Tudorza® Pressair®

(aclidinium bromide inhalation powder)

NDA #202-450

Pulmonary-Allergy Drugs Advisory Committee Meeting

February 23, 2012

Introduction

Lisa Travis, MS, RAC

Senior Director, Regulatory Affairs
Forest Research Institute, Inc.

Aclidinium Bromide

- Novel, potent, long-acting anticholinergic bronchodilator
- Long residence time at M_3 receptor → long duration of action
- Rapid plasma hydrolysis → low systemic exposure and rapid clearance
- Low potential for drug-drug interactions
- Important new treatment option in the armamentarium of COPD therapies
- Demonstrated clinical safety and effectiveness of the 400 µg BID dose

Aclidinium Bromide

Proposed indication statement

Aclidinium bromide inhalation powder 400 µg BID is indicated for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema

Pressair® Dry Powder Inhaler Device

- Convenient and easy to use
  - Small and portable
  - No need to load capsules
  - Press and breathe

- Successful dosing is confirmed
  - Tactile, visual, and auditory cues
- Works reliably in patients including those with advanced COPD

Aclidinium Bromide

Clinical development overview

- **Global program**
  - **26 countries**
  - **5 continents**
- **Large clinical database**
  - **25 clinical studies**
  - **6,490 subjects total**
  - **4,907 patients treated with aclidinium bromide for at least 12 weeks**
  - **60% of patients exposed in North America**

Aclidinium Bromide

Regulatory history

- 2003: File US IND
- 2009: Pre-NDA meeting for QD program
  - FDA recommended further dose assessment with active comparator for benchmarking
- 2009: Start BID program
- 2011: File NDA

Presentation Overview

Introduction	***Lisa Travis, MS, RAC*** Senior Director, Regulatory Affairs Forest Research Institute, Inc.
Medical Need & Introduction to Aclidinium Bromide	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Aclidinium Investigator
Dose Finding & Efficacy	***Cynthia Caracta, MD, FCCP*** Director, Clinical Development - Respiratory Forest Research Institute, Inc.
Safety	***Harry Sacks, MD, FAAP*** Executive Director and Head Clinical Development - Respiratory Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Aclidinium Investigator

Experts Available to Advisory Committee

- **Stephen Rennard, MD, FCCP**
  Professor of Internal Medicine, University of Nebraska Medical Center,
  Aclidinium Bromide Investigator

- **Peter R. Kowey, MD**
  Professor of Medicine and Clinical Pharmacology, Jefferson Medical College,
  Chief - Division of Cardiovascular Diseases, Main Line Health System,
  The William Wikoff Smith Chair in Cardiovascular Research
  Wynnewood, Pennsylvania

- **Gary G. Koch, PhD**
  Department of Biostatistics, University of North Carolina at Chapel Hill,
  Chapel Hill, North Carolina

- **Samy Suissa, PhD**
  Professor of Epidemiology, Biostatistics & Medicine, McGill University,
  Director, Centre for Clinical Epidemiology, Lady Davis Research Institute –
  Jewish General Hospital, Montreal, Quebec

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Medical Need & Introduction to Aclidinium Bromide

Stephen Rennard, MD, FCCP

Professor of Internal Medicine
University of Nebraska Medical Center
Aclidinium Investigator

Prevalence and Impact of COPD in the United States

Prevalence[1]	~12-24 million
Emergency Department visits[2]	~2 million/year
Hospitalizations[3]	~700,000/year
Deaths[1]	~125,000/year

[1] Healthy People 2010. Progress Review; Respiratory Diseases. May 22, 2008.
[2] Ambulatory Medical Care Utilization Estimates for 2007; Vital and Health Statistics, Series 13, Number 169, April 2011.
[3] Breathing in America: Diseases, Progress, and Hope, 2010 (American Thoracic Society).

COPD Therapeutic Goals

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

- Minimize side effects from treatment

COPD Heterogeneity

- Clinical features
- Comorbidities
- Response to treatment
  - Drug preference
  - Drug tolerability

Long Acting Inhaled Bronchodilators a Cornerstone of COPD Management

- LAMA
  - Tiotropium (QD)
- LABA
  - Salmeterol (BID)
  - Formoterol (BID)
  - Arformoterol (BID)
  - Indacaterol (QD)

Long Acting Inhaled Bronchodilators a Cornerstone of COPD Management

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  - Indacaterol (QD)

Challenges with Current Therapies

- Side effects
- Device
- Personalized medicine

Long Acting Inhaled Bronchodilators a Cornerstone of COPD Management

- LAMA
  - Tiotropium (QD)
  - Aclidinium (BID)
- LABA
  - Salmeterol (BID)
  - Formoterol (BID)
  - Arformoterol (BID)
  - Indacaterol (QD)

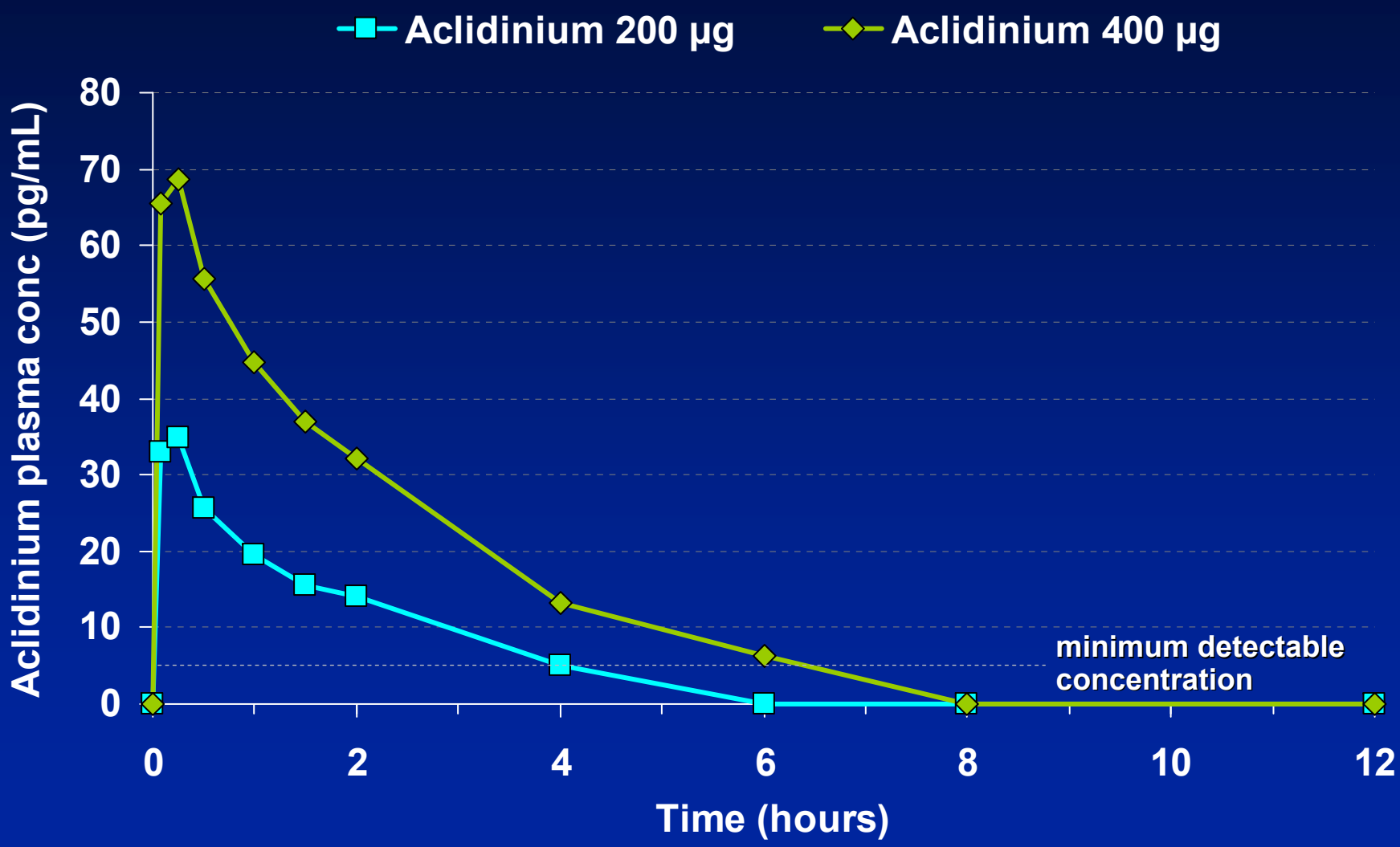
Challenges with Current Therapies

- Side effects
- Device
- Personalized medicine

Clinical Observations are Supported by the Pharmacology of Aclidinium

- High affinity and long residence time at M_3 receptor
- BID bronchodilator
- Rapidly metabolized by plasma cholinesterases
  - Low systemic exposure

Concentration over Time in vivo



Effect of Intrinsic/Extrinsic Factors on PK

- **No food effect**
  - Minimal oral absorption of aclidinium
- **No drug-drug interactions expected**
  - Owing to extremely low (pg/mL) systemic exposure
  - No relevant CYP450 involvement
- **No renal impairment effect on PK**
- **No dose adjustments required for hepatic impairment**
  - No hepatic metabolism
  - Primary route of metabolism is chemical and enzymatic hydrolysis
- **No age or gender effect on PK**

Aclidinium Bromide for COPD Patients

- Long acting anti-muscarinic bronchodilator
- Twice daily treatment option
- Simple device
- Very low systemic exposure
- COPD
  - Common
  - Heterogeneous
  - Treatable
  - Options

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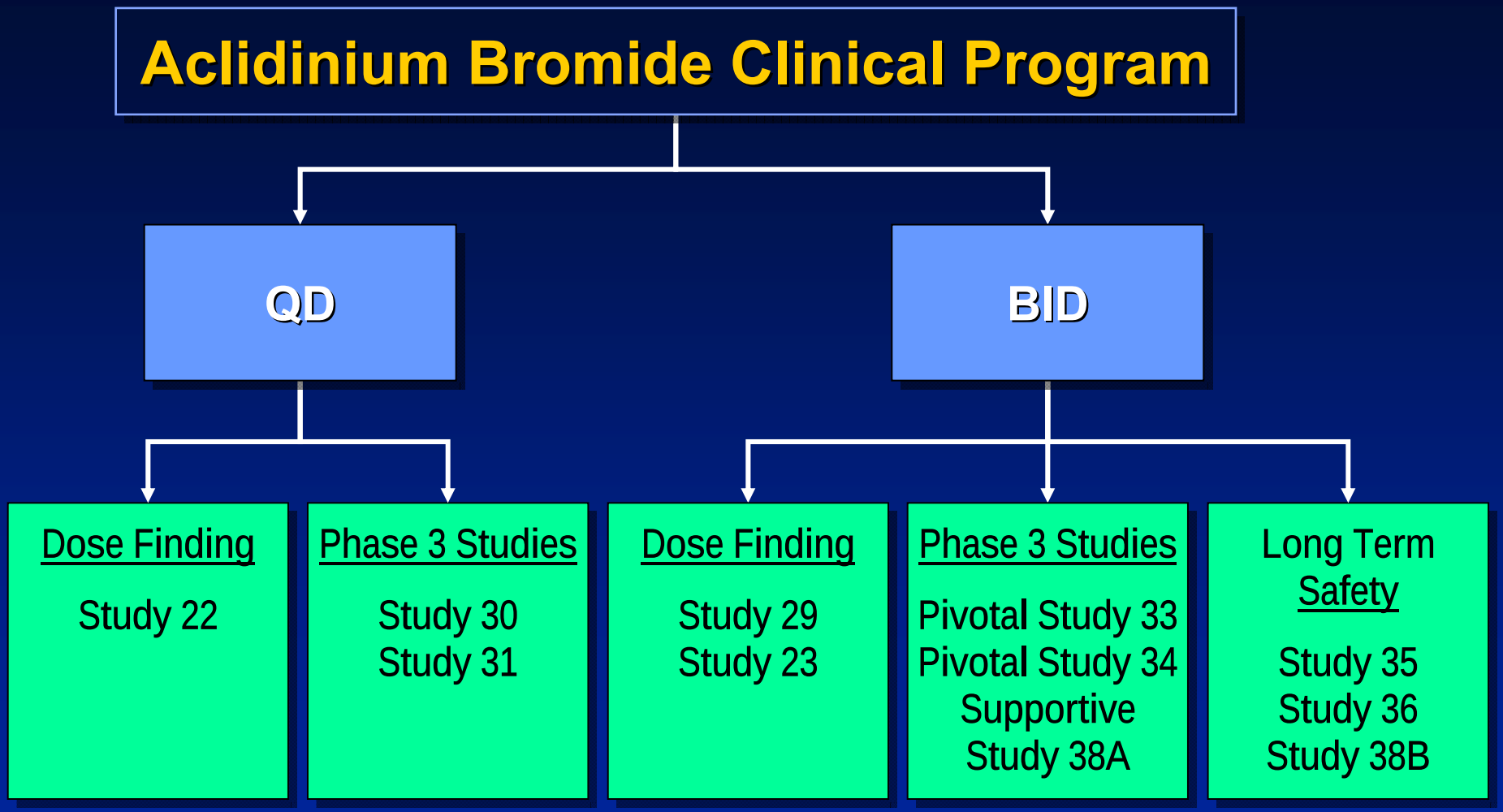
Dose Finding and Efficacy

Cynthia Caracta, MD, FCCP

Director, Clinical Development - Respiratory
Forest Research Institute, Inc.

Aclidinium Bromide Clinical Program



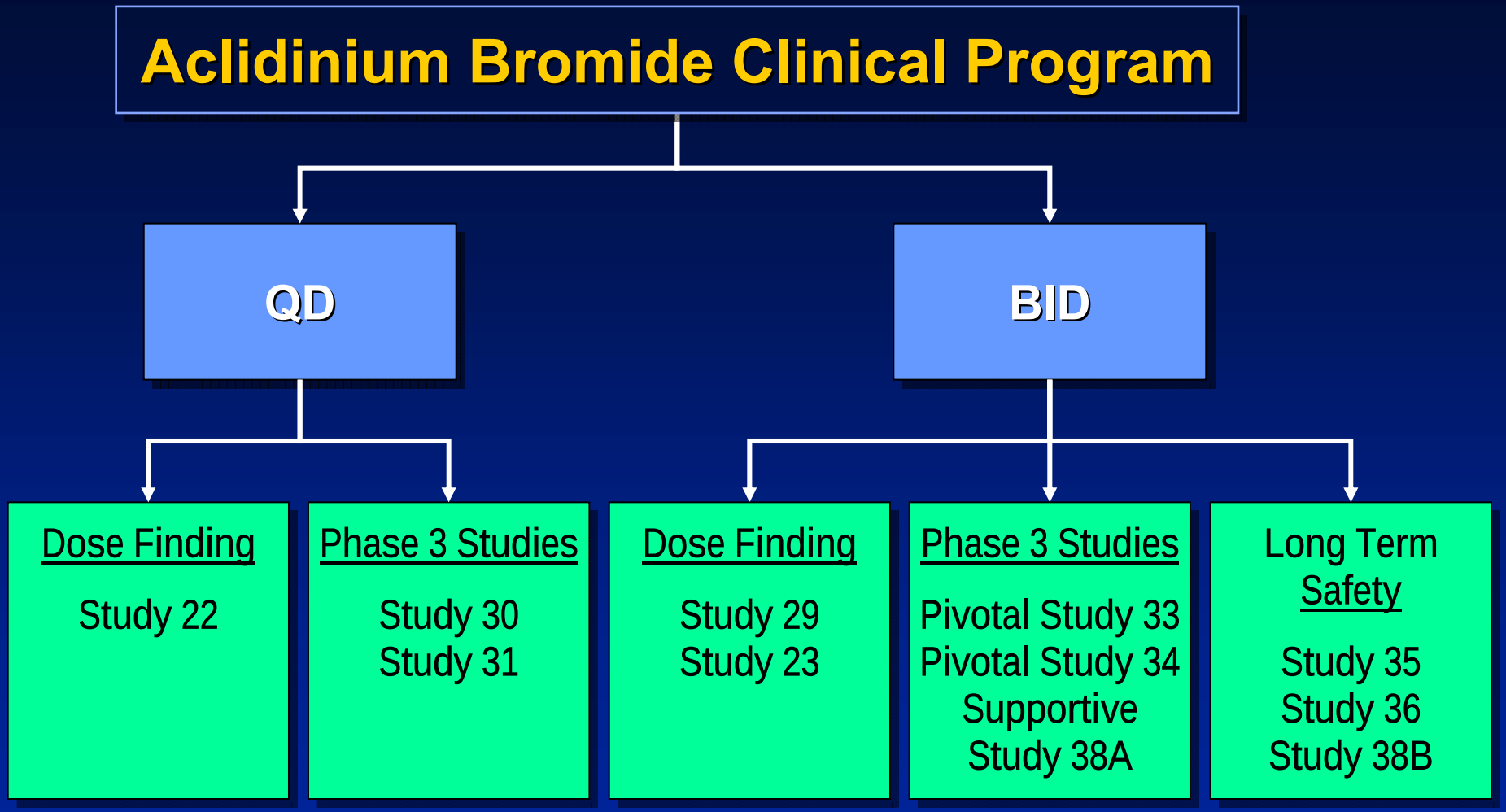
QD = Once-daily, BID = twice-daily

QD Program

Background and Conclusions

- Aclidinium bromide 25 µg - 400 µg QD doses studied in dose finding
  - 200 µg QD was similar to 400 µg QD
    - 200 µg was selected for Phase 3 as the appropriate dose
- Phase 3 studies 30 and 31 did not confirm 200 µg QD as the optimal dose
  - Effect ranged from 60-67 mL
- FDA feedback suggested studying higher and more frequent dosing as well as active comparator for benchmarking

Aclidinium Bromide Clinical Program



QD = Once-daily, BID = twice-daily

BID Dose Finding: Study 29

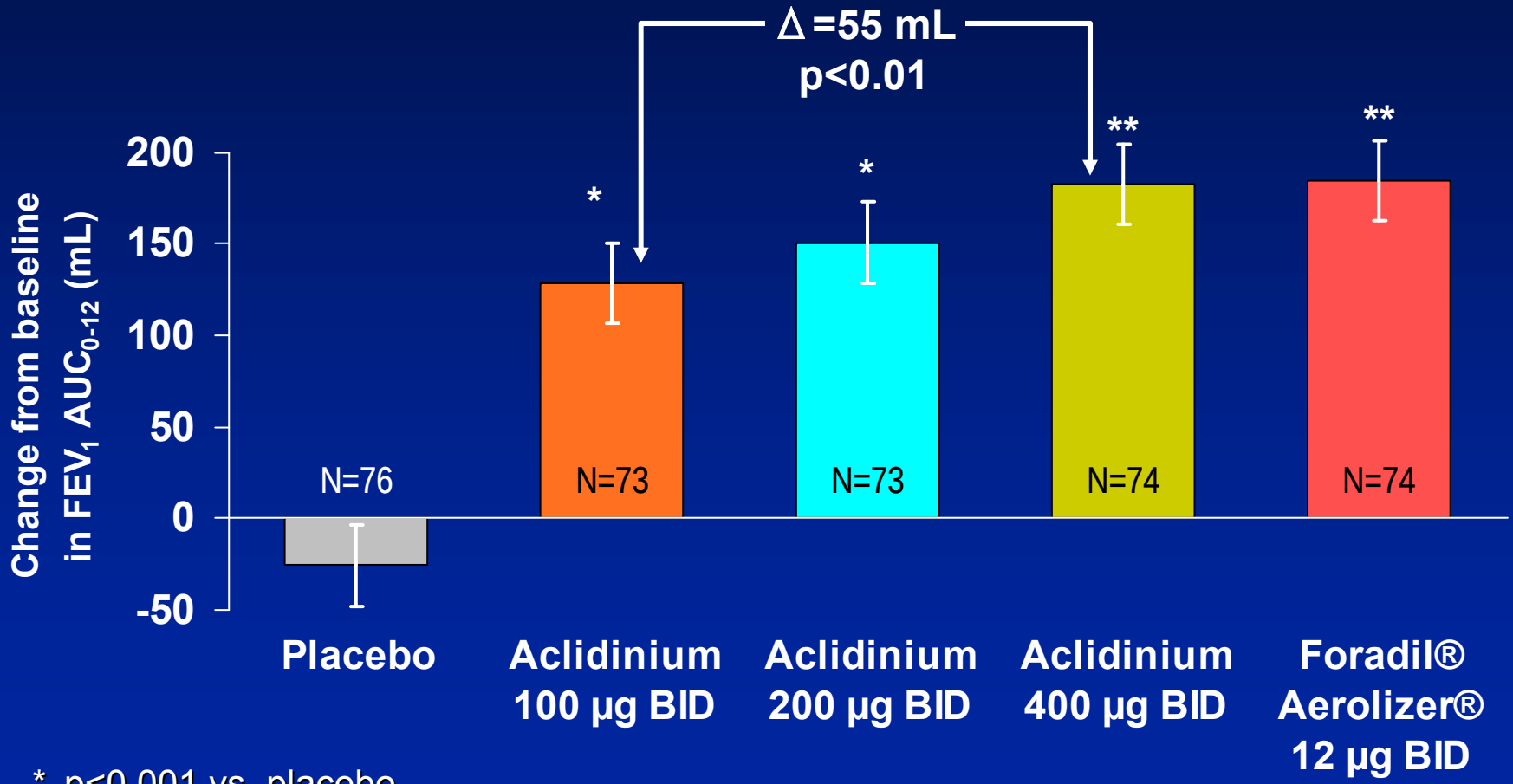
BID Dose Finding: Study 29

Study Design

- Double-blind, double-dummy, randomized, cross-over, placebo and active controlled
- Patient population: moderate to severe COPD
- Treatment for 7 days:
  - Aclidinium bromide 100 µg BID
  - Aclidinium bromide 200 µg BID
  - Aclidinium bromide 400 µg BID
  - Foradil® Aerolizer® 12 µg BID
  - Placebo
- Primary endpoint: FEV_1 $AUC_{0\text{-}12}$

BID Dose Finding: Study 29

Primary Endpoint: Change from Baseline in Normalized FEV_1 AUC_{0-12} (mL) at Day 7: 400 µg Comparable to Foradil and >100 µg (ITT)

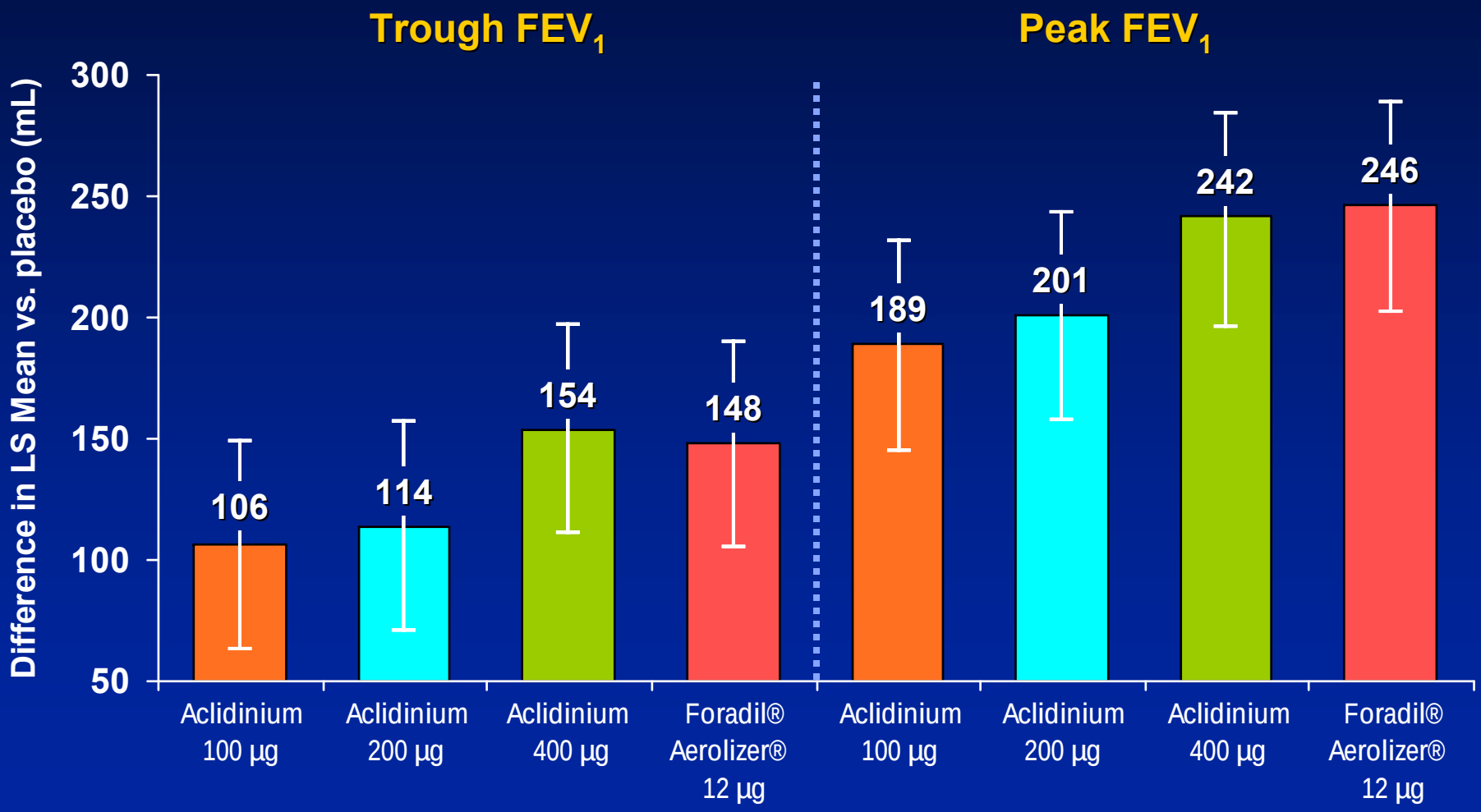


* p<0.001 vs. placebo

** p<0.01 vs. placebo & Aclidinium 100 µg

BID Dose Finding: Study 29

Placebo Adjusted Change from Baseline in Trough and Peak FEV_1 (mL) at Day 7 (ITT)



p<0.0001 for all comparisons vs. placebo

BID Dose Finding: Study 23

Fuhr R, Magnussen H, Sarem K, et al. Efficacy of aclidinium bromide 400 µg BID compared with placebo and tiotropium in patients with moderate-to-severe COPD [published online ahead of print September 8, 2011]. *Chest*. doi:10.1378/chest.11-0406.

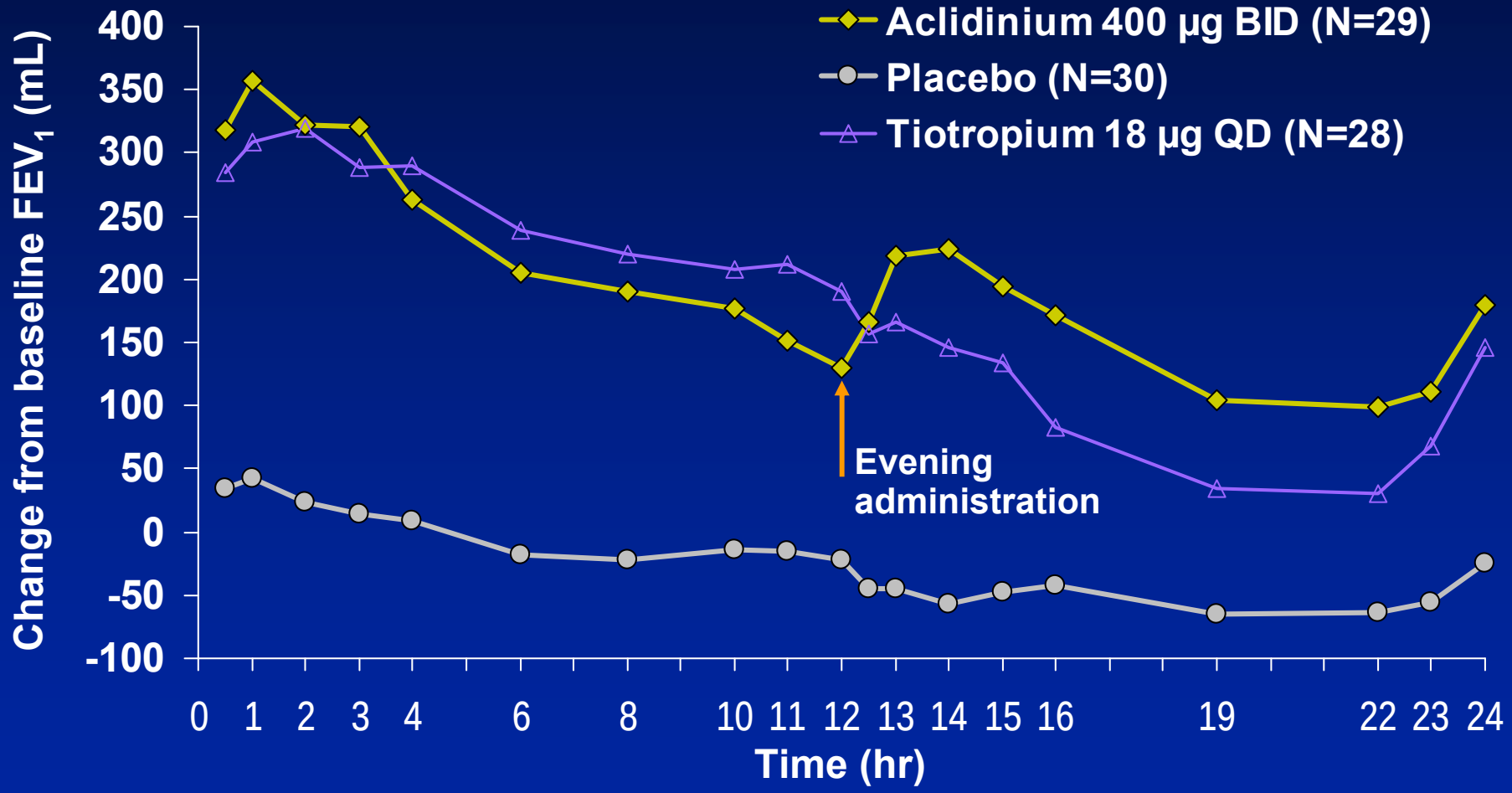
BID Dose Finding: Study 23

Study Design: Active Controlled Study

- Phase 2A 15 day multiple dose, randomized, double-blind, double-dummy, 3 period cross-over, placebo- and active- controlled
- Patient population: moderate to severe COPD
- Treatment for 15 days:
  - Aclidinium bromide 400 µg BID
  - Tiotropium 18 µg QD
  - Placebo
- Primary endpoint: FEV_1 AUC_{0-12}

BID Dose Finding: Study 23

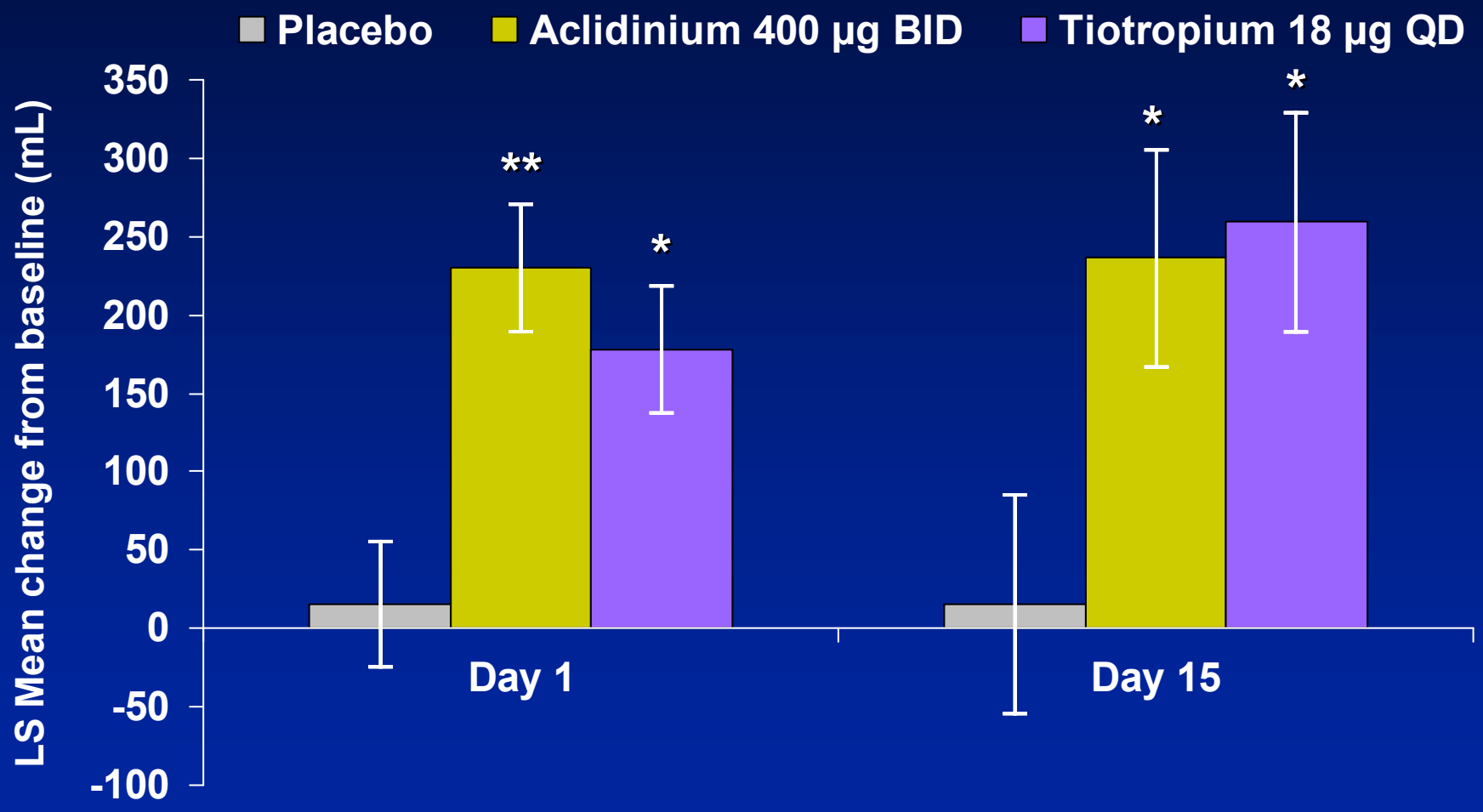
Change from Baseline FEV_1 (mL) at Day 15: Aclidinium 400 µg Similar to Tiotropium (ITT)



Both active treatments are statistically significant vs. placebo ($p<0.05$)

Study 23

Primary Endpoint: Change from Baseline in Normalized FEV_1 AUC_{0-12} (mL) at Day 15

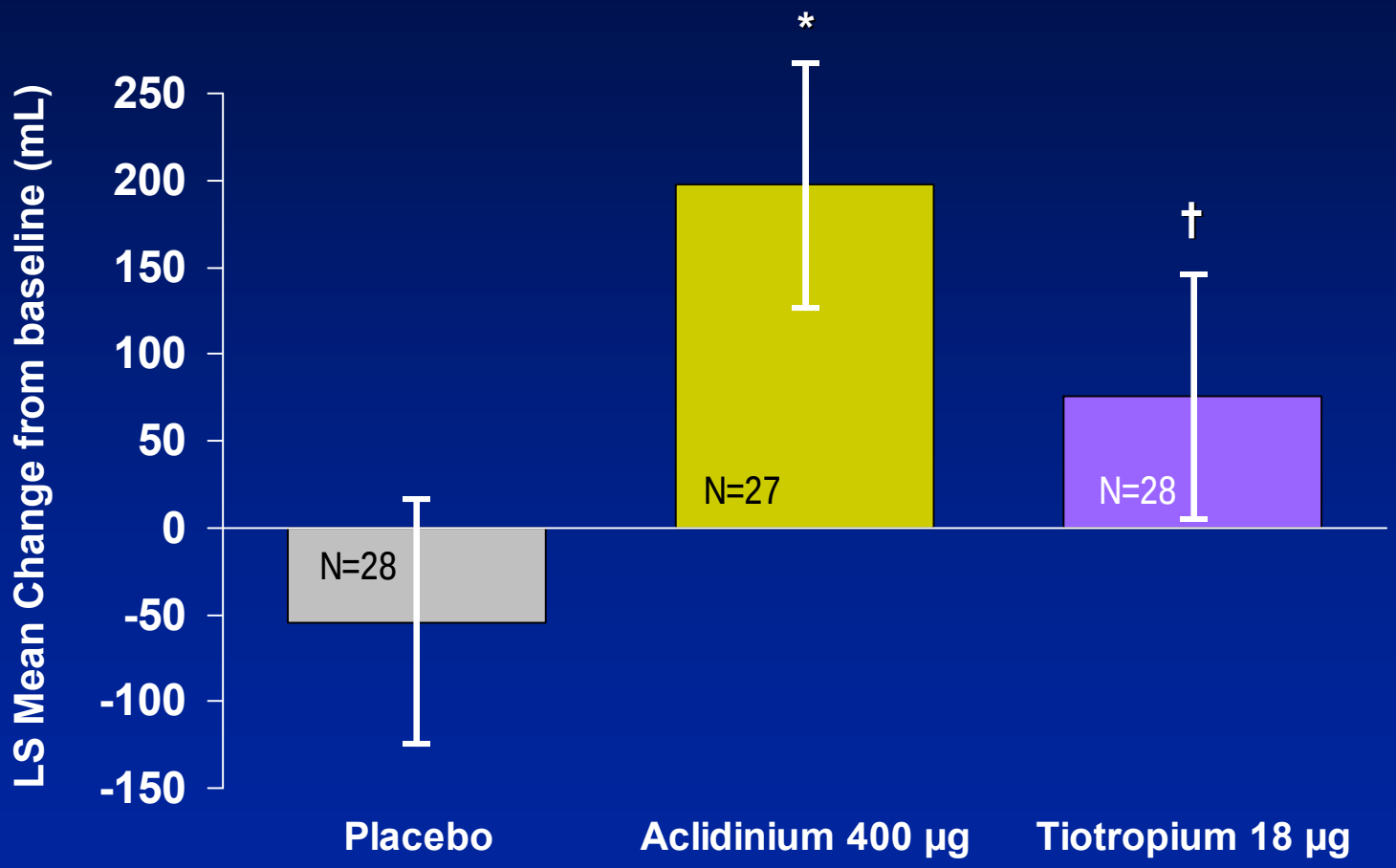


* p<0.05 vs. placebo

** p<0.05 vs. placebo and vs. tiotropium

BID Dose Finding: Study 23

Change from Baseline in Normalized FEV_1 $AUC_{12\text{-}24}$ (mL) at Day 15



* p<0.0001 vs. placebo

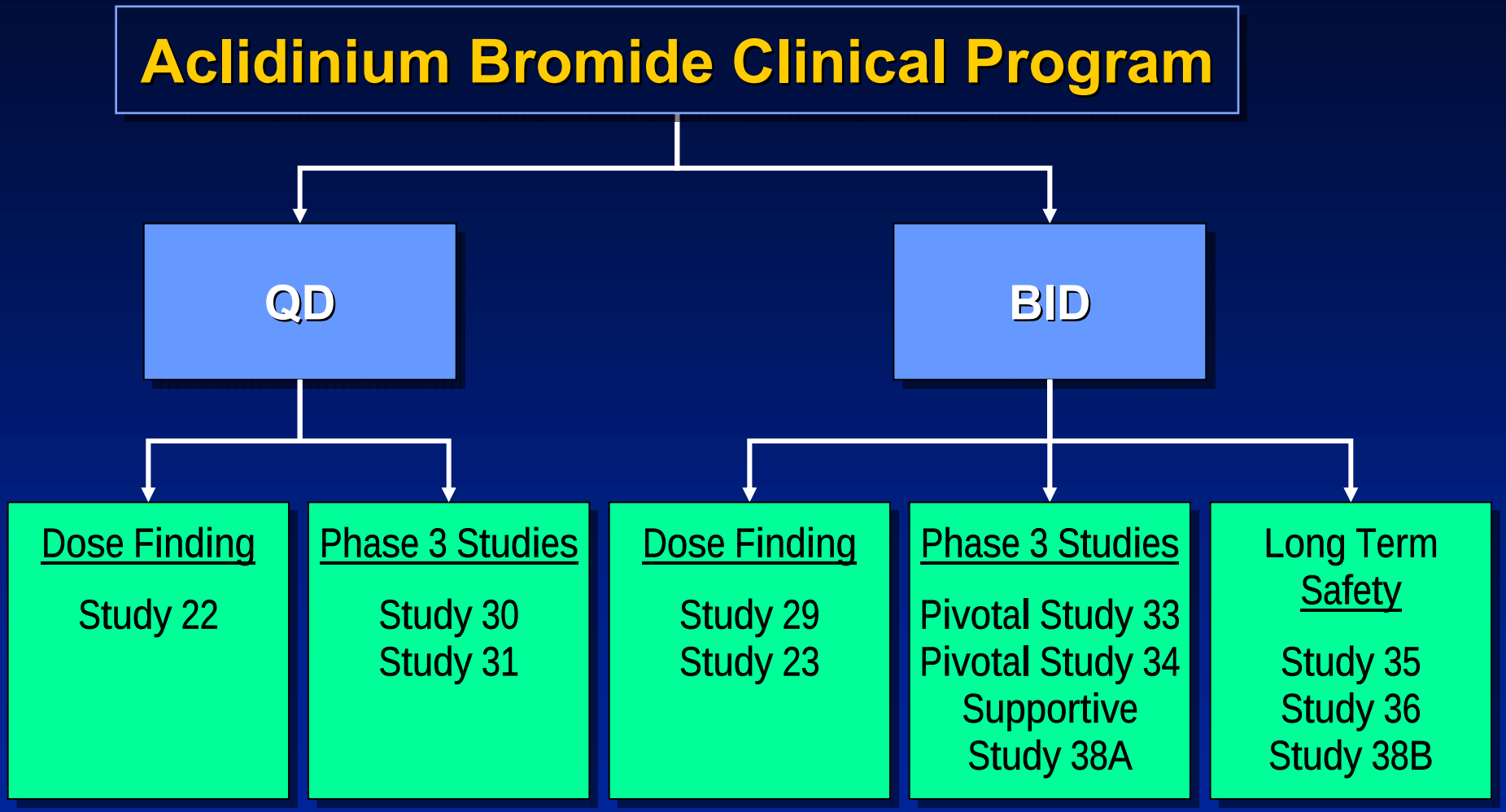
† p=0.0003 vs. placebo

Summary: Aclidinium Bromide Dose Finding and Active Controlled Studies

- A dose-response was observed with aclidinium bromide BID
  - 100, 200 and 400 µg BID were statistically significantly higher than placebo
  - 400 µg BID has statistical significance compared to 100 µg BID
- 400 µg BID dose showed comparable efficacy to approved bronchodilators (Foradil® Aerolizer® and Spiriva® HandiHaler®)
- Safety and tolerability of both doses were acceptable

Efficacy

Aclidinium Bromide Clinical Program



QD = Once-daily, BID = twice-daily

Pivotal Studies 33 and 34

Study Population

- Meets GOLD stage II/III moderate to severe COPD
  - Postbronchodilator FEV_1/ FVC ratio <70% at Visit 1*
  - Postbronchodilator FEV_1 ≥30% to <80% of the predicted value*
- Male/female outpatients ≥40 years of age
- Current or former smokers with a smoking history ≥10 pack-years
- Allowable respiratory treatment: SABA, ICS, long acting theophylline, stable dose oral prednisone, O_2 ≤15 hours

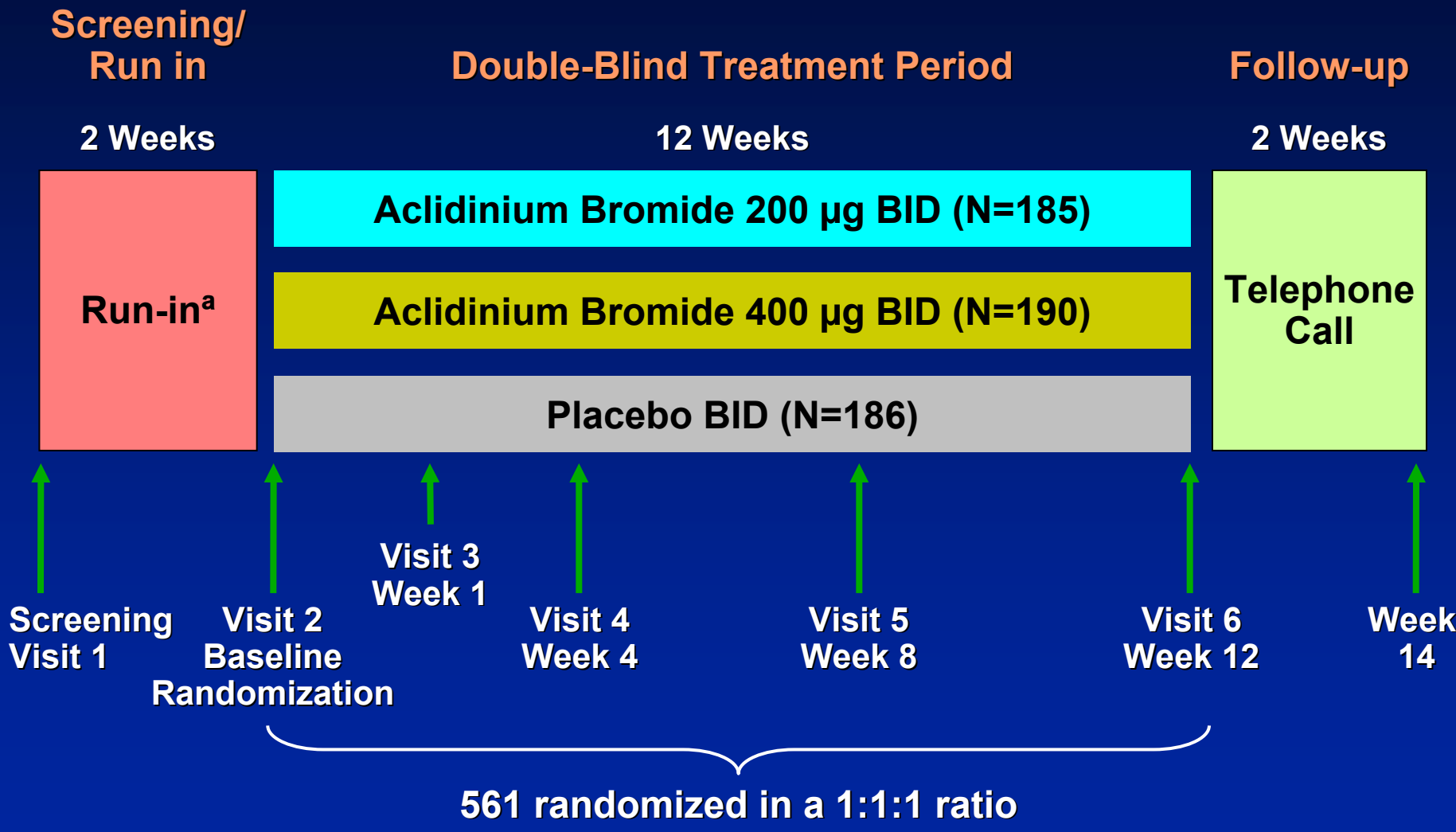
* As defined by ATS/ERS 2004.

Pivotal Study 33

Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil EG, Caracta CF. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I) [published online ahead of print February 9, 2012].

Pivotal Study 33

Aclidinium Bromide Pivotal Study 1: Design



[a] A washout period preceding run-in was required for patients who were taking prohibited medications

Pivotal Study 33

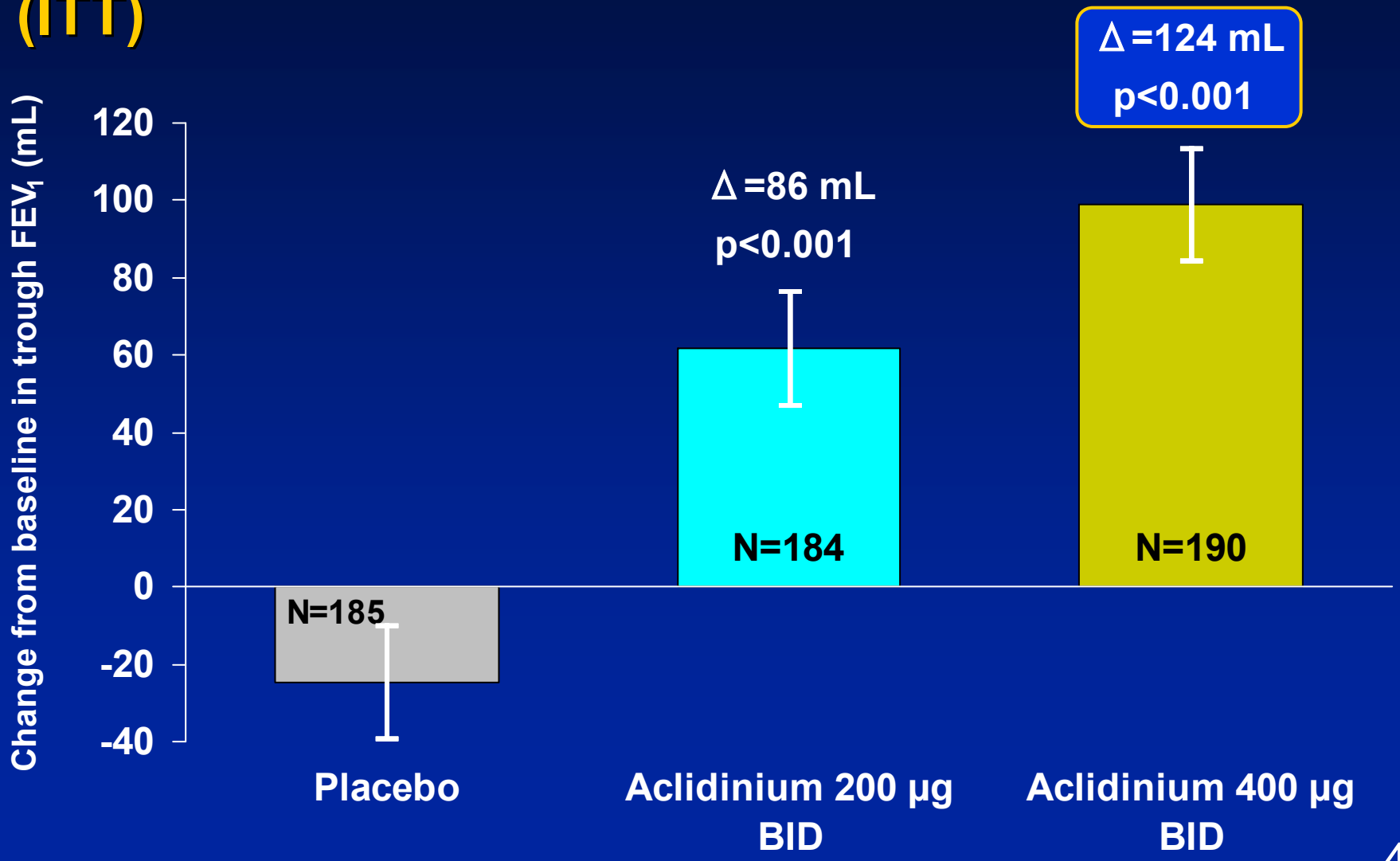
Demographic and Baseline Characteristics

Safety population

		Aclidinium Bromide	
	Placebo (N=186)	200 µg BID (N=184)	400 µg BID (N=190)
Age – mean (yrs)	65.1	63.1	64.9
Male	51.6%	54.9%	52.6%
COPD severity			
Severe	39.2%	43.5%	35.8%
Current smoker	46.8%	45.7%	42.1%
Pre-BD			
FEV_1 – mean (L)	1.38	1.35	1.35
FEV_1 % predicted – mean (%)	48.1	46.1	47.5
Post-BD			
FEV_1 % predicted – mean (%)	54.7	52.8	54.1

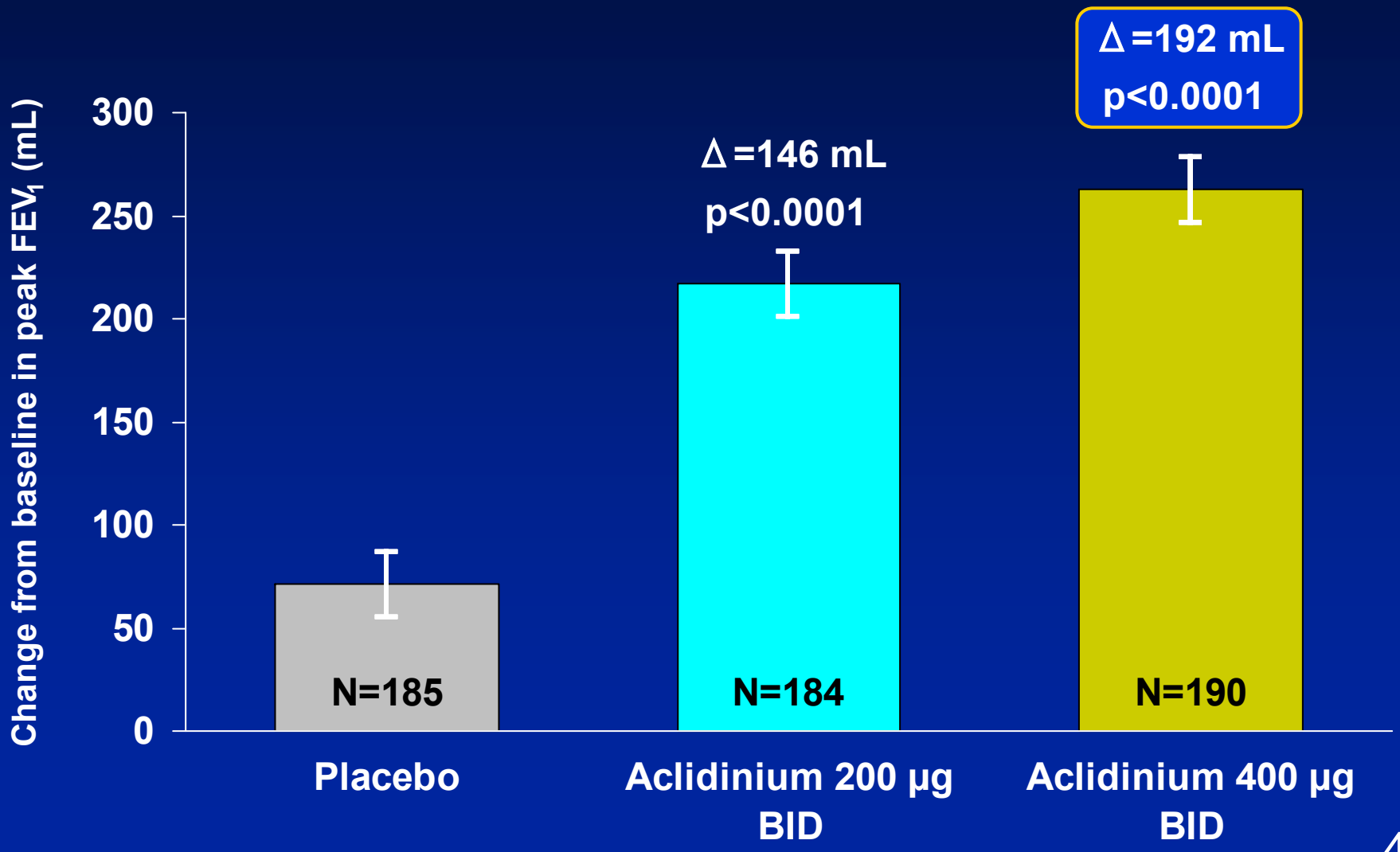
Pivotal Study 33

Primary Endpoint: Change from Baseline in Trough FEV_1 at Week 12: 400 µg BID >200 µg BID (ITT)



Pivotal Study 33

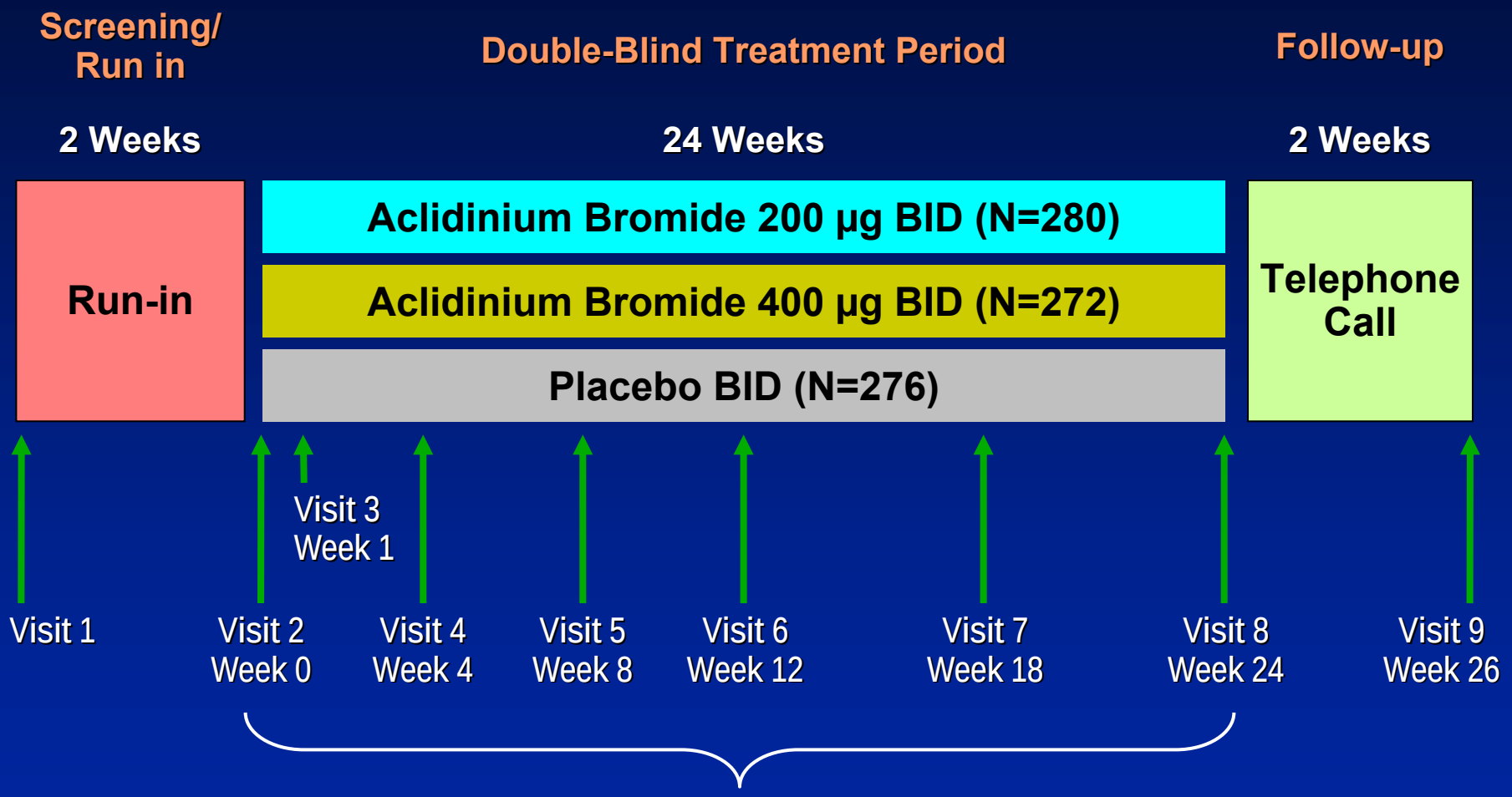
Change from Baseline in Peak FEV_1 at Week 12: 400 µg BID >200 µg BID (ITT)



Pivotal Study 34

Pivotal Study 34

Aclidinium Bromide Pivotal Study 2: Design



Pivotal Study 34

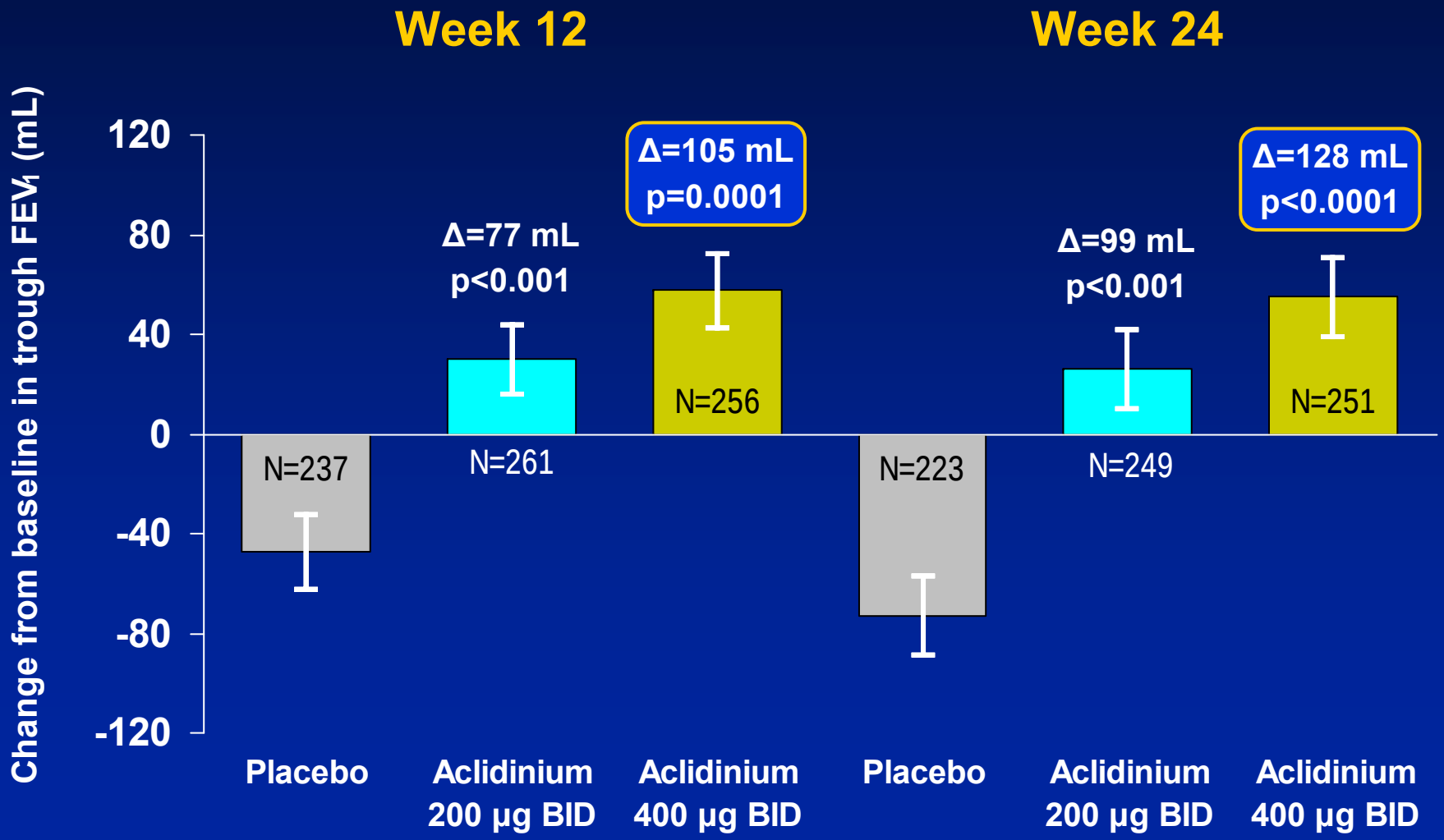
Demographic and Baseline Characteristics

Safety population

		Aclidinium Bromide	
	Placebo (N=273)	200 µg BID (N=277)	400 µg BID (N=269)
Age – mean (yrs)	62.0	62.3	62.9
Male	69.2%	65.3%	67.7%
COPD severity			
Severe	34.1%	30.4%	31.3%
Current smoker	52.8%	50.5%	55.0%
Pre-BD			
FEV_1 – mean (L)	1.48	1.49	1.48
FEV_1 % predicted – mean (%)	51.5	52.0	51.2
Post-BD			
FEV_1 % predicted – mean (%)	56.6	57.6	56.2

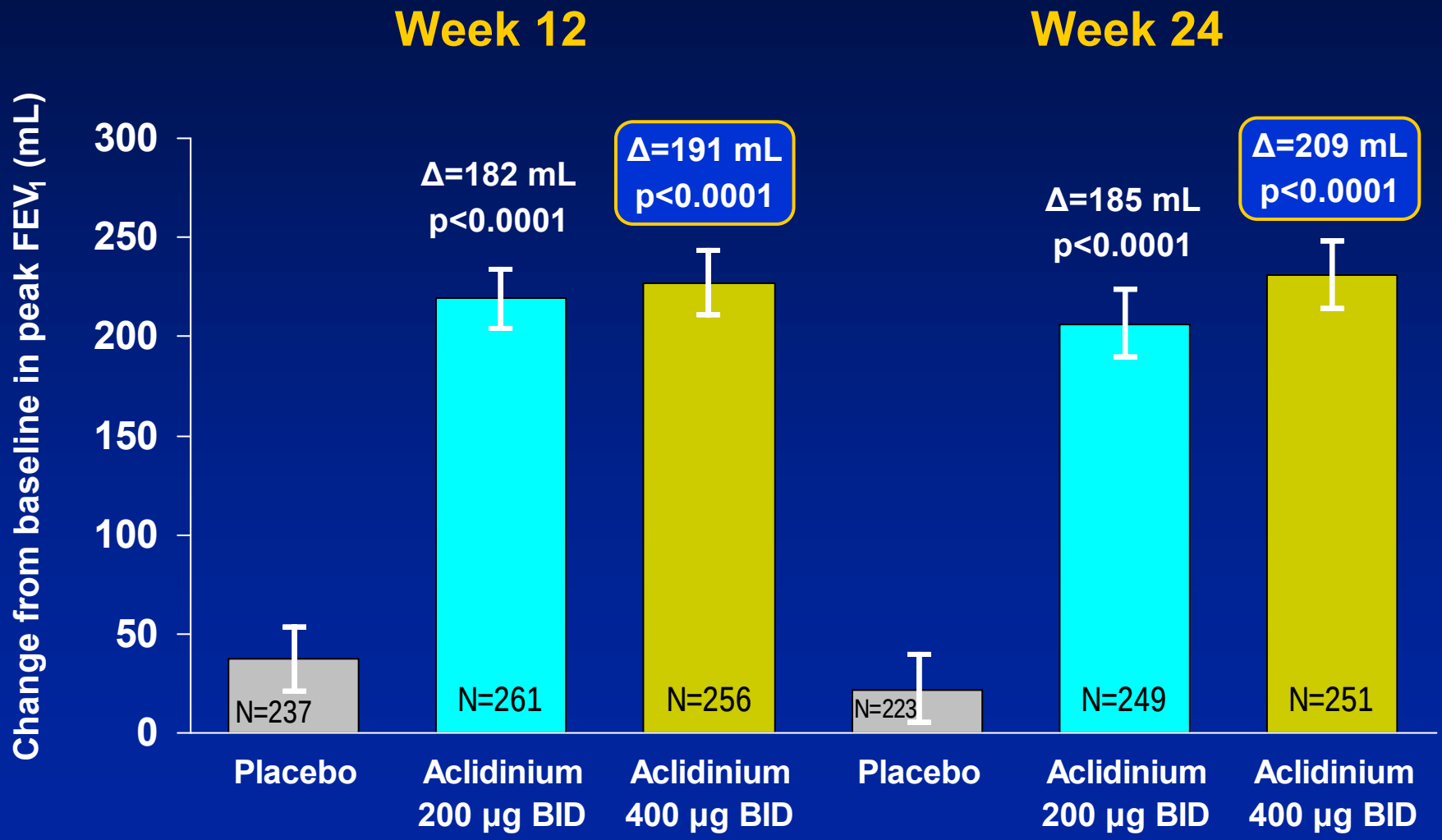
Pivotal Study 34

Primary Endpoint: Change from Baseline in Trough FEV_1: 400 µg BID >200 µg BID (ITT)



Pivotal Study 34

Change from Baseline in Peak FEV_1: 400 µg BID >200 µg BID (ITT)

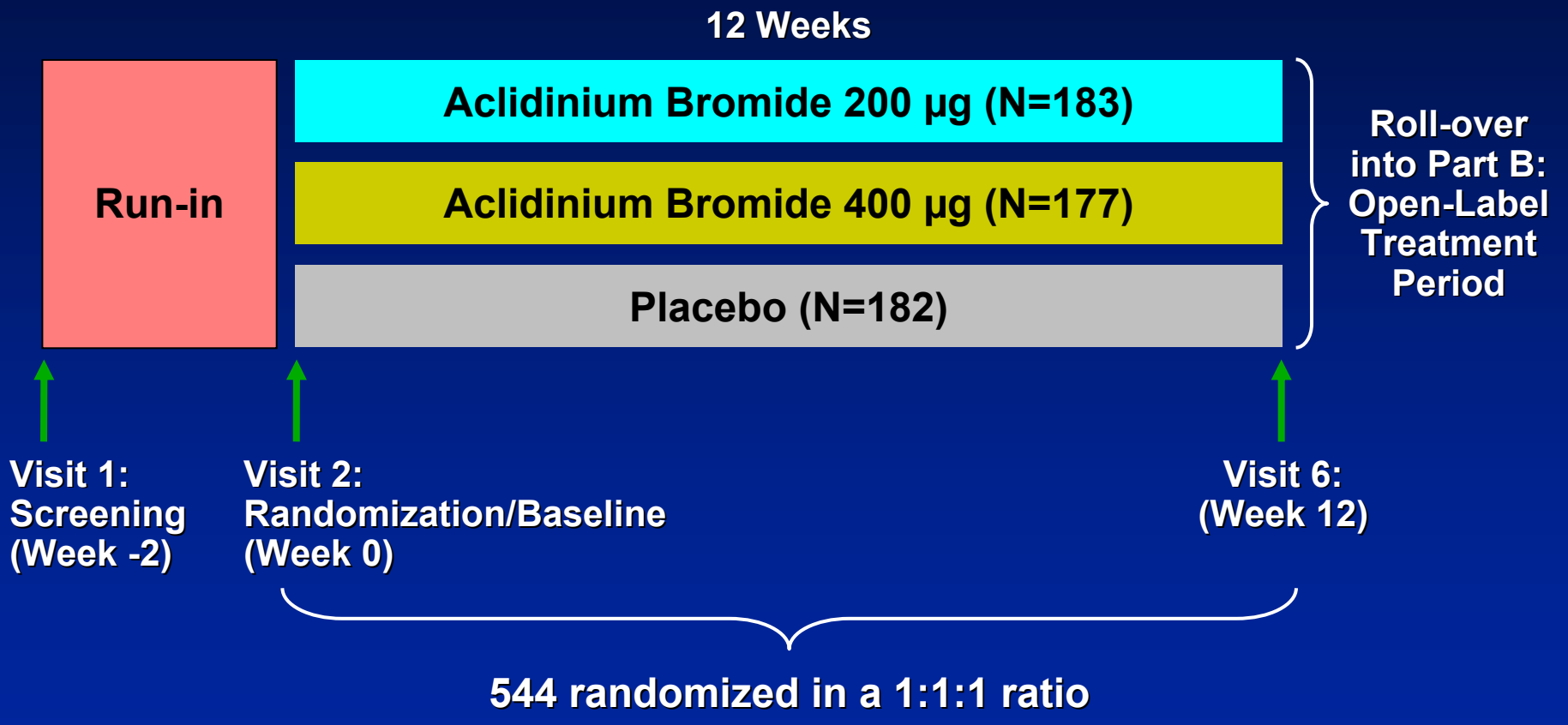


Supportive Study 38A

Supportive Study 38A

Study Design

Part A: 12 week double-blind treatment period



Supportive Study 38A

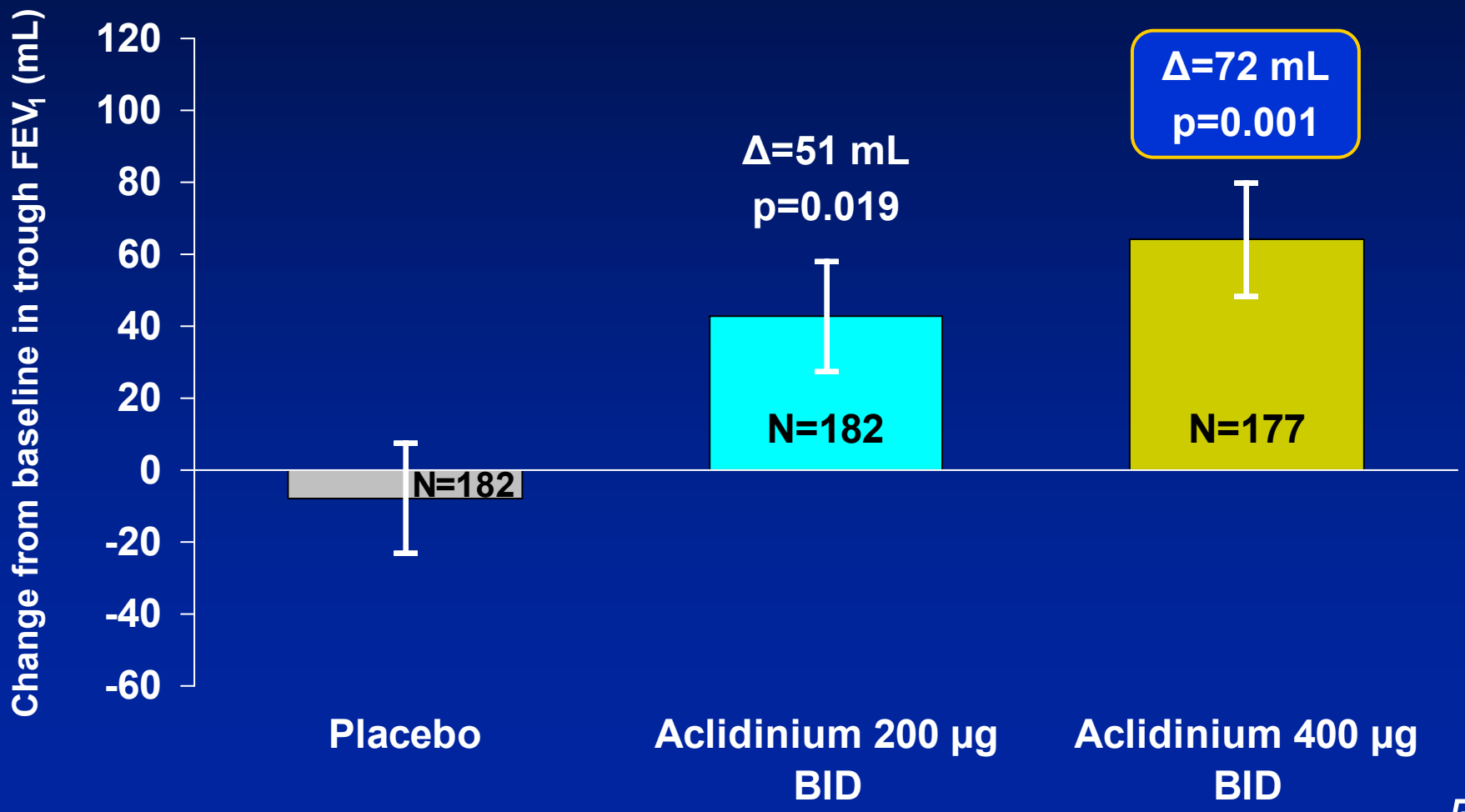
Demographic and Baseline Characteristics

Safety population

		Aclidinium Bromide		
	Placebo (N=182)	200 µg (N=183)	400 µg (N=177)	p-value
Age – mean (yrs)	61.7	63.4	63.2	0.1435
Male	54.9%	54.1%	50.3%	0.6426
Current smoker	56.0%	53.6%	50.3%	0.5487
COPD severity				
Severe	36.8%	46.4%	54.2%	0.0027
Baseline (Visit 2) FEV_1 mean (L)	1.46	1.40	1.25	0.0009
Pre-BD FEV_1 mean (L)	1.45	1.36	1.26	0.0044
Pre-BD FEV_1 % predicted – mean (L)	48.5	46.3	43.6	0.0035
Post-BD FEV_1 % predicted mean (L)	55.2	52.0	50.2	0.0016

Supportive Study 38A

Primary Endpoint: Change from Baseline in Trough FEV_1 at Week 12: 400 µg BID >200 µg BID (ITT)



Supportive Study 38A
Conclusions

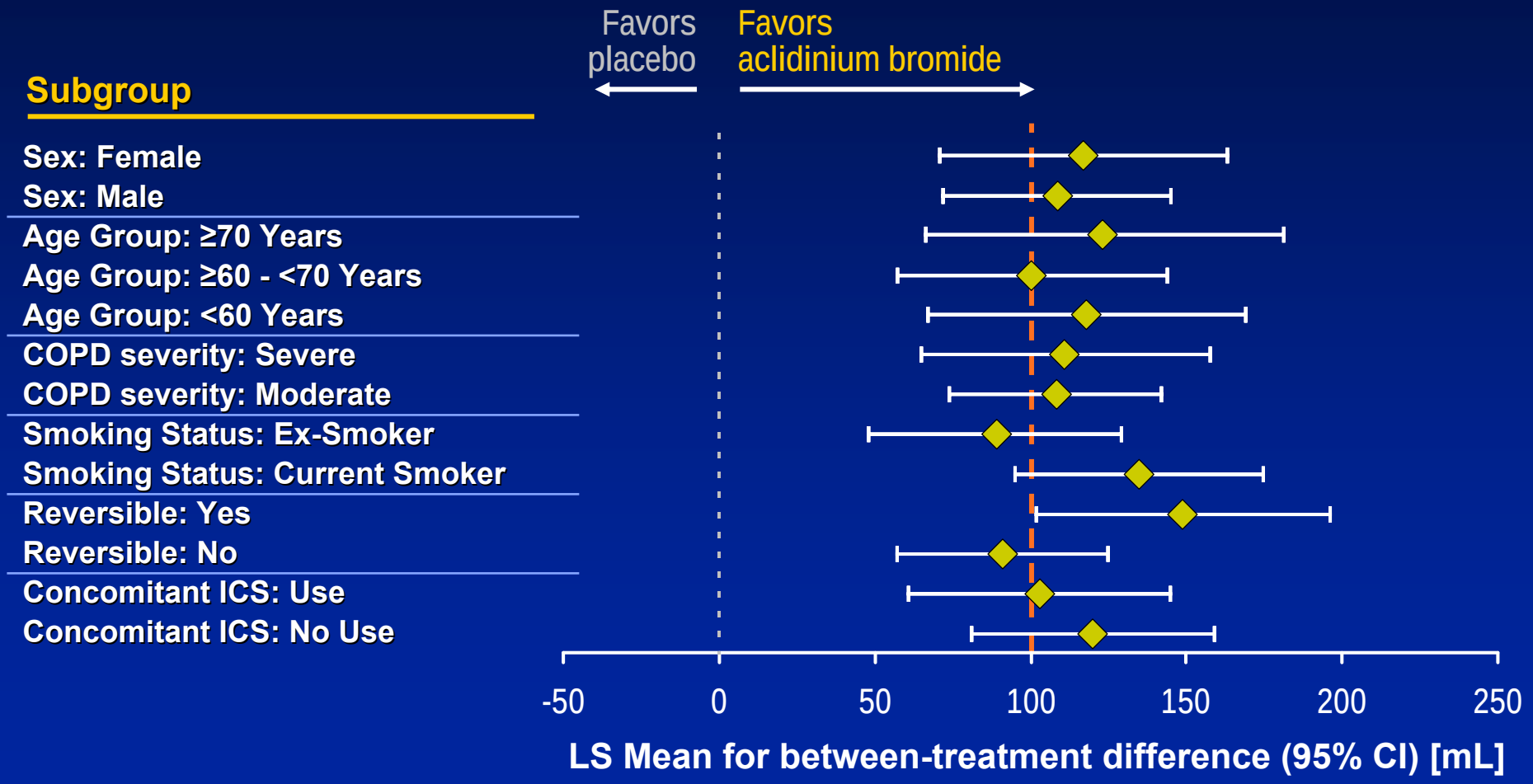
- Although the comparison between placebo and Aclidinium was statistically significant, the effect size for 400 µg (72 mL) was lower than other studies
- Results showed an imbalance but a reasonable treatment effect was demonstrated
- Study 38A results are supportive of indication
  - Both doses are statistically significant vs. placebo
  - 400 µg BID outperformed 200 µg BID

Subgroup Analysis

Pivotal Studies 33 and 34

Subgroup Analysis: Change from Baseline to Week 12 in Trough FEV_1

Aclidinium bromide 400 µg vs. placebo



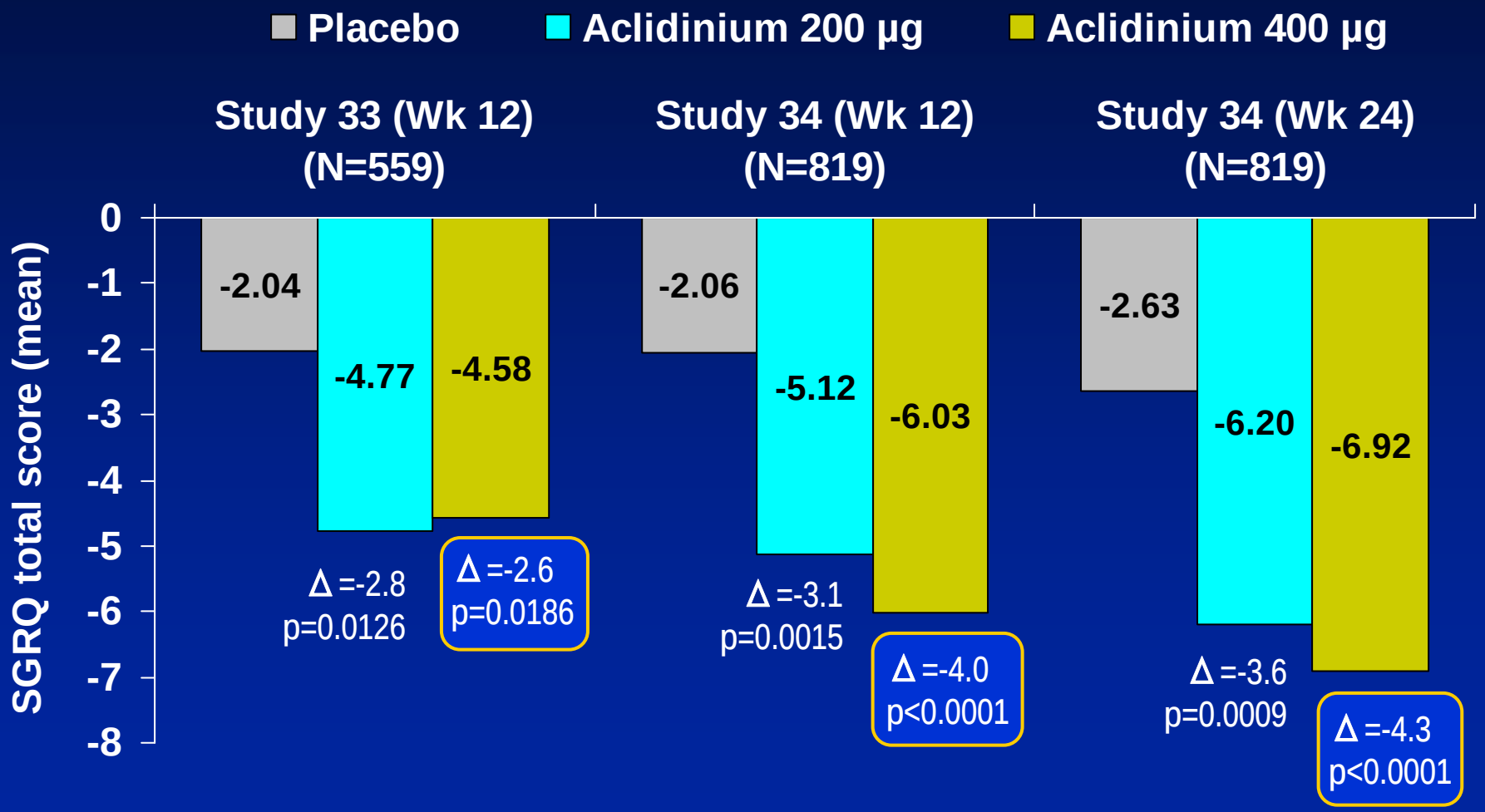
CI = confidence interval; FEV_1 = forced expiratory volume in 1 second.

Supportive Key Clinical Endpoints: Comparison across Pivotal Studies

SGRQ

Pivotal Studies 33 and 34

SGRQ Total Score: 400 µg Shows Improvement from Baseline (ITT)

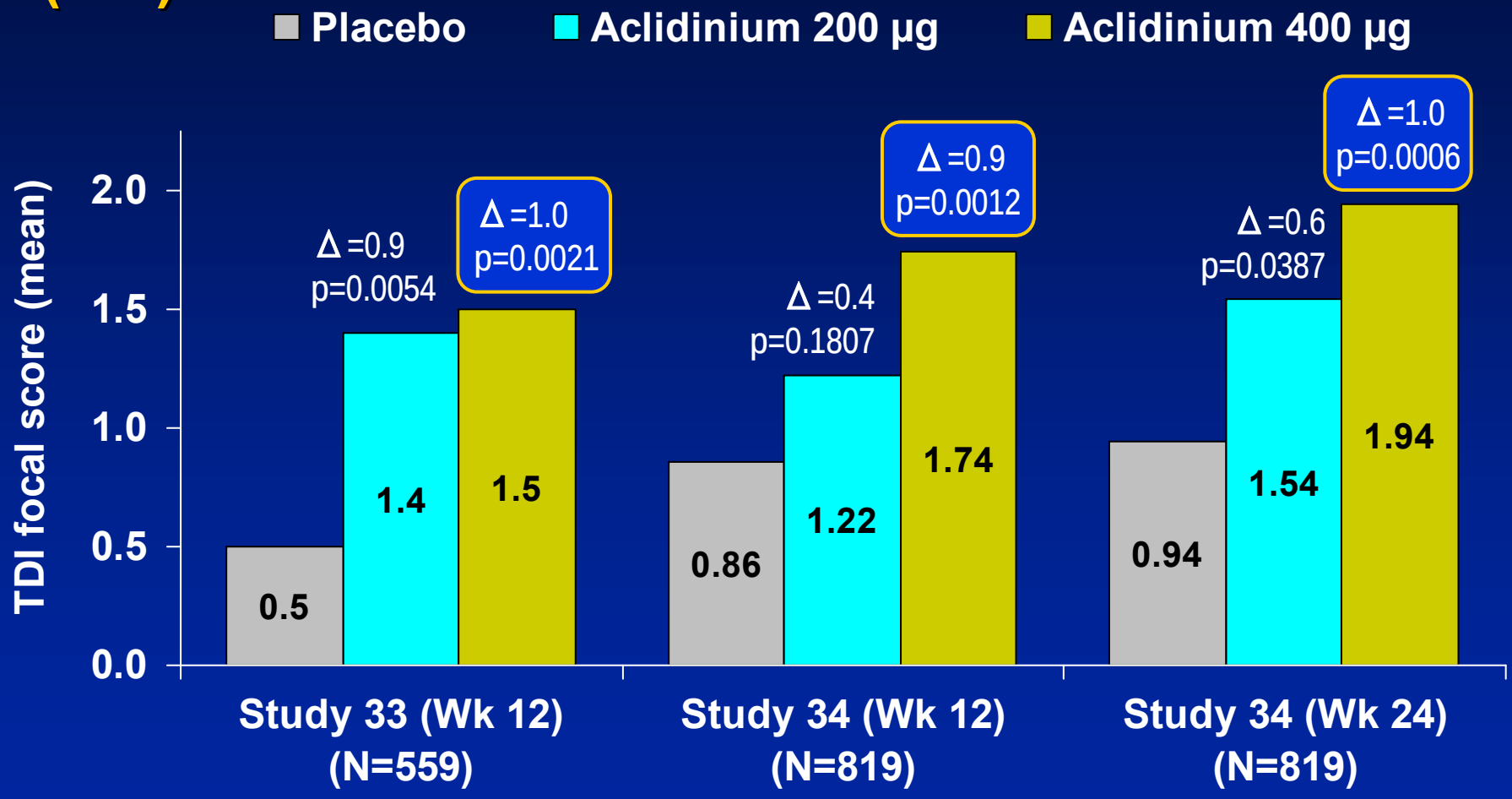


4 unit difference is considered clinically relevant

TDI

Pivotal Studies 33 and 34

TDI Total Score: 400 µg Shows Clinically Relevant Symptom Improvement from Baseline (ITT)



1 unit improvement is considered clinically relevant

COPD Exacerbations

COPD Exacerbations

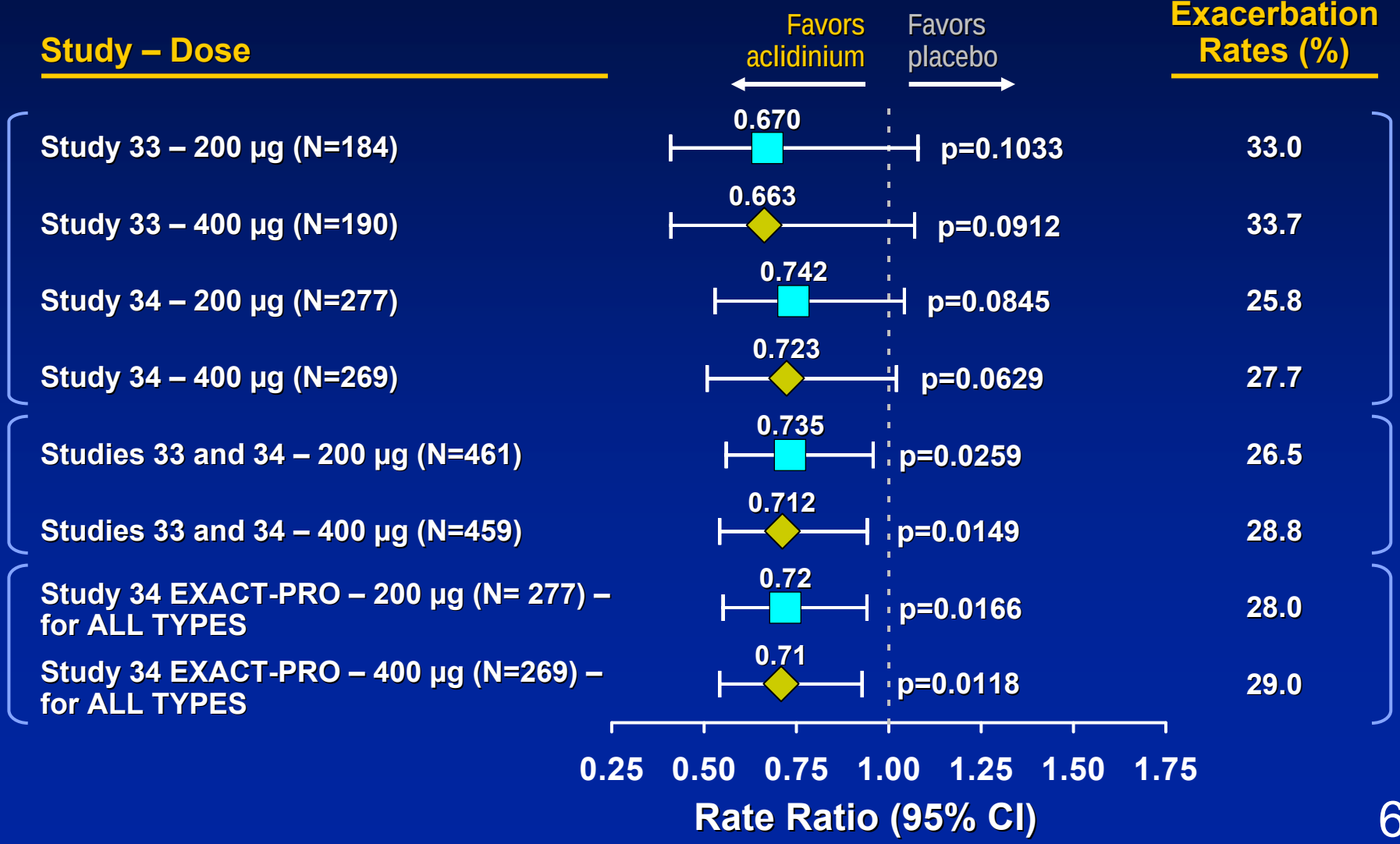
- Increase in COPD symptoms (e.g., dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days with severity characterized as:

Severity	Definition
Mild	Self-managed by the patient at home by increasing short-acting bronchodilator and/or ICS use
Moderate	Did not lead to hospitalization but was treated with antibiotics and/or systemic corticosteroids
Severe	Led to hospitalization (overnight stay at hospital or emergency room)

Pivotal Studies 33 and 34

Rate Ratio of Moderate or Severe COPD Exacerbations per Patient/Year

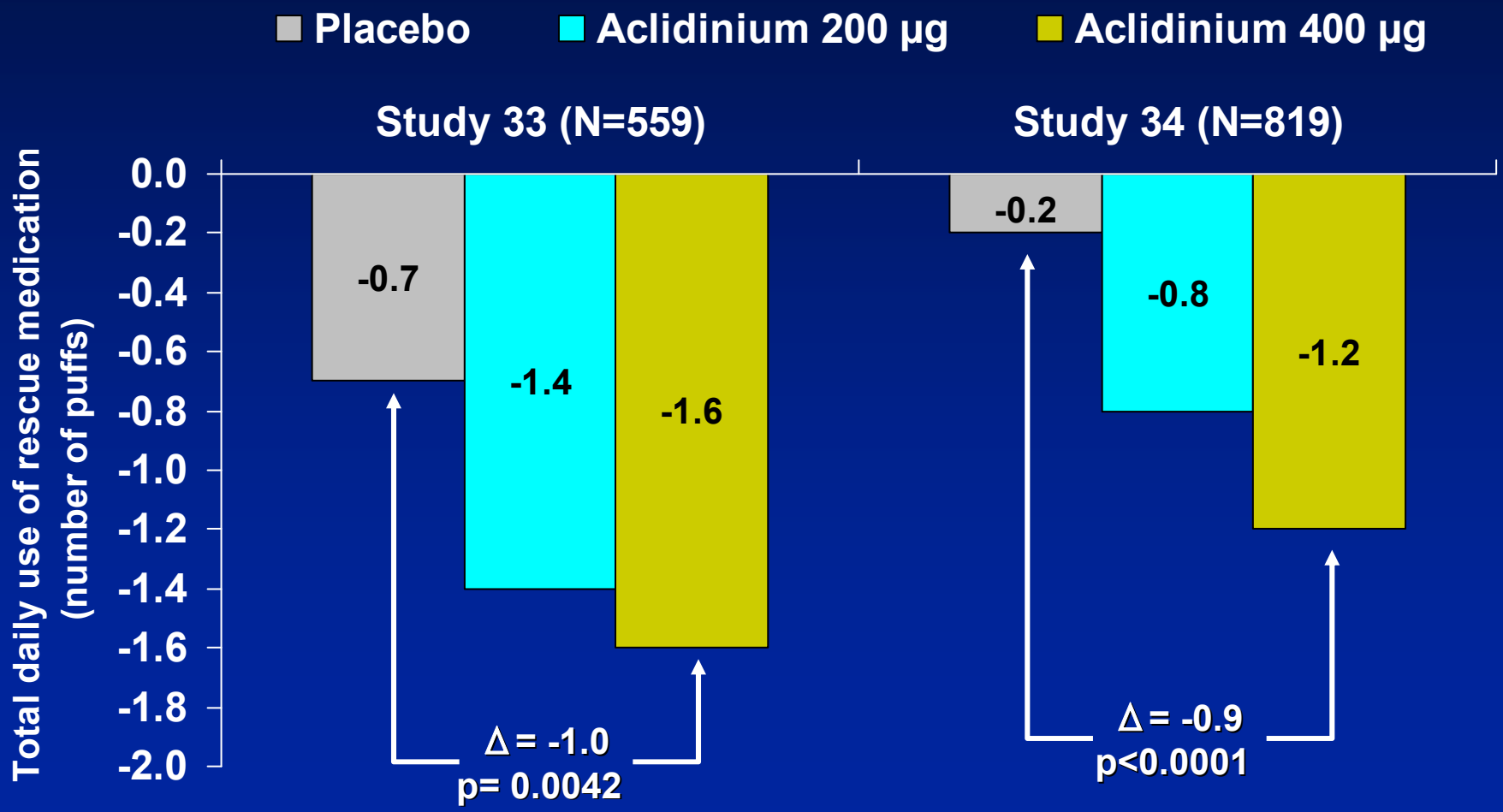
Trend towards reduced exacerbations



Rescue Medication Use

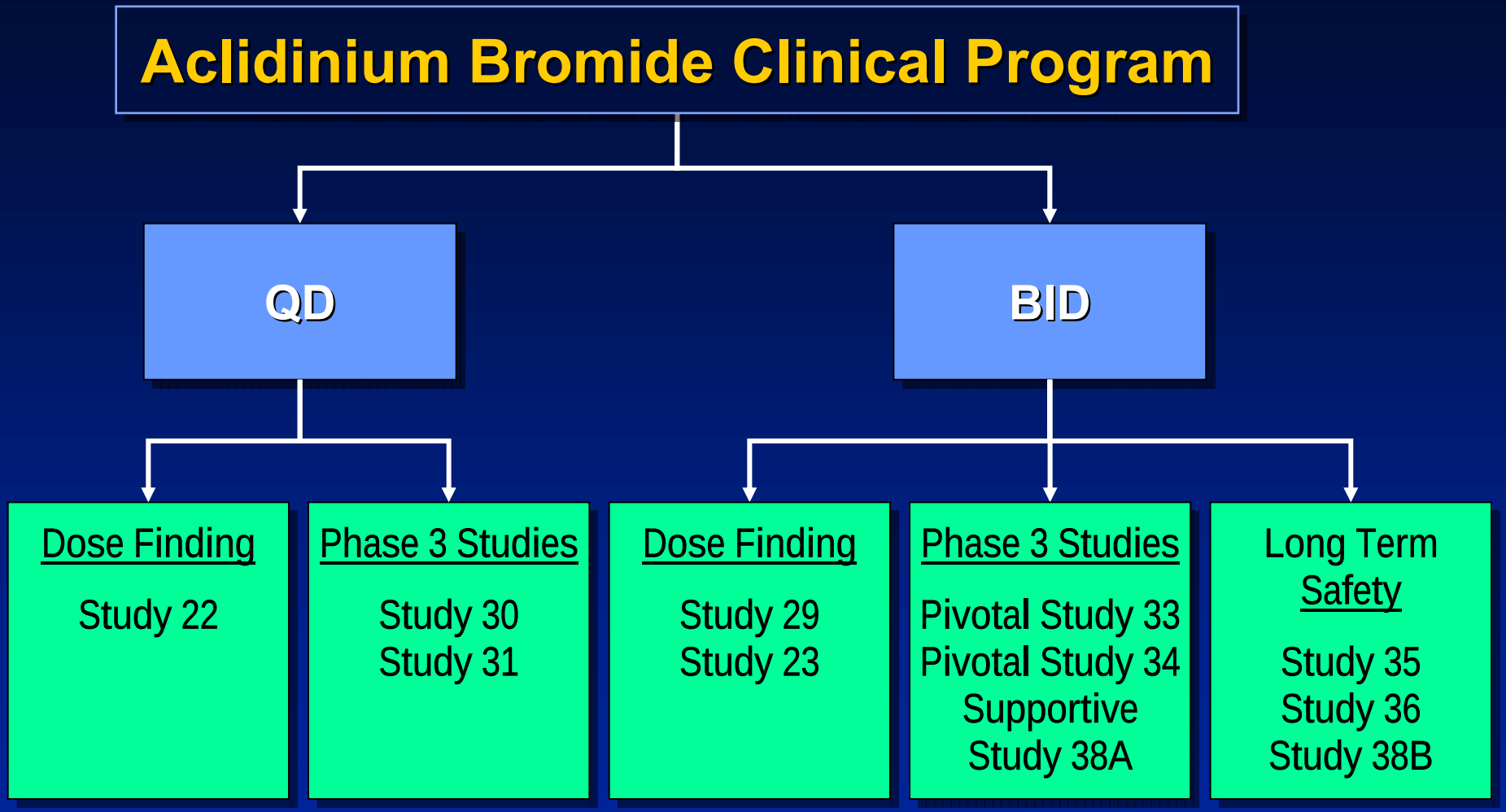
Pivotal Studies 33 and 34

Change from Baseline in Total Daily Use of Rescue Medication (Puffs/Day) over Treatment Duration (ITT)



Persistence of Effect: Study 35

Aclidinium Bromide Clinical Program



QD = Once-daily, BID = twice-daily

Study 35

Study Design

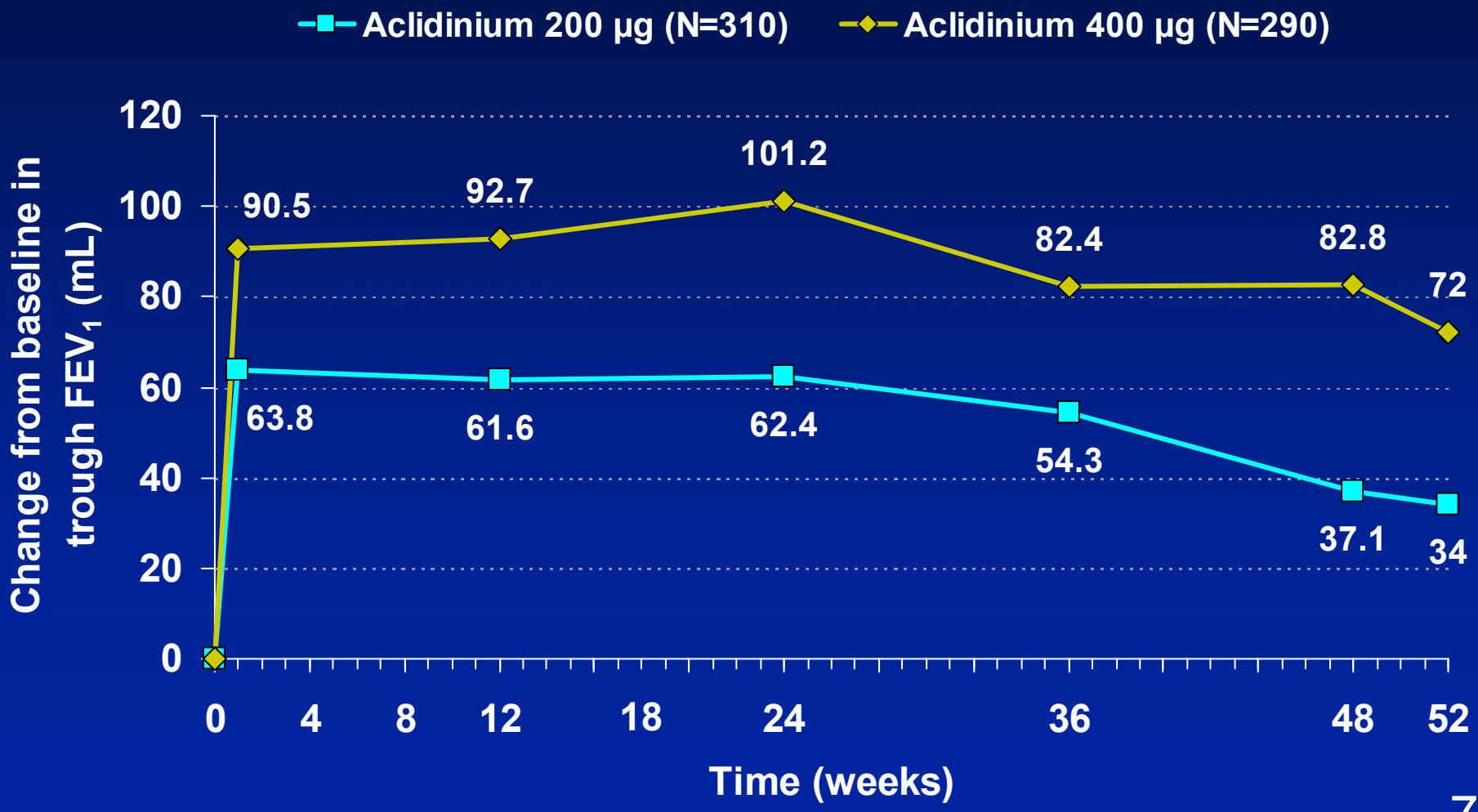
Persistence of effect

- 52 week, randomized, double-blind, multicenter, parallel-group safety study
- Patient population: moderate to severe COPD
- Randomization 1:1 to:
  - AB 200 µg BID (N=311)
  - AB 400 µg BID (N=291)

Study 35

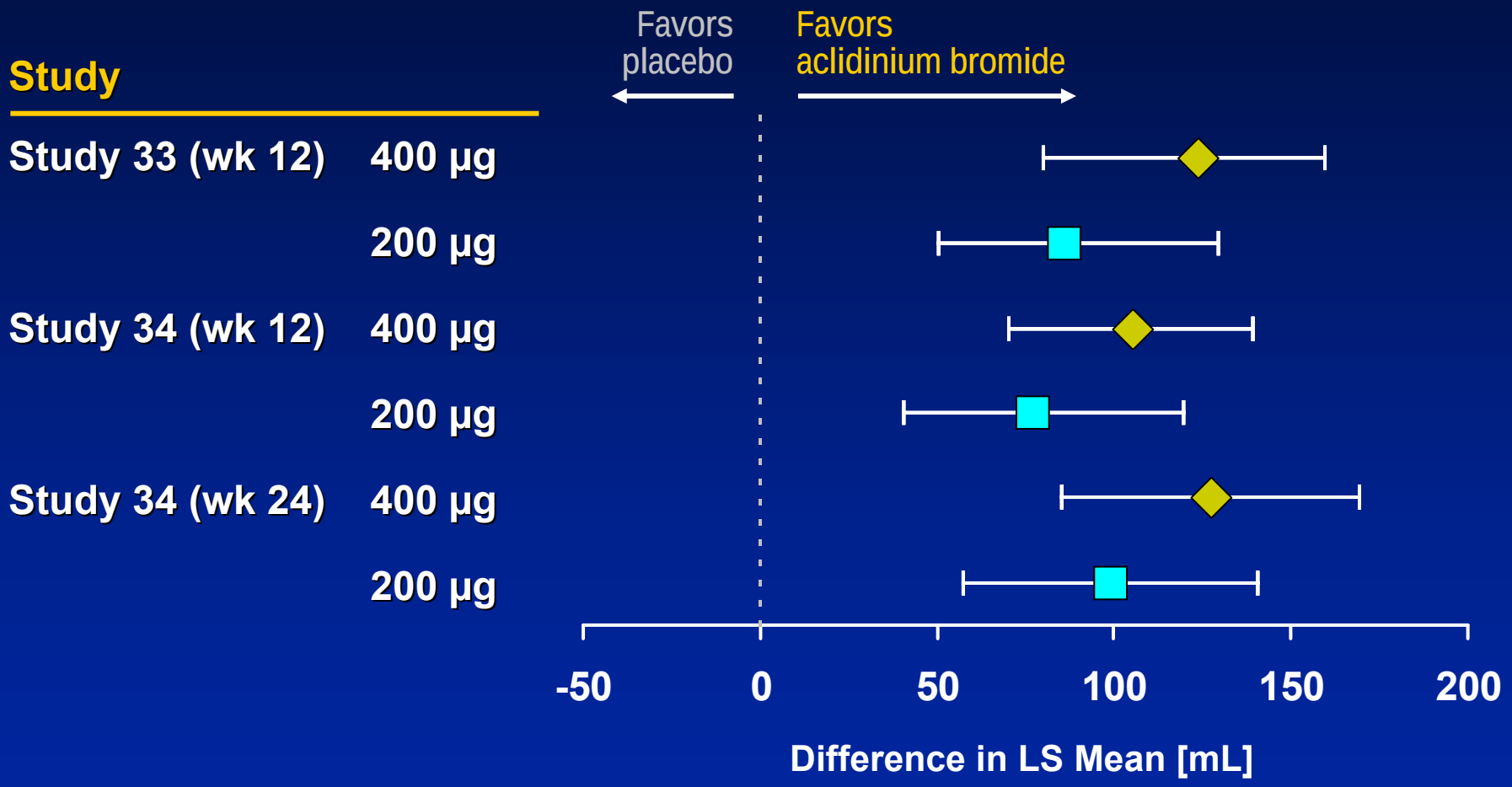
Change from Baseline in Trough FEV_1 over Time (ITT)

Persistence of effect



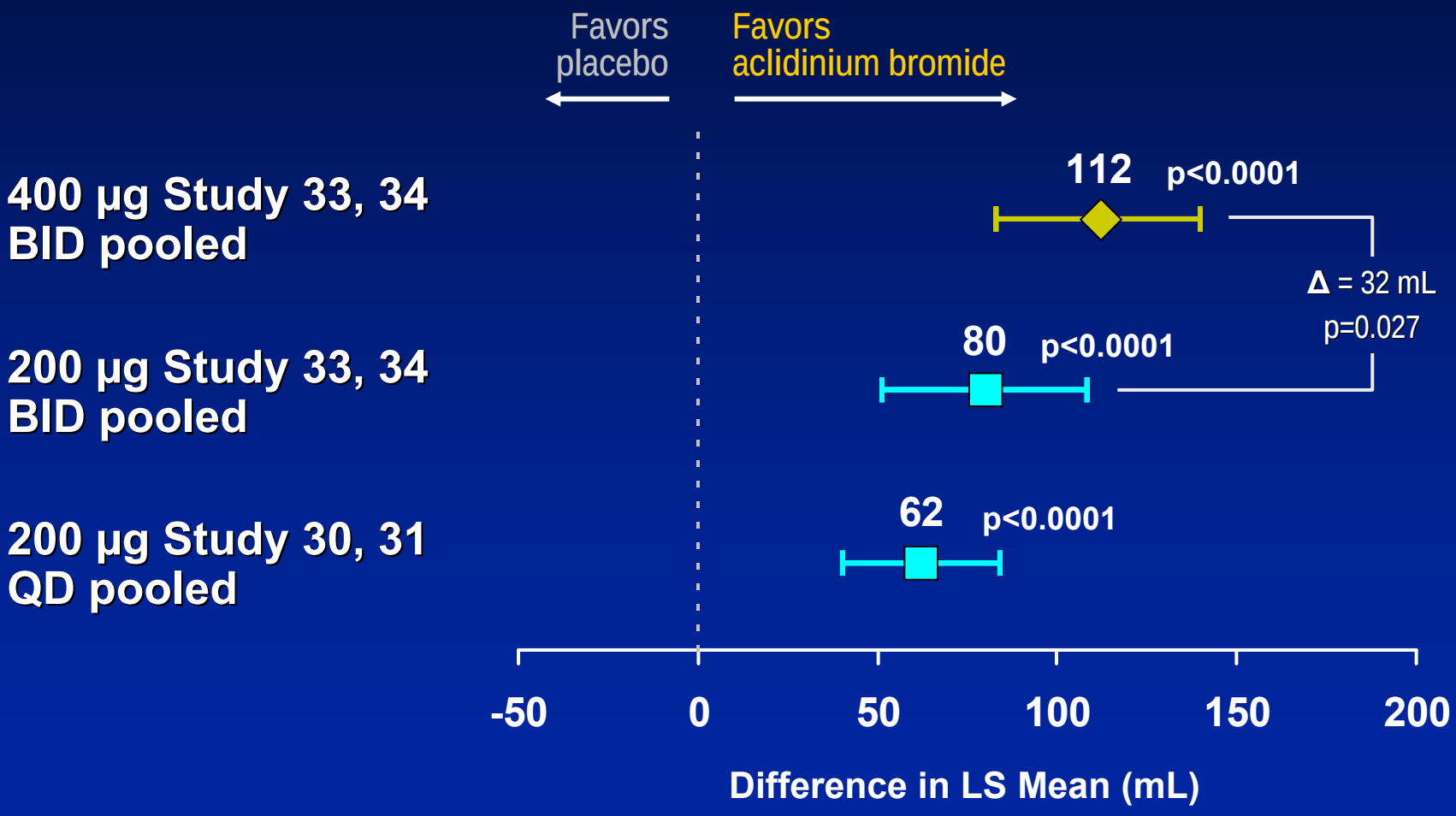
Summary
Totality of Evidence

Totality of Evidence: Change from Baseline in Trough FEV_1 (ITT)



p≤0.0001 for all comparisons vs. placebo

Totality of Evidence: Pooled Analysis Change from Baseline in Trough FEV_1 at Week 12



Summary of Clinical Efficacy – Lung Function

- BID Program established 400 µg BID as the lowest effective dose to achieve clinically meaningful improvements in lung function
  - Maximum bronchodilation after the first dose and persistence of effect
  - Effect similar to tiotropium and formoterol
  - Effect demonstrated in all sub-groups
- Other spirometric endpoints were consistent with trough FEV_1 results

Summary of Clinical Efficacy – Supportive Clinical Endpoints

- Consistent improvements observed with AB 400 µg BID in SGRQ
  - Study 34 (24 weeks) showed clinically relevant improvements (MCID)
- Clinically relevant improvement (MCID) in dyspnea as measured by TDI in AB 400 µg BID that was not observed in 200 µg BID
- Statistically significant reduction in rescue medication use was observed compared to placebo
- In all studies, there was a consistent trend toward reduction in exacerbations

Presentation Overview

Introduction	***Lisa Travis, MS, RAC*** Senior Director, Regulatory Affairs Forest Research Institute, Inc.
Medical Need & Introduction to Aclidinium Bromide	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Aclidinium Investigator
Dose Finding & Efficacy	***Cynthia Caracta, MD, FCCP*** Director, Clinical Development - Respiratory Forest Research Institute, Inc.
Safety	***Harry Sacks, MD, FAAP*** Executive Director and Head Clinical Development - Respiratory Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Aclidinium Investigator

Safety

Harry Sacks, MD

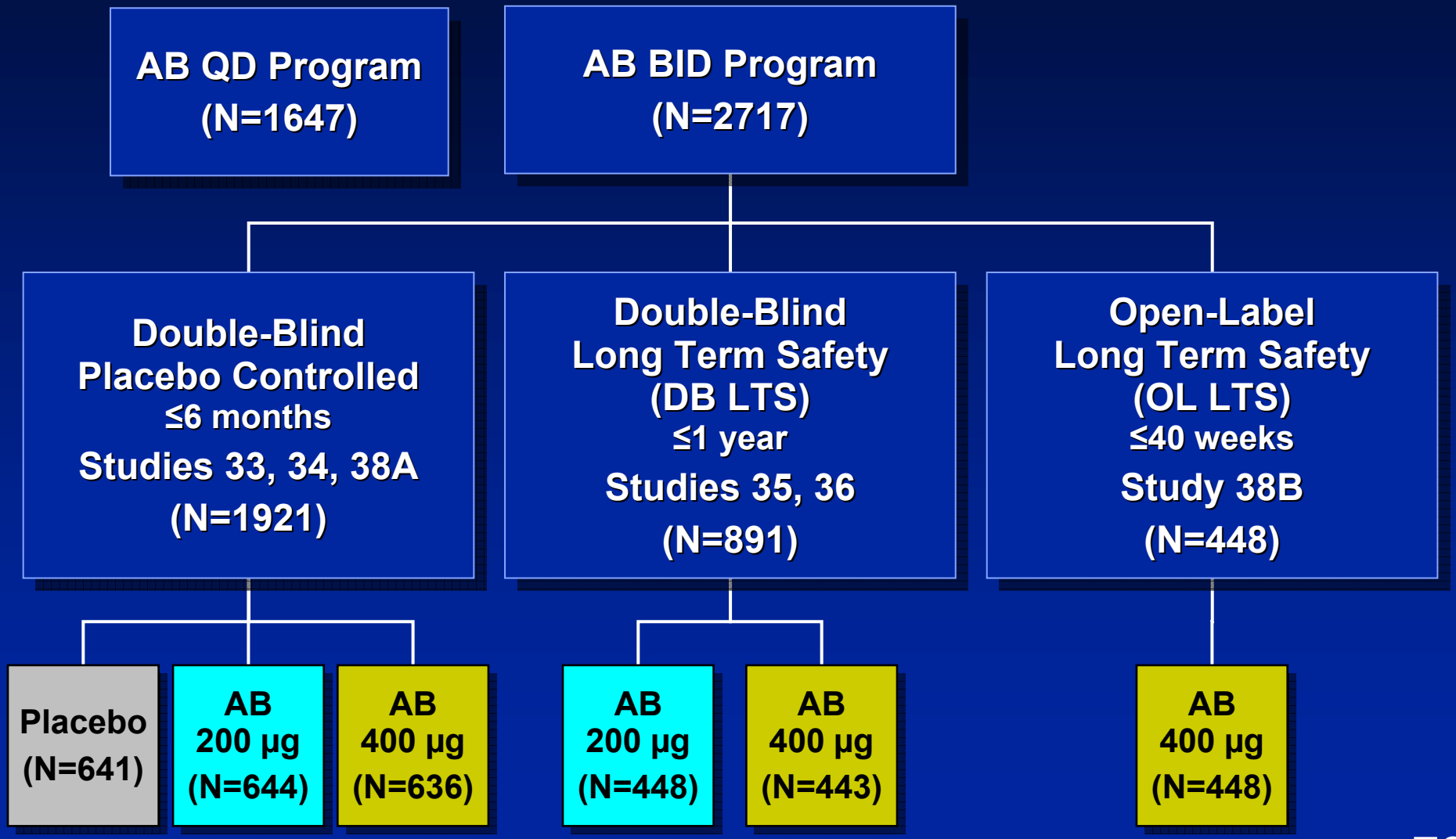
Executive Director,
Clinical Development - Respiratory
Forest Research Institute, Inc.

Aclidinium Bromide: Safety Overview

- Patient Groupings and Exposure
- Treatment Emergent Adverse Events (TEAEs)
- Discontinuations due to Adverse Events
- Serious Adverse Events (SAEs)
- All Cause Mortality
- Adverse Events of Special Interest
  - Cardiovascular Safety
  - Pneumonia
  - Anticholinergic Side Effects

Aclidinium Bromide Development Program

Safety groups (N=4364)



Extent of Exposure

Safety population

Exposure, n	ICH Guidelines	Aclidinium Bromide 400 µg BID	Tiotropium Registration Trials
Total Exposure	1500	1471	1308
≥84 days (12 weeks)		1141	1179
≥168 days (24 weeks)	300-600	970	1152
≥330days (47 weeks)	100	395	562

Long Term Safety Study Designs

Study 35 (52 wks)

Study 35 (52 wks)
Aclidinium 200 µg BID
Aclidinium 400 µg BID

Study 36 (64 wks)

Study 33 (12 wks)	Study 36 (52 wks)
AB200	Aclidinium 200 µg BID
AB400	Aclidinium 400 µg BID
Placebo	Aclidinium 200 µg BID
	Aclidinium 400 µg BID

Study 38 (52 wks)

Study 38A (12 wks)	Study 38B (Open-label 40 wks)
AB200	Aclidinium 400 µg BID
AB400	
Placebo	

Aclidinium Bromide: Safety Overview

- Patient Groupings and Exposure
- ***Treatment Emergent Adverse Events (TEAEs)***
- Discontinuations due to Adverse Events
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Placebo Controlled Studies
Overview

		Aclidinium Bromide	
	Placebo BID (N=641) n (%)	200 µg BID (N=644) n (%)	400 µg BID (N=636) n (%)
Patients with at least 1 TEAE	344 (53.7)	321 (49.8)	319 (50.2)
Overall discontinuation due to AE	31 (4.8)	26 (4.0)	27 (4.2)
Patients with at least 1 SAE	20 (3.1)	14 (2.2)	15 (2.4)
MACE composite	2 (0.3)	2 (0.3)	2 (0.3)
Mortality	2 (0.3)	1 (0.2)	3 (0.5)

Placebo Controlled Studies

Treatment Emergent Adverse Events ≥2%

Preferred Term	Placebo BID (N=641) n (%)	Aclidinium Bromide 200 µg BID (N=644) n (%)	Aclidinium Bromide 400 µg BID (N=636) n (%)
Patients with at least 1 TEAE	344 (53.7)	321 (49.8)	319 (50.2)
COPD (exacerbation)	100 (15.6)	77 (12.0)	75 (11.8)
Headache	32 (5.0)	43 (6.7)	42 (6.6)
Nasopharyngitis	25 (3.9)	40 (6.2)	35 (5.5)
Cough	14 (2.2)	17 (2.6)	19 (3.0)
Diarrhea	9 (1.4)	12 (1.9)	17 (2.7)
Hypertension	16 (2.5)	8 (1.2)	10 (1.6)
Back pain	12 (1.9)	18 (2.8)	8 (1.3)
Bronchitis	13 (2.0)	5 (0.8)	7 (1.1)

Long Term Safety Studies
Overview

	DB LTS		OL LTS
	200 µg BID (N=448) n (%)	400 µg BID (N=443) n (%)	400 µg BID (N=448) n (%)
Patients with at least 1 TEAE	300 (67.0)	304 (68.6)	289 (64.5)
Overall discontinuation due to AE	46 (10.3)	39 (8.8)	29 (6.5)
Patients with at least 1 SAE	23 (5.1)	24 (5.4)	25 (5.6)
MACE composite	7 (1.6)	6 (1.4)	7 (1.6)
Mortality	2 (0.4)	2 (0.5)	3 (0.7)

Long Term Safety Studies

TEAEs ≥3%

Any treatment group

Preferred Term	DB LTS		OL LTS
	200 µg BID (N=448) n (%)	400 µg BID (N=443) n (%)	400 µg BID (N=448) n (%)
Patients with at least 1 TEAE	300 (67.0)	304 (68.8)	289 (64.5)
COPD (exacerbation)	95 (21.2)	91 (20.5)	81 (18.1)
Nasopharyngitis	24 (5.4)	25 (5.6)	21 (4.7)
Sinusitis	22 (4.9)	16 (3.6)	19 (4.2)
Upper respiratory tract tnfection	20 (4.5)	16 (3.6)	26 (5.8)
Cough	19 (4.2)	16 (3.6)	10 (2.2)
Headache	15 (3.3)	15 (3.4)	13 (2.9)
Urinary tract infection	13 (2.9)	15 (3.4)	11 (2.5)
Back pain	9 (2.0)	14 (3.2)	10 (2.2)
Nausea	17 (3.8)	8 (1.8)	14 (3.1)

Aclidinium Bromide: Safety Overview

- Patient Groupings and Exposure
- Treatment Emergent Adverse Events (TEAEs)
- ***Discontinuations due to Adverse Events***
- Serious Adverse Events (SAEs)
- All Cause Mortality
- Adverse Events of Special Interest
  - Cardiovascular Safety
  - Pneumonia
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Placebo Controlled Studies

Discontinuation Due to AEs ≥2 Patients

Preferred Term	Placebo BID (N=641) n (%)	Aclidinium Bromide 200 µg BID (N=644) n (%)	Aclidinium Bromide 400 µg BID (N=636) n (%)
Overall discontinuation due to AE	31 (4.8)	26 (4.0)	27 (4.2)
COPD (exacerbation)	16 (2.5)	9 (1.4)	12 (1.9)
Dyspnea	3 (0.5)	1 (0.2)	3 (0.5)
Dizziness	2 (0.3)	–	–
Ventricular tachycardia	1 (0.2)	–	2 (0.3)

Long Term Safety Studies

Discontinuation Due to AEs ≥2 Patients

Any treatment group

Preferred Term	DB LTS		OL LTS
	200 µg BID (N=448) n (%)	400 µg BID (N=443) n (%)	400 µg BID (N=448) n (%)
Overall discontinuation due to AE	46 (10.3)	39 (8.8)	29 (6.5)
COPD (exacerbation)	13 (2.9)	10 (2.3)	8 (1.8)
Cough	–	2 (0.5)	2 (0.4)
Headache	–	2 (0.5)	–
Pruritus	1 (0.2)	2 (0.5)	–
Syncope	–	2 (0.5)	–
Non-cardiac chest pain	1 (0.2)	1 (0.2)	2 (0.4)
Fatigue	2 (0.4)	–	–
Dizziness	2 (0.4)	–	–
Dyspnea	1 (0.2)	–	2 (0.4)
Acute myocardial infarction	–	–	2 (0.4)

Aclidinium Bromide: Safety Overview

- Patient Exposure and Groupings
- Treatment Emergent Adverse Events (TEAEs)
- Discontinuations due to Adverse Events
- *Serious Adverse Events (SAEs)*
- All Cause Mortality
- Adverse Events of Special Interest
  - Cardiovascular Safety
  - Pneumonia
  - Anticholinergic Side Effects

Placebo Controlled Studies

SAEs in ≥2 Patients

Preferred Term	Placebo BID (N=641) n (%)	Aclidinium Bromide 200 µg BID (N=644) n (%)	Aclidinium Bromide 400 µg BID (N=636) n (%)
Patients with at least 1 SAE	20 (3.1)	14 (2.2)	15 (2.4)
COPD (exacerbation)	17 (2.7)	9 (1.4)	10 (1.6)
Acute respiratory failure	1 (0.2)	–	2 (0.3)
Cardiac failure congestive	–	–	2 (0.3)
Angina pectoris	–	2 (0.3)	1 (0.2)
Pneumonia	2 (0.3)	–	1 (0.2)
Suicidal ideation	1 (0.2)	2 (0.3)	1 (0.2)
Lung adenocarcinoma	–	2 (0.3)	–
Bipolar disorder	–	2 (0.3)	–
Depression	–	2 (0.3)	–

Long Term Safety Studies

SAEs in ≥3 Patients

Preferred Term	DB LTS		OL LTS
	200 µg BID (N=448) n (%)	400 µg BID (N=443) n (%)	400 µg BID (N=448) n (%)
Patients with at least 1 SAE	23 (5.1)	24 (5.4)	25 (5.6)
COPD (exacerbation)	10 (2.2)	13 (2.9)	14 (3.1)
Pneumonia	6 (1.3)	4 (0.9)	2 (0.4)
Acute myocardial infarction	4 (0.9)	3 (0.7)	2 (0.4)
Respiratory failure	1 (0.2)	3 (0.7)	–
Coronary artery disease	2 (0.4)	1 (0.2)	4 (0.9)

Aclidinium Bromide: Safety Overview

- Patient Groupings and Exposure
- Treatment Emergent Adverse Events (TEAEs)
- Discontinuations due to Adverse Events
- Serious Adverse Events (SAEs)
- ***All Cause Mortality***
- Adverse Events of Special Interest
  - Cardiovascular Safety
  - Pneumonia
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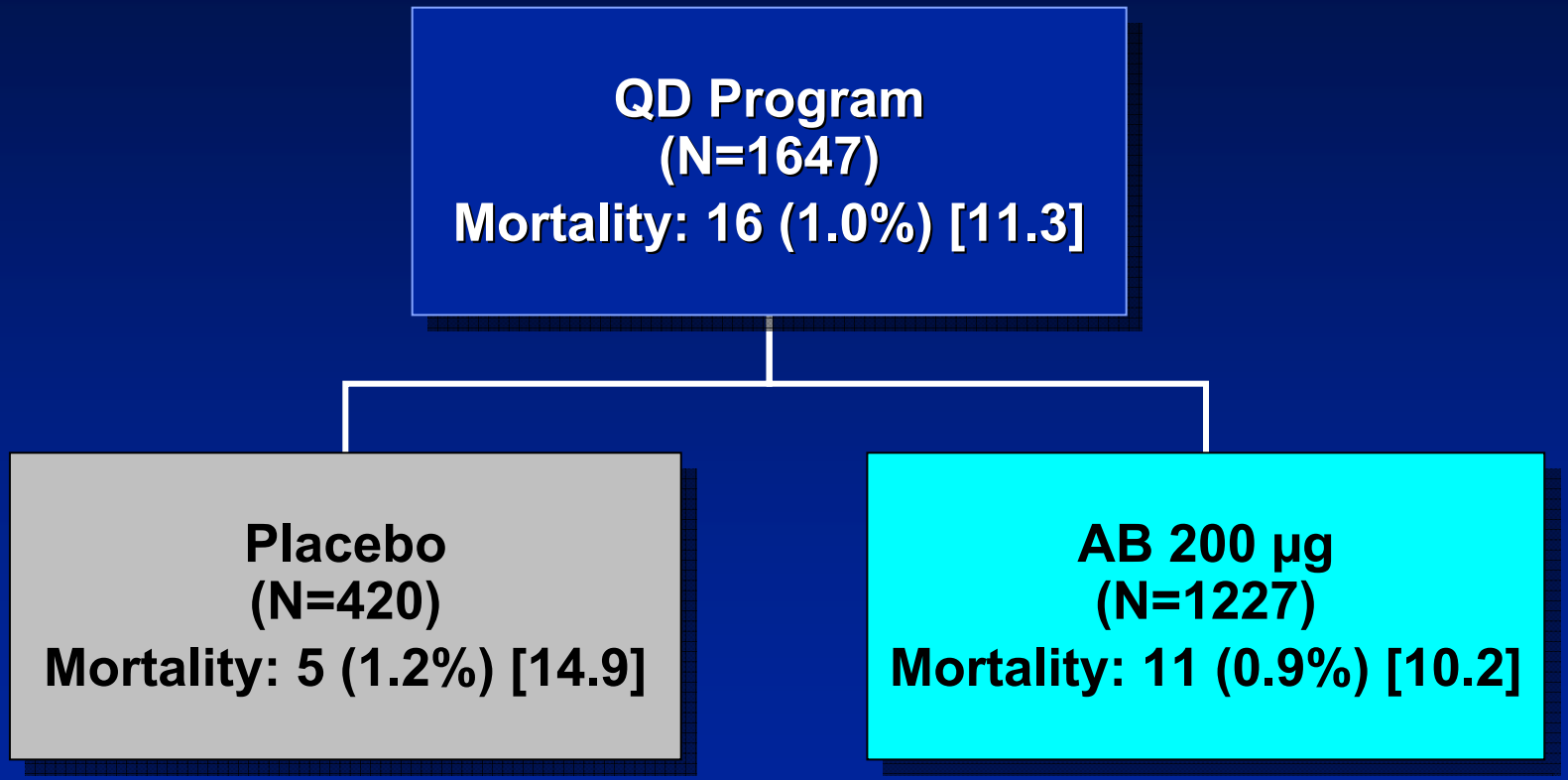
QD Program

Overview of All Cause Mortality

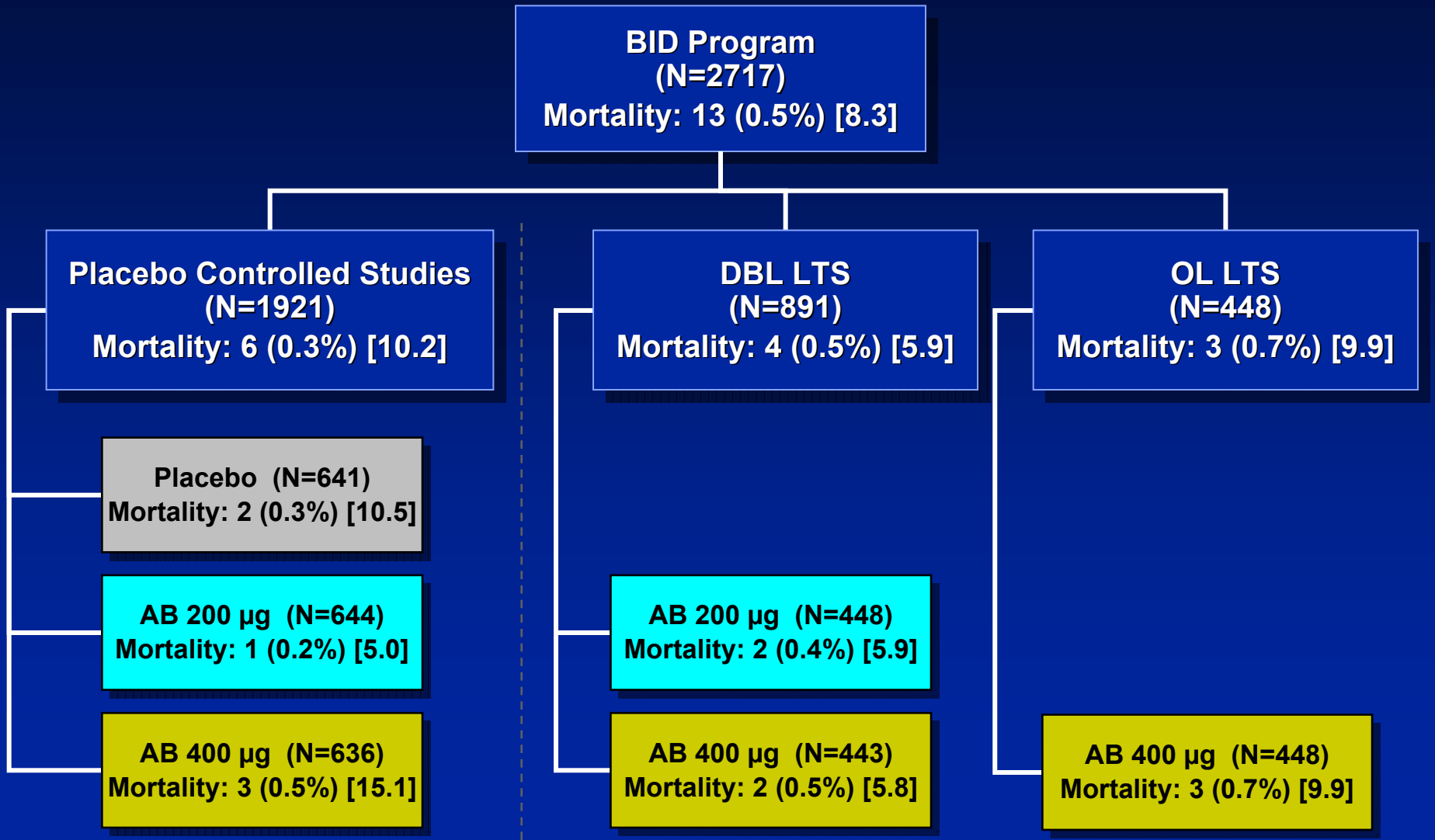
Safety population



BID Program

Overview of All Cause Mortality

Safety population



Cumulative Incidence of Mortality in BID Development Program

Treatment Group	Deaths per 1000 PY
Placebo (N=641)	10.5
Aclidinium Bromide 200 µg (N=999)	8.6
Aclidinium Bromide 400 µg (N=1274)	11.5

Includes deaths recorded during the study, within 30 days of last dose of investigational product, or that followed AE or discontinuation within 30 days

Summary of All Cause Mortality

- There was no increase in mortality for Aclidinium compared to placebo
- Death occurred infrequently and sporadically throughout studies
- There was no imbalance between treatment arms
- Causes of death were variable and as expected in a COPD population

Aclidinium Bromide: Safety Overview

- Patient Groupings and Exposure
- Treatment Emergent Adverse Events (TEAEs)
- Discontinuations due to Adverse Events
- Serious Adverse Events (SAEs)
- All Cause Mortality
- ***Adverse Events of Special Interest***
  - ***Cardiovascular Safety***
  - Pneumonia
  - Anticholinergic Side Effects

Evaluation of Cardiovascular Safety

- Low systemic exposure
- Holter sub-studies and thorough QT Study
- ECG data
- Vital Signs – no change in mean BP and HR
- MACE (Major Adverse Cardiac Events)
- Standard MedDRA Queries (SMQs)

Holter Sub-studies and TQT Study: Results

- Holter sub-study in ~170 patients/ group
  - No clinically relevant findings
  - Non-sustained SVT most frequent finding
- Negative TQT Study

Treatment	Maximal Change from Baseline in QTc	95% Confidence Interval
Moxifloxacin	15.2 msec	11.6, 18.8
AB 200 µg QD	3.3 msec	-0.4, 6.9
AB 800 µg QD	2.0 msec	-1.6, 5.6

ECG Assessment

- ~13,000 ECGs performed
- No drug related changes in intervals
- No imbalances of clinically relevant events
- 4 discontinued cases of non-sustained VT
  - 1 in placebo
    - (M/63); prior to study drug administration
  - 3 in AB 400 µg BID
    - (M/69); prior to study drug administration
    - (M/66); prior to study drug administration
    - (M/54); day 6 of the Study 38B
      - Previously treated for 81 days on AB 400 µg BID in Study 38A
- 1 atrial fibrillation in placebo
- 1 atrial fibrillation and 1 atrial flutter in 400 µg BID of LTS
- 1 sick sinus syndrome in the 200 µg of LTS

Placebo Controlled Studies

MACE

Serious only

	Placebo BID (N=641) [PY=190.6] n (%) [per 1000 PY]	Aclidinium Bromide 200 µg BID (N=644) [PY=199.4] n (%) [per 1000 PY]	Aclidinium Bromide 400 µg BID (N=636) [PY=198.4] n (%) [per 1000 PY]
MACE composite	2 (0.3) [10.5]	2 (0.3) [10.0]	2 (0.3) [10.1]
CV death[a]	–	1 (0.2) [5.0]	1 (0.2) [5.0]
Non-fatal myocardial infarction	1 (0.2) [5.2]	–	–
Non-fatal stroke	1 (0.2) [5.2]	1 (0.2) [5.0]	1 (0.2) [5.0]
FDA MACE composite[b]	4 (0.6) [21.0]	2 (0.3) [10.0]	2 (0.3) [1.01]

[a] Includes information from blinded external adjudication.

[b] Includes information from blinded internal adjudication.

Placebo Controlled Studies

Cardiac SMQ

Serious only

SMQ Categories	Placebo BID (N=641) [PY=190.6] n (%) [per 1000 PY]	Aclidinium Bromide 200 µg BID (N=644) [PY=199.4] n (%) [per 1000 PY]	Aclidinium Bromide 400 µg BID (N=636) [PY=198.4] n (%) [per 1000 PY]
TOTAL	6 (1.1) [31.5]	9 (1.5) [45.1]	6 (1.1) [30.2]
Cardiac failure	1 (0.2) [5.2]	1 (0.2) [5.0]	3 (0.5) [15.1]
Ischemic heart disease	2 (0.3) [10.5]	4 (0.6) [20.1]	1 (0.2) [5.0]
Other ischemic heart disease	1 (0.2) [5.2]	3 (0.5) [15.0]	1 (0.2) [5.0]
Bradyarrhythmia	–	–	1 (0.2) [5.0]
Myocardial infarction	1 (0.2) [5.2]	1 (0.2) [5.0]	–
Supraventricular tachyarrhythmias	1 (0.2) [5.2]	–	–

Long Term Safety Studies
MACE
Serious only

	DB LTS		OL LTS
	200 µg BID (N=448) [340.6] n (%) [per 1000 PY]	400 µg BID (N=443) [PY=341.9] n (%) [per 1000 PY]	400 µg BID (N=448) [PY=302.3] n (%) [per 1000 PY]
MACE composite	7 (1.6) [20.6]	6 (1.4) [17.5]	7 (1.6) [23.2]
CV death[a]	–	1 (0.2) [2.9]	2 (0.4) [6.6]
Non-fatal myocardial infarction	5 (1.1) [14.7]	3 (0.7) [8.8]	2 (0.4) [6.6]
Non-fatal stroke	2 (0.4) [5.9]	2 (0.5) [5.8]	4 (0.9) [13.2]
FDA MACE composite[b]	8 (1.8) [23.5]	7 (1.6) [20.5]	12 (2.7) [39.7]

[a] Includes information from blinded external adjudication.

[b] Includes information from blinded internal adjudication.

Long Term Safety Studies

Cardiac SMQ

Serious only

Category	DB LTS		OL LTS
	200 µg BID (N=448) [340.6] n (%) [per 1000 PY]	400 µg BID (N=443) [PY=341.9] n (%) [per 1000 PY]	400 µg BID (N=448) [PY=302.3] n (%) [per 1000 PY]
TOTAL	17 (3.8) [49.9]	15 (3.5) [43.9]	15 (3.2) [49.6]
Ischemic heart disease	7 (1.6) [20.6]	5 (1.1) [17.1]	6 (1.3) [19.8]
Other ischemic heart disease	3 (0.7) [8.8]	3 (0.7) [12.4]	5 (1.1) [16.5]
Myocardial infarction	5 (1.1) [14.7]	3 (0.7) [7.8]	2 (0.4) [6.6]
Cardiac failure	1 (0.2) [2.9]	2 (0.5) [6.2]	2 (0.4) [6.6]
Supraventricular tachyarrhythmias	–	2 (0.5) [3.1]	–
Bradyarrhythmia	1 (0.2) [2.9]	–	–

Cardiovascular Events Conclusions

- MACE events were rare and evenly distributed between treatment arms
- Cardiac failure and conduction defects were rare and balanced between treatment arms
- TQT study revealed no prolongation of QT interval nor conduction abnormalities of clinical concern
- Cerebrovascular events including stroke were rare and balanced between treatment arms
- Nature of serious events occurred as expected in the general COPD population

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  - Cardiovascular Safety
  - ***Pneumonia***
  - ***Anticholinergic Side Effects***

Pneumonia

Placebo Controlled Studies		Aclidinium Bromide	
	Placebo BID (N=641) n (%)	200 µg BID (N=644) n (%)	400 µg BID (N=636) n (%)
Patients with at least 1 pneumonia related TEAE	5 (0.8)	4 (0.6)	2 (0.3)

Long Term Safety Studies	DB LTS		OL LTS
	200 µg BID (N=448) n (%)	400 µg BID (N=443) n (%)	400 µg BID (N=448) n (%)
Patients with at least 1 pneumonia related TEAE	14 (3.1)	13 (2.9)	8 (1.8)

Placebo Controlled Studies

Potential Anticholinergic Events >2 Patients and >Placebo

Preferred Term	Placebo BID (N=641) n (%)	Aclidinium Bromide 200 µg BID (N=644) n (%)	Aclidinium Bromide 400 µg BID (N=636) n (%)
Dry mouth	4 (0.6)	7 (1.1)	5 (0.8)
Dysphonia	–	2 (0.3)	3 (0.5)
Urinary tract infection	6 (0.9)	11 (1.7)	6 (0.9)
Palpitations	1 (0.2)	4 (0.6)	1 (0.2)
Pyrexia	3 (0.5)	2 (0.3)	5 (0.8)
Dizziness	5 (0.8)	7 (1.1)	4 (0.6)

Overall Conclusions

Aclidinium Bromide in COPD

Efficacy

- Aclidinium bromide 400 µg BID showed clinically meaningful effects in Lung Function and other important supportive outcomes:
  - SGRQ
  - TDI
  - Rescue medication
  - Exacerbations

Safety

- Safety database meets regulatory standards and demonstrates aclidinium is well tolerated
- No imbalance vs. placebo nor consistent dose response in safety outcome rates including all-cause mortality, SAEs, TEAEs, ADOs
- No difference in overall MACE score vs. placebo or across doses despite small and inconsistent imbalances in individual components

Benefit / Risk Conclusions

- Totality of data consistently show aclidinium 400 µg BID is safe and effective with a positive benefit risk profile that can be clearly communicated in the label
- Forest is committed to an ongoing assessment of efficacy and safety of aclidinium bromide throughout the life of the product
  - Forest plans to evaluate the effect of aclidinium on exacerbations and confirm CV safety in a Phase IV study

Presentation Overview

Introduction	***Lisa Travis, MS, RAC*** Senior Director, Regulatory Affairs Forest Research Institute, Inc.
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Dose Finding & Efficacy	***Cynthia Caracta, MD, FCCP*** Director, Clinical Development - Respiratory Forest Research Institute, Inc.
Safety	***Harry Sacks, MD, FAAP*** Executive Director and Head Clinical Development - Respiratory Forest Research Institute, Inc.
Risk/Benefit & Clinician Perspective	***Stephen Rennard, MD, FCCP*** Professor of Internal Medicine University of Nebraska Medical Center Aclidinium Investigator

Risk/Benefit & Clinician Perspective

Stephen Rennard, MD, FCCP

Professor of Internal Medicine
University of Nebraska Medical Center
Aclidinium Investigator

There is pressing need to develop new drugs for COPD...

FDA 2007 Draft Guidance for Industry

"Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment"

Aclidinium Bromide

- 400 µg BID
  - Effective bronchodilator
  - Supportive efficacy
    - Health status
    - Exacerbations
    - Dyspnea
- Risks
  - Tolerability
  - Safety
  - Exposure

Long Acting Inhaled Bronchodilators a Cornerstone of COPD Management

- LAMA
  - Tiotropium (QD)
  - Aclidinium (BID)
- LABA
  - Salmeterol (BID)
  - Formoterol (BID)
  - Arformoterol (BID)
  - Indacaterol (QD)

Long Acting Inhaled Bronchodilators a Cornerstone of COPD Management

- LAMA
  - Tiotropium (QD)
  - Aclidinium (BID)
- LABA
  - Salmeterol (BID)
  - Formoterol (BID)
  - Arformoterol (BID)
  - Indacaterol (QD)

Challenges with Current Therapies

- Side effects
- Device
- Personalized medicine

Aclidinium Bromide and COPD Management

- New LAMA
- Twice daily
- Device
- Side effects
  - Experience
  - Anxiety

COPD Heterogeneity

- Clinical features
- Comorbidities
- Response to treatment
  - Drug preference
  - Drug tolerability

There is pressing need to develop new drugs for COPD...

FDA 2007 Draft Guidance for Industry

"Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment"

Q&A Slides

FDA CDER

Pulmonary-Allergy Drugs Advisory Committee Meeting

February 23, 2012

Aclidinium Affinity for Muscarinic Receptors Is Higher than Ipratropium and Similar to Tiotropium

	M_1	M_2	M_3	M_4	M_5
Aclidinium	**0.09**	**0.10**	**0.12**	**0.25**	**0.16**
Tiotropium	**0.13**	**0.09**	**0.14**	**0.38**	**0.18**
Ipratropium	**1.29**	**1.01**	**1.25**	**2.11**	**3.22**

Data are Ki values in nM concentration

Residence Time on Human M_3 Receptor

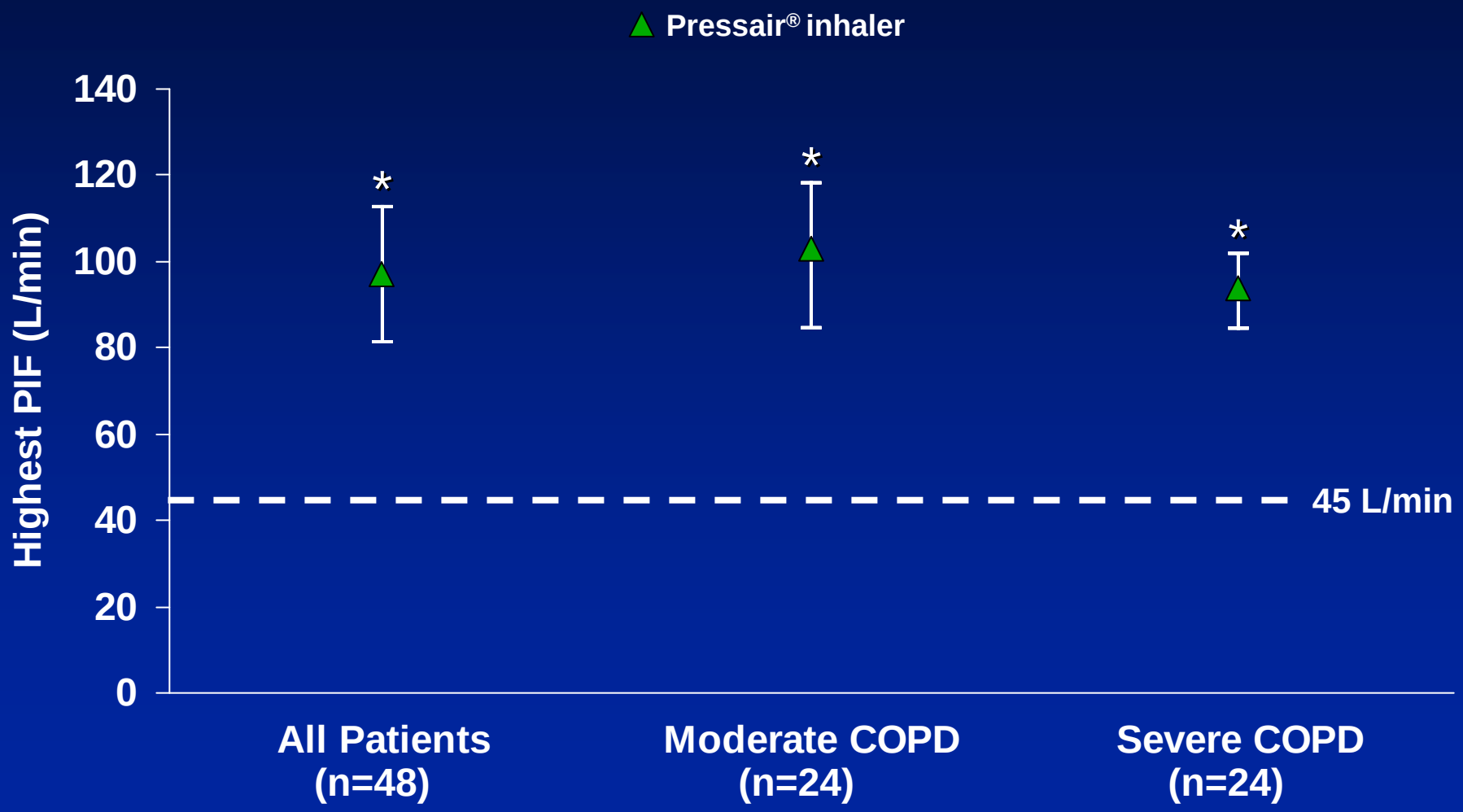
	M_3 Dissociation Half-life (h)
Aclidinium	29.2
Tiotropium	62.2
Ipratropium	0.47

Aclidinium Kinetic Selectivity of M_3 Receptors over M_2 Receptors

	M_2 Dissociation Half-life (h)	M_3 Dissociation Half-life (h)	M_3/M_2 Ratio
Aclidinium	4.7	29.2	6.2
Tiotropium	15.1	62.2	4.1
Ipratropium	0.08	0.47	5.9

Study CL-07

Patients with COPD Can Generate Enough Peak Inspiratory Flows to Successfully Actuate Pressair®



Magnussen et al, Respir Med. 2009

Comparison across Phase 3 Studies: Baseline & Demographics

Safety population

	Study 33 (N=560)	Study 34 (N=819)	Study 38A (N=542)	Total
Age (years) (mean, SD)	64.3 (9.4)	62.4 (8.0)	62.8 (8.9)	63.1 (8.8)
Gender (% male)	53.0 %	67.4 %	53.1 %	59.2%
Race (%)				
Caucasian	93.8 %	95.2 %	90.6 %	93.5%
African-American	5.2 %	0.2 %	8.3 %	4.0%
Others	0.4 %	4.2 %	0.4 %	2.0%
BMI (Kg/m^2) (mean, SD)	27.5 (5.1)	26.7 (4.9)	27.6 (5.8)	27.2% (5.2)
COPD severity (GOLD stages) (%)				
Stage II (Moderate)	58.4 %	68.1 %	53.0 %	60.8%
Stage III (Severe)	39.5 %	31.9 %	45.8 %	38.0%
Stage IV (Very severe)	0.9 %	0 %	0.2 %	0.3%
Current smoker (%)	44.8 %	52.8 %	53.3 %	50.6%
Smoking history (pack-years) (mean, SD)	54.3 (26.8)	40.2 (19.8)	53.8 (29.1)	48.2% (25.7)

BID Program – Studies 33, 34, 35, and 38A

Medical History: SOC ≥20%

System Organ Class	Placebo (N=641) n (%)	Aclidinium Bromide 200 µg (N=955) n (%)	Aclidinium Bromide 400 µg (N=927) n (%)	Aclidinium Bromide Overall (N=1882) n (%)
Vascular disorders	362 (56.5)	548 (57.4)	529 (57.1)	1077 (57.2)
Surgical and medical procedures	317 (49.5)	494 (51.7)	487 (52.5)	981 (52.1)
Musculoskeletal and connective tissue disorders	299 (46.6)	472 (49.4)	494 (53.3)	966 (51.3)
Metabolism and nutrition disorders	270 (42.1)	422 (44.2)	413 (44.6)	835 (44.4)
Gastrointestinal disorders	254 (39.6)	390 (40.8)	383 (41.3)	773 (41.1)
Psychiatric disorders	184 (28.7)	300 (31.4)	305 (32.9)	605 (32.1)
Nervous system disorders	159 (24.8)	279 (29.2)	272 (29.3)	551 (29.3)
Infections and infestations	151 (23.6)	274 (28.7)	274 (29.6)	548 (29.1)
Cardiac disorders	148 (23.1)	237 (24.8)	254 (27.4)	491 (26.1)
Respiratory, thoracic, and mediastinal disorders	141 (22.0)	231 (24.2)	225 (24.3)	456 (24.2)
Immune system disorders	130 (20.3)	223 (23.4)	228 (24.6)	451 (24.0)

Phase 3 Studies

Prior Medications for COPD

Safety population

Treatment	Study 34			Study 33			Study 38A		
	AB 400 µg (N=269)	AB 200 µg (N=277)	Placebo (N=273)	AB 400 µg (N=190)	AB 200 µg (N=184)	Placebo (N=186)	AB 400 µg (N=177)	AB 200 µg (N=183)	Placebo (N=182)
Any Medication	237 (88.1)	248 (89.5)	251 (91.9)	161 (84.7)	145 (78.8)	149 (80.1)	144 (81.4)	143 (78.1)	132 (72.5)
SABAs	141 (52.4)	135 (48.7)	137 (50.2)	127 (66.8)	118 (64.1)	114 (61.3)	97 (54.8)	92 (50.3)	95 (52.2)
LABA+ICS	38 (14.1)	37 (13.4)	42 (15.4)	73 (38.4)	73 (39.7)	64 (34.4)	54 (30.5)	57 (31.1)	55 (30.2)
LAMAs	77 (28.6)	86 (31.0)	58 (21.2)	53 (27.9)	60 (32.6)	56 (30.1)	51 (28.8)	49 (26.8)	43 (23.6)
ICSs	100 (37.2)	97 (35.0)	115 (42.1)	16 (8.4)	12 (6.5)	19 (10.2)	21 (11.9)	26 (14.2)	16 (8.8)
Oxygen	2 (0.7)	2 (0.7)	3 (1.1)	11 (5.8)	10 (5.4)	12 (6.5)	N/A	N/A	N/A
SAMAs	41 (15.2)	45 (16.2)	45 (16.5)	16 (8.4)	7 (3.8)	5 (2.7)	2 (1.1)	8 (4.4)	3 (1.6)
LABAs	81 (30.1)	77 (27.8)	90 (33.0)	6 (3.2)	9 (4.9)	12 (6.5)	11 (6.2)	10 (5.5)	4 (2.2)
Xanthines	50 (18.6)	62 (22.4)	59 (21.6)	5 (2.6)	1 (0.5)	2 (1.1)	6 (3.4)	6 (3.3)	6 (3.3)
SABA+SAMA	30 (11.2)	32 (11.6)	26 (9.5)	2 (1.1)	–	–	25 (14.1)	24 (13.1)	16 (8.8)

Studies 33 and 38A

Patient Population by Race

Race	Placebo BID (N=368) n (%)	Aclidinium Bromide 200 µg BID (N=367) n (%)	Aclidinium Bromide 400 µg BID (N=367) n (%)
White	343 (93.21)	332 (90.46)	341 (92.92)
Black	22 (5.98)	30 (8.17)	22 (5.99)
Asian	1 (0.27)	1 (0.27)	2 (0.54)
American Indian/ Alaska native	1 (0.27)	1 (0.27)	2 (0.54)
Other	1 (0.27)	3 (0.82)	–

Placebo Controlled Studies

Overview – African American Population

Event	Placebo (N=22) n (%)	Aclidinium Bromide 200 µg BID (N=32) n (%)	Aclidinium Bromide 400 µg BID (N=22) n (%)
Patients with at least 1 TEAE	7 (31.8)	12 (37.5)	6 (27.3)
Overall discontinuation due to AE	2 (9.1)	1 (3.1)	2 (9.1)
Patients with at least 1 SAE	1 (4.5)	1 (3.1)	1 (4.5)
MACE composite [a]	–	–	–
Mortality	–	–	–

a: Includes serious events only

Study 23

Overview of Adverse Events (AEs) by Treatment Group

	Aclidinium Bromide 400 µg BID (N=29) n (%)	Placebo (N=30) n (%)	Tiotropium (N=28) n (%)
Number (%) of patients with TEAEs	7 (24.1%)	8 (26.7%)	3 (10.7%)
Number (%) of patients with SAEs	0	1 (3.3%)	0
Number (%) of patients with fatal AEs	0	0	0
Number (%) of patients with AEs leading to discontinuation	0	3 (10.0%)	0

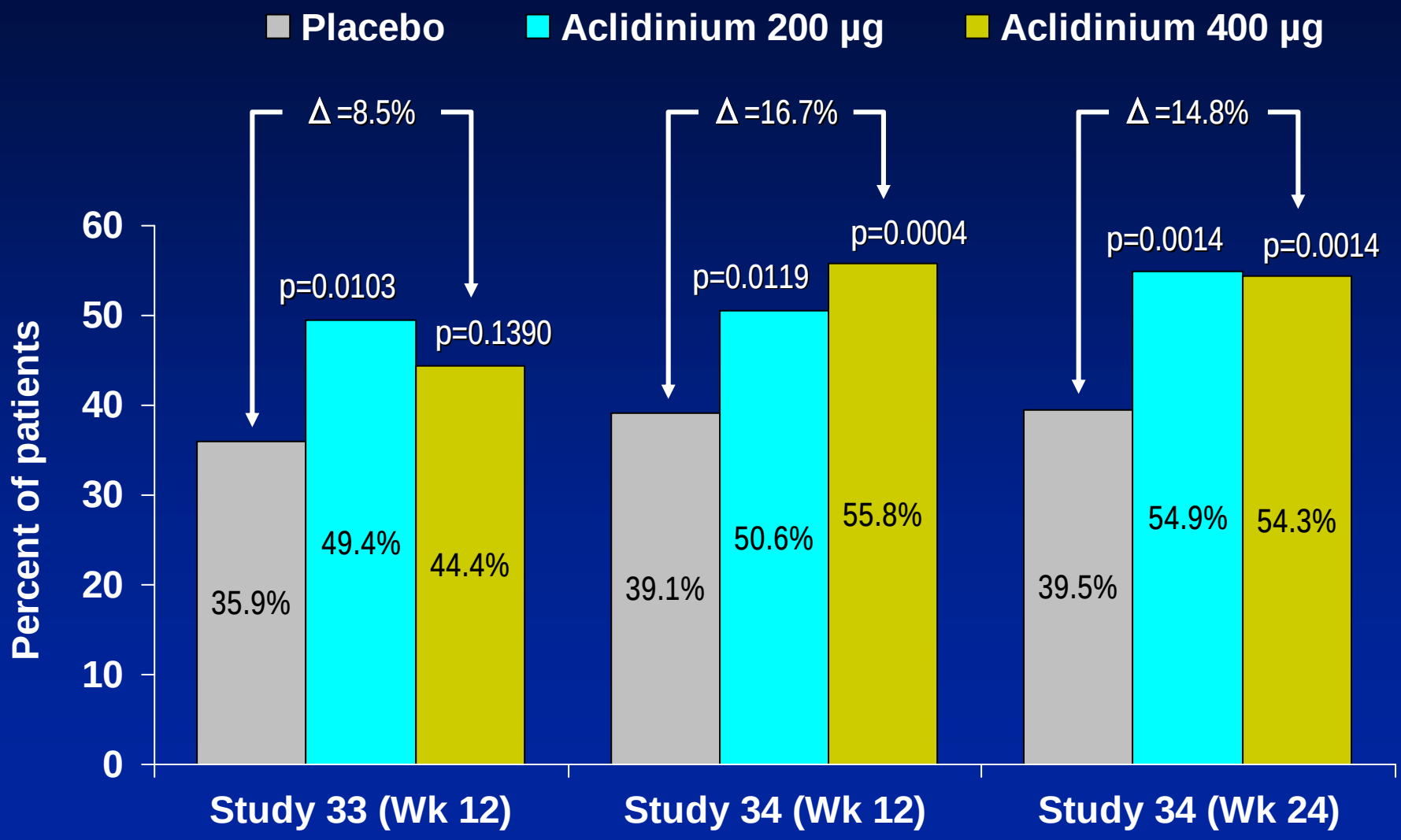
n = Number of patients belonging to the category; N = Number of patients evaluated.

SGRQ: Health Status Measurement

- **The questionnaire contains 50 items divided in two parts comprising three sections:**
  - ***Symptoms*** **concerned with respiratory symptoms, their frequency and severity**
  - ***Activity*** **concerned with activities that cause or are limited by breathlessness**
  - ***Impacts*** **which covers a range of aspects related to social functional and psychological disturbances resulting from the disease**
- **Total score = Symptoms + Activity + Impacts**
  - **Scale: 0 to 100**
  - **Decrease in score indicates improvement**
- **4 unit improvement is considered clinically relevant**

Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2:75-9.

SGRQ Total Score Comparison across Pivotal Studies: Responders (4 Unit Improvement)



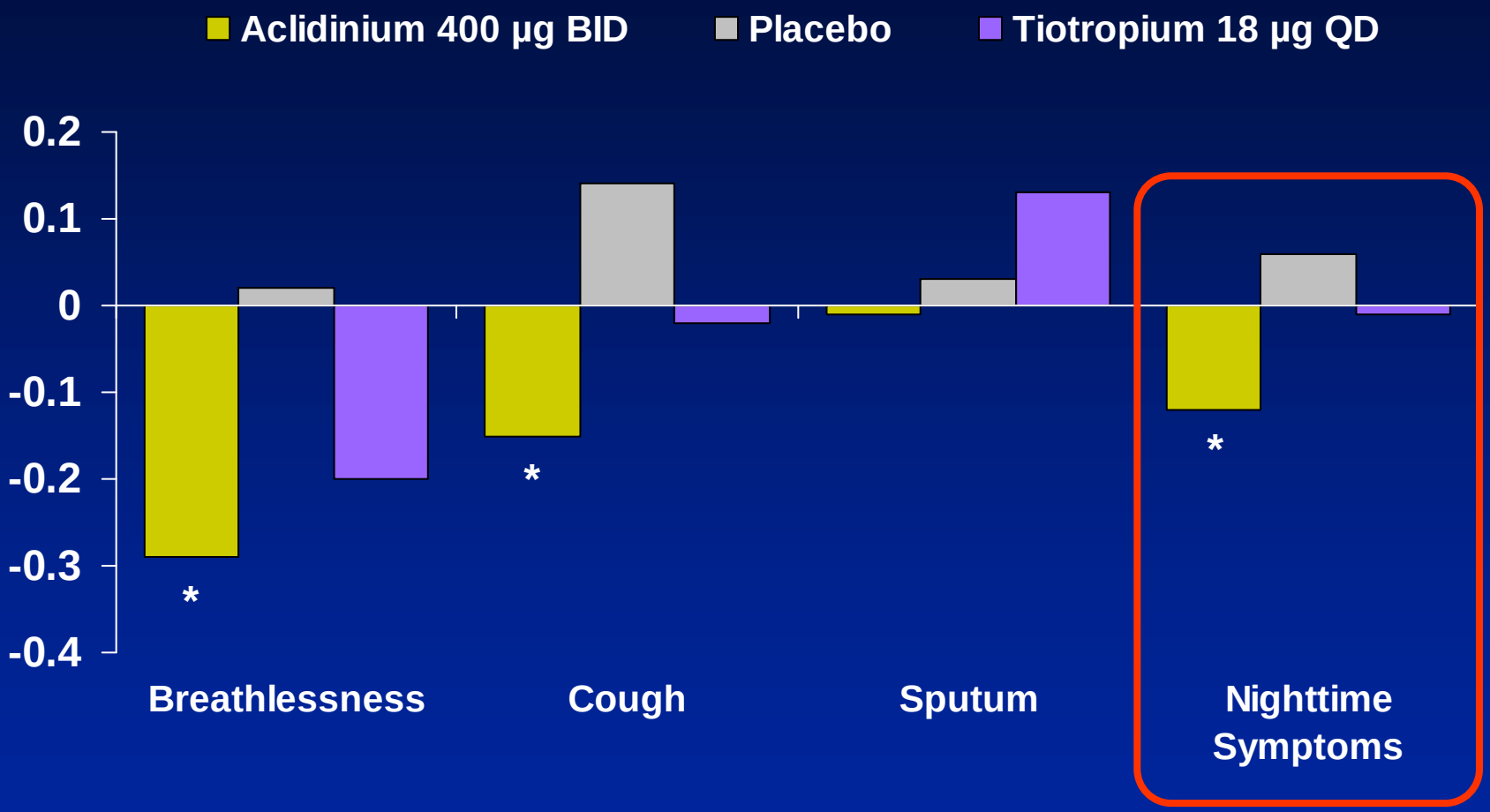
Placebo-Controlled Studies

Cardiac Failure SMQ

Serious only

SMQ/ Preferred Term	Placebo BID (N=641) n (%)	Aclidinium Bromide 200 µg BID (N=644) n (%)	Aclidinium Bromide 400 µg BID (N=636) n (%)
Cardiac failure	**1 (0.2)**	**1 (0.2)**	**3 (0.5)**
Cardiac failure congestive	–	–	2 (0.3)
Cardiac failure acute	–	–	1 (0.2)
Acute pulmonary edema	–	1 (0.2)	–
Left ventricular failure	1 (0.2)	–	–

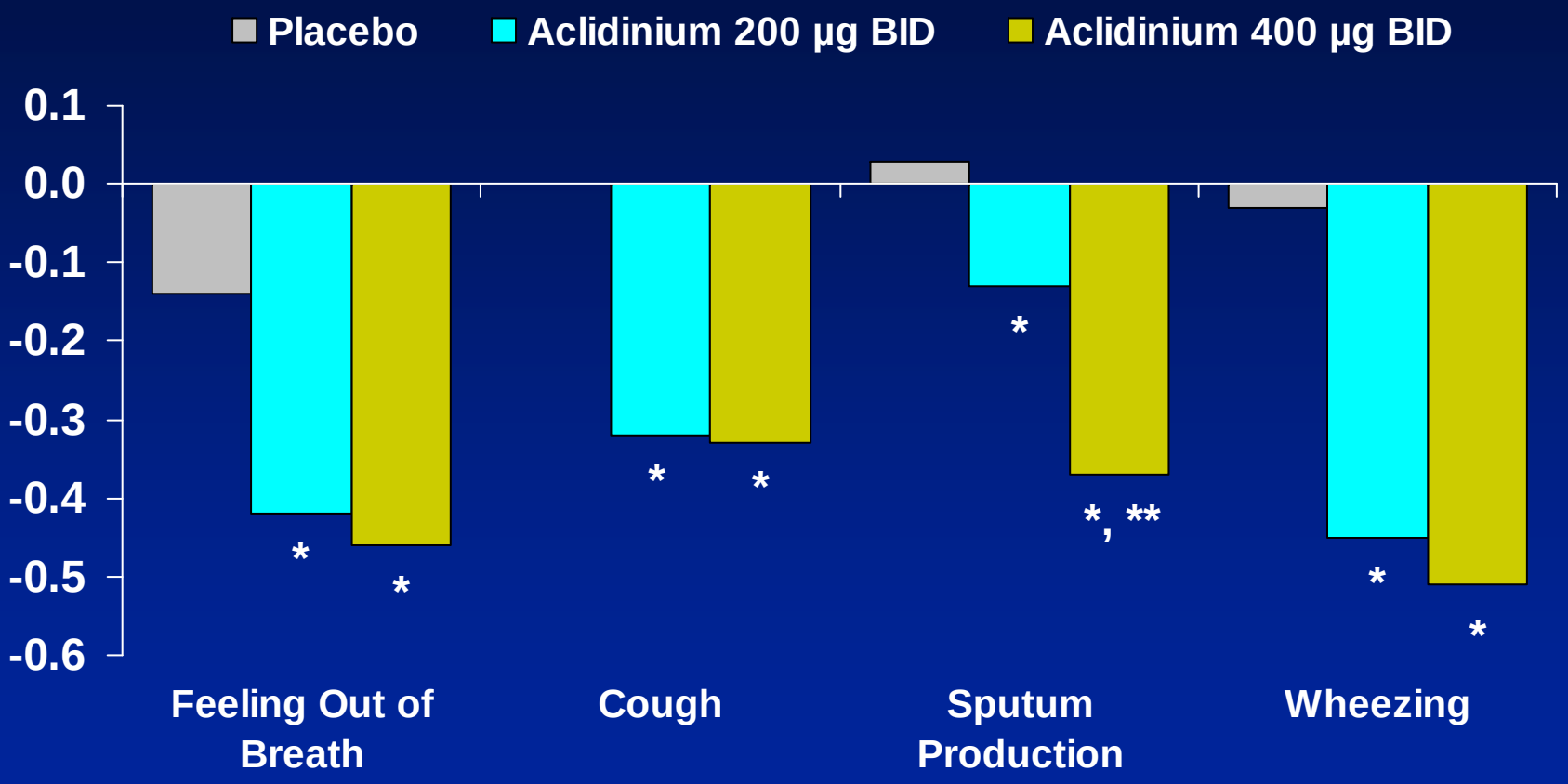
Study 23
COPD Symptoms



*p<0.05 vs placebo
Score: 0 = None; 1 = Present; 2 = Mild; 3 = Moderate; 4 = Severe
Fuhr et al, Chest 2011

Study 33

Nighttime Symptoms: Average Daily Frequency Change from Baseline



0 = Never, 1 = 1-2 times, 2 = 3-4 times, 3 = 5-6 times, 4 = 7 or more times; Recall period: previous night

* $p<0.05$ vs placebo; ** $p<0.05$ vs aclidinium 200 µg BID

Aclidinium Bromide vs. Tiotropium Registration Studies

Mortality and Cardiac Adverse Events

	Aclidinium Bromide Studies [a] (3-6 Months)			Tiotropium Studies [b] (12 Months)	
	Placebo BID (N=641) n (%)	200 µg BID (N=644) n (%)	400 µg BID (N=636) n (%)	Placebo (N=371) n (%)	Tiotropium (N=550) n (%)
Mortality [c]	2 (0.3)	1 (0.2)	3 (0.5)	7 (1.9)	7 (1.3)
Cardiac Failure	2 (0.3)	1 (0.2)	5 (0.8)	4 (1.1)	5 (0.9)
Bradycardia	–	–	2 (0.3)	1 (0.3)	1 (0.2)
Supraventricular tachycardia	4 (0.6)	4 (0.6)	1 (0.2)	1 (0.3)	2 (0.4)
Myocardial infarction	1 (0.2)	1 (0.2)	–	2 (0.5)	3 (0.5)

a: Includes only serious events.

b: Tiotropium studies include 1-year, placebo-controlled studies 205.114 and 205.115.

c: Aclidinium Bromide Studies include deaths recorded during the study, within 30 days of last dose of investigational product, or that followed AE or discontinuation within 30 days

Pulmonary-Allergy Drugs Advisory Committee Meeting. NDA 21-395 Spiriva® (tiotropium bromide) Inhalation Powder for COPD. Clinical Briefing Document, September 6, 2002.

Aclidinium Bromide vs. Tiotropium Registration Studies

Baseline Characteristics and Demographics

	Aclidinium Bromide			Tiotropium	
	Study 33 (N=560)	Study 34 (N=819)	Study 38A (N=542)	Study 114 (N=470)	Study 115 (N=451)
Age – mean (yrs)	64.3	62.4	62.8	65.18	65.19
Male – n (%)	296 (53.0)	552 (67.4)	288 (53.2)	307 (65.3)	292 (64.7)
Race – n (%) Caucasian (White)	524 (93.7)	780 (95.2)	490 (90.6)	432 (91.9)	432 (96.7)
Smoking history – mean	41.0	40.2	40.7	62.9	59.3
Duration of COPD – mean (yrs)	8.6	6.8	8.0	8.99	7.84
Post- BD FEV_1 – mean (L)	1.358	1.48	1.358	1.02	1.03
FEV_1/FVC x 100 – mean	51.7	49.6	51.2	46.19	45.14

Pulmonary-Allergy Drugs Advisory Committee Meeting. NDA 21-395 Spiriva® (tiotropium bromide) Inhalation Powder for COPD. Clinical Briefing Document, September 6, 2002.

Placebo Controlled Studies

Vital Signs

Test	Placebo BID (N=641)		Aclidinium Bromide 200 µg BID (N=644)		Aclidinium Bromide 400 µg BID (N=636)	
	Baseline Mean (SD)	Mean Change from Baseline (SD)	Baseline Mean (SD)	Mean Change from Baseline (SD)	Baseline Mean (SD)	Mean Change from Baseline (SD)
Systolic blood pressure, mm Hg	129.1 (14.7)	-1.4 (14.7)	129.5 (14.9)	-0.3 (14.1)	130.0 (15.2)	-1.2 (14.5)
Diastolic blood pressure, mm Hg	77.6 (9.5)	-1.0 (9.1)	78.1 (9.6)	-0.5 (9.3)	77.9 (9.3)	-0.6 (9.2)
Heart rate	73.3 (12.5)	-3.0 (11.0)	73.5 (12.9)	-3.7 (11.1)	73.9 (13.0)	-3.0 (11.6)

Aclidinium Bromide Post-marketing Study Proposal
Overview

- Double blind, randomized, parallel study of 4000 patients over 3 years
  - Randomization 1:1 to:
    - AB 400 µg BID
    - placebo + standard of care BID
  - Patients must have a history of COPD exacerbations during the past year
  - Allowed prior medications: ICS, LABA, ICS/LABA, theophylline, and Daliresp
  - Prohibited prior medications: LAMA and SAMA

- Primary efficacy endpoint: rate of moderate or severe COPD exacerbations during the first year of treatment

- Primary safety endpoint: time to first MACE event
  - Null hypothesis: hazard ratio is at or above 1.5 for aclidinium relative to placebo; rejected if the upper bound of the 95% CI is below 1.5

- Secondary safety endpoint: time to first MACE or other serious cardiac events of interest (i.e. SMQs for cardiac disorders, conductions disorders, and cerebrovascular disorders)

SGRQ: Key Protocol Elements

Study 33

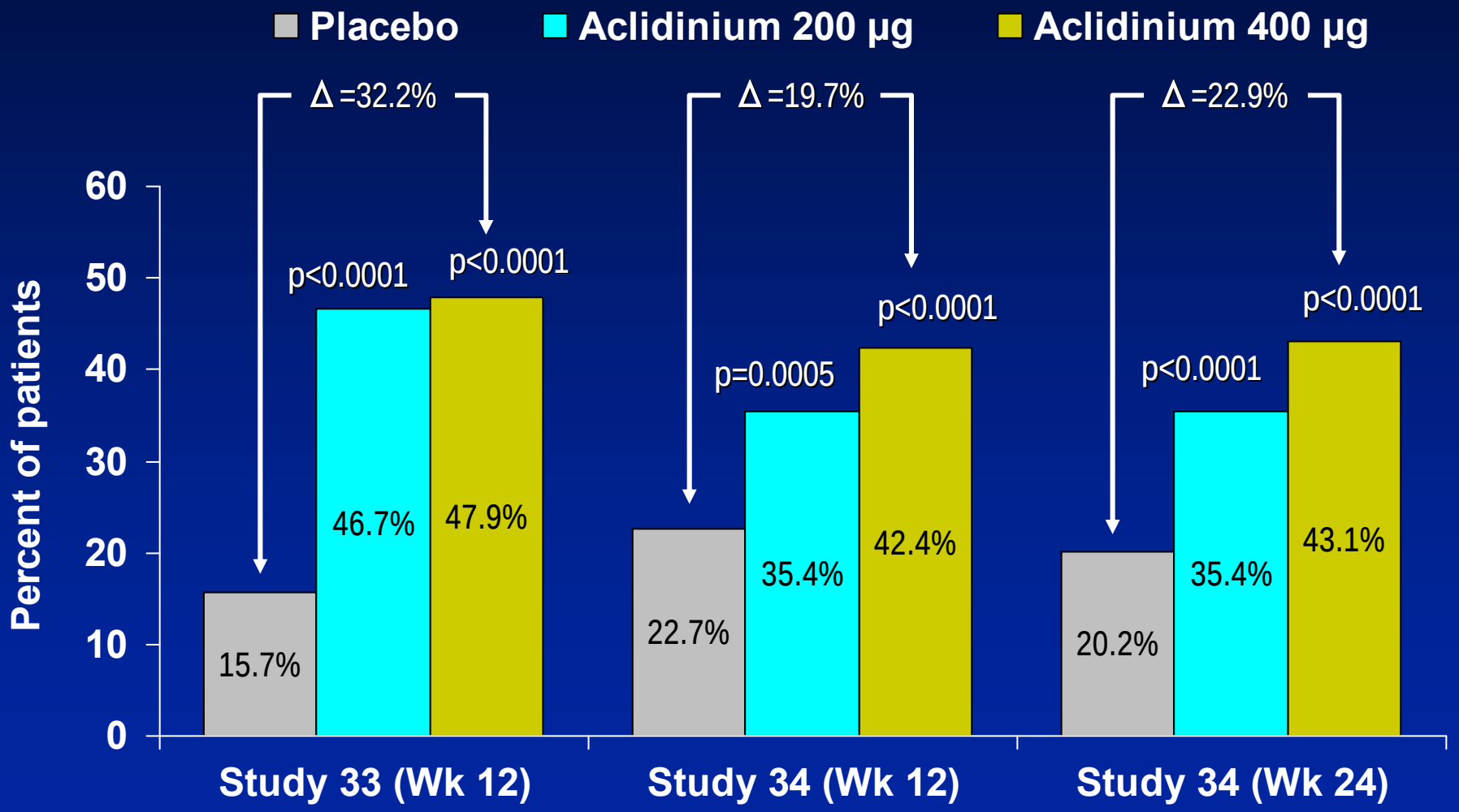
- SGRQ at Visits 2, 4, 5 and 6 (Weeks 0, 4, 8 and 12 respectively) or following premature discontinuation
- SGRQ completed after BDI/TDI

Study 34

- SGRQ at Visits 2, 4, 6 and 8 (Weeks 0, 4, 12, 24 respectively) or following premature discontinuation
- SGRQ completed after BDI/TDI

Studies 33 and 34

Change from Baseline in Trough FEV_1 Responders (≥100 mL Increase)



Study 35

Change from Baseline in Peak FEV_1 by Visit over 52 Weeks (LOCF)

ITT population