Indacaterol
NDA 22-383

Pulmonary-Allergy Drugs Advisory Committee Meeting

March 8, 2011

Novartis Pharmaceuticals Corporation

Introduction and Background

Trevor Mundel, M.D. Ph.D.

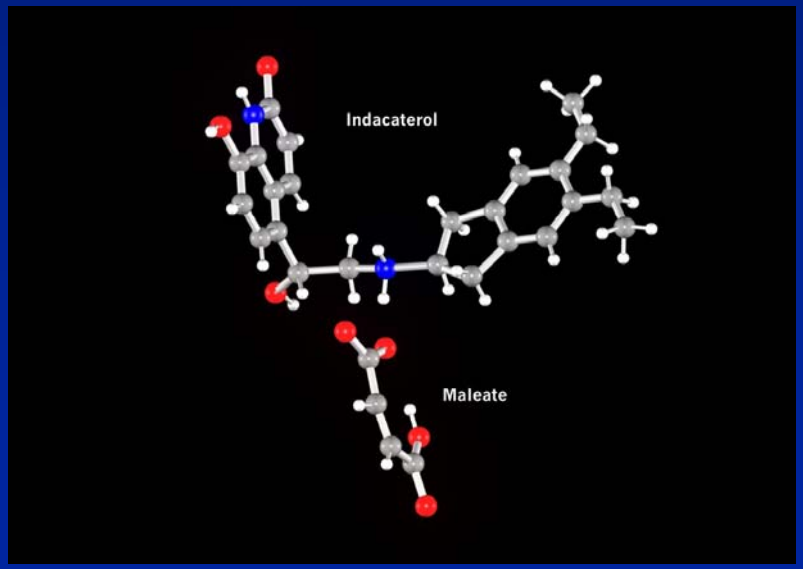
Head of Development
Novartis Pharma AG

Novartis is Committed to Patients with COPD

- Products in Phase 3 with planned COPD only indications
  - LAMA - Glycopyrronium Bromide
  - LABA/LAMA - Indacaterol and Glycopyrronium Bromide
- Currently there are 9 studies with 9500 patients enrolled in COPD studies

Indacaterol – Next Generation Beta$_2$-Agonist

- Rapid onset of effect sustained over 24-hours
- No loss of efficacy over time (tachyphylaxis) or loss of response to rescue medication
- Low systemic exposure with a wide therapeutic index



Proposed Indication

Long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Important Limitations of Use:

- **Not indicated to treat acute deteriorations of chronic obstructive pulmonary disease**
- **Not indicated to treat asthma. The safety and effectiveness in asthma have not been established.**

Product Description

- Administered using a low-resistance single-dose dry powder inhaler

- Multiple feedback to patient that a dose has been taken
  - See: Empty capsule
  - Hear: Whirring sound
  - Experience: Sweet taste

Development and Regulatory History

- In clinical development since November 2000 with more than 15,000 subjects in 61 clinical studies, including over 4,700 patients treated with indacaterol for at least 12 weeks
- Original NDA and European MAA filed in December 2008
  - Doses of 150 µg and 300 µg once daily
- First world-wide approval in November 2009 (EU)
  - Doses of 150 µg and 300 µg once daily approved in more than 50 countries worldwide
  - Post-approval marketing safety experience from 16 countries where launched with no new safety concerns based on 56,000 patient-years

FDA Review History

- Following FDA review of NDA Complete Response letter received in October 2009
  - Conduct clinical studies to further assess dose and dosing frequency, including doses less than 150 µg
  - Address potential higher frequencies of cardiovascular and cerebrovascular (CCV) serious adverse events (SAE)
  - Address possible risk of asthma-related deaths
- Resubmission to FDA in September 2010 proposing 75 µg and 150 µg once daily doses
  - Includes:
    - Integrated dose response analyses across 8000 patients
    - New clinical studies in ~2700 patients
    - Pooled safety and efficacy analyses, including a comprehensive safety analysis with external adjudication

Agenda

Perspectives on COPD	***James Donohue, M.D.*** Professor and Chief Div. of Pulmonary and Critical Care Medicine University of North Carolina at Chapel Hill
Dose Selection, Efficacy	***David Morris, M.D.*** Head of Respiratory Development Novartis Pharma AG
Safety, Risk Mitigation	***Linda Armstrong, M.D.*** Drug Safety and Epidemiology Novartis Pharmaceuticals Corporation
Benefit-Risk, Clinical Perspective	***James Donohue, M.D.*** Professor and Chief Div. of Pulmonary and Critical Care Medicine University of North Carolina at Chapel Hill

Additional Experts

- **John DiMarco, M.D, Ph.D.**
  Professor of Internal Medicine/Cardiology
  University of Virginia

- **Gary Koch, Ph.D.**
  Professor of Biostatistics and
  Director of the Biometric Consulting Laboratory
  University of North Carolina

- **Malcolm Sears, MB, FRCPC**
  Professor of Medicine
  McMaster University
  Hamilton, Ontario, Canada

Perspectives on Chronic Obstructive Pulmonary Disease (COPD)

James Donohue, M.D.

Professor and Chief, Division of Pulmonary and Critical Care Medicine

University of North Carolina at Chapel Hill

Definition

- COPD is a treatable lung disease in which airflow is limited and not fully reversible
- Due to exposure to noxious agents (i.e., cigarette smoking)
- Airflow limitation is usually progressive
- Caused by a mixture of airway disease (including bronchoconstriction) and parenchymal destruction (emphysema)
- Variable history and not all patients follow the same course
- Third leading cause of death in US for 2008

Prevalence and Impact of COPD in the US

Prevalence[1] (2006)	~12-24 million
Emergency Department visits[1] (2006)	~2 million
Hospitalizations[1] (2006)	661,000
Deaths[2] (2005)	124,583
Direct and indirect Costs[3] (2010)	$49.9 BB

[1] Healthy People 2010. Progress Review: Respiratory Diseases. May 22, 2008.
[2] Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality. April 2009.
[3] nhlbi.nih.gov/about/factbook-09

COPD Impacts Patients' Ability to Work[1]

- 50% of COPD patients are estimated be under 65 years of age[2]
- Loss of productivity associated with disease[2]
  - In one survey, 79% of the employed COPD patients reported that COPD negatively affected their work[2]
  - In a different survey, 40% of those still working agreed COPD limited the types or amount of work they could do[3]

[1] Fletcher et al. ATS New Orleans 2010
[2] Education for health.org. COPD 7 presentation
[3] Hernandez et al. Respir Med 2009

COPD Patients Experience Multiple Symptoms That Have a Real Impact on Their Well-being

Symptoms

- Breathlessness (dyspnea)
- Cough
- Wheezing
- Chest tightness
- Sputum production
- Fatigue

Impact on Well-being

- Activity limitation
- Anxiety and depression
- Apprehension about future events
- Lack of confidence about steps to take action
- Risk of increasing social isolation
- Loss of independence

Assessment of Clinical Benefit

- Lung Function
  - Spirometry, i.e., FEV_1, FVC, AUC FEV_1
- Transition Dyspnea Index
  - Measures breathlessness
  - Breathlessness most disabling symptom of COPD
- Health Status
  - St. George's Respiratory Questionnaire (SGRQ) measures health status
  - Health status worse with disease progression
- Rescue Medication Use
  - Marker of symptomatic status

COPD Treatment

GOLD 2010 guidelines

I: Mild	II: Moderate	III: Severe	IV: Very Severe
• FEV_1/FVC <0.70 • FEV_1 ≥80% predicted	• FEV_1/FVC <0.70 • 50% ≥ FEV_1 <80% predicted	• FEV_1/FVC <0.70 • 30% ≥ FEV_1 <50% predicted	• FEV_1/FVC <0.70 • FEV_1 <30% predicted *or* FEV_1 <50% predicted plus chronic respiratory failure

Active reduction of risk factors: influenza vaccination

Add short-acting bronchodilator (when needed)

Add regular treatment with one or more *long-acting* bronchodilators

Add rehabilitation

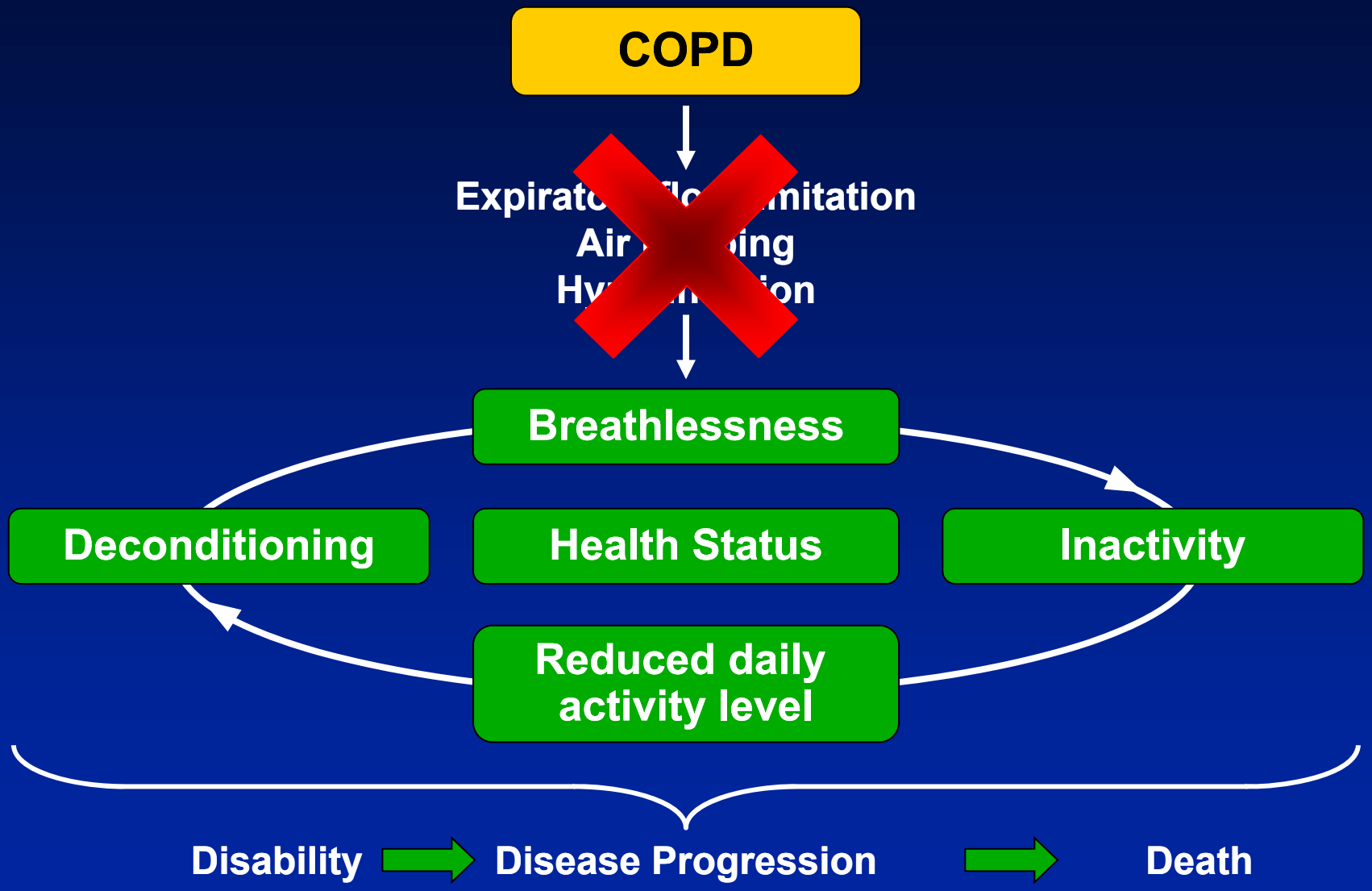
Add inhaled glucocorticosteroids if repeated exacerbations

Add long-term oxygen if chronic respiratory failure

Consider surgical treatments

Adapted from Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2010

Clinical Course of COPD

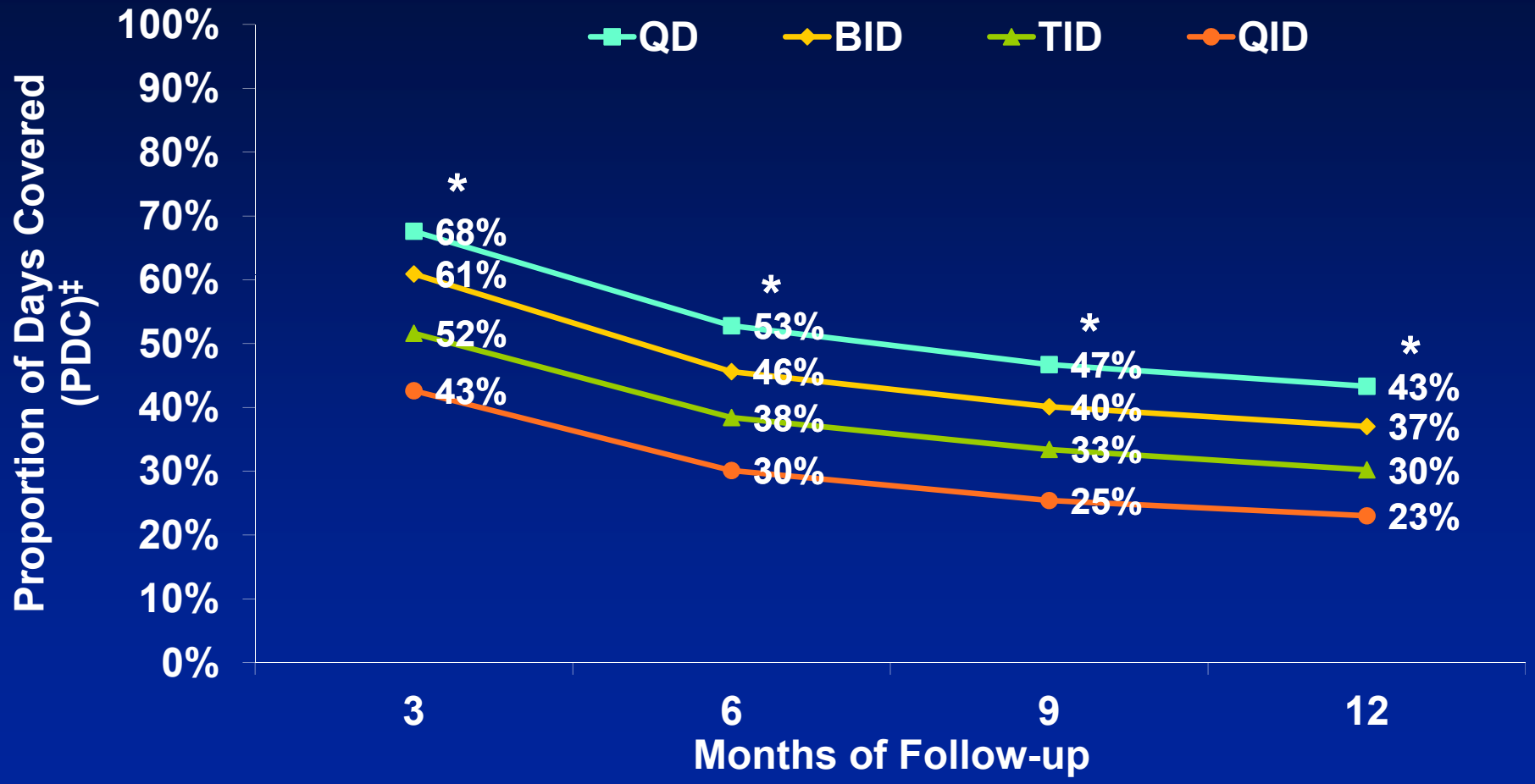


Challenges with Current Therapies

- Multiple dosing over 24 hours associated with breakthrough symptoms[1]
- Onset of action[1]
- Tachyphylaxis or tolerance with long-term use[1]
- Side effects
- Not all patients benefit equally
- Consequences of undertreatment
- Low persistence/compliance with long-term maintenance therapy[2]

1 Tashkin and Fabbri Respiratory Research 2010, 11:149
2 Neugaard Population Health Management Volume 14, Number X, 2011

Once-Daily Dosing Significantly Improves Adherence to COPD Therapy[1]



* p<0.001 for QD vs. BID, QD vs. TID, and QD vs. QID

‡ PDC = ratio of the number of days a patient was covered by a given drug during the observation period to the total number of days in the observation period.

1. Toy EL, et al., *Respiratory Medicine* (2010), doi:10.1016/j.med.2010.09.006

As New Bronchodilators are Introduced There Have Been More Consistent Improvements in Outcomes for Patients with COPD

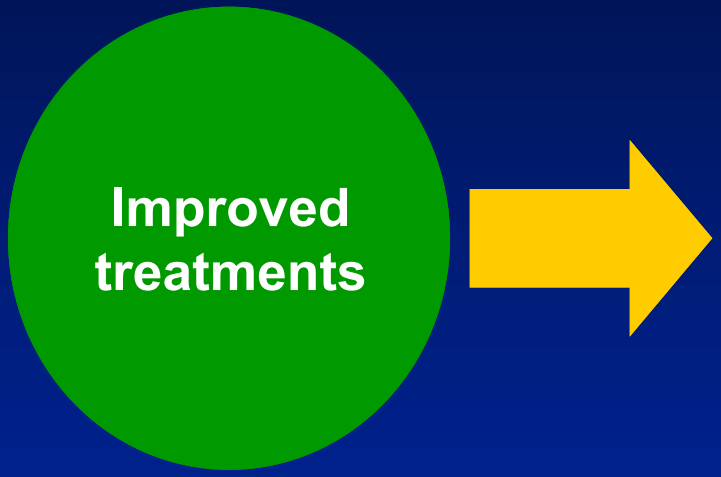
	Duration of action (hours)[1]	Improvement in outcome				
		Lung function[2–8]	Breathlessness[2–8]	Exercise endurance*[1,2]	Health Status[1–14]	Exacerbations[1–3,5,7–14]
Albuterol§	4–6	✓	✓	✓	NA	NA
Ipratropium bromide	6–8	✓	✓	✓	✓	✓
Salmeterol	≥12	✓✓	✓	✓	✓(✓‡)	✓✓
Formoterol	≥12	✓✓	✓✓	✓	✓✓	✓†
Tiotropium	24	✓✓✓	✓✓✓	✓	✓✓(✓‡)	✓✓(✓‡)

✓evidence of effectiveness; ✓✓evidence of effectiveness over SABA or SAMA;
✓✓✓evidence of effectiveness over LABA

*Outcome demonstrated by all bronchodilators, lack of evidence of significant differences between them
†Equivocal evidence depending on formulation[5,10,11] ‡Evidence of numerical improvements over shorter acting comparator[4,8]
§Dependent on dose. NA = evidence not available

1. GOLD 2008; 2. Celli B et al. ERJ 2004; 3. Mahler D et al. Chest 1999; 4. Rennard S et al. AJRCCM 2001; 5. Dahl R et al. AJRCCM 2001
6. Wadbo M et al. ERJ 2002; 7. Vincken W et al. ERJ 2002; 8. Brusasco V et al. Thorax 2003; 9. Rutten van-Molken MPMH et al. Eur J Health Econ 2007; 10. Szafranski W et al. ERJ 2003; 11. Calverley PM et al. ERJ 2003; 12. Calverley PM et al. NEJM 2007
13. Niewoehner D et al. Ann Intern Med 2005; 14. Tashkin D et al. NEJM 2008

How Can We Improve on Current Therapy in COPD?



Longer duration of action is associated with improved outcomes

There is currently no once-daily β_2 agonist, limiting options for combinations

Conclusion

- Optimizing bronchodilation is essential to the management of COPD
- Extending the duration of action of bronchodilators appears to lead to better, more consistent improvements in patient outcomes
- The challenge of COPD will include the need to manage a growing number of younger and more active patients who will live for decades with this disorder
- Newer options are required to provide flexibility and improve overall outcomes for patients

Dose Selection, Efficacy

David Morris, M.D.

Head of Respiratory Development
Novartis Pharma AG

Summary

- Indacaterol is safe and effective for COPD patients
- Indacaterol has a wide therapeutic index and provides consistent 24 hour bronchodilation from first dose out to one year
- Once daily is the optimal dosing regimen
- Indacaterol has a rapid onset of action
- 75 µg is the minimum efficacious dose
- 150 µg is the best single dose for US approval

Outline of Efficacy Data

- Dose selection
  - Dose Ranging
  - Dose Regimen
- Efficacy data from pivotal studies
  - Lung Function
  - Breathlessness
  - Health Status
  - Symptom Relief

Key Placebo-controlled Clinical Studies

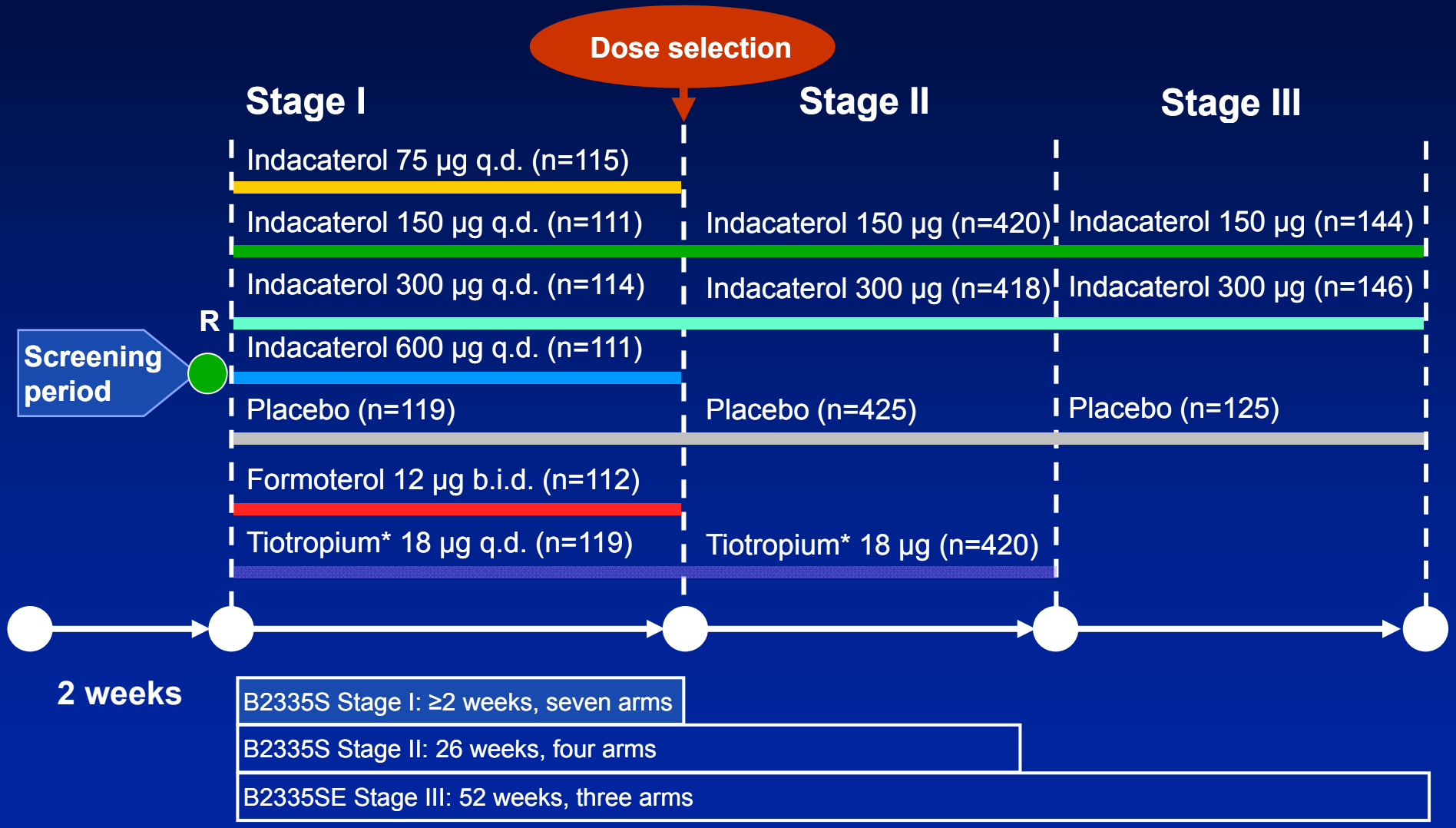
	Study		Indacaterol doses	Comparators	Duration
Dose ranging/ regimen	B2335S (Stage I)	N=801	75, 150 300, 600 µg q.d	Placebo Formoterol 12 µg b.i.d. Tiotropium 18 µg q.d. (open-label)	2 weeks
	B2357 (asthma)	N=511	18.75, 37.5 75, 150 µg q.d	Placebo Salmeterol 50 µg b.i.d.	2 weeks
	B2356	N=552	18.75, 37.5 75, 150 µg q.d	Placebo Salmeterol 50 µg b.i.d.	2 weeks
	B2223 (asthma)	N=191	37.5 µg bid 75 µg q.d 150 µg q.o.d	Placebo	2 weeks
Pivotal 75 µg	B2354	N=323	75 µg q.d.	Placebo	12 weeks
	B2355	N=318	75 µg q.d.	Placebo	12 weeks
Pivotal 150 µg and/or 300 µg	B2346	N=416	150 µg q.d.	Placebo	12 weeks
	B2336	N=998	150 µg q.d.	Placebo Salmeterol 50 µg b.i.d.	26 weeks
	B2335S (Stage II)	N=1,683	150 µg q.d. 300 µg q.d.	Placebo Tiotropium 18 µg q.d. (open-label)	26 weeks
Long-term safety studies	B2334	N=1,728	300 µg q.d. 600 µg q.d.	Placebo Formoterol 12 µg b.i.d.	52 weeks
	B2335SE	N=414	150 µg q.d. 300 µg q.d.	Placebo	52 weeks
	Total	N=7,935			

Outline of Efficacy Data

- Dose selection
  - Dose Ranging
  - Dose Regimen

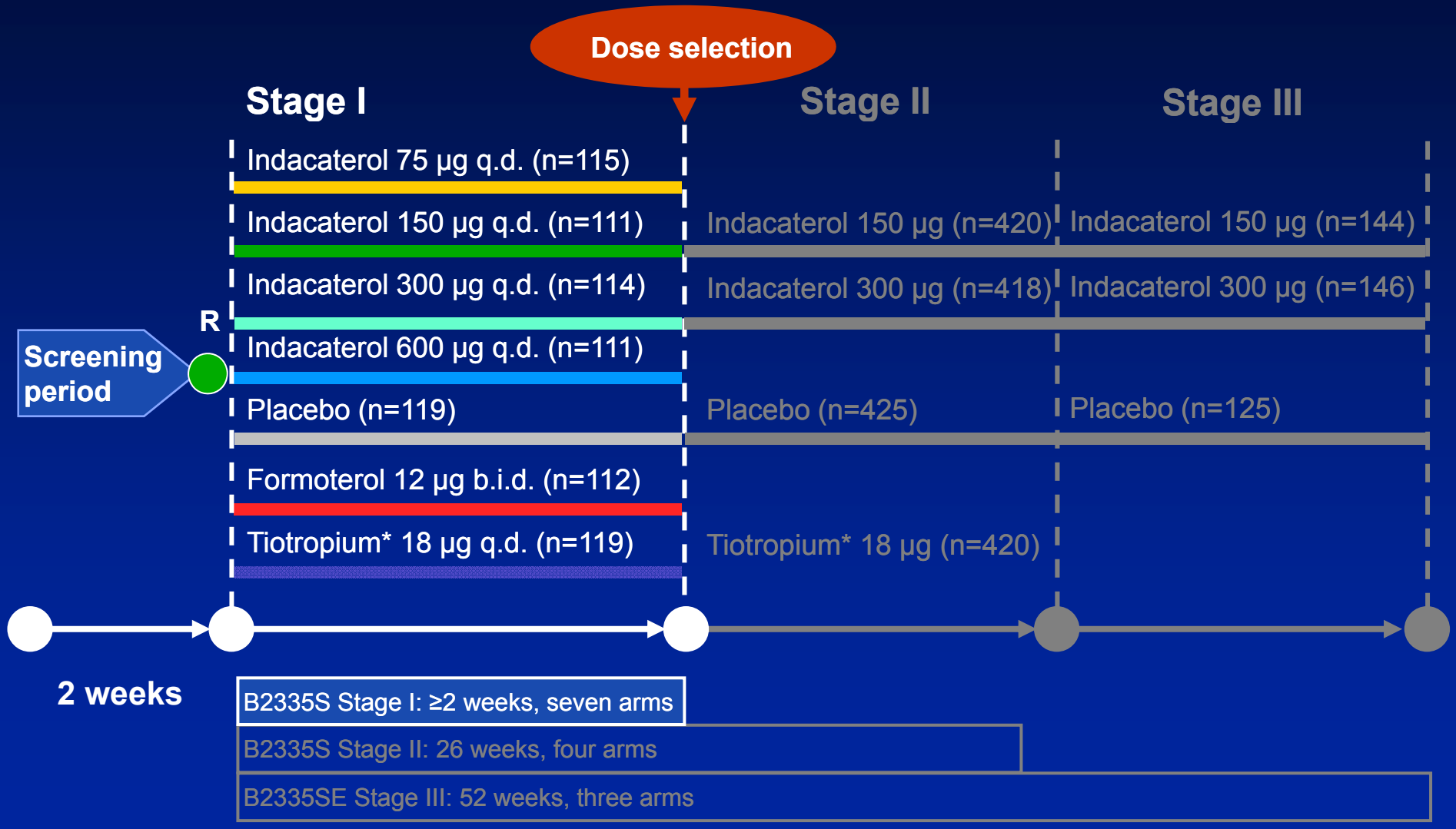
	Study			Comparators	Duration
Dose ranging/ regimen	B2335S (Stage I)	N=801	Dose ranging (COPD)	Placebo Formoterol 12 µg b.i.d. Tiotropium 18 µg q.d. (open-label)	2 weeks
	B2357	N=511	Dose ranging (asthma)	Placebo Salmeterol 50 µg b.i.d.	2 weeks
	B2356	N=552	Dose ranging (COPD)	Placebo Salmeterol 50 µg b.i.d.	2 weeks
	B2223	N=191	Dose regimen (asthma)	Placebo	2 weeks

Identifying an Optimal Dose Using an Adaptive Seamless Design (B2335S/SE)



*** Open-label. All drugs were delivered via proprietary single-dose dry powder inhalers (SDDPI)**

Identifying an Optimal Dose Using an Adaptive Seamless Design (B2335S/SE)



B2335S Stage I: ≥2 weeks, seven arms

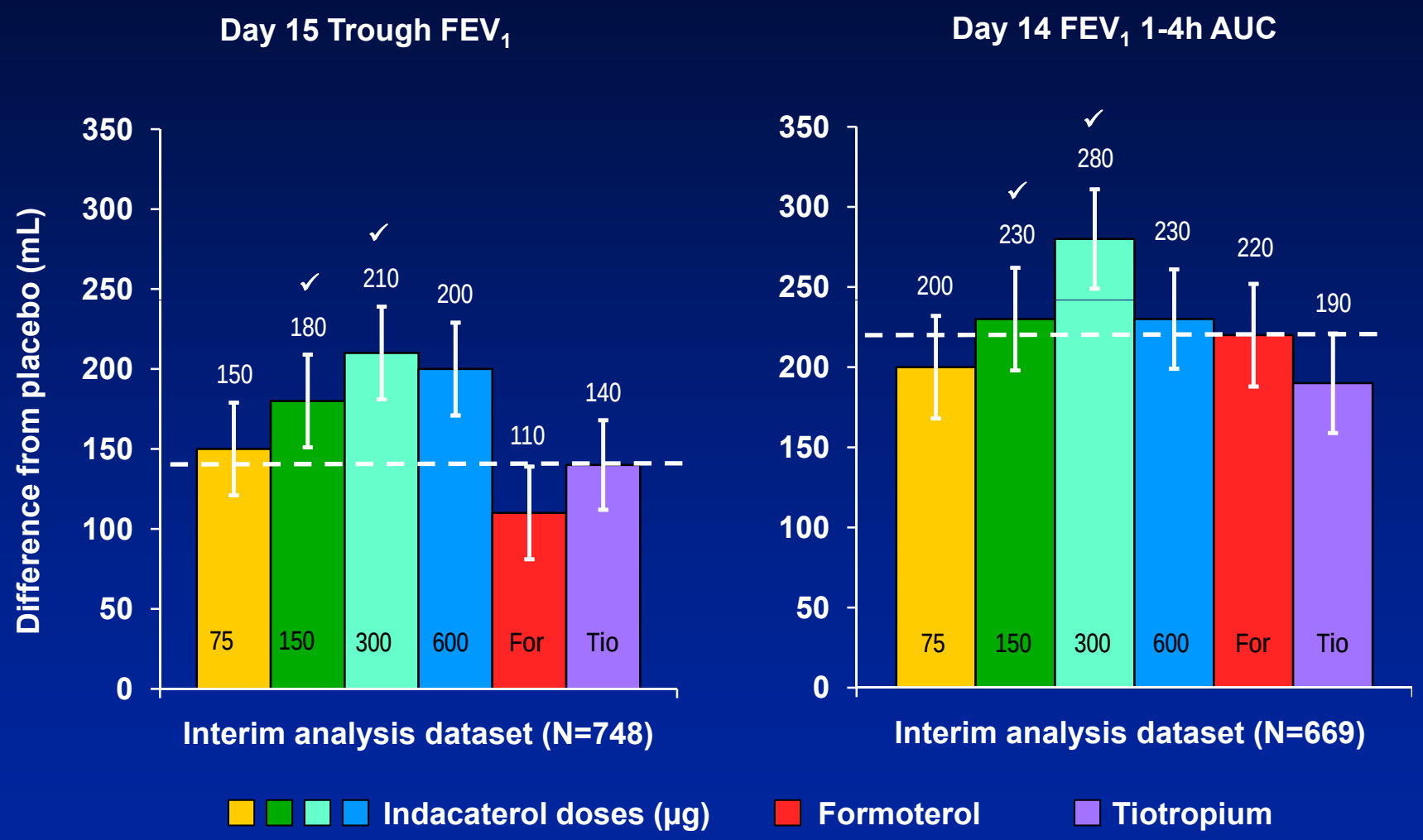
B2335S Stage II: 26 weeks, four arms

B2335SE Stage III: 52 weeks, three arms

*** Open-label. All drugs were delivered via proprietary single-dose dry powder inhalers (SDDPI)**

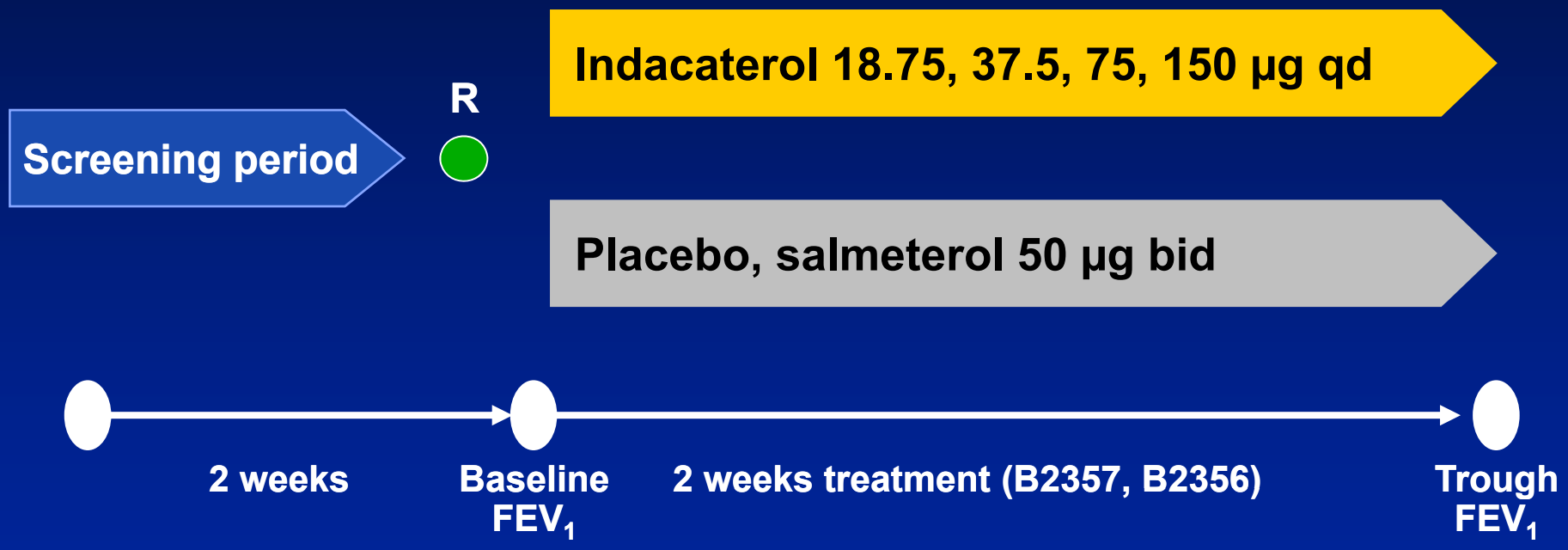
COPD 2 Week Dose Ranging (B2335S)

Independent Data Monitoring Committee selected 150 µg & 300 µg



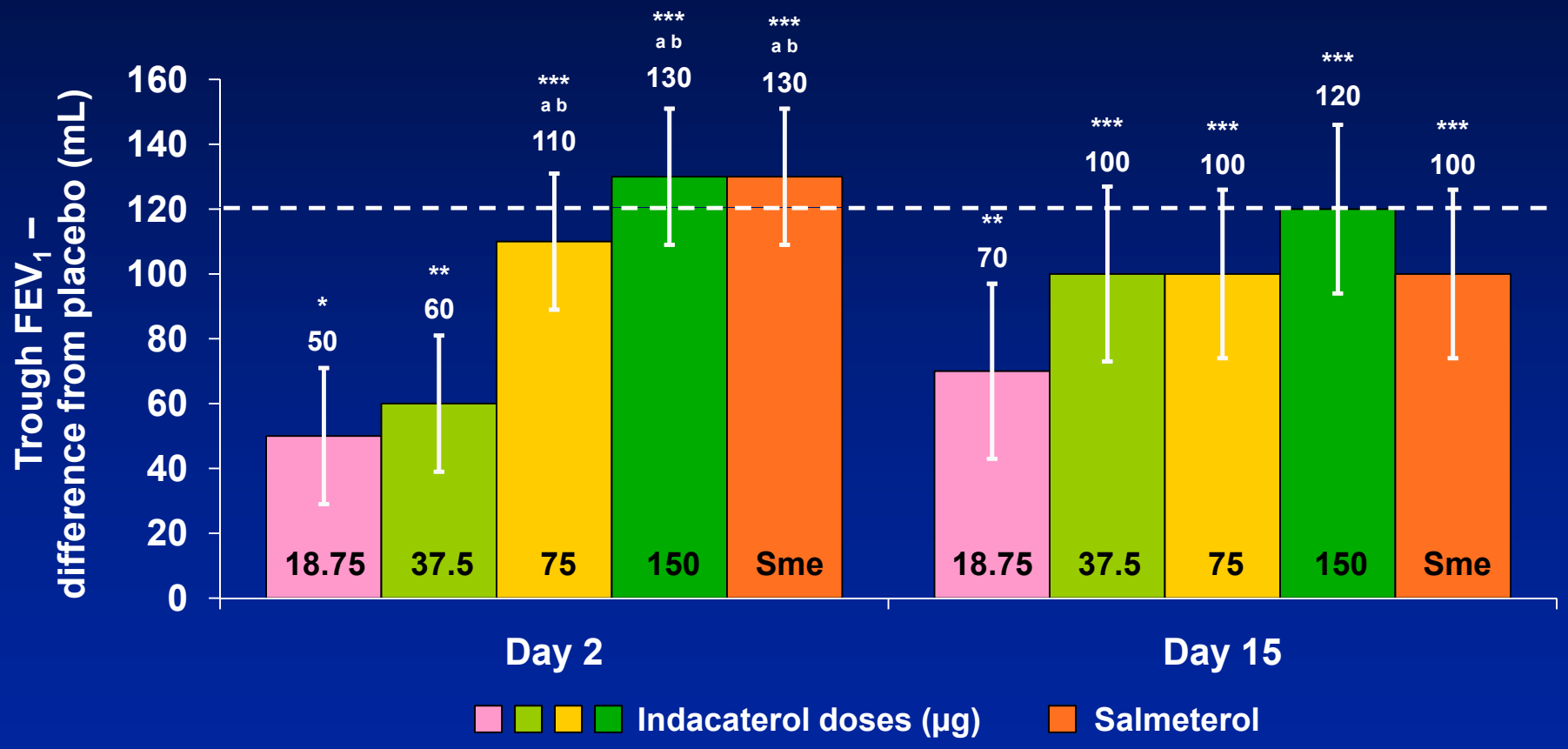
Interim analysis dataset: basis for independent Data Monitoring Committee dose selection decision, imputed with LOCF; Data are least squares means ± SE. N = sum of all arms including placebo. Average number of patients per treatment group N=107 (trough) and N=97 (AUC)

Study Design for COPD and Asthma Dose Ranging



COPD 2 Week Dose Ranging (B2356): Trough FEV_1

150 µg achieves MCID at Day 15, 18.75 µg is a non-effective dose

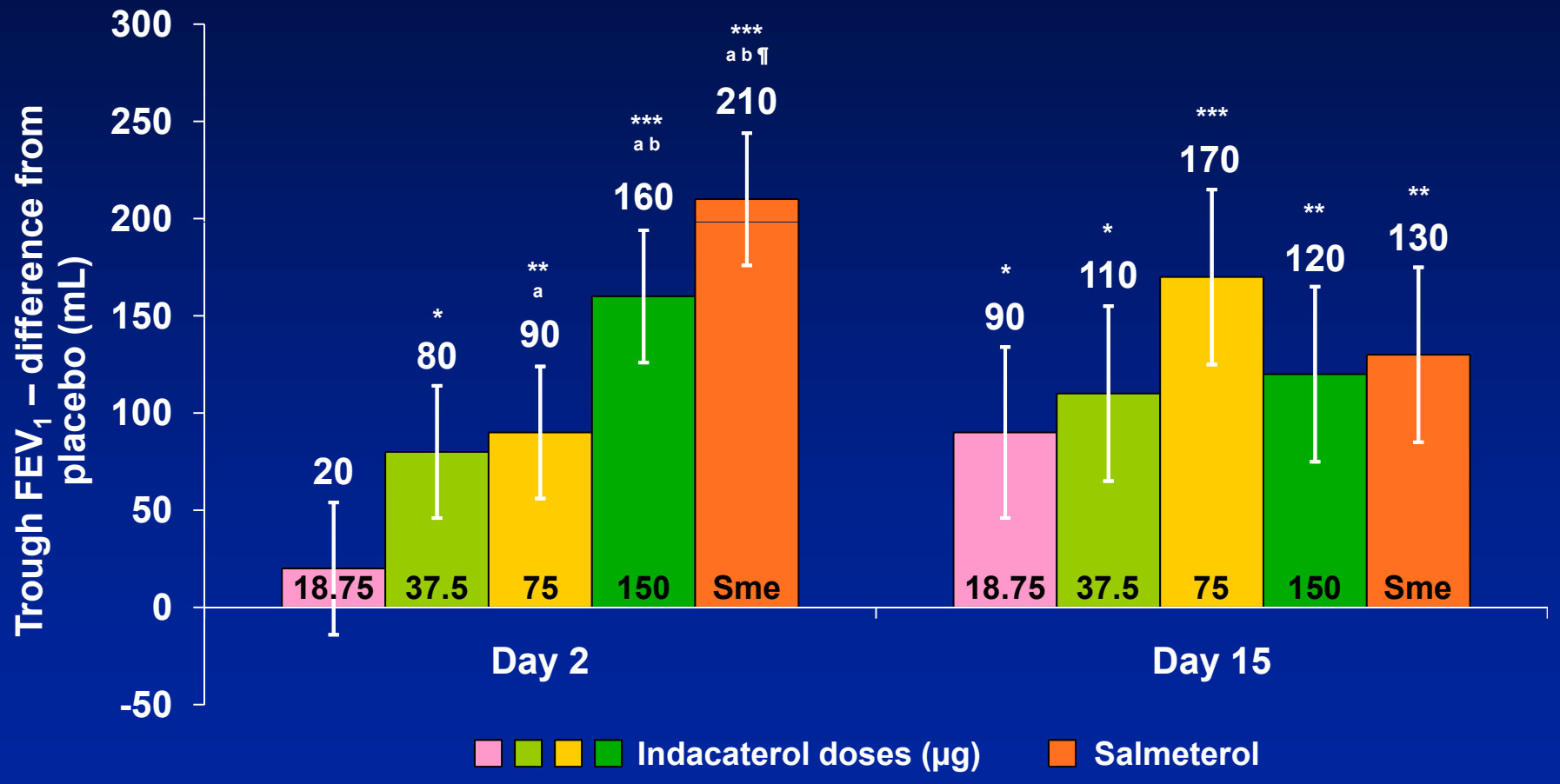


*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=88 (Day 2) and N=86 (Day 15).

Dotted line shows prespecified 120 mL level of clinically important difference

Asthma 2 Week Dose Ranging (B2357): Trough FEV_1

150 µg effective from first dose, 18.75 µg is a non-effective dose



*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; ¶p<0.05 vs 75 µg; Data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=80

Dose Ranging Conclusions

- The minimum efficacious dose is 75 µg as defined by the asthma dose ranging study (B2357)
- In COPD the 150 µg dose meets the MCID of 120 mL from first dose (B2356)

Is Optimal Indacaterol Dosing Once Daily?

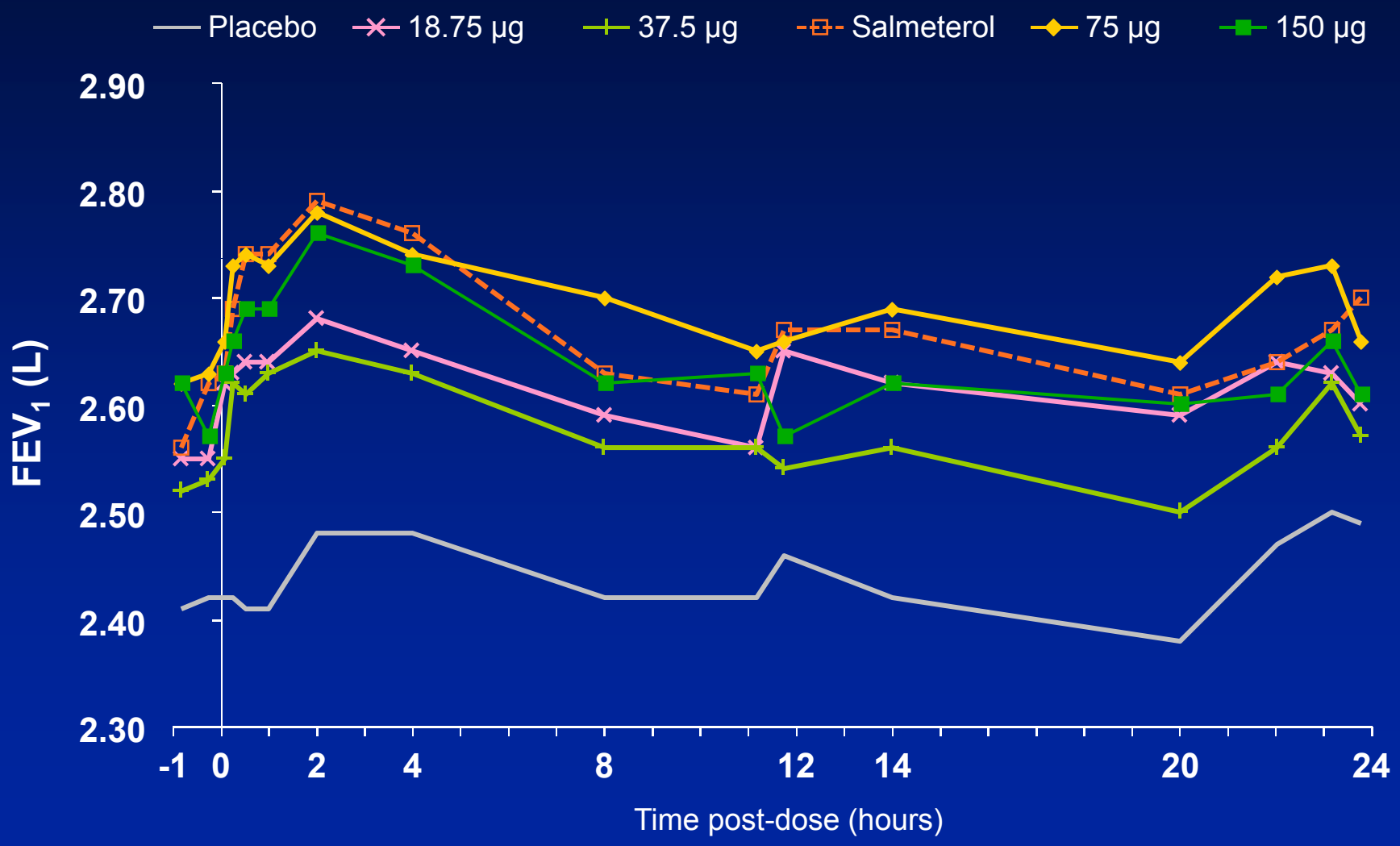
- Does indacaterol provide 24-hour bronchodilation?
- Will twice daily dosing provide better efficacy?

Study Designs

- Dose Ranging Study (B2357)
  - Doses evaluated at 18.75, 37.5, 75, 150 µg qd
  - Study population: asthma
- Dose Regimen Study (B2223)
  - Dose regimens evaluated:
    - Twice daily (bid)
    - Once daily (qd)
    - Every other day (qod)
  - 75 µg per day as average dose to allow greatest discrimination between regimens
  - Study population: asthma

Indacaterol Efficacy Maintained over 24-hour Period

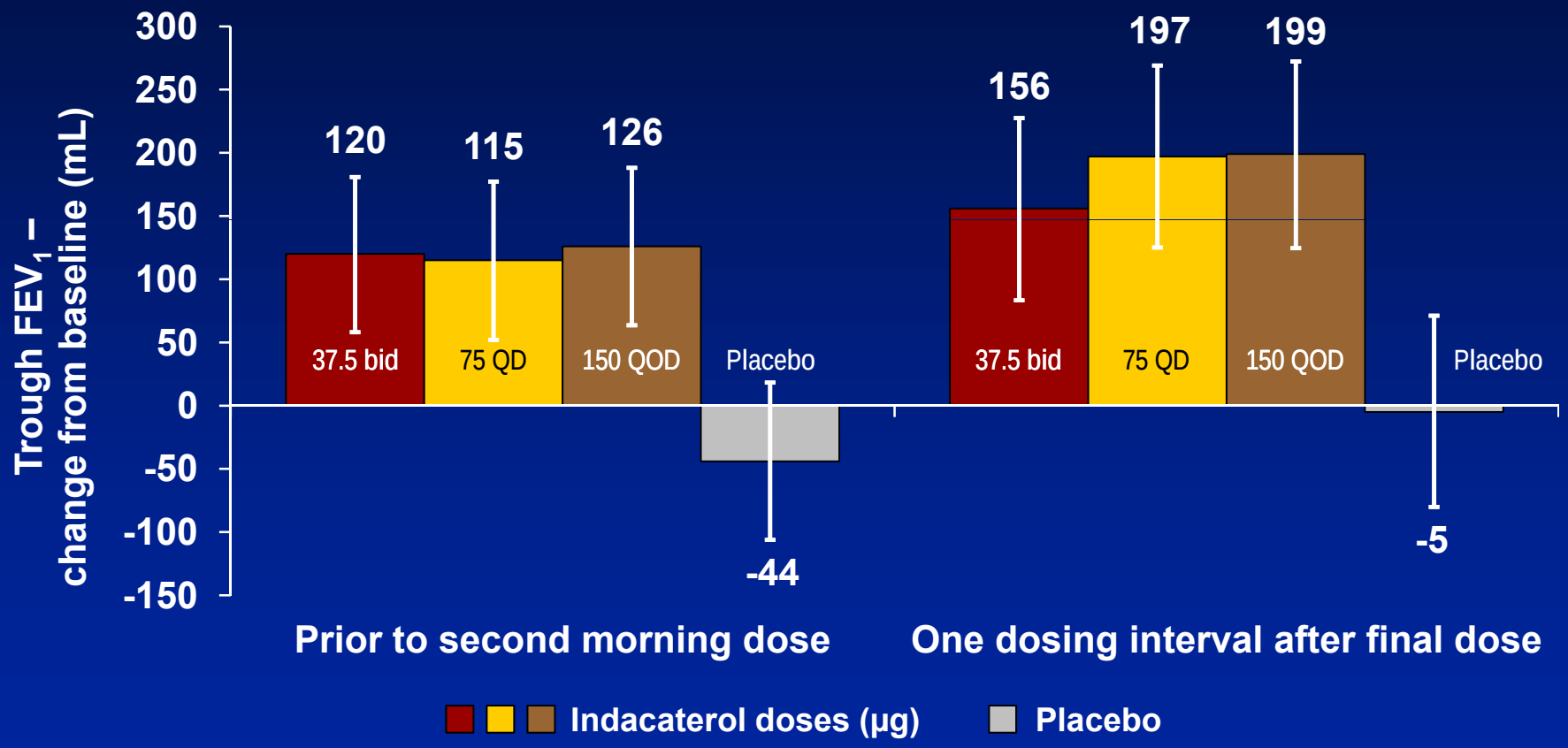
Asthma Study B2357 two weeks treatment



Data are least squares means (LSM)

Divided Dosing Offers No Advantage on Trough FEV_1

Asthma Study B2223 trough FEV_1 change from baseline



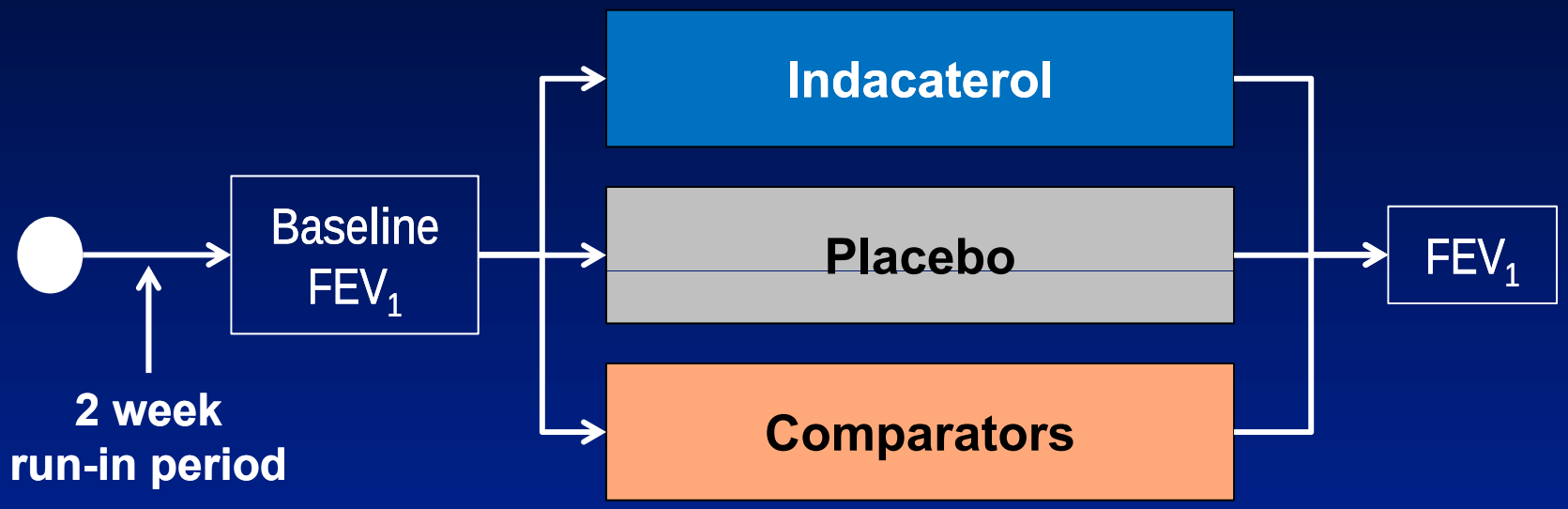
Data are unadjusted means and 90% confidence intervals; Baseline = mean of D-1 profiles matching D15+16/ D1 pre-dose; Trough = mean of 23h 10m and 23h 50m on D17 48 h after last qod dose, 24h after last qd dose and 12h after last bid dose. Average number of patients per treatment group N=47 (left hand plot) and N=44 (right hand plot)

Outline of Efficacy Data

- Efficacy data from pivotal studies
  - Lung Function
  - Breathlessness
  - Health Status
  - Symptom Relief

	Study		Indacaterol doses	Comparators	Duration
Pivotal 75 µg	B2354	N=323	75 µg q.d.	Placebo	12 weeks
	B2355	N=318	75 µg q.d.	Placebo	12 weeks
Pivotal 150 µg and/or 300 µg	B2346	N=416	150 µg q.d.	Placebo	12 weeks
	B2336	N=998	150 µg q.d.	Placebo Salmeterol 50 µg b.i.d.	26 weeks
	B2335S	N=1,683	150 µg q.d. 300 µg q.d.	Placebo Tiotropium 18 µg q.d. (open-label)	26 weeks

Phase III General Study Design



12 weeks (B2346, B2354, B2355)
26 weeks (B2335S, B2336)
52 weeks (B2334, B2335SE)

Baseline Demographics for Pivotal Studies *(1)*

Overall population is representative of COPD population

Demographic		75 µg o.d.		150 µg o.d.		
		B2354 N=323	B2355 N=318	B2346 N=416	B2336 N=998	B2335S N=1665
Age (years)	Mean [range]	64.0 [40 - 90]	61.4 [40 - 86]	63.0 [40 - 89]	63.5 [41 - 89]	63.6 [40 - 88]
Gender	Male (%)	176 (54.5)	172 (54.1)	218 (52.4)	745 (74.6)	1046 (62.8)
	Female (%)	147 (45.5)	146 (45.9)	198 (47.6)	253 (25.4)	619 (37.2)
Race	Caucasian (%)	291 (90.1)	298 (93.7)	385 (92.5)	759 (76.1)	1410 (84.7)
	Black (%)	20 (6.2)	16 (5.0)	22 (5.3)	2 (0.2)	43 (2.6)
Ethnicity						
	Hispanic/Latino (%)	4 (1.2)	4 (1.3)	16(3.8)	83 (8.3)	152 (9.1)
	Other (%)	319 (98.8)	314 (98.7)	400 (96.2)	915 (91.7)	1513 (90.9)
Smoking history, n (%)	Ex-smoker	181 (56.0)	131 (41.2)	200 (48.1)	542 (54.3)	913 (54.8)
	Smoker	142 (44.0)	187 (58.8)	216 (51.9)	456 (45.7)	752 (45.2)

Baseline Demographics for Pivotal Studies *(2)*

Overall population is representative of COPD population

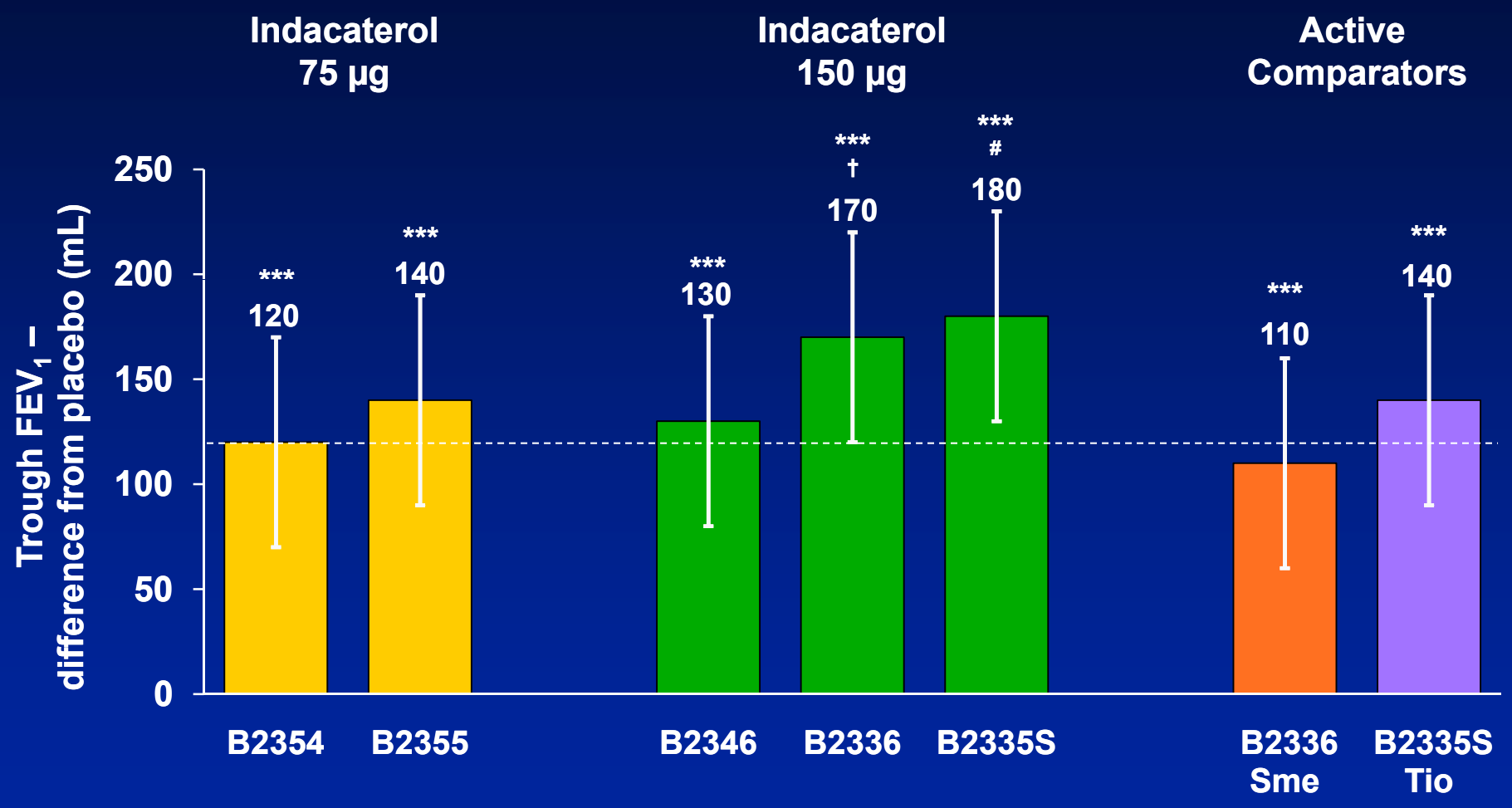
Demographic		75 µg o.d.		150 µg o.d.		
		B2354 N=323	B2355 N=318	B2346 N=416	B2336 N=998	B2335S N=1665
Severity of COPD (GOLD), n (%)	Moderate	185 (57.3)	196 (61.6)	236 (56.7)	535 (53.6)	928 (55.7)
	Severe	136 (42.1)	120 (37.7)	160 (38.5)	425 (42.6)	654 (39.3)
	Other	2 (0.6)	2 (0.6)	20 (4.8)	38 (3.8)	83 (5.0)
ICS use, n (%)		146 (45.2)	119 (37.4)	131 (31.5)	436 (43.7)	624 (37.5)
FEV_1 (%) predicted*	Mean (SD)	53.5 (13.09)	54.6 (13.22)	55.1 (13.73)	53.4 (13.94)	55.6 (14.73)
FEV_1/FVC (%)*	Mean (SD)	52.4 (10.05)	52.5 (10.08)	53.5 (10.09)	52.8 (10.32)	52.9 (10.07)
SABA reversibility (%)	Mean (SD)	16.1 (13.28)	16.9 (15.34)	16.5 (18.37)	11.8 (16.24)	15.5 (16.66)

*Post-bronchodilator

Outcomes

	Parameter	Characteristics
Primary endpoint		
Lung function	FEV_1 Trough at 24 hours	Level of bronchodilation at the end of the dosing interval
Secondary endpoints		
Lung function	FEV_1	Assesses onset of action; bronchodilation from first dose; tachyphylaxis over time
Breathlessness	Transition Dyspnea Index (TDI)	Assesses patient well being
Health Status	St. George's Respiratory Questionnaire (SGRQ)	
Symptom Relief	Rescue Medication	

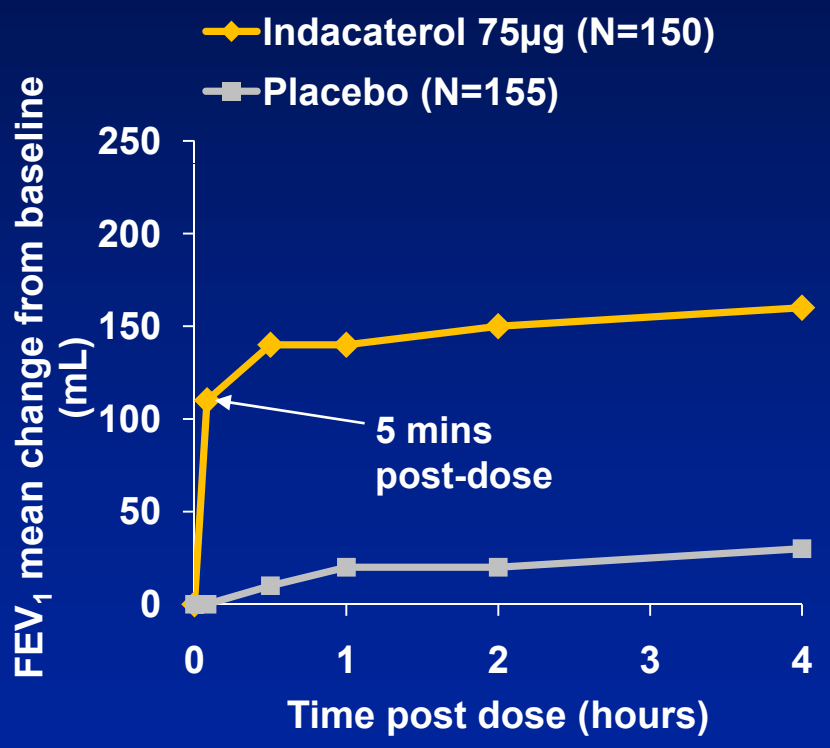
Lung Function Comparisons – Trough FEV_1 at Week 12: Primary Endpoint vs. Placebo



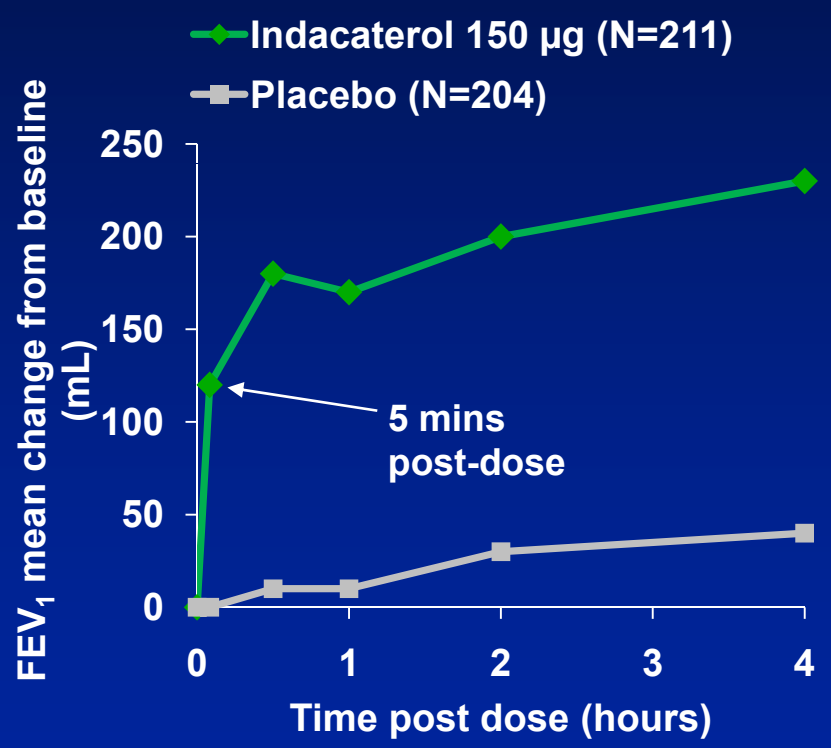
Data are least squares means with 95% confidence intervals. Dotted line shows prespecified 120 mL level of clinically important difference. ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study); #p<0.05 vs tiotropium (within study)

150 µg Demonstrates Fast Onset and Maximal Efficacy from the First Dose

75 µg Study B2355



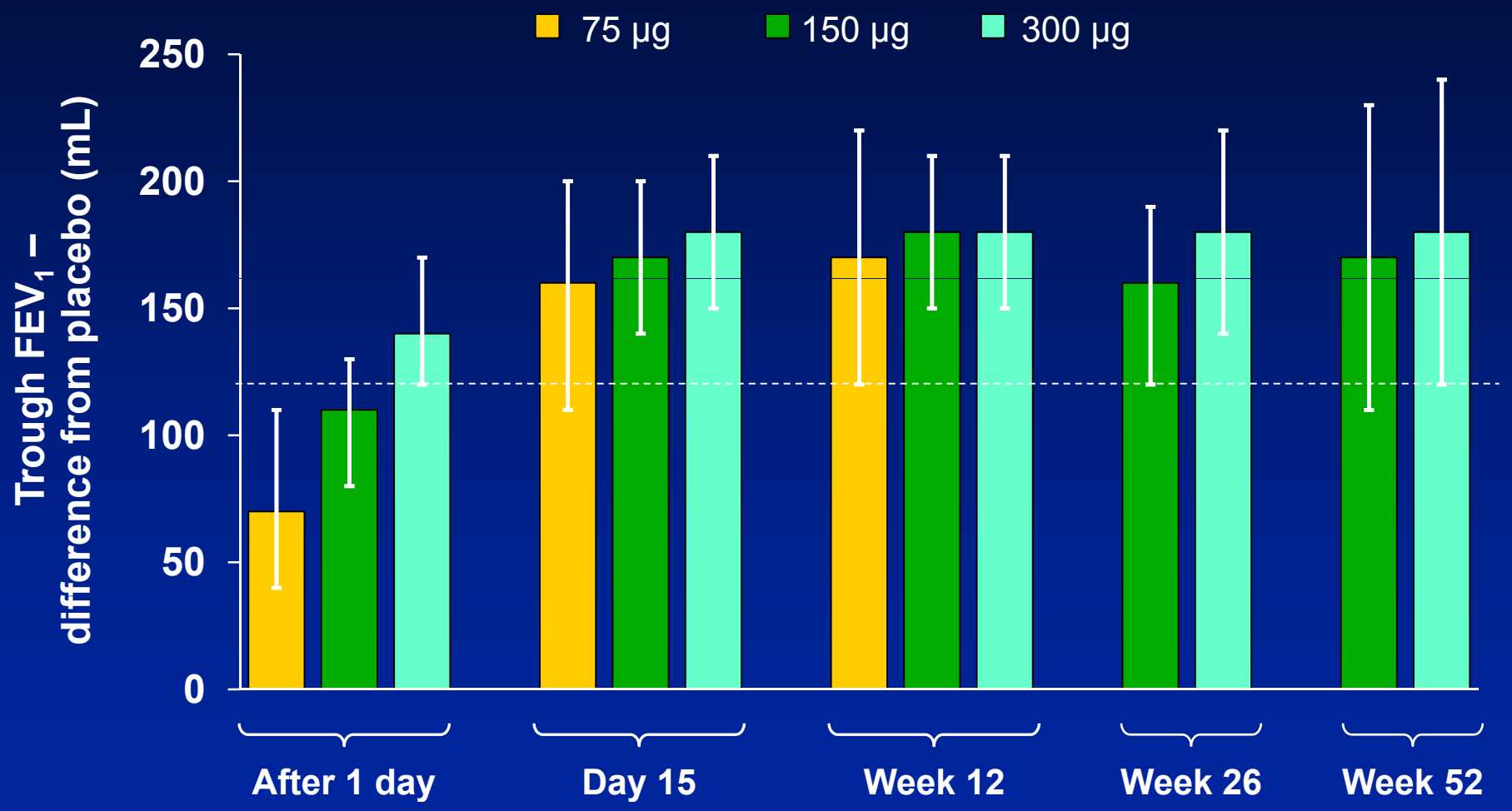
150 µg Study B2346



Feldman et al. BMC Pulmon Med 2010
Data are unadjusted means

Lack of Tachyphylaxis over 52 Weeks

Study B2335S/SE



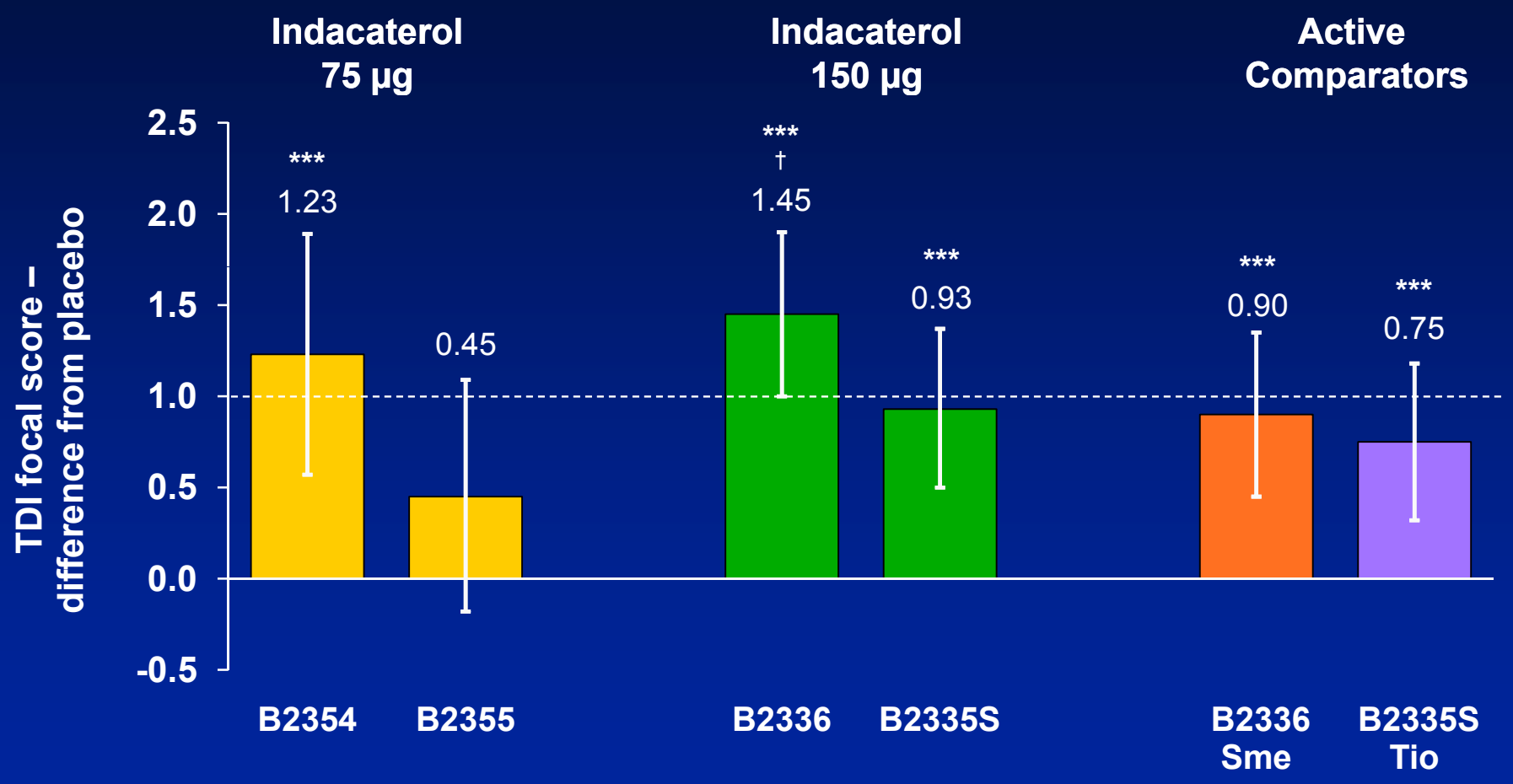
All p<0.001 vs placebo

Dotted line shows prespecified 120 mL level of clinically important difference

Trough FEV_1 = mean of measurements at 23 h 10 min and 23 h 45 min post-dose

Health Outcome Comparisons – TDI at Week 12

Differences from placebo



Data are least squares means with 95% confidence intervals. TDI not assessed in B2346.
Dotted line indicates MCID (≥1.0). ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study)

TDI: Responder Analysis vs Placebo at 1 Unit and 2 Unit Improvement Thresholds

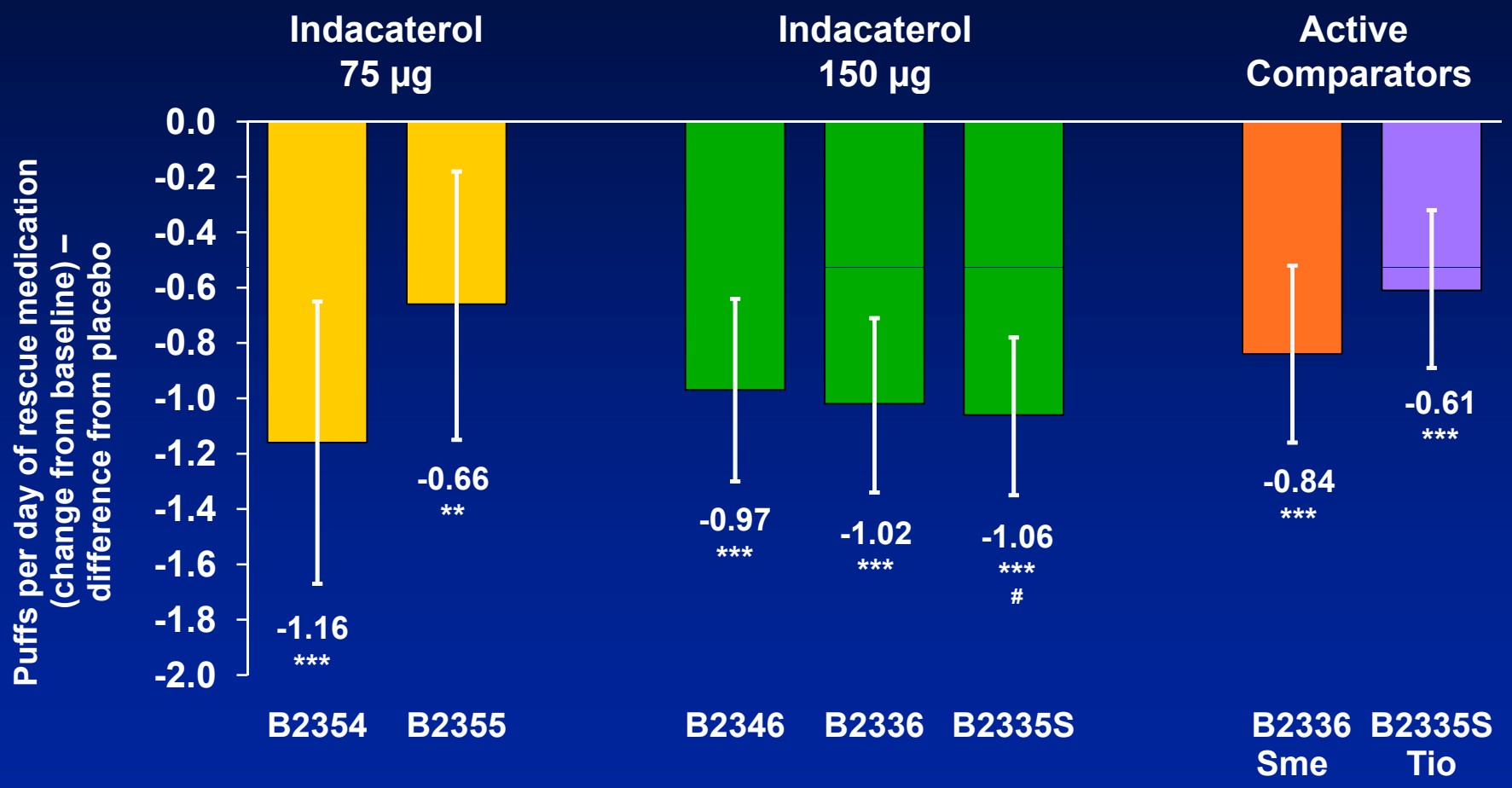
3 month efficacy population

		TDI focal score ≥1		TDI focal score ≥2	
	N	%	OR (95% CI)*	%	OR (95% CI)*
Ind 75	411	49.6	1.97 (1.51, 2.56)	41.4	1.80 (1.38, 2.37)
Ind 150	1526	58.6	2.46 (2.03, 2.99)	52.8	2.44 (2.01, 2.97)
Ind 300	850	62.9	2.79 (2.27, 3.41)	56.2	2.60 (2.12, 3.18)
For	480	55.8	2.16 (1.69, 2.76)	48.8	1.99 (1.55, 2.55)
Tio	1113	51.6	1.78 (1.43, 2.23)	46.2	1.81 (1.44, 2.26)
Sme	303	51.2	1.88 (1.37, 2.58)	46.2	1.97 (1.43, 2.71)
Pbo	1396	38.8		34.1	

*All comparaisons p=<0.001

Use of Rescue Therapy over Study Duration

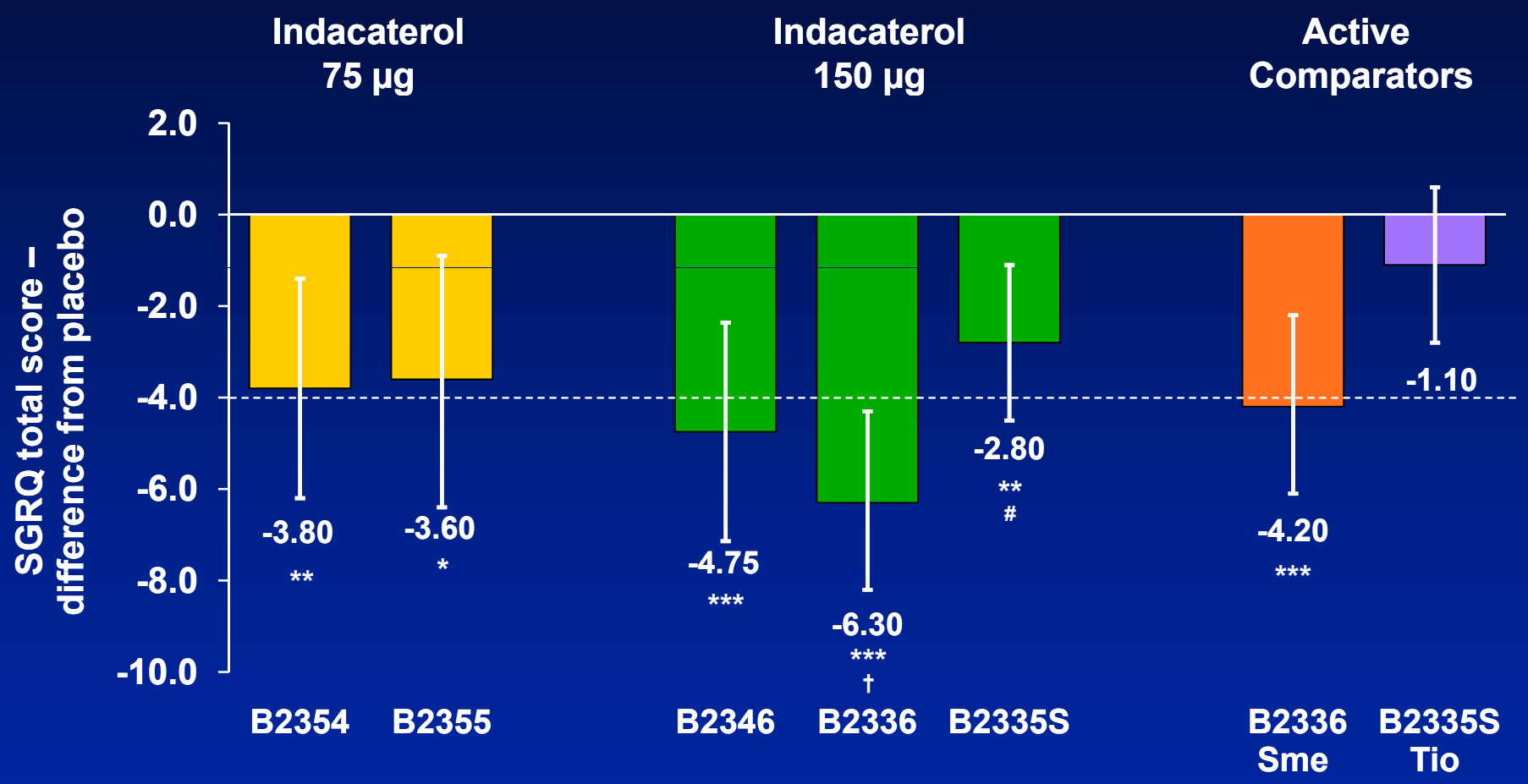
Differences from placebo



Data are least squares means with 95% confidence intervals.
**p<0.01, ***p<0.001 vs placebo (within study); #p<0.05 vs tiotropium (within study)

Health Outcome Comparisons – SGRQ at Wk 12

Differences from placebo



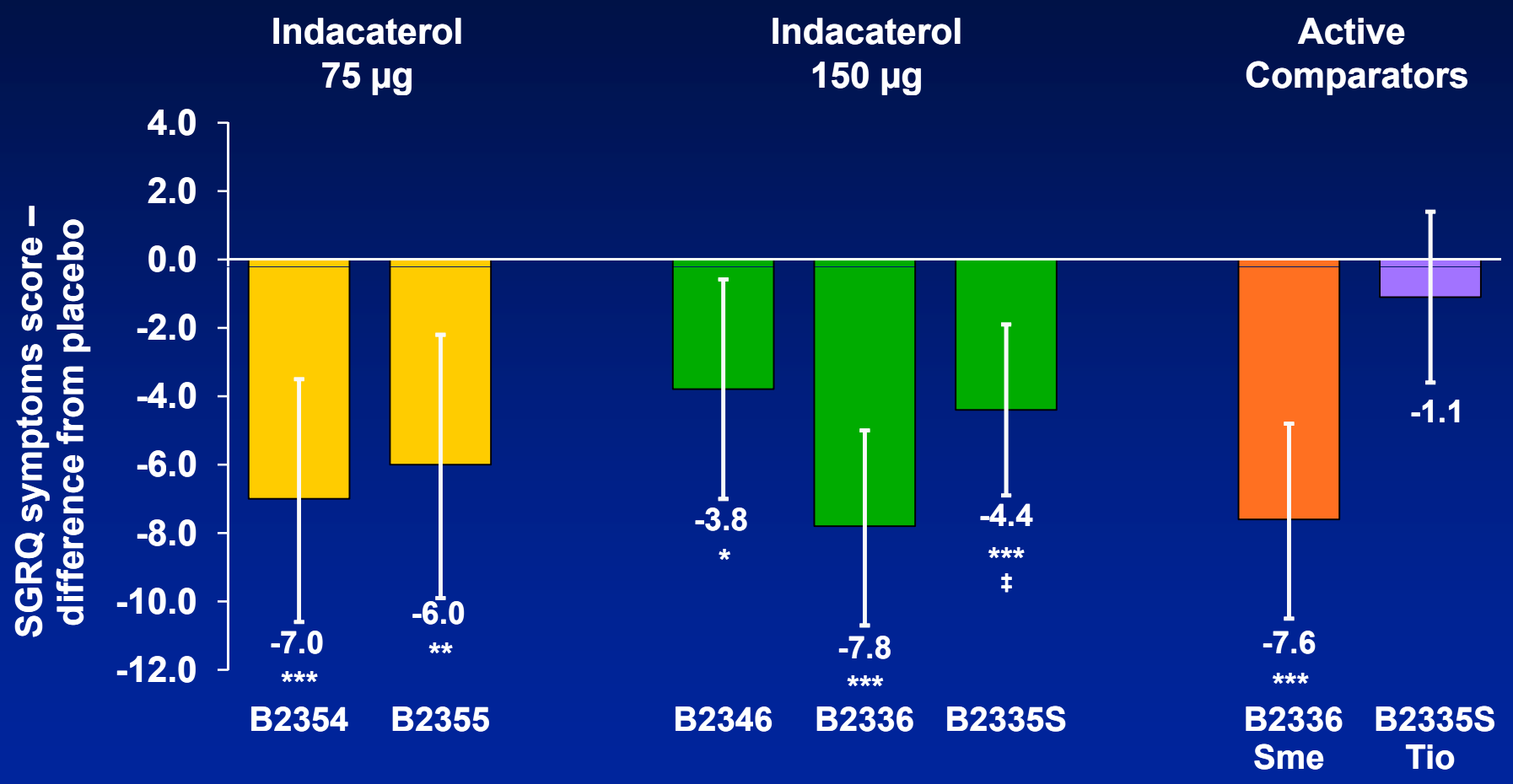
Data are least squares means with 95% confidence intervals. Dotted line indicates MCID (≤-4.0).

*p<0.05, **p<0.01, ***p<0.001 vs placebo (within study);

†p<0.05 vs salmeterol (within study); #p<0.05 vs tiotropium (within study)

Health Status – SGRQ at Week 12

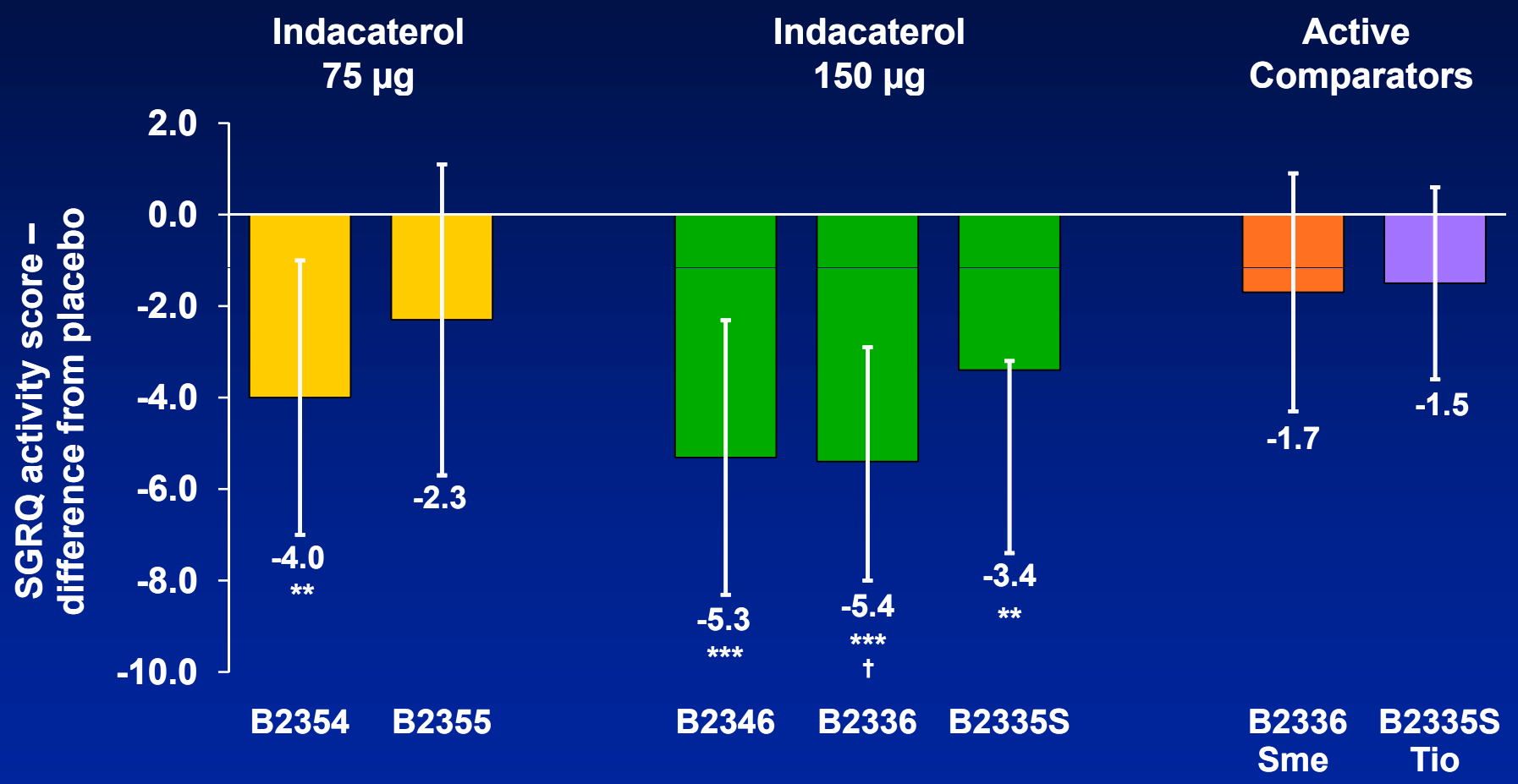
Differences from placebo – symptoms component



Data are least squares means with 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (within study); ‡p<0.05 vs tiotropium (within study)

Health Status – SGRQ at Week 12

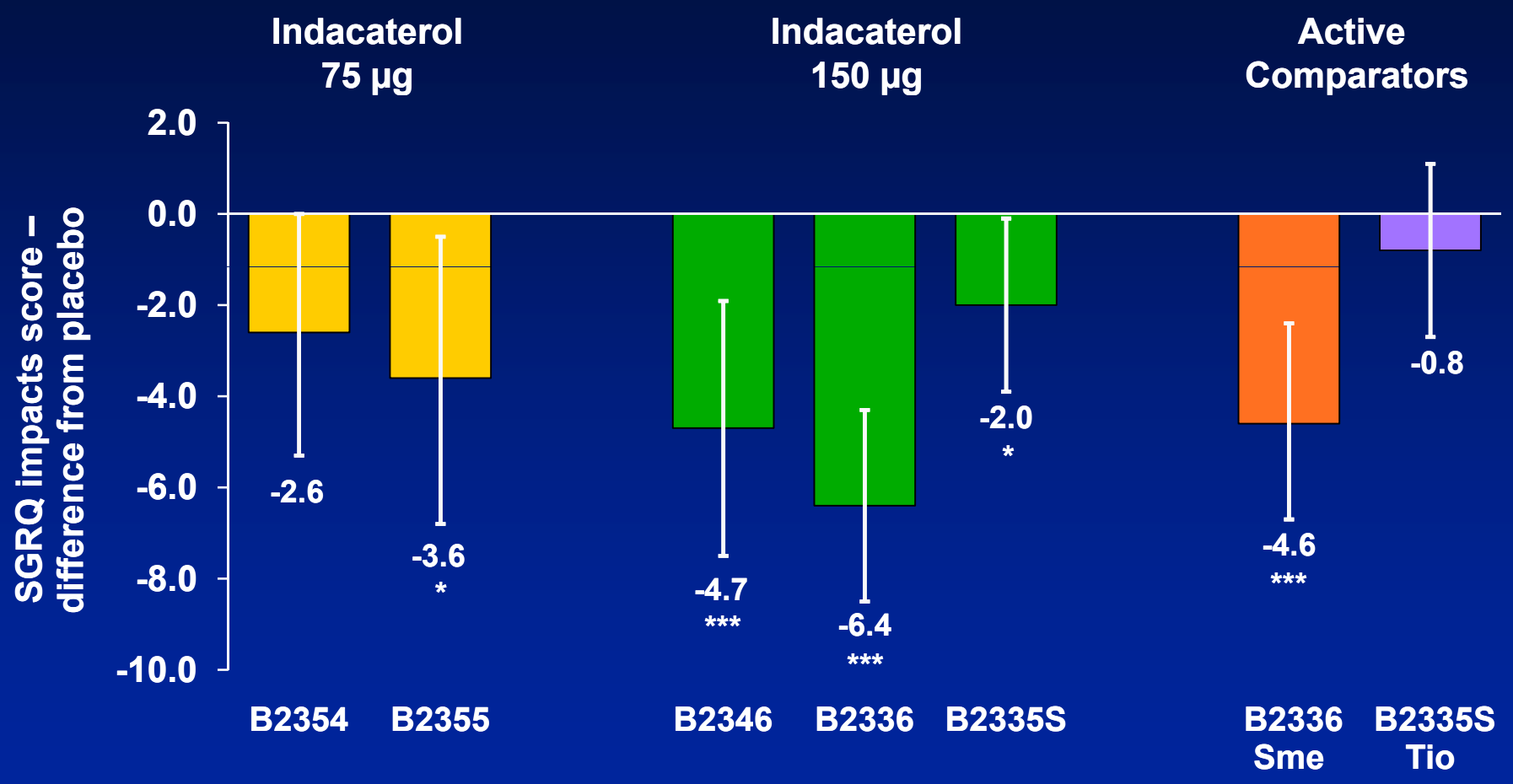
Differences from placebo – activity component



Data are least squares means with 95% confidence intervals.
**p<0.01, ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study)

Health Status – SGRQ at Week 12

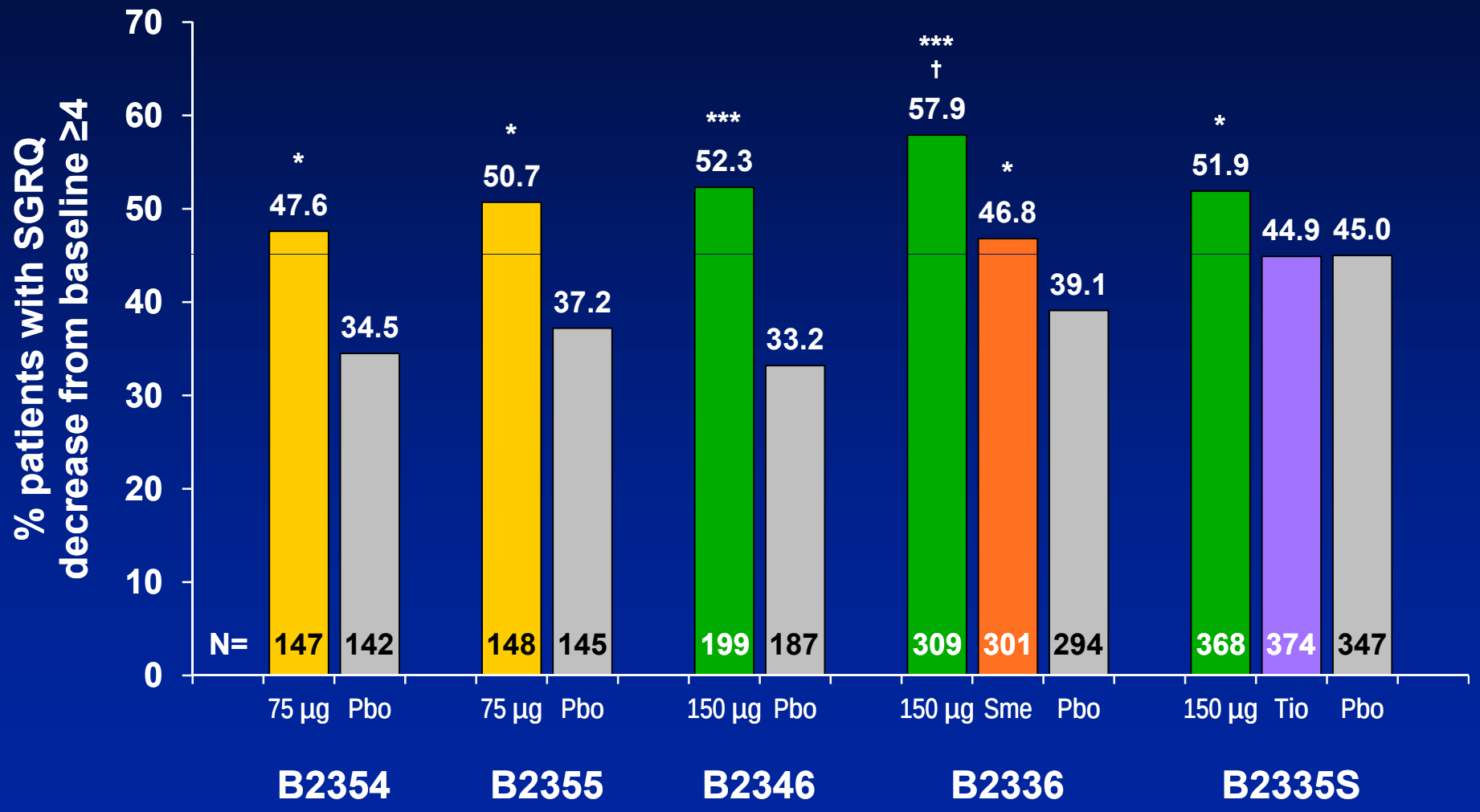
Differences from placebo – impacts component



Data are least squares means with 95% confidence intervals.
*p<0.05, **p<0.01, ***p<0.001 vs placebo (within study)

Health Status – SGRQ at Week 12

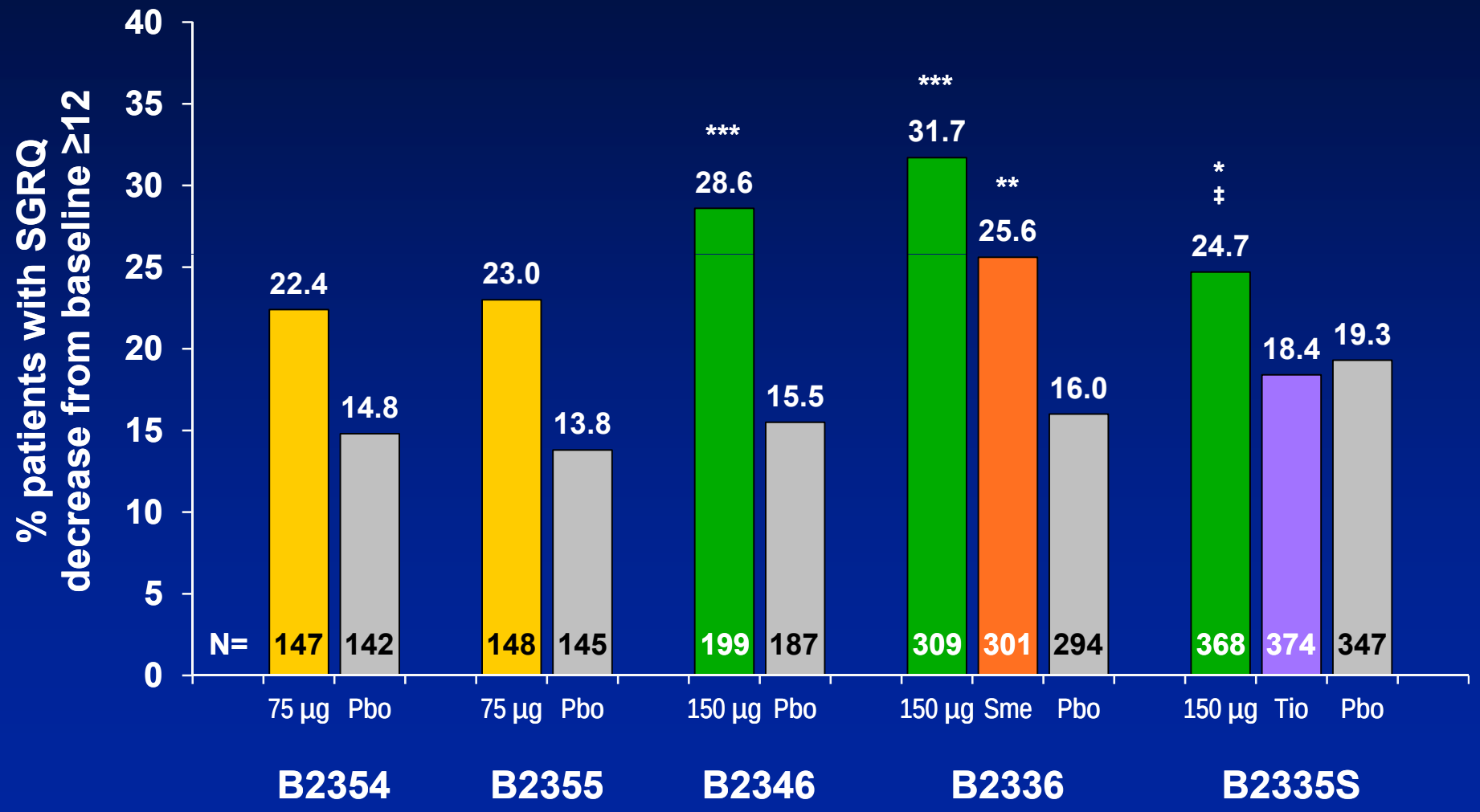
Responder analysis – ≥4 unit decrease from baseline



*p<0.05, ***p<0.001 vs placebo; †p<0.05 vs salmeterol

Health Status – SGRQ at Week 12

Responder analysis – ≥12 unit decrease from baseline

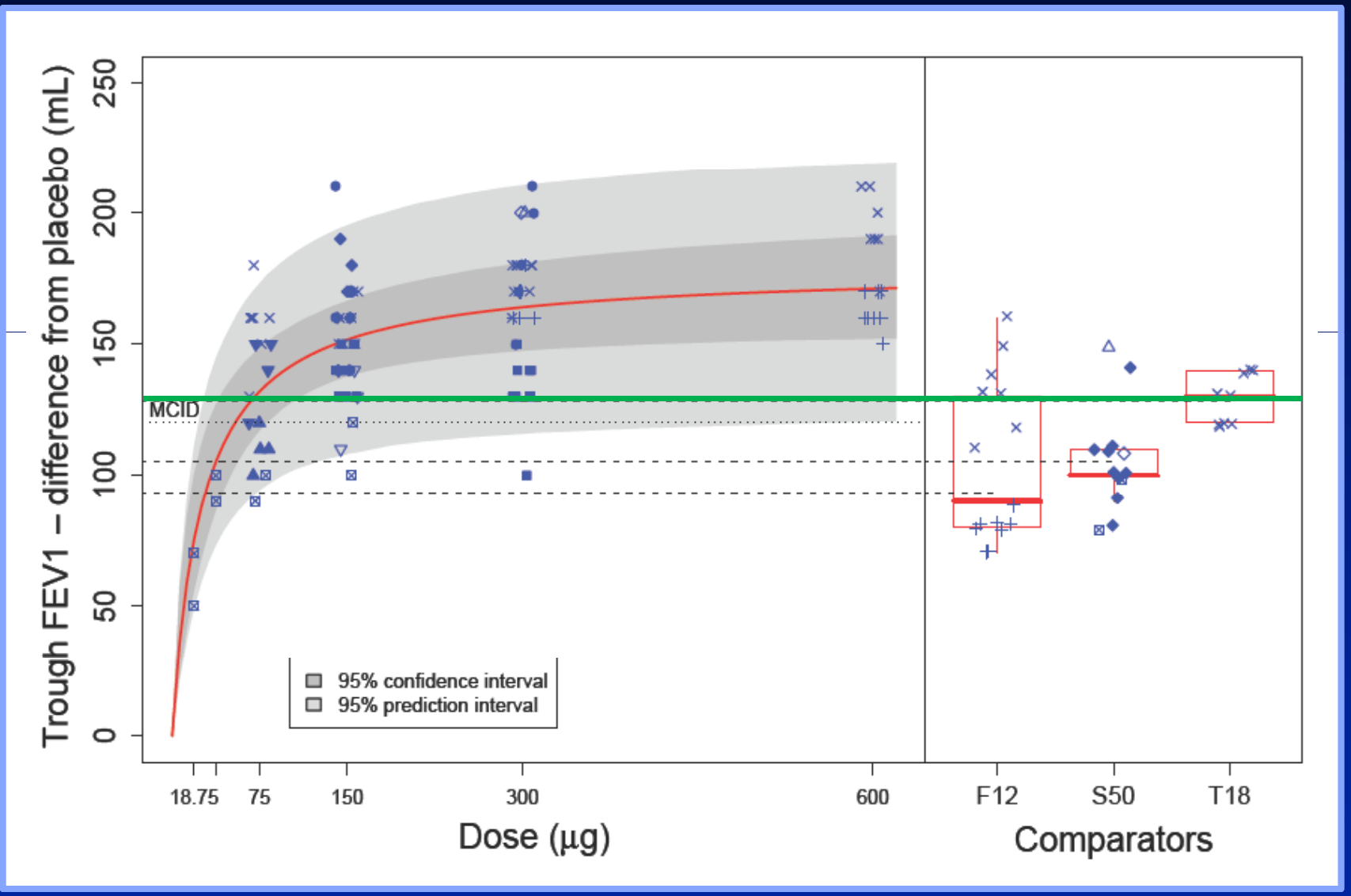


*p<0.05, **p<0.01, ***p<0.001 vs placebo; ‡p<0.05 vs tiotropium (within study)

Integrated Analysis of COPD Efficacy

- Integrates relevant FEV_1 data across studies while accounting for within- and between-study differences
- Integrated study-level analysis
  - 12 studies of very similar design, 8,111 patients, doses between 18.75 and 600 µg
  - Data: Trough FEV_1 mean differences from placebo and their standard errors for each steady-state visit
  - E_{max} model to describe dose response
  - Inter-study and inter-arm variability on maximum effect (E_{max})
  - Responses of active comparators included

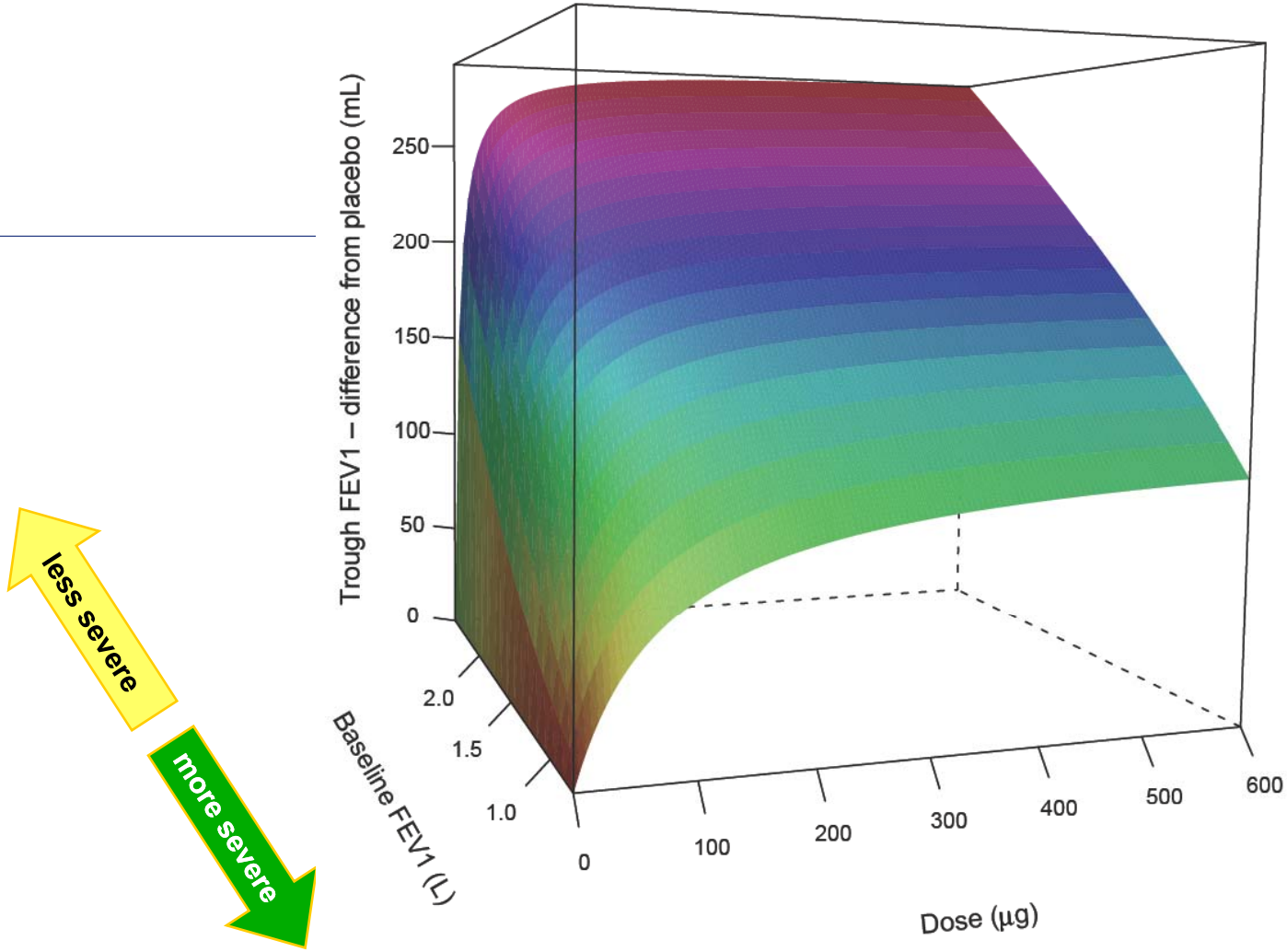
Dose Response: Indacaterol and Comparators



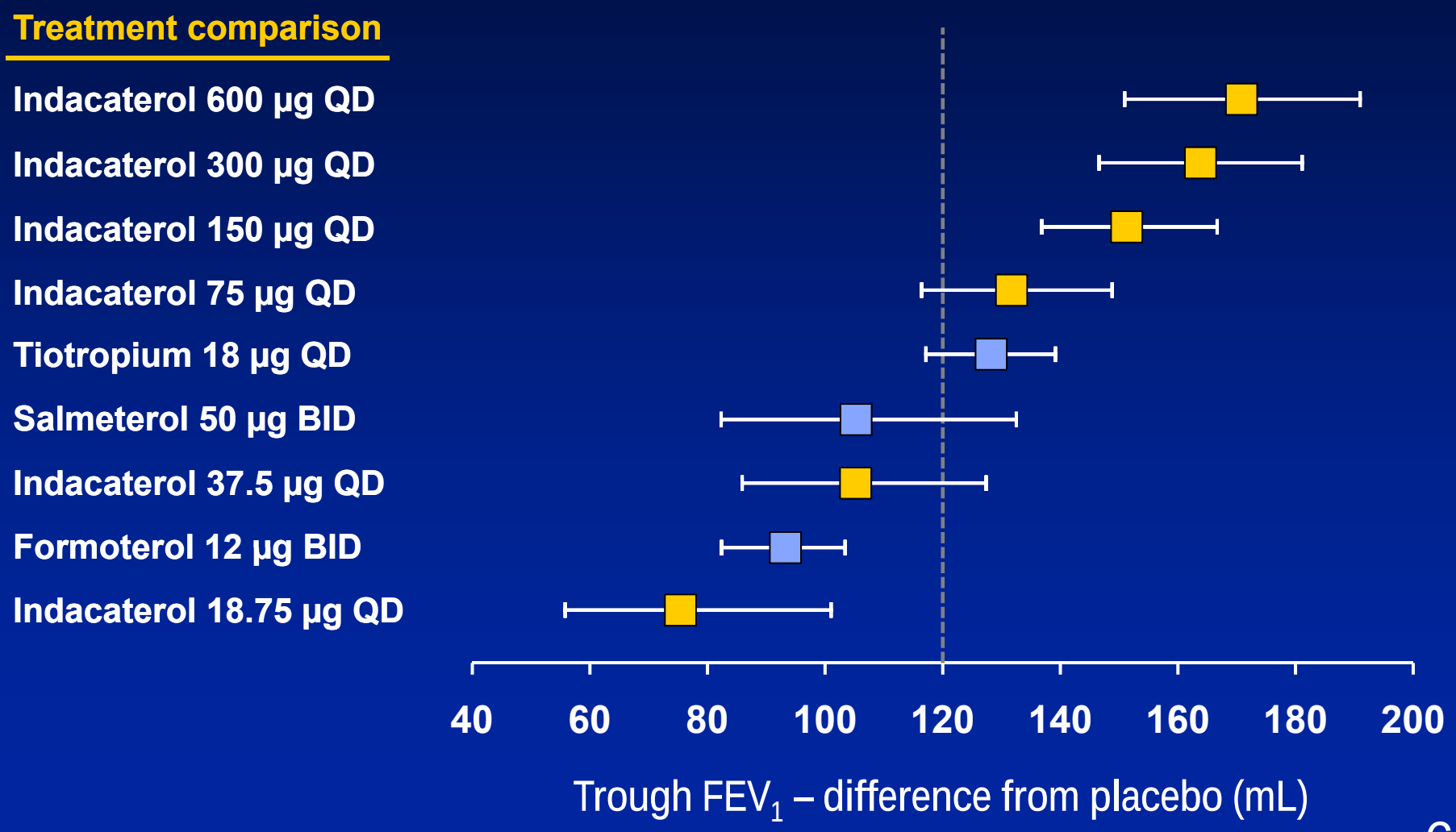
F12=Formoterol 12 µg BID S50=Salmeterol 50 µg BID T18=Tiotropium 18 µg

Predicted Impact of Disease Severity on Dose Response

Severe Patients Benefit More from Higher Dose



COPD Pooled Study-level Analysis: Predicted Response at Each Dose Level



Efficacy Summary

- Indacaterol demonstrates significant clinical benefit in replicate COPD pivotal trials for 75 µg and 150 µg
- Indacaterol provides consistent 24-hour bronchodilation
- Indacaterol dosed once daily is the optimal dose regimen
- Indacaterol has a rapid onset of action
- Indacaterol 150 µg dose is superior to current therapies

Safety

Linda Armstrong, M.D.

Drug Safety & Epidemiology
Novartis Pharmaceuticals Corporation

Safety Agenda

- Indacaterol Development Program: size, duration and patient characteristics
- Adverse Events
- Areas of special interest
  - Cardiovascular + cerebrovascular events
  - Cough after inhalation
  - Asthma safety
  - Acute respiratory events
- Post-marketing experience
- Risk Evaluation and Management for Indacaterol

Indacaterol Development Program

	Total Program (N)	Indacaterol (N)
All treated	15192	9243
COPD Safety Population	9441	4764
COPD 3-month population includes 75 µg, 150 µg, 300 µg, and 600 µg doses	9441	4764
COPD 12-month population includes 150 µg, 300 µg, and 600 µg doses	2142	1152

Patient Exposure by Treatment: >4000 Patient-years

COPD safety population (N=9441)

	Indacaterol Treatment Groups				Control Treatment Groups			
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	Pbo N=2012	For N=556	Tio N=1214	Sme N=895
Exposure (days)								
Mean	85.5	120.3	232.7	263.4	167.7	260.3	107.7	112.2
Patient-years	**105.06**	**859.72**	**736.97**	**394.49**	**923.60**	**396.21**	**357.97**	**274.93**
6 - <12 months	0	583 (22.3)	539 (46.59)	191 (34.92)	687 (34.15)	190 (34.17)	240 (19.77)	230 (25.70)
≥12 months	0	77 (2.95)	256 (22.13)	167 (30.53)	240 (11.93)	168 (30.22)	0	0

Baseline Co-existing Conditions

COPD safety population

	Indacaterol Treatment Groups				Control Treatment Groups			
Baseline co-existing conditions	75 µg N=449 n (%)	150 µg N=2611 n (%)	300 µg N=1157 n (%)	600 µg N=547 n (%)	For N=556 n (%)	Tio N=1214 n (%)	Sme N=895 n (%)	Pbo N=2012 n (%)
Cardio-vascular disease	101 (22.5)	476 (18.2)	195 (16.9)	114 (20.8)	114 (20.5)	242 (19.9)	181 (20.2)	382 (19.0)
Diabetes mellitus	41 (9.1)	280 (10.7)	103 (8.9)	52 (9.5)	52 (9.4)	129 (10.6)	95 (10.6)	224 (11.1)
Hyper-tension	262 (58.4)	1334 (51.1)	550 (47.5)	270 (49.4)	278 (50.0)	634 (52.2)	464 (51.8)	986 (49.0)
>3 CV risk factors	217 (48.3)	1084 (41.5)	407 (35.2)	217 (39.7)	225 (40.5)	514 (42.3)	368 (41.1)	800 (35.8)

Overview of Adverse Events

Common Adverse Events

COPD 3 month population ≥4% in 75 or 150 µg groups

	Indacaterol Treatment Groups				Control
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	Pbo N=2012
Total AEs n (%)	231 (51.5)	1067 (40.9)	556 (48.1)	252 (46.1)	867 (43.1)
Severe AEs n (% of all events)	17 (3.8)	100 (3.8)	37 (3.2)	22 (4.0)	101 (6.0)
COPD†	38 (8.5)	239 (9.2)	136 (11.8)	56 (10.2)	269 (13.4)
	5 (1.1)	25 (1.0)	7 (0.6)	5 (0.9)	27 (1.3)
Nasopharyngitis	24 (5.4)	114 (4.4)	67 (5.8)	43 (7.9)	89 (4.4)
	1 (0.2)	3 (0.1)	0	0	0
Cough	29 (6.5)	104 (4.0)	60 (5.2)	27 (4.9)	72 (3.6)
	1 (0.2)	1 (<0.1)	1 (0.1)	1 (0.2)	7 (0.4)
Headache	23 (5.1)	80 (3.1)	26 (2.3)	16 (2.9)	44 (2.2)
	1 (0.2)	4 (0.2)	2 (0.2)	0	1 (0.1)
Muscle Spasms	6 (1.3)	38 (1.5)	25 (2.2)	22 (4.0)	15 (0.8)
	0	7 (0.3)	0	2 (0.4)	1 (0.1)

† Progressive disease/exacerbations

Common Adverse Events

COPD 12 month population ≥10%

	Indacaterol Treatment Groups			Control
	150 µg N=144	300 µg N=583	600 µg N=425	Pbo N=556
Total AEs n (%)	110 (76.4)	422 (72.4)	276 (64.9)	351 (63.1)
Severe AEs n (% of all events)	19 (13.2)	60 (10.3)	43 (10.1)	64 (11.5)
COPD†	35 (24.3)	179 (30.7)	117 (27.5)	184 (33.1)
	3 (2.1)	17 (2.9)	11 (2.6)	22 (4.0)
Nasopharyngitis	24 (16.7)	99(17.0)	80 (18.8)	75 (13.5)
	1 (0.7)	19 (3.3)	0	2 (0.4)
Cough	17 (11.8)	47(8.1)	27 (6.4)	27 (4.9)
	1 (0.7)	1 (0.2)	1 (0.2)	1 (0.2)
Upper RTI	17 (11.8)	41(7.0)	20 (4.7)	21 (3.8)
	2 (1.4)	0	0	0
Headache	15 (10.4)	25(4.3)	21 (4.9)	24 (4.3)
	2 (1.4)	0	0	1 (0.2)

† Progressive disease/exacerbations

Indacaterol Adverse Event Experience (COPD)

COPD safety population

		Indacaterol Treatment Groups				Control Treatment Groups			
		75 µg	150 µg	300 µg	600 µg	Pbo	For	Tio	Sme
Total Exposure	N	449	2611	1157	547	2012	556	1214	895
	patient-year	105.1	859.7	737.0	394.5	923.6	396.2	358.0	275.0
Adverse Events	n	237	1226	767	351	1093	352	576	340
	n/patient-year	5.4	4.1	3.9	3.6	3.9	2.9	4.5	3.0
Serious Adverse Events	n	17	135	117	56	155	73	64	35
	n/patient-year	0.25	0.24	0.24	0.21	0.27	0.32	0.33	0.18
Deaths	n	0	4	2	1	14	4	4	1
	n/patient-year	0	0.01	<0.01	<0.01	0.02	0.01	0.01	<0.01

Most Commonly Reported SAEs by SOC Adjusted for Exposure (>1.0 Events Per 100 Patient Years)

COPD safety population

	Indacaterol Treatment Groups				Control Treatment Groups			
	75 µg N=449	150 µg N=2611	300 µg N=1157	600 µg N=547	Pbo N=2012	For N=556	Tio N=1214	Sme N=895
Total SAEs/100 patient-year exposure	24.7	23.5	24.4	20.5	31.8	33.2	18.2	27.0
Respiratory, thoracic & mediastinal disorders	6.7	5.2	8.7	3.5	8.6	12.1	6.1	5.5
Infections & Infestations	4.8	4.0	3.5	2.3	4.8	7.6	5.3	3.6
Cardiac Disorders	3.8	3.4	3.4	3.0	2.8	1.8	4.7	3.3
Nervous System Disorders	1.9	1.9	1.4	0.8	1.1	1.0	2.8	1.5
General disorders & administration site conditions	1.9	0.6	0.3	0.3	1.1	0.3	0.8	0.4
Blood and Lymphatic system disorders	1.9	0.2	0.1	0.3	0.2	0	0	0
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1.0	1.4	2.0	2.3	1.5	1.8	1.7	0.4
Gastrointestinal disorders	1.0	1.4	0.5	2.5	1.8	0.8	1.7	1.1
Injury, poisoning & procedural complications	0	2.0	1.6	1.8	1.0	1.3	3.6	0.4

Fatal SAEs

COPD safety population (N=9441)

- **Control Groups (23/4677 patients)**

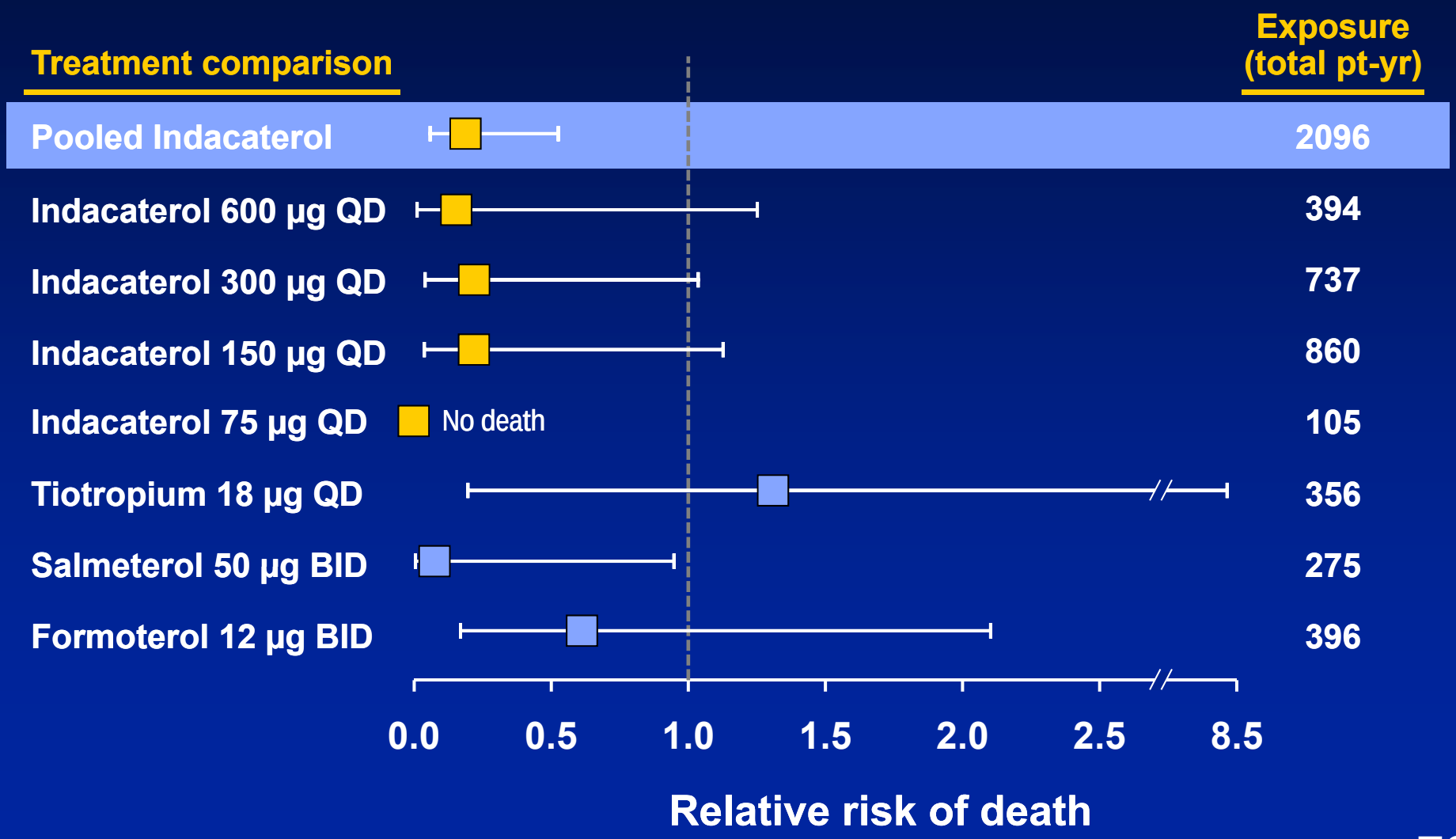
Group	Fatal Events (n)	Reported Cause of Death
Placebo	14	2 Aortic Aneurysm Ruptures, 1 Cardiac Arrest, 3 Sudden Death, 1 Cardio-respiratory Arrest, 3 MIs, 1 Death cause unknown, 1 Multi-organ Failure, 1 Accident, 1 COPD
Formoterol	4	Multi-organ Failure, Respiratory failure, Sudden Death, Death cause unknown
Salmeterol	1	Respiratory Failure
Tiotropium	4	Arteriosclerosis, Cardiac Arrest, Respiratory Arrest, Sepsis

- **Indacaterol Treatment Groups (7/4764 patients)**

Group	Fatal Events (n)	Reported Cause of Death
75 µg	0	–
150 µg	4	Sudden Death, Cardiac Arrest, MI, Cancer
300 µg	2	Cardiac Arrest, MI
600 µg	1	COPD Exacerbation

Safety over Dose Range – Mortality

Relative risks (to placebo) adjusted for time on treatment
COPD safety population

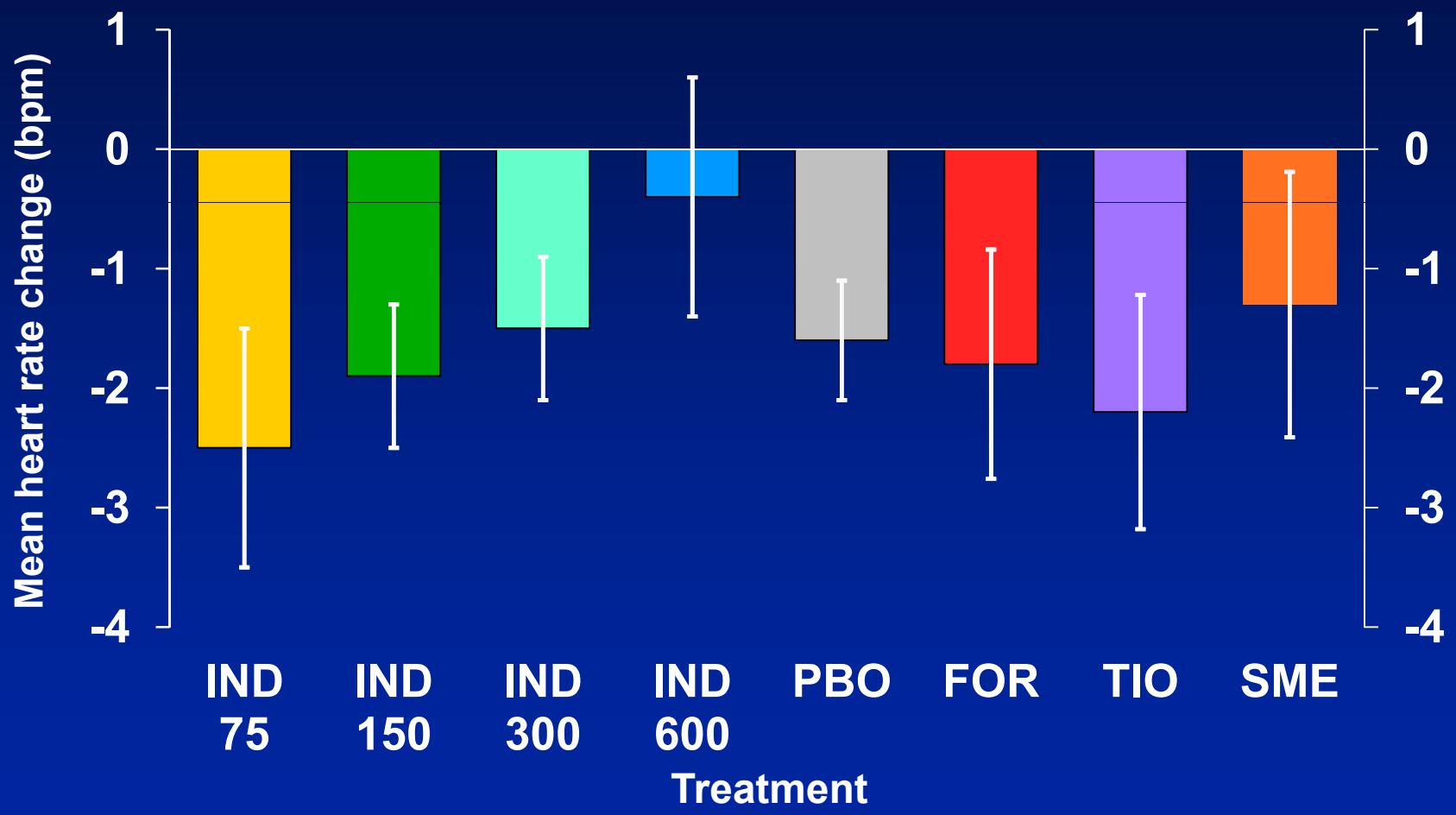


Areas of Special Interest

- Cardio-cerebrovascular events
- Cough after inhalation
- Safety in asthma
- Respiratory composite endpoint

Mean Pulse Rate (bpm) Change from Baseline

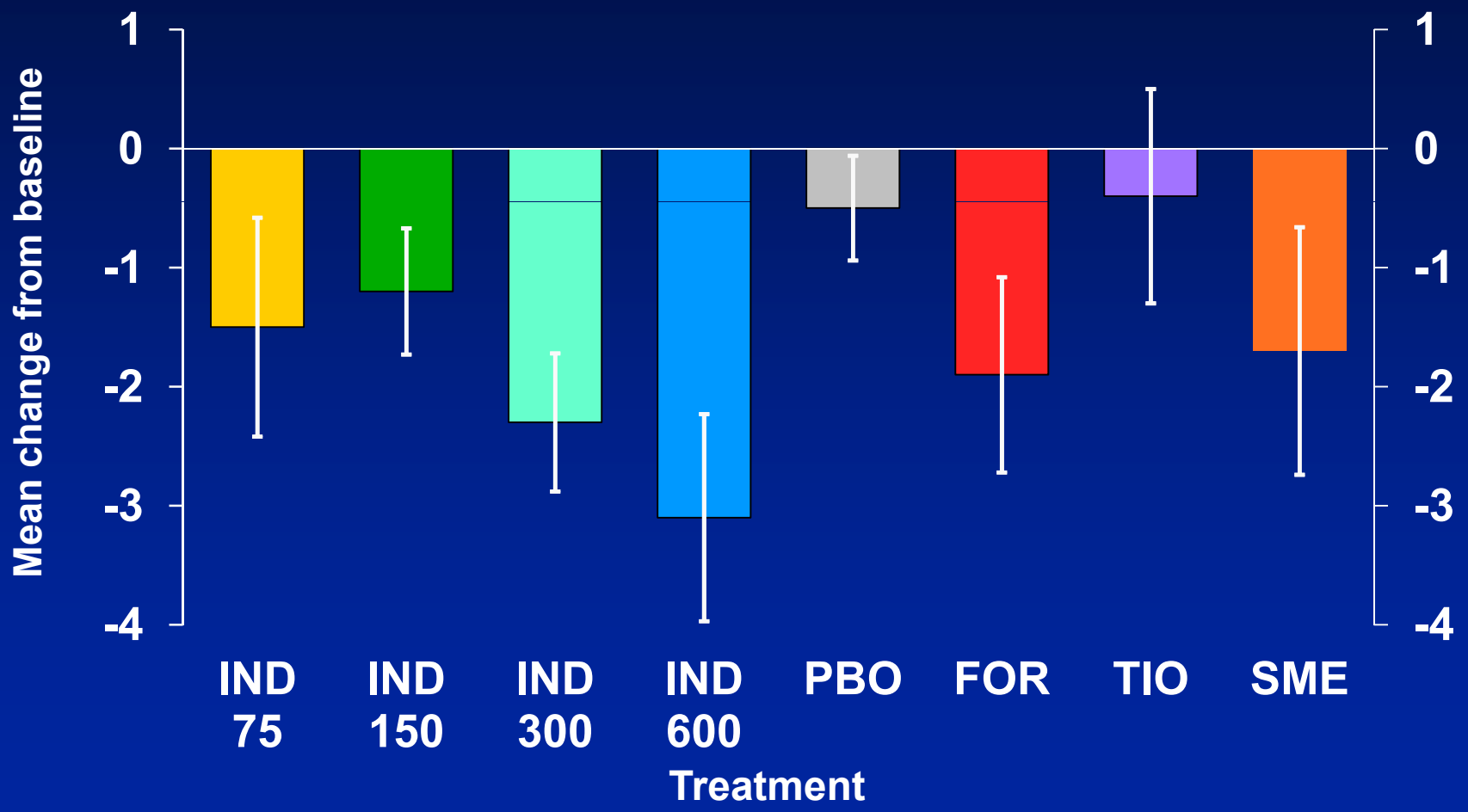
COPD safety population week 12



Data are least squares means with standard error

Mean Diastolic Blood Pressure (mmHg) Change from Baseline

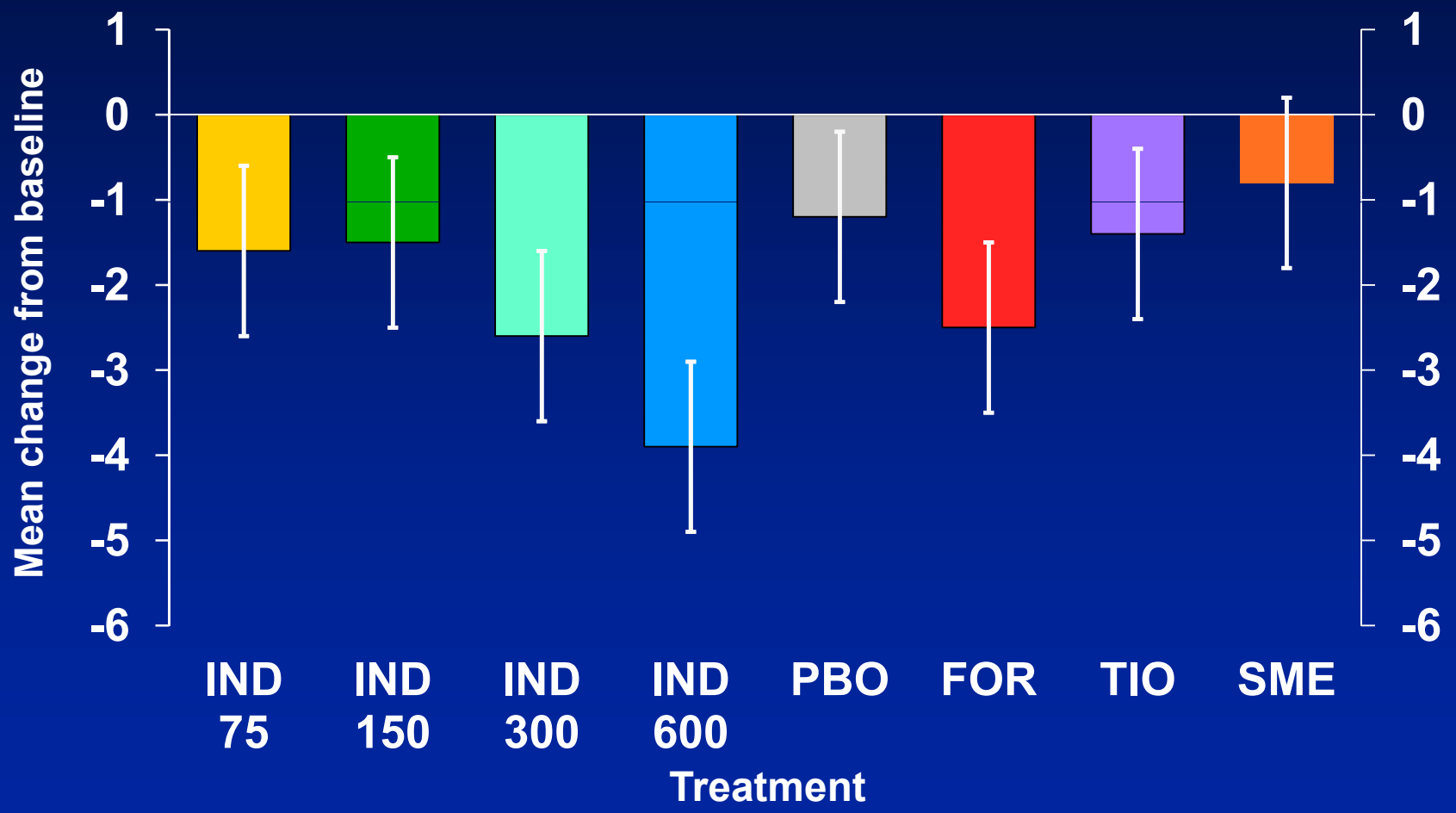
COPD safety population week 12



Data are least squares means with standard error

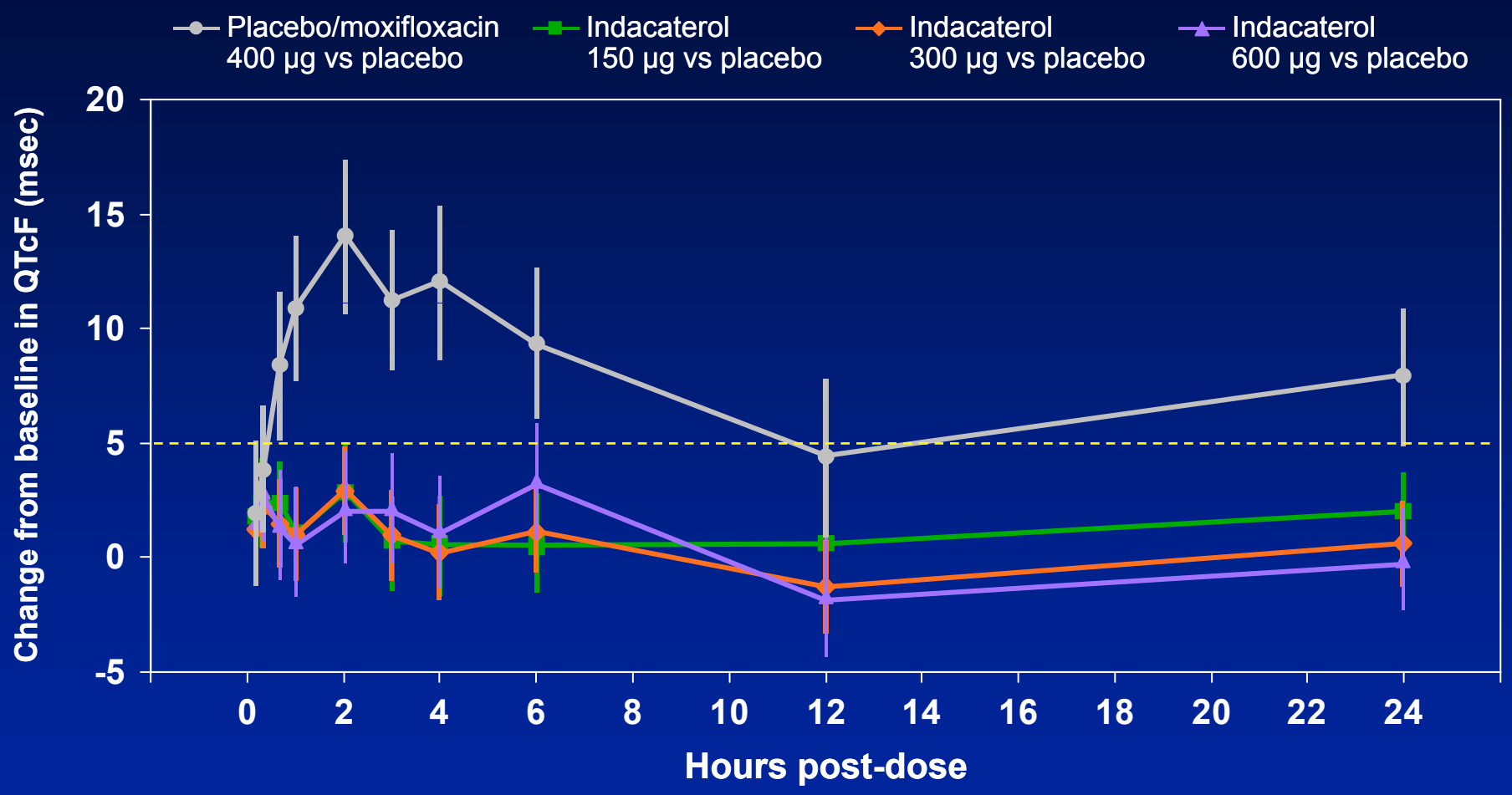
Mean Systolic Blood Pressure (mm Hg) Change from Baseline

COPD safety population week 12



Data are least squares means with standard error

QTc F- Change from Baseline Day 14



B2339 study

Confidence intervals are based on a one-sided t-test at the 5% significance level using data from the respective timepoint and pair of treatment groups only

Definition of CCV Events

- Standardized query (SMQ) composed of 257 preferred terms related events with varied pathology
  - Cardiac Arrhythmias
  - Cardiac Failure
  - Cerebrovascular Disorders
  - Ischemic Heart Disease
    - Myocardial infarction
    - Other ischemic heart disease
- Additional analyses performed to evaluate risk of specific cardiovascular and cerebrovascular events

Serious Cardiovascular (CCV) Events in 1 Year Studies

Study B2334	Indacaterol Treatment Groups		Control Treatment Groups	
	300 µg	600 µg	For	Pbo
Total population, N	437	425	434	432
Patients with ≥ 1 event, n	15	11	6	4
(%)	3.43	2.59	1.38	0.93
Total pt-yr	372.21	361.58	361.38	338.05
# of event per pt-yr	0.04836	0.03872	0.02490	0.01479

Study B2335SE	Indacaterol Treatment Groups		Control Tx Group
	150 µg	300 µg	PBO
Total population, N	144	146	124
Patients with ≥ 1 event, n	1	3	4
(%)	0.69	2.05	3.23
Total pt-yr	140.70	143.54	120.21
# of event per pt-yr	0.0071	0.0209	0.0333

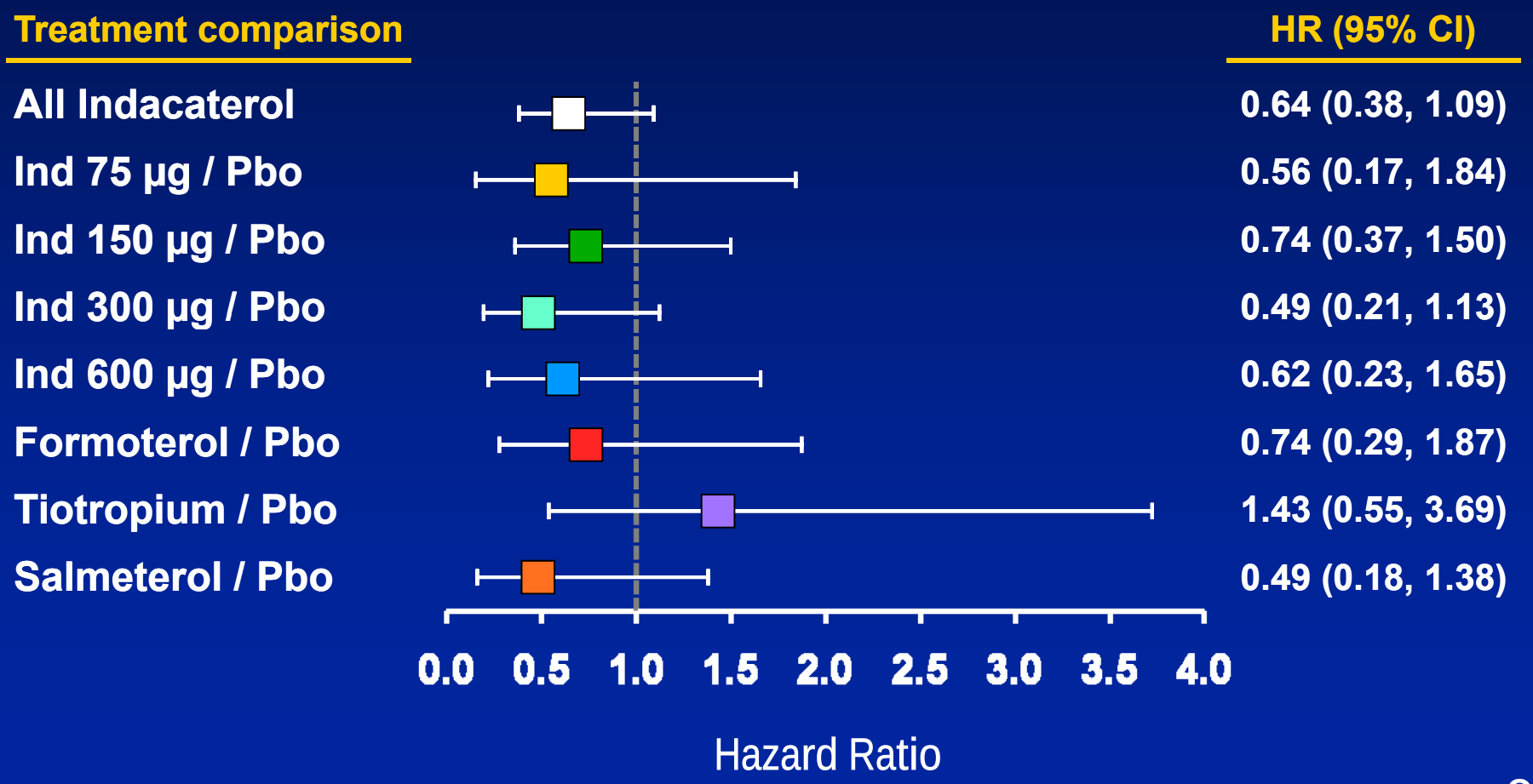
Definition of Major Cardiac and Cerebrovascular Events (MACE)

- Includes predefined search terms for stroke, myocardial infarction and cardiac death
- Fatal events externally adjudicated to identify cardiovascular deaths
- 2 MACE searches:
  - Broad MACE
    - SMQs for myocardial infarction, central nervous system hemorrhage, cerebrovascular accidents
  - Custom MACE
    - Subset of preferred terms selected by FDA

CCE: Major Adverse Cardiovascular Events

COPD safety population (N=9441)

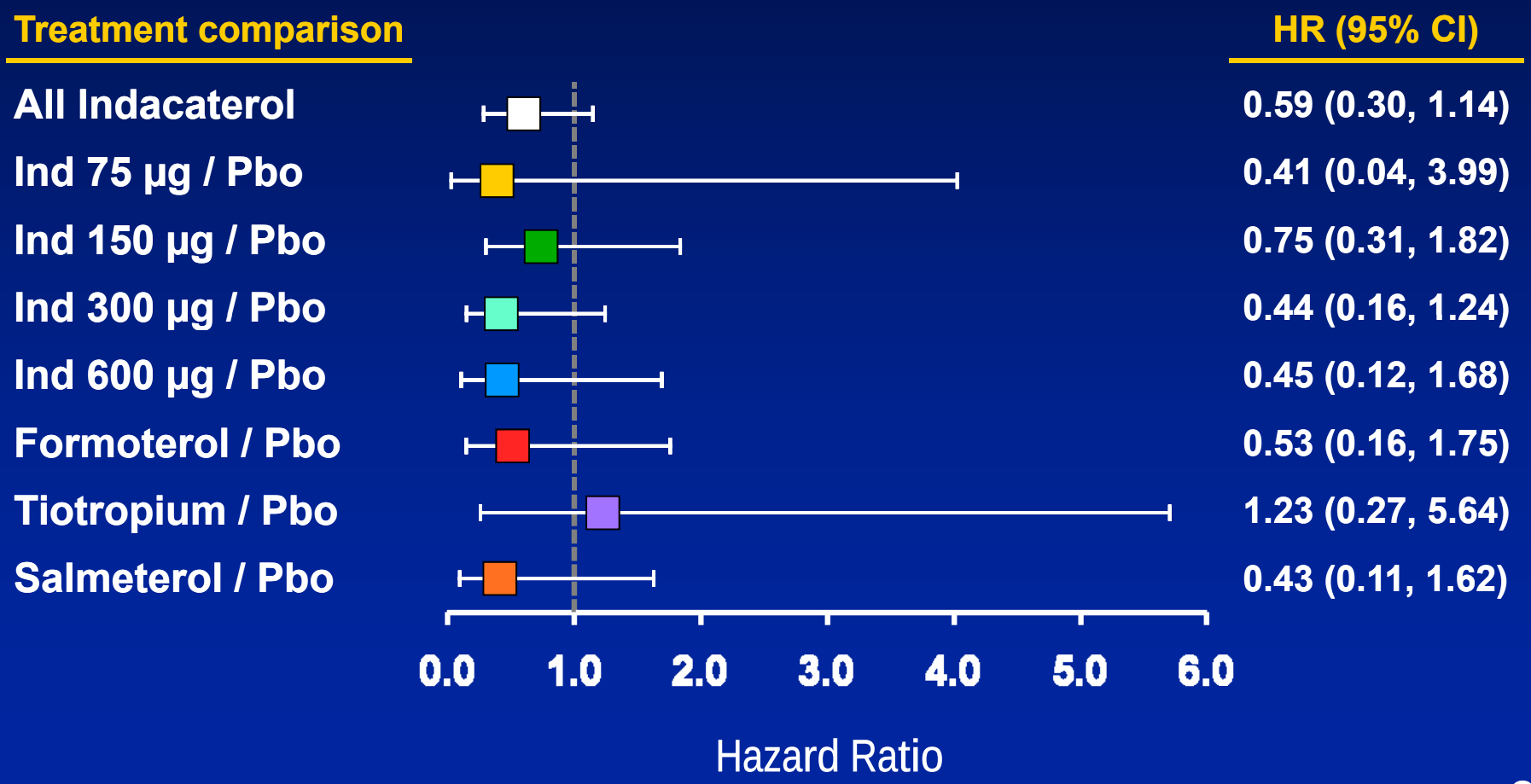
Myocardial Infarction, Stroke and Vascular Death (Broad MACE)



CCE: Major Adverse Cardiovascular Events

COPD safety population (N=9441)

Myocardial Infarction, Stroke and Vascular Death (Custom MACE)



Summary CCV Events

- Imbalance in CCV SAEs in Study 2334 due to less severe and subjective events
- MACE analyses do not show an increase risk of myocardial infarction, stroke, or cardiac death among patients receiving any dose of indacaterol

Areas of Special Interest

- Cardio-cerebrovascular events (CCV)
- **Cough after inhalation**
- Safety in asthma
- Respiratory composite endpoint

Cough Following Inhalation

- Investigator reported
- Reported as AEs if identified by patient
- 15% of patients experienced a sporadic cough after inhalation of indacaterol
  - Short-lasting, typically 5 seconds
  - Higher frequency among females and current smokers
- Most cough AEs were mild/moderate in severity
- No evidence of an association with bronchospasm, exacerbations, or loss of efficacy
- 1 discontinuation due to cough after inhalation at the proposed doses

Areas of Special Interest

- Cardio-cerebrovascular events
- Cough after inhalation
- Safety in asthma
- Adjudication of SAEs and Respiratory composite endpoint

Fatal Events Do Occur in Asthma Clinical Trials

Drug	TTE	Patient Age/Sex	Cause of Death
Ciclesonide[1]	102 days	14F	Cardiorespiratory arrest at school
Ciclesonide[2]	N/A	75F	Found dead at home, likely sudden death
Formoterol/ Budesonide[3]	26 days	13M	Respiratory Failure
Salmeterol/ Fluticasone[4]	3 months	25M	Status Asthmaticus

[1,2] Medical Review NDA 21-658www.accessdata.fda.gov/scripts/cder/drugsatfda/
[3] Sears ERJ 2008
[4] Bateman Ann Int Med 2008; 149:33-42

Safety in Asthma Indacaterol Study: B2338

- Novartis is NOT seeking an Asthma indication of indacaterol monotherapy
- 6 month safety study
- 750 patients randomized 1:1:1
  - Indacaterol 300 µg
  - Indacaterol 600 µg
  - Salmeterol 50 µg bid
- No placebo arm
- Patients instructed to continue previous ICS
  - ICS was NOT randomized

B2338: Asthma-Related Adverse Events – Preadjudication

Type of AEs*	Ind 300 µg N=268 n (%)	Ind 600 µg N=268 n (%)	Sme N=269 n (%)
All AEs	147 (54.9)	178 (66.4)	181 (67.3)
All SAEs	5 (1.9)	11 (4.1)	8 (3.0)
Asthma-related AEs	31 (11.6)	42 (15.7)	40 (14.9)
Asthma AE leading to d/c	4 (1.5)	6 (2.2)	2 (0.7)
Asthma-related hospitalizations	2 (0.7)	2 (0.7)	1 (0.4)
Asthma-related intubation	0	0	0
Asthma-related death	1 (0.4)	0	0

- Hospitalization rate in Indacaterol arms consistent with rate in FDA 2008 meta analysis (1.3%)[1]

* Not mutually exclusive [1] Levinson Statistical Briefing Document for 2008 PADAC table 5

Safety in Asthma Study B2338: All-Cause Deaths (300 µg)

- Asthma Exacerbation
  - 60 year old man who visited an ER on study day 165 complaining of asthma symptoms after exposure to organic solvents. He was treated with systemic corticosteroids then discharged on no additional steroids. 4 days later, he complained of worsening asthma symptoms and arrested on the way to the hospital.
- Cardiac Arrest
  - 75 year old woman with a history of hypertension. On study day 118, patient was asymptomatic. On day 119 she experienced sudden onset of dyspnea with cardiac arrest. CPR was performed. On intubation, airway pressures were normal.
    Treating physician believed event cardiac in nature.
    On adjudication, noted that patient was likely to have had COPD.

Spontaneous Report of Fatal Event in Patient with History of Asthma

44 year old woman with a history of asthma and current COPD

- Past Medical History: Baseline FEV_1 53% of predicted
  - Current smoker, history of noncompliance with medication
  - Multiple exacerbations requiring systemic corticosteroids
- Concomitant Medications: Fluticasone and Tiotropium, changed to Indacaterol and Tiotropium +/- prednisolone by specialist, subsequently put on BUD by GP who did not continue indacaterol

Four days prior to the event, she started clarithromycin for the treatment of a URI. On the day of her arrest, she complained of increasing dyspnea. Her death was initially described as "status asthmaticus after severe worsening of COPD", cause of death (per death certificate) listed as cardiac arrest.

Analysis of Respiratory Composite Endpoint

- FDA requested analysis of a Respiratory Composite Endpoint
- Includes all blinded, randomized, controlled asthma and COPD studies ≥7 days in which indacaterol was administered via single dose dry powder inhaler
- Blinded external adjudication of all SAEs to determine which events primarily represent:
  - Asthma-related death, intubation, hospitalization
  - COPD-related death, intubation, hospitalization
  - Pneumonia related death, intubation, hospitalization

Studies Included in Meta Analysis of Acute Respiratory Events

- 7 asthma studies, B2338 and 6 placebo-controlled short term studies ≥7 days in duration
  - Range of doses 18.75 - 800 µg QD
  - Range of treatment Duration 1-4 weeks
  - Total enrolled = 1,914
- 23 COPD studies of ≥7 days
  - Range of doses from 18.75 - 800 µg QD
  - Range of treatment Duration 1-52 weeks
  - Total enrolled = 11,755

Asthma Related Adverse Events

Asthma SDDPI studies

	18.75 N=84	37.5 N=81	75 N=131	150 N=85	300 N=268	600 N=268	Pbo N=254	Sme N=353
Pt year	3.45	3.35	5.54	3.47	119.56	119.18	9.2	127.5
Asthma Composite Endpoint * population I n (n/pt yr)	0	0	0	0	2 0.02	2 0.02	0	1 0.01

- No dose response in active controlled study

* Adjudicated Hospitalizations, intubations and Death

Acute COPD-Related Hospitalizations

COPD SDDPI studies

FDA Addendum Table 3- without adjustment for differences in study length

	75 N=543	150 N=2745	300 N=1422	600 N=584	Ind All N=6863	Pbo N=2484	For N=556	Tio N=842	Sme N=1010
n	5	36	40	13	108	47	29	5	10
%	0.9	1.3	2.8	2.2	1.6	1.0	5.2	0.6	1.0

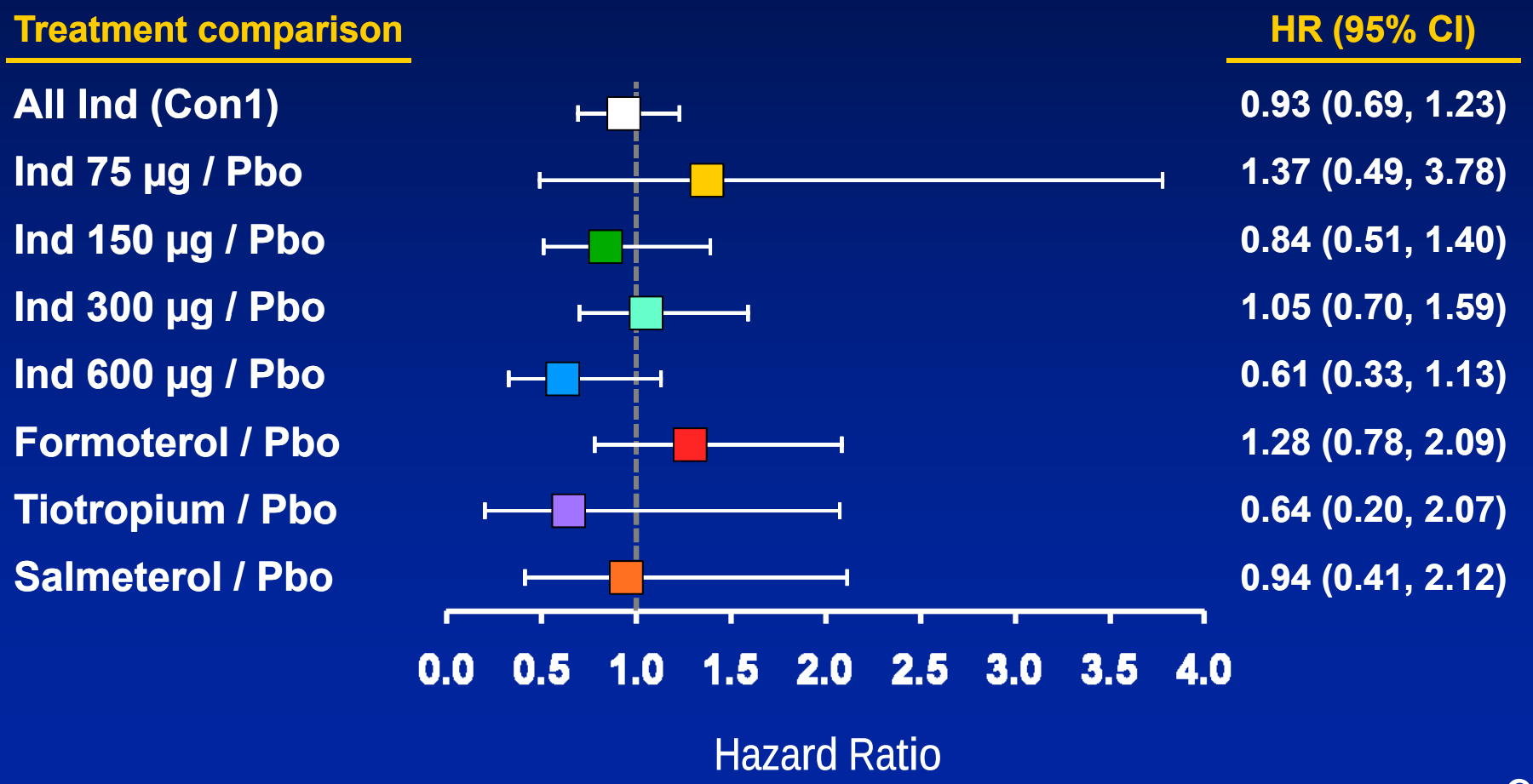
Hospitalizations adjusted by Exposure

	75 N=543	150 N=2745	300 N=1422	600 N=584	Ind All N=6863	Pbo N=2484	For N=556	Tio N=842	Sme N=1010
n	5	36	40	13	108	47	29	5	10
n/100 pt year	4.59	4.51	6.02	3.29	4.93	5.53	8.58	3.34	3.58

Acute Respiratory Composite Endpoint

COPD safety population

Acute Respiratory Composite Endpoint for COPD



Summary Clinical Trial Data

- Extensive program with studies up to a year in duration
- No dose response at doses up to 600 µg
- Small number of serious events in asthma studies
- No increase in acute respiratory events in COPD studies
- The safety profile does not limit dose selection

Post-Marketing Experience

Spontaneous Event Reporting

- Voluntary reporting by patients, family members or Healthcare providers to Novartis
- Reports from health authorities
- Media or literature reports
- Reports Solicited by calls to patients for Novartis sponsored patient support programs
- Increase in spontaneous reporting in the first 2 years after launch is known as the Weber effect

Weber JCP In Rainsford KD ed. Advances in Inflammation Research, vol 6. New York:Raven Press, 1984:1-6

COPD Post-Marketing Experience: ~56,000 Patient-years

- December 1, 2009 to November 30, 2010
- 275 cases
- 562 events
- Most reports describe non serious events
- Indication for use
  - 258 COPD, bronchitis, emphysema or not available
  - 11 asthma
  - 6 other

COPD Post-Marketing Experience: Most Common Adverse Events (Spontaneous Reports) ~56,000 Patient-years

Most Common Events (Non serious)	N
Cough	67
Dyspnea	21
Headache	20
Peripheral edema	17
Dizziness	12

Most Common Serious Events	N
Angina	7
Dyspnea	7
COPD	6
Circulatory collapse*	5
Arrhythmia	4

* Syncope (2), presyncope (2), hyperglycemia, DM (1)
November 30, 2009 - November 30, 2010

COPD Post-Marketing Experience: ~56,000 Patient-years

- **Fatal outcomes: 34 Cases**
  - 14 spontaneously reported
  - 20 collected by a call center as part of Patient Support Program in Mexico
- **Patients had significant underlying co-morbidities contributing to fatal outcomes**
  - 13 COPD disease progression/pneumonia
    - 1 respiratory arrest in patient w/ concomitant asthma
  - 10 Cardiac (CHF, Cardiac arrest, MI)
  - 3 malignancy
  - 2 unknown
  - 2 pulmonary emboli
  - 2 complications of DM (sepsis, circulatory collapse)
  - 1 GI hemorrhage
  - 1 Wegener's Granulomatosis

November 30, 2009 – February 7, 2011

Risk Evaluation and Management for Indacaterol

Objectives of Risk Evaluation and Management for Indacaterol

- In labeling, describe appropriate use of indacaterol
- Accurately communicate risks to prescribers and patients
- Evaluate occurrence of events of special interest
- Minimize off-label use

Proposed US Risk Evaluation and Mitigation Strategy (REMS)

- Goals of Proposed REMS:
  - To inform healthcare providers about:
    - The increased risk of asthma-related death in patients taking LABAs and the appropriate use of indacaterol in patients with COPD
  - To inform patients about:
    - Other serious risks associated with the use of indacaterol
- Medication Guide for Patients
  - Included in packaging so each patient will receive one with every prescription and refill
- Communication Plan for Prescribers
  - DHCP Letter; information on a website; letter to professional societies

Safety Risk Management Plan to Optimize Active and Passive Surveillance

- Enhanced Pharmacovigilance to improve quality of data collected for spontaneous events
- Further evaluation of indacaterol safety in clinical practice through active surveillance:
  - Two 3-year, Post-authorization safety studies (PASS)
    - General Practitioner Research Database (UK) – *ongoing*
    - US claims database – *proposed*
  - Events to be monitored include:
    - Off-label use in asthma
    - Cardiovascular events
    - LABA class effects

Ongoing Evaluation of Safety of Indacaterol (and its Combinations)

- Randomized Control Trials
  - COPD: 3500 patient 1-year study of COPD exacerbations
  - Asthma: 1500 QMF patient study comparing the fixed dose combination of indacaterol and mometasone furoate (an ICS) to mometasone furoate alone for 12-18 months
- Observational Studies
  - COPD: 15,000 patients to be enrolled in various national observational studies

Safety Conclusions

- Wide therapeutic index
- Similar SAE profile to comparators
- No increased risk of major cardiovascular or cerebrovascular events
- No increased risk of acute respiratory events
- No new signals identified in post marketing experience
- Comprehensive risk management strategy
- The safety profile does not limit the selection of an optimal dose

Indacaterol Benefit Risk Clinical Perspective

James Donohue, M.D.

Professor and Chief, Division of Pulmonary and Critical Care Medicine

University of North Carolina at Chapel Hill

COPD Treatment

GOLD 2010 guidelines

I: Mild	II: Moderate	III: Severe	IV: Very Severe
• FEV_1/FVC <0.70 • FEV_1 ≥80% predicted	• FEV_1/FVC <0.70 • 50% ≥ FEV_1 <80% predicted	• FEV_1/FVC <0.70 • 30% ≥ FEV_1 <50% predicted	• FEV_1/FVC <0.70 • FEV_1 <30% predicted *or* FEV_1 <50% predicted plus chronic respiratory failure

Active reduction of risk factors: influenza vaccination

Add **short-acting bronchodilator (when needed)**

Add **regular treatment with one or more *long-acting* bronchodilators to optimize bronchodilation**

Add **rehabilitation**

Add **inhaled glucocorticosteroids if repeated exacerbations**

Add **long-term oxygen if chronic respiratory failure**

Consider **surgical treatments**

Adapted from Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2010

150 µg Studies: vs. Comparators

Study	B2336 N=998	B2335S N=1665
	Indacaterol vs Salmeterol	Indacaterol vs Tiotropium
FEV_1 Trough	60 mL (20, 100)	50 mL (10, 90)*
TDI	0.55 (0.11, 1.00)	0.18 (-0.24, 0.61)
SGRQ	-2.1 (-4.0, -0.2)	-1.7 (-3.4, -0.1)

* Results are from the non-inferiority analysis for trough FEV_1, other endpoints are from the superiority analyses

Safety

- LABA class effects in COPD not typically seen with indacaterol
  - Heart rate increase
  - QTc prolongation
- Cardio-cerebrovascular profile of indacaterol in COPD similar to other LABAs
- Indacaterol has a wide therapeutic index with safety demonstrated up to 1 year at 4-8 times the proposed doses
- LABA safety in asthma (not proposed indication)
  - Addressed with appropriate labeling for COPD only, REMS communication plan, and post-marketing surveillance studies

Use of Indacaterol 75 and 150 µg in Patients with COPD

- Both doses are safe and effective
- The optimal dose is the 150 µg dose based on the totality of the efficacy and safety data
- The 150 µg dose would be preferable as the starting dose

Q&A Slides Presented

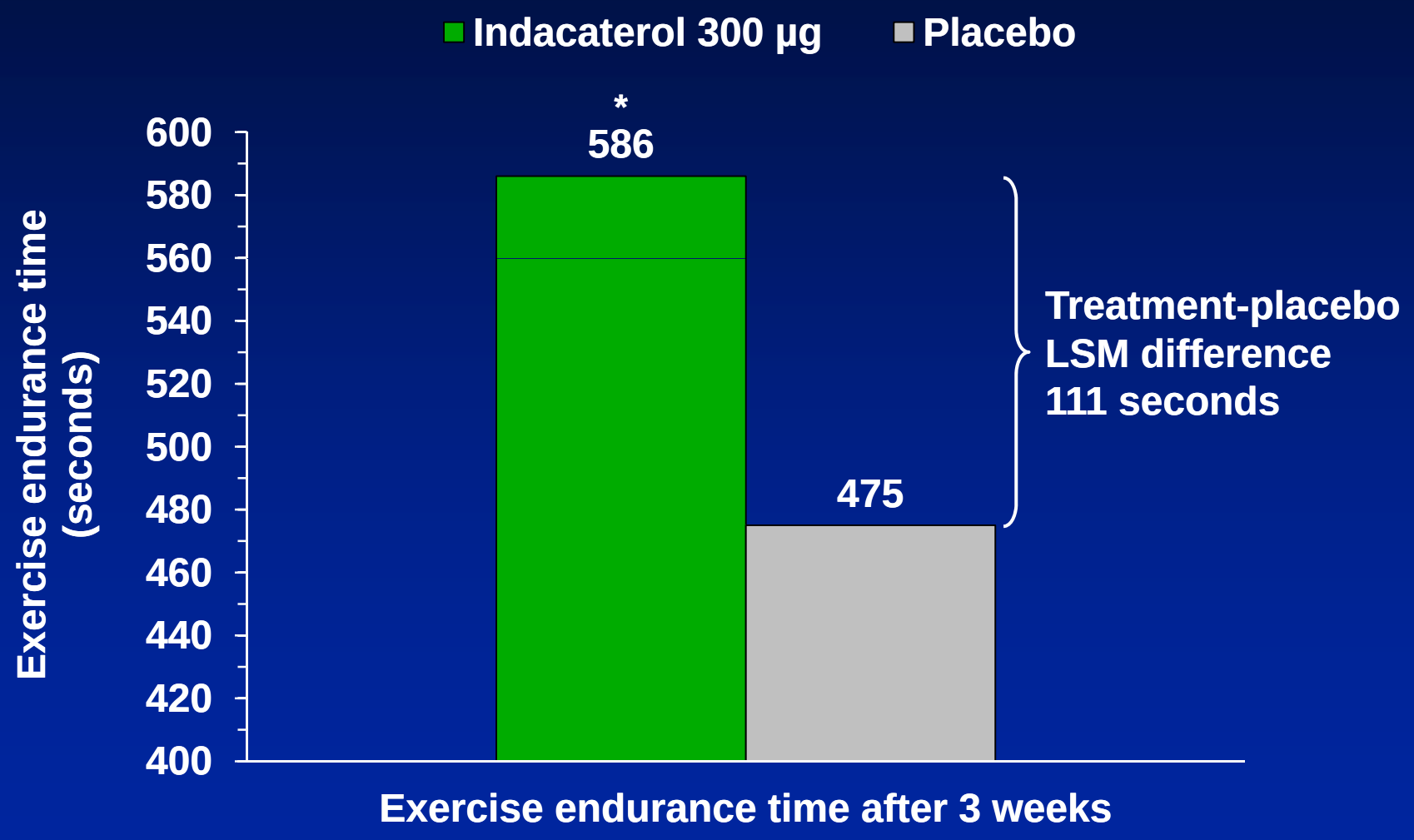
FDA CDER

Pulmonary-Allergy Drugs Advisory Committee Meeting

March 8, 2011

B2311: Exercise Endurance Time after 3 Weeks

mITT population

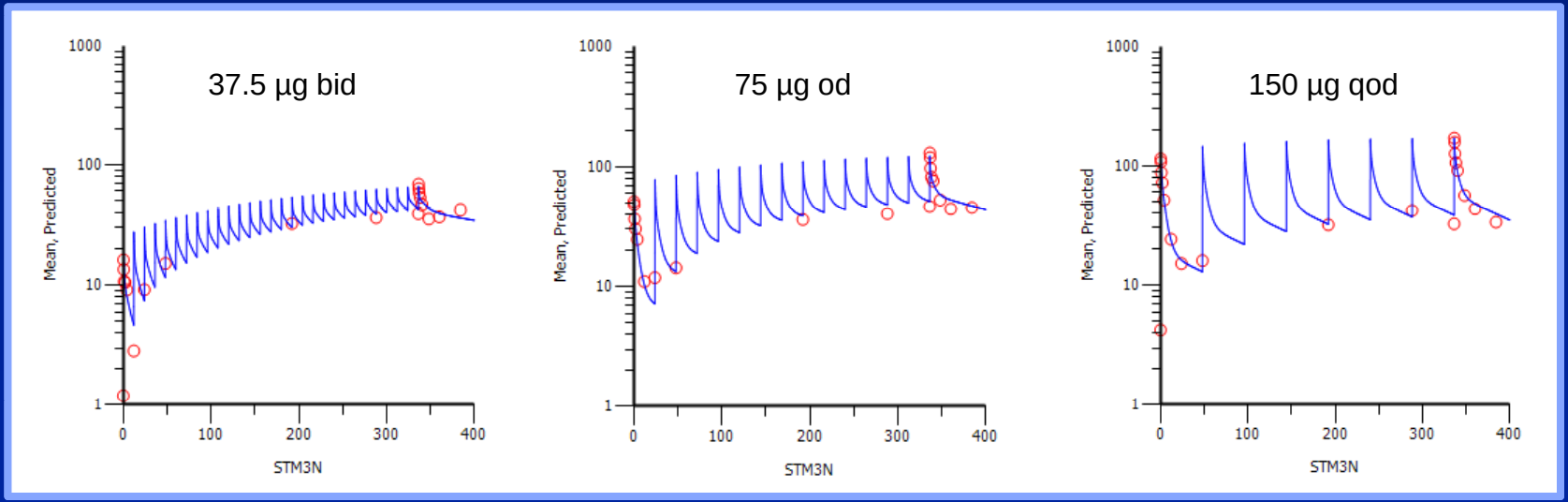


Data are LSM. *p<0.05 vs placebo

Steady State Serum Levels for Different Dosage Regimens

- B2223 data confirm, that different dosing regimens have impact on $C_{max,ss}$ but they result in similar $C_{min,ss}$ and $C_{av,ss}$

		Day 15, Steady State		
	Dose Regimen	C_{max}	C_{min}	$C_{av,ss}$
Study data from B2223	37.5 µg bid	76.2	34.4	50.3
	75 µg od	143	39.8	60.4
	150 µg qod	220	34.3	61.9



Line represents PK model fit to the observed data (circles)

Impact of Demographic Variables on the PK of Indacaterol

- Pooled dataset was used for population PK analysis including impact of demographic covariates
- Age, body weight, gender and Asian ethnicities were identified as major demographic covariates; systemic exposure increases with age, but decreases with BW

Age	C_{max} is 15% higher at 95 percentile age (77 y) than at median age (62 y)
BW	C_{max} is 18% higher at 5 percentile BW (49.2 kg) than at median BW (73.2 kg).
Gender	C_{max} is 8% higher in females
Japanese	Japanese subjects have a 25% higher C_{max} than average
Korean	Korean subjects have a 17% higher C_{max} than average

Drug Interactions Summary

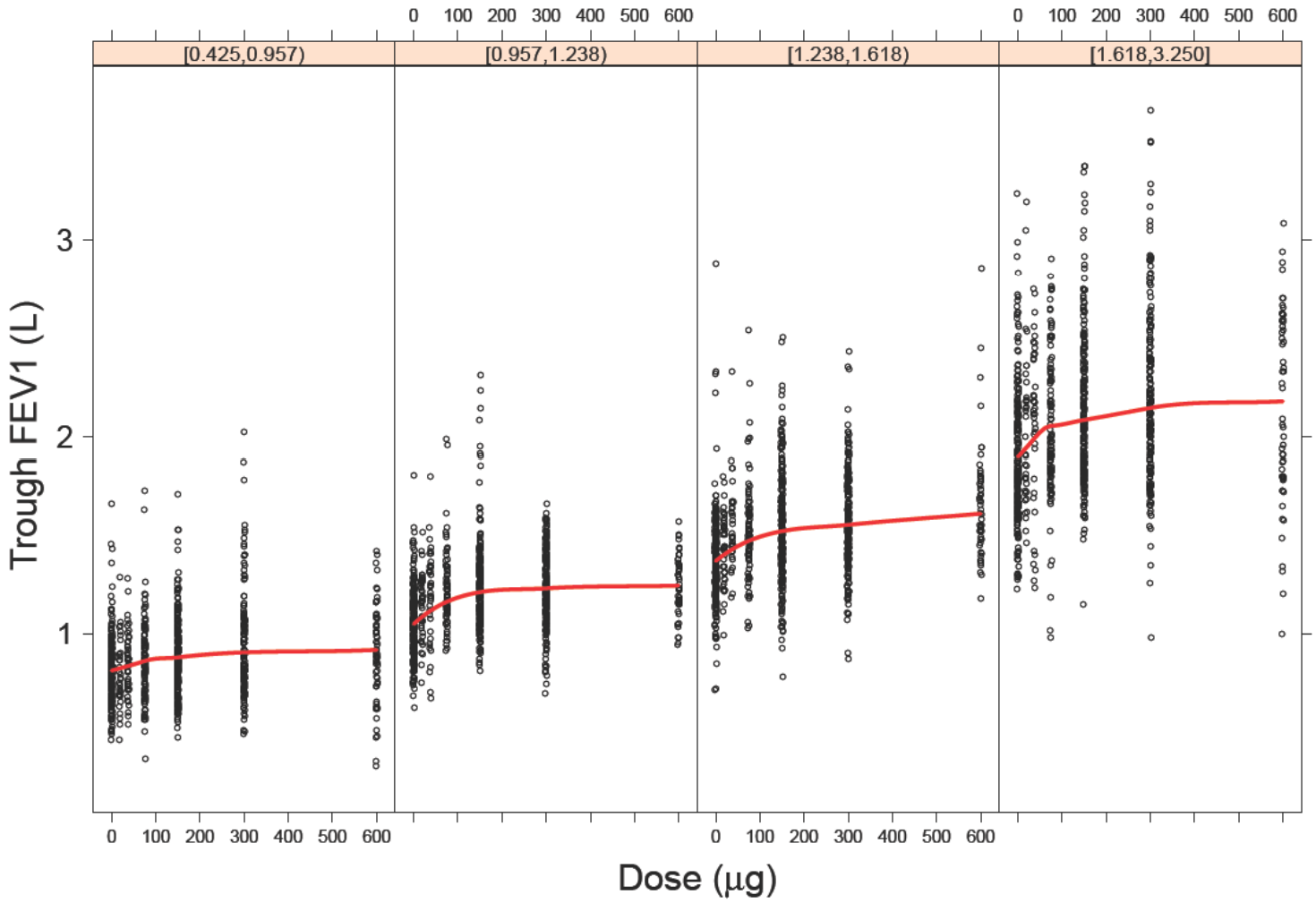
- Comprehensive drug interaction program performed that addressed the key elimination pathways, i.e., CYP3A4 and P-gp
- Maximum increase by a combined strong inhibitor of CYP3A4 and P-gp (i.e., ketoconazole) doubles AUC_{last}. Biggest changes in C_{max} observed with verapamil (1.53-fold)

Inhibitor Drug	C_{max}	AUC_{last}
Ketoconazole	1.31 (1.16, 1.48)	1.95 (1.78. 2.13)
Erythromycin	1.15 (1.00, 1.32)	1.59 (1.41, 1.80)
Verapamil	1.53 (1.34, 1.76)	1.47 (1.32, 1.64)
Ritonavir	1.08 (0.99, 1.18)	1.77 (1.60, 1.97)

Ratio of geometric means (90% confidence interval) for the comparison of indacaterol co-administered with an inhibitor drug to indacaterol administered alone

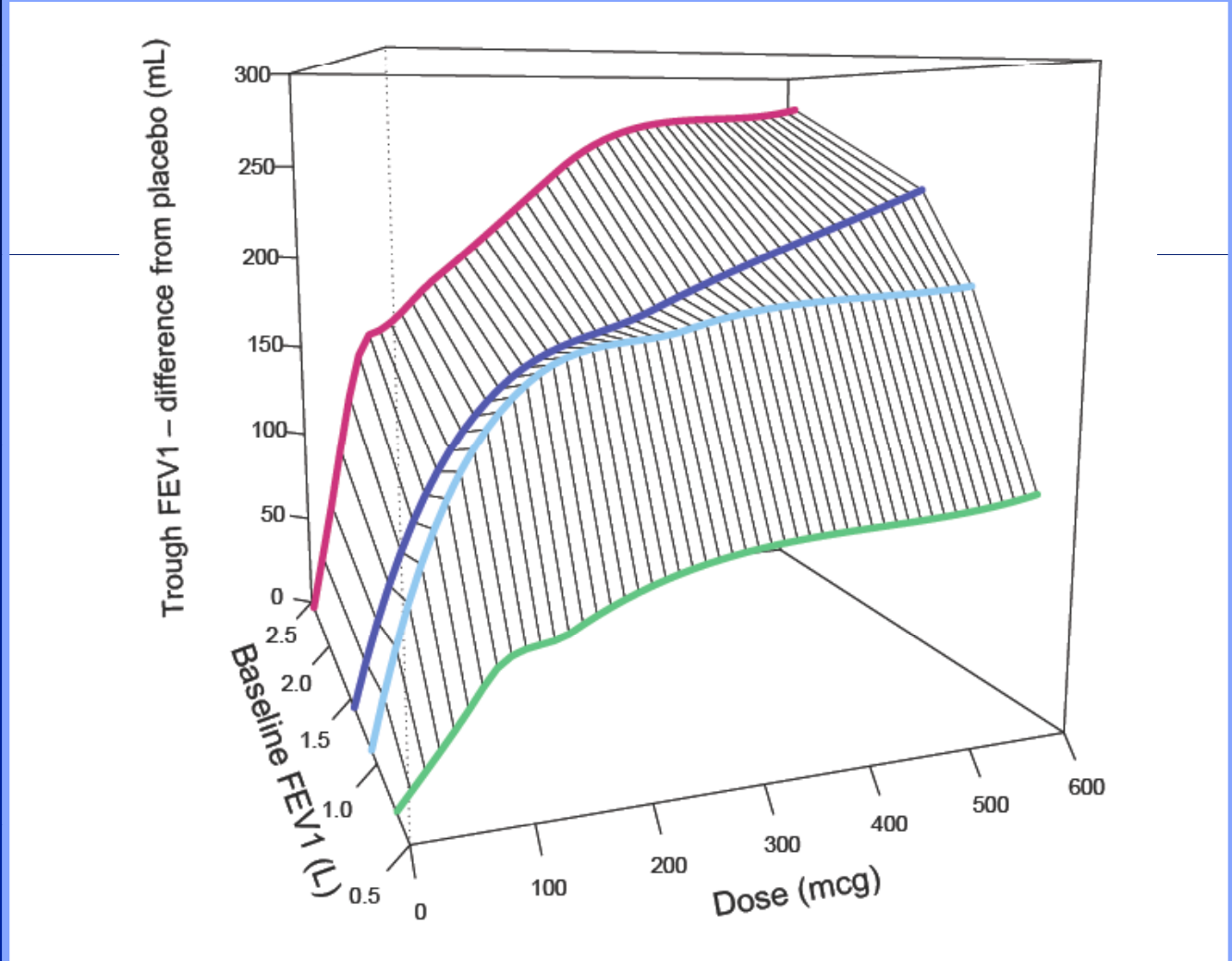
Patient-level Dose Response Data by Baseline

Studies B2335S and B2356



Mean Patient-level Dose Response Data by Baseline

Studies B2335S and B2356



Adverse Events Adjusted by Race
COPD safety population

Caucasian

	Ind 75µg N=414	Ind 150µg N=2026	Ind 300µg N=772	Ind 600µg N=503	For N=511	Tio N=1110	Sme N=736	Pbo N=1502
Patient years	96.9	642.3	568.6	363.2	364.6	322.1	223.7	713.6
AEs per patient year	5.5	4.5	4.1	3.4	2.9	4.6	2.9	4.0
SAEs per patient year	0.27	0.26	0.27	0.21	0.33	0.36	0.19	0.27

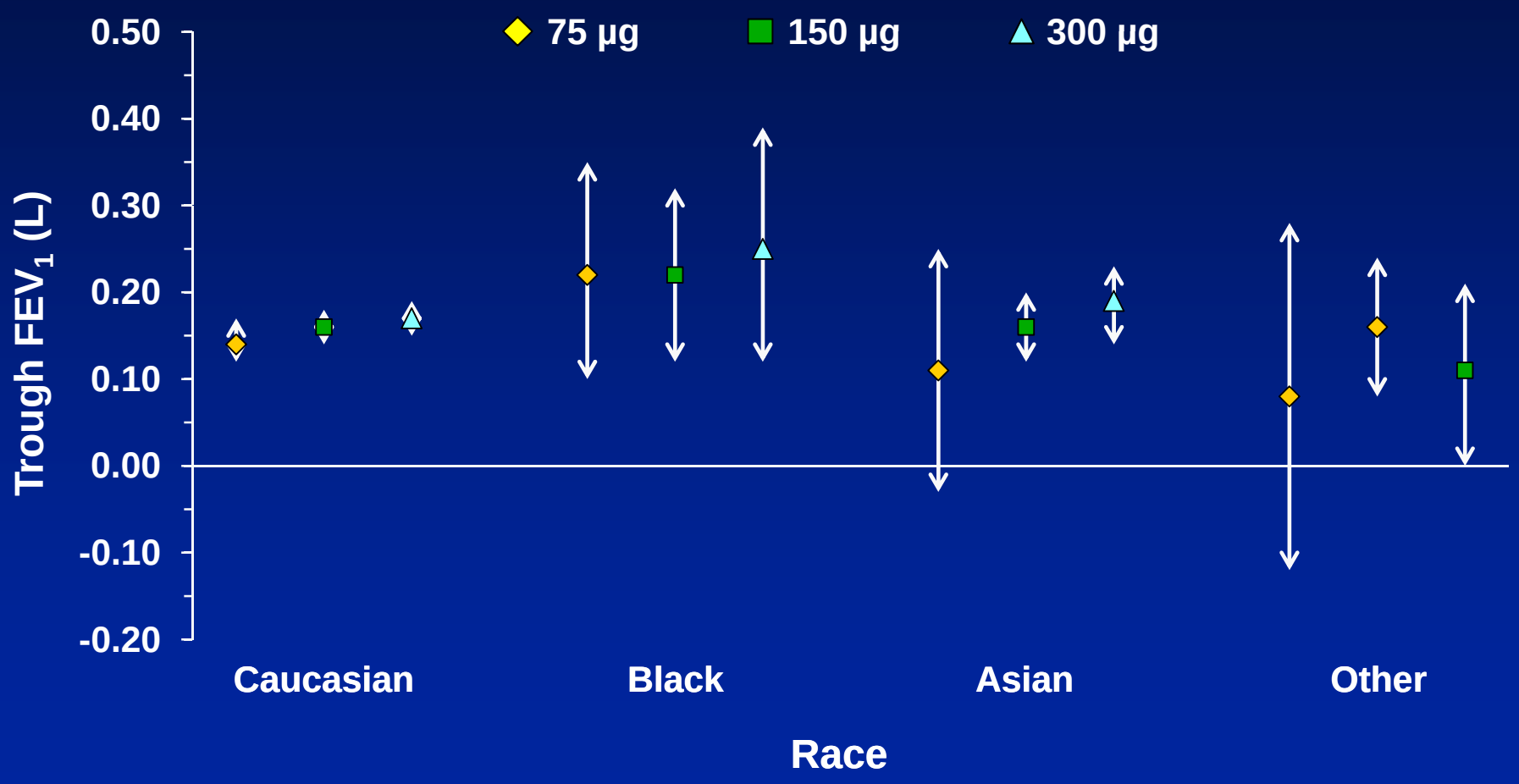
Black

	Ind 75µg N=19	Ind 150µg N=56	Ind 300µg N=13	Ind 600µg N=6	For N=3	Tio N=18	Sme N=11	Pbo N=38
Patient years	4.3	16.0	9.1	1.8	0.7	6.0	2.4	11.3
AEs per patient year	4.2	6.0	3.6	1.6	4.5	5.6	4.9	6.4
SAEs per patient year	0	0.13	0	0	0	0	0	0.62

Asian

	Ind 75µg N=11	Ind 150µg N=462	Ind 300µg N=348	Ind 600µg N=15	For N=13	Tio N=52	Sme N=120	Pbo N=415
Patient years	2.7	178.6	140.6	9.2	5.3	20.6	36.9	167.2
AEs per patient year	4.0	2.7	2.9	3.7	6.2	3.8	3.3	3.3
SAEs per patient year	0	0.18	0.14	0	0.38	0.20	0.19	0.26

Indacaterol-Placebo Differences in Trough FEV_1 at Week 12 by Subgroup



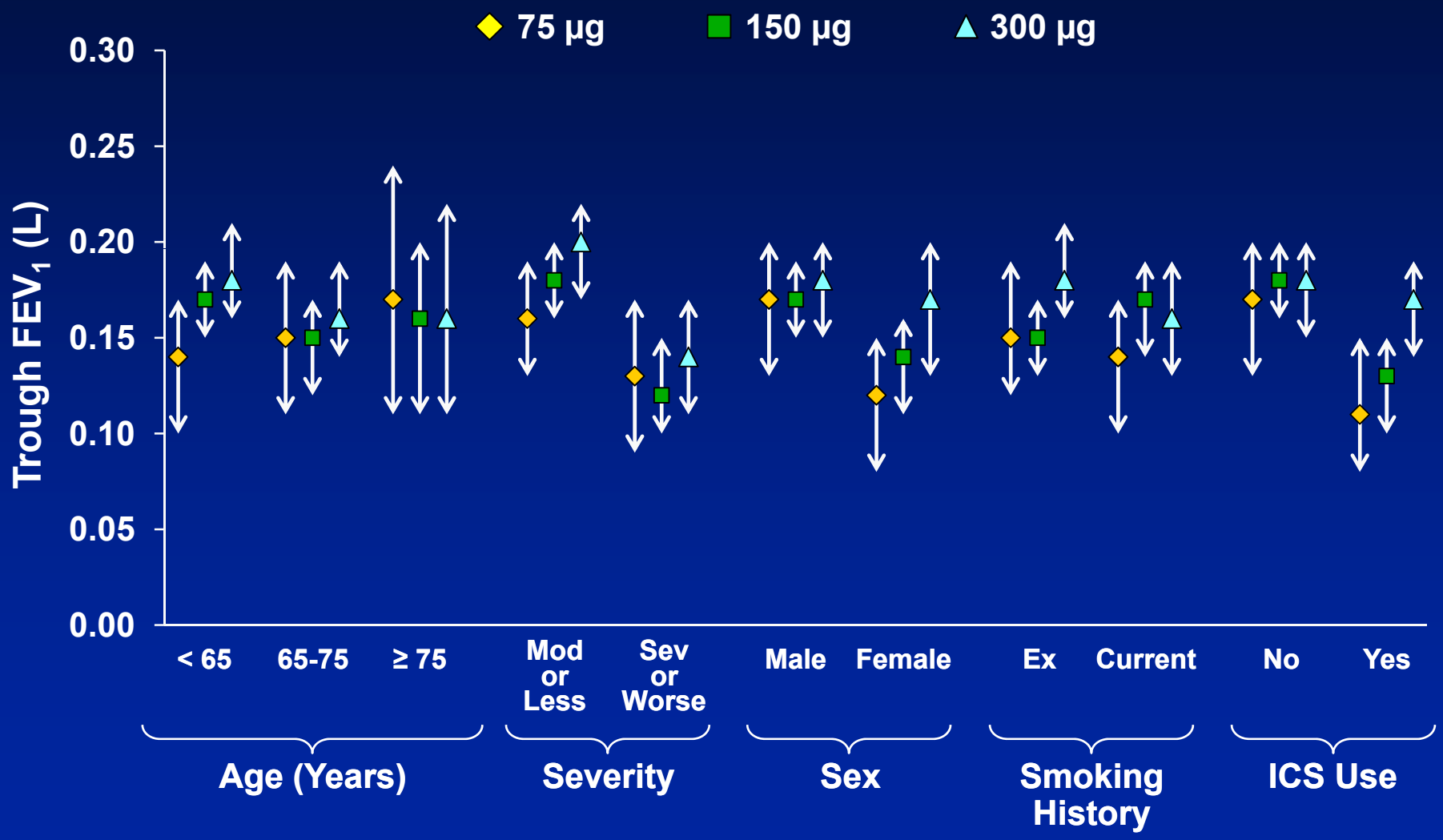
Data are least squares means and 95% confidence intervals

Use of Steroids at Baseline in Indacaterol Pivotal Studies – Balanced across Treatment Arms

		Ind 75 µg	Ind 150 µg	Ind 300 µg	Sme	Tio	Pbo
B2354 - n (%)	Yes	70 (42.9)	---	---	---	---	76 (47.5)
	No	93 (57.1)	---	---	---	---	84 (52.5)
B2355 - n (%)	Yes	63 (39.6)	---	---	---	---	56 (35.2)
	No	96 (60.4)	---	---	---	---	103 (64.8)
B2335S* - n (%)	Yes	---	159 (38.2)	155 (37.3)	---	145 (34.9)	165 (39.5)
	No	---	257 (61.8)	261 (62.7)	---	270 (65.1)	253 (60.5)
B2336 - n (%)	Yes	---	149 (45.2)	---	152 (45.6)	---	135 (40.3)
	No	---	181 (54.8)	---	181 (54.4)	---	200 (59.7)
B2346 - n (%)	Yes	---	61 (28.9)	---	---	---	70 (34.1)
	No	---	150 (71.1)	---	---	---	135 (65.9)
3 month pooled efficacy – n (%)	Yes	187 (41.6)	1138 (43.6)	480 (42.7)	411 (45.9)	589 (48.5)	809 (40.9)
	No	262 (58.4)	1472 (56.4)	643 (57.3)	484 (54.1)	625 (51.5)	1167 (59.1)

* Limited to treatment arms continued into Stage 2 only

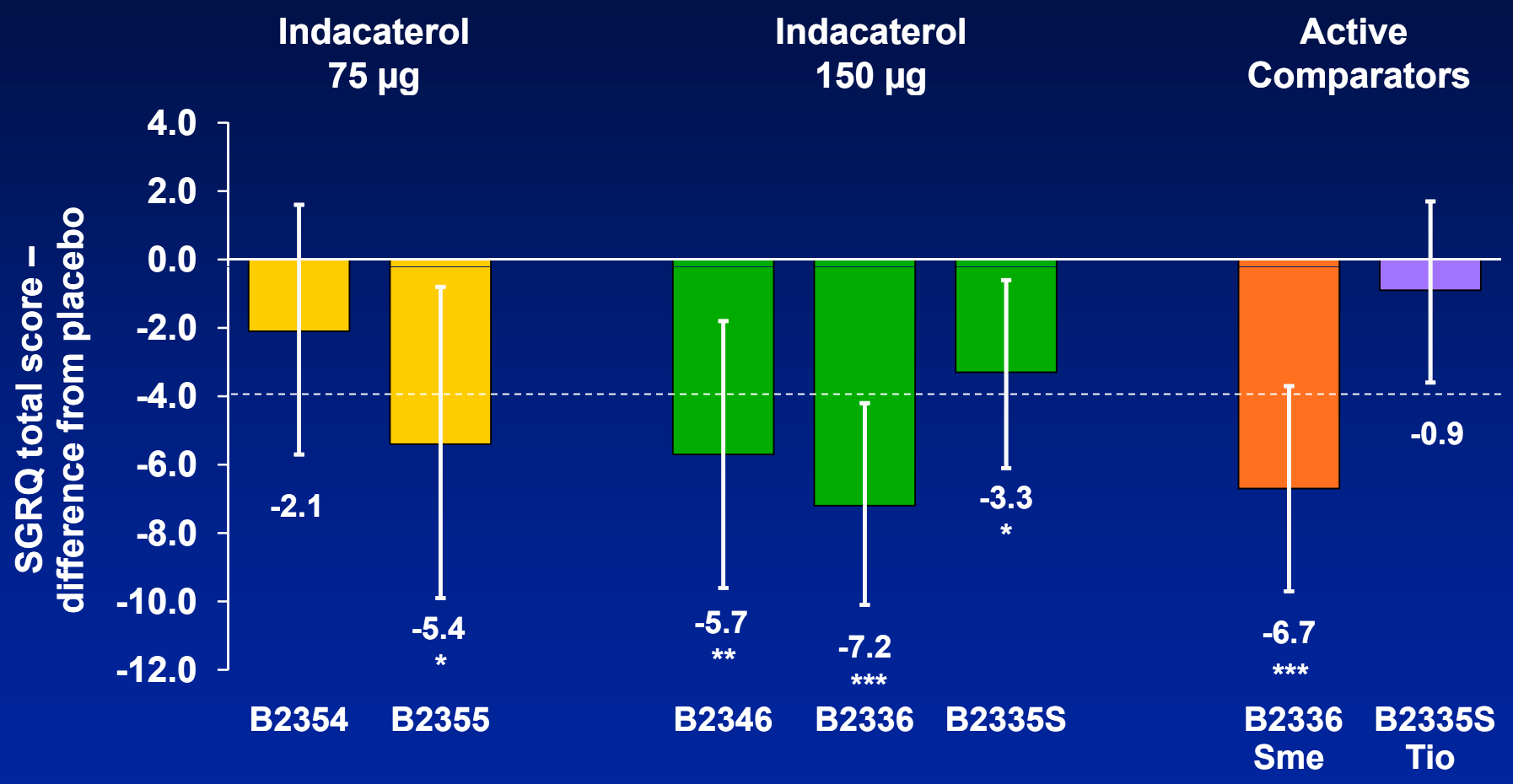
Indacaterol-Placebo Differences in Trough FEV_1 at Week 12 by Subgroup



Data are least squares means and 95% confidence intervals

Health Status – SGRQ at Week 12

Differences from placebo – severe or worse



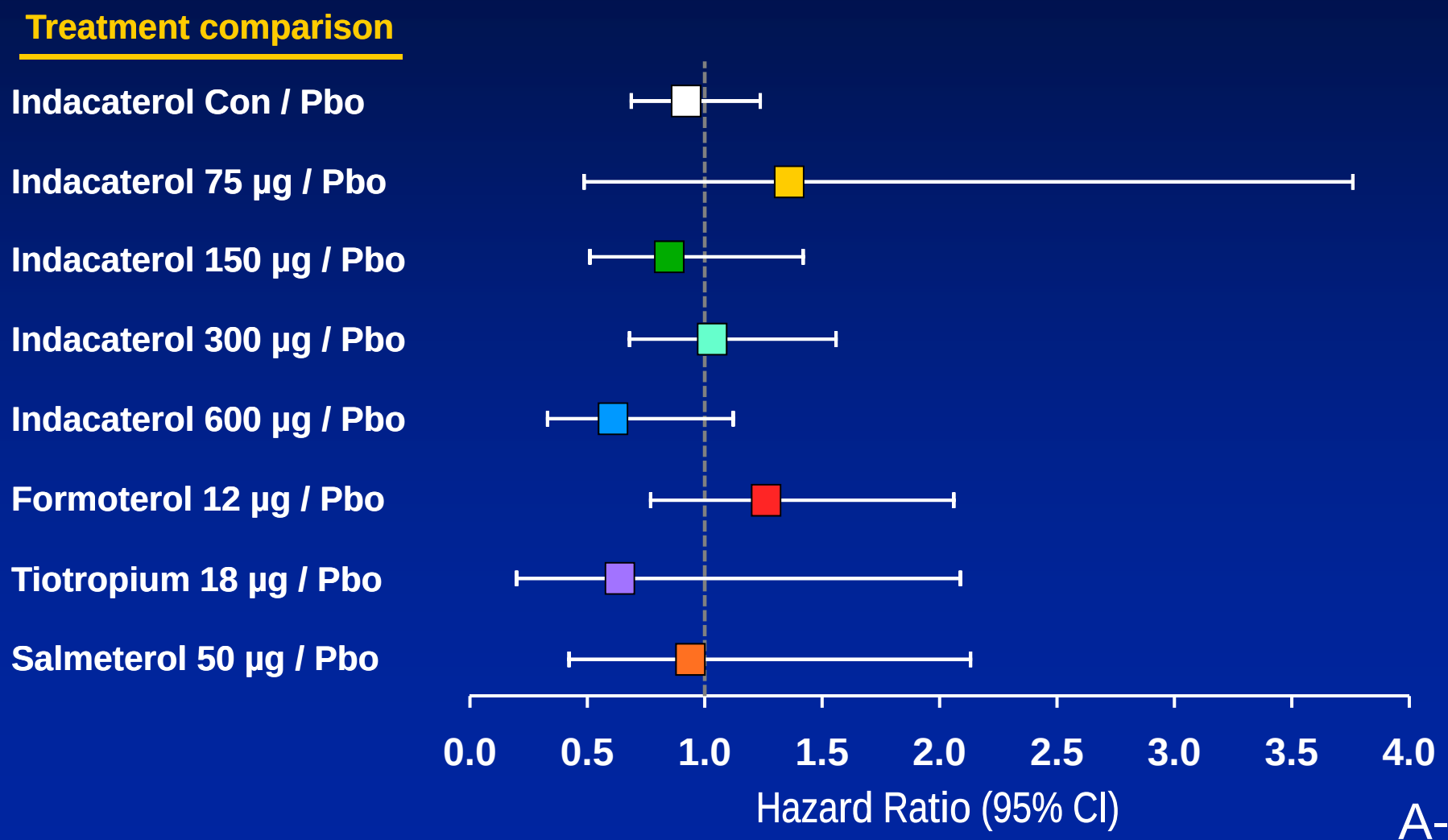
Data are least squares means with 95% confidence intervals. Dotted line indicates MCID (≤-4.0).
*p<0.05, **p<0.01, ***p<0.001 vs placebo (within study)

Percentage Rates of Discontinuation from Pivotal Trials

	Indacaterol Treatment Groups			Control Treatment Groups			
	75 µg o.d.	150 µg o.d.	300 µg o.d.	Placebo	For 12 µg b.i.d.	Tio 18 µg o.d.	Sme 50 µg b.i.d.
B2346 (12 week)		11.8		13.2			
B2335S (26 week)		22.6	18.4	30.8		21.2	
B2336 (26 week)		13.2		20.9			15.0
B2334 (52 week)			22.7	31.7	25.7		
B2354 (12 weeks)	11.7			18.8			
B2355 (12 weeks)	6.9			10.7			

Time to Acute Respiratory Related Hospitalization

COPD safety population I



SGRQ Total Score after 3 Months Treatment (LOCF) by Region

COPD 3 month efficacy population

	Treatment Differences by Region			
Comparison	LS Mean	SE	95% CI	p-value
Region=USA: Ind 75 - Placebo	-3.2	0.82	(-4.8, -1.6)	<0.001
Region=Non-USA: Ind 75 - Placebo	-6.4	1.99	(-10.3, -2.5)	0.0012
Region=USA: Ind 150 - Placebo	-4.2	0.78	(-5.8, -2.7)	<0.001
Region=Non-USA: Ind 150 - Placebo	-4.8	0.61	(-6.0, -3.6)	<0.001
Region=USA: Ind 300 - Placebo	-3.2	1.08	(-5.3, -1.1)	0.0028
Region=Non-USA: Ind 300 - Placebo	-4.2	0.63	(-5.5, -3.0)	<0.001

SGRQ Total Score – Difference from Placebo *(LOCF where available)*

Study	Dose	Week 4	Week 8	Week 12	Week 24/26	Week 44	Week 52
B2354	75 µg	-2.9 (-5.0, -0.9) p=0.005		-3.8 (-6.2, -1.4) p=0.002			
B2355	75 µg	-2.0 (-4.3, 0.2) p=0.081		-3.6 (-6.4, -0.9) p=0.010			
B2346	150 µg	-3.8 (-5.8, -1.8) p<0.001	-4.5 (-6.8, -2.2) p<0.001	-4.8 (-7.1, -2.4) p<0.001			
B2336	150 µg	-3.6 (-5.3, -1.8) p<0.001	-4.1 (-6.0, -2.2) p<0.001	-6.3 (-8.2, -4.3) p<0.001	-5.0 (-7.2, -2.9) p<0.001		
B2335S	150 µg	-3.5 (-5.1,-2.0) p<0.001	-2.9 (-4.6,-1.2) p<0.001	-2.8 (-4.5,-1.1) p=0.001	-3.3 (-5.1,-1.5) p<0.001		
	300 µg	-3.0 (-4.6,-1.5) p<0.001	-2.7 (-4.4,-1.0) p=0.002	-2.5 (-4.2,-0.8) p=0.003	-2.4 (-4.2,-0.6) p=0.008		
B2334	300 µg	-3.3 (-4.9, -1.7) p<0.001	-4.6 (-6.3, -2.9) p<0.001	-3.8 (-5.6, -2.1) p<0.001	-4.4 (-6.2, -2.5) p<0.001	-4.5 (-6.6, -2.5) p<0.001	-4.7 (-6.7, -2.7) p<0.001

Data are LSM (95% CI) and p values

External Adjudicators Have Reviewed Fatal Cases

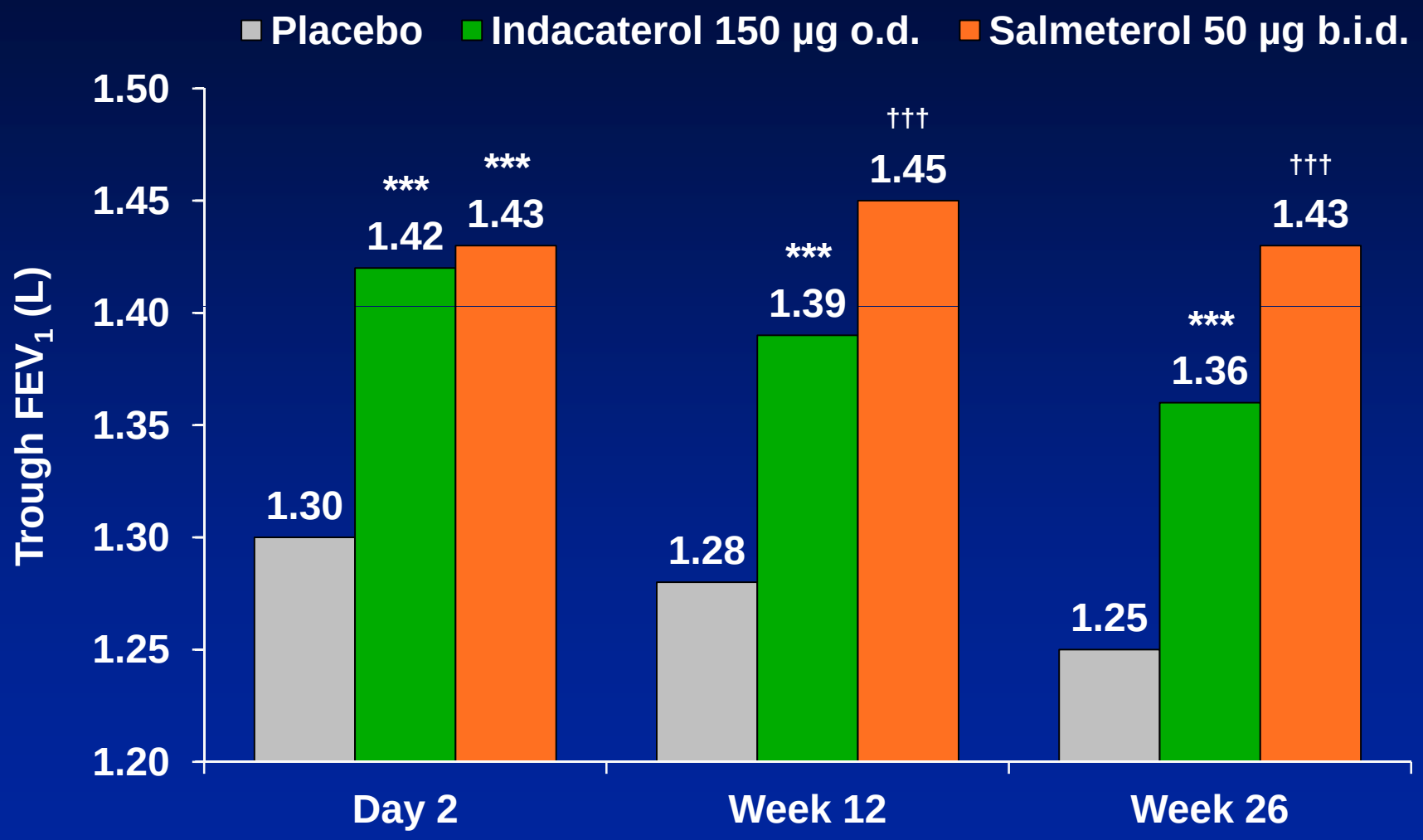
Cause of Death	Number of Patients	Age (Range)	TTE (Range)	Comments
COPD Progression	5	44-98	3-74	44 yo had alpha-1 anti trypsin deficiency. 5 had discontinued indacaterol prior to event
Pneumonia	4	57-84	2-26	All on concomitant ICS. One had d/c'd indacaterol
Cardiac	6 (3 unk but possible)	56-86	5-28	For one patient, external reviewers felt multiple LABAs may have contributed to events
Other	5	72-91	3-39	GIB, sepsis, PE, liver Ca, lymphoma 1 had d/c'd indacaterol prior to event

Causes of Death and Mortality Rate in Mexico PSP is Consistent with Epidemiological Data

Epidemiological Data	Findings in Mexico PSP
Expected number of Deaths in patients > 65 years of age over 5 months =16 National Mortality Data 2008 (Mexico)	17 deaths in patients >65 years of age
Expected number of CV deaths among patients with Severe COPD over 5 months= 6 Sidney et al 2005	3 confirmed cardiac deaths 3 unknown
In Mexico, peak of pneumonia related deaths occurred from October-February Kuri-Morales et al 2006	Program ran between September-January

B2336 – Trough FEV_1 over 26 Weeks

Legend is incorrect:
Green bars = Salmeterol,
Orange bars = Indacaterol



***p<0.001 vs placebo; †††p<0.001 vs salmeterol
Data are Least Squares Means

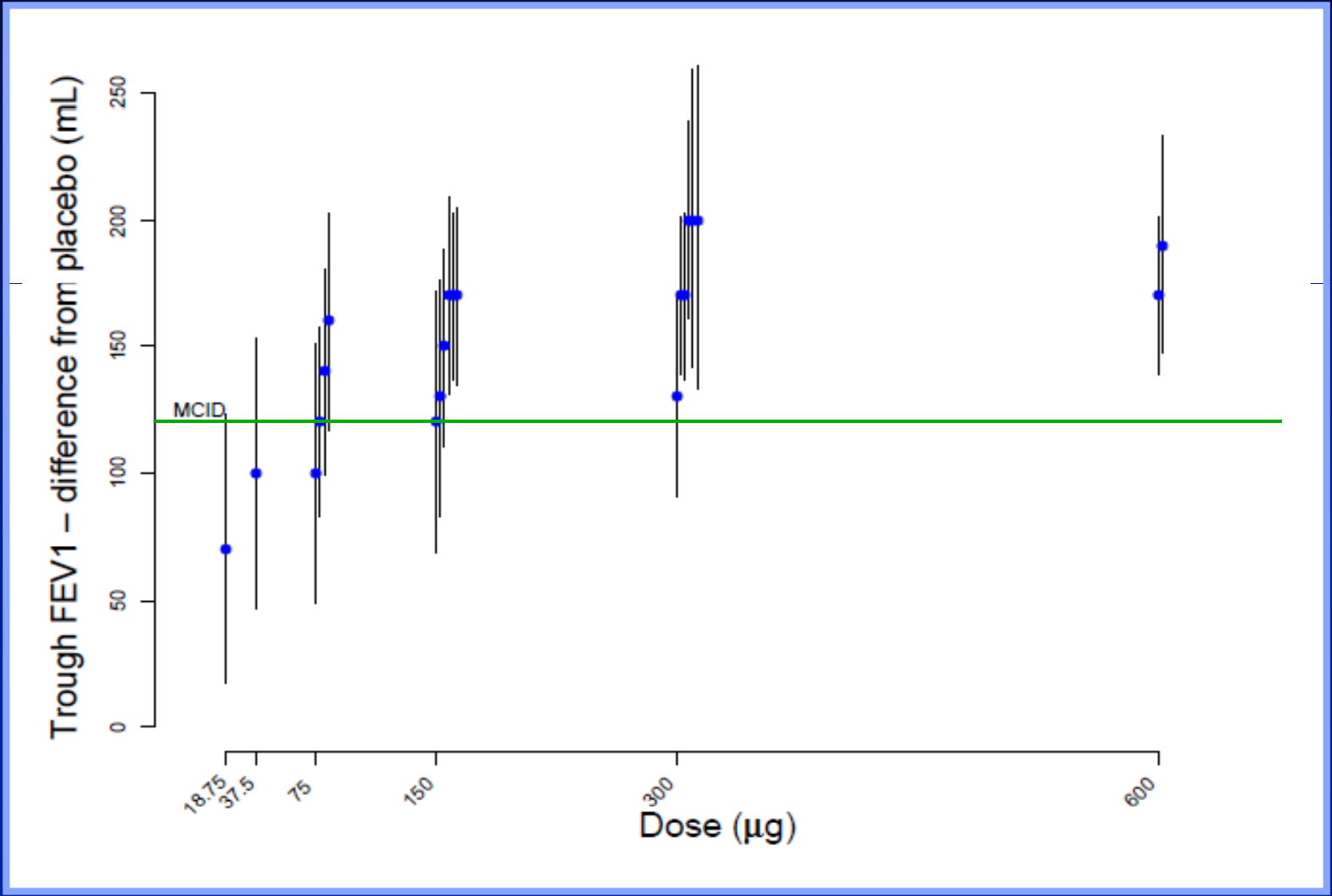
ST-147

B2336 – Trough FEV_1 after 12 Weeks of Treatment

Treatment	n Randomized	LOCF n ITT	Non-LOCF n ITT	Treatment Comparison	LOCF LS mean 95% CI	Non-LOCF LS mean 95% CI	LS mean 95% CI*
Ind 150	333	320	295	Ind 150-Pbo	0.17 (0.13, 0.20)	0.16 (0.13, 0.20)	0.18 (0.14, 0.21)
				Ind 150-Salm	0.06 (0.02, 0.10)	0.06 (0.03, 0.10)	0.07 (0.03, 0.10)
Salm	334	317	289	Salm-Pbo	0.11 (0.07, 0.14)	0.10 (0.06, 0.14)	0.11 (0.07, 0.15)
Pbo	335	316	269				

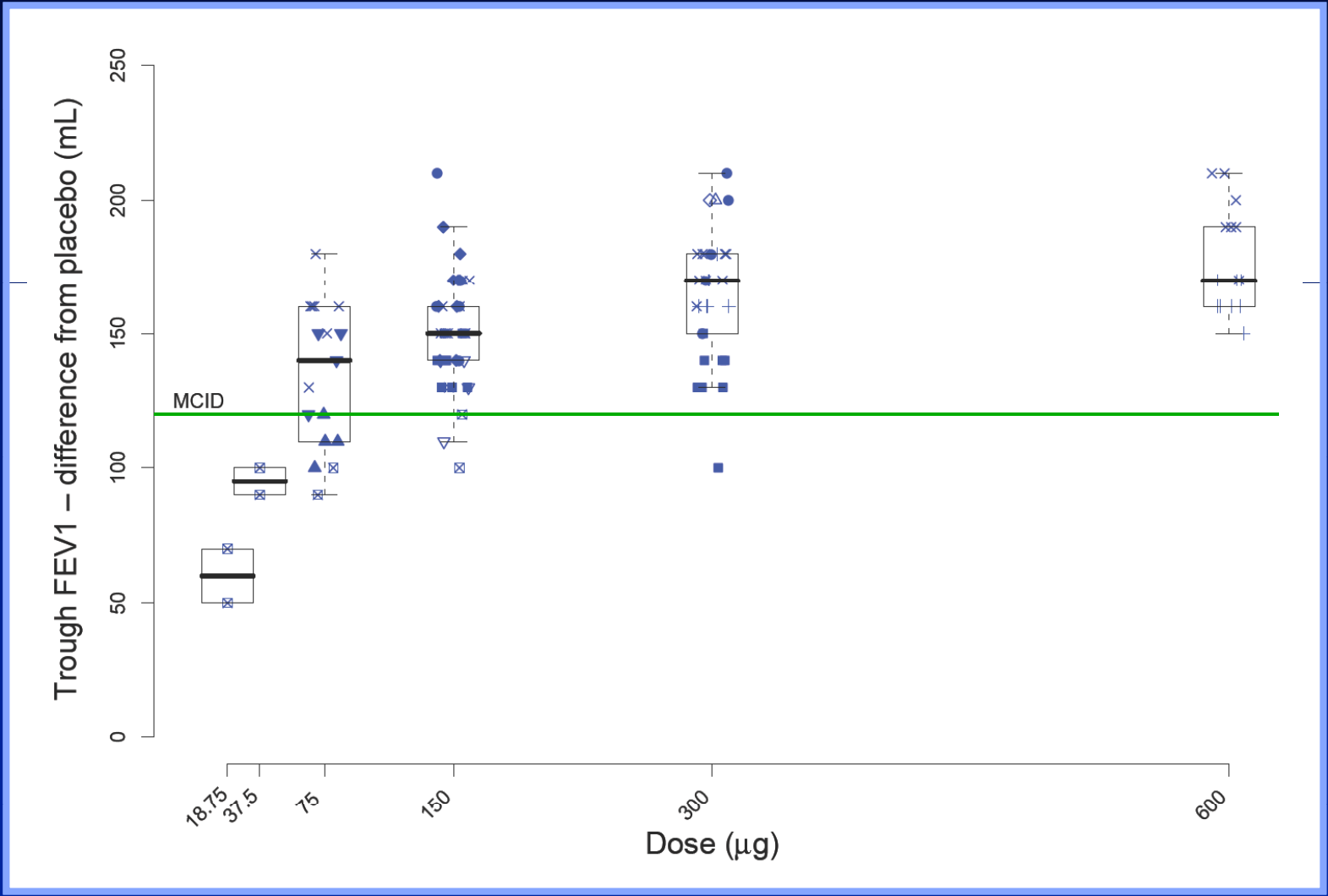
*From a repeated measures analysis

Trough FEV_1 Contrasts (Primary Endpoint) Across Studies



Note: data points were jittered for improved readability

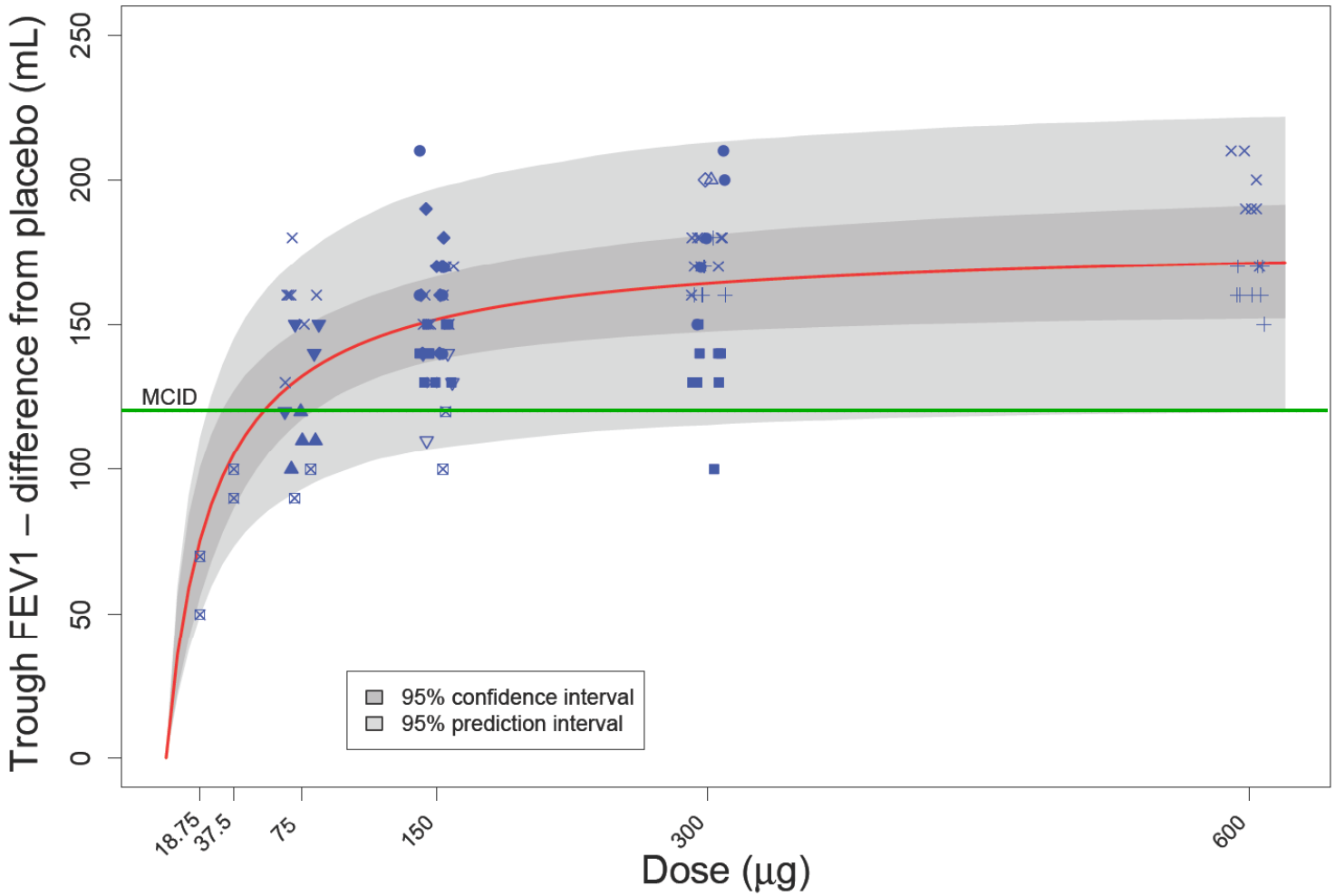
Trough FEV_1 Contrasts (All Study Visits) Across Studies



Note: data points were jittered for improved readability

Study-Level Dose Response Relationship

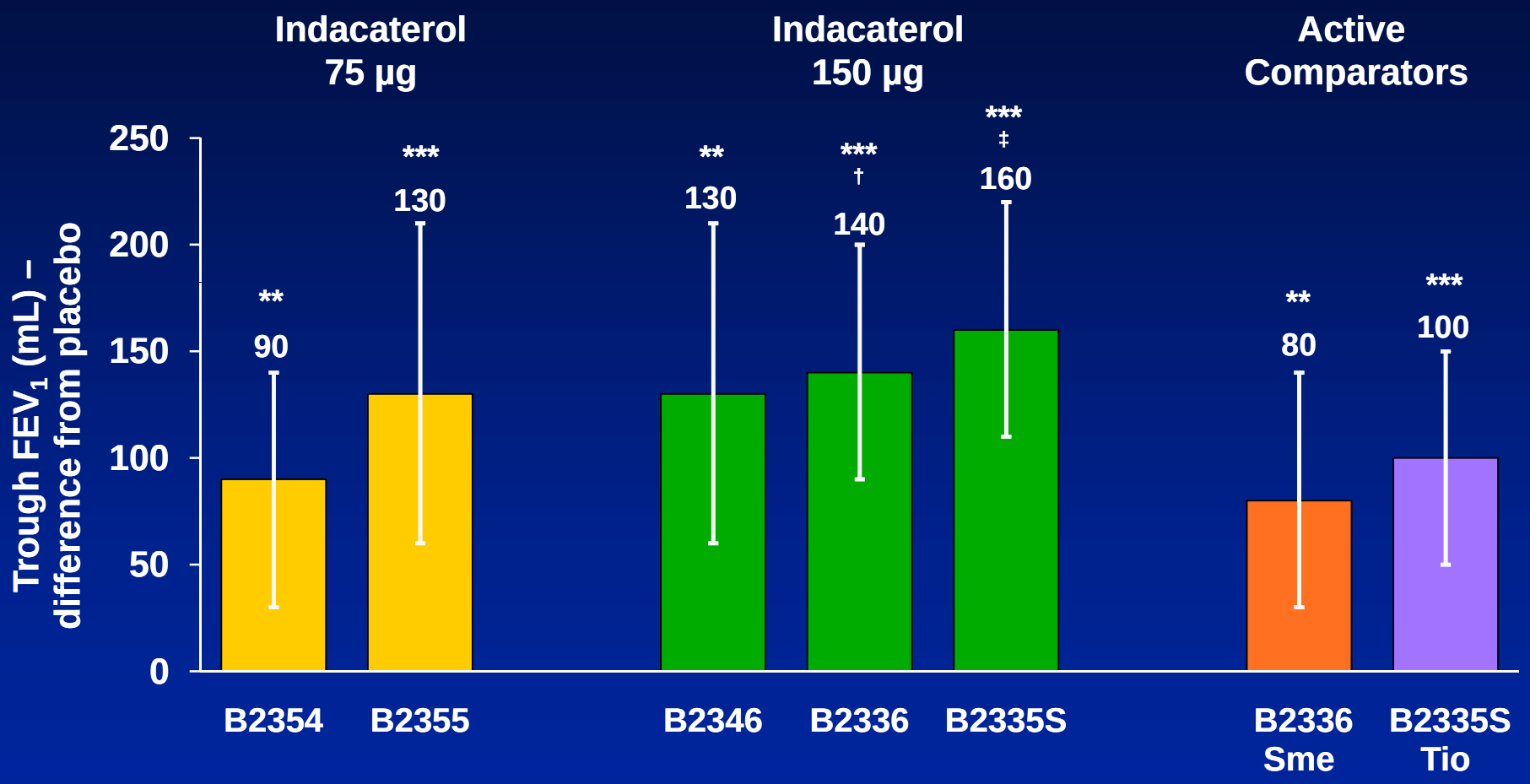
Final analysis

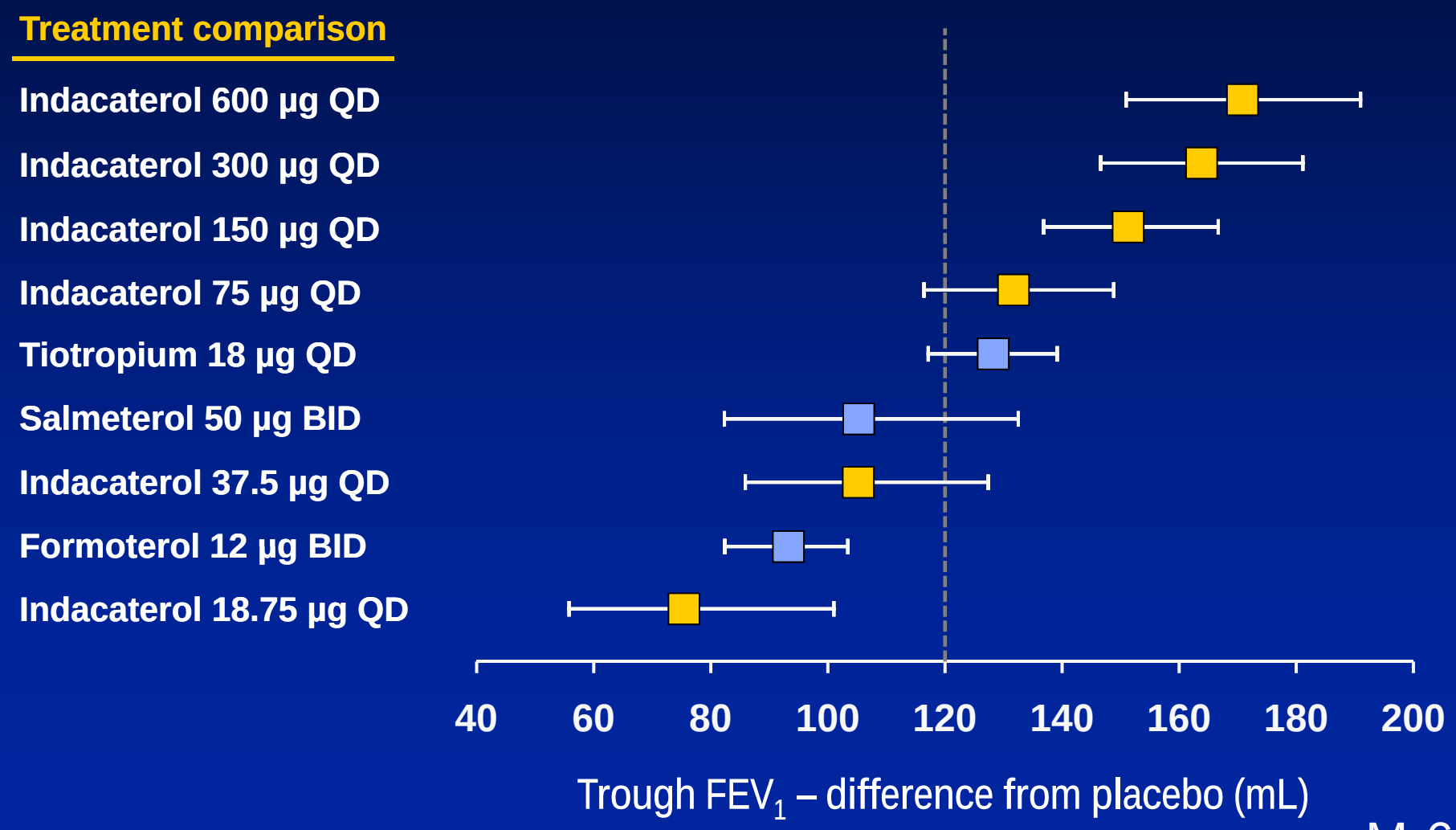


Note: data points were jittered for improved readability

Lung Function – Trough FEV_1 at Week 12

Differences from placebo – severe or worse



Data are least squares means with 95% confidence intervals. **p<0.01, ***p<0.001 vs placebo (within study); †p<0.05 vs salmeterol (within study); ‡p<0.05 non-inferiority vs tiotropium (within study)

COPD Pooled Study-level Analysis: Predicted Response at Each Dose Level