Bronchitol®
Inhaled Dry Powder Mannitol (DPM) for Adult Patients with Cystic Fibrosis

Chiesi USA, Inc.

Pulmonary-Allergy Drug Advisory Committee

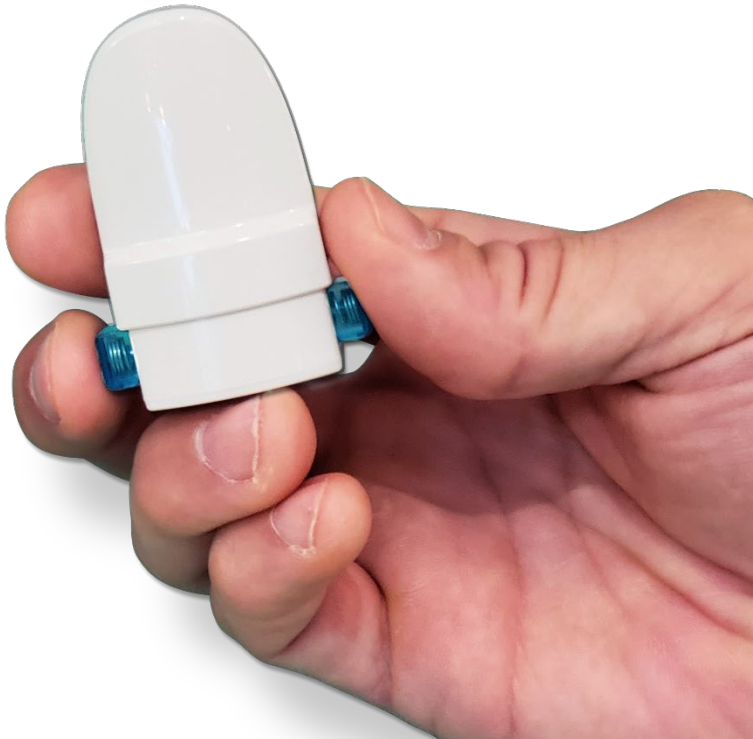
May 8, 2019

Introduction

Mark Parry-Billings, PhD

Head of Corporate Drug Development

Chiesi Farmaceutici S.p.A.

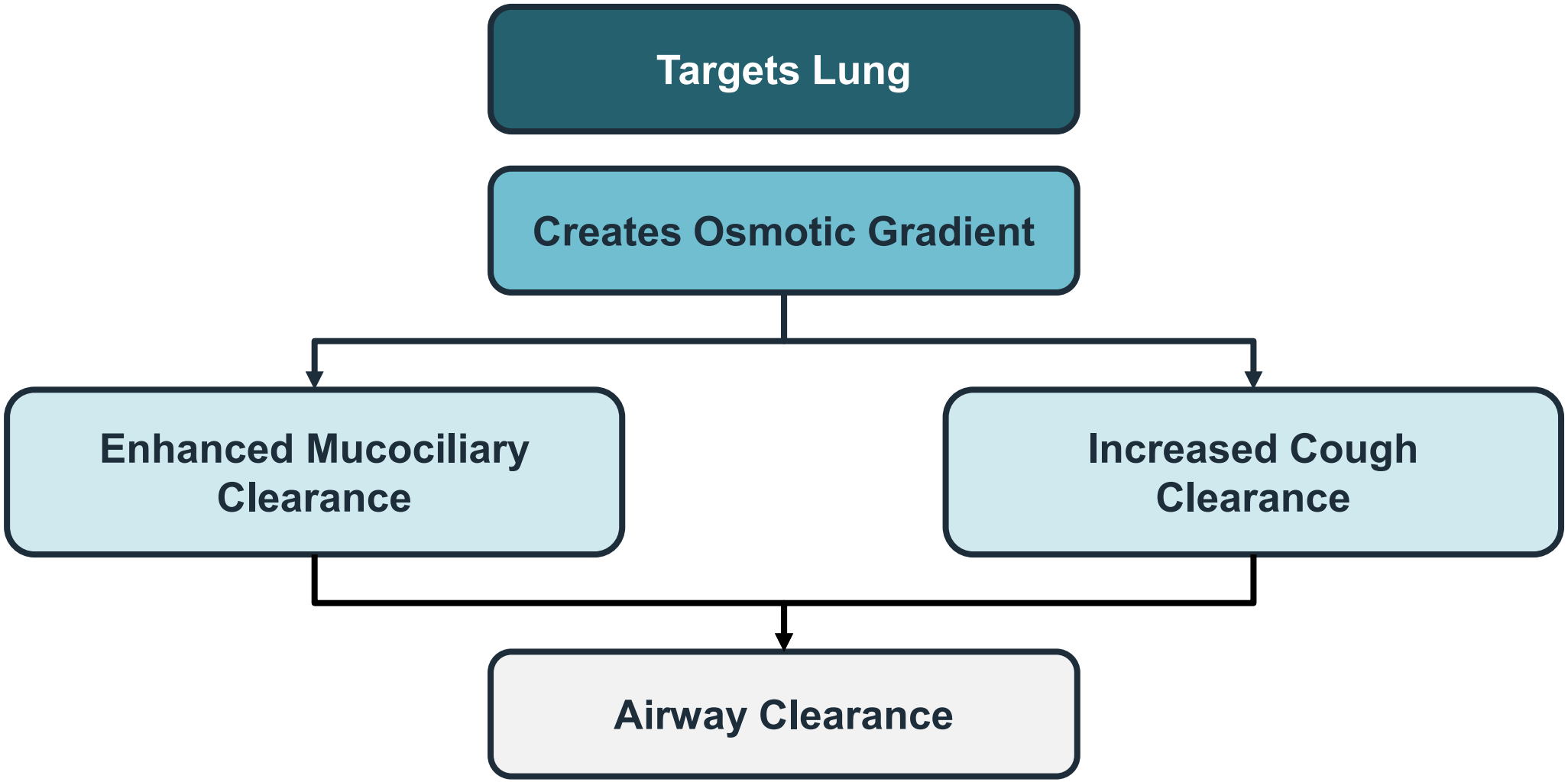


Bronchitol Introduction

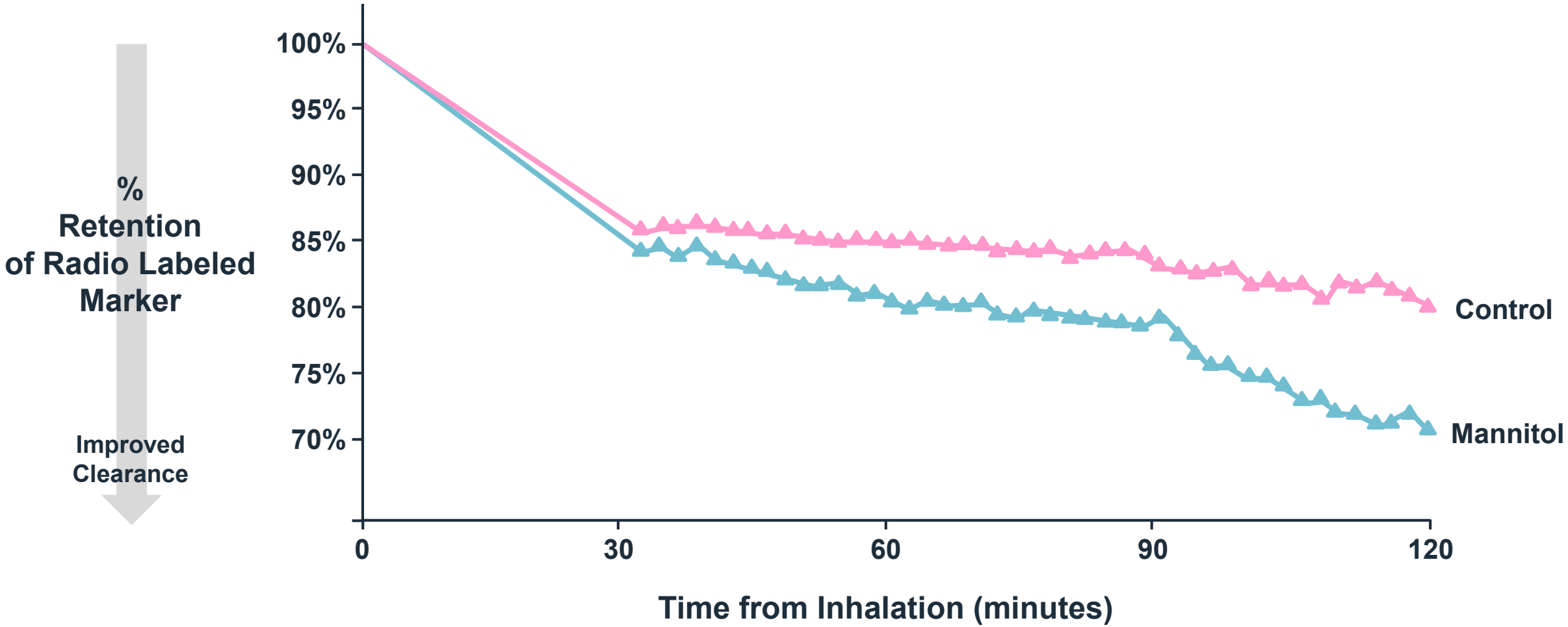
- Clinical profile
  - Unique mechanism to improve lung function
  - Naturally-occurring osmotic agent, GRAS*
  - FEV_1 is prognostic indicator for morbidity and mortality in CF
  - Generally well-tolerated safety profile
- Evidence base includes
  - Consistent FEV_1 improvement across three Phase 3 trials
  - 8 years of worldwide post-approval clinical experience
- Easy-to-use inhaled dry powder form of mannitol
- Treatment option for adult patients with CF

*Generally recognized as safe

Bronchitol Clinically-Impactful MoA: Airway Clearance



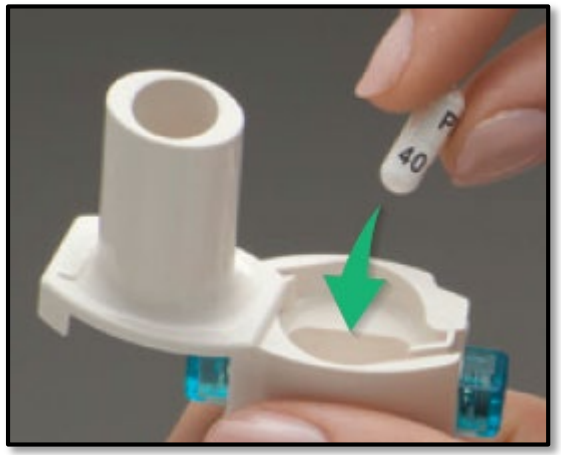
Airway Clearance-Targeted Mechanism of Action Confirmed in CF Patients

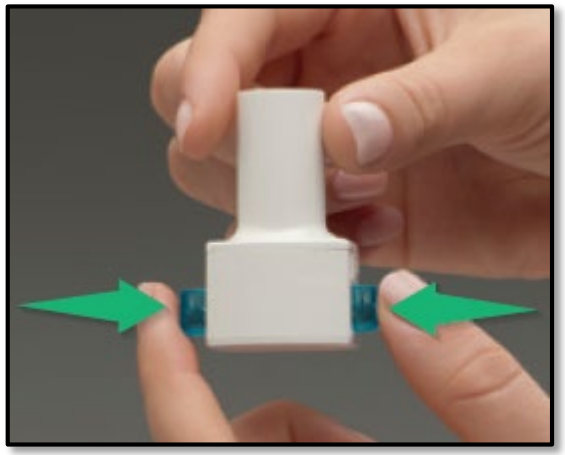


*p < 0.01 for mannitol vs. control on both post intervention clearance and cough clearance

Adapted from Robinson, 1999.

Bronchitol Administered Using Easy-to-Use Dry Powder Inhaler





Global Bronchitol Experience

- First approved in Australia in 2011
- Approved in 35 countries for treatment of adult patients with CF
  - Markets include UK, Germany, Italy, and Spain
  - Approximately 8,000 patients treated
  - No notable safety concerns

Bronchitol Proposed Indication

- …for the management of cystic fibrosis to improve pulmonary function in patients 18 years and older in conjunction with standard therapies.

US Regulatory History (2012 - 2013)

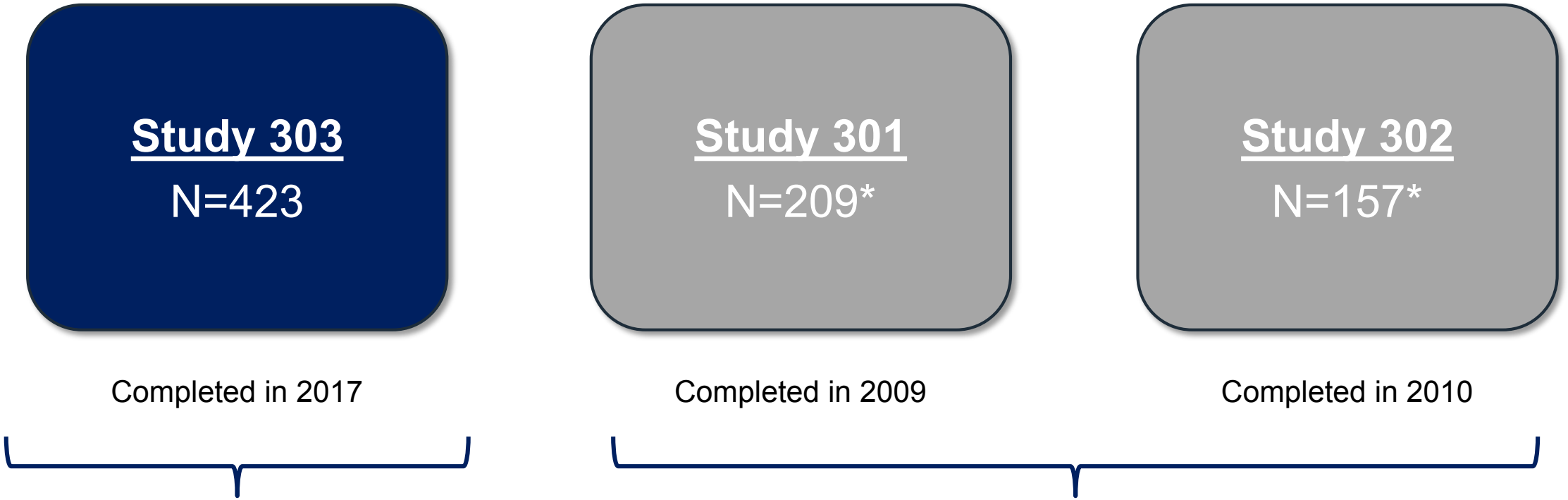
- NDA submission 2012 by Pharmaxis
  - Patients aged 6 years and older
  - Two phase 3 studies (301 and 302) in both pediatric and adult patients
- PADAC, CRL and End-of-Review Conference 2013
  - Two phase 3 studies not adequate
    - Study 302 missed primary endpoint
    - Study 301 statistical analysis did not account for frequent early dropouts
    - Hemoptysis concerns in pediatric patients
  - Third phase 3 study in adults requested

US Regulatory History (2018)

- December 2018: NDA resubmission
  - In line with pre-submission meeting
  - Focused on new Phase 3 Study 303
  - Adults only
  - Drop outs minimized and accounted for in analysis
  - Earlier studies (301 and 302) reassessed using prespecified statistical plan for Study 303
  - Integrated analysis for safety and efficacy

Benefit-Risk Supported By Three Randomized, Double-Blind, Controlled Phase 3 Studies

789 adult patients with CF randomized in Phase 3 studies



*Adult patients from study that enrolled pediatric and adult patients

Agenda

Unmet Need & Disease Background

Scott H. Donaldson, MD
Professor of Medicine, Division of Pulmonary and Critical Care
University of North Carolina at Chapel Hill
Director, Adult Cystic Fibrosis Center

Efficacy of Bronchitol

Carmen Dell'Anna, MD
Vice President, Medical Affairs
Chiesi USA, Inc.

Safety of Bronchitol

W. James Alexander, MD, MPH
Senior Medical Affairs Consultant
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Clinical Perspective

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Additional Experts

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North Marston, Buckinghamshire

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Head Adult Cystic Fibrosis Centre,
Lung-Transplantation Program
Charité – Universitätsmedizin Berlin

Alexandra Quittner, PhD
Senior Scientist
Miami Children's Research Institute

Unmet Need and Disease Background

Scott H. Donaldson, MD

Professor of Medicine

University of North Carolina at Chapel Hill

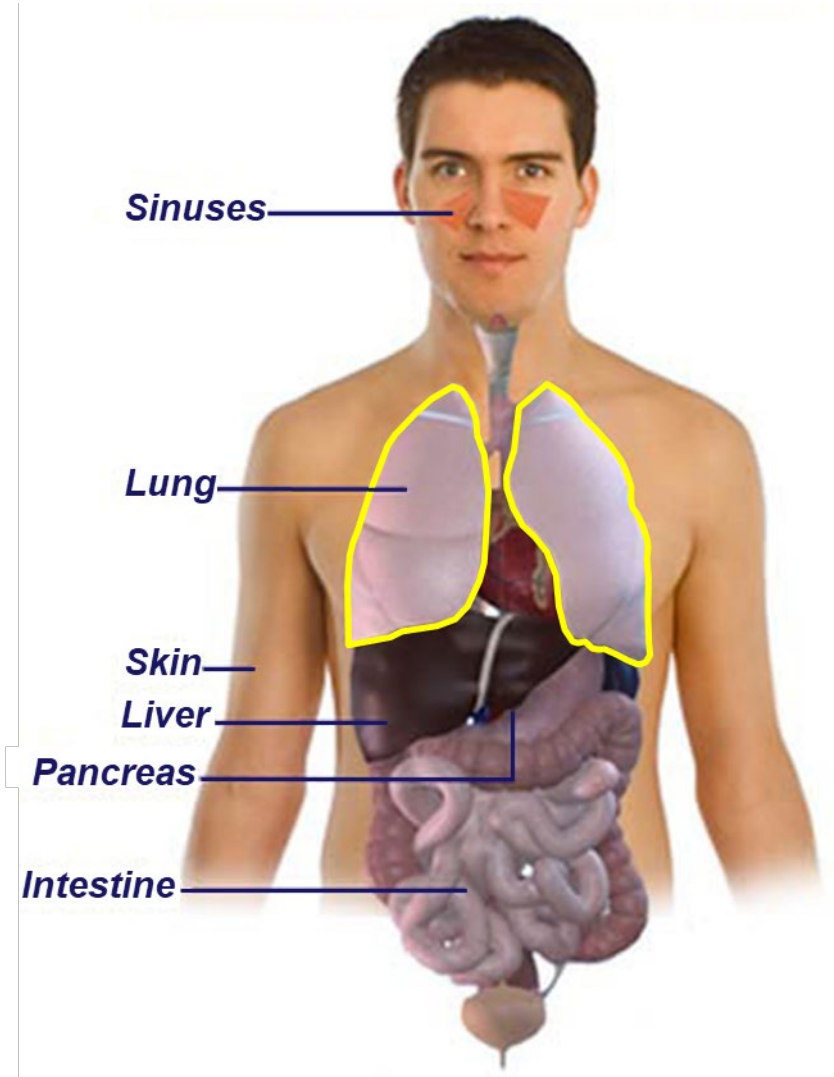
CF is a Life Shortening Genetic Disease[1]

- > 30,000 patients in the US
  - Adults represent 54% of CF population
- Single gene, autosomal recessive disorder
- > 90% Caucasians
- Median predicted survival increased 11 years since 2002
- 2017 average age at death ~ 30 years

1. Cystic Fibrosis Foundation Patient Registry, Annual Data Report 2017

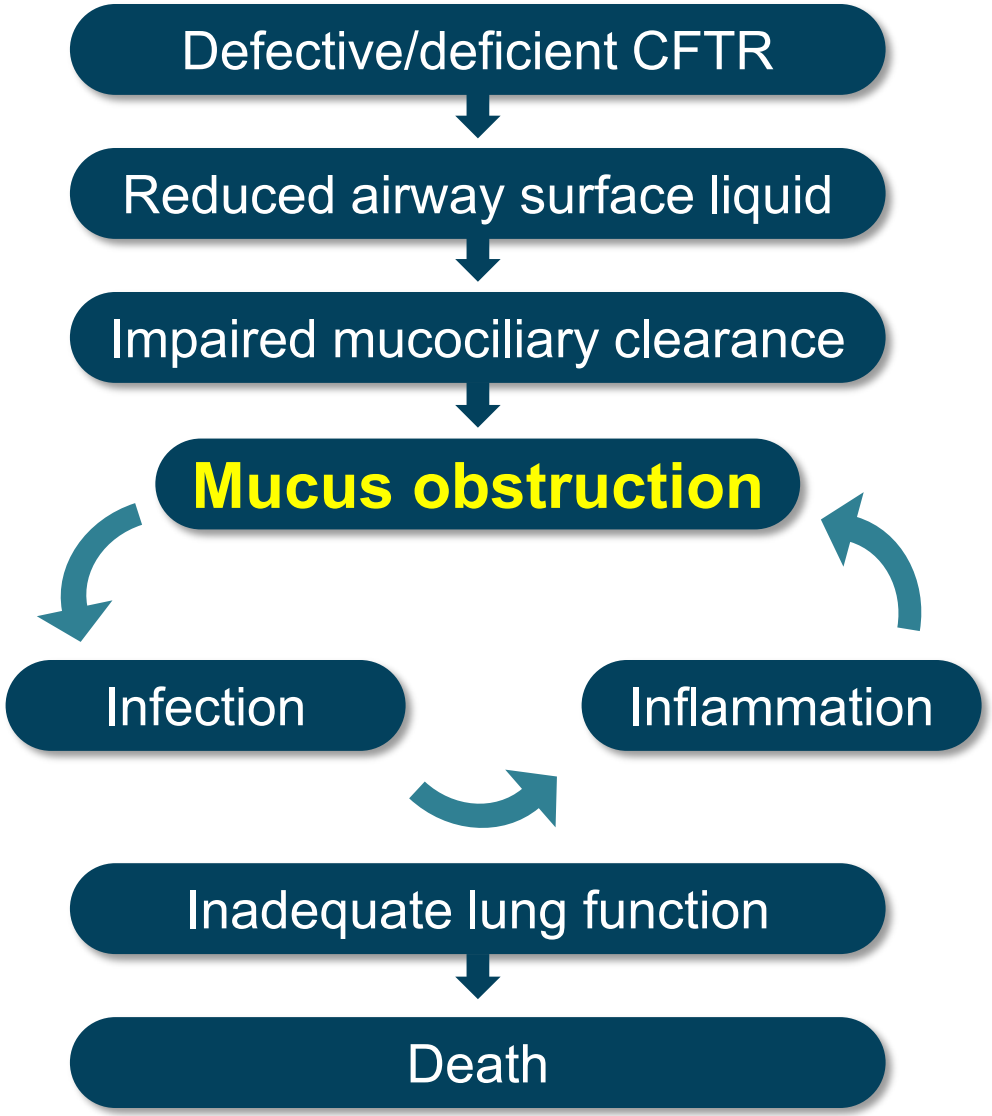
CF Disease Focuses on Airways[1]

- Multi-organ disease
- Lung is primary organ impacted
  - Bronchiectasis with chronic, polymicrobial infection
  - Structure and function of lung progressively declines
- Respiratory failure accounts for > 80% of mortality[2]

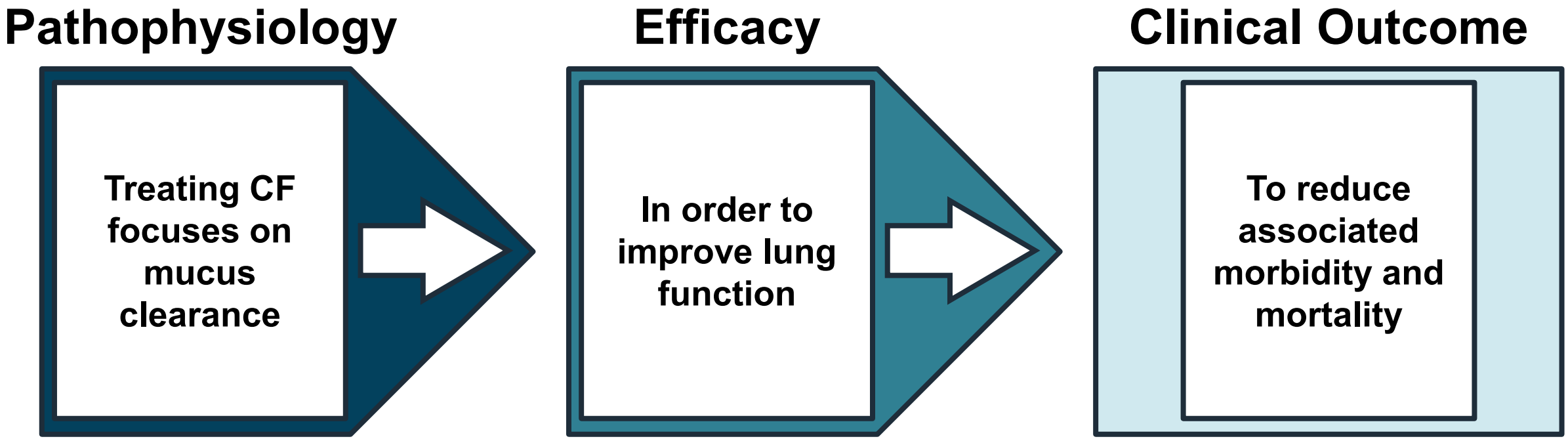


1. Orenstein, 2003; 2. Flume, 2012.

CF Pathophysiology



Treating Airway Clearance Improves Clinical Outcome

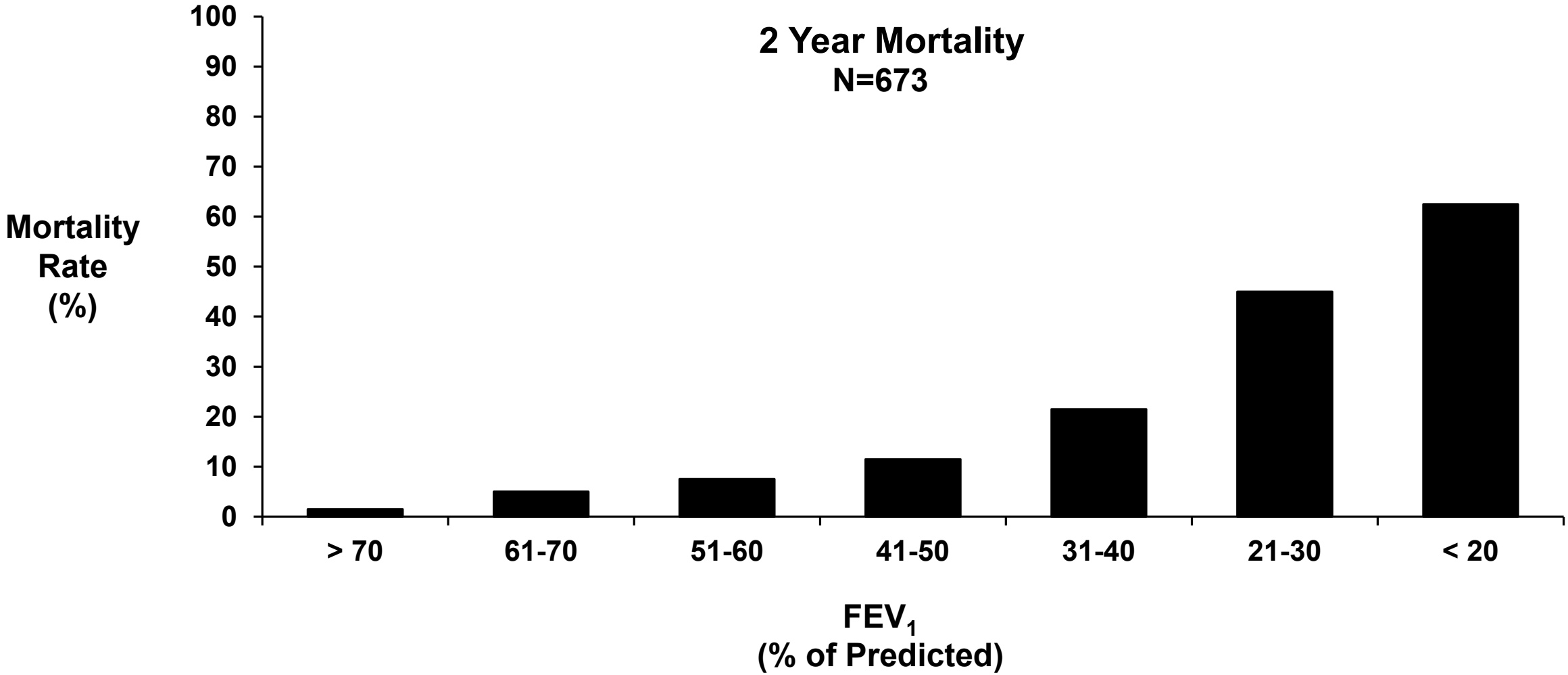


FEV_1 Accepted Measure of Lung Function, Predictor of Morbidity and Mortality

- FEV_1 is primary spirometric parameter of interest
  - Strong relationship between FEV_1 and structural lung damage[1]
  - Strongest clinical predictor of exercise capacity and survival[2]

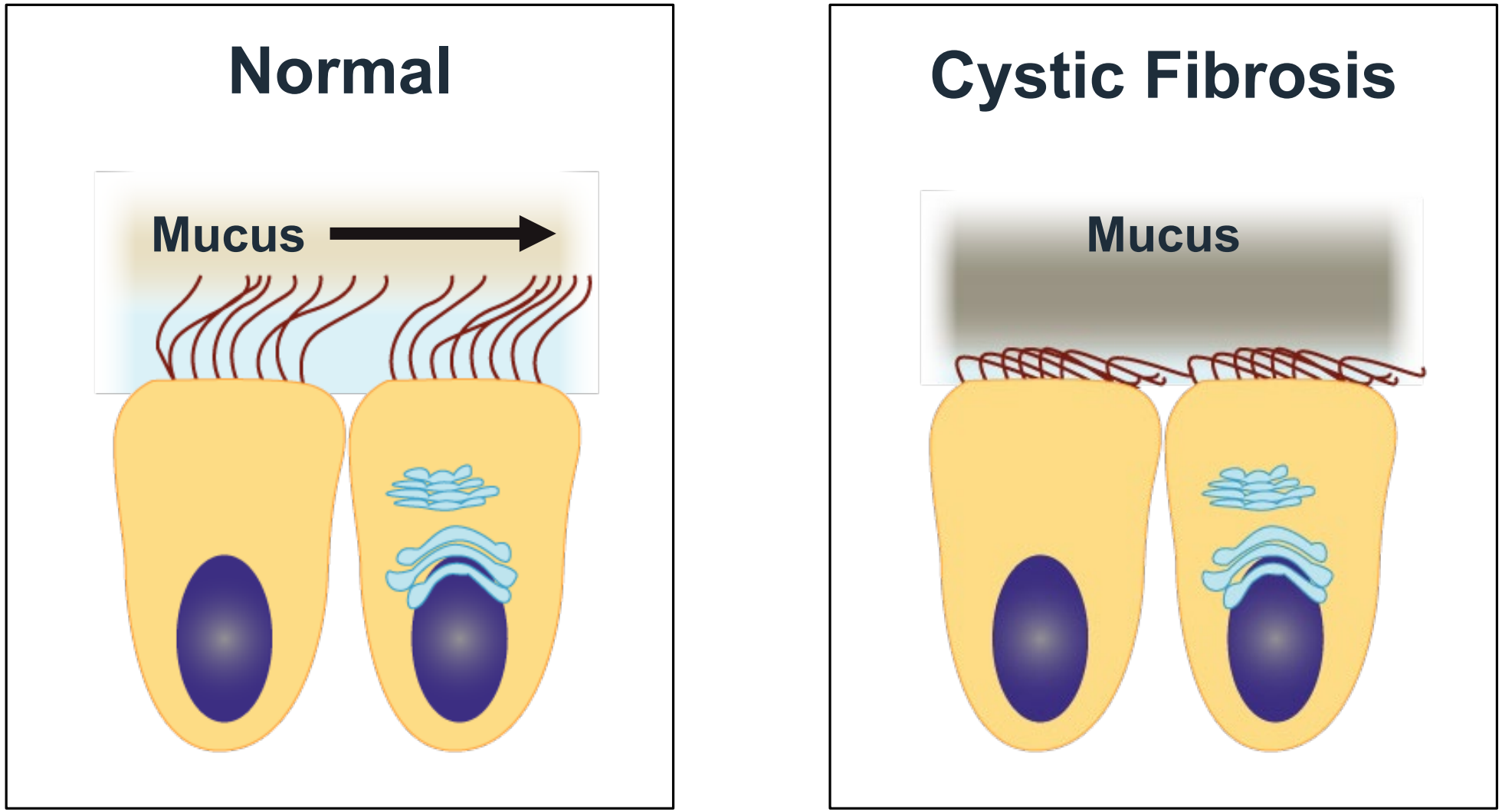
1. Liou, 2010; 2. Demirkazik, FB 2001.

FEV_1 Key Predictor of Morbidity and Mortality Well Established in Literature



Figured recreated from Kerem, NEJM 1992.

Mucociliary Clearance in CF



Mucus Plugging of CF Airways

Resected lung with mucus

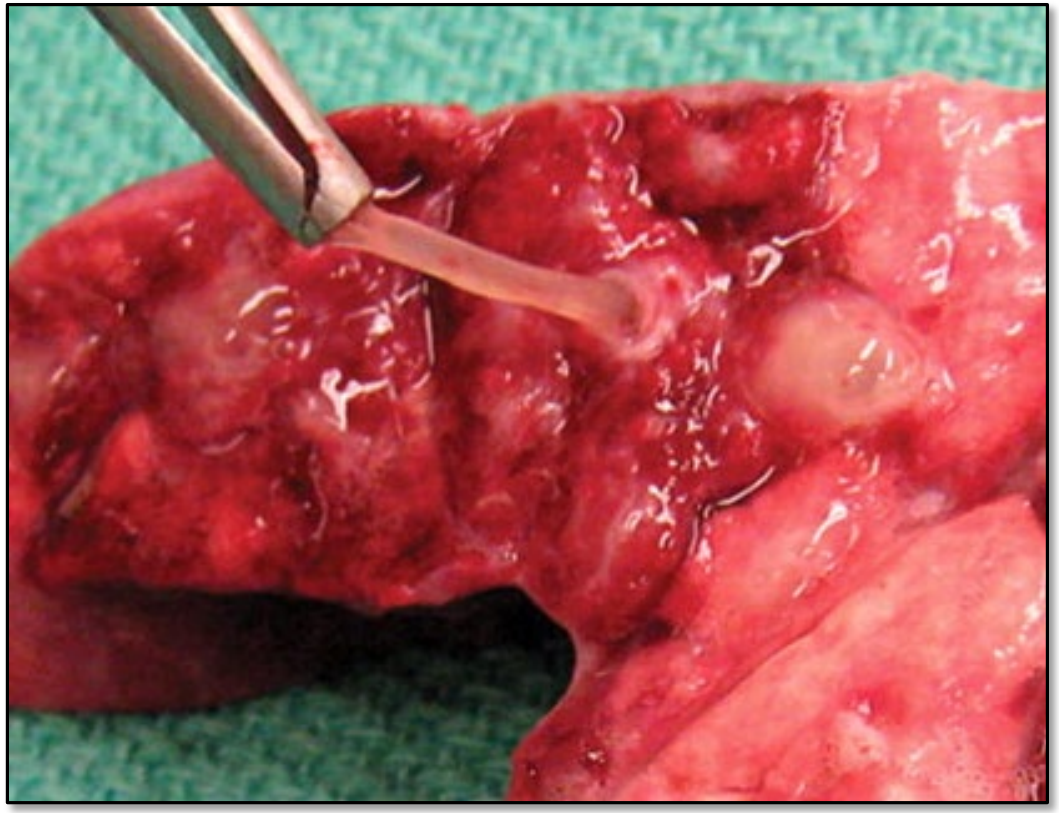
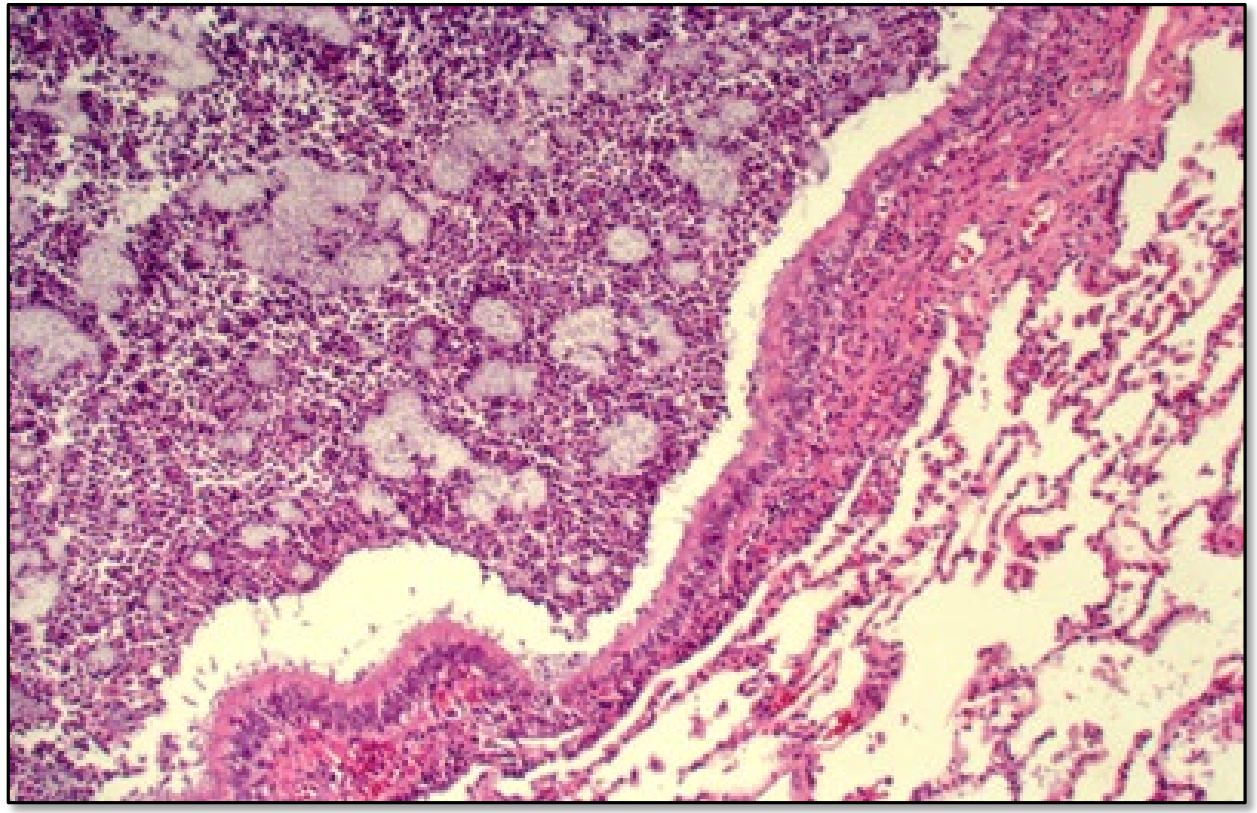
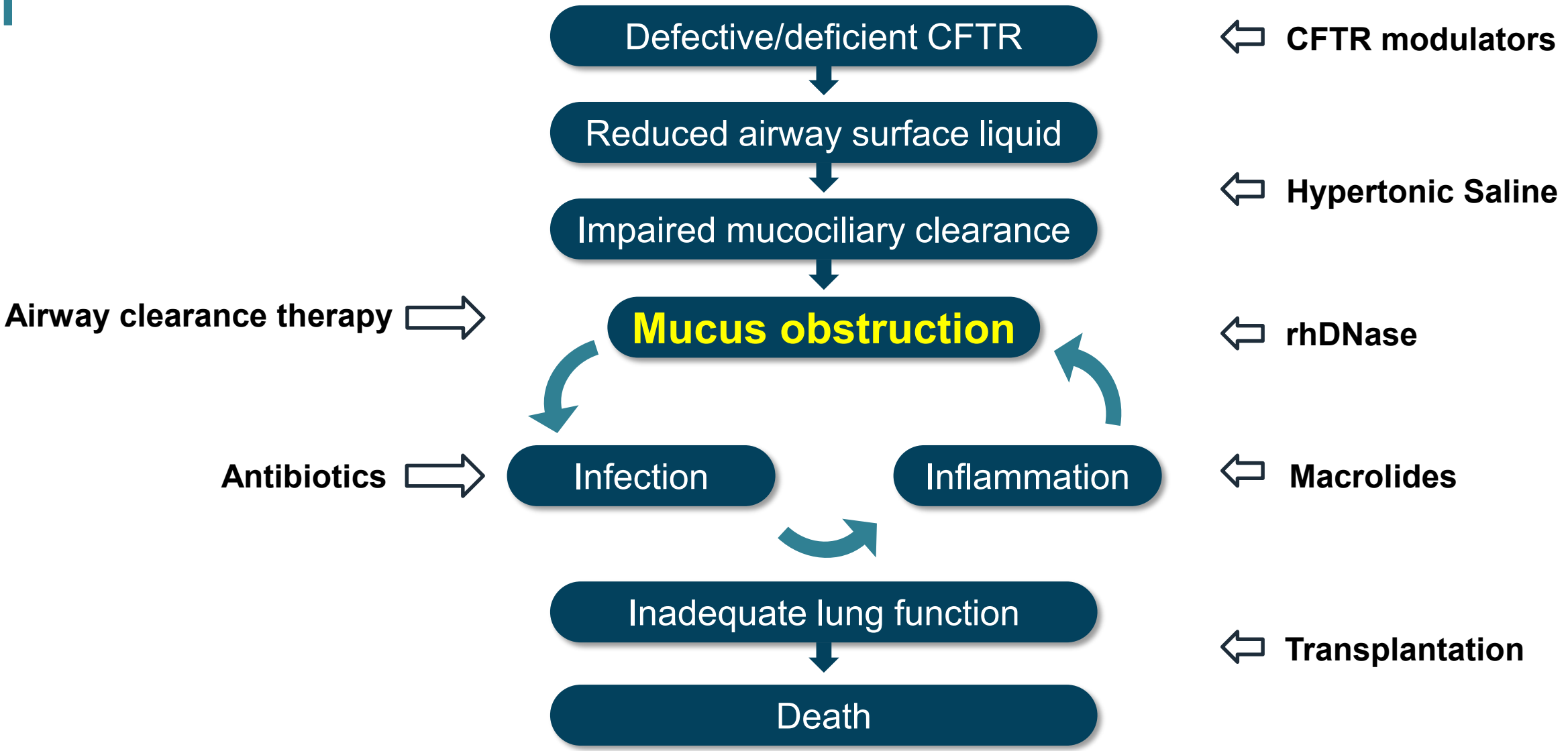


Photo micrograph of CF airway



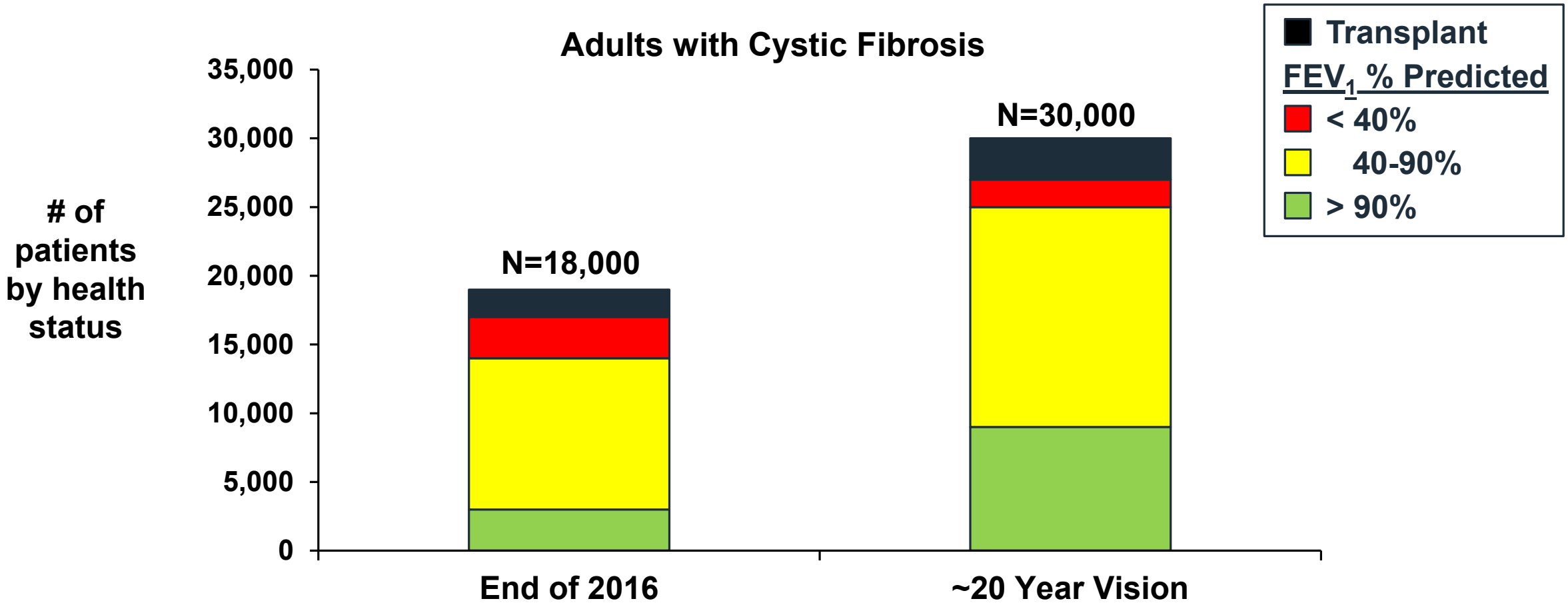
Therapies Recommended in CF Guidelines



CFTR Modulators to Treat People with Cystic Fibrosis

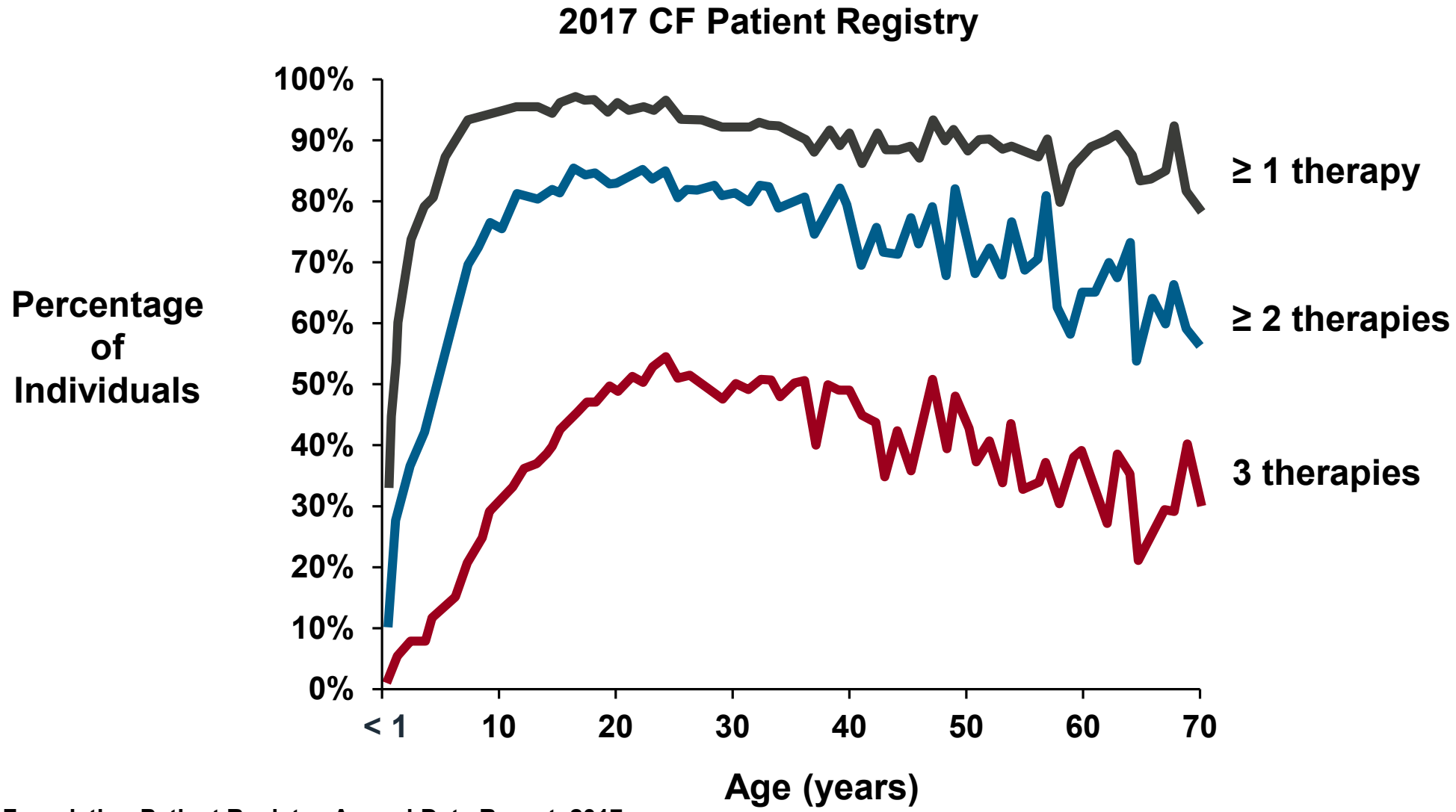
- CFTR modulators effective in proportion of CF population
- Some not eligible for CFTR modulator therapies
- Slows, but does not stop progression of lung disease
- Ongoing need for downstream treatments focused on airway clearance

US Adult CF Population Expected to Increase Dramatically



Adapted from 2018 Revised Model for July 2018 CFF Medical Strategy Retreat

Treatment Burden



Cystic Fibrosis Foundation Patient Registry, Annual Data Report, 2017.

Treatment Burden Reduces Adherence and is Associated with Worse Clinical Outcomes

- Nebulized medication adherence: ~ 36%[1]
- Adherence to inhaled medications varies with difficulty
  - 36% with HS; 62% with rhDNase[2]
- Clinical outcomes correlate with adherence[2]

1. Daniels, 2011; 2. Quittner, 2014

What do People with CF Tell Us?

- Surveys of CF community to establish research priorities
- Treatment burden is research priority for patients and providers
  - James Lind Alliance: 1st out of 10 (N=677)[1]
  - Cystic Fibrosis Foundation: 3rd out of 12 (N=135)[2]
- Patients want effective therapies that take less time

1. Rowbotham, 2018; 2. Hollin, 2019.

A Patient Story – Meet Kim

- 30-year old female
- Married, 2 children, employed
- Chronic airway infection and pancreatic insufficiency
- Bronchiectasis with FEV_1 50% predicted

A Typical Day for Kim – Juggling Every Day Activities While Managing CF

Morning

- Wakeup - 5am
- Begins therapy
  - Inhaled bronchodilator
  - Hypertonic saline
  - Airway clearance
  - rhDNase
  - Inhaled tobramycin
- Cleans devices
- Gets ready for work
- Gets kids ready for school
- Eats breakfast
- Goes to work

Evening

- Leaves work
- Arrives home
- Dinner preparation
- Homework review
- Children's bedtime
- Begins therapy
  - Inhaled bronchodilator
  - Hypertonic saline
  - Airway clearance
  - Inhaled tobramycin
- Cleans devices
- Bedtime - 10pm

Adults with CF Need Effective, Efficient Treatment Options

- Lung disease progression persists in adults despite intensive treatment regimens
- Feasible treatments more likely to be used, and achieve real world efficacy
- Ongoing goal: improve airway clearance and lung function
- Options that reduce treatment burden and increase portability demanded by people with CF and caregivers

Efficacy in Adult Patients with Cystic Fibrosis

Carmen Dell'Anna, MD

Vice President, Medical Affairs

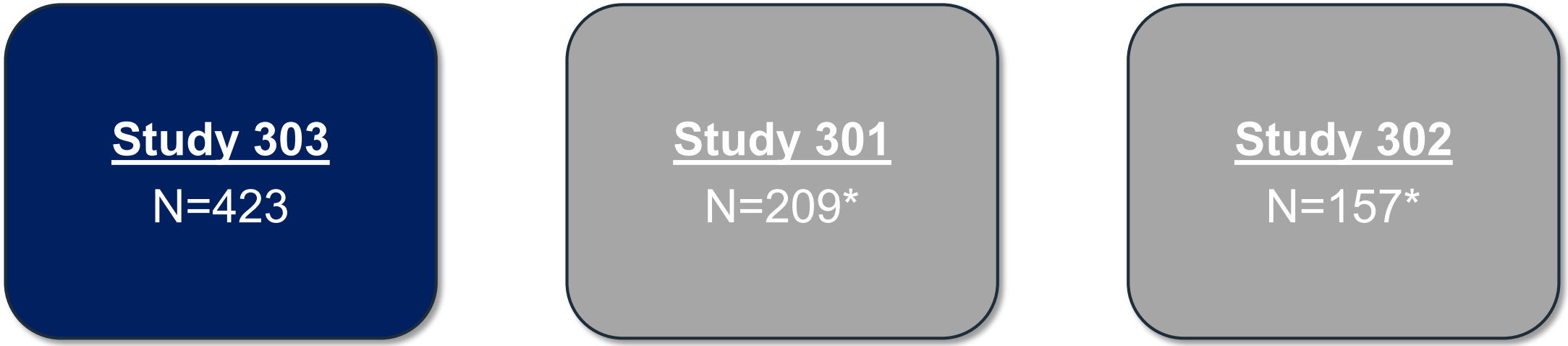
Chiesi USA, Inc.

Efficacy Agenda

- Overview of Phase 3 clinical studies
- Primary study results
- Sensitivity / responder analyses
- Other pulmonary function endpoint results
- Other clinical endpoint results (PDPE and CFQ-R)

Bronchitol Efficacy Supported by 3 Randomized, Double-Blind Controlled Phase 3 Studies

789 adult patients with CF randomized in Phase 3 studies



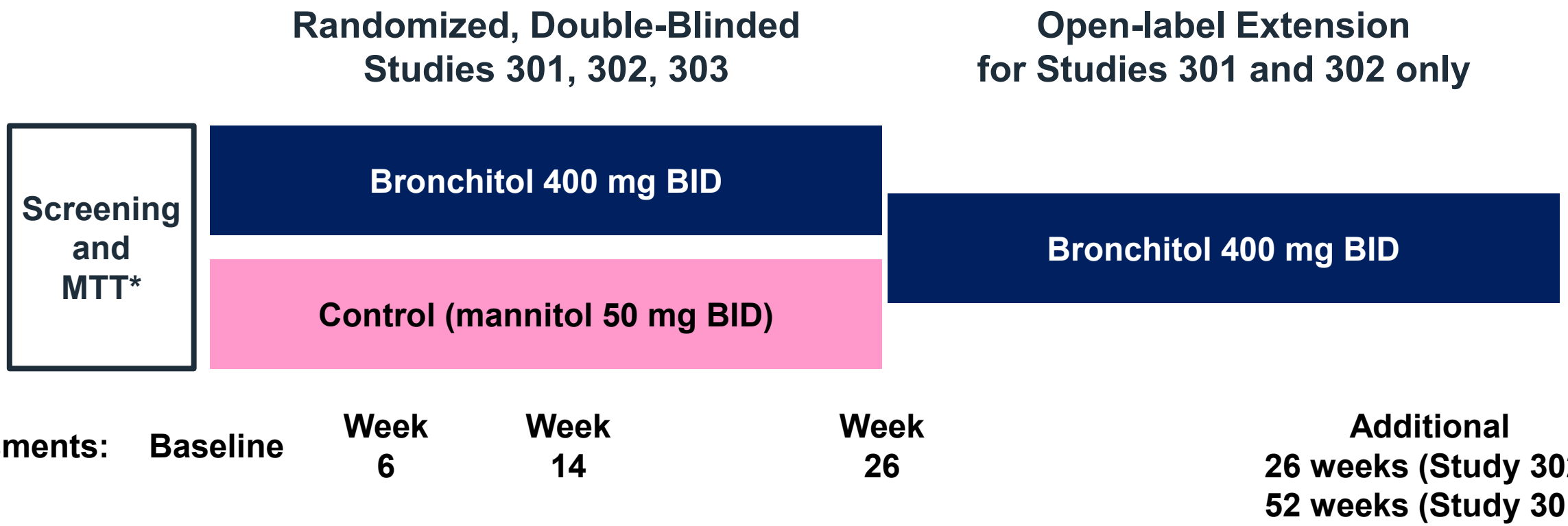
Completed in 2017

Completed in 2009

Completed in 2010

*Adult patients from study that enrolled pediatric and adult patients

Similar Design Across Phase 3 Studies



*Mannitol Tolerance Test administered under medical supervision (~ 92% of patients pass MTT)

Low Dose Mannitol 50 mg Used as Control to Protect Blind

- Same taste and appearance
- Phase 2 supported a lack of response with low dose
- Selection discussed with FDA

Key Enrollment Criteria for Adults in Phase 3 Studies

Key Inclusion Criteria	Study 303	Study 301	Study 302
% predicted FEV_1 at screening	> 40% and < 90%	≥ 30% and < 90%	≥ 40% and < 90%
Permitted maintenance therapies	Established antibiotics and / or rhDNase treatments		
Key Exclusion Criteria			
Prohibited therapies	Nebulized hypertonic saline for maintenance and non-selective oral β-blockers		
Mannitol Tolerance Test (MTT)	Failure to successfully complete the MTT		

Primary and Secondary Endpoints in Phase 3 Studies

- Primary endpoint
  - Change from baseline in FEV_1 over 26-weeks
- Other pulmonary function endpoints
  - Change from baseline in FVC over 26-weeks
  - Change from baseline in FEF_{25-75} over 26-weeks
- Other clinical endpoints
  - Rate of PDPE over 26-weeks
  - Change from baseline in CFQ-R respiratory domain

FEV_1=Forced expiratory volume in 1 second; FVC=Forced vital capacity; FEF_{25-75}=Forced expiratory flow in middle half of an expiration
PDPE=Protocol defined pulmonary exacerbation; CFQ-R=Cystic Fibrosis Questionnaire Revised

Statistical Analysis Accounted for Missing Data

- Analysis population ITT: all adult patients randomized
- Handling of missing data for patients who withdrew from study
  - Due to AE, death, lack of efficacy or physician decision; missing values imputed with BOCF*
  - Due to other reasons; no formal imputation
- Primary analysis: Mixed Model Repeated Measures (MMRM)
- Analysis included all available data, regardless of discontinuation of study medication

*Baseline Observation Carried Forward

Multiple Sensitivity Analyses to Confirm Robustness of Primary Endpoint

- Pattern Mixture Modeling (PMM)
  - Multiple imputation based on reason for study withdrawal
  - Multiple imputation regardless of reason for study withdrawal
- MMRM without imputation of missing data
- Tipping point analysis
- Responder analysis

Patient Disposition: Study 303 Withdrawal Lower and Balanced

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Treated with drug	**99%**	**> 99%**	92%	89%	96%	97%	96%	97%
Completed study	**88%**	**89%**	57%	61%	72%	83%	75%	81%
Study Withdrawal	**12%**	**11%**	43%	39%	28%	17%	25%	19%
AE	**5%**	**3%**	19%	14%	9%	3%	10%	6%
Withdraw consent	**6%**	**6%**	15%	20%	10%	10%	9%	10%
Physician decision	**0**	**0**	4%	1%	2%	2%	2%	< 1%
Sponsor decision	**0**	**0**	4%	2%	0	0	1%	< 1%
Lack of efficacy	**< 1%**	**< 1%**	0	0	0	0	< 1%	< 1%
Other	**< 1%**	**2%**	< 1%	1%	6%	2%	2%	2%

Study 303: 18% Bronchitol, 21% Control patients stopped drug

Demographics in Adults Across Three Phase 3 Studies

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Age and Gender								
Mean age, years	**27**	**29**	29	29	27	29	28	29
Male	**56%**	**50%**	59%	46%	61%	62%	58%	51%
Race								
White	**97%**	**98%**	98%	99%	99%	100%	97%	98%
Other	**3%**	**2%**	2%	1%	1%	0	3%	2%
BMI, kg/m^2								
Mean	**22**	**22**	23	22	22	22	22	22
Region								
US	**27%**	**28%**	-	-	59%	60%	27%	26%
Non-US	**73%**	**72%**	100%	100%	41%	40%	73%	74%

Baseline Disease Characteristics

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Lung Function at Baseline								
Mean FEV_1 (L)	**2.45**	**2.38**	2.27	2.10	2.38	2.30	2.38	2.30
Mean % Predicted	**63%**	**63%**	58%	58%	61%	60%	61%	61%
% Predicted FEV_1								
≤ 50%	**24%**	**22%**	31%	34%	24%	35%	32%	31%
> 50% to ≤ 70%	**39%**	**48%**	43%	34%	44%	35%	41%	42%
> 70%	**36%**	**31%**	26%	32%	32%	30%	26%	27%
Symptoms at Baseline								
Median CFQ-R score	**66.7**	**66.7**	66.7	72.2	72.2	61.1	66.7	66.7
Score > 50	**78%**	**78%**	80%	78%	79%	71%	79%	77%
Presence of Pseudomonas aeruginosa								
% at screening	**44%**	**43%**	60%	67%	59%	57%	52%	51%

Exacerbation History Within 12 Months of Study

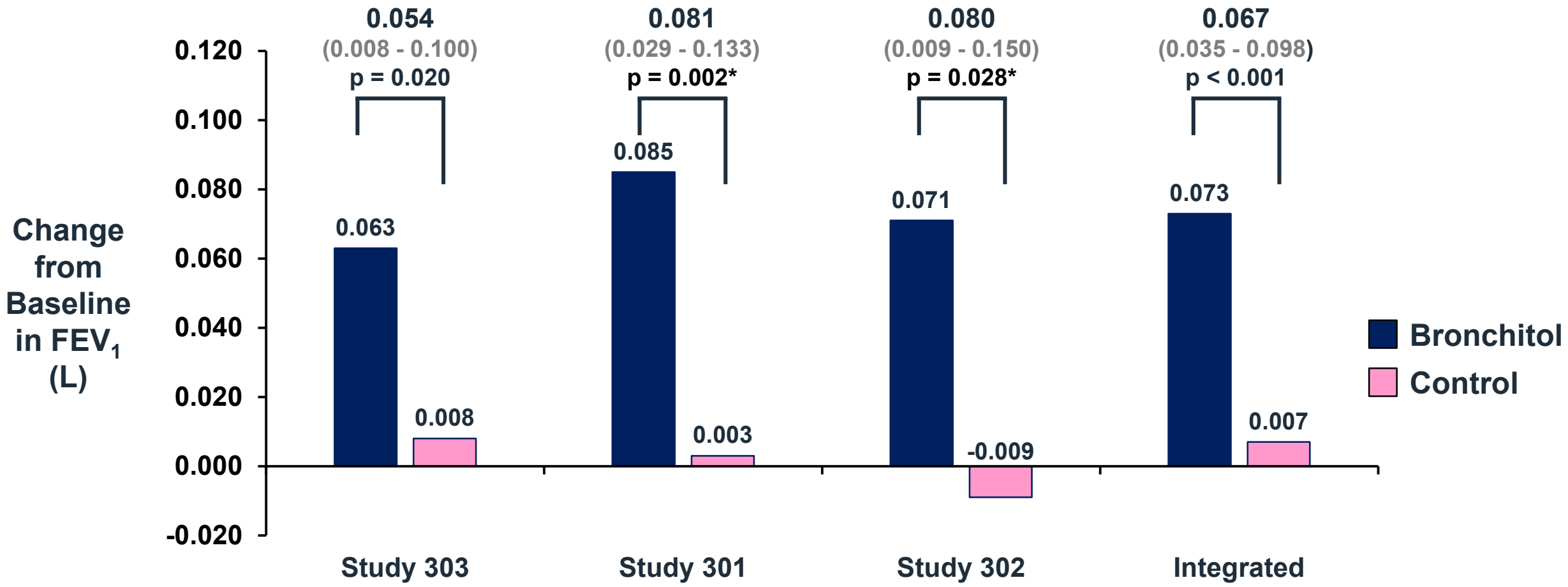
	Study 303		Study 301*		Study 302		Integrated*	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
PE Hospitalization								
0	**58%**	**63%**	-	-	61%	65%	-	-
≥ 1	**42%**	**37%**	-	-	39%	35%	-	-
PE with IV antibiotics								
0	**52%**	**56%**	-	-	55%	62%	-	-
≥ 1	**48%**	**44%**	-	-	45%	38%	-	-

*Not collected in Study 301

Efficacy Agenda

- Overview of Phase 3 clinical studies
- Primary study results
- Sensitivity / responder analyses
- Other pulmonary function endpoint results
- Other clinical endpoints (PDPE and CFQ-R)

Primary Endpoint: Significant Change from Baseline FEV_1 Over 26-Weeks (ITT)



MMRM with BOCF based on dropout reasons
*Analysis for study 301 and 302 performed post-hoc

Efficacy Agenda

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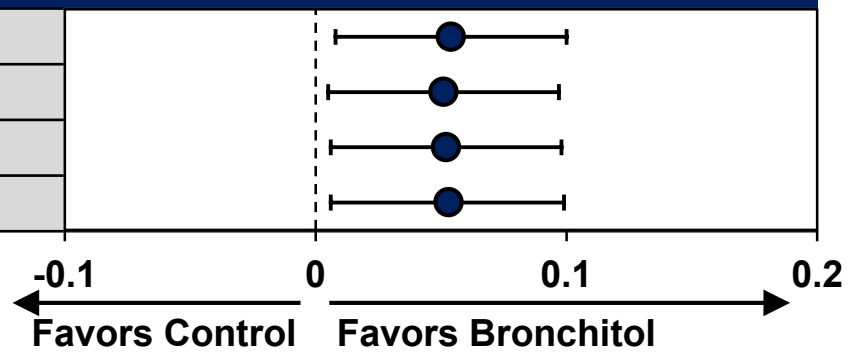
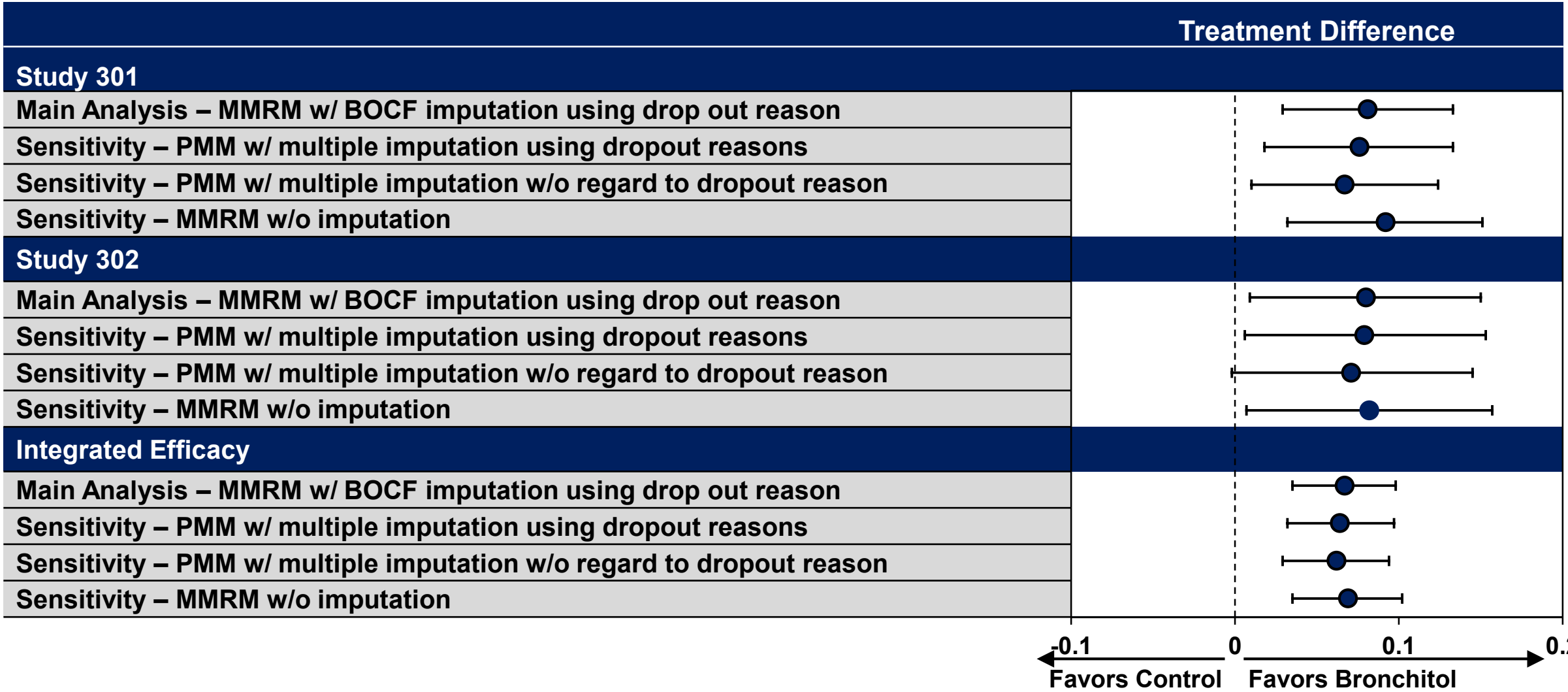
Sensitivity Analyses Support Robust Results (Study 303)

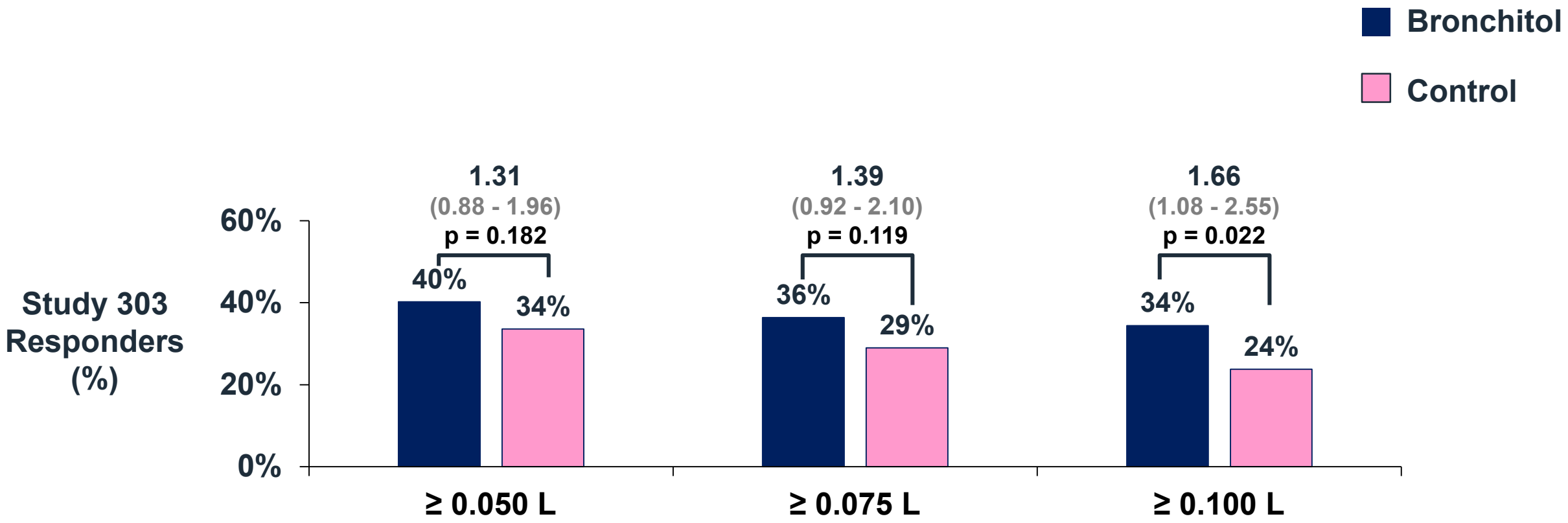
	Treatment Difference
Study 303	
Main Analysis – MMRM w/ BOCF imputation using drop out reason	
Sensitivity – PMM w/ multiple imputation using dropout reasons	
Sensitivity – PMM w/ multiple imputation w/o regard to dropout reason	
Sensitivity – MMRM w/o imputation	



Sensitivity Analyses Support Robust Results (Studies 301, 302, and Integrated)

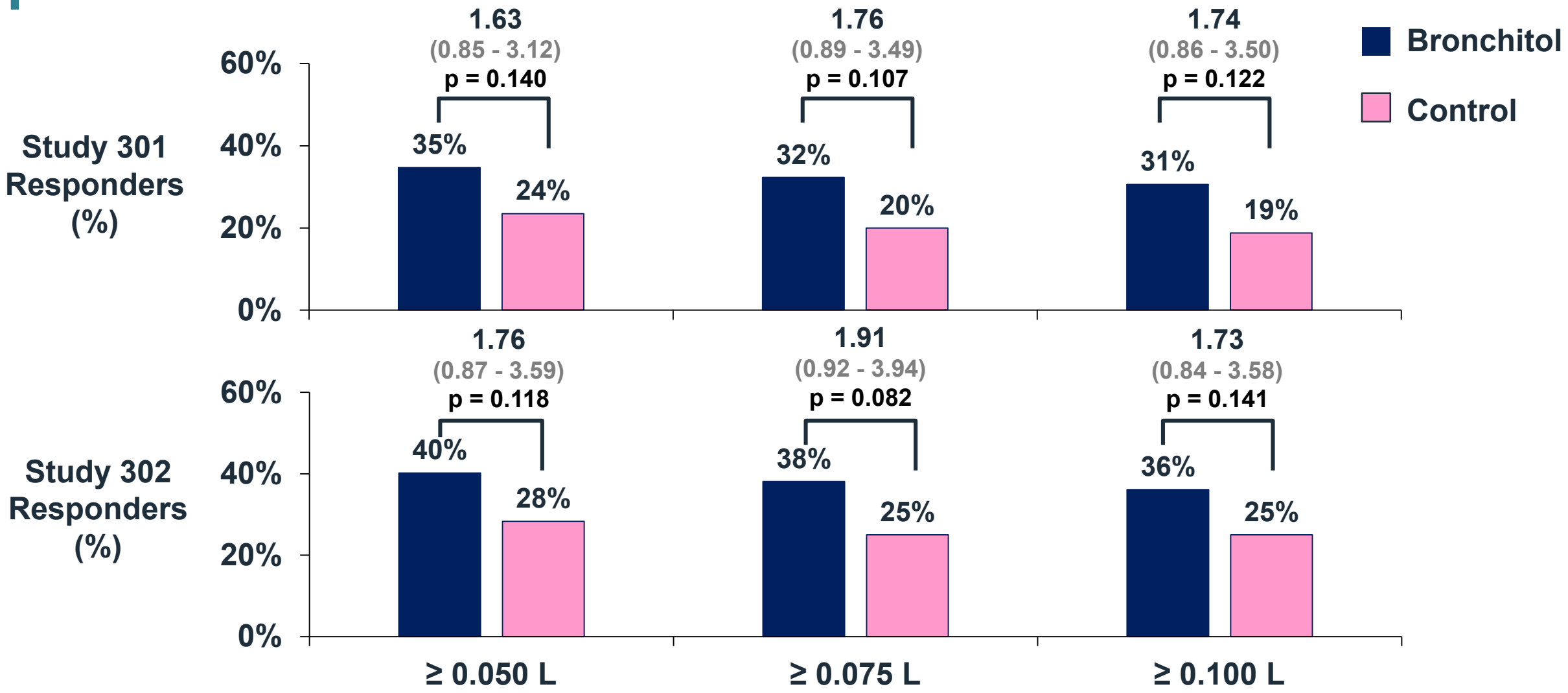


Bronchitol Provided Improved FEV_1 Responder Rate at Week 26 (Study 303)

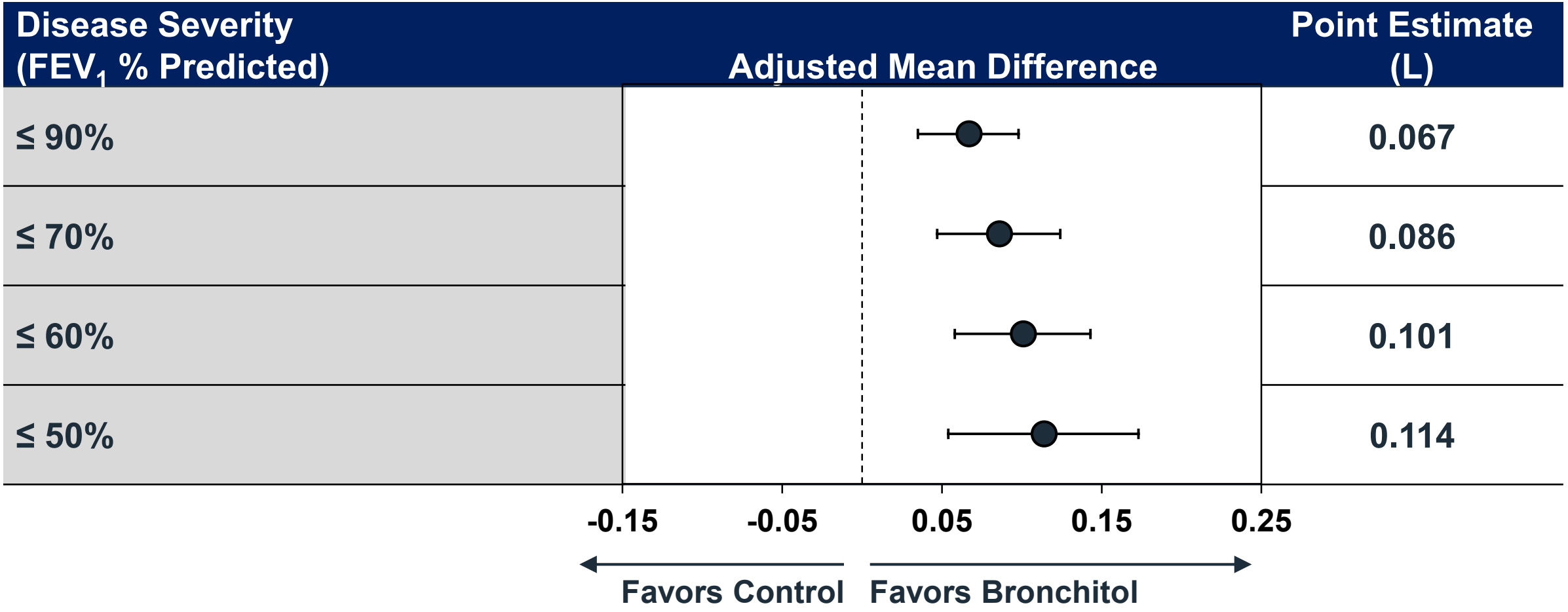


Logistic regression model: patients without week 26 data considered non-responders

Studies 302 and 301 Similar Results to Study 303: Improved FEV_1 Responder Rate at Week 26



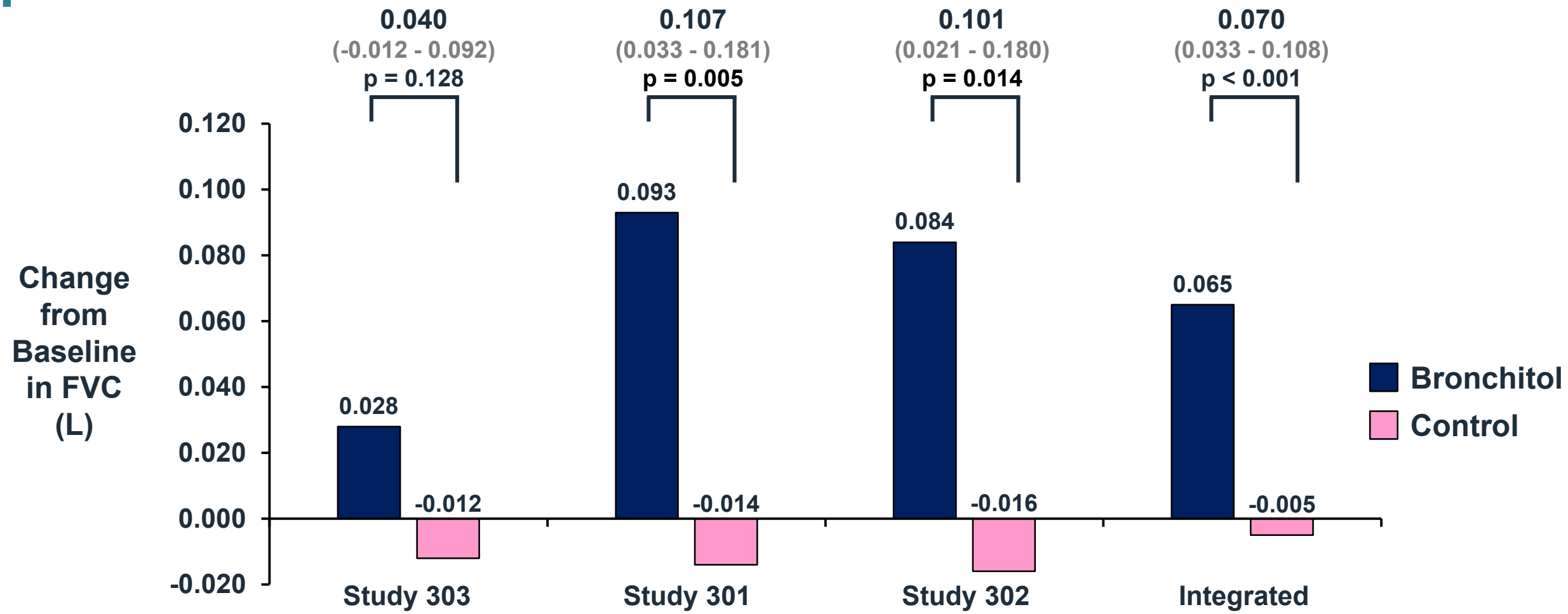
Treatment Effect By Severity Over 26-Weeks (Integrated Analysis)



Efficacy Agenda

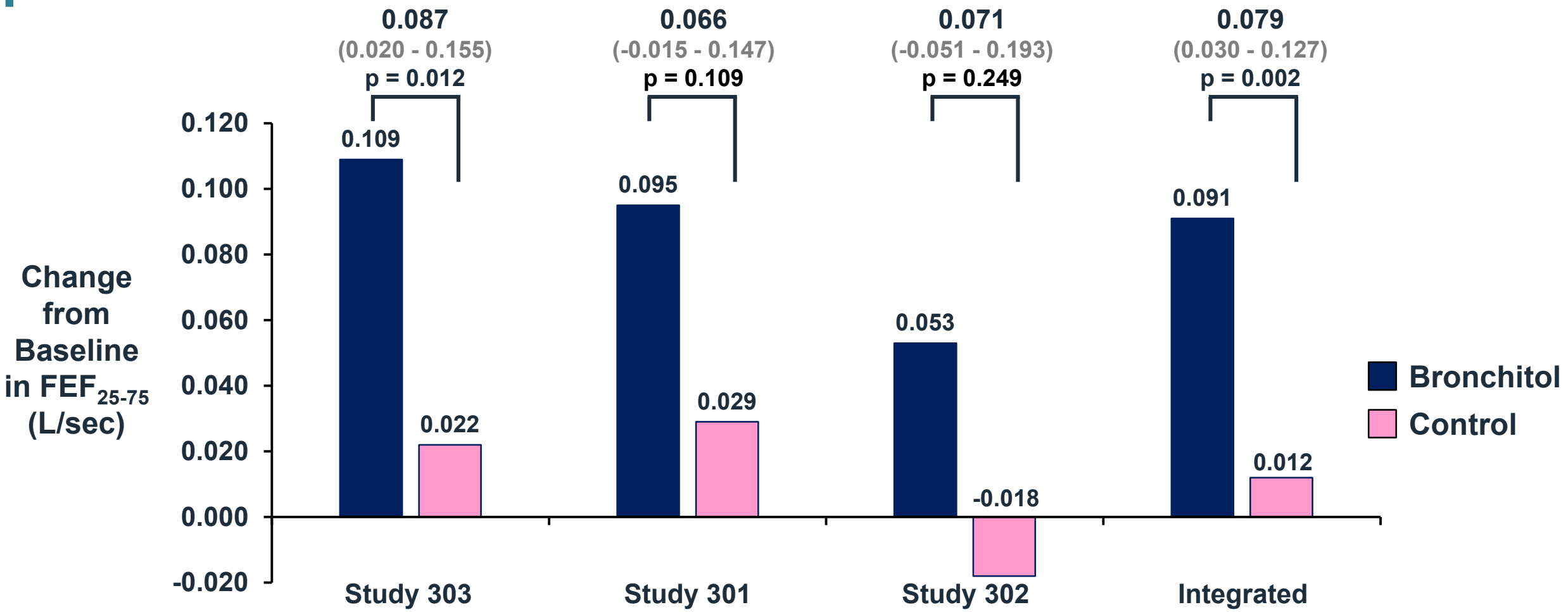
- Overview of Phase 3 clinical studies
- Primary study results
- Sensitivity analyses
- Other pulmonary function results
- Other clinical endpoints (PDPE and CFQ-R)

FVC Improvement Over 26 Weeks Supports Consistent Benefit of Bronchitol



MMRM with BOCF based on dropout reasons

FEF_{25-75} Improvement Over 26 Weeks Supports Benefit of Bronchitol



MMRM with BOCF based on dropout reasons

Efficacy Agenda

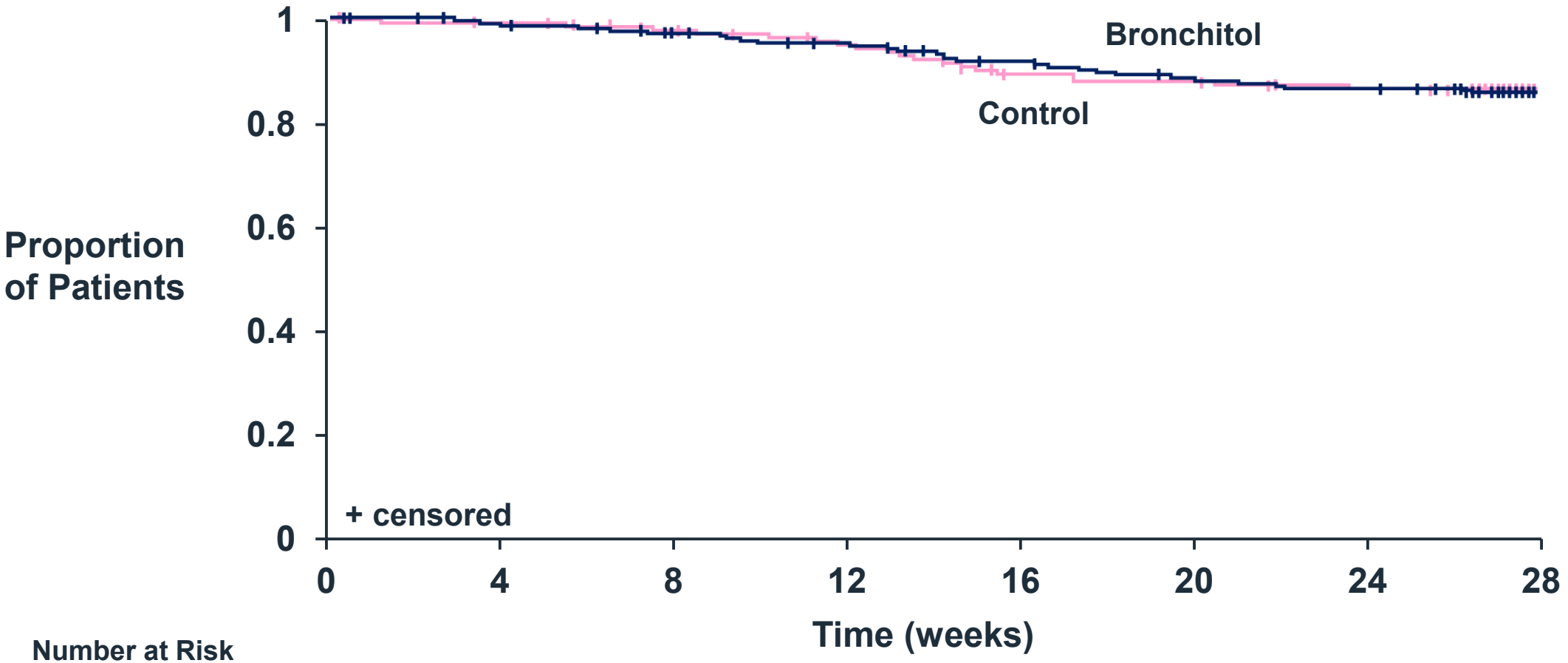
- Overview of Phase 3 clinical studies
- Primary study results
- Sensitivity / responder analyses
- Other pulmonary function results
- Other clinical endpoints (PDPE and CFQ-R)

Low Rate of PDPEs

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Reported PDPEs								
% of patients ≥ 1 PDPE	**13%**	**14%**	21%	32%	15%	13%	16%	18%
# of PDPE events	**34**	**29**	**35**	**37**	**18**	**8**	**87**	**74**
PDPE Rate								
Adjusted PDPE rate per patient / year	**0.257**	**0.215**	0.719	0.995	0.350	0.221	0.393	0.388
Adjusted rate ratio (95% CI) p-value	**1.194 (0.714, 1.997) p = 0.499**		0.723 (0.425, 1.231) p = 0.232		1.582 (0.681, 3.672) p = 0.286		1.014 (0.725, 1.420) p = 0.934	

Negative binomial model without imputation

No Difference in Time to First PDPE (Study 303)



Number at Risk								
Bronchitol	209	201	192	184	173	165	161	75
Control	214	210	203	194	176	173	168	82

Change in CFQ-R Respiratory Domain Over 26 Weeks

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=209	**Control N=214**	Bronchitol N=124	Control N=85	Bronchitol N=97	Control N=60	Bronchitol N=430	Control N=359
Change from Baseline over 26 Weeks								
Adjusted Mean	**-0.94**	**-1.86**	-2.10	-4.25	0.02	-0.56	-0.19	-0.34
Adjusted Mean Difference (95% CI) p-value	**0.58 (-1.76, 2.92) p = 0.627**		0.92 (-3.43, 5.28) p = 0.676		2.15 (-13. 66, 17.97) p = 0.748		0.16 (-1.77, 2.09) p = 0.871	

MMRM without imputation

CFQ-R Change from Baseline Over 26 Weeks – More Symptomatic Patients (Baseline CFQ-R Score ≤ 50)

	Study 303		Study 301		Study 302		Integrated	
	Bronchitol N=45	**Control N=46**	Bronchitol N=17	Control N=14	Bronchitol N=18	Control N=17	Bronchitol N=80	Control N=77
Baseline (mean)	**42.0**	**36.7**	37.6	34.9	38.9	37.6	40.3	36.6
Change from baseline								
Adjusted mean	**16.4**	**11.9**	10.4	7.6	19.6	15.6	15.7	11.3
Adjusted mean difference (95% CI)	**4.50 (-1.13, 10.14)**		2.91 (-10.24, 16.05)		4.00 (-7.01, 15.00)		4.42 (-0.12, 8.96)	

MMRM without imputation

Quittner, A, 2009. MCID of 4.0 on CFQ-R

Summary of Bronchitol Efficacy

- Demonstrated clear, consistent, improvements in FEV_1
  - Greater improvement seen in more severe patients
  - Results confirmed in multiple sensitivity and responder analyses
- Secondary lung function endpoints support primary results
- PDPE: similar between arms
  - Very few exacerbations during study
- CFQ-R: similar between arms
  - Improvement seen in more symptomatic patients

Safety of Bronchitol

W. James Alexander, MD, MPH

Chiesi Medical Affairs

Senior Medical Consultant

Safety Profile of Bronchitol is Well Characterized in Adults with CF

- Three Phase 3 studies similar designs, pooled data
- Overall safety profile
- Safety profile in open-label extension
- Adverse events of special interest
  - Pulmonary exacerbations* in US and non-US subpopulations

*Coded as condition aggravated

508 Adult Patients Treated with Bronchitol 400 mg BID in Phase 3 Studies

	Patients (N)
Underwent mannitol tolerance test (MTT)	896
Passed mannitol tolerance test (MTT)	824
Randomized and treated with Bronchitol in double-blind phase (DBP)	414
Control patients treated with Bronchitol in open-label extension (OLE)	94
Total patients treated with Bronchitol 400 mg BID (study or extension)	508

Overall AE Profile was Similar Between Bronchitol and Control

Patients with	Bronchitol N=414	Control N=347
≥ 1 AE	78%	74%
≥ 1 severe AE	13%	13%
≥ 1 SAE	19%	18%
≥ 1 AE leading to discontinuation of study drug	12%	9%
AE with fatal outcome	0	0.3%

Similar Incidence of AEs (≥ 5% of Patients) with Bronchitol or Control

Patients with	Bronchitol N=414	Control N=347
≥ 1 AE	78%	74%
Pulmonary exacerbation*	32%	33%
Cough	15%	11%
Headache	11%	14%
Hemoptysis	10%	10%
Nasopharyngitis	7%	7%
Pharyngolaryngeal pain**	7%	4%
Bacteria sputum identified	7%	5%
Upper respiratory tract infection	6%	6%
Lower respiratory tract infection	4%	5%

*Coded as condition aggravated
**Coded as oropharyngeal pain

Similar Occurrence of SAEs with Bronchitol or Control (≥ 1% of Patients)

Patients with	Bronchitol N=414	Control N=347
≥ 1 SAE	19%	18%
Pulmonary exacerbation*	13%	11%
Hemoptysis	1%	1%
Lower respiratory tract infection	1%	0.9%
Pneumonia	0.2%	1%

*Coded as condition aggravated

AEs Leading to Study Drug Discontinuation

Patients with	Bronchitol N=414	Control N=347
≥ 1 AE leading to study drug discontinuation	12%	9%
Cough	5%	3%
Pulmonary exacerbation*	3%	3%
Hemoptysis	2%	1%
Chest discomfort	1%	1%
Wheezing	0.2%	1%
Bronchospasm	0.5%	0
Pharyngolaryngeal pain**	0.5%	0

*Coded as condition aggravated
**Coded as oropharyngeal pain

Overall AE Profile of Bronchitol Treatment During 6-12 Month Open Label Extension

Patients with	Bronchitol OLE N=224
≥ 1 AE	87%
≥ 1 severe AE	15%
≥ 1 SAE	25%
≥ 1 AE leading to discontinuation of study drug	7%
AE with fatal outcome	0

Patients from Studies 301 and 302

Safety Profile of Bronchitol is Well-Characterized in Adults with CF

- Three Phase 3 studies similar, pooled data
- Overall safety profile
- Safety profile in open-label extension
- Adverse events of special interest
  - Pulmonary exacerbations* in US and non-US subpopulations

*Coded as condition aggravated

Adverse Events of Special Interest

Patients with ≥ 1 AE	Bronchitol N=414	Control N=347
Cough and/or productive cough	17%	12%
Pharyngolaryngeal pain*	7%	4%
Hemoptysis	10%	10%
Bronchospasm	1%***	0.6%
Pulmonary exacerbation**	32%	33%

*Coded as oropharyngeal pain
**Coded as condition aggravated
***Preferred terms of bronchospasm and bronchial hyperreactivity

FDA Briefing Book Table 33: Studies 301, 302, and 303 Pooled, Exacerbations, US and Non-US Subgroups, Patients ≥ 18 Years

CF Exacerbations	Studies 301, 302, 303 Pooled			
	US Population		Non-US Population	
	Bronchitol N=110	Control N=93	Bronchitol N=304	Control N=254
SAEs	23 (21%)	10 (11%)	32 (11%)	29 (11%)
Any exacerbation	42 (38%)*	33 (36%)	90 (30%)	81 (32%)

*Denotes correction, FDA Table 33 reported 42 (24%)

More US Bronchitol Patients had Prior History of PE

Baseline Characteristics	US Population		Non-US Population*	
	Bronchitol N=110	Control N=93	Bronchitol N=190	Control N=178
≥ 1 PE hospitalization in 12 months prior to screening	45%	38%	38%	35%
≥ 2 PE hospitalization in 12 months prior to screening	20%	14%	13%	15%

- Similar imbalance seen in US patients with PE requiring IV antibiotics in 12 months prior to screening

*Includes studies 303 and 302, no data on previous hospitalizations or administration of IV antibiotics available for study 301

Most Exacerbation SAEs Occurred in Patients with Prior History of PE

Patients with CF Exacerbations	US Population		Non-US Population*	
	Bronchitol N=110	Control N=93	Bronchitol N=190	Control N=178
SAEs	23 (21%)	10 (11%)	10 (5%)	12 (7%)
History of ≥ 1 PE hospitalization in 12 months prior to screening	21	6	9	7

*Includes studies 303 and 302, no data on previous hospitalizations available for study 301

Pulmonary Exacerbations: Not a Unique Risk Related to Bronchitol in US Patients

- US subpopulation data need to be interpreted with caution
- Imbalances at baseline in US patients for prior PEs further confound interpretation of this small subset
- Overall safety population shows no increase in risk of PE with Bronchitol treatment

Summary of Bronchitol Safety in Adult CF Patients

- Bronchitol was generally well-tolerated
- Cough and pharyngolaryngeal pain more frequent with Bronchitol
  - Cough expected due to mechanism of action
  - Pharyngolaryngeal pain expected due to local mucosal effects
- Other AESIs similar between arms
  - Hemoptysis
  - Bronchospasm
  - Pulmonary exacerbations
- Safety supported by 8 years of post-marketing data and 5-year registry study conducted by UK CF trust

Bronchitol: A Clinician's Perspective

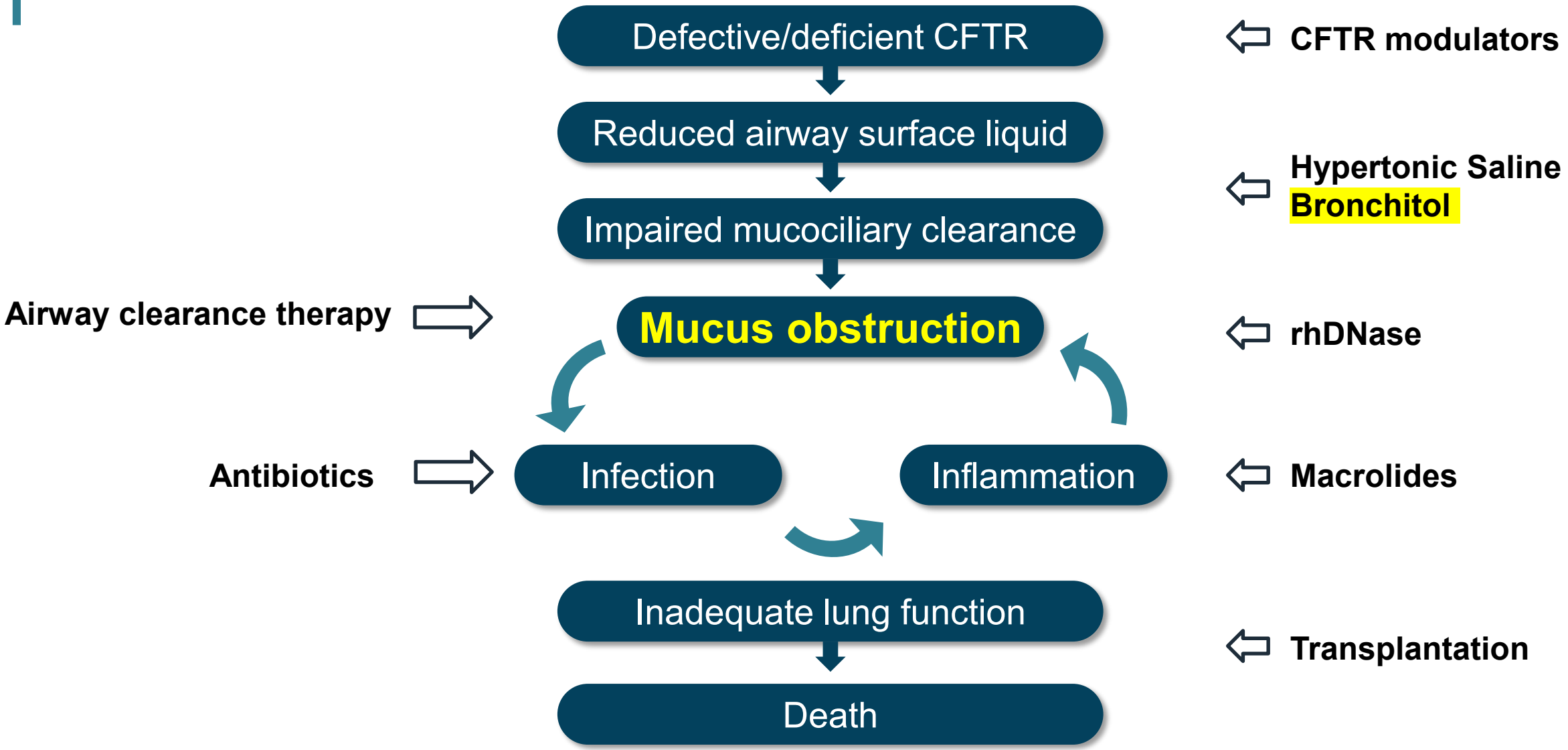
Patrick A. Flume, MD

Professor of Medicine and Pediatrics

Medical University of South Carolina

The Powers-Huggins Endowed Chair for Cystic Fibrosis

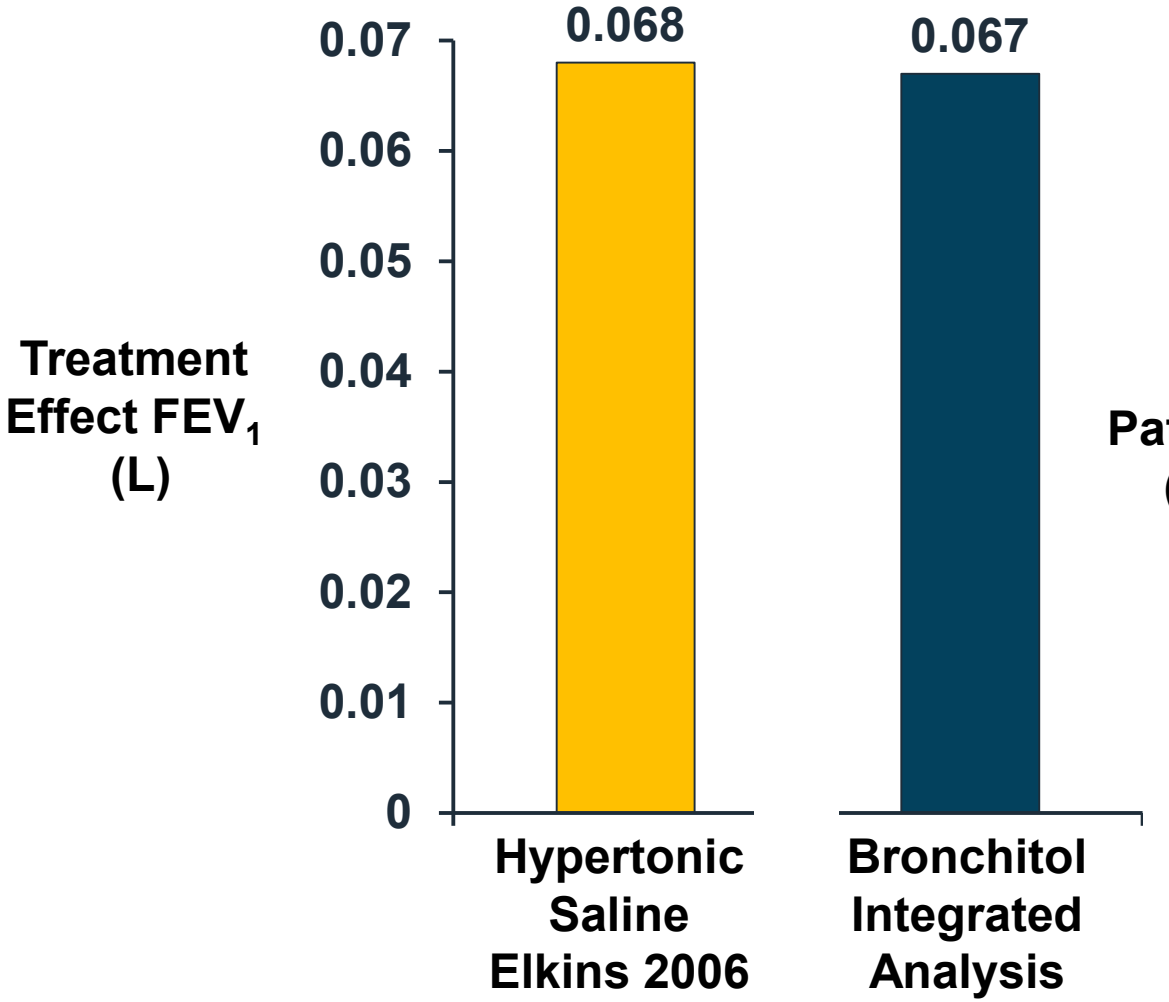
Bronchitol Targets Airway Clearance Complementing Other Recommended Therapies

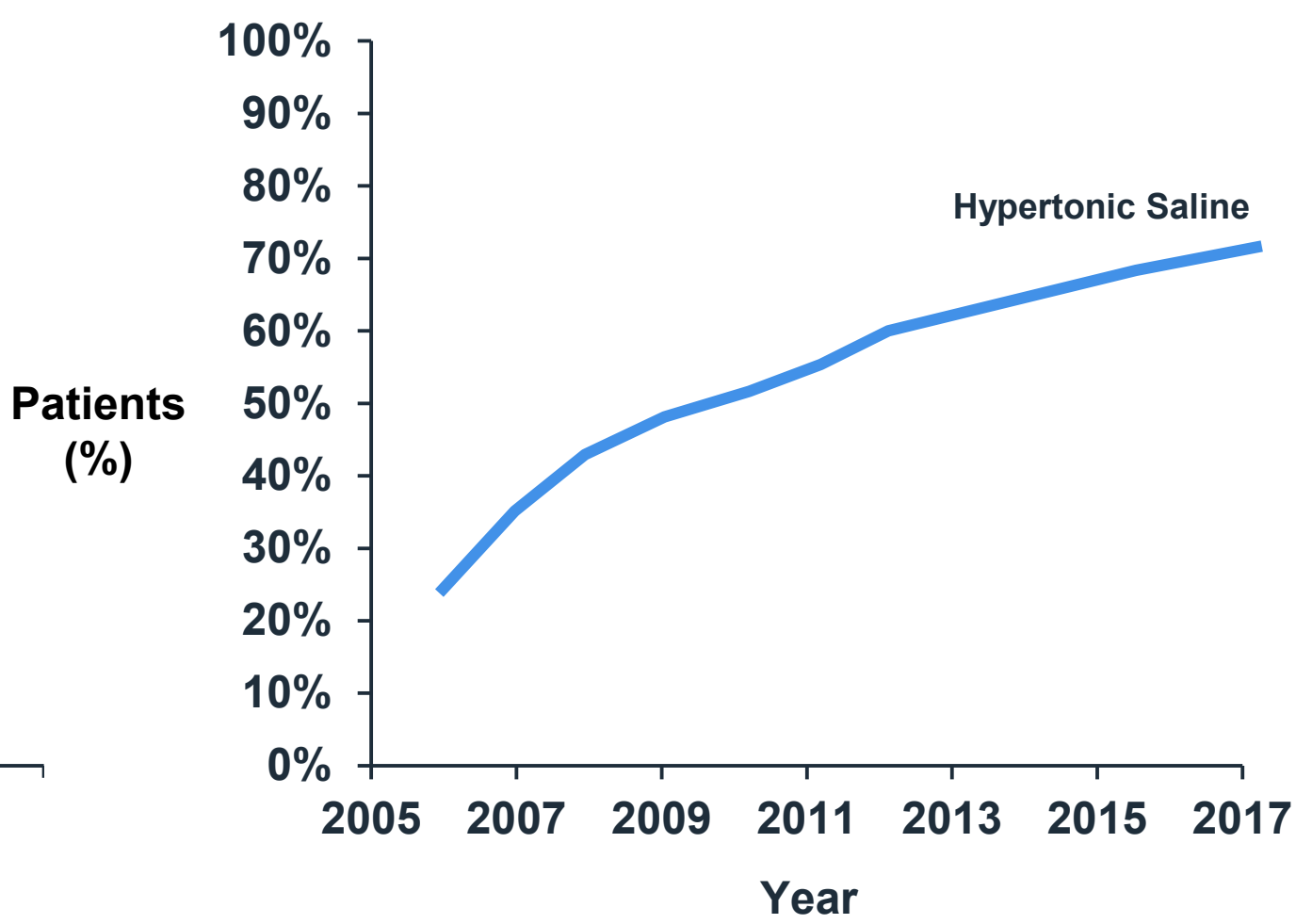


How the CF Clinician Looks at a New Therapeutic Option

- What is the evidence for efficacy?
- What is the safety and tolerability of the therapy?
- When and how will I introduce it into my patient's regimen?

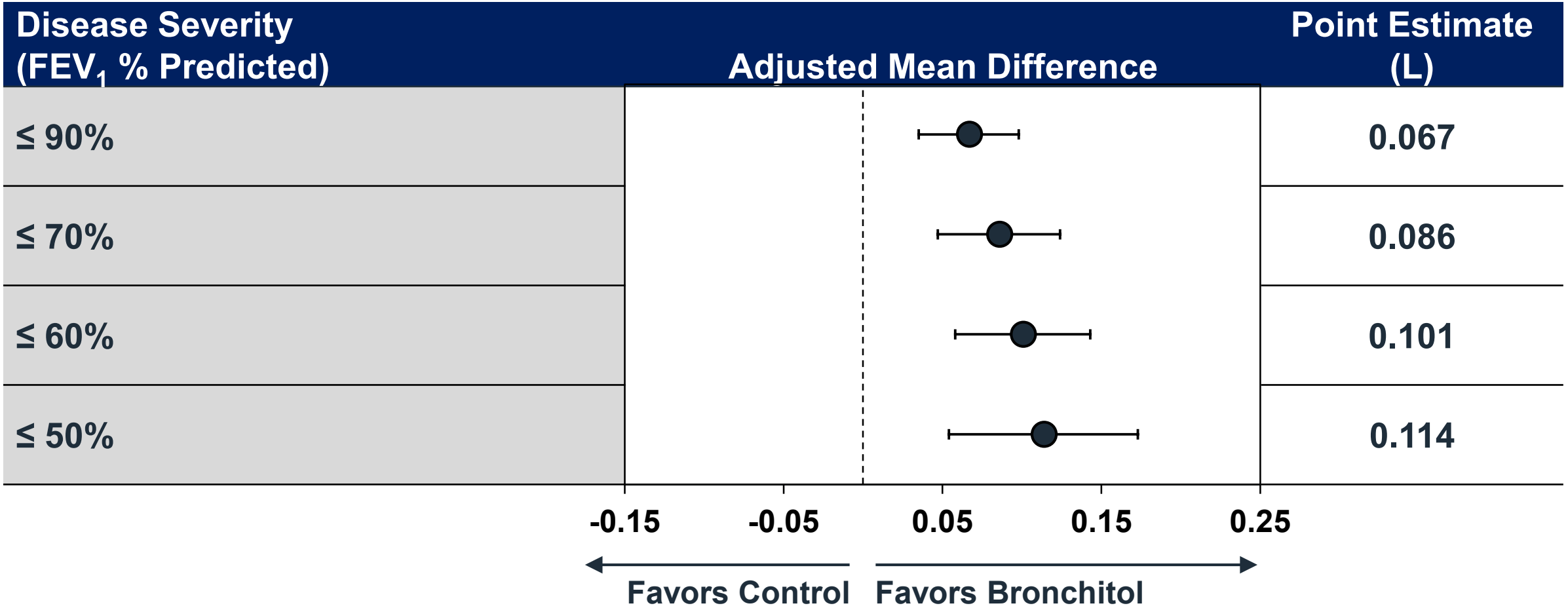
Evidence to Support a Clinically Meaningful FEV_1 Improvement





Cystic Fibrosis Foundation Patient Registry, Annual Data Report, 2017.

Treatment Effect by Severity Over 26-Weeks (Integrated Analysis)



How the CF Clinician Looks at a New Therapeutic Option

- What is the evidence for efficacy?
- What is the safety and tolerability of the therapy?
- When and how will I introduce it into my patient's regimen?

Safety and Tolerability of New Therapy

- Some patients cannot tolerate introduction of a medication, whether by nebulized solution or by powder
  - Can be mitigated with information and improvement in patient techniques
  - Mannitol tolerance test identifies patients who experience bronchospasm and those patients will not receive treatment

No Differences in Risk of Pulmonary Exacerbations

Integrated Safety Dataset (% of Patients)	Bronchitol N=414	Control N=347
Pulmonary exacerbation* (any)	32%	33%
Pulmonary exacerbation* (SAEs)	13%	11%

*Coded as condition aggravated

How the CF Clinician Looks at a New Therapeutic Option

- What is the evidence for efficacy?
- What is the safety and tolerability of the therapy?
- When and how will I introduce it into my patient's regimen?

Physician / Patient Discussion Regarding Current Regimens

- CFTR modulators shown great results
- Patients ask what therapies they may stop
- Patients most interested in stopping therapies that
  - Take the most time
  - Require most effort in setup and cleaning
- Need options to individualize therapy

Advantages of Bronchitol Therapy

- Low treatment burden
  - Portable
  - ~ 5 minute treatment
  - Minimal set-up
  - Minimal cleaning
  - No refrigeration required
- Conveniently fits lifestyle of patients

Why Would Patients Choose Bronchitol?

- Reduced treatment time
- Portable option
- Discrete
- Does not require a nebulizer
- May increase adherence to therapy

Bronchitol: Viable Treatment Option with Positive Benefit-Risk Profile

Mechanism	Efficacy	Safety	Patient Utility
Bronchitol's MoA confirmed to clear mucus	Consistent and clinically relevant improvements in FEV_1	Acceptable safety and tolerability	Easy to use, short administration time, portable

Bronchitol®
Inhaled Dry Powder Mannitol (DPM) for Adult Patients with Cystic Fibrosis

Chiesi USA, Inc.

Pulmonary-Allergy Drug Advisory Committee

May 8, 2019

Back-up Slides

Baseline Characteristics of US Patients with SAEs of Pulmonary Exacerbation (PE)*

	Bronchitol N=23	Control N=10
Percent predicted FEV_1, mean	56%	56%
Number of hospitalizations for PE in 12 months prior to screening:		
None	2	4
1	4	3
2	11	0
3	5	2
4	1	1
Prevalence of *P. aeruginosa* at screening	65%	50%

*Coded as condition aggravated

SAE of Pulmonary Exacerbation (PE)* -- 3-Fold Lower In Bronchitol Patients Without Prior History of Hospitalization (Pooled – Study 303 and 302)

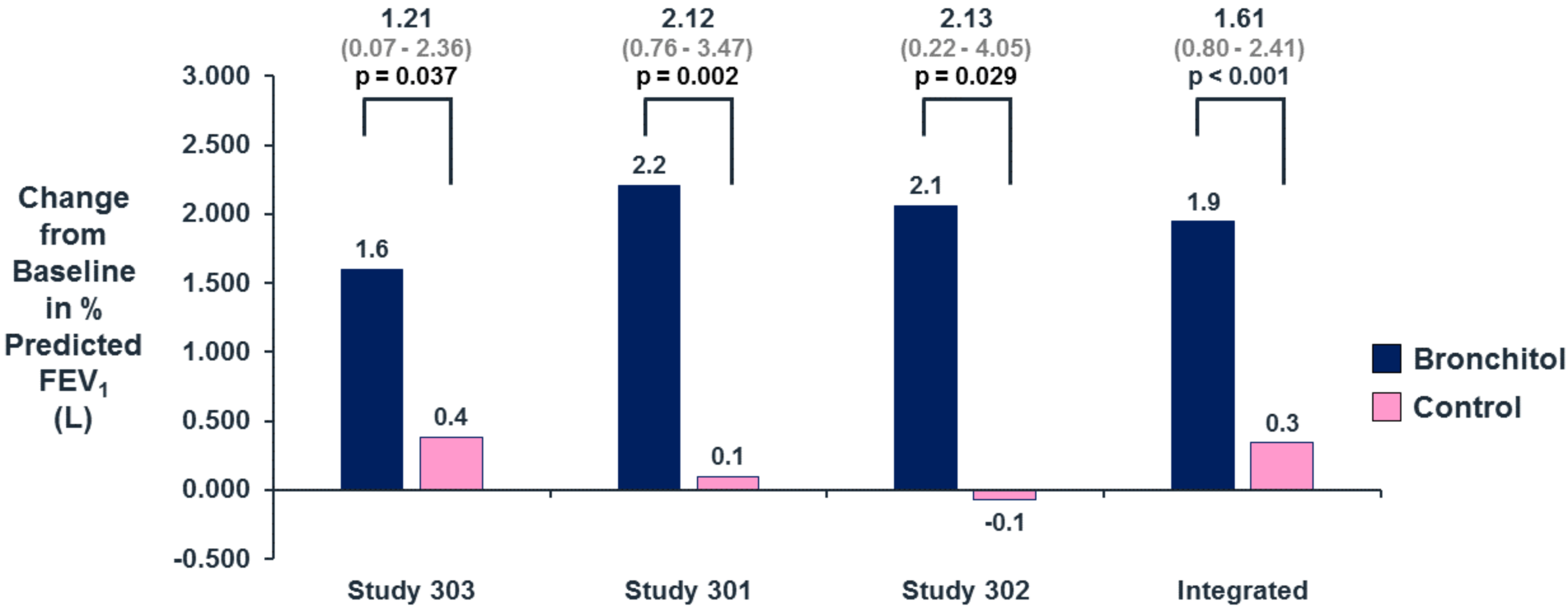
Patients in Studies 302 and 303 with:	Bronchitol	Control
NO hospitalization for PE in prior 12 months	178	173
One SAE of PE in DBP	3 (1.7%)	9 (5.2%)
Mild	1	1
Moderate	2	5
Severe	0	3
Day of Onset of PE (mean)	105	101
Percent predicted FEV1 (mean) at screening	55.2% [3 Pt]	51.3% [9 Pt]

*Coded as condition aggravated

Sample Size Assumptions (Study 303)

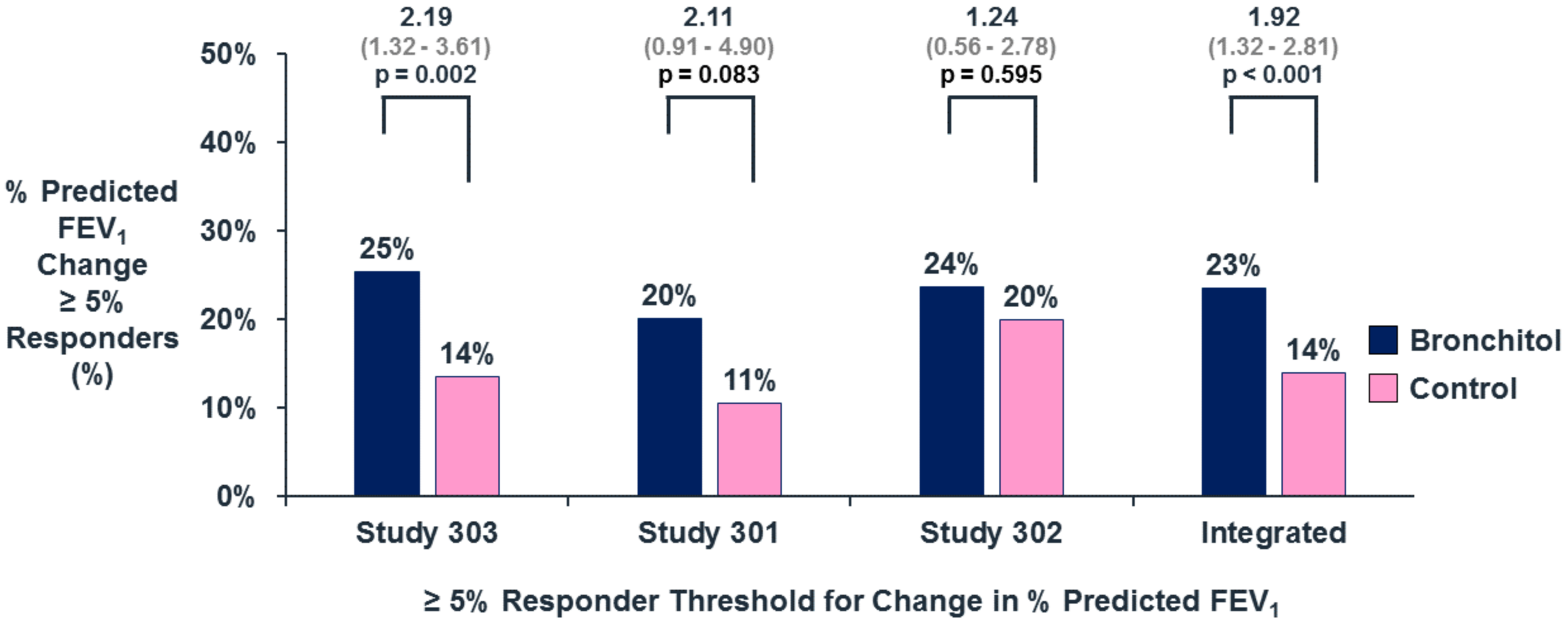
- Treatment difference: 80ml
- Standard deviation: 230ml
- Power: 90%, 2-sided alpha: 0.05
- 350 randomized patients
- Assumptions based on 301, 302 effect and SD observed for completers
- Blinded sample-size reassessment pre-planned due to uncertainty about SD

Change from Baseline in % Predicted FEV_1 Over 26 Weeks Favored Bronchitol

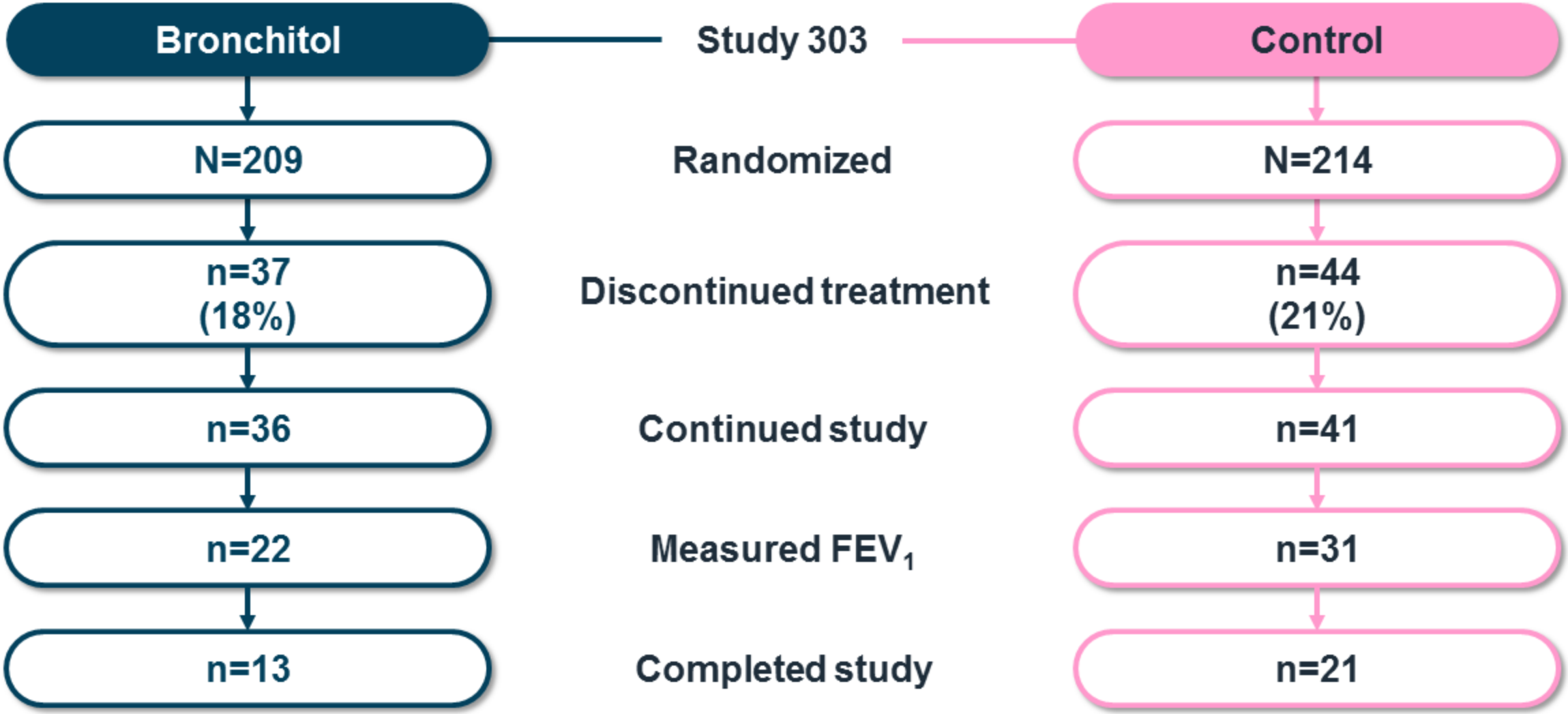


Mixed Model Repeated Measures (MMRM) with BOCF based on dropout reasons

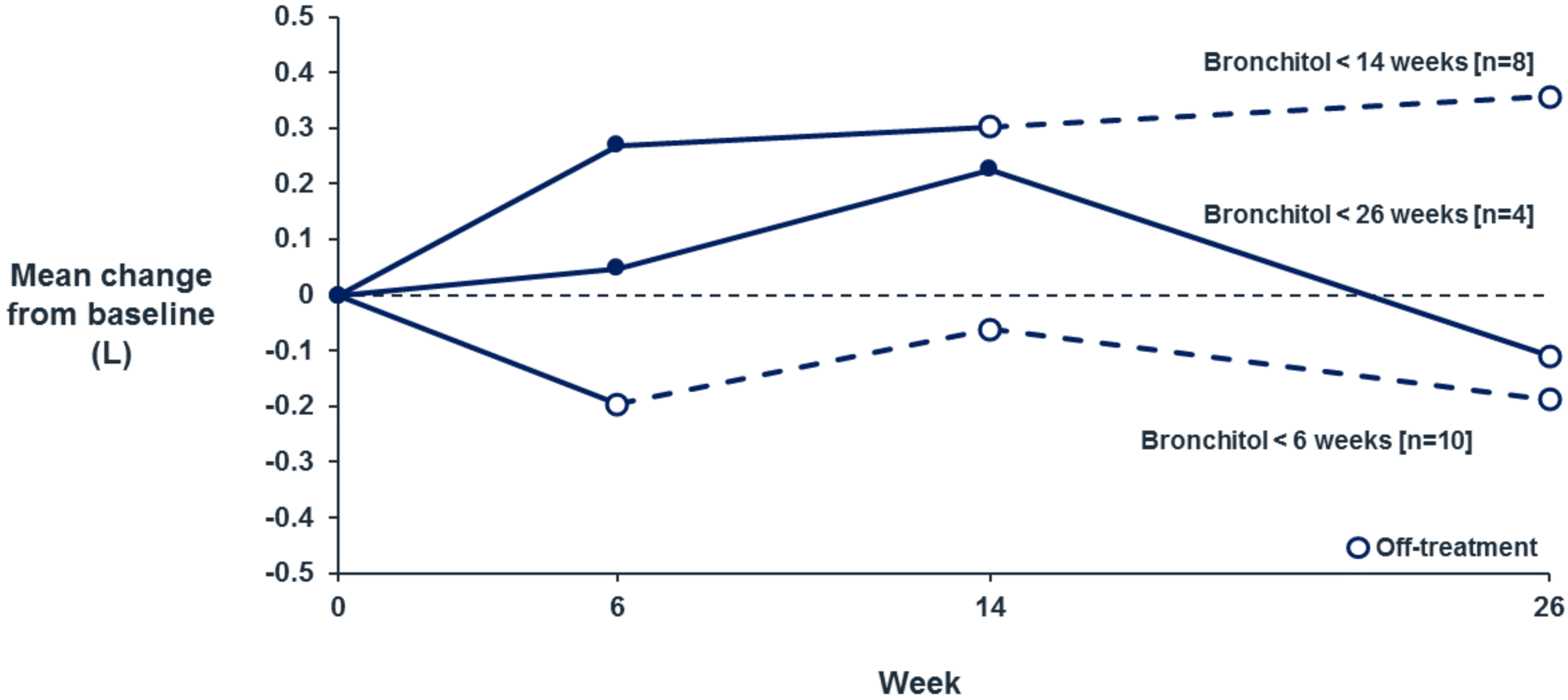
Bronchitol Provided Improved % Predicted FEV_1 ≥ 5% Responder Rate at Week 26



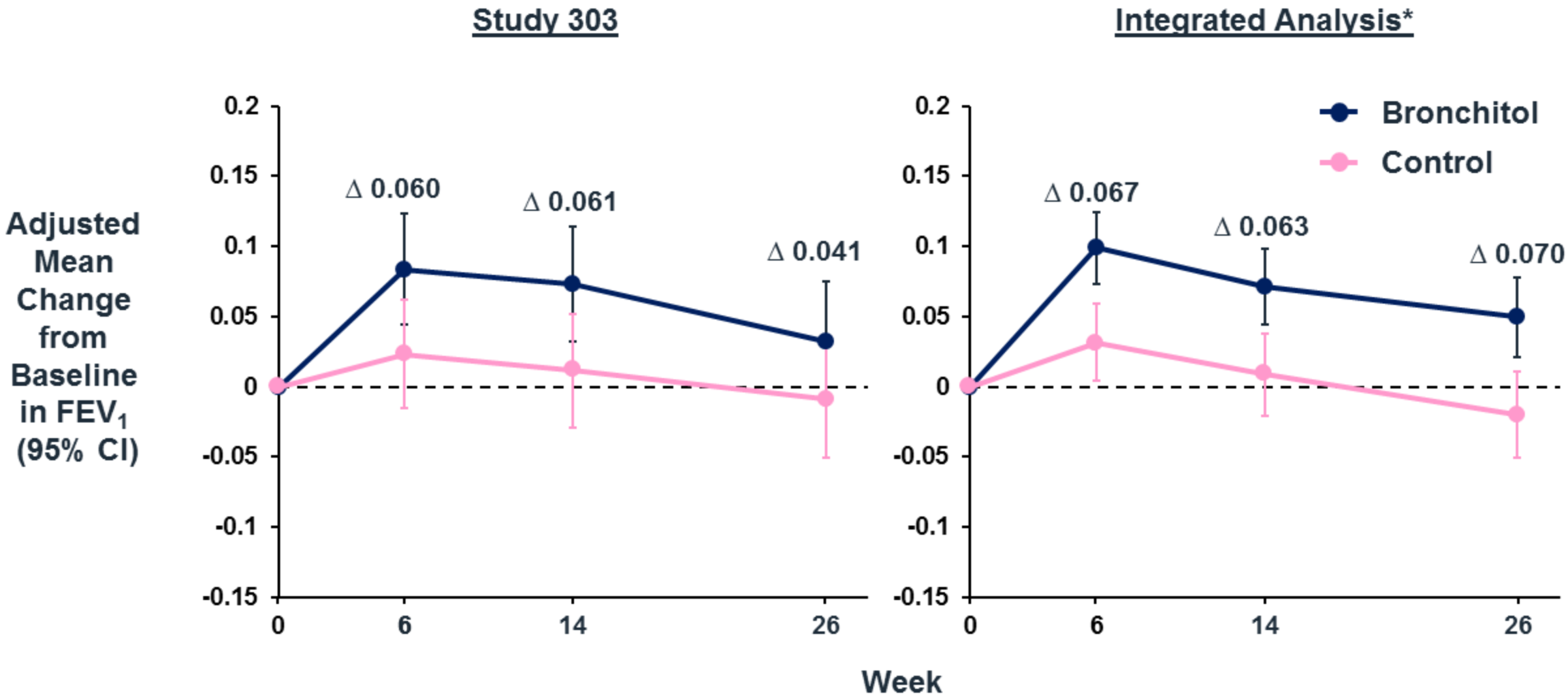
Study 303: Patients Discontinued Treatment But Continued in Study



FEV_1 Trend in Patients Who Discontinued Treatment But Continued in Study – Bronchitol

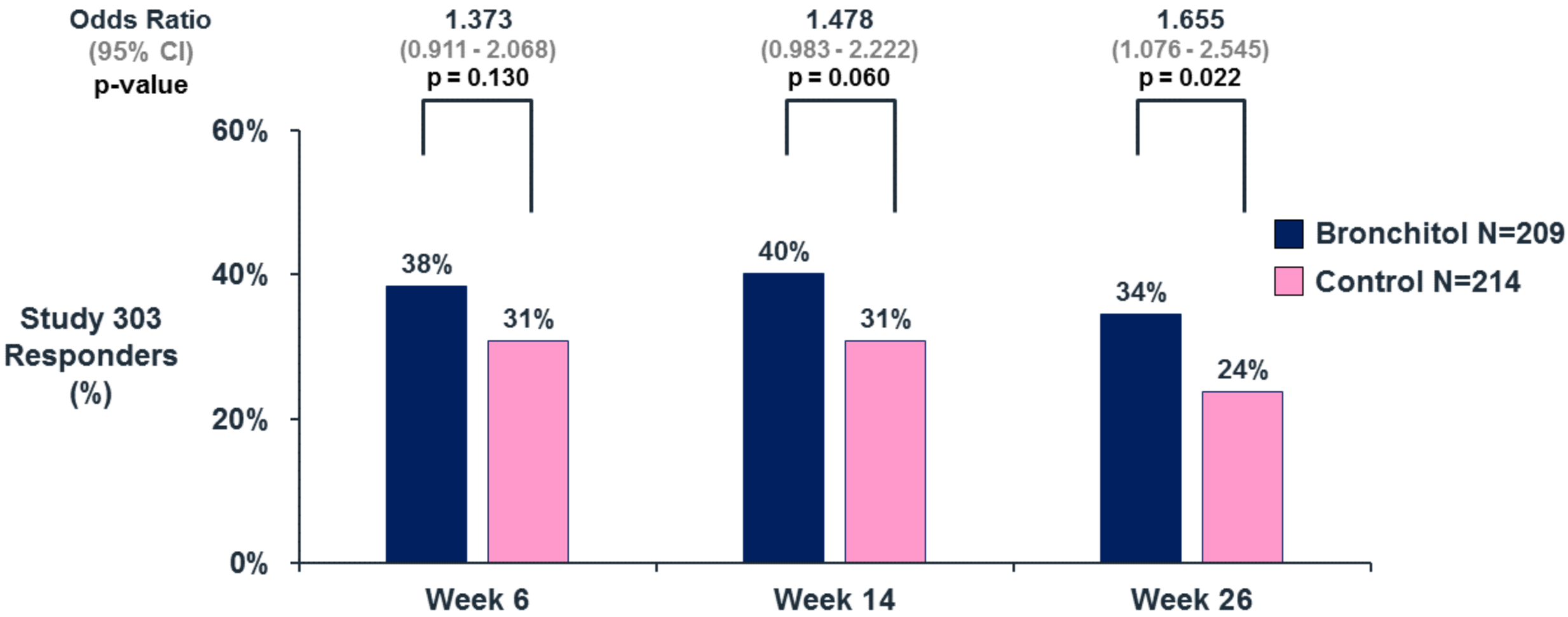


Change from Baseline in FEV_1 Over 26 Weeks (Study 303 and Integrated Analysis)

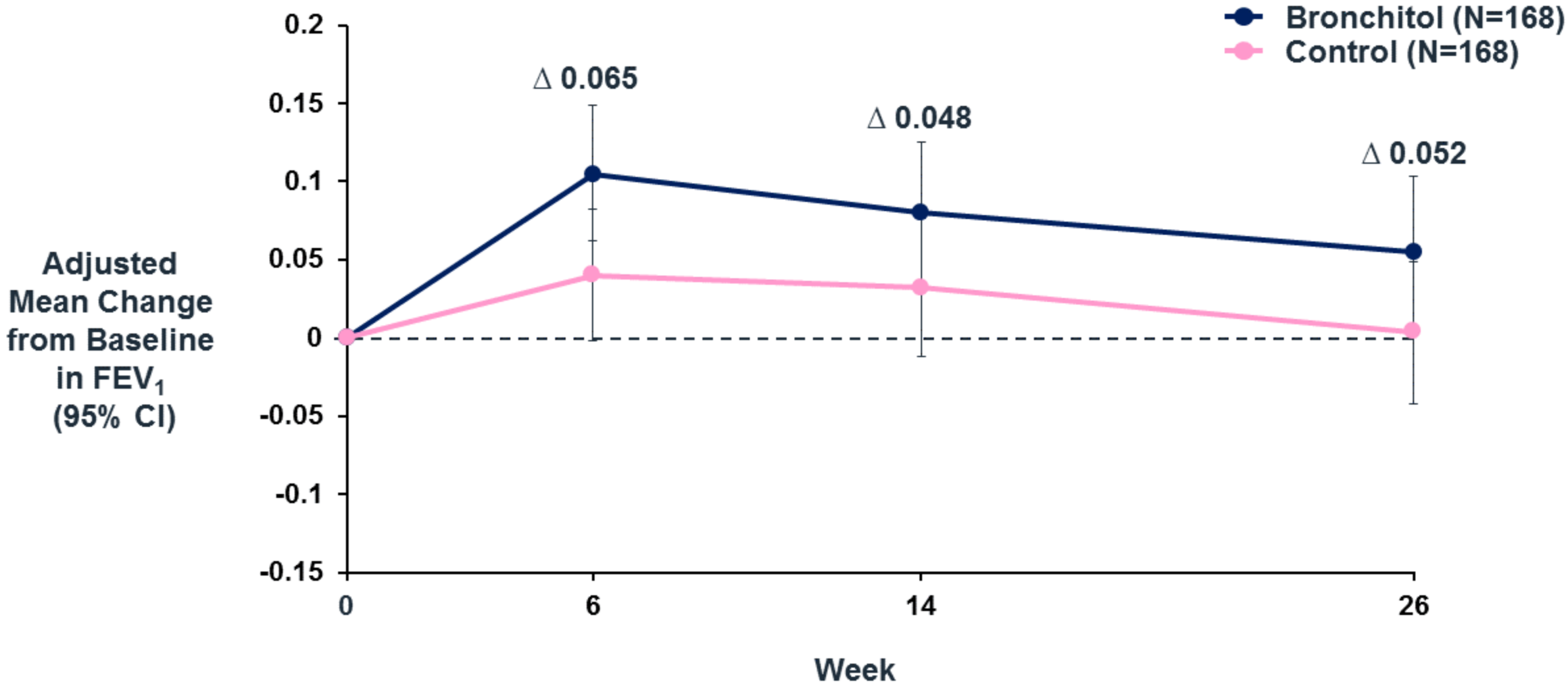


*Includes studies 303, 301 and 302

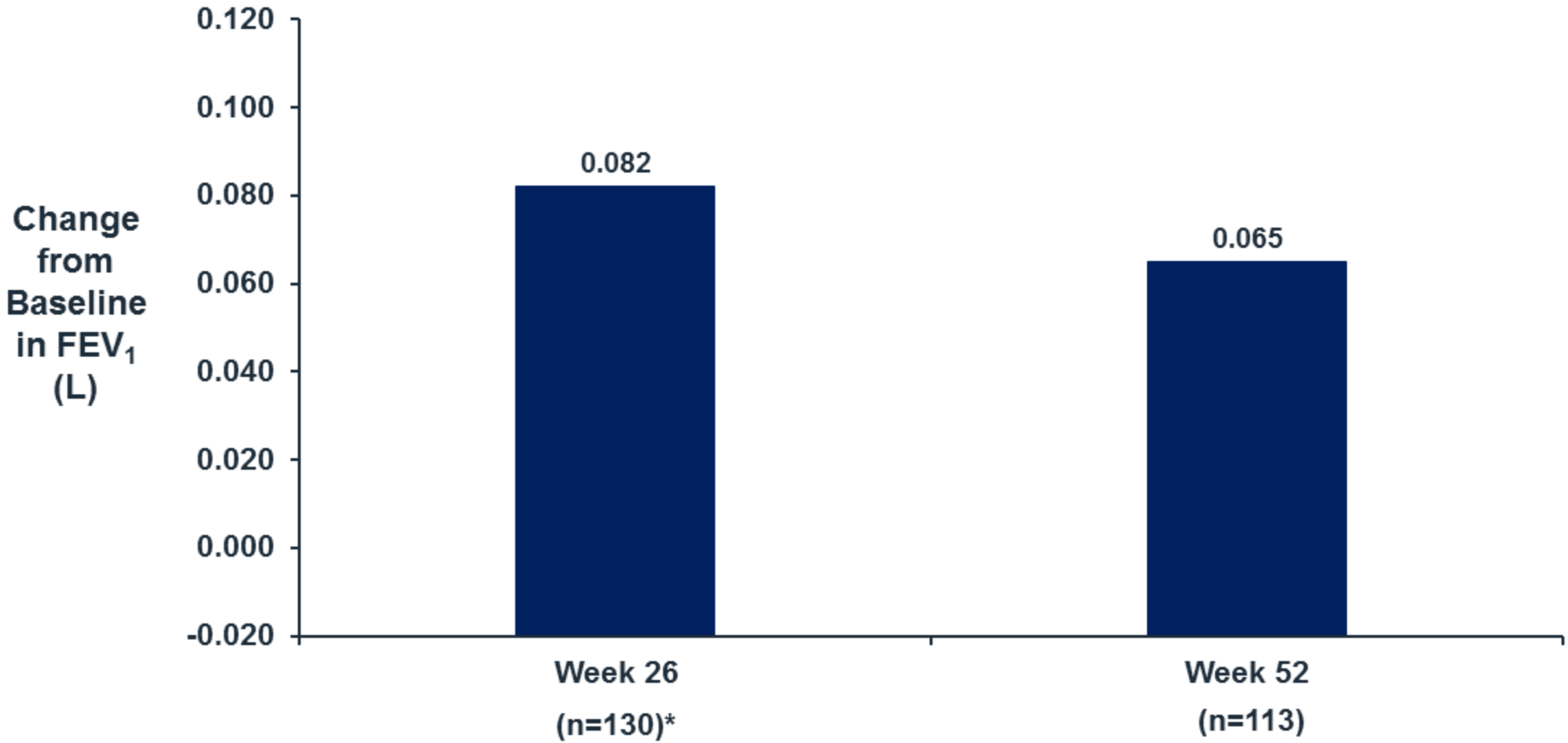
Bronchitol Provided Improved FEV_1 Responder (>100ml) Rate at Each Visit (Study 303)



Treatment Completers Analysis Supports Sustained Benefit at Each Visit (Study 303)



Long-Term Effect in Open-label Phase for Bronchitol (Pooled Study 301 and 302)



*Only subjects continuing the study in OLP are considered

Tipping Point Analysis Support Robustness of FEV_1 Results (Study 303)

- Penalties assigned for missing data to lose statistical significance

Penalty to control	Penalty required to Bronchitol for non-significance (p > 0.05)
0 L	- 0.100 L
- 0.020 L	- 0.100 L
- 0.040 L	- 0.120 L
- 0.060 L	- 0.140 L
- 0.080 L	- 0.140 L
- 0.100 L	- 0.160 L
…	…
- 0.240 L	- 0.240 L

Disease Characteristics - US and Non-US Patients (Study 303)

	US Patients		Non-US Patients	
	Bronchitol N=57	Control N=59	Bronchitol N=152	Control N=155
Mean time since diagnosis, years	24	24	18	19
Mean age at diagnosis, years	5	9	8	8
CFTR Mutation, (%)				
Both deltaF508	28%	29%	26%	20%
One deltaF508	58%	53%	38%	37%
% with PE treated with IV in last 12 months	51%	34%	47%	48%
% with PE requiring hospitalization in last 12 months	42%	30%	42%	39%
% with prior diagnosis of bronchiectasis	60%	59%	66%	68%
% with presence pseudomonas aeruginosa at screening	63%	60%	38%	37%

Lung Function and Symptoms at Baseline - US and Non-US (Study 303)

	US Patients		Non-US Patients	
	Bronchitol N=57	Control N=59	Bronchitol N=152	Control N=155
Mean FEV_1 at Baseline (L)	2.31	2.41	2.51	2.37
Mean % Predicted FEV_1 at Baseline	62%	65%	64%	62%
% Predicted FEV_1 at Baseline				
≤ 50%	23%	17%	25%	23%
> 50% to ≤ 70%	44%	44%	38%	49%
> 70%	33%	39%	38%	28%
Median baseline CFQ-R score	72	72	67	61

US and Non-US Patients: AE Profile (Pooled – All Phase 3 Studies)

Pulmonary exacerbation	US		Non-US	
	Bronchitol N=110	Control N=93	Bronchitol N=304	Control N=254
Any AE of Pulmonary exacerbation	38%	36%	30%	32%
SAE, n (%)	23 (21%)	10 (11%)	10 (5%)	12 (7%)
History of ≥ 1 PE hospitalization in 12 months prior to screening, n	21	6	9	7
Prevalence of P. aeruginosa	65%	50%	na	na

- Small number of events drove difference in SAE rate in US
- Pseudomonas rate higher in US - IV antibiotic use drives hospitalization
- Hospitalization results in AE coding of “Serious”
- Majority of events assessed as mild or moderate

Rate of PDPE Sensitivity Analyses (Study 303)