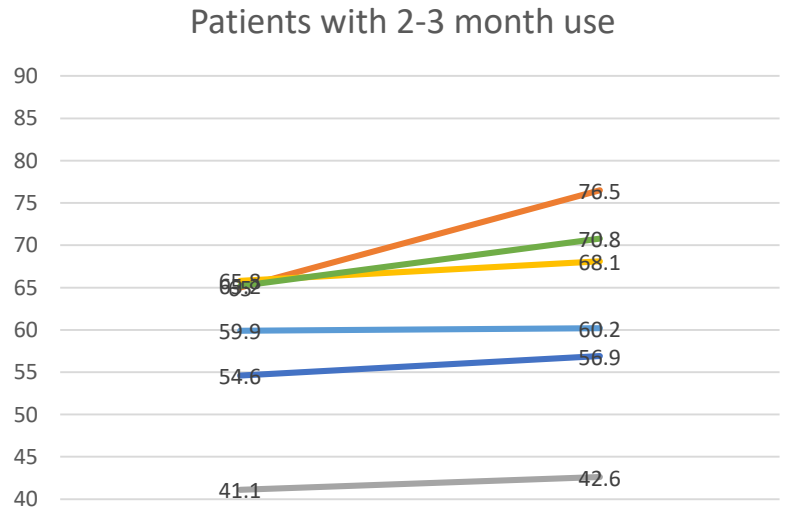


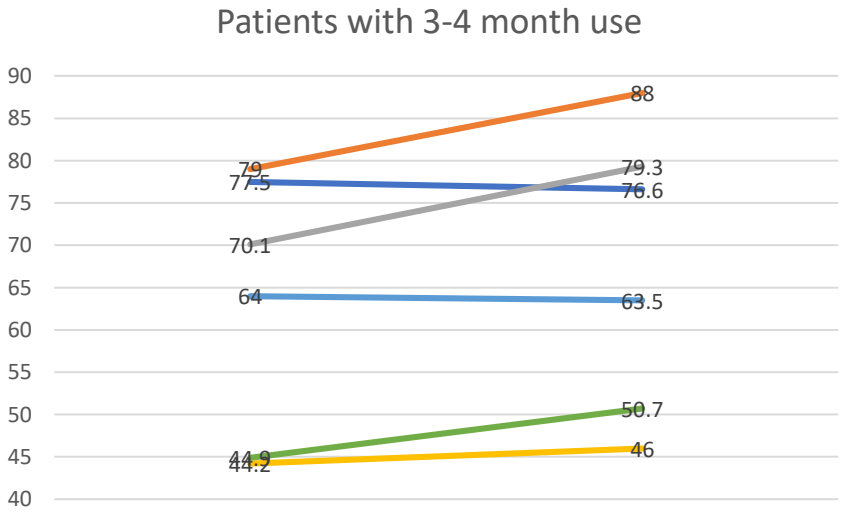
Weight

- Measurements (kilograms) 0-3 months before starting Trikafta and 0-4 months after starting Trikafta





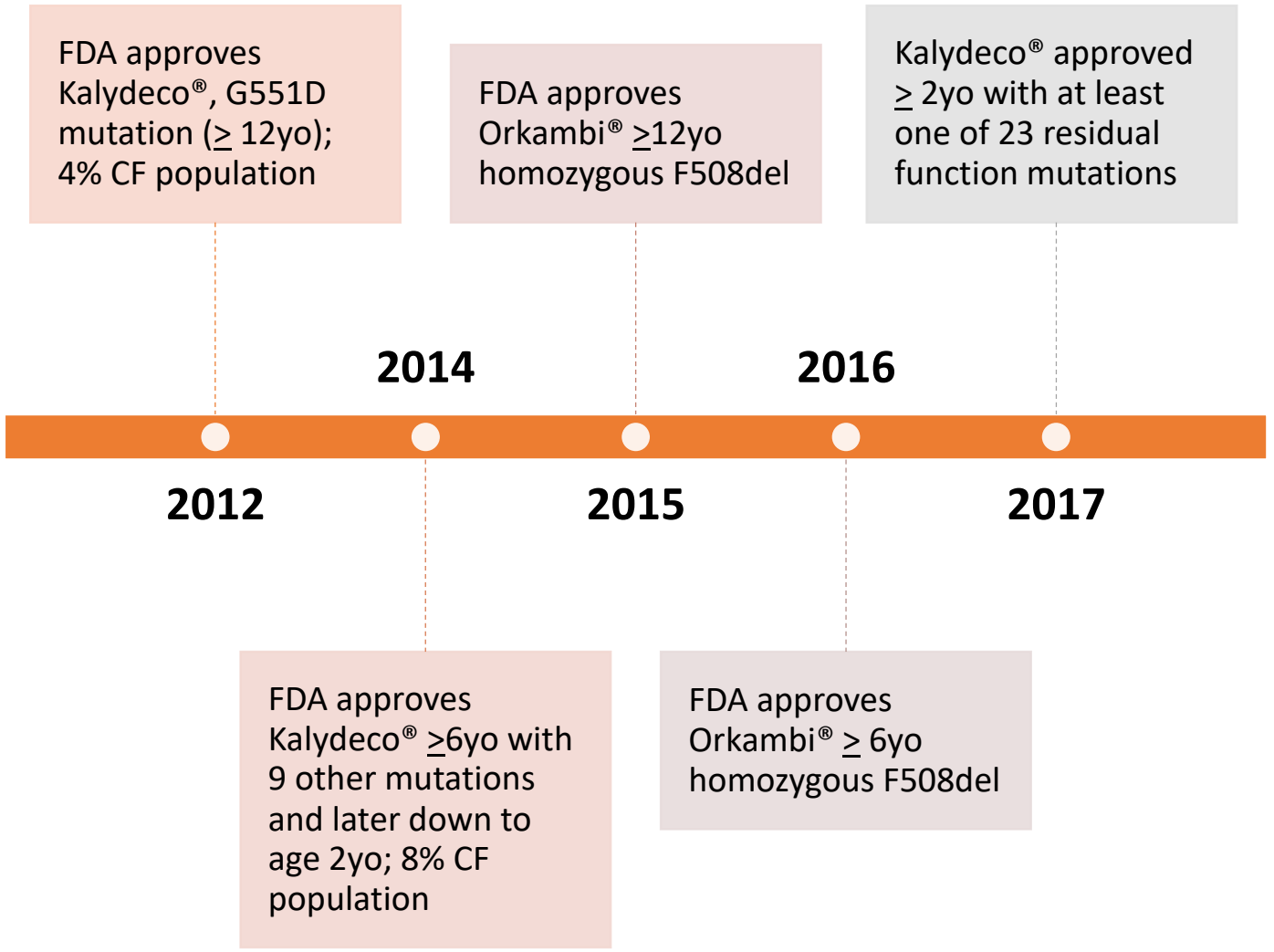




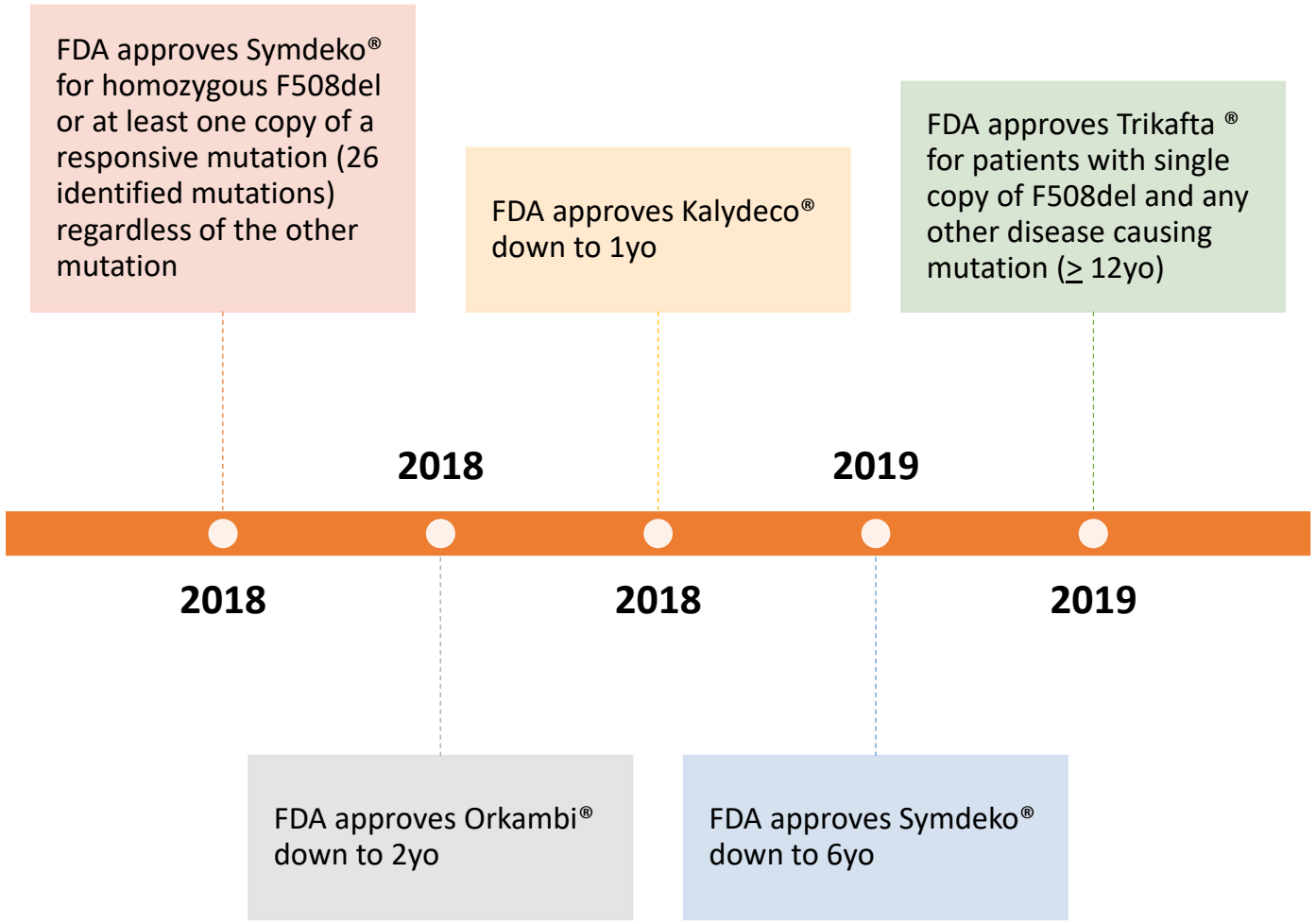
Amplifiers

- Increase the amount of CFTR protein that the cell makes
- Many CFTR mutations produce insufficient CFTR protein
- If more CFTR protein, potentiators + correctors may allow more chloride to cross the cell membrane
- Not yet available
- Phase II Trials, PTI-428

Drug Development Pipeline



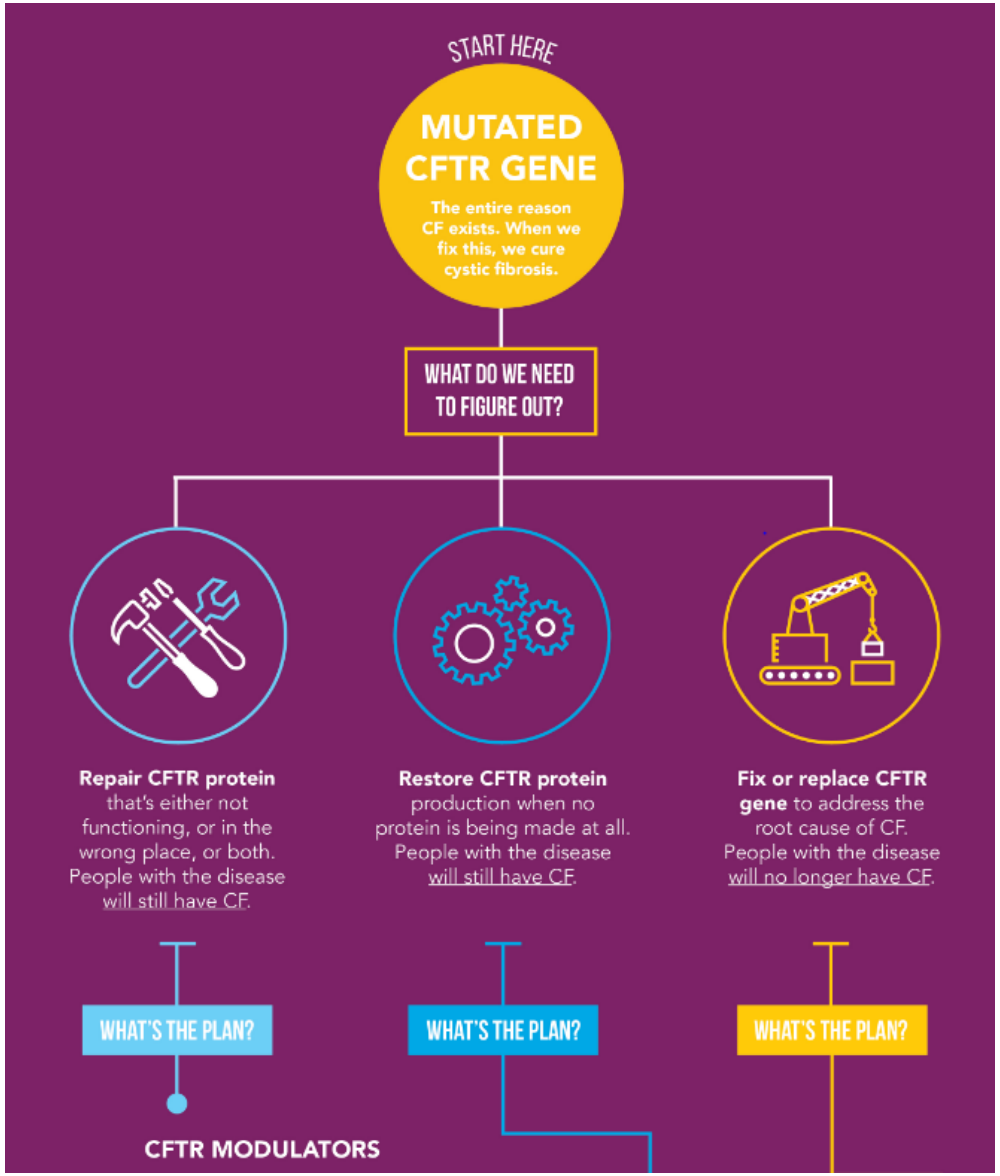
Drug Development Pipeline



Cystic Fibrosis Foundation Launches $500 Million Path to a Cure

Nonprofit issues challenge to accelerate treatments for every person with CF

https://youtu.be/WWZAJ7PHW4I



Cystic Fibrosis and COVID-19

ELSEVIER

Journal of Cystic Fibrosis

Available online 25 April 2020

In Press, Journal Pre-proof

A MULTINATIONAL REPORT TO CHARACTERISE SARS-CoV-2 INFECTION IN PEOPLE WITH CYSTIC FIBROSIS

Rebecca Cosgriff [a], Susannah Ahern [b], Scott C. Bell [c], Keith Brownlee [a], Pierre-Régis Burgel [d], Cass Byrnes [e], Harriet Corvol [f], Stephanie Y. Cheng [g], Alexander Elbert [h], Albert Faro [h], Christopher H. Goss [i], Vincent Gulmans [j], Bruce C. Marshall [h], Edward McKone [k], Peter G. Middleton [l], Rasa Ruseckaite [b], Anne L. Stephenson [f, m], Siobhán B Carr [n]

- Report on the outcomes of 40 people with CF positive for SARS-CoV-2
- Cohort is heterogeneous and includes 11 lung transplant patients
- Data collected through Registries of 8 participating countries
- Clinical course of SARS-CoV-2 in CF appears similar to the general population
- Outcomes of early cases have been better than predicted

Study Results

- Eight countries: Australia, Canada, France, Ireland, Netherlands, New Zealand, UK and U.S.
- 40 people with CF infected with SARS-CoV-2
- 0.07 percent in CF compared to 0.15 percent in general population
- Mean age 33 yrs (range 15-59 yrs)
- Mean FEV1pp 70 (range 18-114)
- FEV1pp <40 (5 patients)
- 31 (78%) had symptoms when tested, and 24 (60%)had fever
- 15 (38%) with CFRD
- 14 patients on CFTR modulators
- 11 patients post lung transplant
- 1 patient pregnant – delivered healthy baby
- 13 (33%) needed oxygen and 1 required ventilation (transplant patient)
- 70% recovered, 30% unresolved at time of reporting, and no deaths

Why the lower incidence in CF?

- Earlier and more effective “shielding”, “protective self-isolation” or “cocooning”
- ‘Primed’ for reducing risk of exposure due to learned behaviors or standard of care therapies

SARS-CoV-2 in the US as of 5/14/19

- CF Registry reported cases (US)
  - Tests conducted 600
  - Confirmed positive 34
    - Pediatric: 5
    - Hospitalized: 10
    - Advanced lung disease: 6
    - Post-lung transplant: 5
    - Deaths: 2 (1 transplant, 1 advanced lung disease)

- UMass Memorial Medical Center (Pediatric and Adult) Data
  - Confirmed positive 2

CF and Intensive Care

- Pre FDA approval of Trikafta: median survival for patients with CF and FEV1 <30% predicted is over 6.5 years
- Improving critical care outcomes: unanticipated survival and functional recovery from respiratory failure precipitated by influenza and other acute infections
- 2020 CF Foundation consensus guidelines for the care of individuals with advanced CF recommend individuals be considered eligible for intensive care

Improved Prognosis in Cystic Fibrosis: Consideration for Intensive Care During the COVID-19 Pandemic. Am J Resp Crit Care Med. April 2020

Conclusion

- Cystic Fibrosis is a multisystem disease impacting many organ systems
- CFTR quantity and dysfunction lead to disease
- New CFTR modulators impacting outcomes and likely survival
- CF and SARS-CoV-2 outcomes hopeful

Thank-you to our Cystic Fibrosis Care Team!

- Physicians
  - Ted Kremer, MD
  - Michelle Trivedi, MD
  - Fei Jamie Dy, MD
  - Evan Bailey, MD
  - Oren Schaefer, MD
  - David Fish , MD
  - Christine Bielick-Kotkowski, MD
  - Amy Darukhanavala, MD (Endocrine)
- Psychologist
  - Stella Lopez, PsyD
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  - Diane Waitkevich, PNP
  - Emily Young, PNP
  - Chris Dell'Erba, RN
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- Nutrition
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- Secretaries
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