ORKAMBI (Lumacaftor/Ivacaftor) Treatment for Cystic Fibrosis

Vertex Pharmaceuticals Incorporated

Pulmonary and Allergy Drugs
Advisory Committee

May 12, 2015

Introduction

Jeffrey Chodakewitz, MD

Chief Medical Officer
Executive Vice President, Clinical Development

Vertex Pharmaceuticals Incorporated

Agenda for Vertex Presentation

Introduction	**Jeffrey Chodakewitz, MD** Chief Medical Officer Executive Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Disease Background and Medical Need	**Michael W. Konstan, MD** Vice Dean for Translational Research, Professor of Pediatrics Case Western Reserve University School of Medicine UH Rainbow Babies and Children's Hospital
Mechanism of Action	**Fredrick Van Goor, PhD** Principal Research Fellow Vertex Pharmaceuticals Incorporated
Clinical Development Program **Clinical Efficacy and Safety**	**Charlotte McKee, MD** Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Clinical Perspective	**Bonnie Ramsey, MD** Endowed Professor of Pediatrics, University of Washington School of Medicine Director, Center for Clinical and Translational Research, Seattle Children’s Hospital

Additional Experts

- **Janet Wittes, PhD**
  President
  Statistics Collaborative, Inc.
- **Willis C. Maddrey, MD**
  Professor of Internal Medicine and Hepatology
  University of Texas Southwestern Medical Center at Dallas

Lumacaftor/Ivacaftor (LUM/IVA) Development – Highlights

- Cystic Fibrosis is a systemic, life-shortening, orphan, genetic disease which affects more than 30,000 people in the US
- Ivacaftor (KALYDECO) was originally approved in January 2012
  - To treat patients with the *G551D* mutation (~4% of CF patients)
  - Ivacaftor did not provide clinically meaningful benefit in a trial of patients homozygous for *F508del* and therefore is not indicated in this population
- LUM/IVA Regulatory Highlights
  - Awarded breakthrough therapy designation (Dec 2012)
  - Frequent interactions with FDA to develop LUM/IVA
  - LUM/IVA clinical development program:
    - » 2 Pivotal Phase 3 Trials in >1100 CF patients
  - LUM/IVA NDA submitted (Nov 2014)

LUM/IVA Targets Underlying Cause of Cystic Fibrosis

- LUM/IVA is the first treatment developed to address the underlying cause of CF in *F508del* homozygous patients, with the potential to change the course of disease
  - The clinical program demonstrates rapid, sustained and consistent respiratory and systemic benefits: FEV_1, pulmonary exacerbations and BMI
  - Favorable safety profile in >1100 CF patients

- Both LUM and IVA required for maximal clinical effect in *F508del*
  - Disease biology
  - Mechanism of action of LUM and IVA
  - Effects in preclinical models and translation to patients
  - Pattern and confidence in clinical benefit for patients

Positive benefit/risk profile supports approval in F508del homozygous patients aged 12 years and older

Positive Benefit/Risk Profile Supports Approval of LUM/IVA

<u>Proposed indication</u>:

The treatment of cystic fibrosis in patients homozygous for the *F508del-CFTR* mutation, aged 12 years and over

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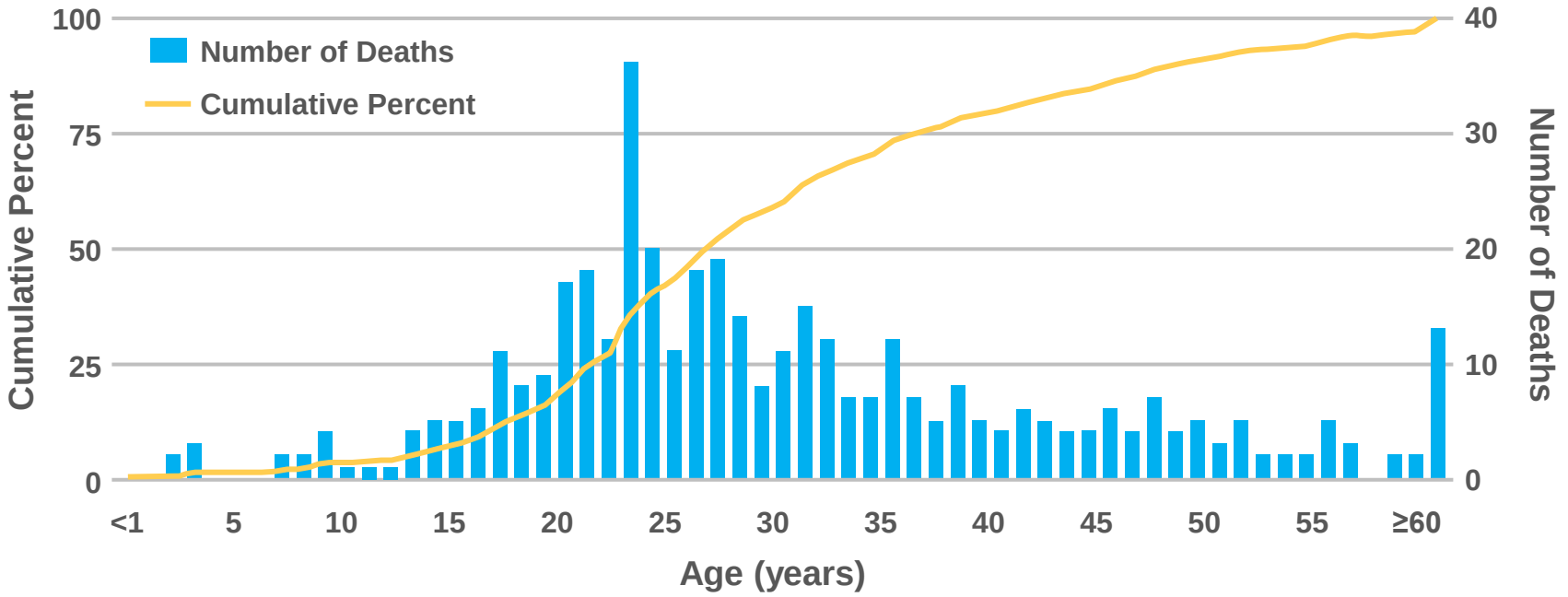
Disease Background and Medical Need

Michael W. Konstan, MD

Vice Dean for Translational Research
Professor of Pediatrics
Case Western Reserve University School of Medicine
UH Rainbow Babies and Children's Hospital

CF Is a Life-Shortening Orphan Genetic Disease

Age at Death



Approximately 30,000 people in the US[1]

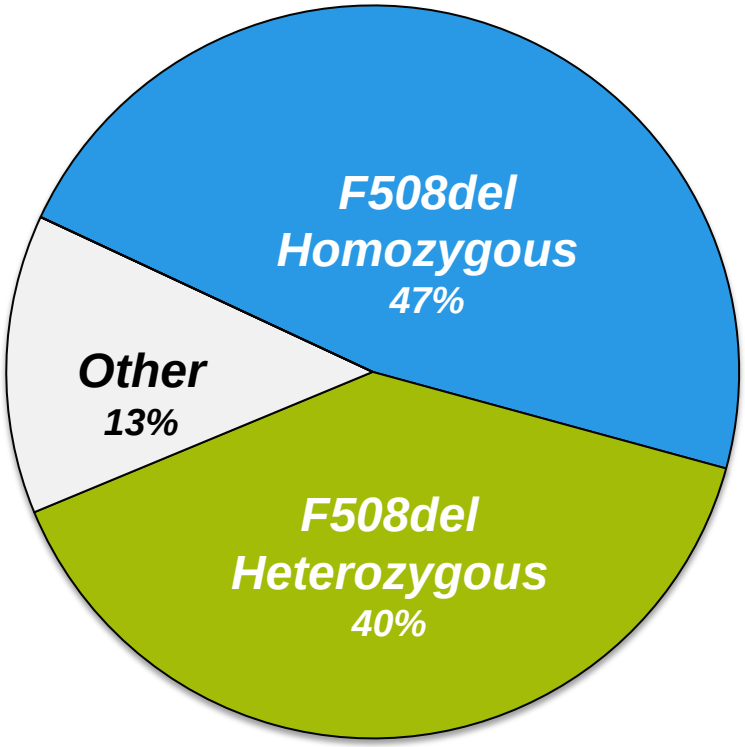
- Median age at death: 27.5 years[1]

[1]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014.

The *F508del-CFTR* Homozygous Genotype Is Associated with a Severe Clinical Phenotype

- Almost half of CF patients are homozygous for *F508del-CFTR*[1]

- *F508del* homozygous:
  - Severe phenotype[2,3]
  - Early onset of progressive lung disease[2,3]
  - Shortened life expectancy compared to the overall CF population[4]

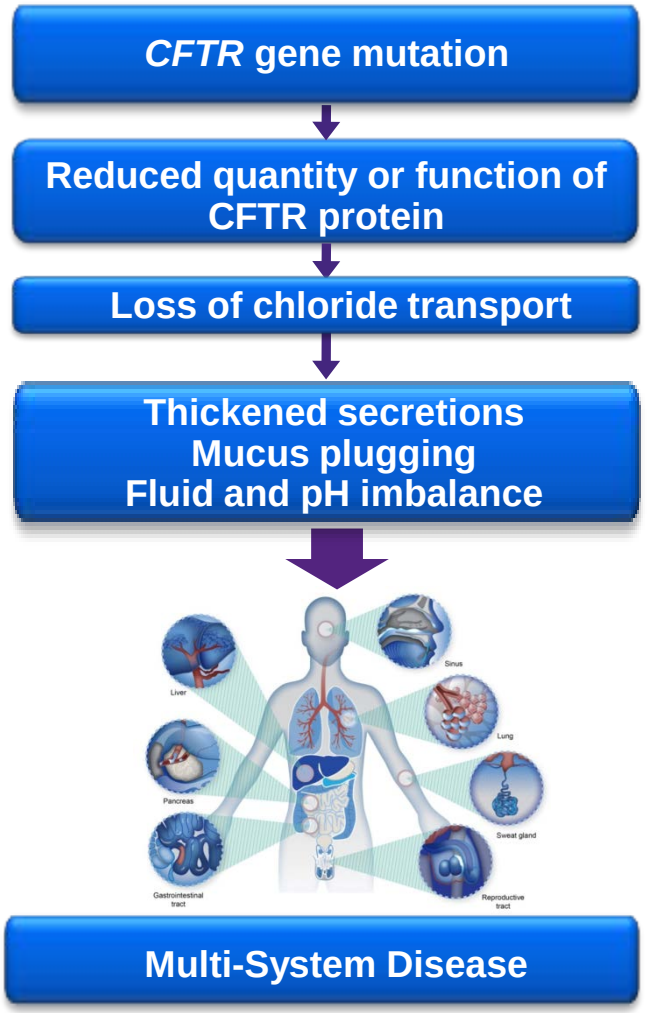


[1]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014. [2]The Clinical and Functional TRanslation of CFTR (CFTR2);http://cftr2.org.2015. [3]Kerem E et al. *N Engl J Med.* 1990. [4]MacKenzie T et al. *Ann Intern Med.* 2014.

The Underlying Cause of CF Is Loss of CFTR Protein Activity

- Reduced CFTR activity results in a loss of chloride transport causing abnormalities in tissues where CFTR protein is present[1]

Pathophysiologic Cascade of CF Disease[2,3]



[1]Rowe SM et al. *N Engl J Med*. 2005;352:1992-2001. [2]Ratjen F. *Respir Care*. 2009. [3]O'Sullivan BP, Freedman SD. *Lancet*. 2009.

CF Is a Multi-System Disease

Liver disease

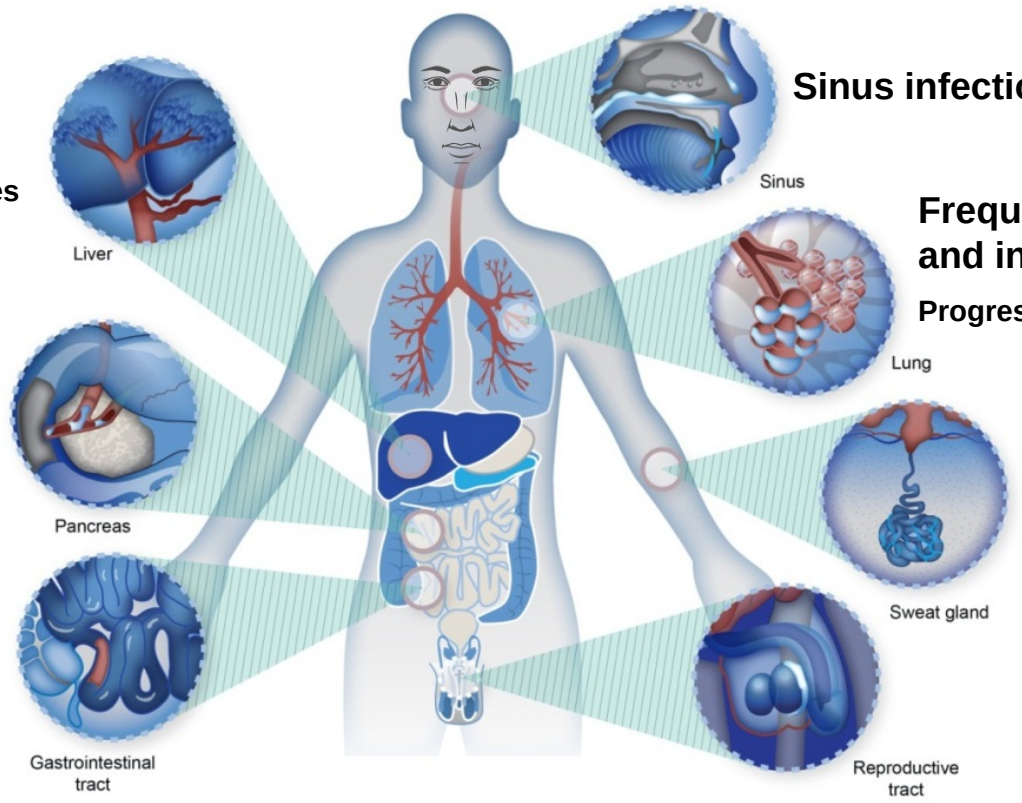
↑ **transaminases, gallbladder abnormalities**

Pancreatic insufficiency

CF-related diabetes

Digestive problems

Failure to thrive



Sinus infections, nasal polyps

Frequent lung infections and inflammation

Progressive lung disease

Salty sweat

Fertility issues

Progressive loss of lung function is the major cause of morbidity and mortality[1,2]

[1]O'Sullivan BP, Freedman SD. *Lancet*. 2009. [2]Cystic Fibrosis Foundation (CFF) Patient Registry. *2013 Annual Data Report*. CFF; 2014.

Primary Goals of CF Care

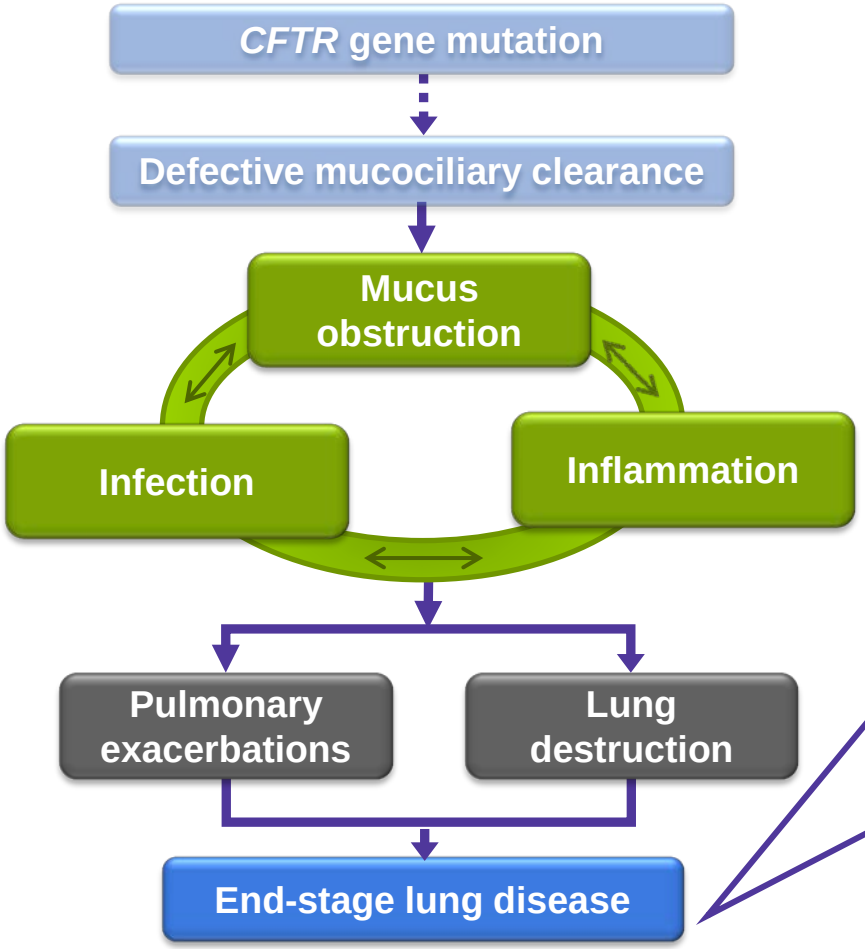
The primary goals of CF treatment include the following:[1-3]

1. Maintain lung function
2. Reduce pulmonary exacerbations
3. Improve nutritional status

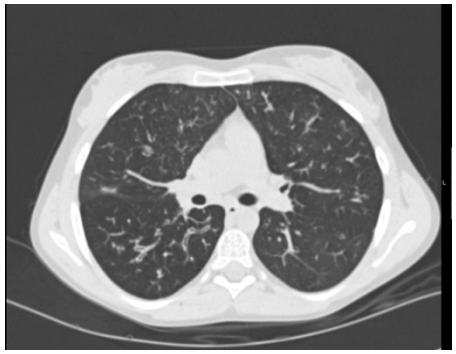
[1]Stallings et al. *Journal of the American Dietetic Association.* 2008. [2]Mogayzel et al. *Am J Respir Crit Care Med.* 2013. [3]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014.

CF Is Characterized by Progressive Lung Disease

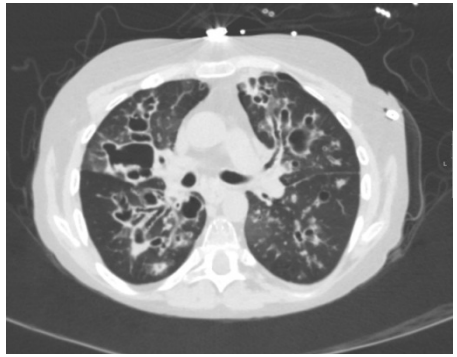
Pathophysiologic Cascade of CF in the Lungs[1,2]



Progression of lung disease[3]



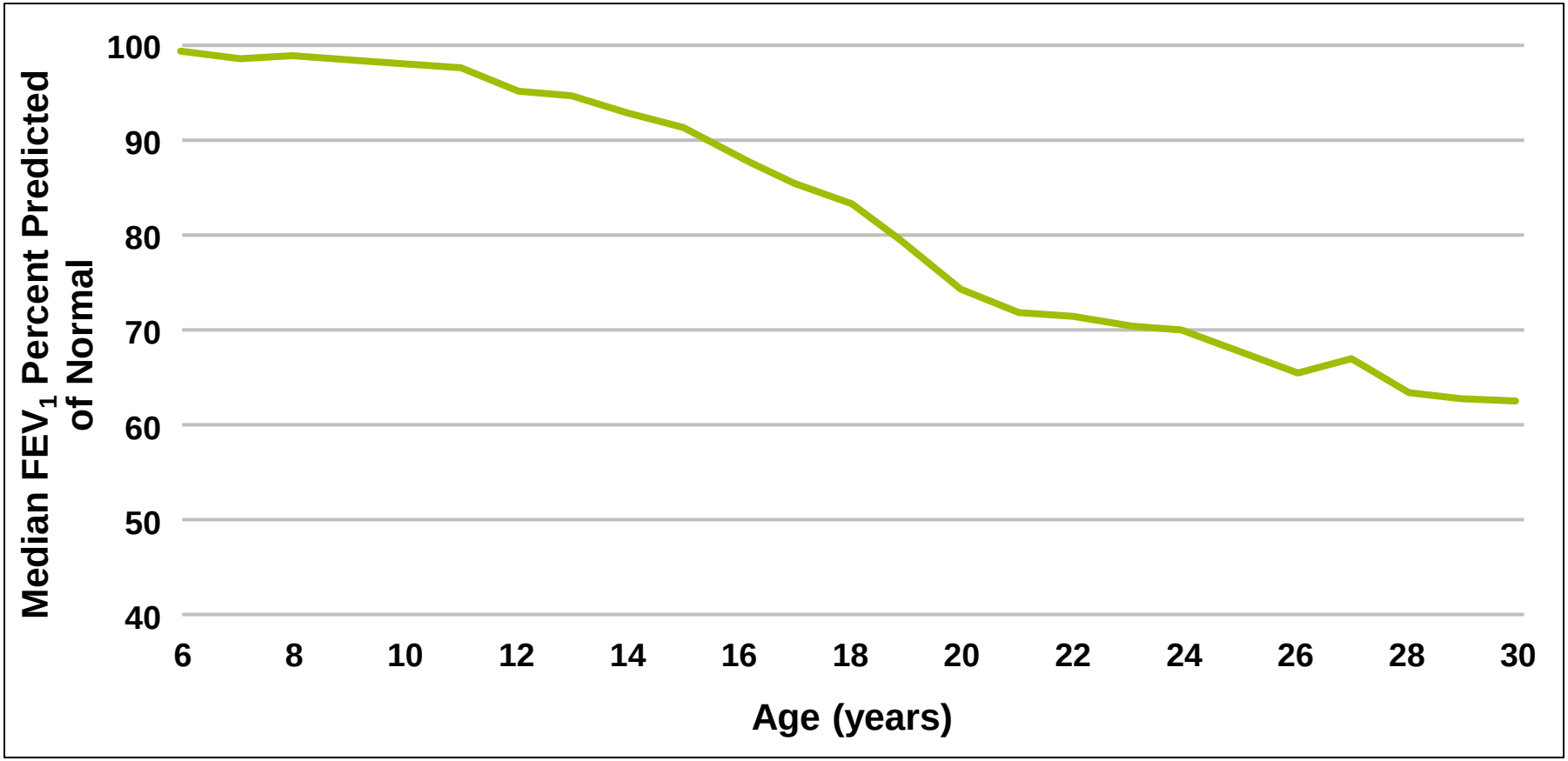
Age 16



Age 23

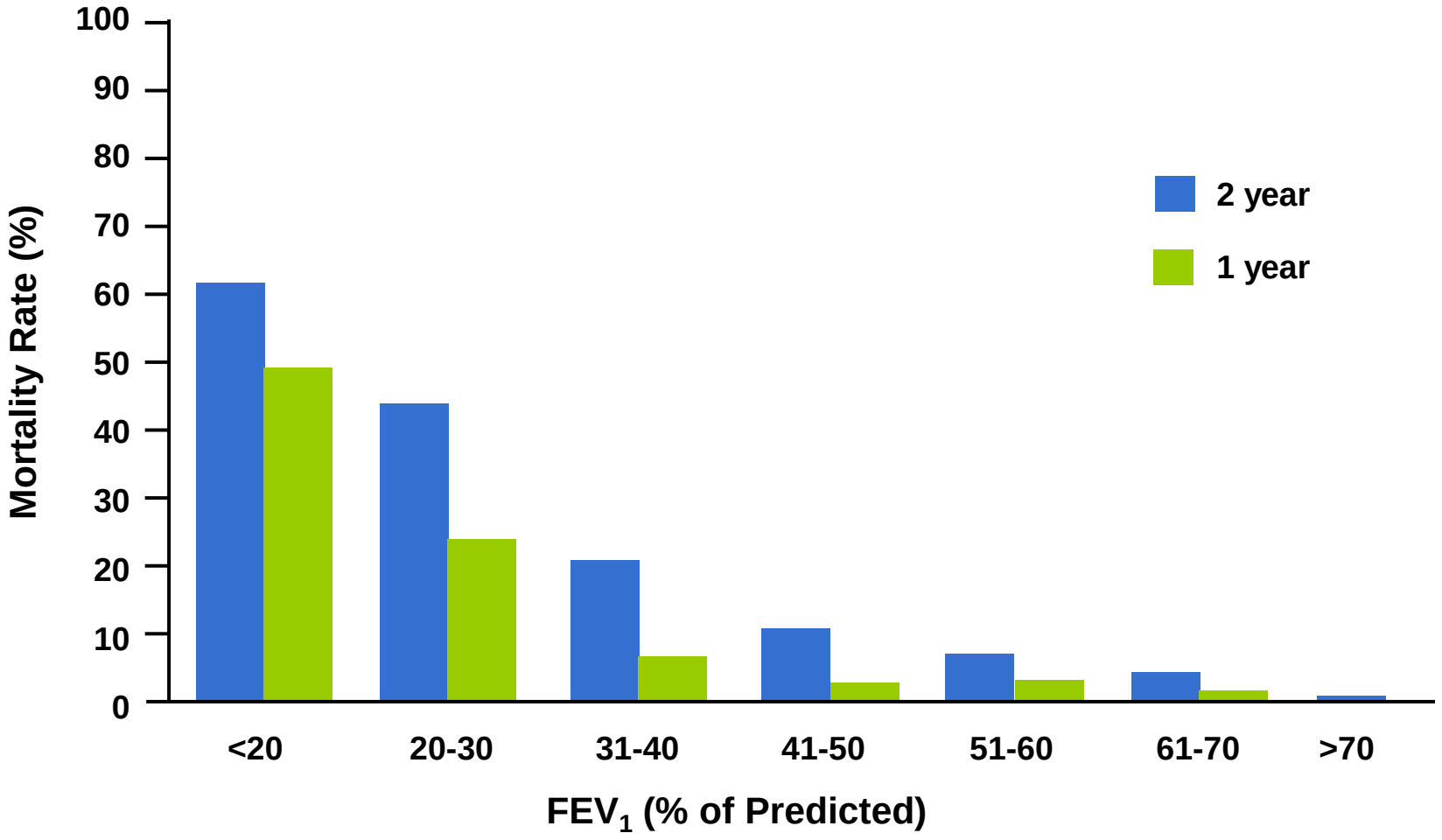
[1]Ratjen F. *Respir Care.* 2009;54:595-605. [2]Liou TG, Adler FR, *Am J Epidemiol* 2001. [3]Images courtesy of Dr. Michael W Konstan

CF Patients Develop Progressive Lung Disease at an Early Age Despite Current Therapies



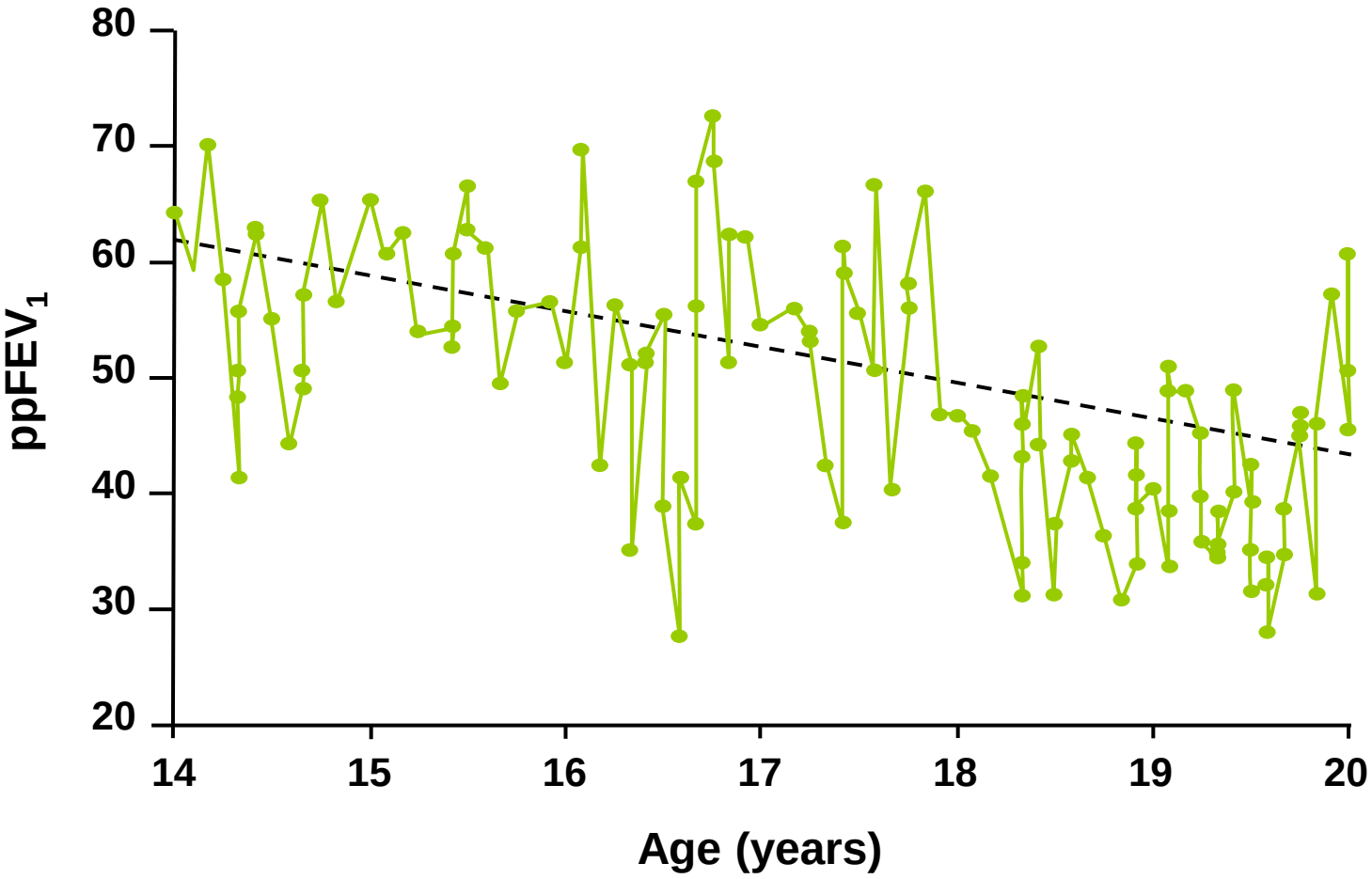
Cystic Fibrosis Foundation (CFF) Patient Registry. *2012 Annual Data Report*. Bethesda, MD: CFF; 2013.

FEV_1 Is the Strongest Predictor of Mortality in CF



Kerem E et al. *N Engl J Med.* 1992.

Progressive Lung Disease in a Patient Homozygous for *F508del*



Nutritional Status Is Poor in CF and Correlates with Lung Function and Survival

- In CF, nutritional deficiency is common due to pancreatic insufficiency and malabsorption[1]
- Lower body mass index (BMI) is associated with reduced lung function[2]
- Poor nutritional status is a predictor of reduced survival[3,4]

[1]O'Sullivan BP, Freedman SD. *Lancet*. 2009. [3]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014. [3]Liou TG, Adler FR, *Am J Epidemiol* 2001.[4]Stephenson et al. *Eur Resp J ;* 2014.

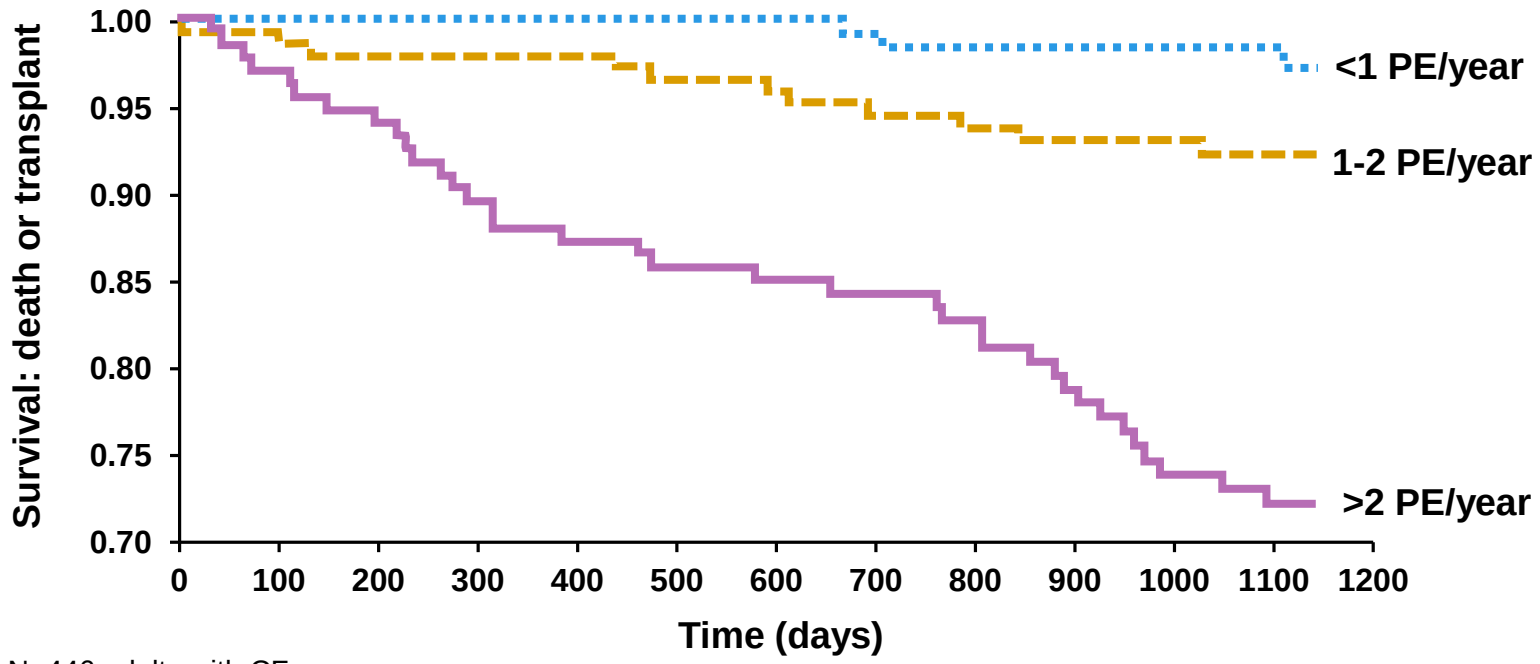
Pulmonary Exacerbations Are Serious Life Events for a CF Patient

- Occur and increase throughout the life of a CF patient[1,2]
- Characterized by worsening respiratory symptoms (cough, sputum production, shortness of breath)[1,2]
  - Typically require treatment with antibiotics
  - Often result in hospitalization (average of 19 days/year), absence from school or work
- Major clinical consequences
  - Irreversible and progressive loss of lung function[3-6]
  - Increased risk for future exacerbations[7]
  - Reduced health-related quality of life[8]
  - Increased risk of death[9,10]

[1]CFF Patient Registry. Annual Report to the Center Directors, 2013. [2]Goss and Burns. Thorax 2007. [3]Sanders et al. *Am J Respir Crit Care Med* 2010. [4]Sanders et al. *Ped Pulm* 2010. [5]Waters et al. *J Cystic Fibrosis* 2012. [6]Collaco et al, *Am J Respir Crit Care Med* 2010. [7]Van Devanter et al. *J Cystic Fibrosis* 2015. [8]Britto et al. *Chest* 2002. [9]de Boer et al. *Thorax* 2011. [10]Liou et al. *Am J Epidemiol* 2001.

Pulmonary Exacerbations Are Associated with Increased Mortality

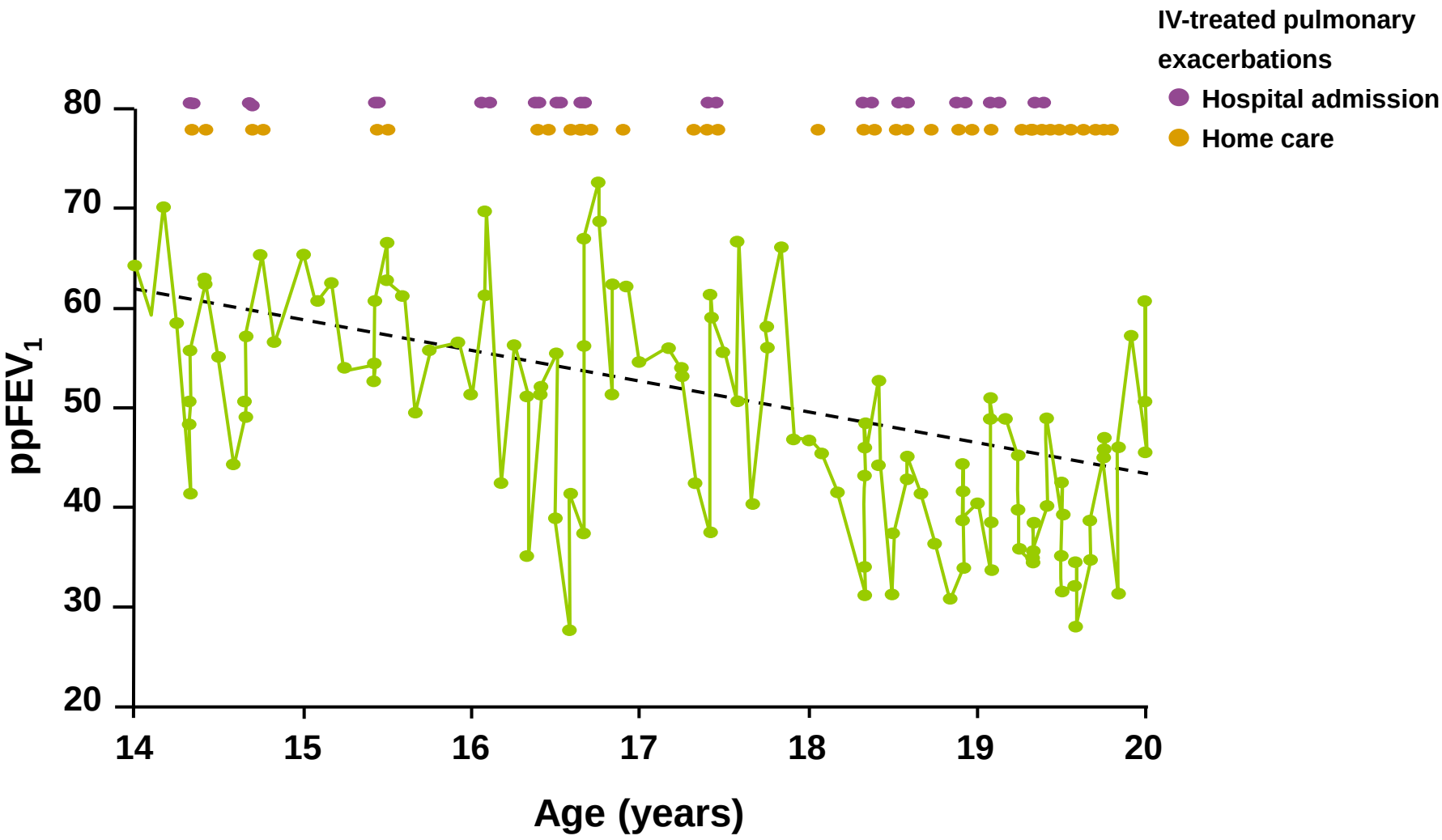
Survival: Death or Transplant by Number of Pulmonary Exacerbations (PE)[5]



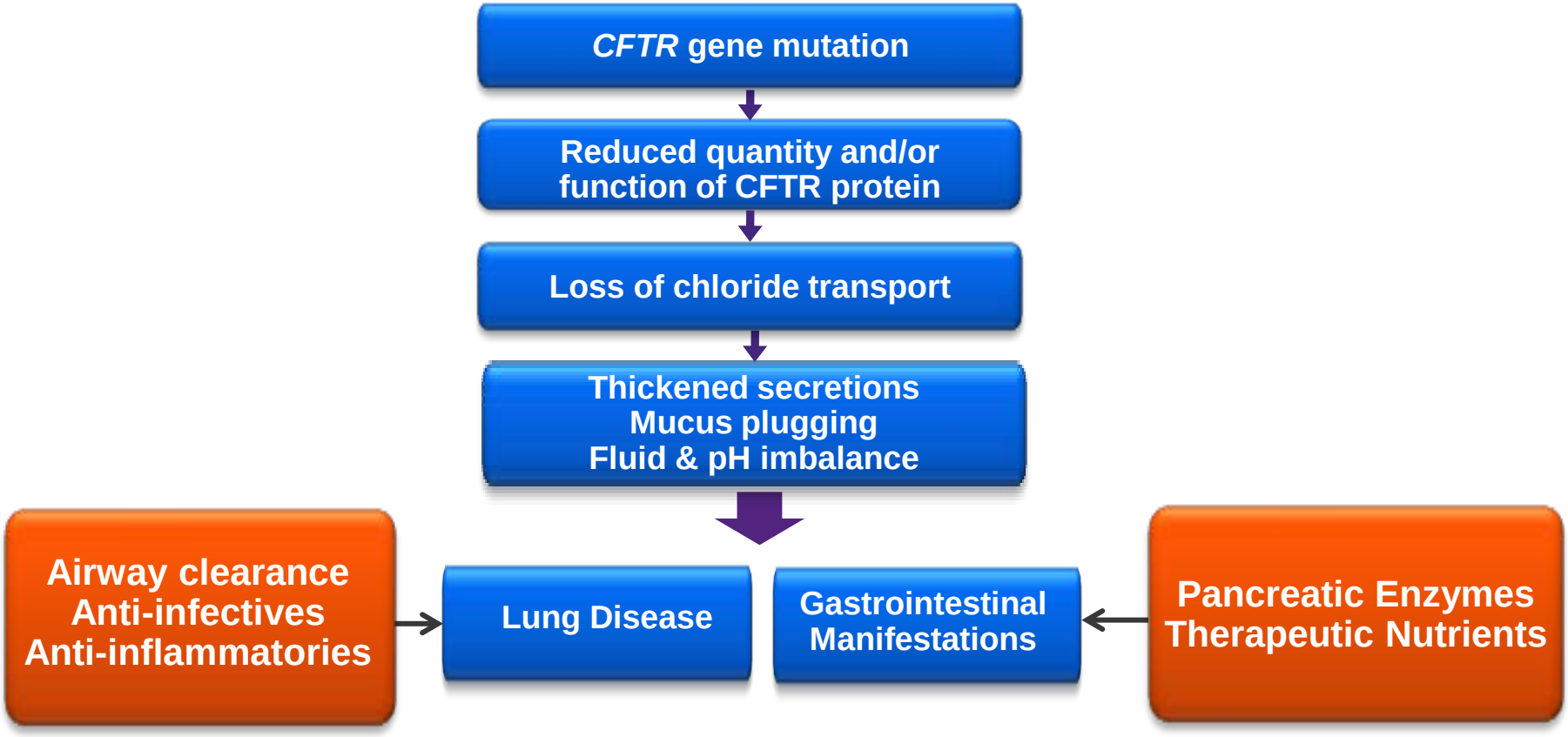
N=446 adults with CF

deBoer K et al. *Thorax*. 2011.

Progressive Lung Disease and Exacerbations in a Patient Homozygous for *F508del*



Current Therapies Do Not Treat the Underlying Cause of Disease in *F508del* Homozygous Patients



Ratjen F. *Respir Care.* 2009. O'Sullivan BP, Freedman SD. *Lancet*. 2009. Davis et al., *Am J Respir Crit Care Med*. 1996. Mogayzel. *Am J Respir Crit Care*. 2013. Stallings et al. *Journal of the American Dietetic Association.* 2008.

CFTR Modulators Treat the Underlying Cause of Disease

F508del/F508del

~ 47% of CF patients

***CFTR* gene mutation**

↓

Reduced quantity and/or function of CFTR protein

↓

Loss of chloride transport

↓

Thickened secretions
Mucus plugging
Fluid & pH imbalance

↓

Lung Disease

Gastrointestinal Manifestations

Gating Mutations

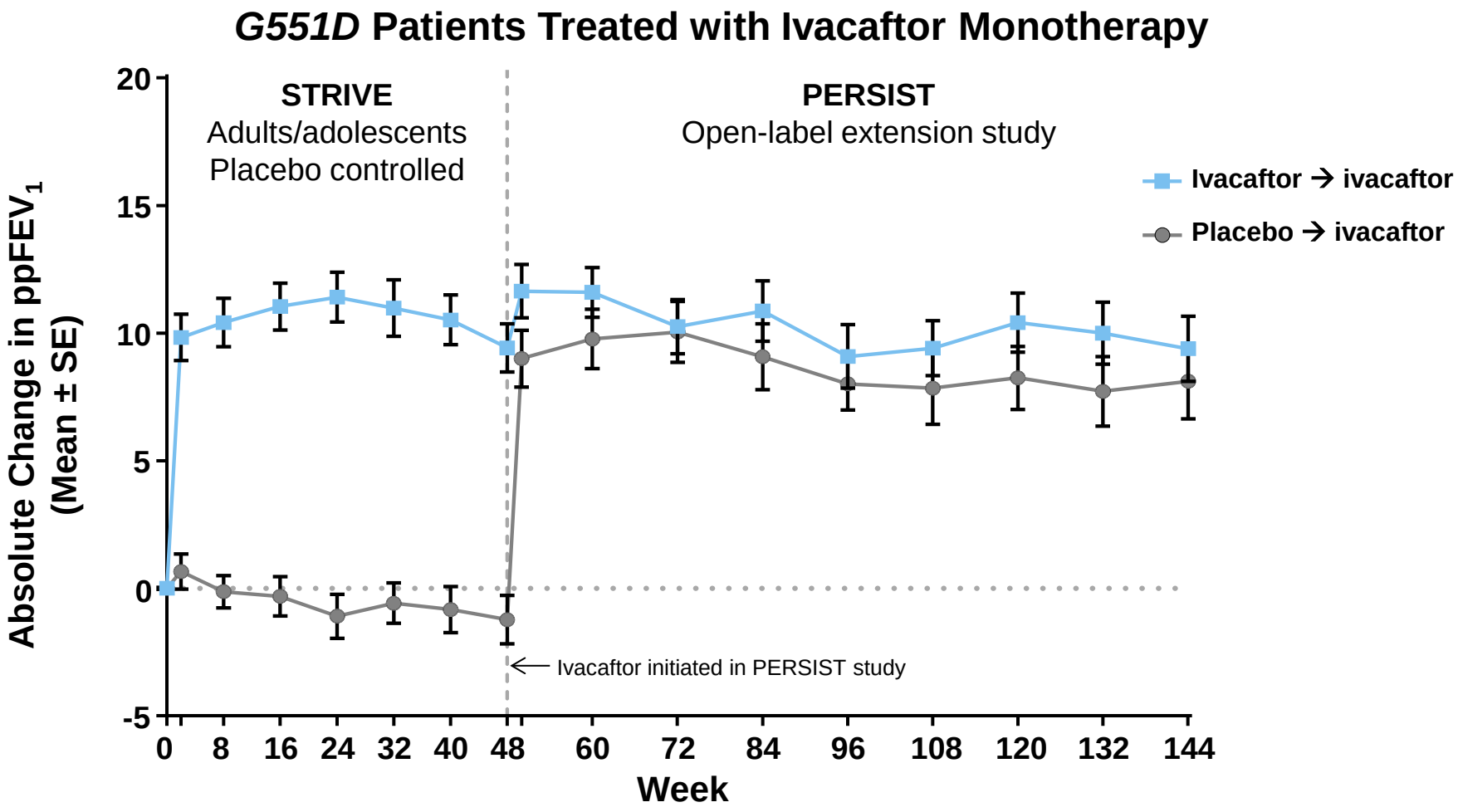
~ 8% of CF patients

Ivacaftor

- Improved FEV_1[1-3]
- Decreased rate of lung function decline[4]
- Decreased pulmonary exacerbations[1,3]
- Improved nutritional status[1-3]
- Reduced *P. aeruginosa* culture rate[5]

[1]Ramsey B et al. *N Engl J Med* 2011. [2]Davies J et al. *Am J Resp Crit Care Med* 2013. [3]McKone E et al. *Lancet Resp Med* 2014. [4]Sawicki G et al. *Presented at ECFS* 2014. [5]Rowe S et al. *Am J Respir Crit Care Med*. 2014. [6]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014.

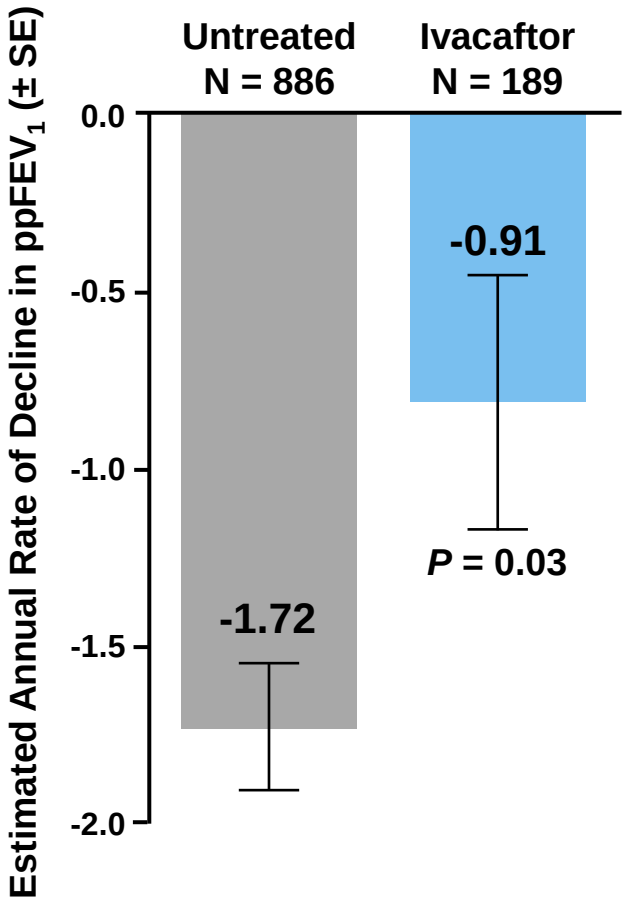
Restoring CFTR Function Results in Improved FEV_1

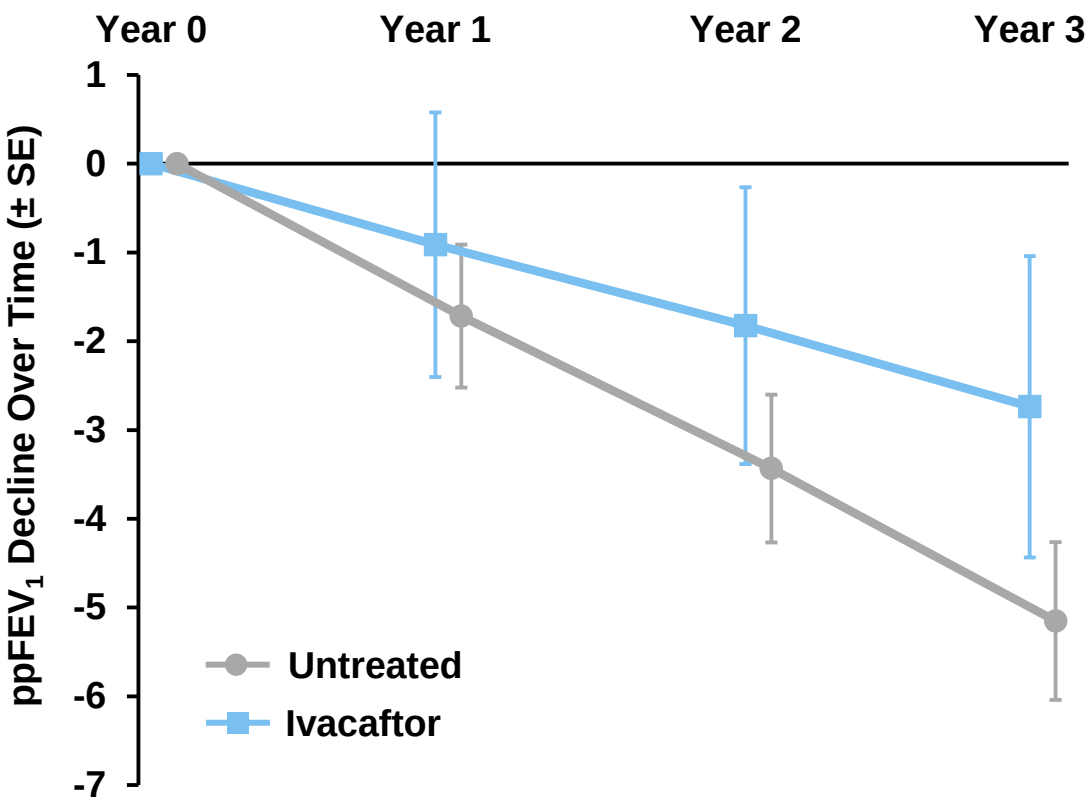


1. Acute improvement in $ppFEV_1$ **2. Sustained effect on $ppFEV_1$**

McKone E et al. *Lancet Resp Med.* 2014.

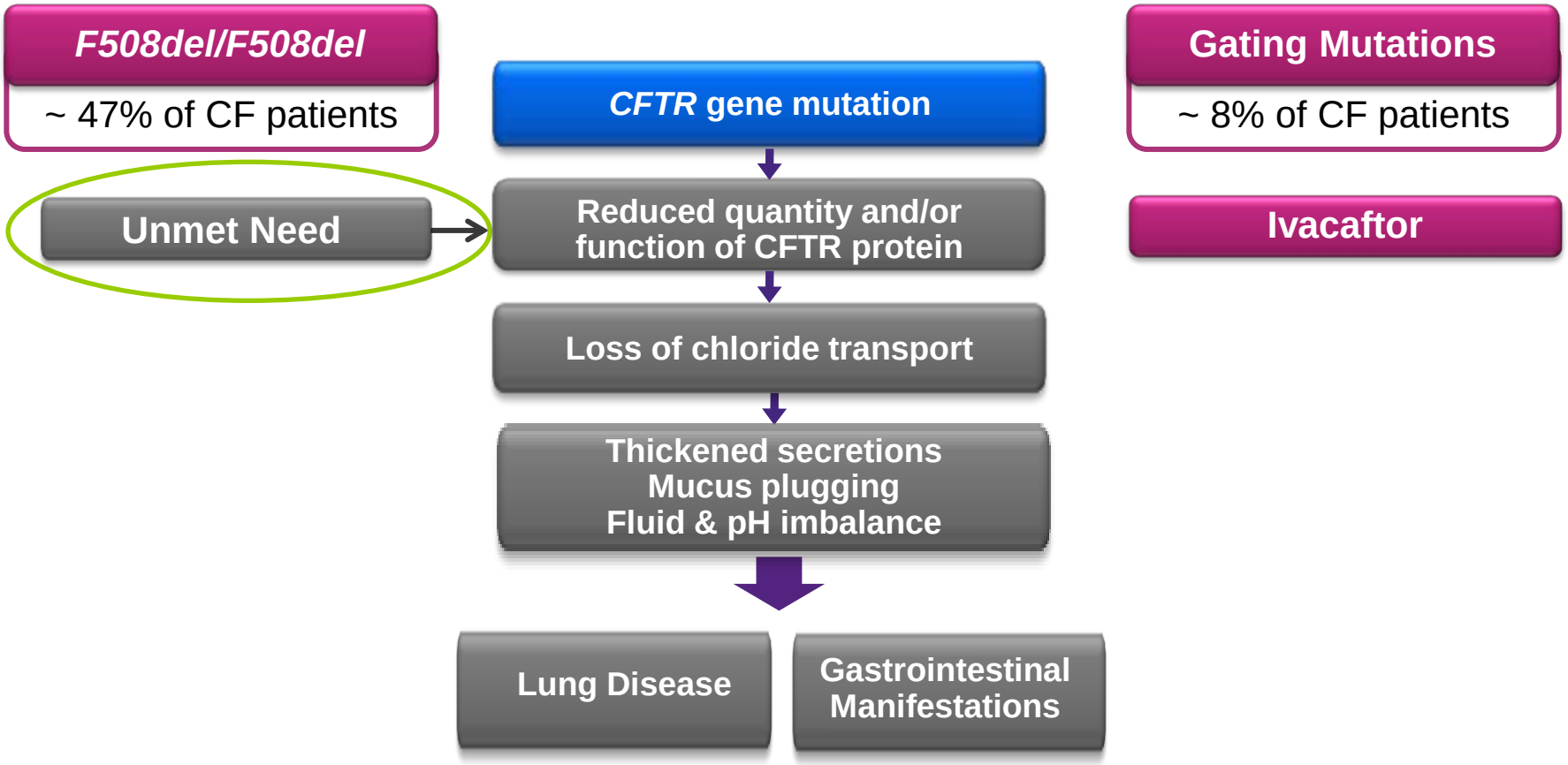
CFTR Modulation with Ivacaftor Reduces the Rate of Lung Function Decline in Patients with *G551D*





Modified From: Sawicki G. Presented at the 37th Meeting of the European Cystic Fibrosis Society at Gothenburg, Sweden, June 12, 2014. Vertex Pharmaceuticals Data on File.

CFTR Modulators Treat the Underlying Cause of Disease



Ratjen F. *Respir Care.* 2009. O'Sullivan BP, Freedman SD. *Lancet*. 2009. Mogayzel. *Am J Respir Crit Care*. 2013.

Summary

- CF is a multi-system, life-shortening disease that is caused by defects in CFTR protein activity
- The *F508del* homozygous genotype is associated with a severe clinical phenotype, rapid disease progression, and reduced survival
- FEV_1, pulmonary exacerbations and nutritional status are key measures in assessing clinical response and disease stage
- Today, there is no CFTR modulator therapy for these patients

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Mechanism of Action

Fredrick Van Goor, PhD

Principal Research Fellow

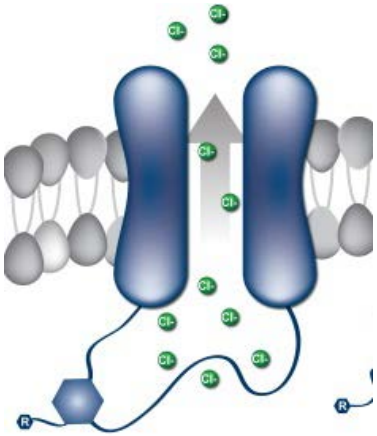
Vertex Pharmaceuticals

Introduction

- It is well established that defects in the CFTR protein cause CF
- The molecular defect associated with *F508del* is well understood
- This drove the discovery of two complementary medicines to target the underlying molecular defect in CFTR caused by *F508del*

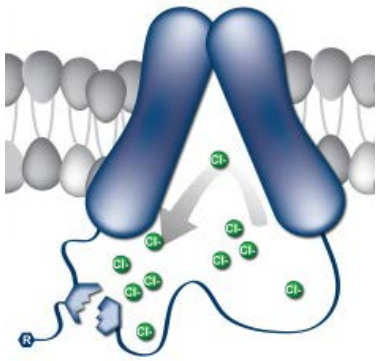
CF Is Caused by Molecular Defects in the CFTR Chloride Ion Channel

Normal

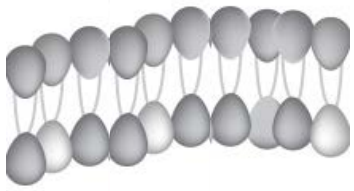


CF

Molecular defects caused by *CFTR* mutations are well understood



and/or

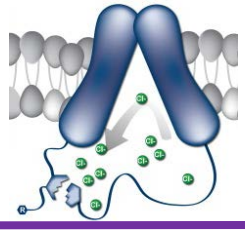


Decreased Function

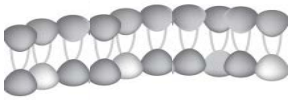
Decreased Quantity

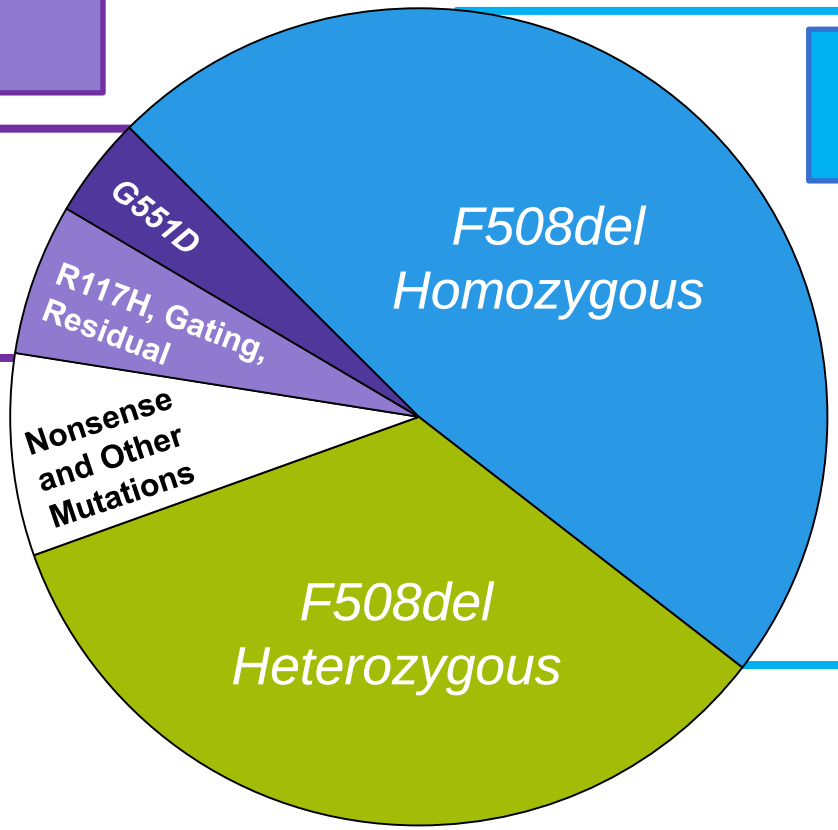
Two Complementary Medicines to Address Defects Caused by CFTR Mutations

Potentiator
e.g., IVA



Corrector + Potentiator
e.g., LUM + IVA





Decreased Function

Decreased Quantity

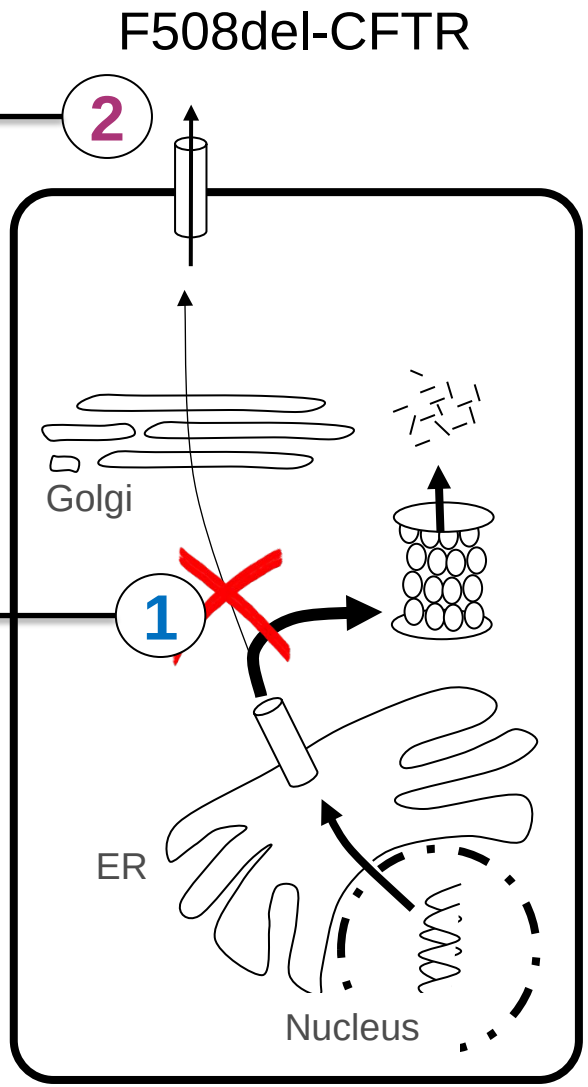
The Molecular Defect Caused by *F508del* Is Well Understood

Consequence

Less than 5% of normal CFTR at the cell surface, resulting in almost complete loss of chloride transport

Molecular defect caused by *F508del*

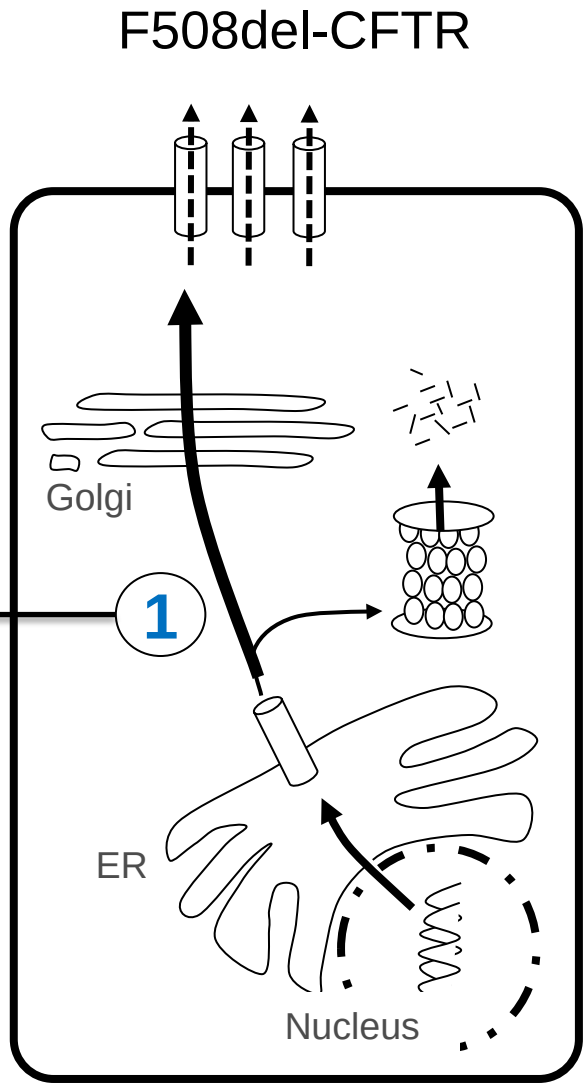
Severe defect in the processing and trafficking of F508del-CFTR



LUM Addresses the Underlying Molecular Defect Caused by *F508del*

LUM

Facilitates the processing and trafficking of F508del-CFTR to increase its amount at the cell surface



IVA Improves the Function of F508del-CFTR Delivered to the Surface by LUM

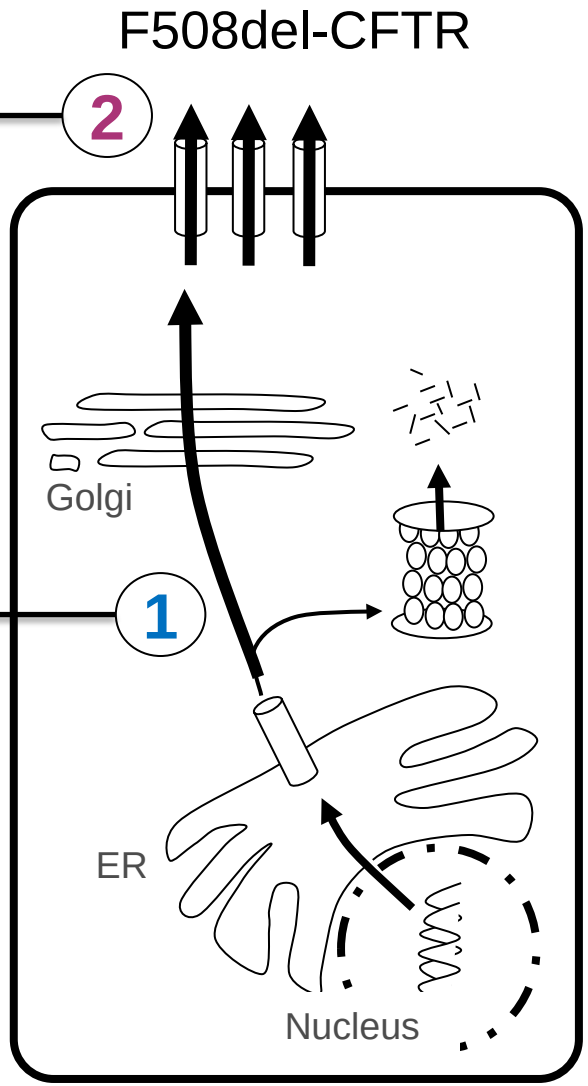
IVA

Potentiates the channel-open probability of F508del-CFTR delivered to the cell surface by LUM

+

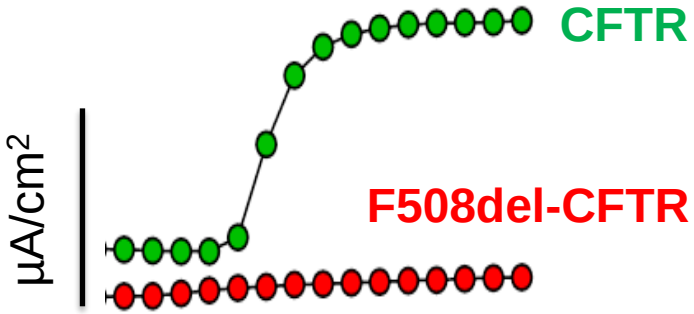
LUM

Facilitates the processing and trafficking of F508del-CFTR to increase its amount at the cell surface

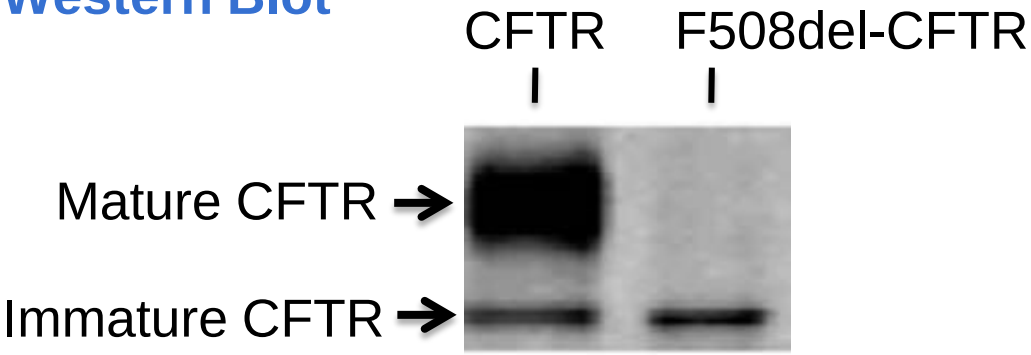


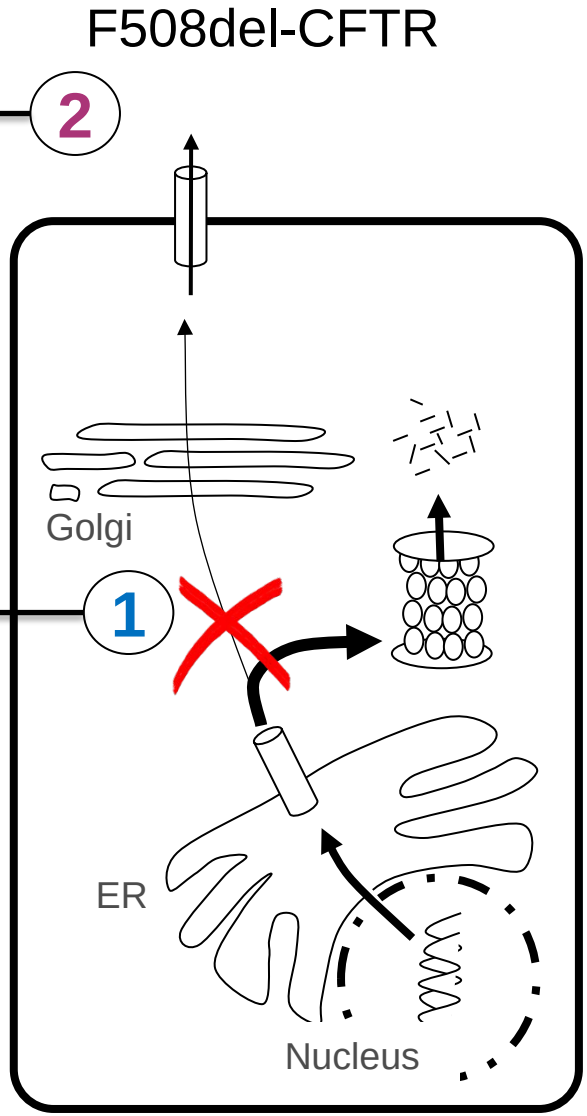
Methods Established to Measure the Underlying Defect in *F508del* Human Bronchial Epithelial Cells

Ussing Chamber



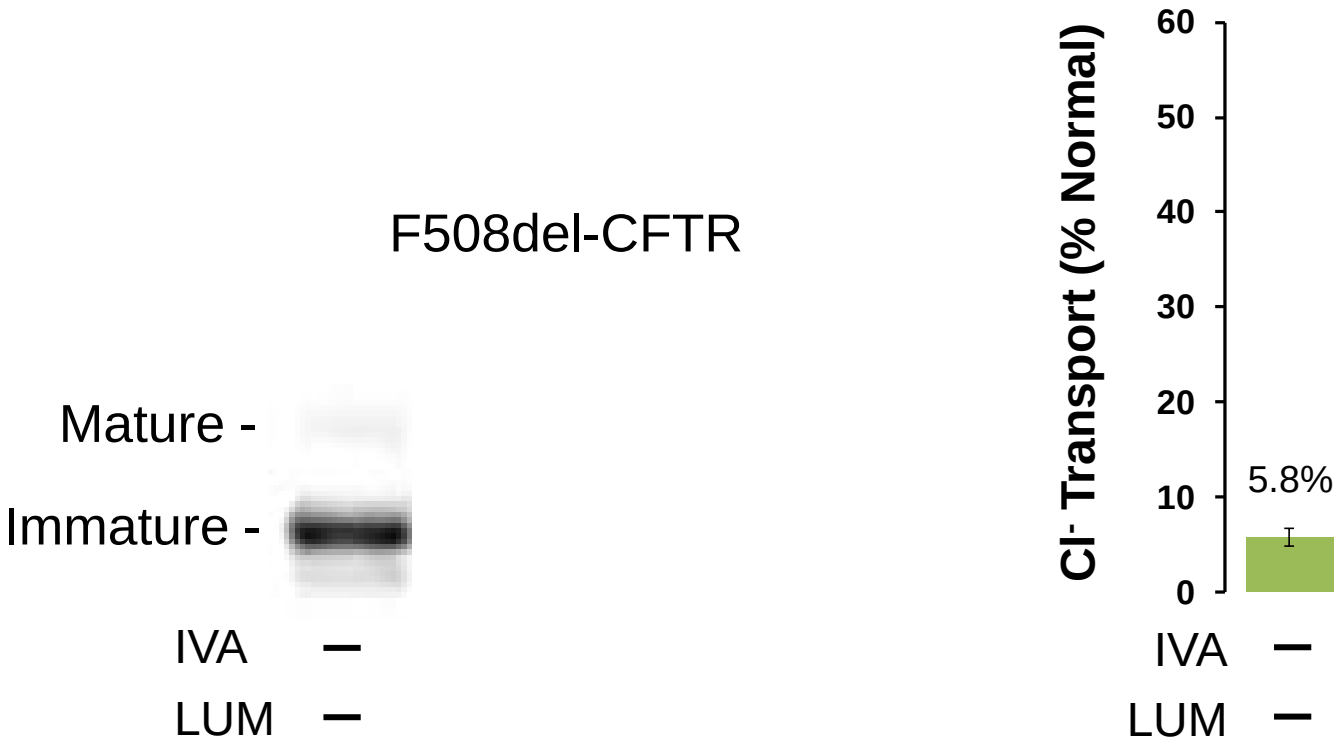
Western Blot





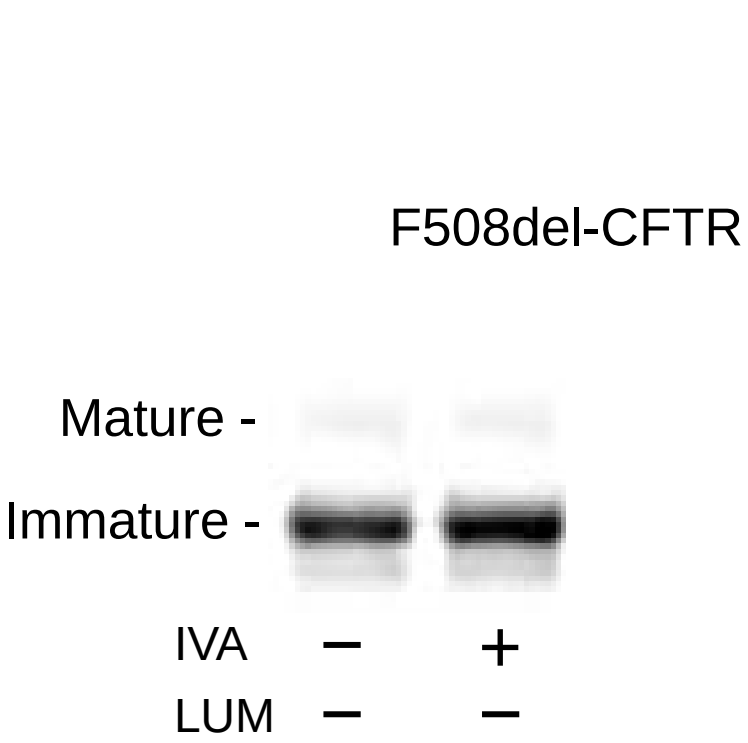
There is Little-to-no F508del-CFTR Protein at the Cell Surface

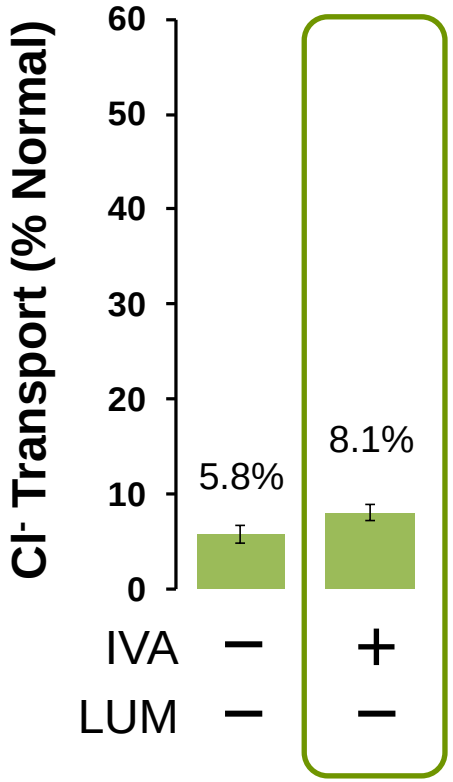
- Due to severe defect in CFTR processing and trafficking
- Causes almost complete loss of chloride transport in epithelial cells



IVA Does Not Address the Underlying Molecular Defect Caused by F508del-CFTR

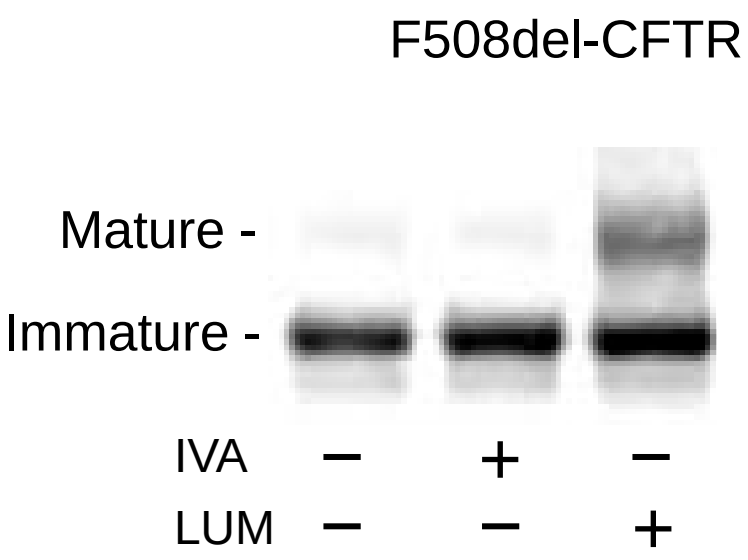
- IVA does not improve the processing and trafficking of F508del-CFTR
- IVA has minimal effect on chloride transport because there is little-to-no CFTR at the cell surface

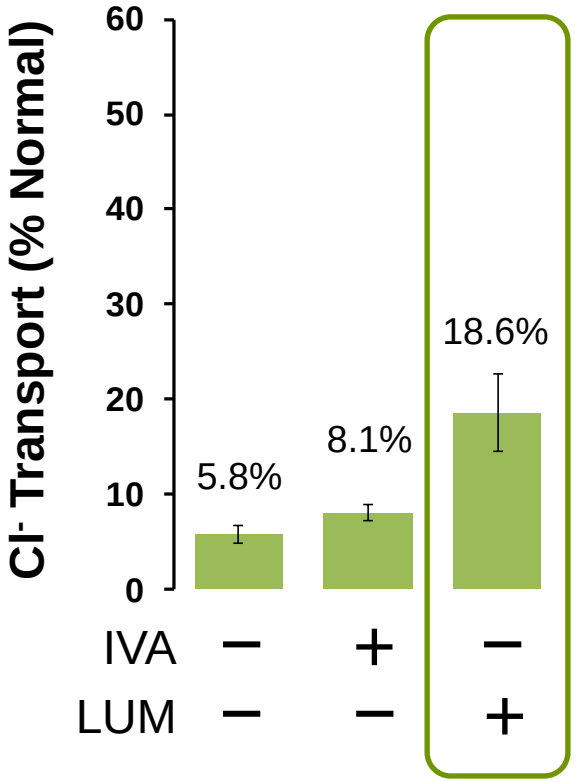




LUM Is Essential to Address the Underlying Defect Caused by F508del-CFTR

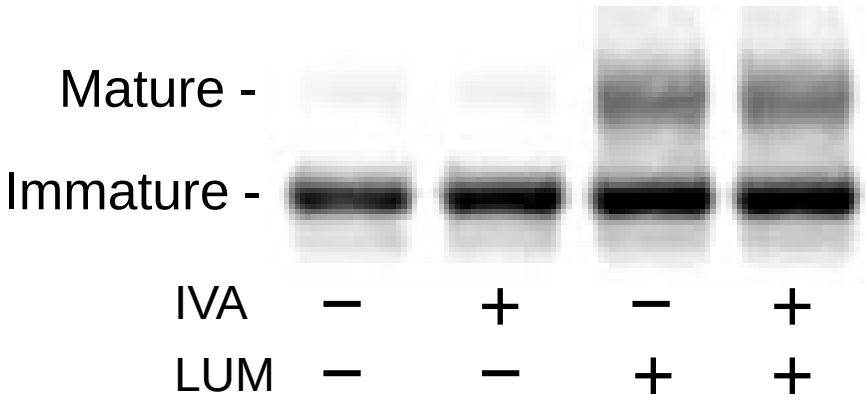
- LUM improves the processing and trafficking of CFTR to increase the amount of F508del-CFTR at the cell surface
- Results in an increase in chloride transport

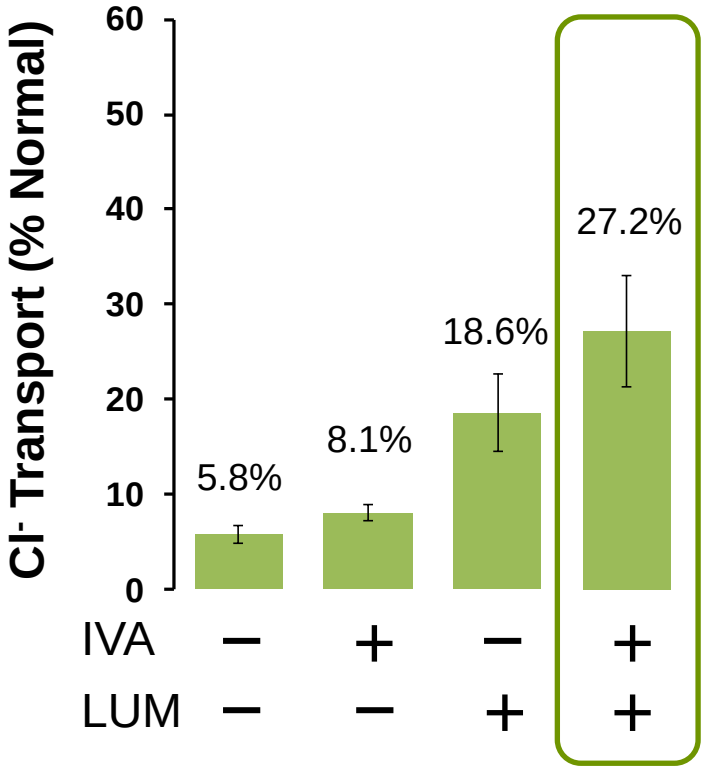




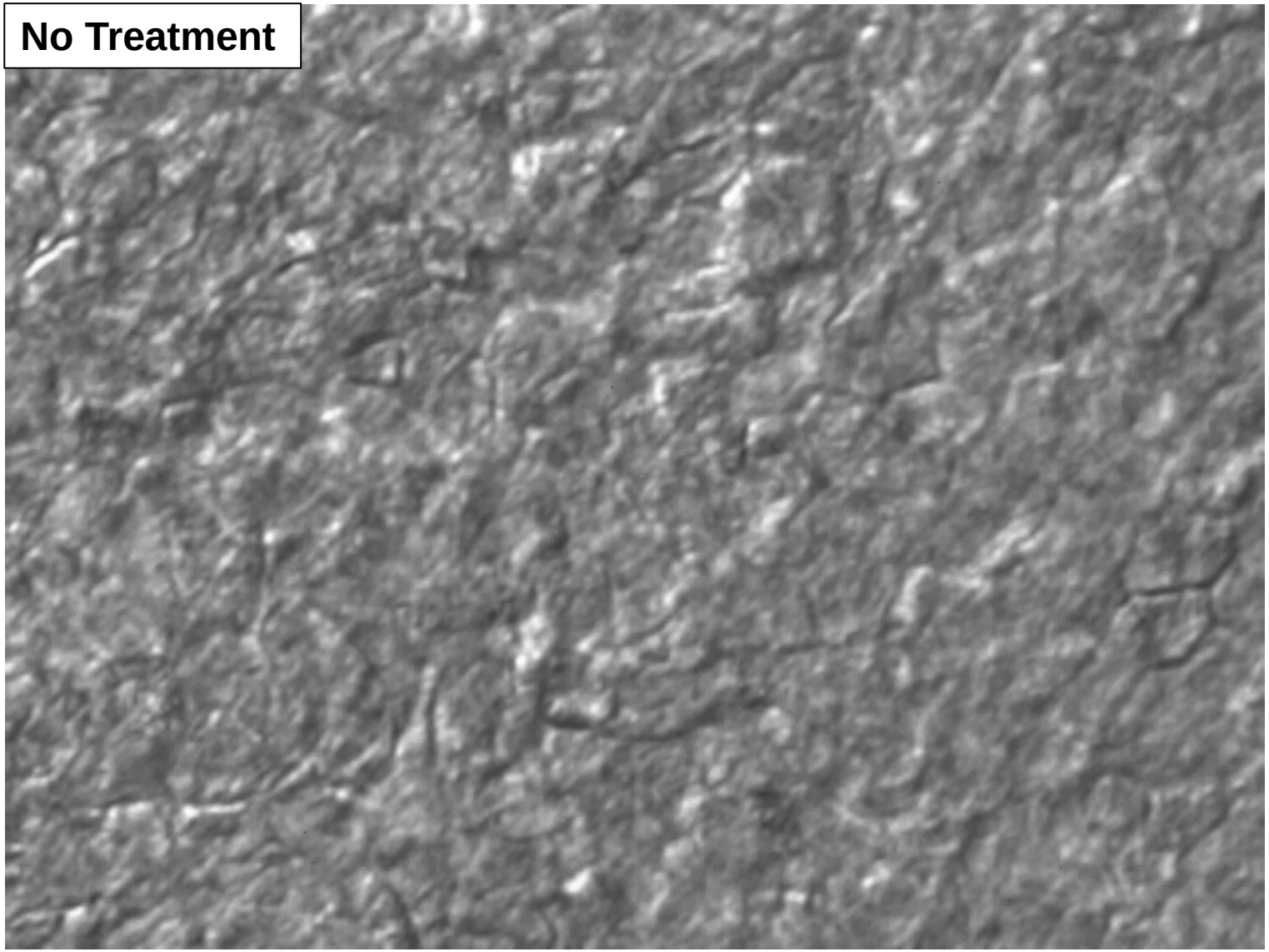
LUM/IVA Combination Provides a Maximal Increase in Chloride Transport

- The F508del-CFTR delivered to the cell surface by LUM is potentiated by IVA, leading to a further enhancement of chloride transport

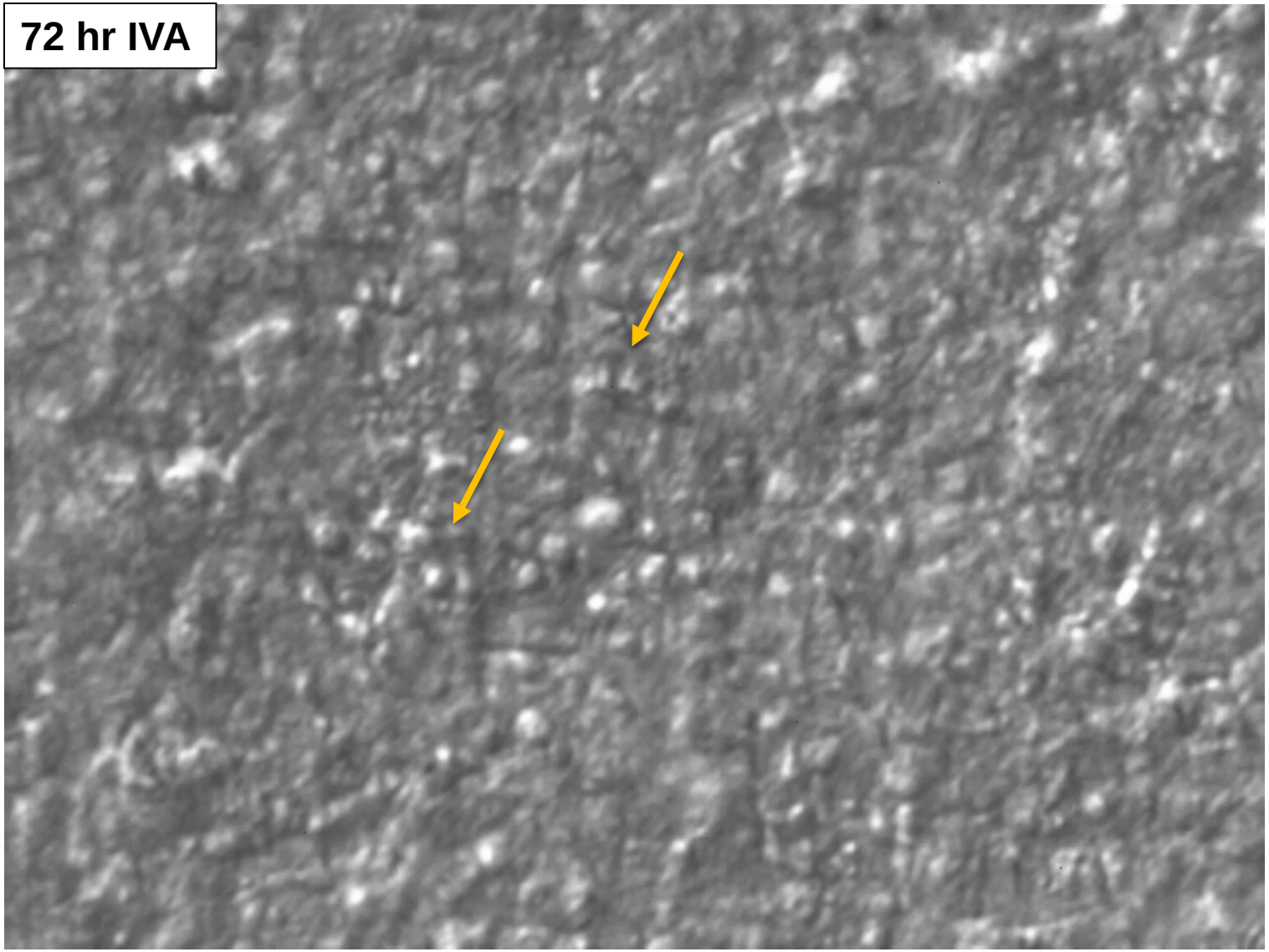




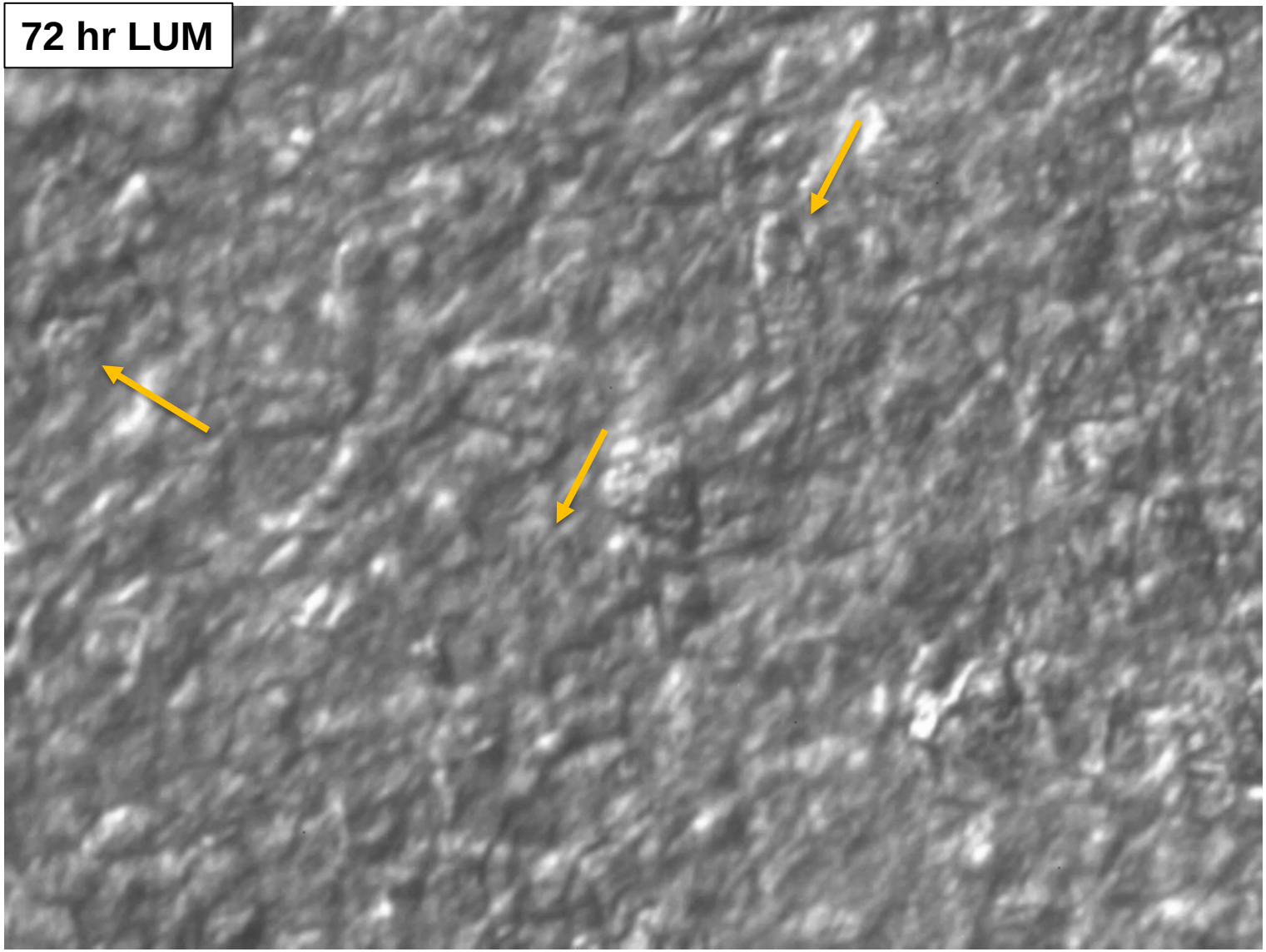
Ciliary Beat Frequency in *F508del* HBE Cells: No Treatment



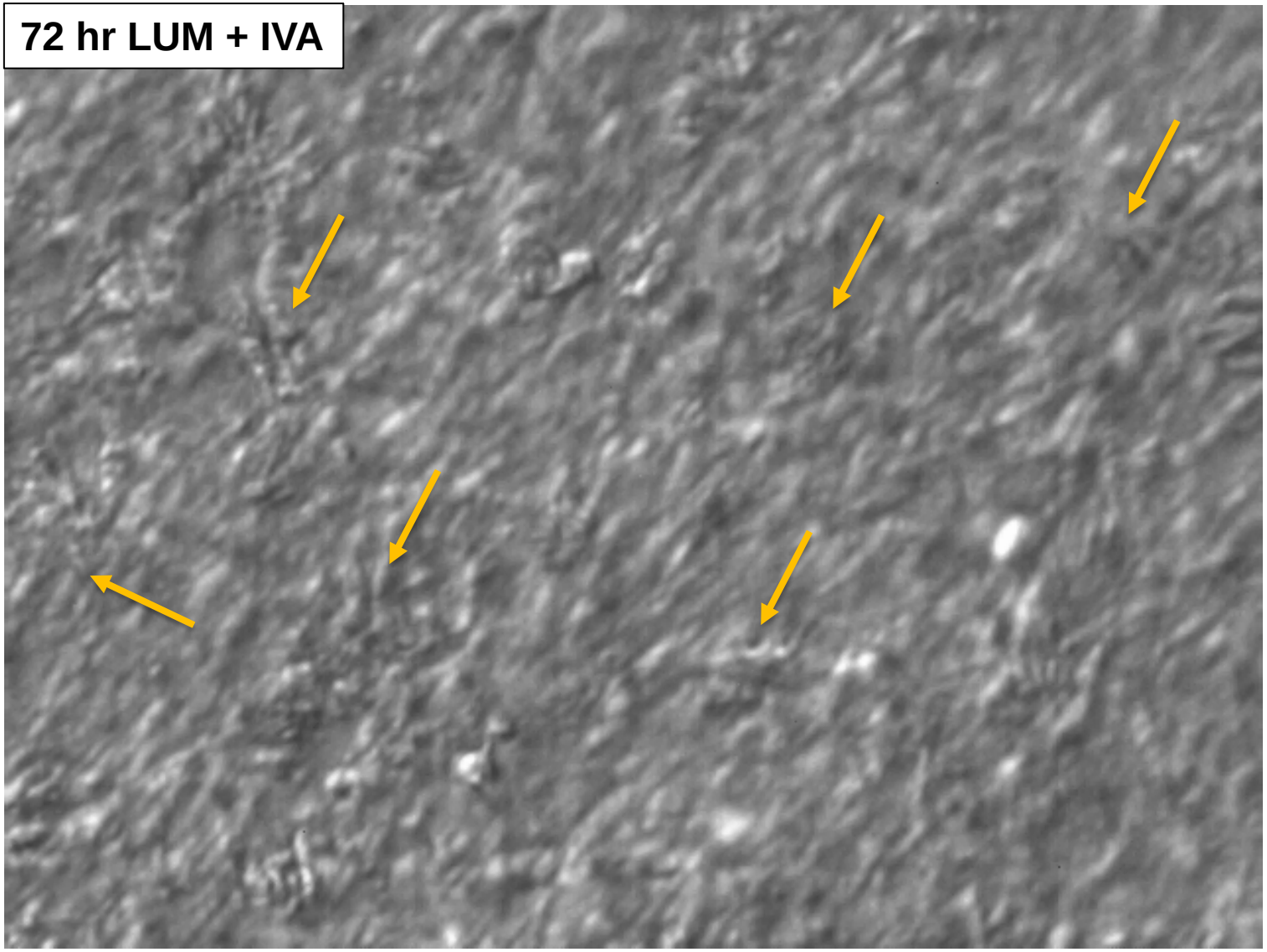
Ciliary Beat Frequency in *F508del* HBE Cells: IVA Alone



Ciliary Beat Frequency in *F508del* HBE Cells: LUM Alone



Ciliary Beat Frequency – LUM + IVA Provides Maximum Improvement



LUM is Essential to Address the Underlying Defect in F508del-CFTR

- *F508del* causes a severe defect in CFTR processing and trafficking
- IVA had a minimal effect on chloride transport in vitro, consistent with little-to-no F508del-CFTR at the cell surface
- LUM improves F508del-CFTR processing and trafficking thereby increasing CFTR at the cell surface
- The F508del-CFTR delivered to the cell surface by LUM was potentiated by IVA
- The combination provides superior increases in chloride transport and ciliary beat frequency

Agenda for Vertex Presentation

Introduction	**Jeffrey Chodakewitz, MD** Chief Medical Officer Executive Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Disease Background and Medical Need	**Michael W. Konstan, MD** Vice Dean for Translational Research, Professor of Pediatrics Case Western Reserve University School of Medicine UH Rainbow Babies and Children's Hospital
Mechanism of Action	**Fredrick Van Goor, PhD** Principal Research Fellow Vertex Pharmaceuticals Incorporated
Clinical Development Program **Clinical Efficacy and Safety**	**Charlotte McKee, MD** Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Clinical Perspective	**Bonnie Ramsey, MD** Endowed Professor of Pediatrics, University of Washington School of Medicine Director, Center for Clinical and Translational Research, Seattle Children’s Hospital

Clinical Development Program

Charlotte McKee, MD

Vice President, Clinical Development

Vertex Pharmaceuticals

LUM/IVA Phase 1/2 Objectives

Determine whether in vitro LUM/IVA findings translate to F508del homozygous patients

1. Confirm that maximum benefit is observed with LUM/IVA combination compared with either drug alone

2. Identify effective dose(s)

   - Sweat chloride pharmacodynamic endpoint: direct measure of CFTR function
   - FEV_1 clinical endpoint: direct measure of lung function

3. Preliminary evaluation of safety profile

LUM/IVA Phase 1/2 Overview

LUM/IVA Program:

- Phase 1: 12 studies in over 400 subjects
- Phase 2: 189 patients homozygous for *F508del*

LUM monotherapy 28d → LUM/IVA combination 28d

  - LUM doses studied:
    200qd, 400qd, 600qd, 400q12h
  - IVA doses studied: 150q12h and 250q12h

- IVA monotherapy (150q12h; 16 wks)
  - 140 patients homozygous *F508del*

IVA Monotherapy: Minimal Effect in *F508del* Homozygous Patients

Endpoint	Treatment Difference (95% CI)	*P*-Value
Absolute change in ppFEV$_1$	**1.72** (-0.63, 4.08)	0.1509
Sweat chloride	**-2.9** (-5.6, -0.2)	0.04

- Primary efficacy endpoint not met
- Minimal improvement in sweat chloride
- Secondary endpoints not statistically significant
  - Pulmonary exacerbations
  - CFQ-R Respiratory Domain
  - BMI

Biology, mechanism of action, *in vitro* data, and clinical results all indicate that IVA alone does not provide clinically meaningful benefit in *F508del* homozygous patients

LUM Monotherapy Results

- Improvement in sweat chloride
- Unexpectedly associated with a decline in FEV_1

	LUM200qd N = 21	LUM400qd N = 20	LUM600qd N = 20	LUM400q12h N = 11
Sweat chloride change from baseline at Day 28				
Treatment difference (95% CI)	**-4.9** (-9.5, -0.3)	**-8.3** (-13.0, -3.6)	**-6.1** (-10.8, -1.4)	**-8.2** (-14.1, -2.3)
P-value	0.038	<0.001	0.012	0.007
$ppFEV_1$ absolute change from baseline at Day 28				
Treatment difference (95% CI)	**0.2** (-3.7, 4.2)	**-1.4** (-5.4, 2.6)	**-2.7** (-6.7, 1.4)	**-4.6** (-9.6, 0.4)
P-value	0.904	0.497	0.196	0.069

LUM/IVA Combination: Dose-Dependent Improvements in Sweat Chloride and FEV_1

	LUM200qd/IVA N = 21	LUM400qd/IVA N = 20	LUM600qd/IVA N = 20	LUM400q12h/IVA N = 11
Sweat chloride change from baseline at Day 56				
Treatment difference (95% CI)	**-5.0** (-10.5, 0.5)	**-9.8** (-15.3, -4.3)	**-9.5** (-15.1, -3.9)	**-11.0** (-18.3, -3.7)
P-value	0.073	<0.001	0.001	0.004
$ppFEV_1$ absolute change from baseline at Day 56				
Treatment difference (95% CI)	**3.8** (-0.5, 8.1)	**2.7** (-1.7, 7.0)	**5.6** (1.2, 10.0)	**4.2** (-1.3, 9.7)
P-value	0.082	0.228	0.014	0.137

LUM monotherapy 28d → LUM/IVA combination 28d

Change from baseline to Day 56: net effect of 28 days
LUM/IVA combination preceded by 28 days of LUM monotherapy

Favorable Safety Profile Observed with LUM/IVA

- LUM/IVA was generally well tolerated
- No dose-limiting toxicities identified
- Short-term declines in FEV_1 observed immediately post-dose with LUM/IVA
  - Rarely associated with clinical adverse events
  - FEV_1 returned to/near baseline within 7 days of continued dosing
  - Reversed or largely prevented with bronchodilators

Dose Selection for IVA and LUM

IVA

- IVA exposure reduced when dosed in combination with LUM (compared to monotherapy dose of 150q12h)
  - LUM is a strong inducer of CYP3A
  - IVA is a sensitive substrate of CYP3A
- IVA 250q12h selected for combination therapy

LUM

- LUM 600qd and 400q12h doses showed greatest effects on sweat chloride and FEV_1 endpoints

Phase 2 Conclusions

- Improvements in F508del-CFTR function observed *in vitro* translated to patients
- LUM/IVA combination superior to either drug alone across *in vitro*, pharmacodynamic, clinical endpoints
  - Monotherapy arms not included in Phase 3
- Regimens with LUM 400q12h and 600qd in combination with IVA250q12h chosen for Phase 3
- Favorable safety profile

Phase 2 data supported moving into Phase 3 with LUM/IVA combination therapy

Clinical Efficacy and Safety Results

Charlotte McKee, MD

Vice President, Clinical Development
Vertex Pharmaceuticals Incorporated

Presentation Overview

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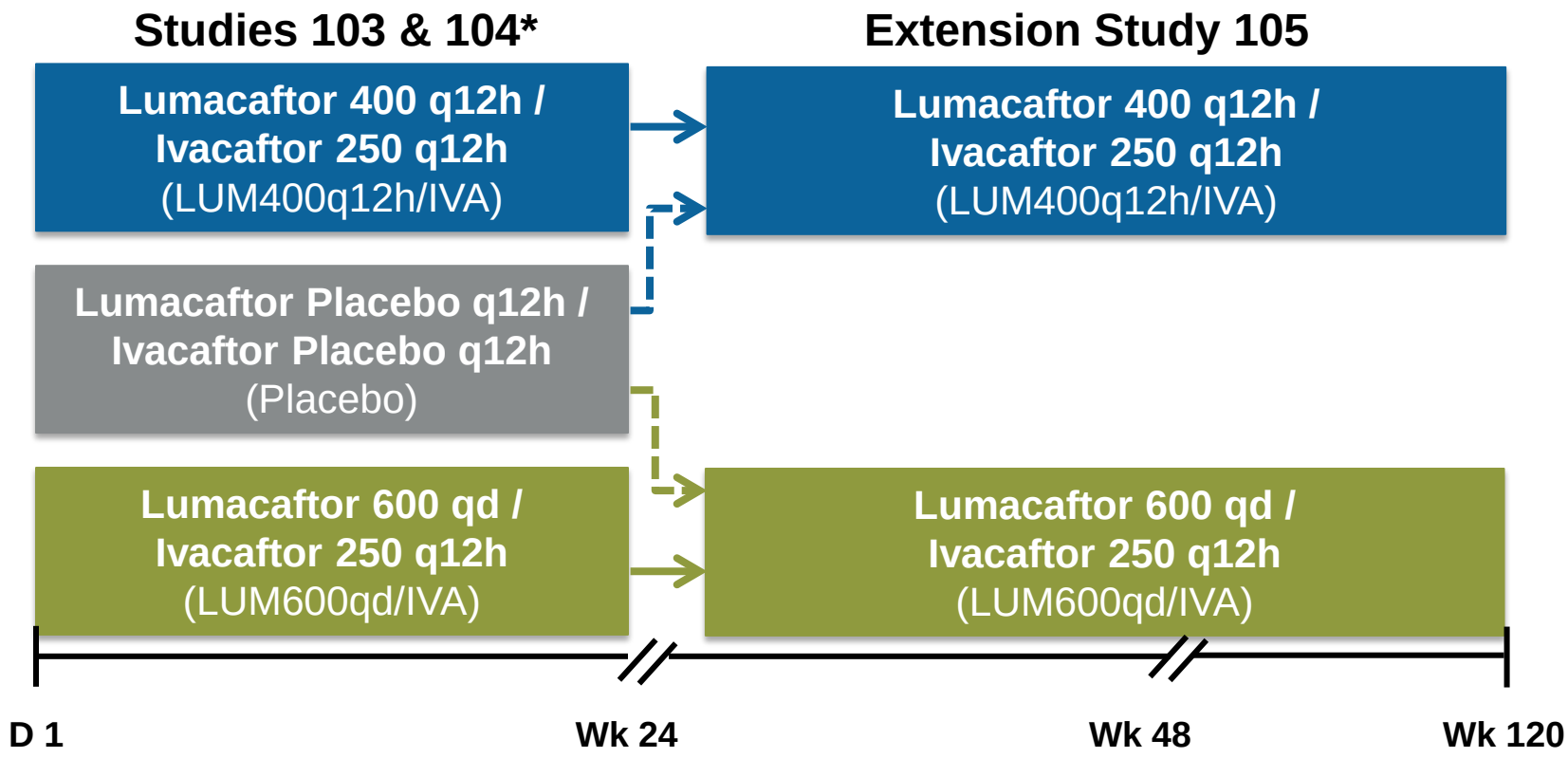
Primary Goals of CF Care

The primary goals of CF treatment include the following:[1-3]

1. Maintain lung function
2. Reduce pulmonary exacerbations
3. Improve nutritional status

[1]Stallings et al. *Journal of the American Dietetic Association.* 2008. [2]Mogayzel et al. *Am J Respir Crit Care Med.* 2013. [3]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014.

Two Phase 3 Studies Conducted



- Randomized, double-blind, placebo-controlled studies
- 187 sites in US, Canada, EU, Australia

*Identical except for the following assessments: ambulatory ECGs in a subset of US subjects in Study 103; intensive PK in a subset of US adolescent subjects in Study 104

Phase 3 Study Endpoints

Primary Objective: Efficacy of LUM/IVA at Week 24 in CF Patients Homozygous for the F508del-CFTR Mutation

Endpoint		Assessment Timing
Primary	Absolute ppFEV$_1$	Wk 24[a]
Key Secondary	Relative ppFEV$_1$	Wk 24[a]
	BMI	Wk 24[c]
	CFQ-R respiratory domain	Wk 24[c]
	≥5% relative ppFEV$_1$	Wk 24[a]
	Pulmonary exacerbations	Wk 24[b]
Selected Secondary	Safety	Throughout Study
	PK	D 1 & 15, Wks 4, 8, 16

[a]Assessed as the average of Wk 16 & Wk 24
[b]Assessed through Wk 24
[c]Assessed at Wk 24
Analysis population: all randomized subjects who received at least one dose of study medication (ITT)

Key Phase 3 Eligibility Criteria

- Homozygous for F508del-CFTR
- Confirmed diagnosis of CF
- Age ≥12 years
- Screening ppFEV$_1$ ≥40 to ≤90
- Exclusions:
  - Screening safety laboratory results outside specified limits
  - Colonization with *B cenocepacia*, *B dolosa*, *M abscessus* (or similar organisms)
  - Transplantation
  - Use of strong inhibitors, moderate or strong inducers of CYP3A

Statistical Analysis Plan

- Absolute and relative change in ppFEV$_1$ endpoints
  - Mixed model for repeated measures (MMRM)
  - Adjusted for sex, age group, lung disease severity
- Secondary Endpoints: Type 1 error control
  - Bonferroni adjustment: $P \leq 0.025$ for each arm
  - Hierarchical testing procedure within each arm to control for multiple secondary endpoints
- Pooled analyses of both studies for pre-specified efficacy and safety endpoints

Patient Disposition

95% of Patients Completed 24 Weeks of Treatment

Patients, N	Placebo	LUM600qd/ IVA	LUM400q12h/ IVA	TOTAL
Randomized	374	372	376	1122
Withdrew	3	4	7	14
Received study dose	371	368	369	1108
Total discontinuations	9	20	25	54
Due to AE	6	14	17	37
Other	3	6	8	17
Completed treatment	362	348	344	1054
Nearly all patients enrolled in extension				
Treated in extension	353	334	340	1027

Baseline Characteristics Well Matched

	Placebo N = 371	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Sex: Female	49%	50%	49%
Age, years	25.4	24.5	25.3
Age (years)			
12 to <18	26%	26%	27%
≥18	74%	74%	73%
$ppFEV_1$	60.4	60.8	60.5
$ppFEV_1$			
<40	8%	7%	8%
≥40 to <70	64%	66%	63%
≥70 to ≤90	26%	27%	27%
>90	1%	1%	1%
BMI, kg/m^2	21.0	21.0	21.5

Study Population Was Treated with Common CF Medications

Therapy	Placebo N = 371	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Bronchodilators (any)	92%	93%	93%
Dornase alfa	76%	79%	74%
Inhaled antibiotics	70%	63%	61%
Azithromycin	63%	63%	58%
Inhaled hypertonic saline	59%	54%	62%
Inhaled corticosteroids	59%	58%	58%

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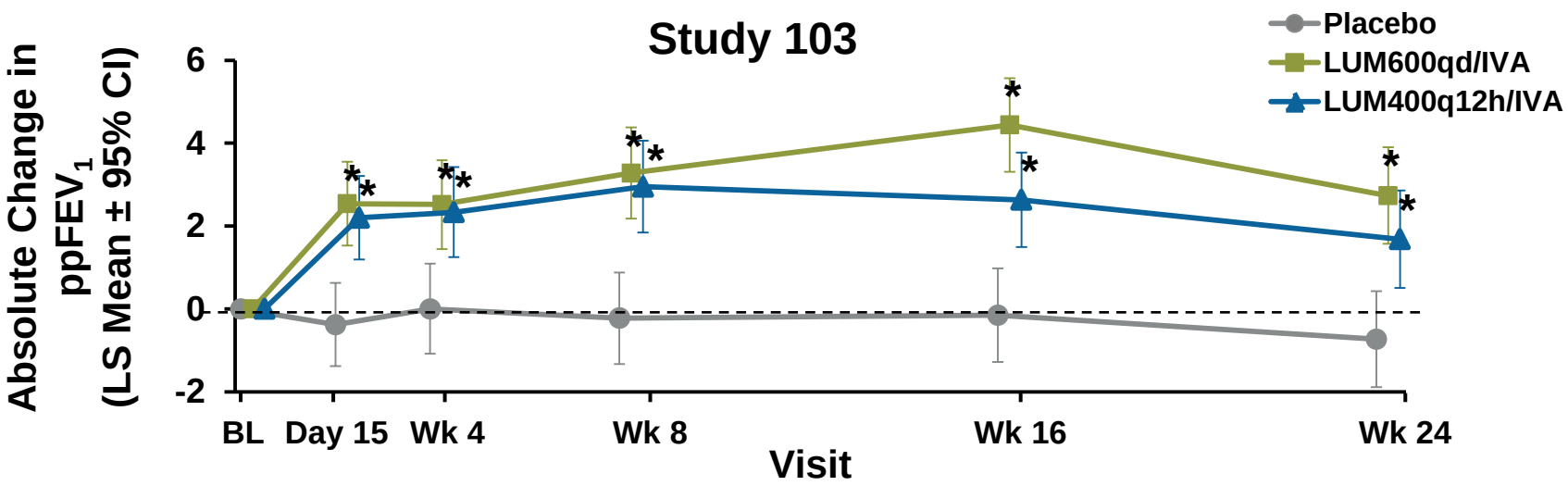
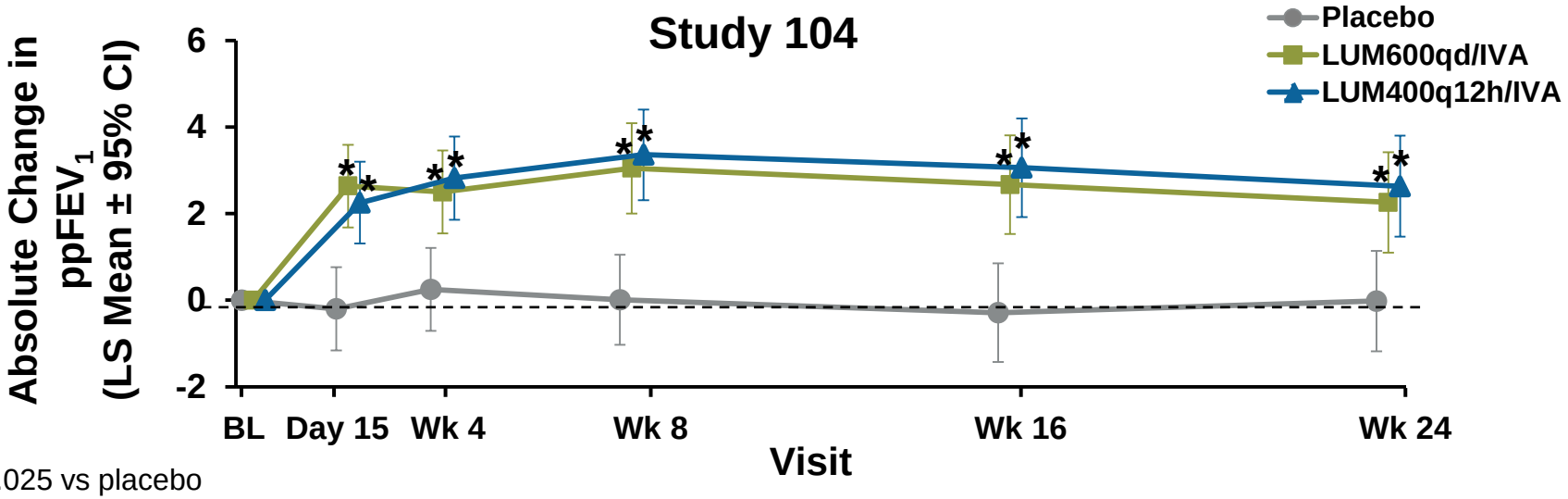
Primary Endpoint Met with High Statistical Significance

Significant in Both Studies and All 4 Active Arms

	Study 103		Study 104	
	LUM600qd/ IVA N = 183	LUM400q12h/ IVA N = 182	LUM600qd/ IVA N = 185	LUM400q12h/ IVA N = 187
Absolute change in $ppFEV_1$ vs. placebo (95% CI)	4.0 (2.6, 5.4)	2.6 (1.2, 4.0)	2.6 (1.2, 4.1)	3.0 (1.6, 4.4)
	P<0.0001	*P*=0.0003	*P*=0.0004	*P*<0.0001

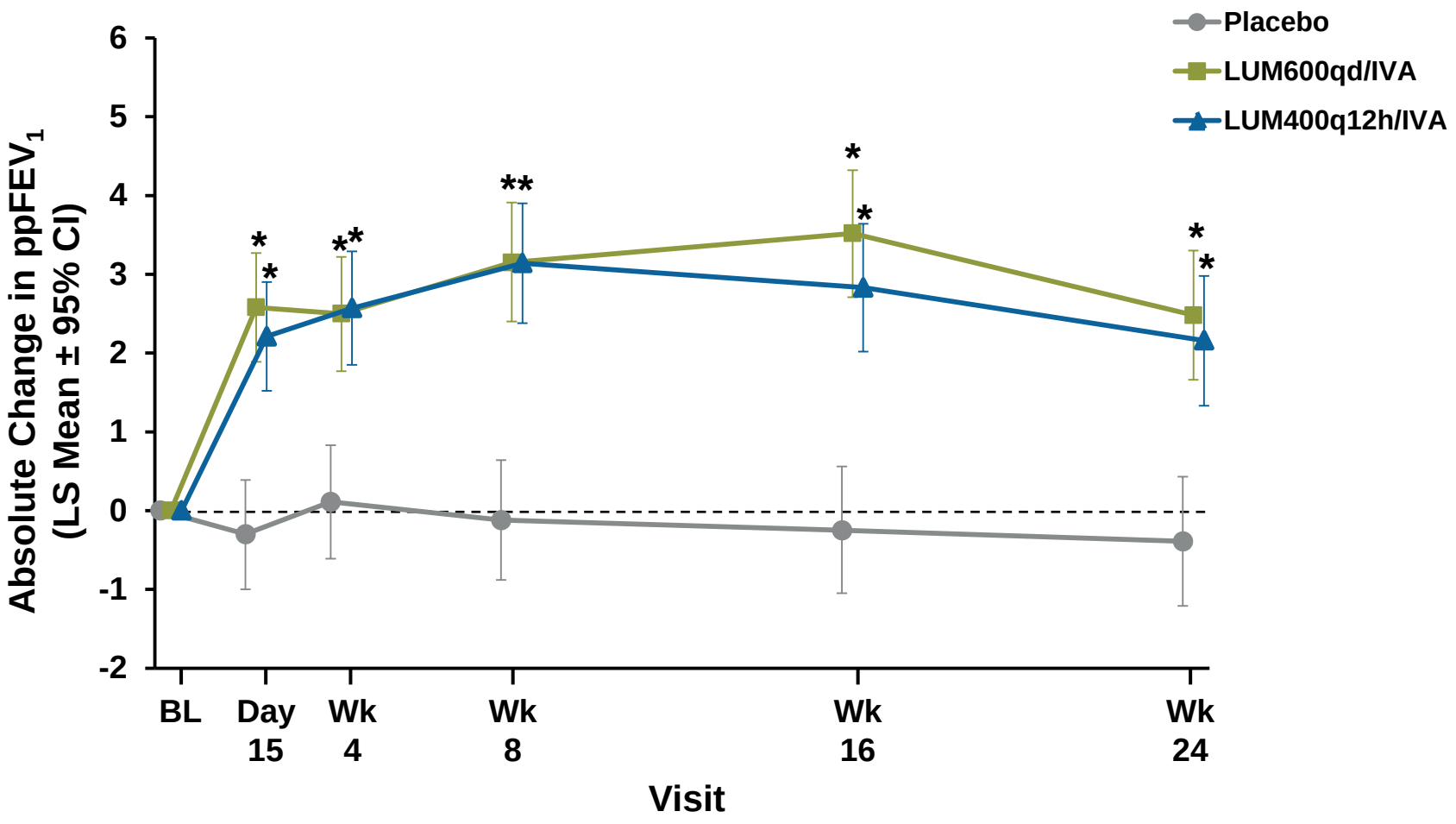
Improvements in FEV_1 Were Rapid, Sustained, and Consistent





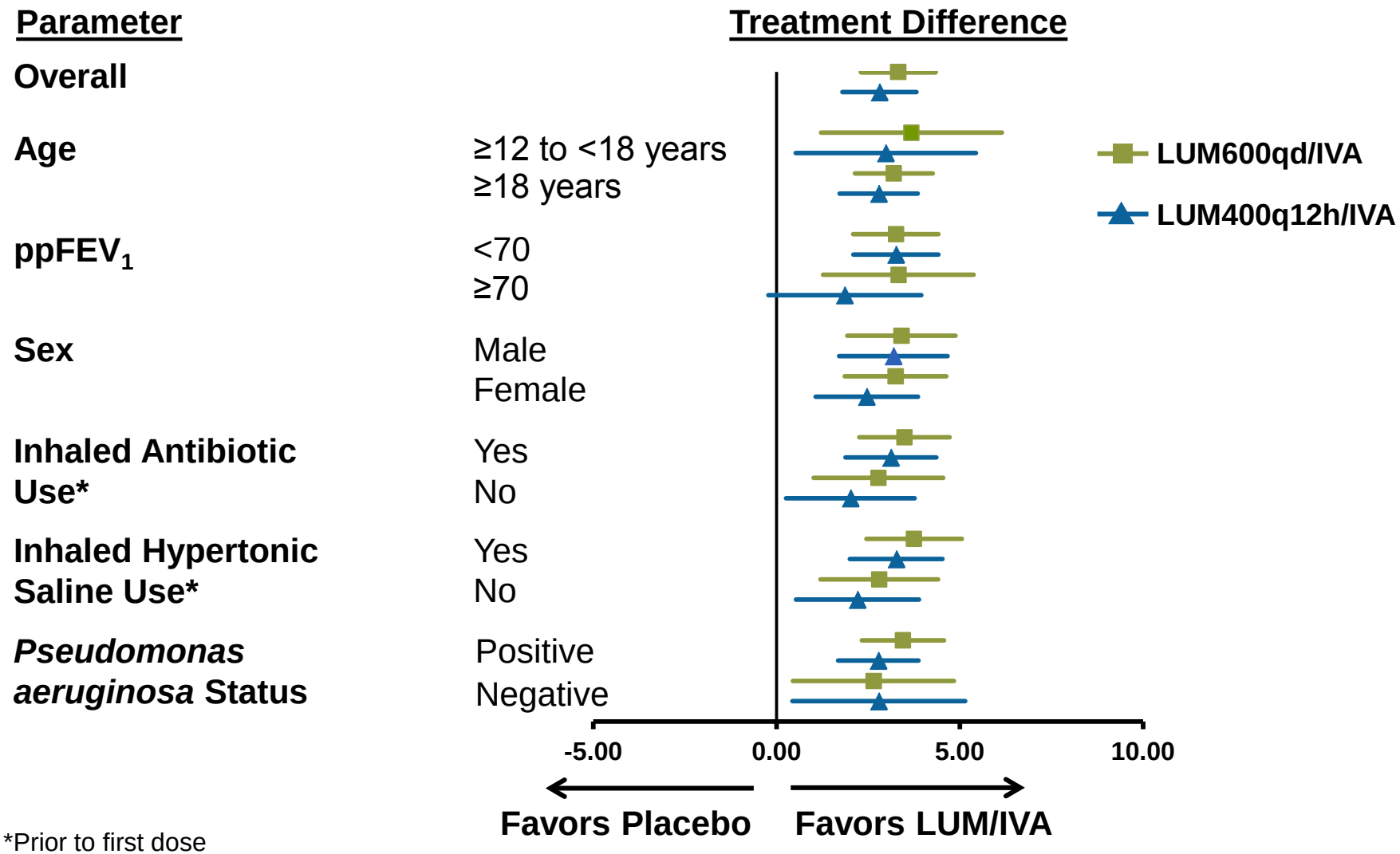
*P<0.025 vs placebo

FEV_1 Improvements Observed with Both Dosing Regimens in Pooled Analysis



*P<0.025 vs placebo

Subgroup Analyses of Change in FEV_1 All Favored Active Treatment



*Prior to first dose

All Key Secondary Endpoints Favored Active Treatment in Both Studies

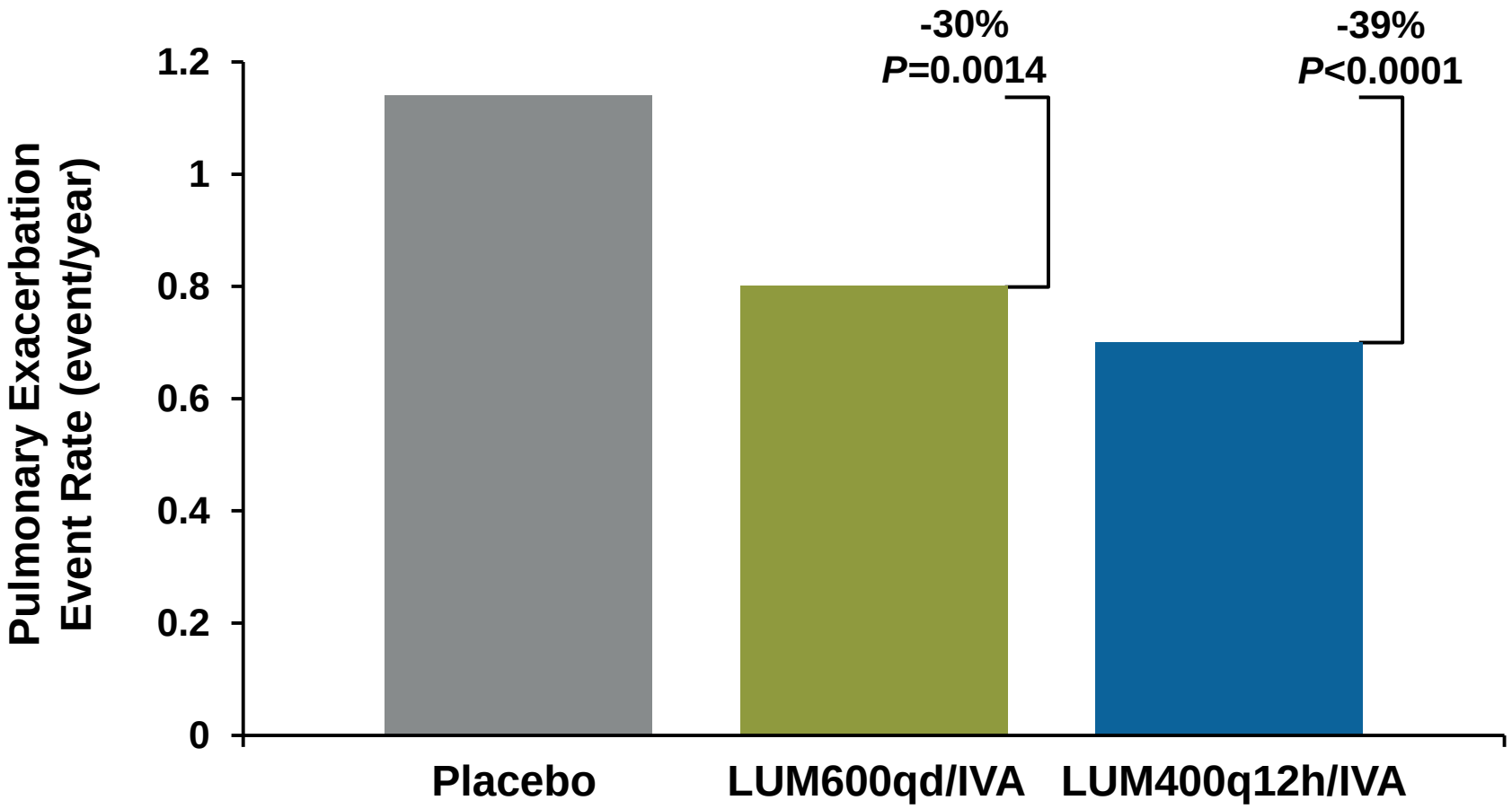
		Study 103		Study 104	
		LUM600qd/ IVA N = 183	LUM400q12h/ IVA N = 182	LUM600qd/ IVA N = 185	LUM400q12h/ IVA N = 187
Relative ppFEV$_1$	Treatment difference	6.7 *P*<0.0001	4.3 *P*=0.0006	4.4 *P*=0.0007	5.3 *P*<0.0001
BMI	Treatment difference	0.16 *P*=0.1122	0.13 *P*=0.1938	0.41 *P*<0.0001	0.36 *P*=0.0001
CFQ-R respiratory	Treatment difference	3.9 *P*=0.0168	1.5 *P*=0.3569	2.2 *P*=0.1651	2.9 *P*=0.0736
≥5% relative ppFEV$_1$	Odds ratio	2.94 *P*<0.0001	2.06 *P*=0.0023	2.96 *P*<0.0001	2.38 *P*=0.0001
Pulmonary exacerbations	Rate ratio	0.72 *P*=0.0491	0.66 *P*=0.0169	0.69 *P*=0.0116	0.57 *P*=0.0002

Shading indicates statistical significance within the hierarchy.

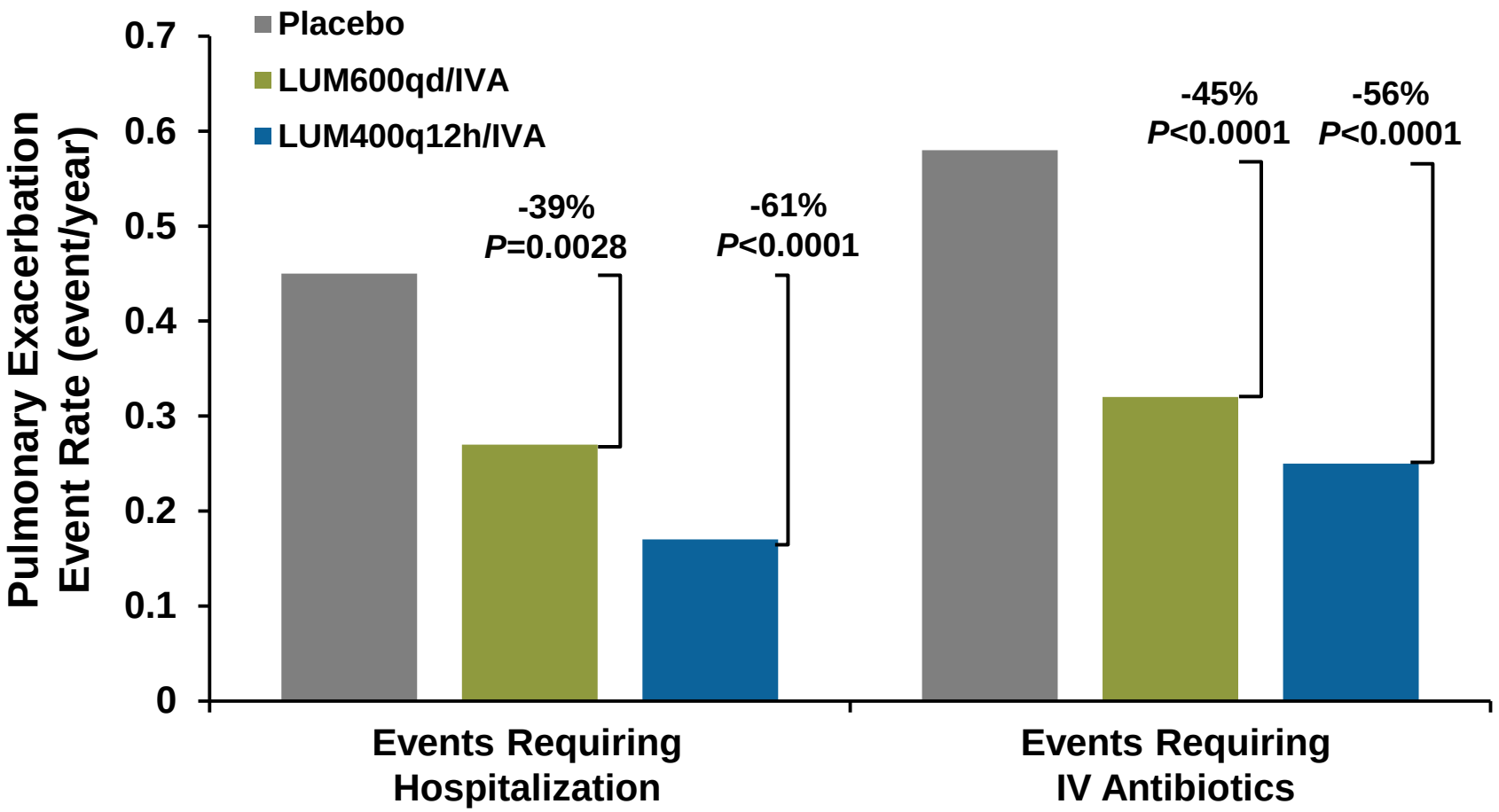
All Key Secondary Endpoints Favored Active Treatment in Pooled Analysis

		LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Relative ppFEV$_1$	Treatment difference	5.6 *P*<0.0001	4.8 *P*<0.0001
BMI	Treatment difference	0.28 *P*<0.0001	0.24 *P*=0.0004
CFQ-R respiratory	Treatment difference	3.1 *P*=0.0071	2.2 *P*=0.0512
≥5% relative ppFEV$_1$	Odds ratio	2.95 *P*<0.0001	2.22 *P*<0.0001
Pulmonary exacerbations	Rate ratio	0.70 *P*=0.0014	0.61 *P*<0.0001

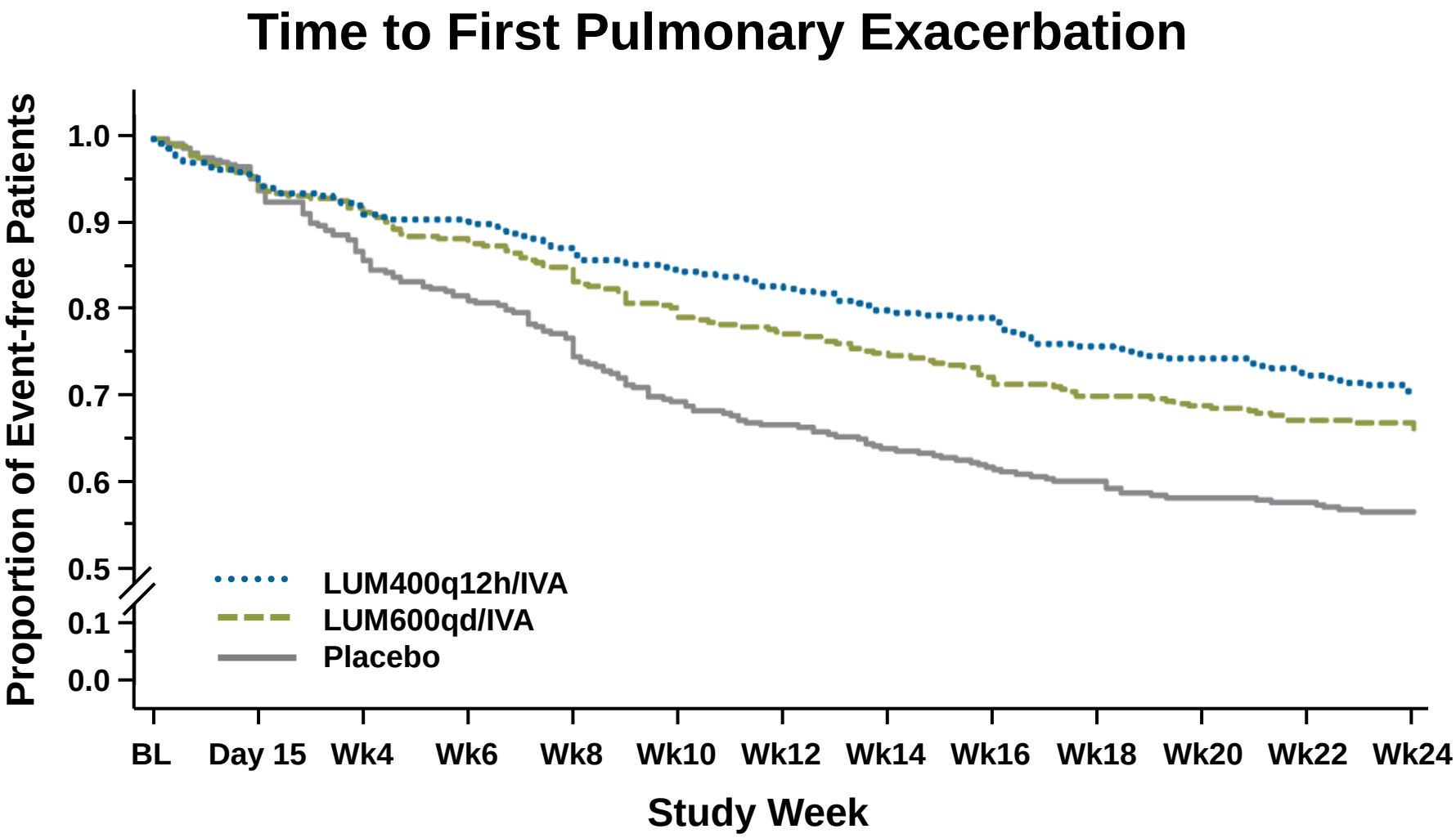
Pulmonary Exacerbations Significantly Reduced



Severe Pulmonary Exacerbations Significantly Reduced

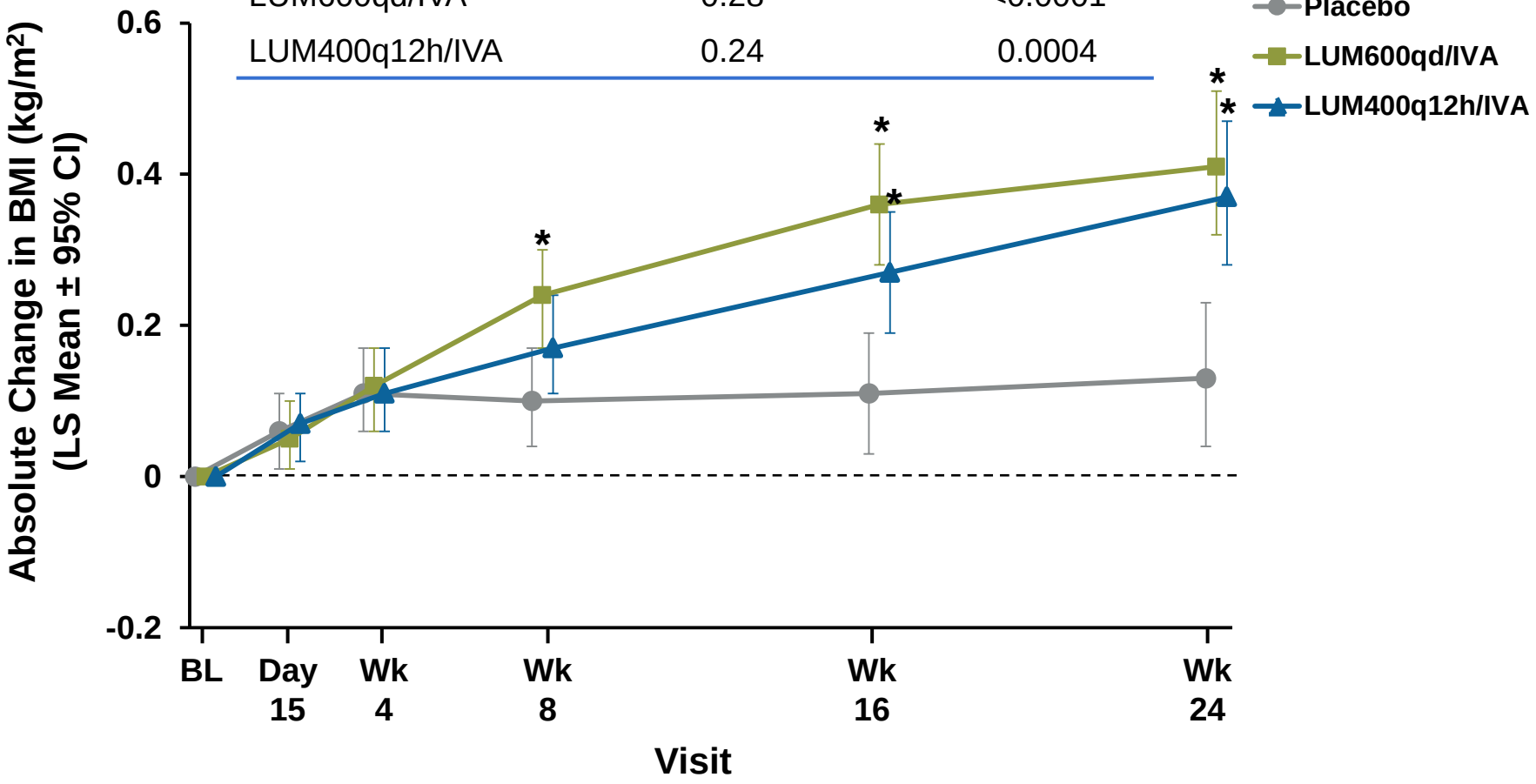


Active Treatment Prolonged Time to First Pulmonary Exacerbations



BMI Improved with Both Dosing Regimens

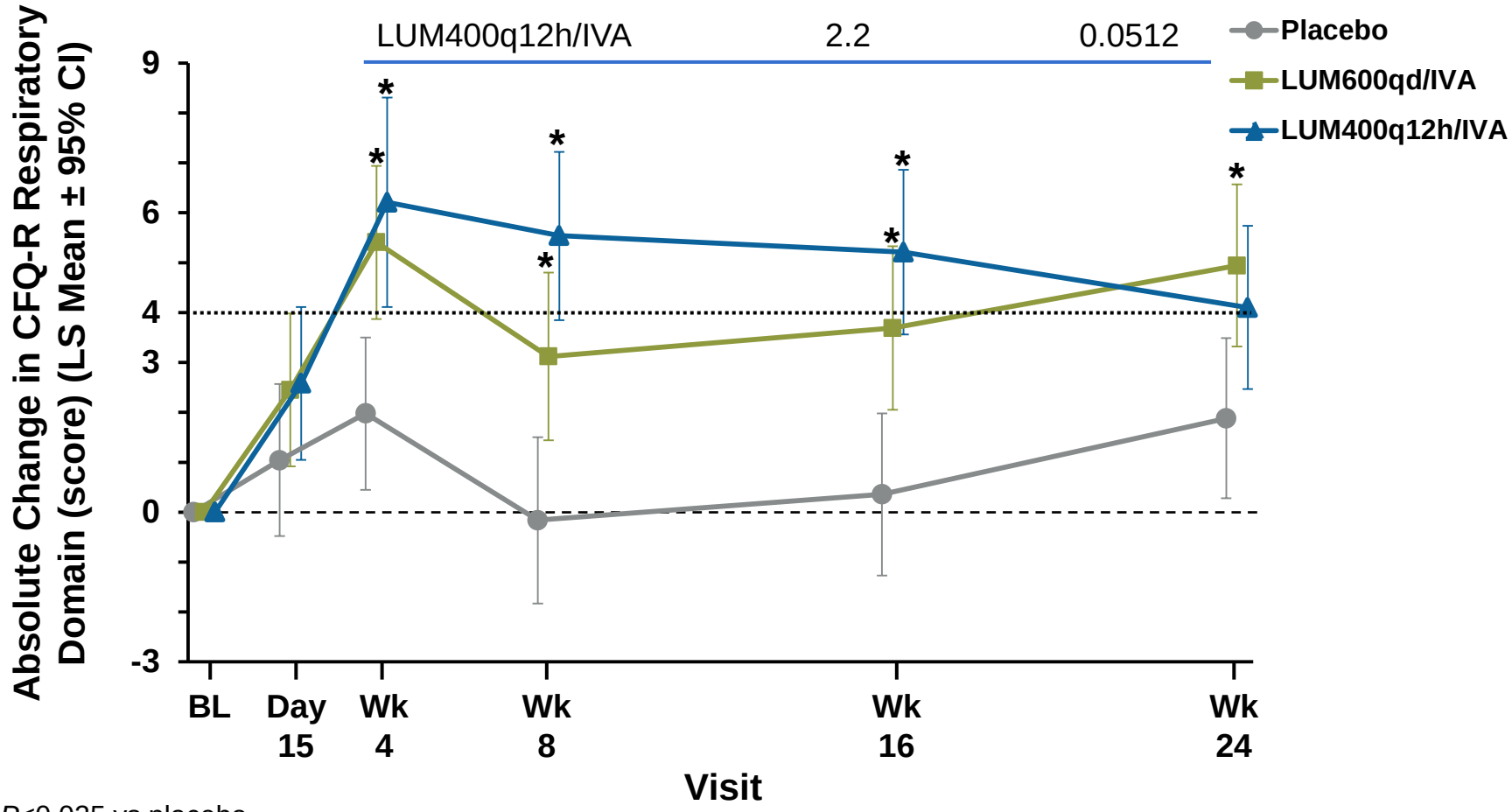
Treatment	Absolute Change at Week 24 from Baseline	*P*-value
LUM600qd/IVA	0.28	<0.0001
LUM400q12h/IVA	0.24	0.0004



*P<0.025 vs placebo

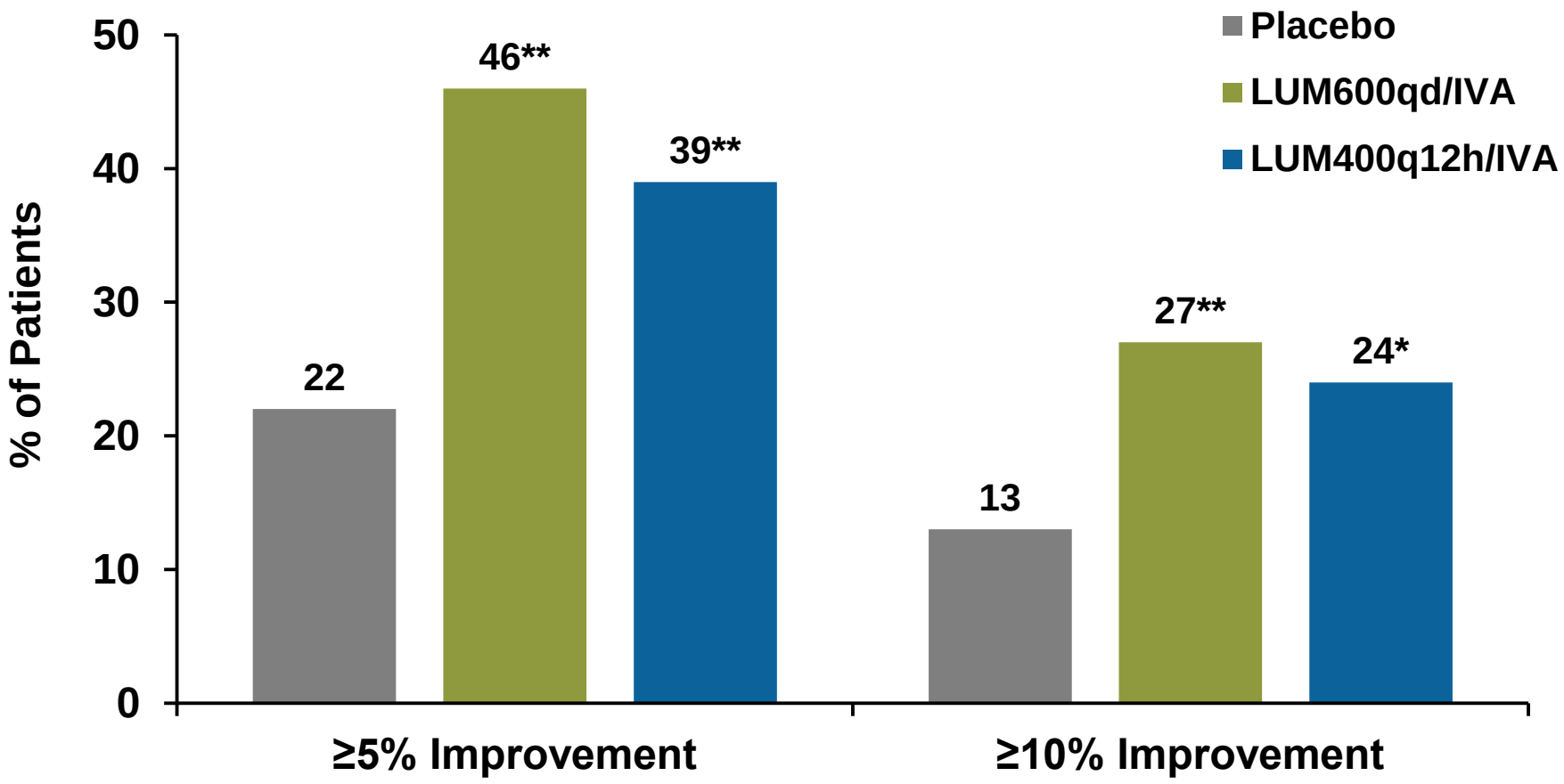
CFQ-R Respiratory Domain Improvements Favored Active Treatment

Treatment	Absolute Change at Week 24 from Baseline	*P*-value
LUM600qd/IVA	3.1	0.0071
LUM400q12h/IVA	2.2	0.0512



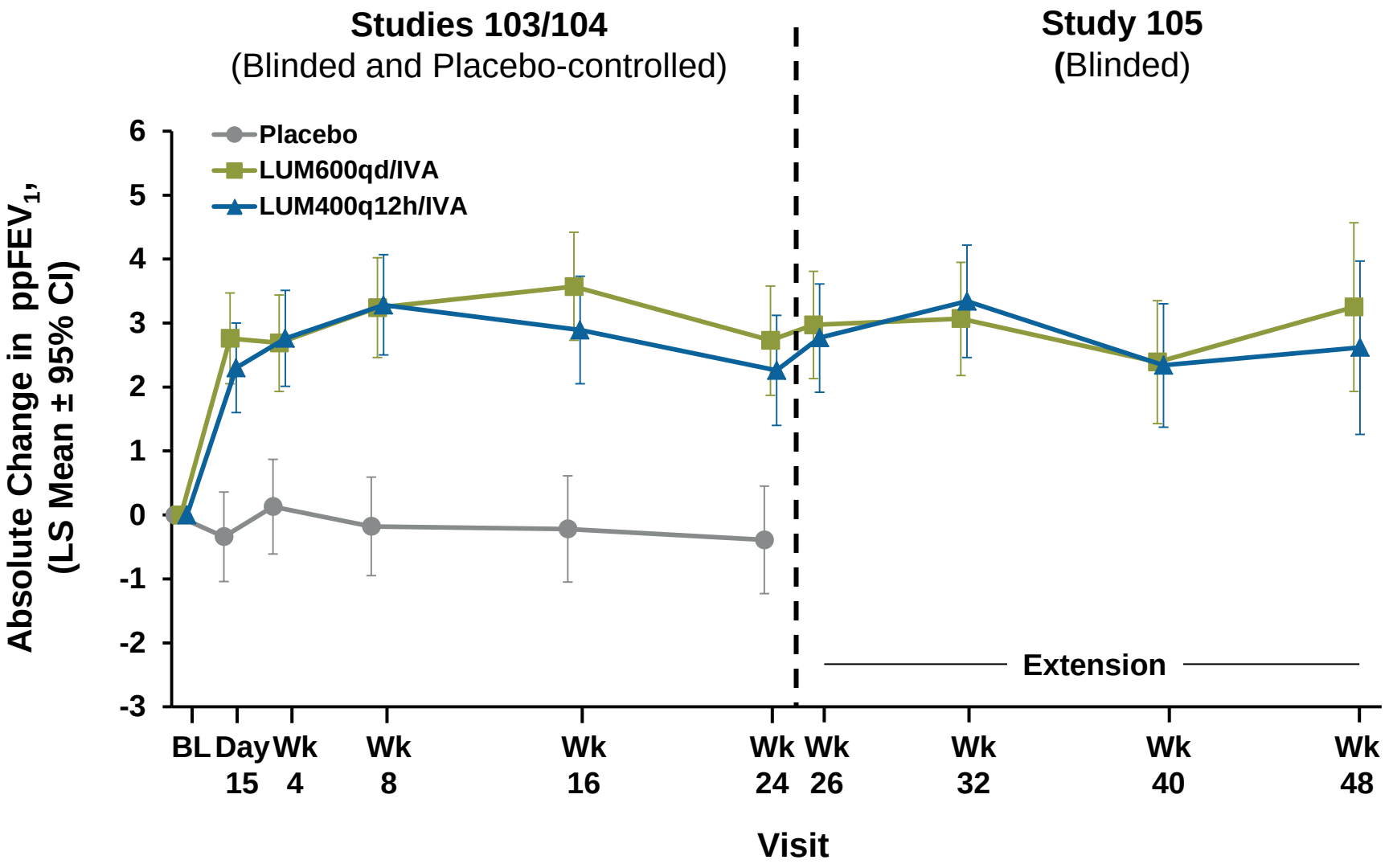
*P<0.025 vs placebo

Substantial Proportion of Patients had Relative Improvement in FEV_1 of ≥5% and ≥10%

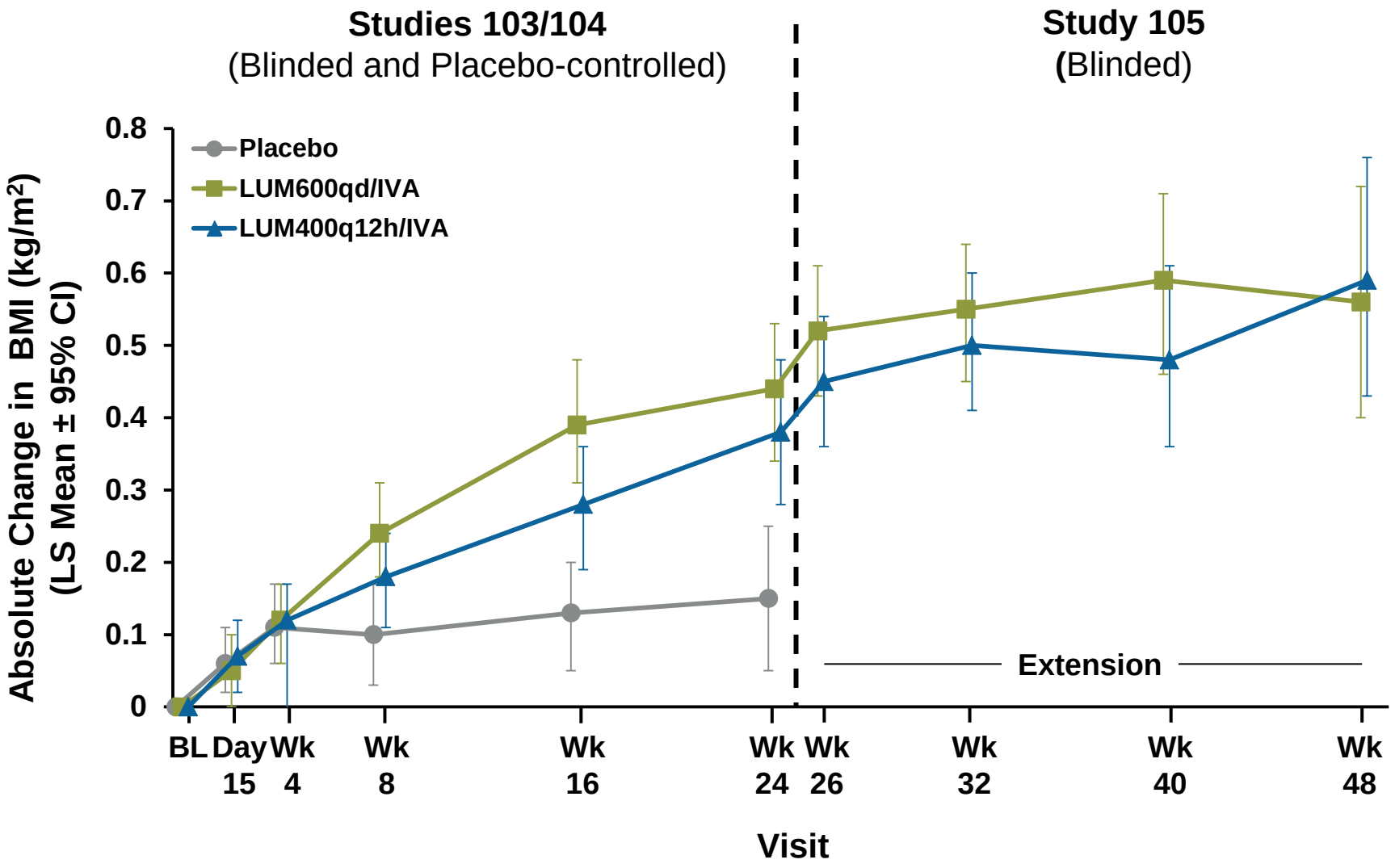


**P<0.0001 vs placebo
*P=0.0003 vs placebo

Improvements in FEV_1 Sustained Through 48 Weeks



Improvements in BMI Continued Through 48 Weeks



LUM/IVA Efficacy Conclusions

- Rapid, clinically meaningful, and statistically significant improvements in lung function
  - Primary endpoint met in both studies and all treatment arms
  - Sustained through 48 weeks
- Substantial reductions in pulmonary exacerbations, especially those requiring hospitalization and IV antibiotics
- Meaningful improvements in BMI through 48 weeks
- CFQ-R improvements favored treatment
- All improvements seen on top of usual CF treatments

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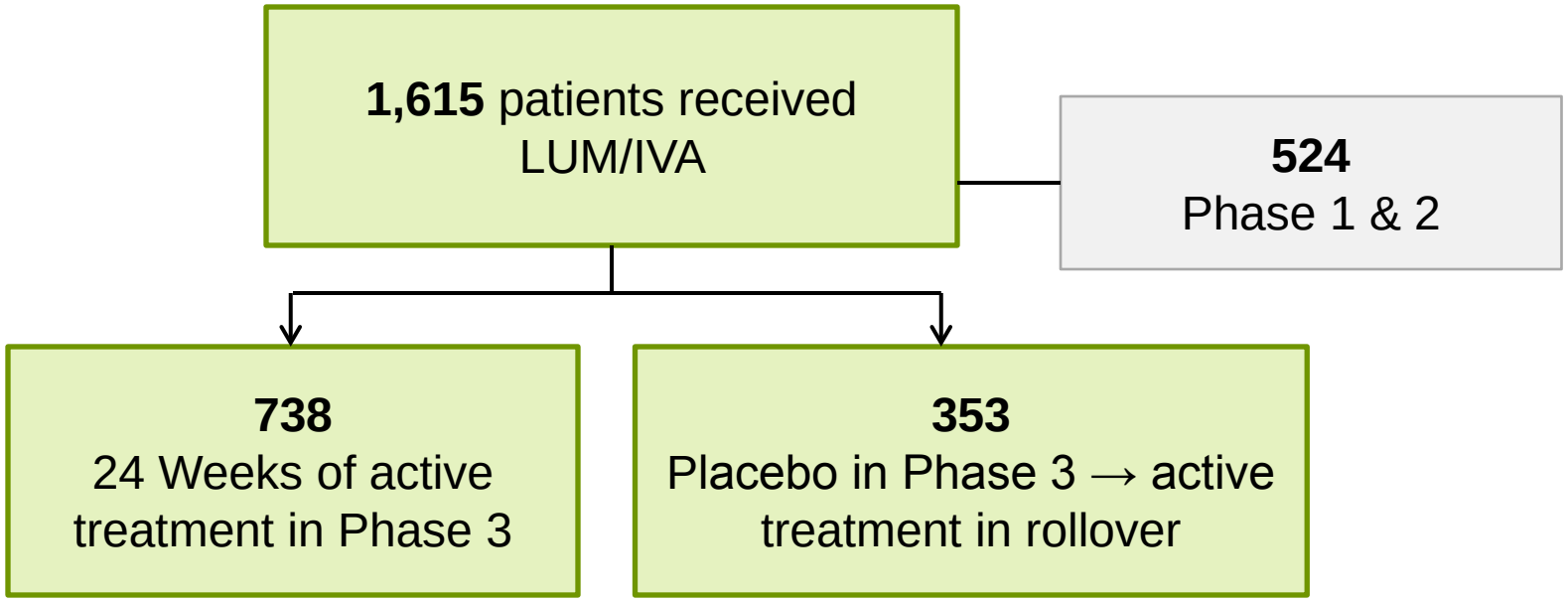
LUM/IVA Has a Robust Safety Database



- Over 1,000 patients exposed to LUM/IVA in Phase 3 (at time of filing):
  - More than 800 patients treated >24 weeks
  - More than 500 patients treated >40 weeks
- Ongoing studies continue to accumulate safety data

Adverse Events Were Common in All Treatment Arms

Adverse Events, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Adverse events	355 (96)	356 (97)	351 (95)	707 (96)
Serious AEs	106 (29)	84 (23)	64 (17)	148 (20)
Grade 3 or 4 AEs	59 (16)	57 (15)	45 (12)	102 (14)
AEs leading to death	0	0	0	0

- Serious adverse events more common in placebo group
- No deaths in either pivotal Phase 3 study

Most Frequent (≥10%) Adverse Events Are Typical for CF Population

Preferred Term, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Pulmonary exacerbation	**182 (49)**	145 (39)	132 (36)	**277 (38)**
Cough	**148 (40)**	121 (33)	104 (28)	**225 (31)**
Headache	**58 (16)**	58 (16)	58 (16)	**116 (16)**
Sputum increased	**70 (19)**	55 (15)	54 (15)	**109 (15)**
Dyspnea	**29 (8)**	55 (15)	48 (13)	**103 (14)**
Hemoptysis	**50 (14)**	52 (14)	50 (14)	**102 (14)**
Diarrhea	**31 (8)**	36 (10)	45 (12)	**81 (11)**
Nausea	**28 (8)**	29 (8)	46 (13)	**75 (10)**
Respiration abnormal	**22 (6)**	40 (11)	32 (9)	**72 (10)**
Nasopharyngitis	**40 (11)**	23 (6)	48 (13)	**71 (10)**
Oropharyngeal pain	**30 (8)**	44 (12)	24 (7)	**68 (9)**
Upper respiratory tract infection	**20 (5)**	24 (7)	37 (10)	**61 (8)**
Nasal congestion	**44 (12)**	33 (9)	24 (7)	**57 (8)**

AE Incidence ≥5% in Active Treatment Groups and More Common (≥3%) than Placebo

AE Incidence Similar Between Dose Groups

Preferred Term, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Dyspnea	**29 (8)**	55 (15)	48 (13)	**103 (14)**
Menstrual abnormality*	**3 (2)**	17 (9)	19 (10)	**36 (10)**
Respiration abnormal	**22 (6)**	40 (11)	32 (9)	**72 (10)**
Flatulence	**11 (3)**	20 (5)	24 (7)	**44 (6)**
Rash	**7 (2)**	16 (4)	25 (7)	**41 (6)**

* Incidence calculated in female patients only

Laboratory Abnormalities Similar Between LUM/IVA and Placebo

- No clinically meaningful differences in mean values or shifts from baseline between LUM/IVA and placebo:
  - Serum chemistry, hematology or coagulation studies
- Lab-related AEs generally similar between groups

Serious Adverse Events Were Less Frequent with LUM/IVA

Preferred Term, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Subjects with any SAE	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
Pulmonary exacerbation	89 (24.1)	55 (14.9)	41 (11.1)	96 (13.0)
Hemoptysis	3 (0.8)	4 (1.1)	5 (1.4)	9 (1.2)
Liver/elevated transaminases	0	4 (1.1)	3 (0.8)	7 (0.9)
Respiratory events	0	4 (1.1)	0	4 (0.5)
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)	2 (0.5)	4 (0.5)

Few Treatment Discontinuations Due to AE

Preferred Term, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Subjects with any AE leading to treatment discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)
Respiratory events	0	5 (1.4)	0	5 (0.7)
Blood CPK increased	0	0	4 (1.1)	4 (0.5)
Liver/elevated transaminases	0	3 (0.8)	1 (0.3)	4 (0.5)
Hemoptysis	2 (0.5)	0	3 (0.8)	3 (0.4)

Respiratory Events Occurred More Often in LUM/IVA Group

Events Were Generally Mild to Moderate

Subjects, n (%) with:	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Respiratory AE*	63 (17.0)	99 (26.8)	95 (25.7)	194 (26.3)
Respiratory SAEs	0	4 (1.1)	0	4 (0.5)
Respiratory AEs leading to discontinuation	0	5 (1.4)	0	5 (0.7)

*Includes dyspnoea, respiration abnormal, wheezing, chest discomfort, asthma, bronchospasm, and bronchial hyperreactivity

Respiratory Events Typically Occurred Early in Dosing Course

Subjects, n (%) with:	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
Any respiratory symptom AE*	51 (13.8)	88 (23.8)	81 (22.0)	169 (22.9)
>0 to ≤1 week	14 (3.8)	66 (17.9)	65 (17.6)	131 (17.8)
>1 to ≤2 weeks	4 (1.1)	6 (1.6)	4 (1.1)	10 (1.4)
>2 to ≤8 weeks	17 (4.6)	6 (1.6)	10 (2.7)	16 (2.2)
>8 to ≤16 weeks	14 (3.8)	11 (3.0)	8 (2.2)	19 (2.6)
>16 to ≤24 weeks	9 (2.4)	12 (3.3)	8 (2.2)	20 (2.7)

*Includes dyspnoea, respiration abnormal, chest discomfort

- Median duration 6 days
- Manageable, few resulted in treatment discontinuation

Liver-related Lab Abnormalities and AEs Were Similar Between Groups

Subjects, n (%)	Placebo N = 370	LUM600qd/IVA N = 369	LUM400q12h/IVA N = 369	Total LUM/IVA N = 738
ALT or AST increased				
>3 × ULN	19 (5.1)	22 (6.0)	16 (4.3)	38 (5.2)
>3 × to ≤5 × ULN	12 (3.3)	12 (3.3)	11 (3.0)	23 (3.1)
>5 × to ≤8 × ULN	5 (1.4)	7 (1.9)	2 (0.5)	9 (1.2)
>8 × ULN	2 (0.5)	3 (0.8)	3 (0.8)	6 (0.8)
Total bilirubin				
>1.5 × to ≤2 × ULN	5 (1.4)	0	0	0
>2 × ULN	1 (0.3)	2 (0.5)	1 (0.3)	3 (0.4)
ALT/AST >3 × ULN and Total bilirubin >2 × ULN	0	2 (0.5)	1 (0.3)	3 (0.4)
AEs	20 (5.4)	20 (5.4)	22 (6.0)	42 (5.7)
SAEs	0	4 (1.1)	3 (0.8)	7 (0.9)

Liver SAE Summary

- Seven liver-related SAEs in active treatment group (n=738) vs. none in placebo group (n=370)
  - Complex cases confounded by alternative etiologies and/or risk factors
- No common patterns or baseline characteristics
  - Six of the 7 patients had a history of liver abnormalities
  - No relationship with LUM/IVA exposure
- All events resolved
- While data do not support a causal association between LUM/IVA and liver events, a contribution cannot be excluded
  - Monitoring recommendations proposed

Long-term Safety Data Were Favorable

- >500 patients treated for ≥40 weeks at Phase 3 doses
- Long-term (≥48 wks) safety consistent with 24-wk data
  - Similar type and incidence of AEs
    - » Low incidence of transaminase elevations
    - » Similar early, transient respiratory events in patients new to treatment
- No new safety concerns

LUM/IVA Safety Conclusions

- Most common adverse events were typical for CF population and similar between treatment groups
  - Most events were mild to moderate and manageable without stopping treatment
  - SAEs more frequent in placebo due to higher exacerbation rate
- Imbalance in respiratory AEs occurred early; generally mild to moderate and resolved without stopping treatment
- Imbalance of liver SAEs without a causal link to treatment
- Overall safety profile favorable and similar for both dose regimens
- Long-term safety profile remained favorable through 48 weeks

Presentation Overview

- Phase 3 Program Overview
- Efficacy Results
- Safety Results
- Conclusion
  - Dosing Recommendation
  - Benefit/Risk Profile
  - LUM/IVA Combination versus IVA Monotherapy

Recommended Dosing Regimen: LUM400q12h/IVA

- Improvements in ppFEV$_1$, BMI, CFQ-R similar with both dose regimens
  - LUM400q12h/IVA yielded greater reductions in pulmonary exacerbations
- Similar safety profiles
- Potential advantages for patient adherence, given the fully matched fixed dose combination regimen

LUM600qd/IVA

Morning	Evening
LUM/IVA	IVA
200/83	125
200/83	125
200/83	

LUM400q12h/IVA

Morning	Evening
LUM/IVA	LUM/IVA
200/125	200/125
200/125	200/125

LUM/IVA Benefit/Risk Profile

- LUM/IVA combination therapy shows clear and compelling evidence of clinical benefit with a favorable safety profile
  - Sustained, meaningful systemic clinical benefits demonstrated across multiple endpoints
  - First treatment to address the underlying cause of CF in this population
  - Potential to change the course of disease

LUM/IVA combination therapy has a highly favorable benefit/risk profile supporting approval in *F508del* homozygous patients aged 12 years and older

Presentation Overview

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Evidence that LUM Contributes to LUM/IVA Combination Efficacy

Biology: F508del-CFTR defect results in little-to-no CFTR at the cell surface

- LUM required to increase delivery of F508del-CFTR to cell surface
- IVA can only potentiate F508del-CFTR on the cell surface

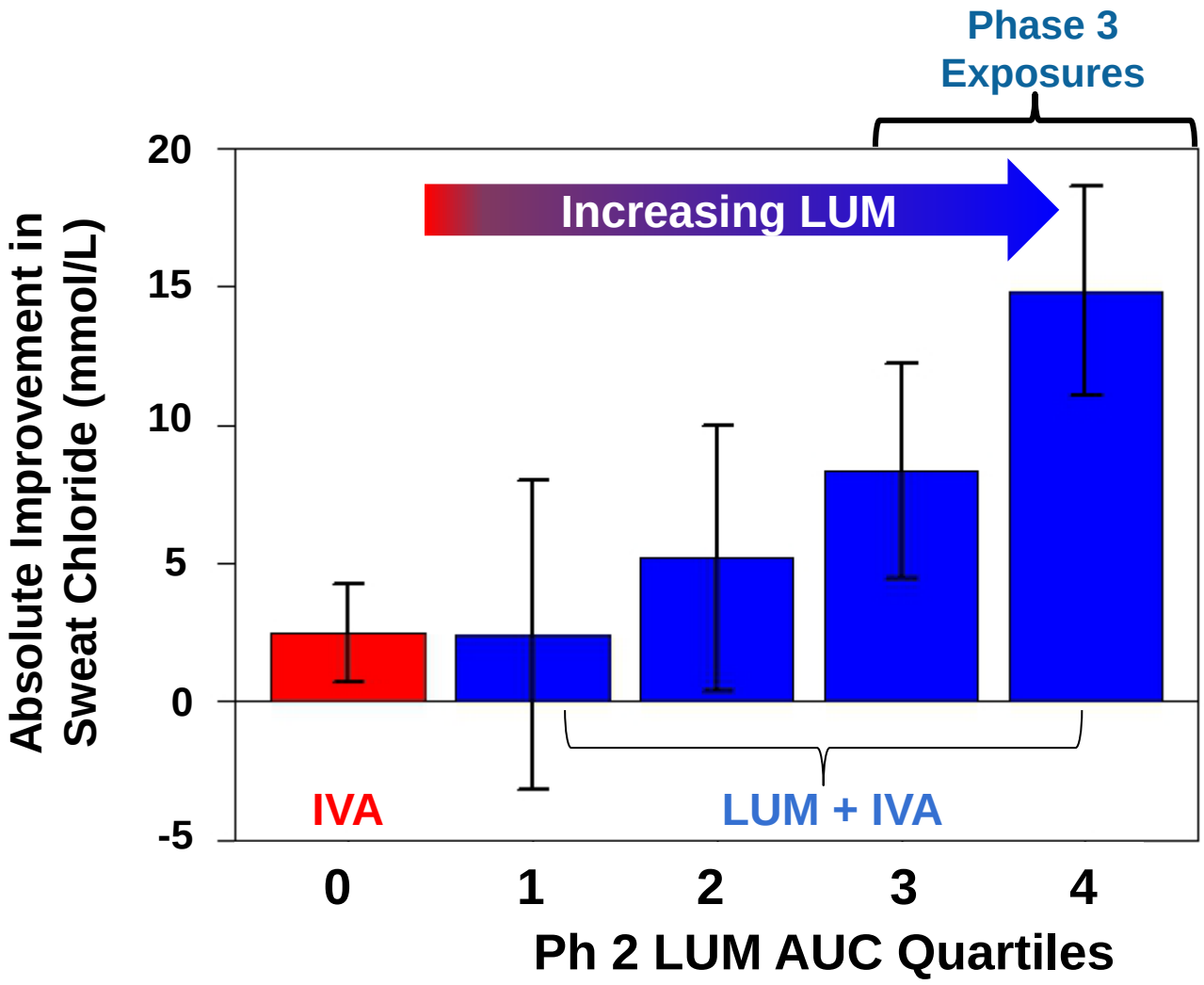
Preclinical/Biomarker:

- IVA: minimal *in vitro* chloride transport and sweat chloride improvements
- LUM/IVA: superior *in vitro* chloride transport and sweat chloride improvements

Clinical:

- IVA: no consistent or statistically significant clinical benefit
- LUM/IVA: consistent, sustained, statistically significant, and clinically meangingful improvements in multiple endpoints

LUM Clearly Contributes to Improvements in Sweat Chloride with Combination Therapy



Major Differences Between LUM/IVA and IVA Clinical Studies

	IVA	LUM / IVA
Year conducted	2009 - 2010	2013 - 2014
Inclusion criteria: $ppFEV_1$	≥40 (Mean BL: 79.7)	40 - 90 (Mean BL: 60.5)
Inclusion criteria: Use of hypertonic saline	Not allowed	Allowed
Placebo randomization	4:1	2:1
Analysis of subjects who discontinued early	Subjects data not collected off-treatment	Subjects data collected and analyzed on- or off-treatment
Calculation of $ppFEV_1$	Knudson	Hankinson and Wang

Comparison of Results from IVA and LUM/IVA Studies

Comparison	IVA Mono (IVA150q12h)	LUM/IVA Combo (LUM400q12h/IVA)
In vitro CFTR activity (HBE, Δ % wild type)	2.1 *P*<0.02	21.4 *P*<0.02
Change in sweat chloride (mmol/L)	-2.9 *P*=0.0384	-11.1 *P*=0.004
Absolute change in ppFEV$_1$ (%)	1.72 *P*=0.1509	2.81 *P*<0.0001
Change in BMI (kg/m^2)	-0.07 *P*=0.6655	0.24 *P*=0.0004
Change in CFQ-R (respiratory domain)	1.31 *P*=0.5408	2.22 *P*=0.0512
Pulmonary exacerbations (rate ratio vs. placebo)	0.68 *P*=0.2795	0.61 *P*<0.0001

LUM/IVA Conclusion

LUM/IVA combination therapy has a highly favorable benefit/risk profile supporting approval in *F508del* homozygous patients age 12 years and older

Agenda for Vertex Presentation

Introduction	**Jeffrey Chodakewitz, MD** Chief Medical Officer Executive Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Disease Background and Medical Need	**Michael W. Konstan, MD** Vice Dean for Translational Research, Professor of Pediatrics Case Western Reserve University School of Medicine UH Rainbow Babies and Children's Hospital
Mechanism of Action	**Fredrick Van Goor, PhD** Principal Research Fellow Vertex Pharmaceuticals Incorporated
Clinical Development Program **Clinical Efficacy and Safety**	**Charlotte McKee, MD** Vice President, Clinical Development Vertex Pharmaceuticals Incorporated
Clinical Perspective	**Bonnie Ramsey, MD** Endowed Professor of Pediatrics, University of Washington School of Medicine Director, Center for Clinical and Translational Research, Seattle Children’s Hospital

Clinical Perspective

Bonnie Ramsey, MD

Endowed Professor of Pediatrics, University of Washington School of Medicine

Director, Center for Clinical and Translational Research, Seattle Children's Hospital

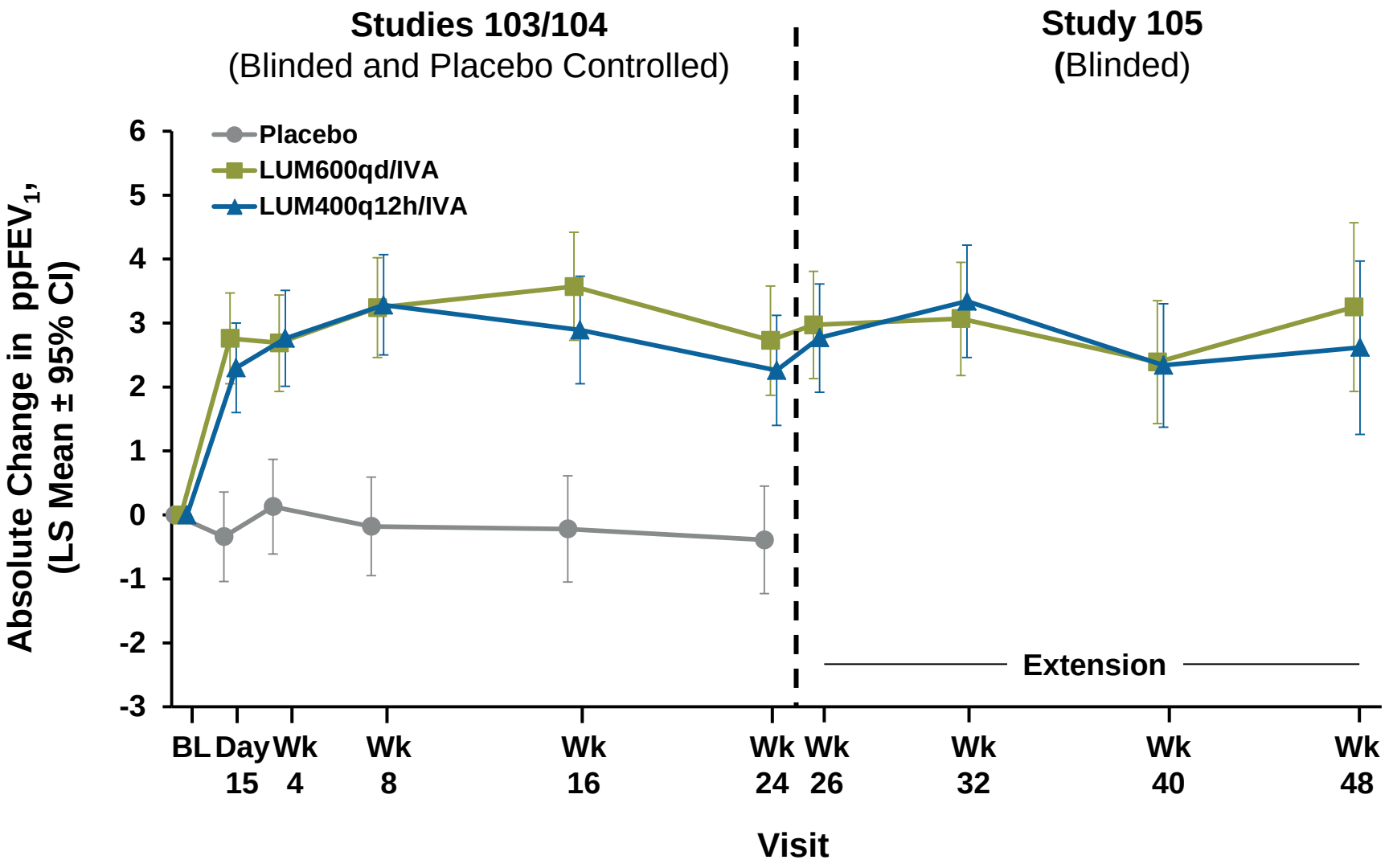
Primary Goals of CF Care

The primary goals of CF treatment include the following:[1-3]

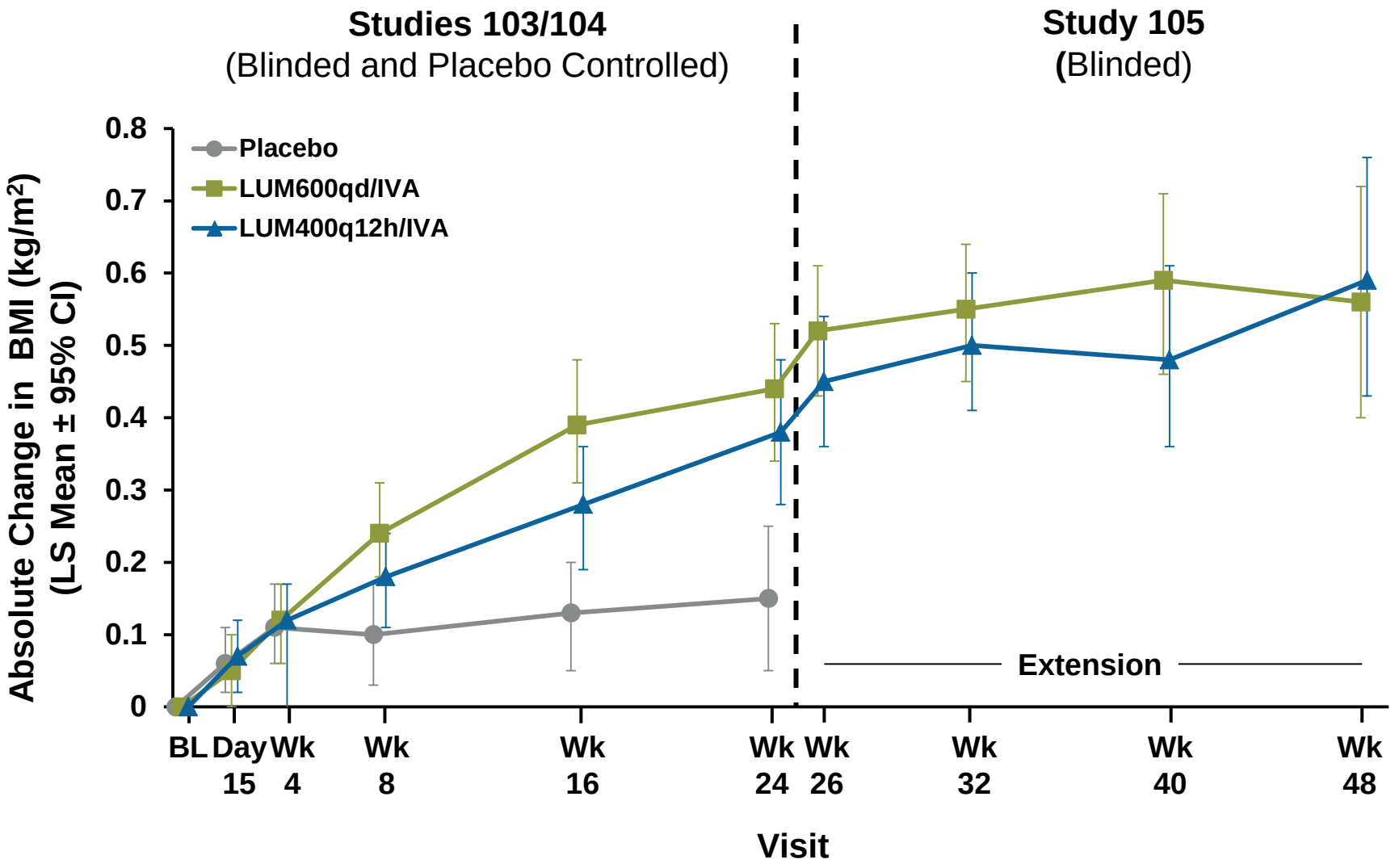
1. Maintain lung function
2. Reduce pulmonary exacerbations
3. Improve nutritional status

[1]Cystic Fibrosis Foundation (CFF) Report to Center Directors. *2013 Annual Data Report*: CFF; 2014.[2]Mogayzel et al. *Am J Respir Crit Care Med.* 2013. [3]Stallings et al. *Journal of the American Dietetic Association.* 2008.

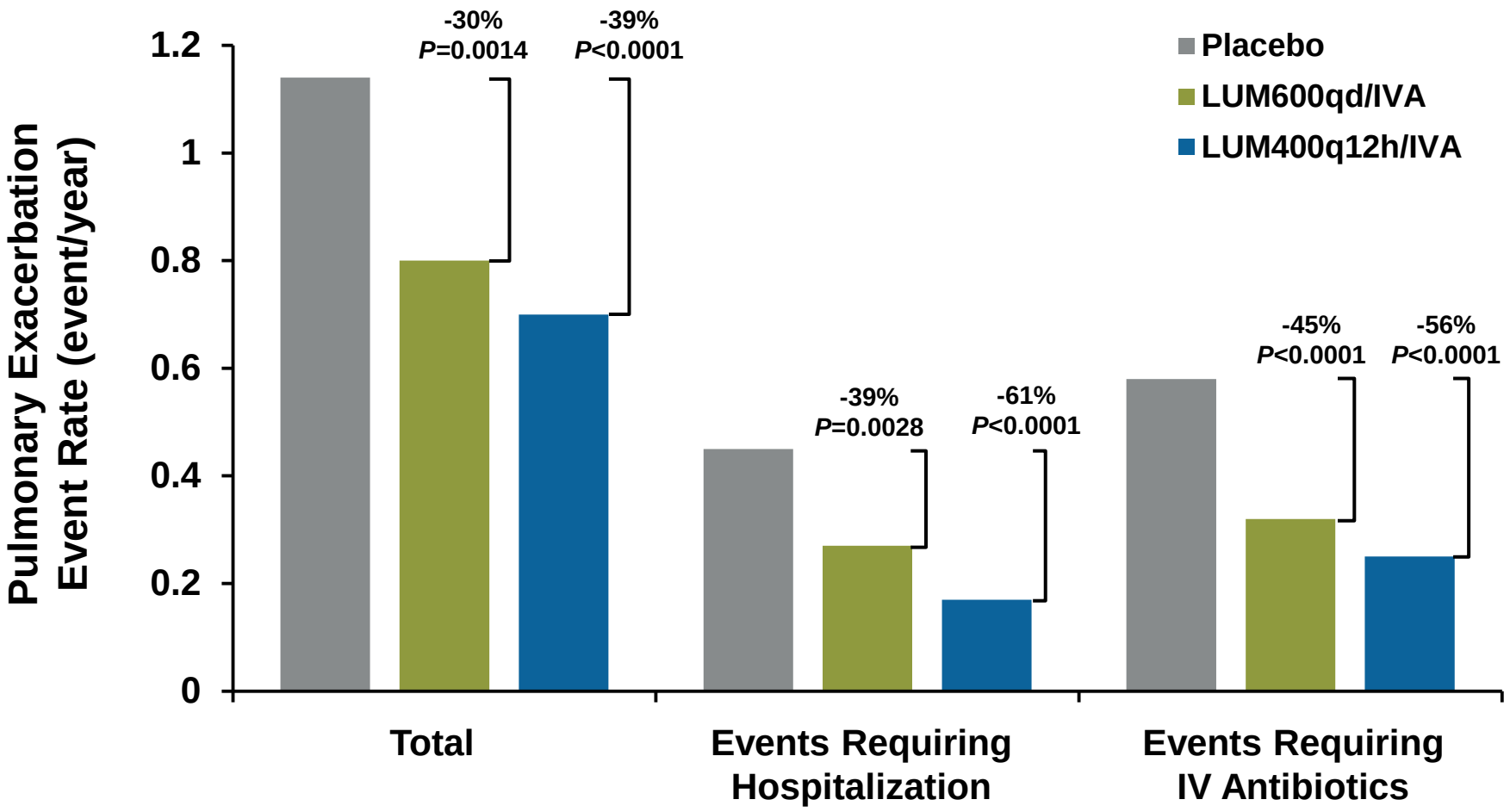
Improvements in FEV_1 Sustained Through 48 Weeks



Improvements in BMI Continued Through 48 Weeks



Pulmonary Exacerbations Significantly Reduced



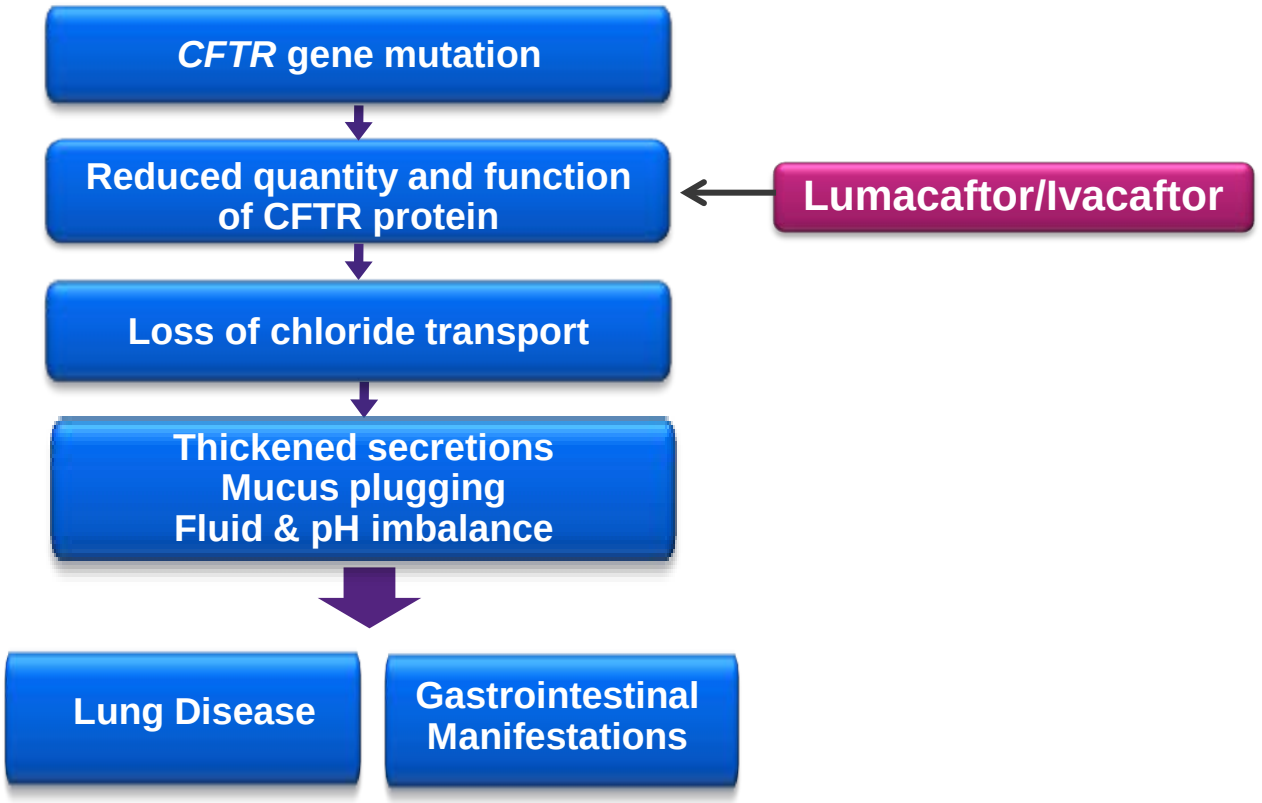
Clinical Relevance of Risks

- Majority of adverse events were mild to moderate and consistent with CF disease
- Respiratory adverse events more common during treatment initiation
  - Some patients discontinued drug but the majority remained on therapy and symptoms resolved
- Although transaminase elevations similar between treatment groups, it was more commonly reported as a serious adverse event in the treatment arms
  - Transaminase elevations are common in this population
  - Proposed management is acceptable

Opportunity to Treat the Underlying Cause of CF in Patients Homozygous for *F508del*

F508del/F508del

~ 47% of CF patients with a current high unmet need



Ratjen F. *Respir Care.* 2009. O'Sullivan BP, Freedman SD. *Lancet*. 2009. Mogayzel. *Am J Respir Crit Care*. 2013.

ORKAMBI (Lumacaftor/Ivacaftor)

Treatment for Cystic Fibrosis

Vertex Pharmaceuticals Incorporated

Pulmonary and Allergy Drugs Advisory Committee

May 12, 2015

Backup Slides Shown

770-104: IVA Monotherapy Results

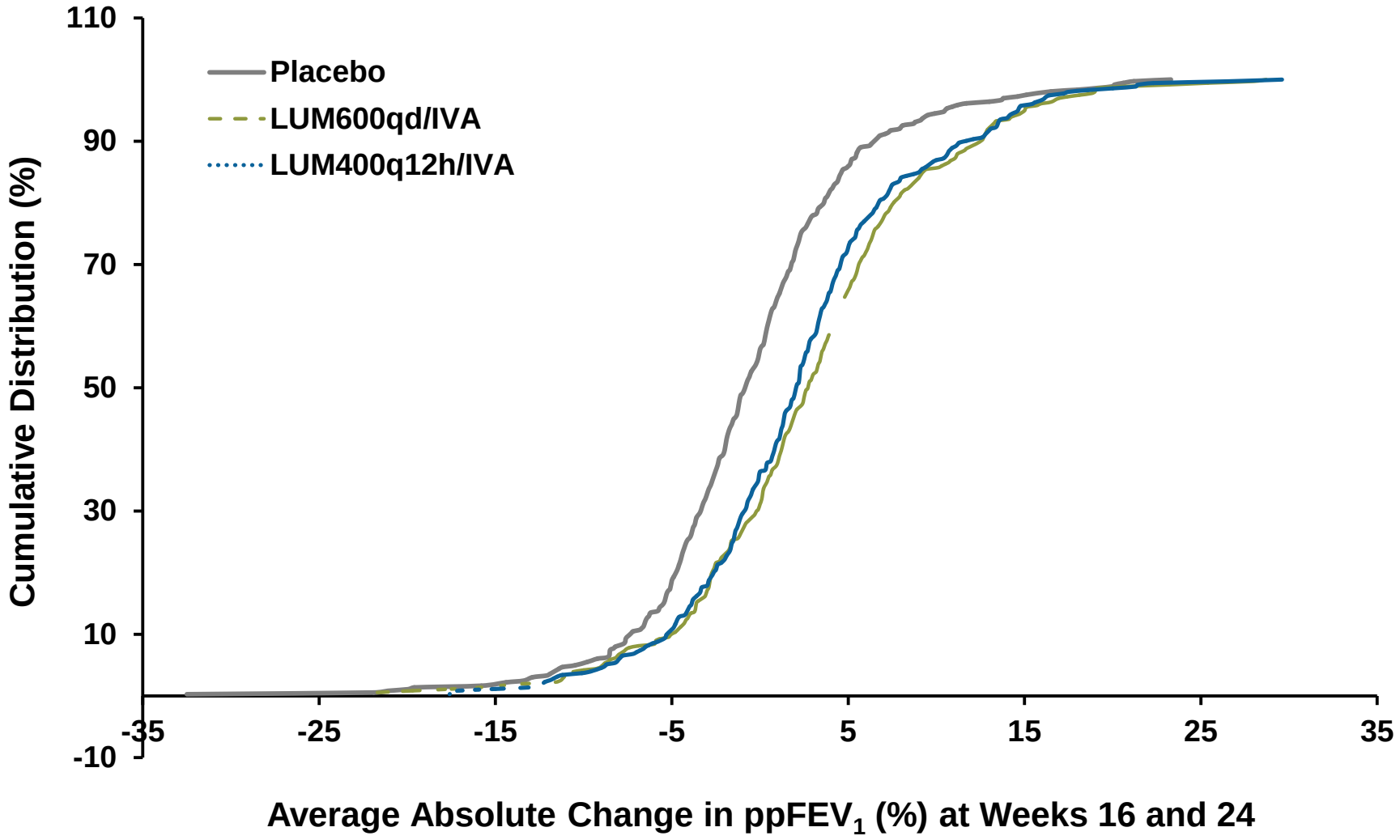
No meaningful clinical benefit in patients homozygous for F508del

Endpoint	Treatment Difference (95% CI)	*P*-Value
Change in sweat chloride (mmol/L)	-2.9 (-5.6, -0.2)	0.04
Average absolute change in ppFEV$_1$	1.72 (-0.63, 4.08)	0.1509
Average absolute change in BMI	-0.07 (-0.36, 0.23)	0.6655
Average absolute change in CFQ-R respiratory domain score	1.31 (-2.92, 5.55)	0.5408
	Rate Ratio (95% CI)	***P*-Value**
Number of pulmonary exacerbations	0.677 (0.334, 1.372)	0.2795

Efficacy Results for Adolescent Population (Pooled)

Endpoint	Comparison	Age Group	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Absolute change in $ppFEV_1$	Treatment difference to placebo	≥12 to <18	3.7 (*P*=0.0036)	3.0 (*P*=0.0178)
		≥18	3.2 (*P*<0.0001)	2.8 (*P*<0.0001)
Relative change in $ppFEV_1$	Treatment difference to placebo	≥12 to <18	5.3 (*P*=0.0093)	4.1 (*P*=0.0440)
		≥18	5.7 (*P*<0.0001)	5.1 (*P*<0.0001)
Change in BMI	Treatment difference to placebo	≥12 to <18	0.39 (*P*=0.0019)	0.33 (*P*=0.0088)
		≥18	0.24 (*P*=0.0022)	0.21 (*P*=0.0081)
Change in CFQ-R	Treatment difference to placebo	≥12 to <18	4.1 (*P*=0.0559)	4.5 (*P*=0.0344)
		≥18	2.8 (*P*=0.0385)	1.5 (*P*=0.2782)
Patients with 5% or greater relative improvement in $ppFEV_1$	Odds ratio to placebo	≥12 to <18	2.91 (*P*=0.0005)	1.89 (*P*=0.0319)
		≥18	2.95 (*P*<0.0001)	2.37 (*P*<0.0001)
Number of pulmonary exacerbations	Rate ratio to placebo	≥12 to <18	0.59 (*P*=0.0385)	0.26 (*P*<0.0001)
		≥18	0.74 (*P*=0.0127)	0.72 (*P*=0.0081)

Cumulative Distribution Plot of $ppFEV_1$ Average Absolute Change from Baseline (FAS)



Pooled Studies: Pulmonary Assessments at Week 24

Endpoint	Comparison	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Absolute change in ppFVC	Treatment difference to placebo	3.1 *P*<0.0001	3.0 *P*<0.0001
Relative change in ppFVC	Treatment difference to placebo	4.1 *P*<0.0001	4.0 *P*<0.0001
Absolute change in FEV_1/FVC ratio	Treatment difference to placebo	0.01 *P*=0.09	0.00 *P*=0.46
Absolute change in ppFEF 25-75	Treatment difference to placebo	3.3 *P*<0.0001	2.2 P=0.0028

Study 102 (Cohort 4) Efficacy Results

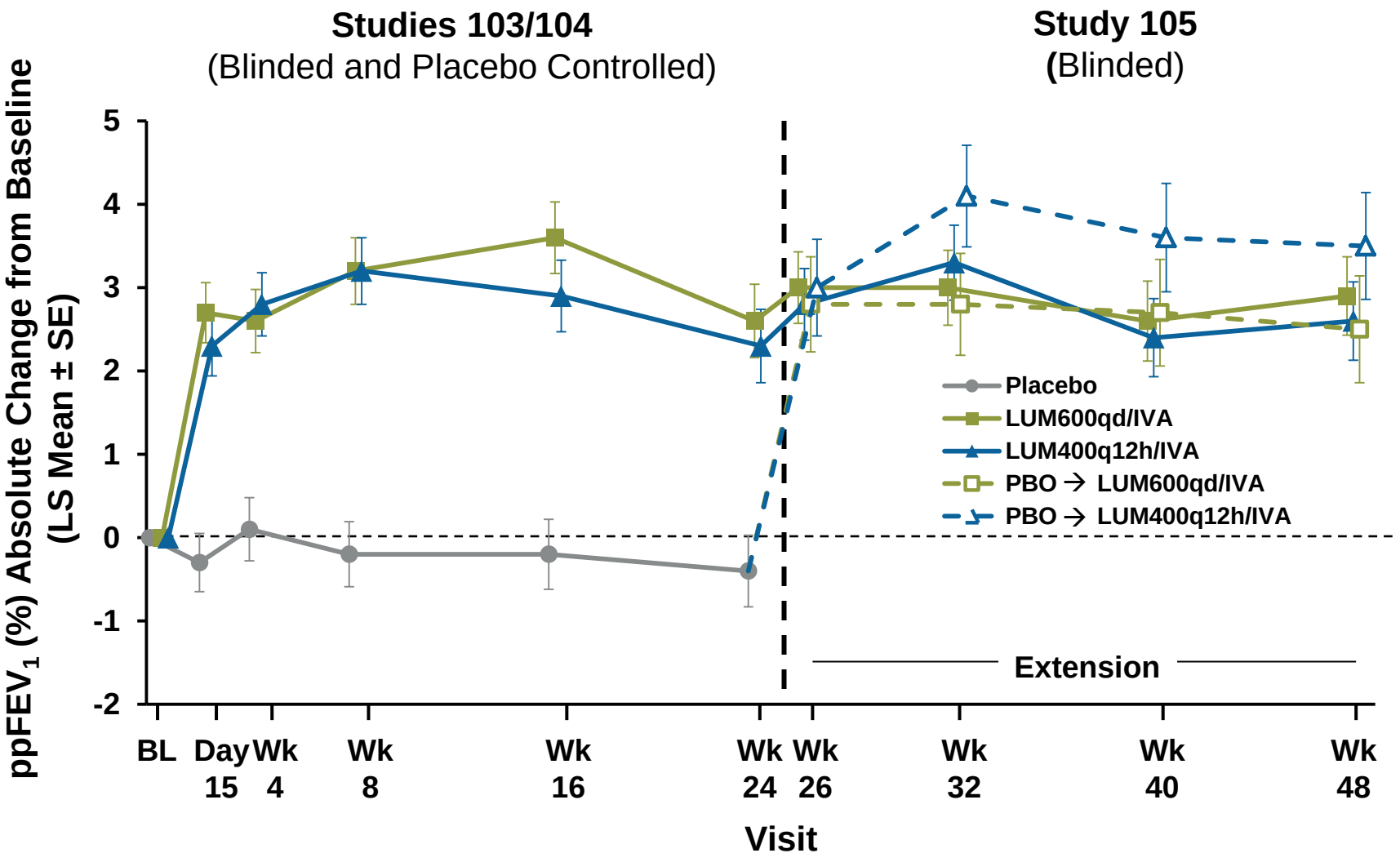
Endpoint	Comparison	Placebo N = 63	LUM400q12h/IVA N = 62
Absolute change in ppFEV$_1$ (percentage points)	Treatment difference to placebo	NA	0.60 (*P*=0.5978)
Relative change in ppFEV$_1$ (%)	Treatment difference to placebo	NA	1.52 (*P*=0.4408)
Change in BMI (mg/kg^2)	Treatment difference to placebo	NA	-0.12 (*P*=0.2588)
Change in CFQ-R (points)	Treatment difference to placebo	NA	6.48 (*P*=0.0131)[a]
Change in weight (kg)	Odds ratio to placebo	NA	-0.27 (*P*=0.3694)
Change in sweat chloride[b] (mmol/L)	Treatment difference to placebo	NA	-11.03 (*P*<0.0001)

[a]Not considered statistically signficant within the framework of the testing hierarchy.
[b]Endpoint was not part of the testing hierarchy.

809 (Pooled): Pulmonary Exacerbations, Hospitalizations, Antibiotics – Number of Events

Event Type		Placebo N = 371	LUM600qd/IVA N = 368	LUM400q12h/IVA N = 369
Pulmonary Exacerbations	Subjects with events	161	123	109
	Number of events (Annualized Event rate)	251 (1.1.4)	173 (0.80)	152 (0.70)
	Rate Ratio		0.70 (*P*=0.0014)	0.61 (*P*<0.0001)
IV Antibiotics for Pulmonary Exacerbations	Subjects with events	115	70	54
	Number of events (Event rate)	149 (0.58)	80 (0.32)	64 (0.25)
	Rate Ratio		0.5521 (*P*<0.0001)	0.4354 (*P*<0.0001)
Unplanned Hospitalizations for Pulmonary Exacerbations	Subjects with events	87	53	37
	Number of events (Event rate)	105 (0.45)	62 (0.27)	40 (0.17)
	Rate Ratio		0.6067 (*P*=0.0028)	0.3858 (*P*<0.0001)

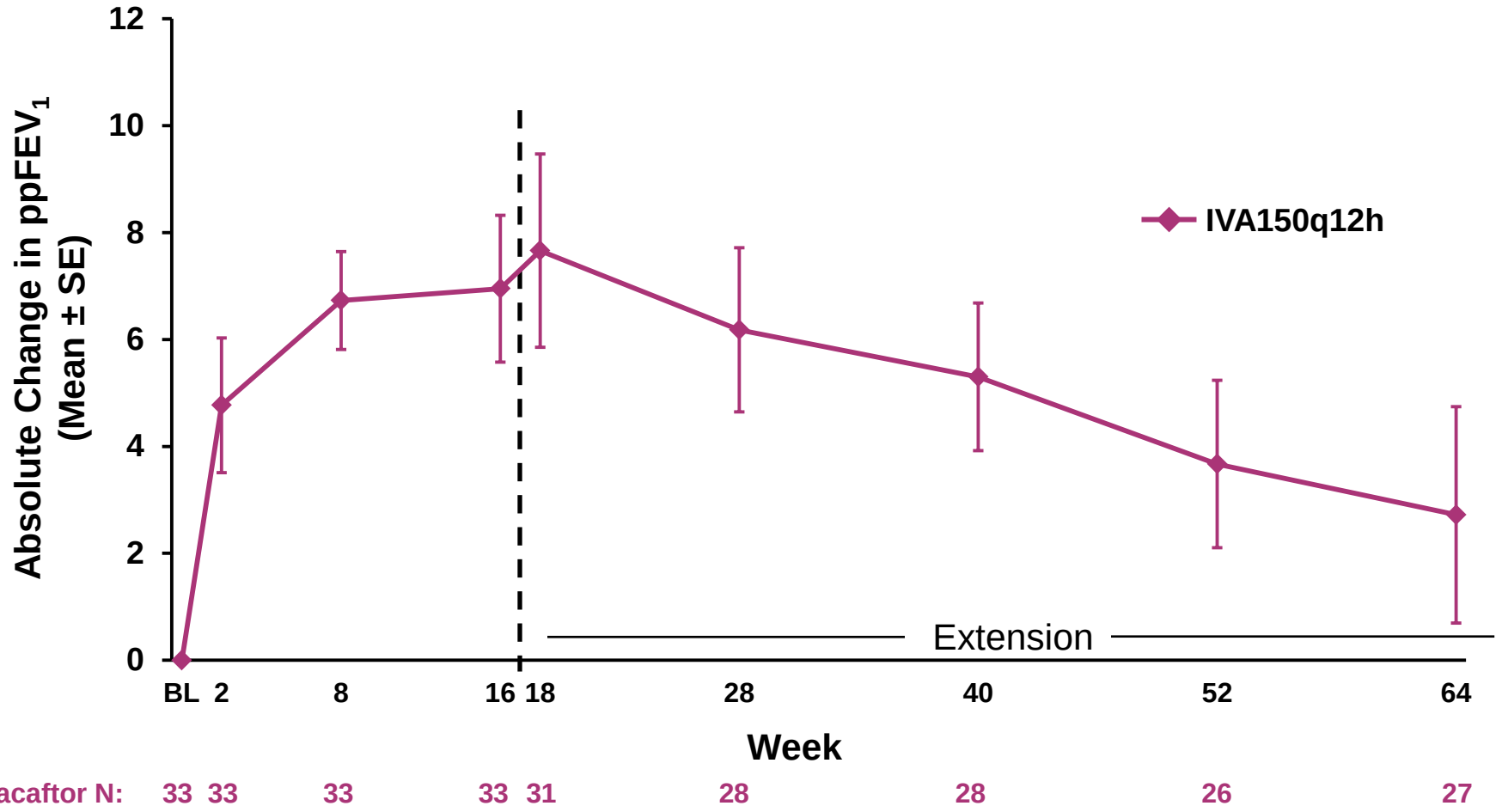
Study 105 IA2 (48 Weeks): ppFEV$_1$ Change from Baseline



Response Analysis of Absolute Change From Baseline in CFQR Respiratory Domain at Each Visit (FAS)

Responders (≥4)	Placebo N = 371 n (%)	LUM400q12h/IVA N = 369 n (%)
Day 15	133 (35.8)	158 (42.8)
Week 4	156 (42.0)	197 (53.4)
Week 8	135 (36.4)	183 (49.6)
Week 16	137 (36.9)	185 (50.1)
Week 24	159 (42.9)	169 (45.8)

IVA: 770-104 Part B Subjects with >10% FEV_1 Response or Sweat Chloride >15mmol/L



LUM/IVA: Sustained Efficacy in Patients with >10% FEV_1 Response (IA2)