BREO™ ELLIPTA™ 100/25 (Fluticasone furoate / Vilanterol)

GlaxoSmithKline

BREO™ ELLIPTA™ 100/25 (Fluticasone furoate / Vilanterol)

Introduction

Katharine Knobil, MD
Vice President, Clinical Development
GlaxoSmithKline

Impact of COPD in the US

- Affects an estimated 27 million Americans[1]
  - Nearly half are undiagnosed
- The 3rd leading cause of death[2,3]
  - 130,000 deaths every year[3]
  - More people die every day from COPD than from breast cancer and diabetes combined[3]
- Patient burden of COPD
  - Significant symptoms and poor physical functioning
  - Social isolation
  - Fear of exacerbations

[1] National Heart, Lung, and Blood Institute. 2012 Chart Book on Cardiovascular, Lung, and Blood Diseases. February 2012.
[2] Kosacz, 2012. MMWR - Chronic Obstructive Pulmonary Disease Among Adults — United States, 2011
[3] Murphy, 2012. Deaths: Preliminary data for 2010. National vital statistics reports; vol 60 no 4. Hyattsville, MD: National Center for Health Statistics.

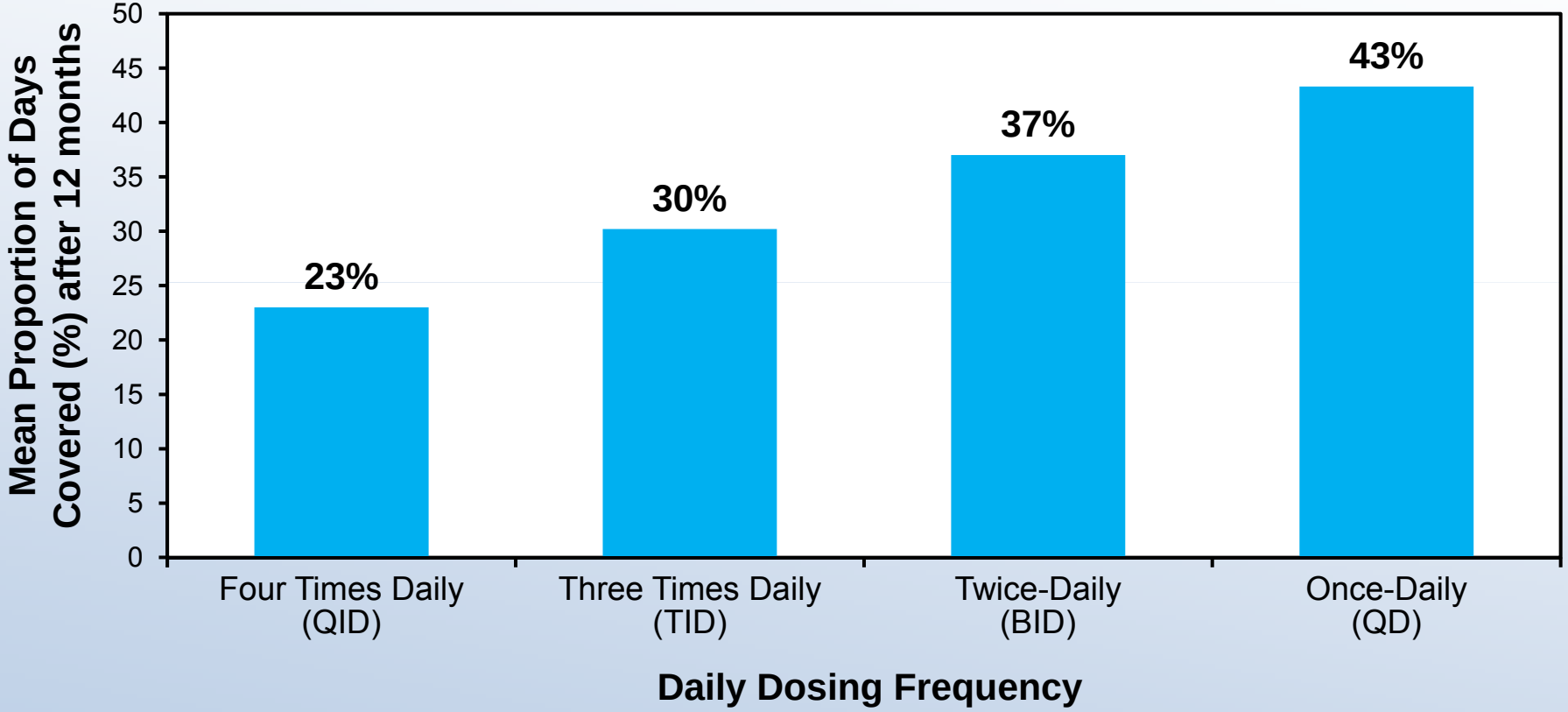
Significant Impact of COPD Exacerbations

- Exacerbations are common
  - Patients of all severity levels experience exacerbations[1] but the frequency of exacerbations per year increases with worsening COPD disease severity[2]
  - History of exacerbations predicts future exacerbations[3]
  - Approximately 30% of those without an exacerbation in a given year will exacerbate in the following year[3]
- Significant economic burden associated with COPD and exacerbations
  - 15.4 million office visits, 739,000 hospitalizations[4]
  - 50%-75% of all COPD costs are for services associated with exacerbations[5]

[1]Balcells, et al. Resp Med. 2009;103:1293-1302. .
[2]Miravitlles, et al. Respir Med 1999;93:173-79.
[3]Hurst, et al. N Engl J Med 2010;363:1128-38.
[4] 2012 NHLBI Morbidity and Mortality Chart Book on Cardiovascular, Lung, and Blood Diseases. Available at: www.nhlbi.nih.gov/resources/docs/cht-book.htm. Accessed 27 February 2013.
[5]Celli, et al. Eur Respir J 2004;23:932–46

Dosing Frequency and Adherence in Patients with COPD

Adherence is poor in the treatment of chronic conditions[1,2]



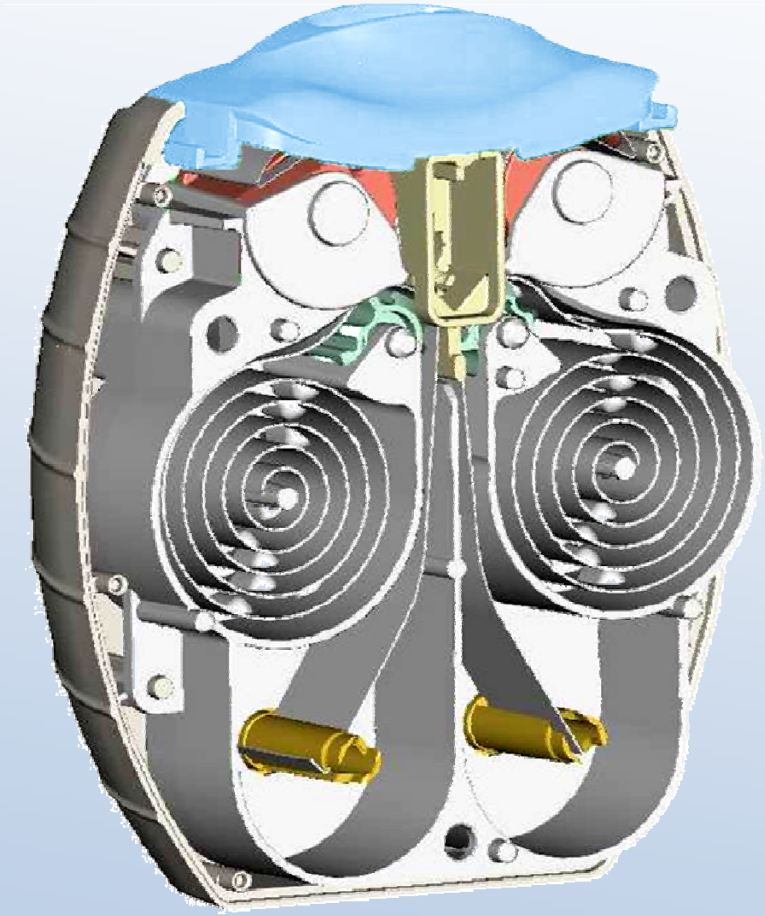
- Patients with COPD with higher adherence experienced fewer hospitalizations and lower Medicare costs than those with lower adherence behavior[3]

[1] DiMatteo, et al. Med Care. 2004;42:200-9.
[2] Toy, et al. Resp Med 2011;105:435-41.
[3] Simoni-Wastila, et al. Am J Geriatr Pharmacother 2012;10:201-10.

BREO ELLIPTA 100/25

- BREO
  - Fluticasone furoate (FF) 100mcg: long-acting inhaled corticosteroid (ICS)
  - Vilanterol (VI) 25mcg: long-acting selective beta$_2$-adrenergic agonist (LABA)
- ELLIPTA
  - Novel dry powder inhaler with two blister strips
  - Consistent dosing even in patients with severe lung function impairment

BREO ELLIPTA 100/25



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BREO ELLIPTA 100/25
Novel Development Strategy

- Develop the combination in parallel with components
  - Improved patient benefit
- Very large patient experience
  - Over 18,000 subjects in the COPD and Asthma programs
  - Nearly 8,000 subjects in the COPD program
  - Over 5,500 in the 4 COPD pivotal trials
- Dose Selection
  - VI dose-ranged in both asthma and COPD
  - 3 strengths of FF taken into phase III to assess benefit/risk based on relevant endpoints for patients with COPD

Topics for Discussion

- Statistical testing hierarchy
- Statistical significance of lung function improvement of BREO ELLIPTA 100/25 over VI alone
- Replication of exacerbation reduction of BREO ELLIPTA 100/25
- Safety profile of BREO ELLIPTA 100/25
  - Pneumonia
  - Fractures
- Benefit/risk assessment

Summary of the BREO ELLIPTA 100/25 Development Program

- Established class of medications for the treatment of COPD
  - Novel once daily LABA combined with once daily ICS
  - Novel inhaler
- Efficacy
  - Significant improvement in lung function with BREO ELLIPTA
  - Significant reduction in COPD exacerbations
  - Improvement in symptoms of COPD
- Safety
  - Extensive safety database
  - Safety profile similar to established ICS/LABA combinations

Advisors

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Mark Dransfield, MD
Associate Professor of Medicine
Medical Director, UAB Lung Health Center
Division of Pulmonary, Allergy and Critical Care Medicine
University of Alabama at Birmingham & Birmingham VA Medical Center
Birmingham, AL

Lionel Mandell, MD, FRCPC, FRCP
Professor Emeritus, Division of Infectious Diseases, Department of Medicine
McMaster University
Hamilton, Ontario

Agenda

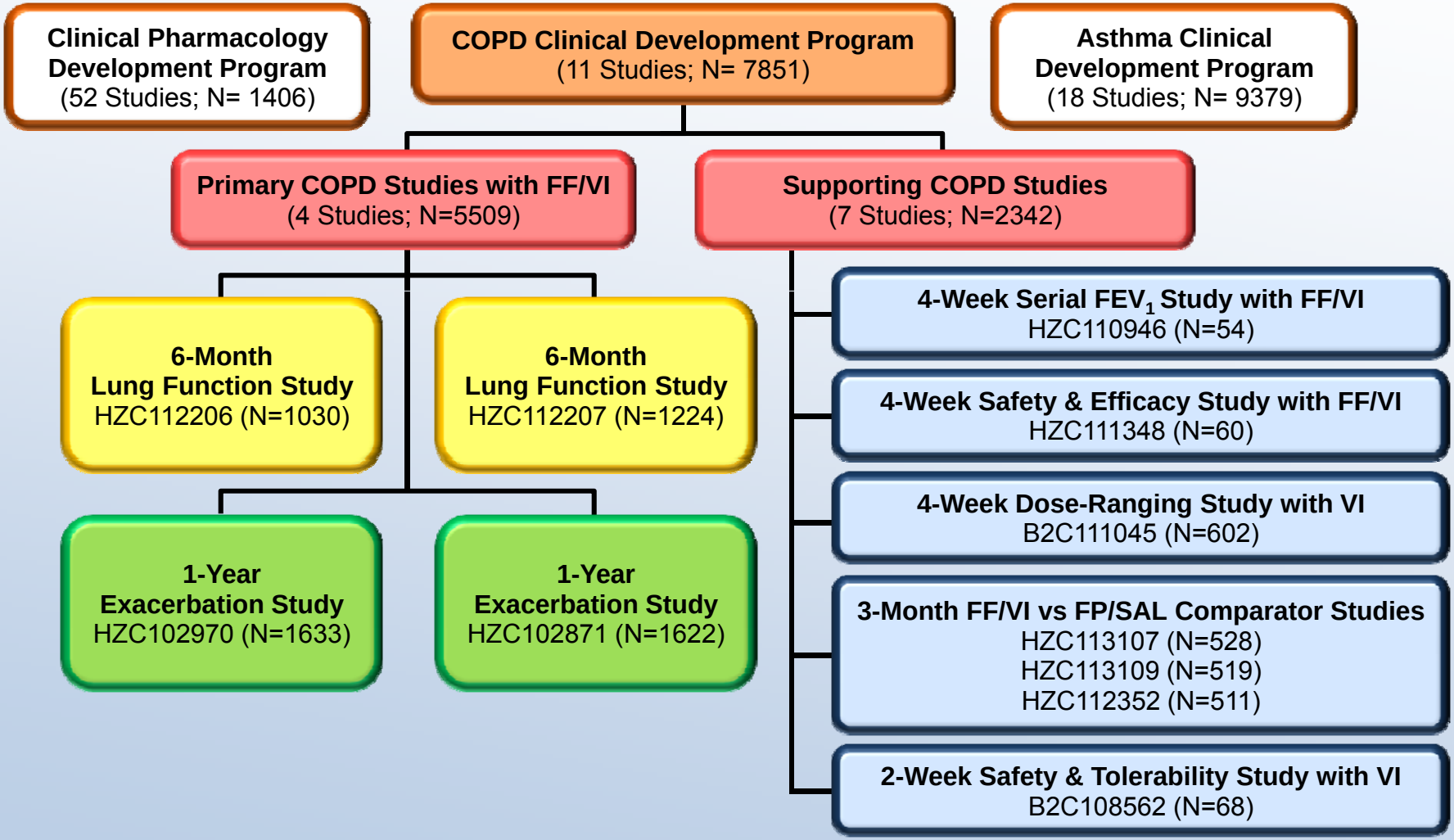
Introduction	**Katharine Knobil, MD** Vice President, Clinical Development GlaxoSmithKline
Clinical Efficacy	**Courtney Crim, MD** Group Director, Clinical Development Respiratory GlaxoSmithKline
Clinical Safety	**Tjark Reblin, MD** VP, Safety Evaluation and Risk Management Global Clinical Safety and Pharmacovigilance GlaxoSmithKline
Physician's Perspective	**Stephen Rennard, MD** Larson Professor of Medicine Division of Pulmonary, Critical Care, Sleep and Allergy University of Nebraska Medical Center
Closing Comments	**Katharine Knobil, MD** Vice President, Clinical Development GlaxoSmithKline

BREO ELLIPTA 100/25
(Fluticasone furoate / Vilanterol)

Efficacy

Courtney Crim, MD
Director of Clinical Development
GlaxoSmithKline

Clinical Development Program



FF=fluticasone furoate; FP=fluticasone propionate; SAL=salmeterol; VI=vilanterol

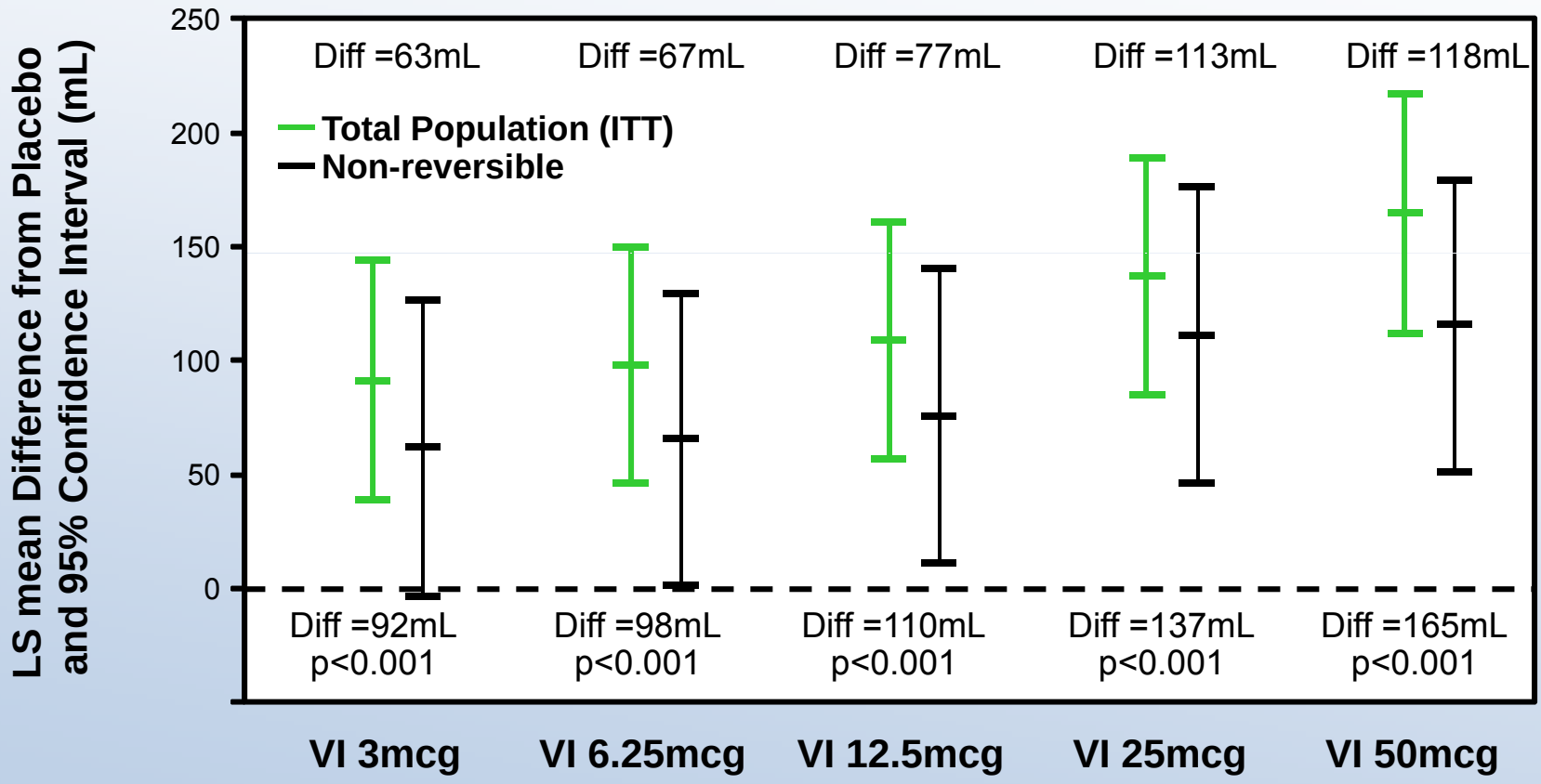
Data Presentation

- **Selection of doses for Phase III**
  - Vilanterol (VI)
  - Fluticasone furoate (FF)
- **Phase III Program for FF/VI**
  - Efficacy of VI monotherapy: FEV_1: 0-4hr and trough
  - Contribution of VI in the combination: FEV_1: 0-4hr
  - Contribution of FF in the combination: Exacerbations, trough FEV_1
  - Efficacy of FF/VI 100/25 on Symptoms
- **Efficacy of FF/VI 100/25 compared with FP/SAL**

Dose Selection of Vilanterol (VI)

- Dose of VI (25mcg) selected for testing in Phase IIIa COPD program was based on a Phase II dose-ranging study in subjects with COPD (B2C111045)
  - VI doses of 3, 6.25, 12.5, 25 and 50 mcg once daily were evaluated
- Phase II dose-ranging study in asthma (B2C109575) also supported 25mcg as appropriate dose of VI to take into Phase III

Vilanterol vs. Placebo on Trough FEV_1 in Patients with COPD (B2C111045)

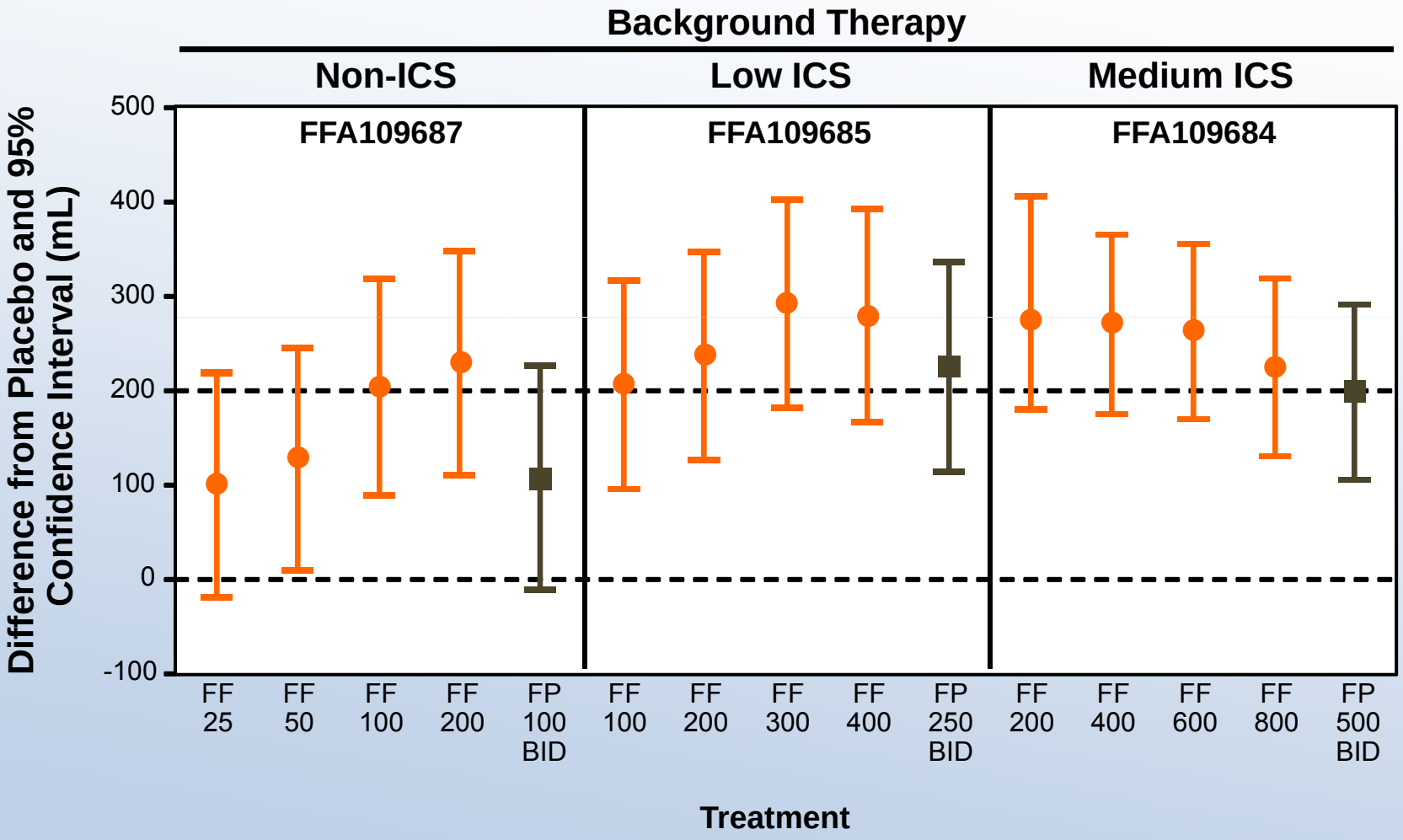


Adapted from Hanania, et al Chest 2012;142:119-27

Selection of Phase III FF Doses in COPD

Based on Phase IIb dose ranging in asthma

Phase IIb Asthma Studies Showed a Plateau at FF 200mcg in Trough FEV_1 Response

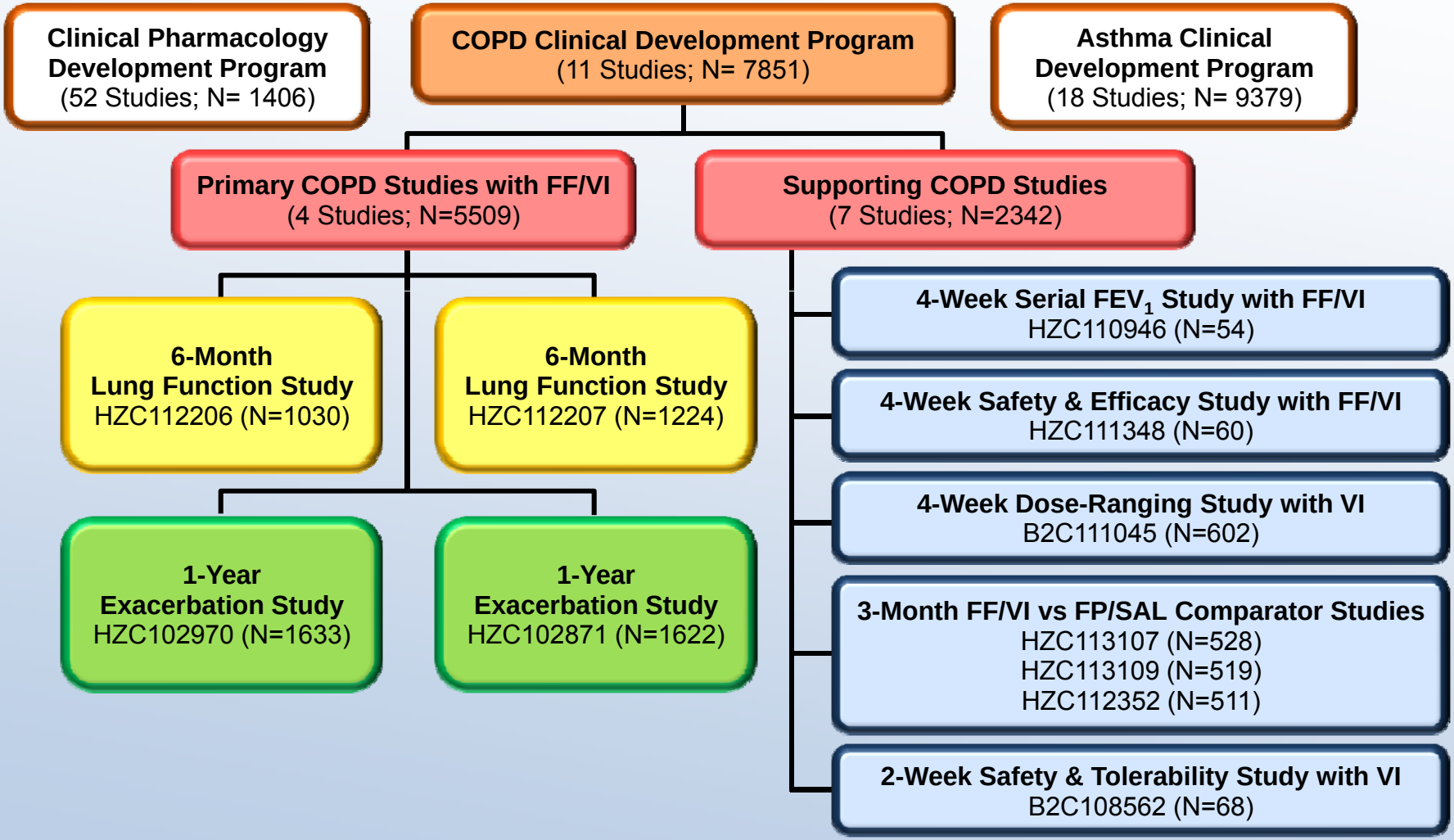


Bateman et al. Respir Med 2012;106:642-50
Adapted from Bleecker et al. Ann Allergy Asthma Immunol 2012;109:353-58
Busse et al. Thorax 2012;67:35-41

Phase IIb Dosing Conclusions

- VI 25mcg once daily determined as optimal dose in patients with COPD
- FF 50mcg, 100mcg, and 200mcg identified as doses to evaluate in Phase III COPD program to identify most effective dose when combined with VI 25mcg in reducing exacerbations
- Additional Phase IIb studies comparing once with twice daily dosing confirmed both VI and FF as once daily products

Clinical Development Program



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  - Efficacy of FF/VI 100/25 on Symptoms
- **Efficacy of FF/VI 100/25 compared with FP/SAL**

Phase III: 6-Month Lung Function Studies (HZC112206 and HZC112207)

HZC112206

- FF/VI 50/25
- FF/VI 100/25
- FF 100mcg
- VI 25mcg
- placebo

HZC112207

- FF/VI 100/25
- FF/VI 200/25
- FF 100mcg
- FF 200mcg
- VI 25mcg
- placebo

Primary Endpoints:

- 0-4hr weighted mean FEV_1 (contribution of LABA, i.e., FF/VI vs. FF)
- Trough FEV_1 (contribution of ICS, i.e., FF/VI vs. VI)

Secondary Endpoints:

- Peak FEV_1 on Treatment Day 1
- Time to onset (increase of 100mL above baseline in FEV_1) on Treatment Day 1

Primary COPD Studies: Demographic and Baseline Characteristics 6-Month Lung Function Studies (HZC112206 and HZC112207)

	6-month lung function studies (206 & 207) (N=2254)	
Age (yrs): Mean (Min-Max)	62.1 (40-85)	
Sex: Female/Male, n (%)	684 (30%) / 1570 (70%)	
Race, n (%)	**ITT**	**US**
Caucasian	1896 (84%)	650 (92%)
Asian	304 (13%)	4 (<1%)
African American/African Heritage	48 (2%)	48 (7%)
Other*	6 (<1%)	6 (<1%)
Body Mass Index (kg/m^2): Mean (Min-Max)	26.32 (13.2-63.0)	
Current Smoker, n (%)	1222 (54%)	
Smoking History-Pack Yrs: Mean (Min-Max)	44.1 (10-200)	

*Includes: American Indian or Alaska Native

Primary COPD Studies: Demographic and Baseline Characteristics 6-Month Lung Function Studies (HZC112206 and HZC112207) – continued

	6-month lung function studies (206 & 207) (N=2254)
Screening Post-albuterol FEV_1 (L) Mean (SD)	1.45 (0.4842)
Screening Post-albuterol FEV_1, % Predicted Mean (SD)	48.1 (12.51)
Screening Post-albuterol FVC (L) Mean (SD)	3.12 (0.8854)
Screening Post-albuterol FEV_1/FVC (%) Mean (SD)	47.2 (11.29)
Screening Reversibility (mL)	148.3 (169.70)
Screening Reversibility, n (%)	695 (31%)
In the Year Prior to Screening, n% Moderate COPD Exacerbation[1] 0 ≥1 Severe COPD Exacerbation[2] 0 ≥1	 1707 (76%) 547 (24%) 2061 (91%) 193 (9%)

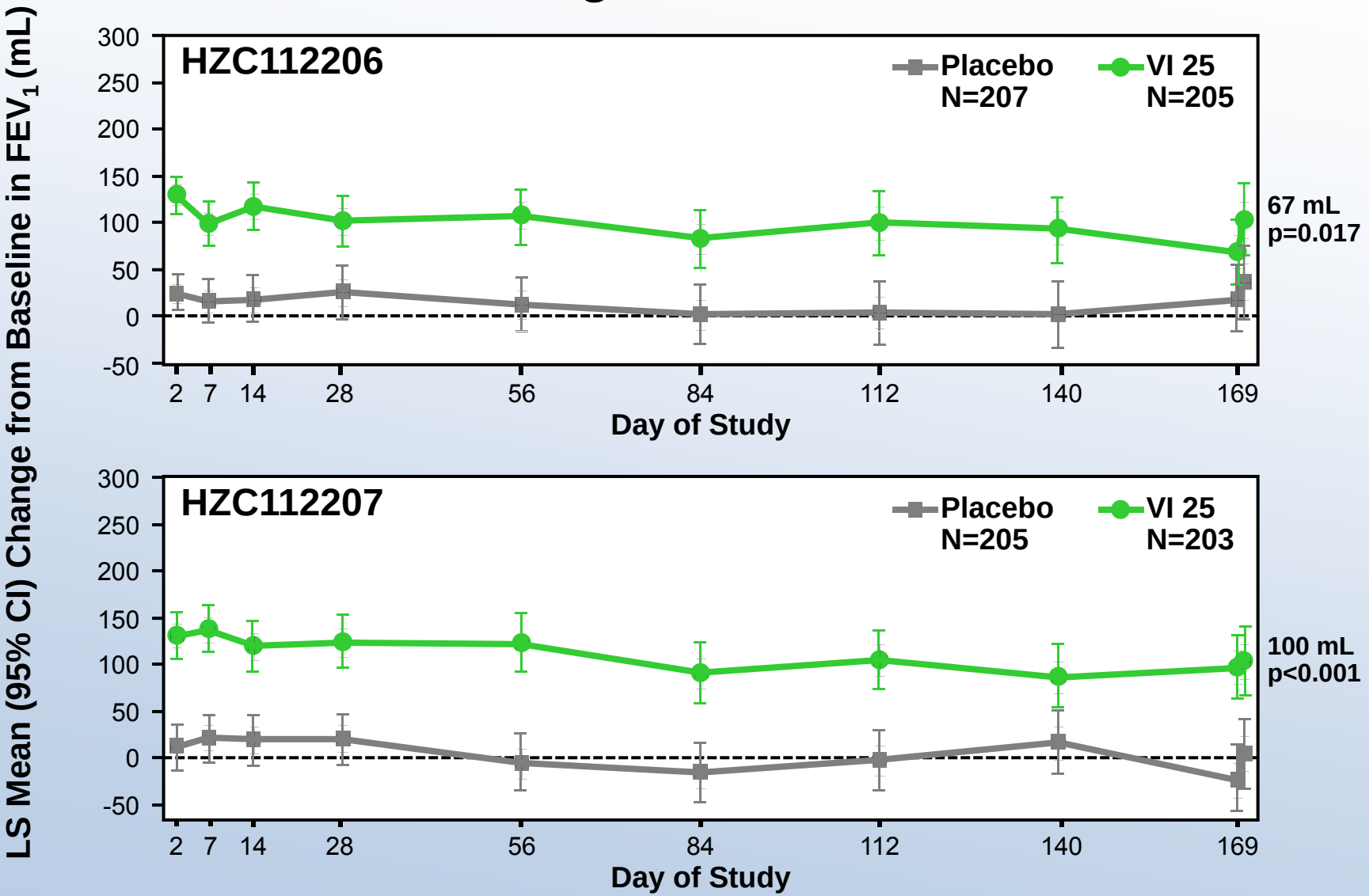
1. Required oral/systemic corticosteroids and/or antibiotics but did not involve hospitalization
2. Required hospitalization

Exacerbation Events in Placebo Subjects Compared with those on Active Treatment 6-Month Studies HZC112206 and HZC112207

	Placebo	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
HZC112206	**N=207**	**N=206**	**N=206**		**N=205**	**N=206**	
Moderate/Severe	21 (10%)	12 (6%)	18 (9%)*		22 (11%)	26 (13%)	
Severe	*3*	*0*	*4*		*7*	*3*	
HZC112207	**N=205**		**N=204**	**N=205**	**N=203**	**N=204**	**N=203**
Moderate/Severe	21 (10%)		13 (6%)	14 (7%)	18 (9%)	4 (2%)	10 (5%)
Severe	*6*		*5*	*6*	*7*	*0*	*3*

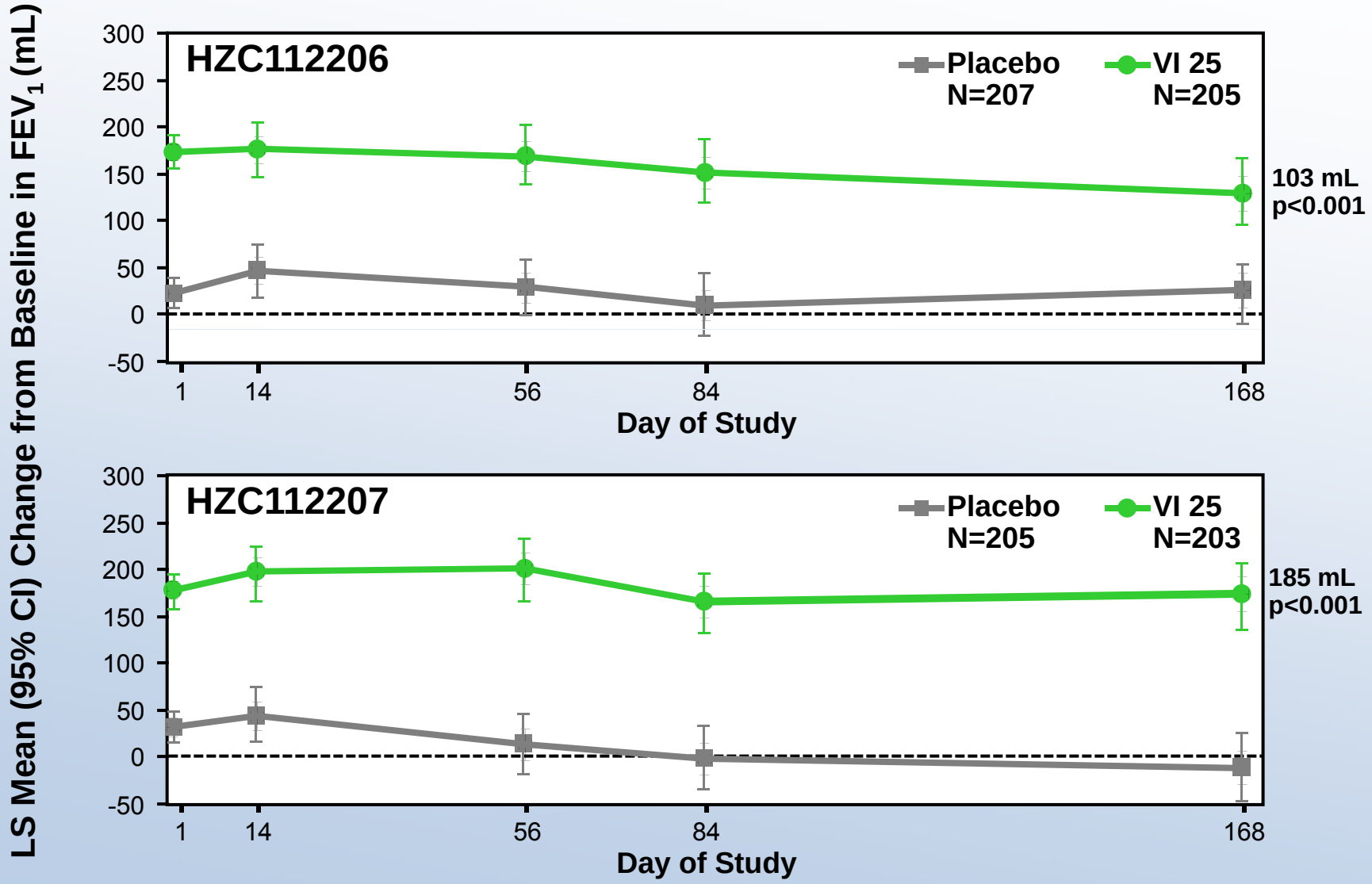
*One subject experienced two exacerbations
Moderate COPD exacerbation defined as requiring systemic corticosteroids and/or antibiotics
Severe COPD exacerbation defined as requiring hospitalization

Efficacy of Vilanterol vs. Placebo on Trough FEV_1 6-Month Lung Function Studies



Martinez et al. Resp Med 2013;107:550-59.
Kerwin et al. Resp Med 2013 ;107:560-69.

Efficacy of Vilanterol vs. Placebo on 0-4hr Weighted Mean FEV_1 6-Month Lung Function Studies



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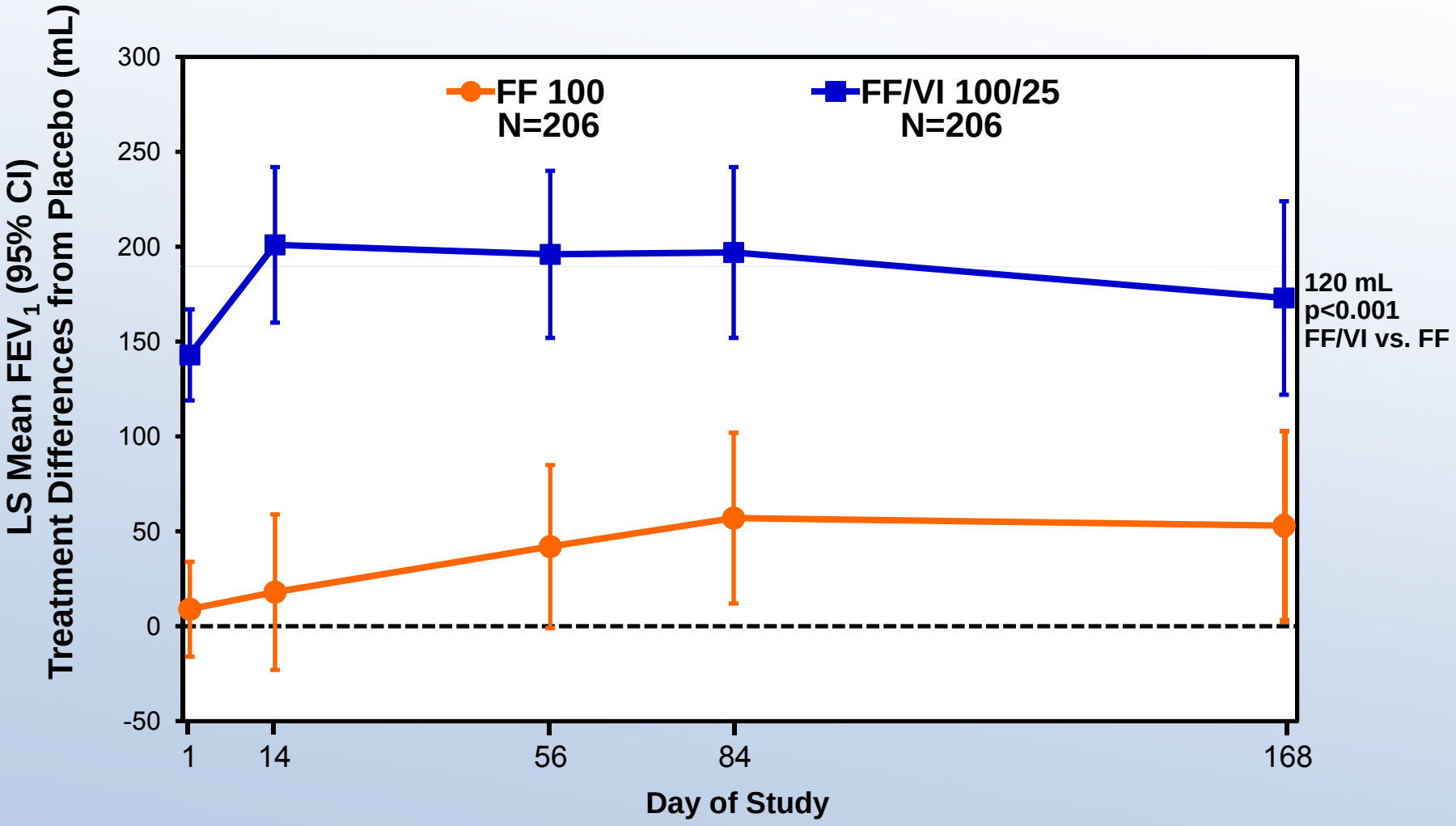
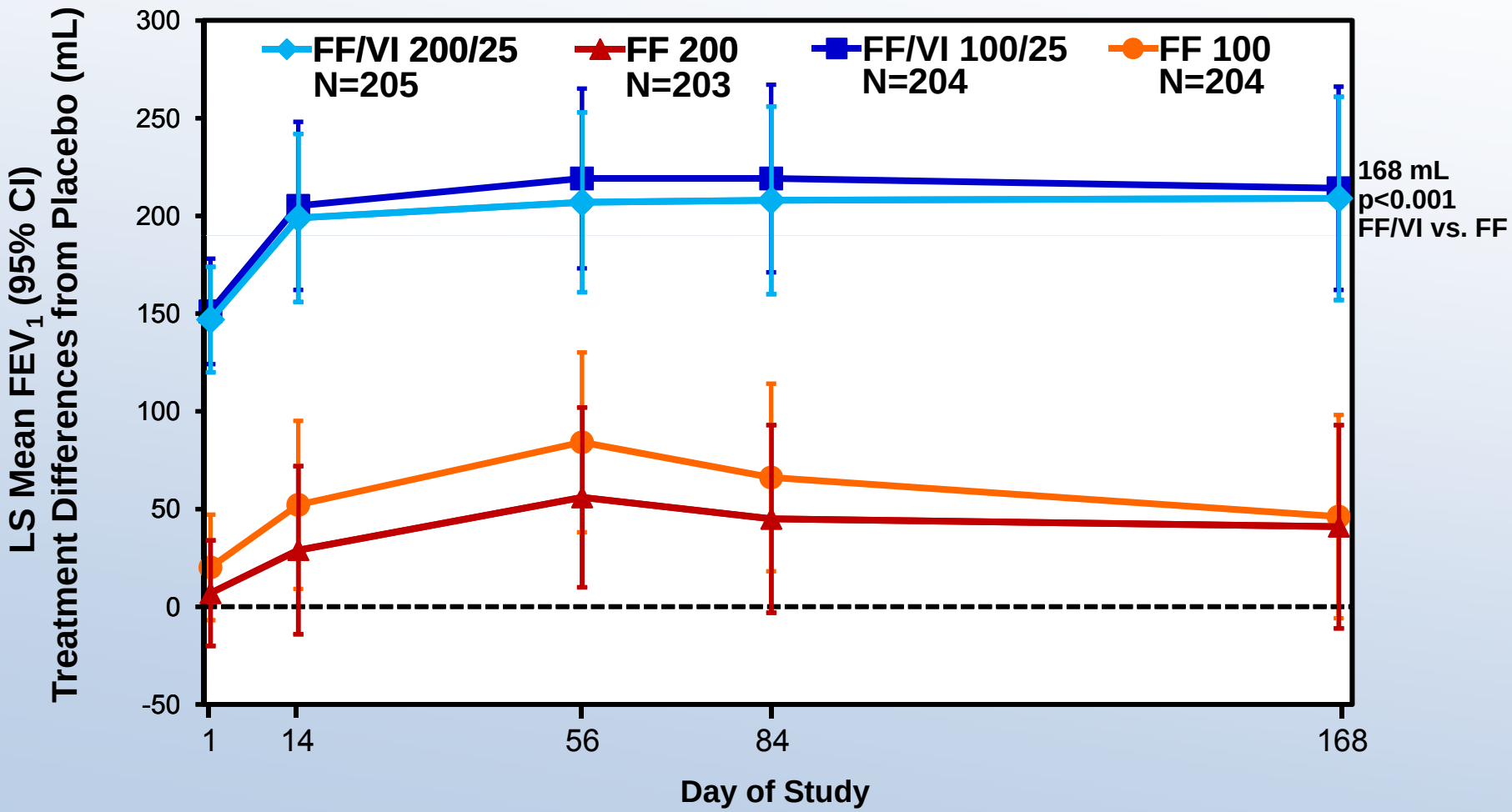
Effect of FF/VI vs. FF
Difference in 0-4hr Weighted Mean FEV_1
6-Month Lung Function Study (HZC112206)



Kerwin et al. Resp Med 2013 ;107:560-69.

Effect of FF/VI vs. FF
Difference in 0-4hr Weighted Mean FEV_1
6-Month Lung Function Study (HZC112207)



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Phase III: 1-Year Exacerbation Studies (HZC102970 and HZC102871)

HZC102970	HZC102871
FF/VI 200/25	FF/VI 200/25
FF/VI 100/25	FF/VI 100/25
FF/VI 50/25	FF/VI 50/25
VI 25mcg	VI 25mcg

Primary Endpoint

- Annual rate of moderate/severe exacerbations

Secondary Endpoints

- Time to first moderate/severe exacerbation
- Annual rate of exacerbations requiring OCS
- Trough FEV_1

- Subjects were required to have at least 1 exacerbation in the year prior to screening
- Subjects were run in on 4 weeks of FP/SAL 250/50
- All moderate/severe exacerbations and pneumonia were to have chest x-rays within 48 hrs
  - Moderate exacerbations: required treatment with oral corticosteroids and/or antibiotics
  - Severe exacerbations: necessitated hospitalizations

Primary COPD Studies: Demographic and Baseline Characteristics 1-Year Exacerbation Studies (HZC102970 and HZC102871)

	1-year exacerbation studies (970 & 871) (N=3255)	
Age (yrs): Mean (Min-Max)	63.7 (40-90)	
Sex: Female/Male, n (%)	1385 (43%) / 1870 (57%)	
Race, n (%)	**ITT**†	**US**
Caucasian	2746 (84%)	1,024 (93%)
Asian	168 (5%)	10 (<1%)
African American/African Heritage	73‡ (2%)	61‡ (6%)
Other	266* (8%)	11 (<1%)
Body Mass Index (kg/m^2): Mean (Min-Max)	26.87 (12.4-63.2)	
Current Smoker, n (%)	1439 (44%)	
Smoking History-Pack Yrs: Mean (Min-Max)	46.2 (10-255)	

* Includes Mixed Race (n=160, 5%), American Indian or Alaskan Native (n=107, 3%) and Native Hawaiian or Other Pacific Islander (n=1, <1%)

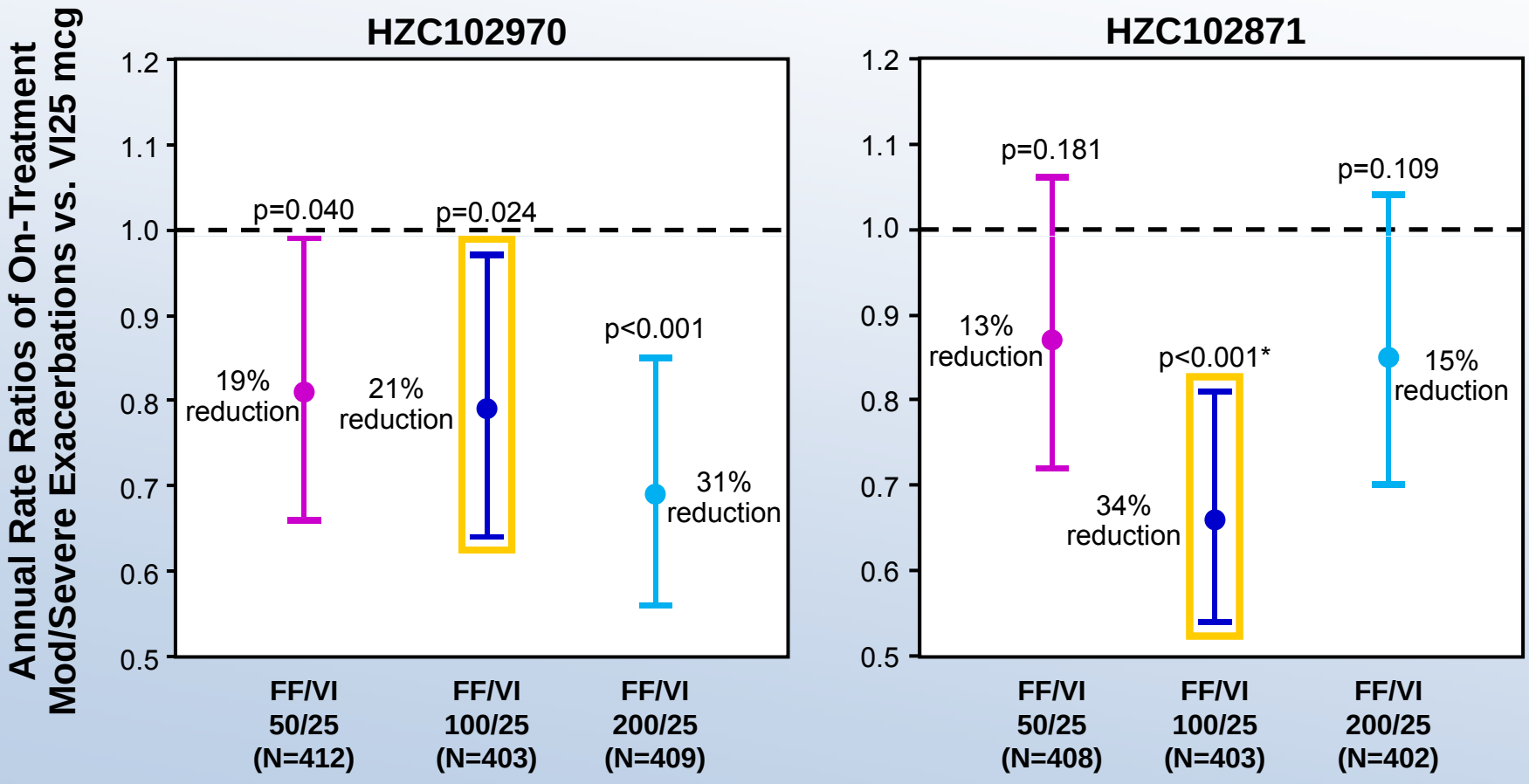
† Race was not reported for 2 subjects

‡ Includes 2 (<1%) subjects reported as African American/African Heritage & White

Primary COPD Studies: Demographic and Baseline Characteristics 1-Year Exacerbation Studies (HZC102970 and HZC102871) – continued

	1-year exacerbation studies (970 & 871) (N=3255)
Frequent Exacerbators	1267 (39%)
Screening Post-albuterol FEV_1 (L) Mean (SD)	1.29 (0.47)
Screening Post-albuterol FEV_1, % Predicted Mean (SD)	45.4 (13.36)
Screening Post-albuterol FVC (L) Mean (SD)	2.86 (0.88)
Screening Post-albuterol FEV_1/FVC (%) Mean (SD)	45.5 (11.62)
Screening Reversibility (mL)	140.4 (161.04)
Screening Reversibility, n (%)	972 (30%)

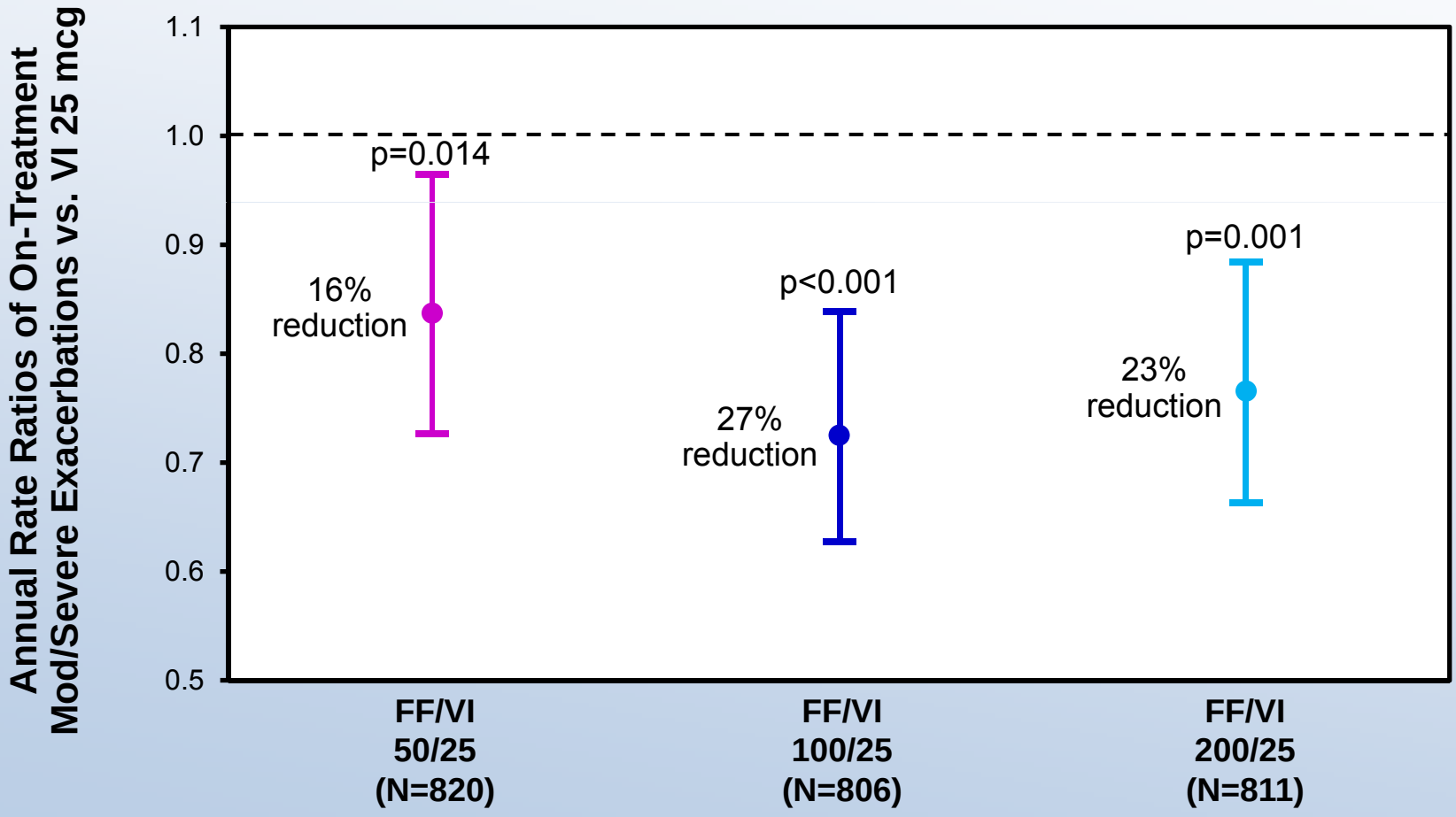
Primary Endpoint: Moderate and Severe Exacerbations Annual Rate Ratios FF/VI vs. VI 25mcg 1-Year Exacerbation Studies



Annual rate for VI is 1.14 in Study HZC102970 and 1.05 in Study HZC102871

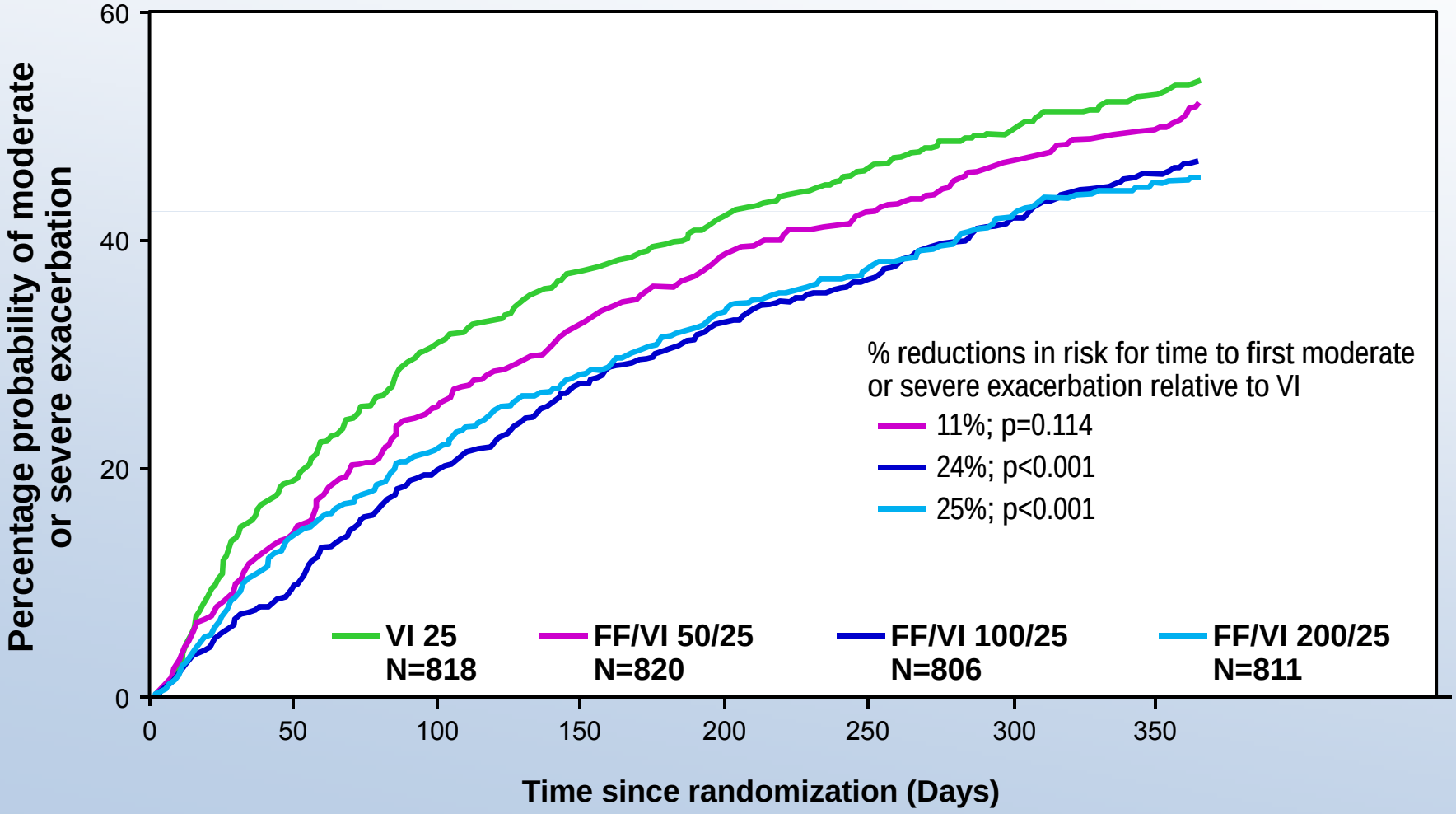
*nominal p-value

Moderate and Severe Exacerbations Annual Rate Ratios FF/VI vs. VI 25mcg Integrated 1-Year Exacerbation Studies (HZC102970 and HZC102871)

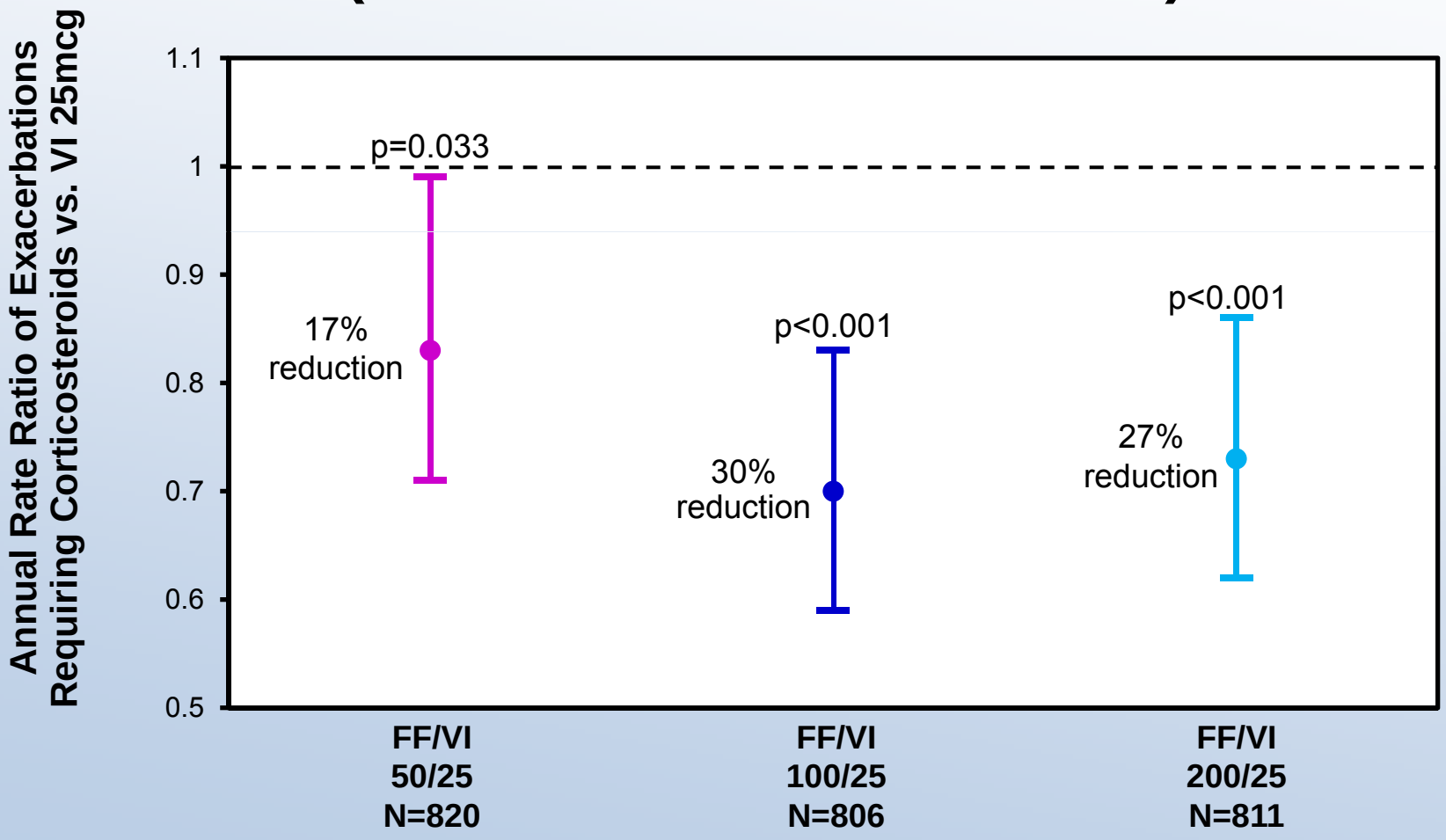


VI exacerbation event rate: 1.11 events per year

Probability of Moderate and Severe Exacerbation Over Time
Integrated 1-Year Exacerbation Studies (HZC102970 and HZC102871)



Annual Rate of Exacerbations Requiring Corticosteroids FF/VI vs. VI 25mcg Integrated 1-Year Exacerbation Studies (HZC102970 and HZC102871)



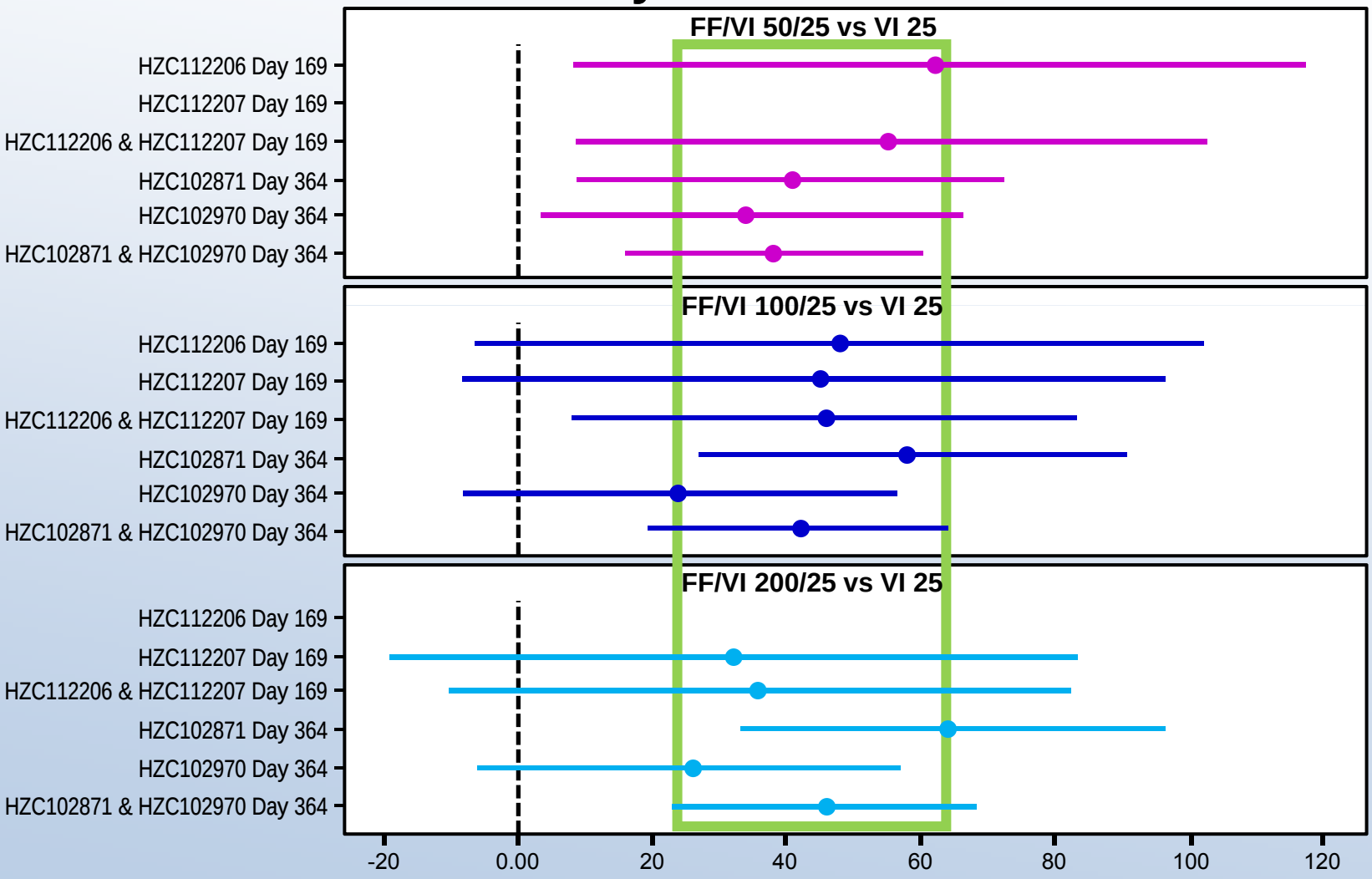
VI exacerbation event rate: 0.87 events per year

NNT: Subject and Event Based FF/VI vs. VI

	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Subject based NNT (NNT to have 1 additional subject with no moderate/severe exacerbations per year)	63.1	14.4	13.8
Event based NNT (NNT to prevent 1 moderate/severe exacerbation per year)	5.6	3.3	3.8

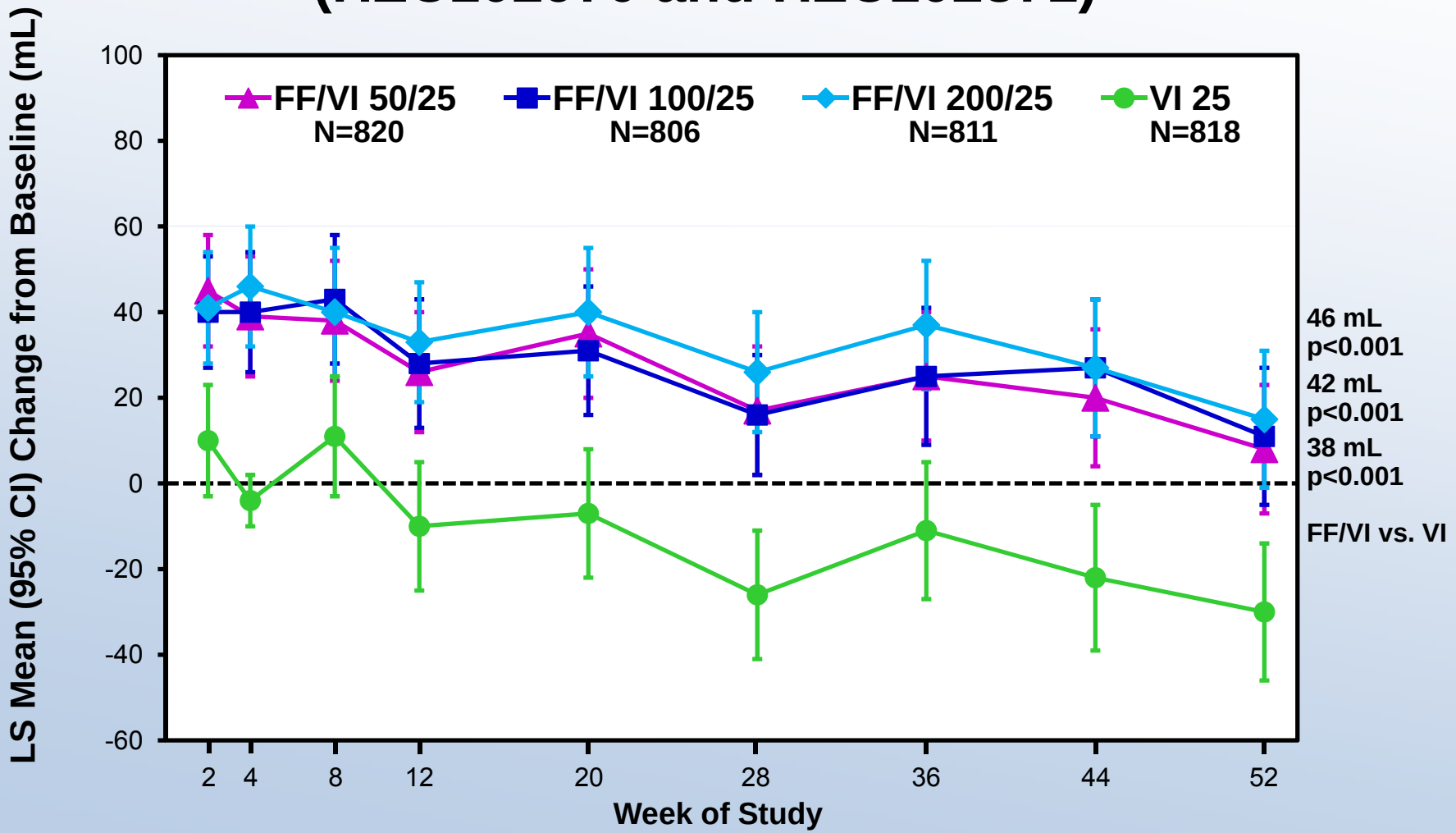
Contribution of FF in the Combination Trough FEV_1

Trough FEV_1: Treatment Differences FF/VI vs. VI 25mcg at Day 169 and 364

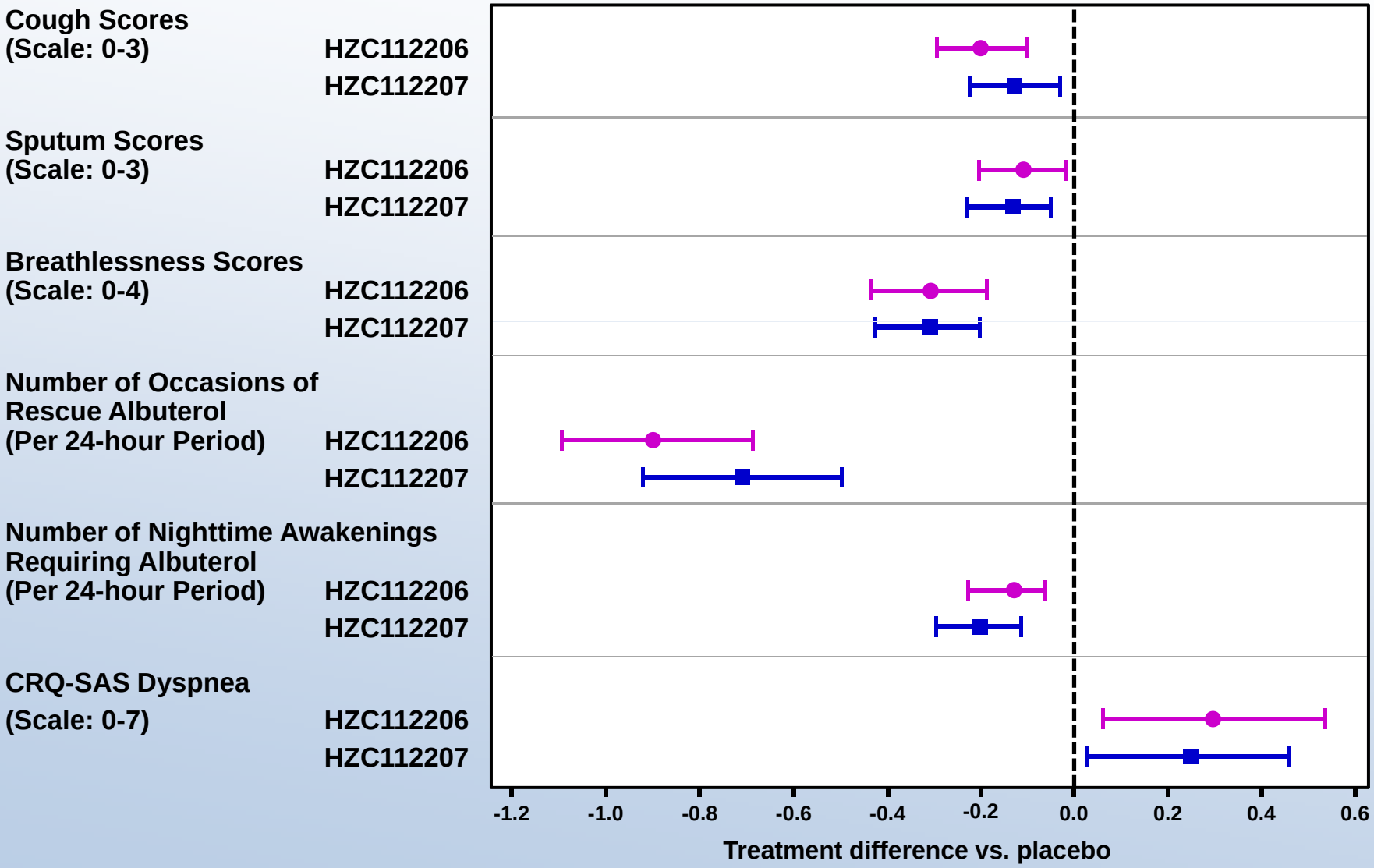


Treatment Difference from VI 25mcg (95% CI) for Change from Baseline Trough FEV_1 (mL)

Effect of FF/VI vs. VI
Change from Baseline in Trough FEV_1
Integrated 1-Year Exacerbation Studies
(HZC102970 and HZC102871)

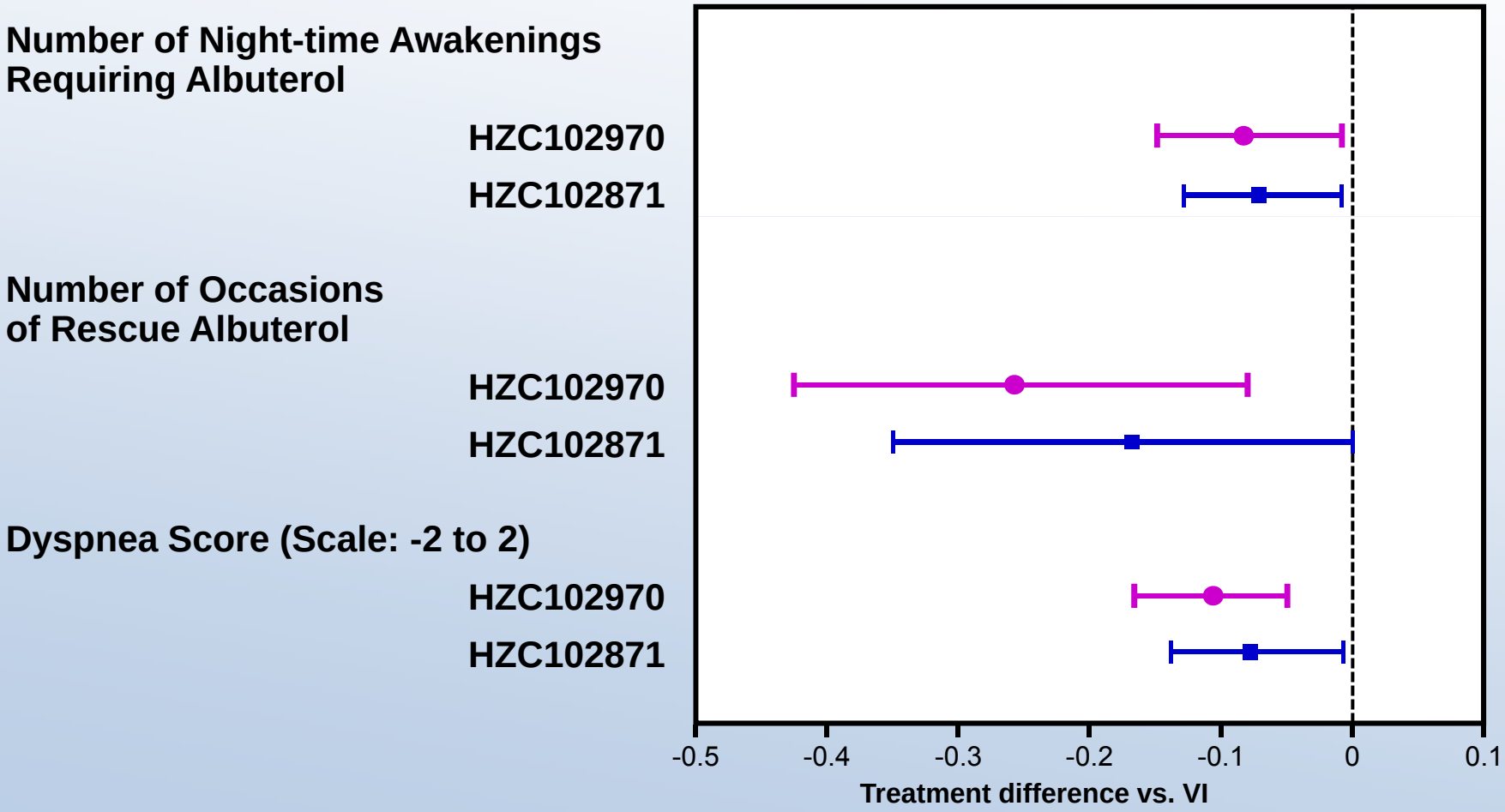


FF/VI 100/25 Improves Symptom-related Parameters Relative to Placebo



HZC112206 FF/VI 100/25 n=206; placebo n=207 / HCZ112207 FF/VI 100/25 n=204; placebo=205

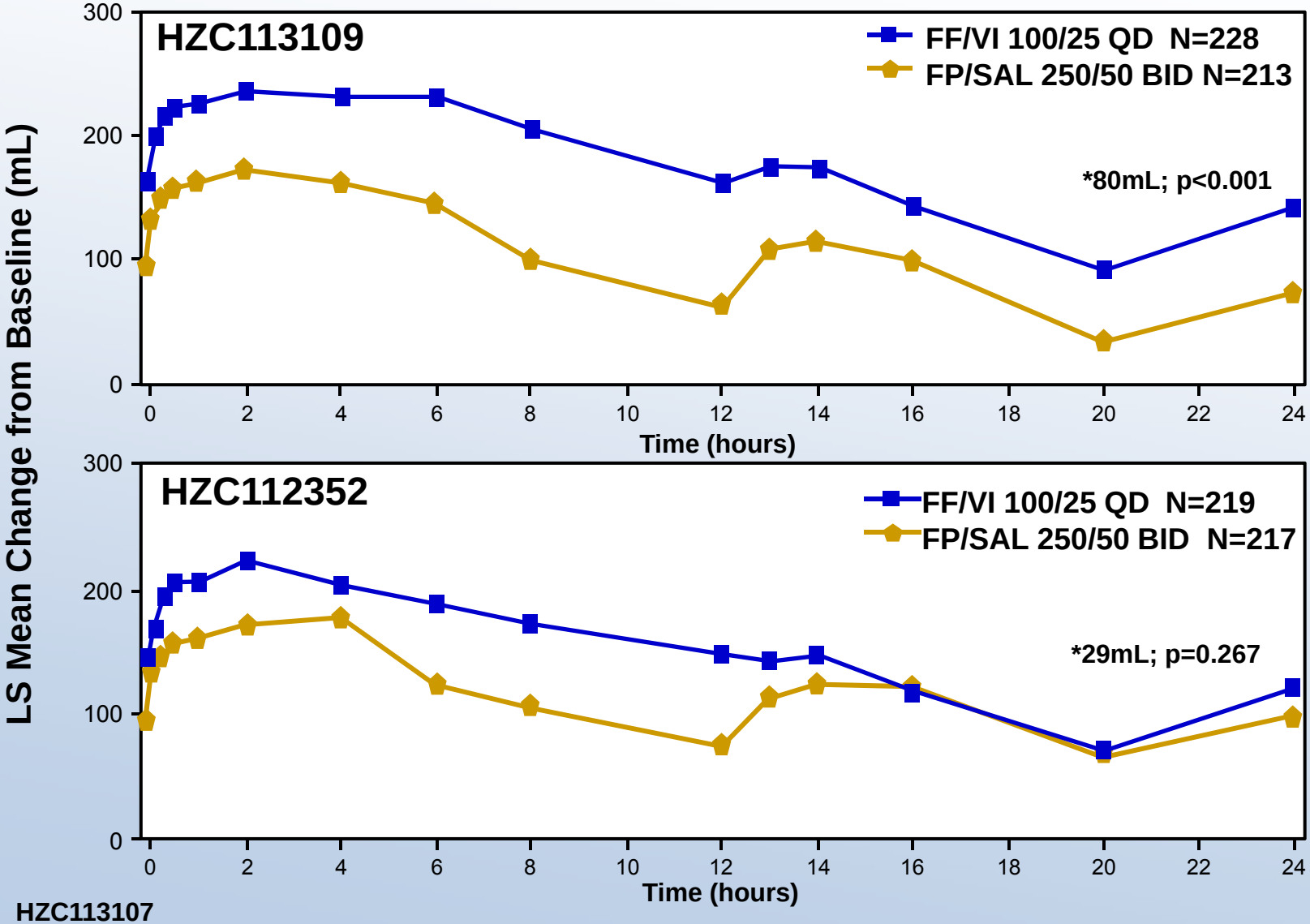
FF/VI 100/25 Improves Symptom-related Parameters Relative to VI 25
Integrated 1-Year Exacerbation Studies



HZC102970 FF/VI 100/25 n=403; VI 25=409 / HZC102871 FF/VI 100/25 n=403; VI 25=409

Comparator Studies with FF/VI 100/25 vs. FP/SAL 250/50 or 500/50 in COPD

24-Hour Serial FEV_1 on Day 84
FF/VI 100/25 vs. FP/SAL 250/50



HZC113107

FF/VI 100/25 (N=224) vs. FP/SAL 500/50 (N=233) difference=*22mL; p=0.282

* 24-hour weighted mean FF/VI vs. FP/SAL

Summary

- VI 25 alone statistically significantly improved lung function compared with placebo
- Contribution of VI to FF/VI demonstrated on 0-4hr weighted mean FEV_1
- Contribution of FF to FF/VI demonstrated by reductions in annual rate of moderate and severe exacerbations
  - FF/VI 50/25 was less efficacious than FF/VI 100/25
  - No incremental benefit observed with FF/VI 200/25 over FF/VI 100/25
- Contribution of FF in combination on lung function not statistically demonstrated throughout the primary studies. However, treatment effect consistent with and comparable to other ICS/LABA products
- Improvements in symptom-related endpoints support efficacy of FF/VI 100/25
- FF/VI 100/25 QD demonstrated similar or greater improvement in lung function compared with FP/SAL 250/50 BID

Conclusion

The breadth of data from our clinical development program demonstrate that VI contributes the bronchodilatation to BREO ELLIPTA 100/25 in alleviating the airflow obstruction in patients with COPD and FF makes its contribution to BREO ELLIPTA in reducing the rate of moderate and severe exacerbations over VI alone

BREO ELLIPTA 100/25
(Fluticasone furoate / Vilanterol)

Safety

Tjark Reblin, MD
Vice President
Global Clinical Safety and Pharmacovigilance
GlaxoSmithKline

Safety of Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies (N=2254)
  - 1 year exacerbation studies (N=3255)
- ICS safety
  - Pneumonia
  - HPA, bone and ocular effects
- LABA safety
  - Cardiovascular effects
- Risk management

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
  - 1 year exacerbation studies
- ICS safety
  - Pneumonia
  - HPA, bone and ocular effects
- LABA safety
  - Cardiovascular effects
- Risk management

Common Adverse Events
6-month Lung Function Studies
(HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N=203
Nasopharyngitis	31 (8%)	14 (7%)	35 (9%)	13 (6%)	41 (10%)	32 (8%)	20 (10%)
Headache	20 (5%)	12 (6%)	29 (7%)	15 (7%)	36 (9%)	30 (7%)	11 (5%)
Upper respiratory infection	13 (3%)	16 (8%)	29 (7%)	7 (3%)	20 (5%)	16 (4%)	5 (2%)
Oral/oropharyngeal candidiasis*	9 (2%)	20 (10%)	22 (5%)	9 (4%)	9 (2%)	13 (3%)	13 (6%)

*Terms/numbers oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal as in proposed US PI table
Note: Table lists preferred terms of AEs seen in ≥3% in FF/VI 100/25 group

On-Treatment Serious Adverse Events 6-month Lung Function Studies (HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N=203
Any event	21 (5%)	6 (3%)	23 (6%)	15 (7%)	31 (8%)	22 (5%)	10 (5%)
Respiratory, Thoracic and Mediastinal Disorders	8 (2%)	0	9 (2%)	7 (3%)	12 (3%)	2 (<1%)	2 (<1%)
Infections and Infestations	2 (<1%)	1 (<1%)	3 (<1%)	4 (2%)	6 (1%)	4 (<1%)	3 (1%)
Cardiac disorders	3 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)	2 (<1%)

Note: Representation only lists MedDRA organ classes with reports from ≥1% of subjects per any of the different treatment groups, with the exception of cardiac. Remaining data for organ classes with fewer than 1% of subjects affected across all groups are listed in the briefing document.

Fatal Events
6-month Studies ITT population*
(HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF200 N=203
Any fatal event	2 (<1%)	2 (<1%)	2 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0
Death	0	0	1 (<1%)	0	0	0	0
Sudden Cardiac death	0	0	0	0	1 (<1%)	0	0
Sudden death	1 (<1%)	0	0	0	0	0	0
Myocardial infarction	0	0	0	1 (<1%)	0	0	0
Myocardial ischemia	1 (<1%)	0	0	0	0	0	0
Accidental poisoning	0	0	0	0	1 (<1%)	0	0
Alcohol poisoning	0	1 (<1%) †	0	0	0	0	0
Cerebral hemorrhage	0	1 (<1%) †	0	0	0	0	0
Thrombotic stroke	0	0	1 (<1%)	0	0	0	0
Gastrointestinal hemorrhage	0	1 (<1%)	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	1 (<1%) ‡	0	0
Pulmonary embolism	0	0	0	0	0	1 (<1%)	0

* includes on and post-treatment
† Both events in same subject,
‡ Determined related to nuclear stress testing

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
  - 1 year exacerbation studies
- ICS safety
  - Pneumonia
  - HPA, bone and ocular effects
- LABA safety
  - Cardiovascular effects
- Risk management

Common Adverse Events
1-year Exacerbation Studies
(HZC102970 and HZC102871)

	FF/VI 50/25 N = 820	FF/VI 100/25 N = 806	FF/VI 200/25 N = 811	VI 25 N = 818
Nasopharyngitis	112 (14%)	128 (16%)	158 (19%)	112 (14%)
Oral/oropharyngeal candidiasis	110 (13%)	87 (11%)	88 (11%)	55 (7%)
Upper respiratory infection	84 (10%)	90 (11%)	75 (9%)	78 (10%)
Headache	61 (7%)	57 (7%)	67 (8%)	60 (7%)
COPD	53 (6%)	56 (7%)	53 (7%)	53 (6%)
Back pain	40 (5%)	54 (7%)	37 (5%)	53 (6%)
Bronchitis	41 (5%)	38 (5%)	47 (6%)	42 (5%)
Sinusitis	47 (6%)	42 (5%)	40 (5%)	36 (4%)
Pneumonia	46 (6%)	49 (6%)	45 (6%)	23 (3%)

Note: Representation only lists preferred terms for terms reported ≥5% in FF/VI 100/25 group . Remaining data for organ classes with fewer subjects affected across all groups are listed in the briefing document

On-Treatment Serious Adverse Events 1-year Exacerbation Studies (HZC102970 and HZC102871)

	FF/VI 50/25 N = 820	FF/VI 100/25 N = 806	FF/VI 200/25 N = 811	VI 25 N = 818
Any event	136 (17%)	123 (15%)	124 (15%)	126 (15%)
Respiratory, Thoracic and Mediastinal Disorders	59 (7%)	63 (8%)	59 (7%)	60 (7%)
Infections and Infestations	35 (4%)	43 (5%)	37 (5%)	20 (2%)
Cardiac disorders	14 (2%)	17 (2%)	10 (1%)	16 (2%)
Neoplasms benign, malignant and unspecified	13 (2%)	7 (<1%)	15 (2%)	10 (1%)
Gastrointestinal Disorders	10 (1%)	6 (<1%)	10 (1%)	8 (<1%)

Note: Representation only lists MedDRA organ classes with reports from ≥1% of subjects per any of the different treatment groups. Remaining data for organ classes with fewer than 1% of subjects affected across all groups are listed in the briefing document.

Fatal Events
1-year Studies ITT Population* (HZC102970 and HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N = 818
Any Fatal Event	16 (2%)	10 (1%)	14 (2%)	13 (2%)
Cardiac Disorders	5 (<1%)	4 (<1%)	3 (<1%)	5 (<1%)
Respiratory, Thoracic and Mediastinal Disorders	3 (<1%)	3 (<1%)	5 (<1%)	3 (<1%)
Infections and Infestations	1 (<1%)	1 (<1%)	6 (<1%)†	3 (<1%)
Neoplasms benign, malignant and unspecified	4 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
Vascular Disorders	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Gastrointestinal Disorders	0	1 (<1%)	0	1 (<1%)
General Disorders and Administration Site Conditions	1 (<1%)	0	0	1 (<1%)
Nervous System Disorders	2 (<1%)	0	0	0
Hepatobiliary Disorders	0	1 (<1%)	0	0
Musculoskeletal and Connective Tissue Disorders	1 (<1%)	0	0	0

* Includes on and post-treatment

† While pneumonia was not reported as the fatal AE (recorded as COPD exacerbation) for one additional subject on FF/VI 200/25 in HZC102871, the investigator completed the pneumonia page in eCRF citing pneumonia at the time of death

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
  - 1 year exacerbation studies
- ICS safety
  - Pneumonia
  - HPA, bone and ocular effects
- LABA safety
  - Cardiovascular effects
- Risk management

Pneumonia Background

- Patients with COPD have increased pneumonia risk[1]
- Increased incidence of pneumonia in patients on ICS combined with LABA versus placebo or LABA alone [2-6]
- Rigorous approach to capture pneumonias:
  - Adverse Events of Special Interest grouping for reporting
  - Chest x-ray required
  - Pneumonia CRF page to capture additional clinical information

1. Mannino, et al. Respir Med 2009;103:224-29
2. Calverly, et al. N Engl J Med 2007; 356: 775–789;
3. Sharafkhaneh, et al. Respir Med 2012;106:257-68;
4. Doherty, et al. Int J COPD 2012;7:57-71
5. Ferguson, et al. Resp Med 2008;102:1099–1108.
6. Anzueto, et al. COPD 2009;6:320-29.

Pneumonia-related Adverse Events 6-month Lung Function Studies (HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N = 203
Pneumonia*, %	3 (0.73)	3 (1.46)	6 (1.46)	4 (1.95)	7 (1.72)	6 (1.46)	3 (1.48)
Event rate/1000 treatment years	19.5	38.3	38.1	48.7	43.4	38.2	37.6
Serious pneumonia*, %	1 (0.24)	1 (0.49)	1 (0.24)	3 (1.46)	5 (1.23)	3 (0.73)	2 (0.99)
Event rate/1000 treatment years	6.5	12.8	6.4	36.5	31.0	19.1	25.1
Fatal pneumonia	0	0	0	0	0	0	0

* Under “pneumonia” a composite of many MedDRA preferred terms is captured

Pneumonia-related Adverse Events 1-year Exacerbation Studies (HZC102970 and HZC102871)

	FF/VI 50/25 N = 820	FF/VI 100/25 N = 806	FF/VI 200/25 N = 811	VI 25 N = 818
Pneumonia*, subjects (%)	48 (5.85)	51 (6.33)	55 (6.78)	27 (3.30)
Event rate/1000 treatment years	78.6	85.7	94.9	42.3
Serious pneumonia*, subjects (%)	24 (2.93)	25 (3.10)	23 (2.84)	8 (0.98)
Event rate/1000 treatment years	37.8	42.9	35.1	12.1
Fatal pneumonia*, subjects (%)	0	1 (0.12)	7† (0.86)	1 (0.12)‡
Event rate/1000 treatment years	0	1.5	10.2	1.5

*Under "pneumonia" a composite of many MedDRA preferred terms is captured
† While pneumonia was not reported as the fatal AE (recorded as COPD exacerbation) for one subject on FF/VI 200/25 in HZC102871, the investigator reported a non-serious pneumonia event and completed the pneumonia page in eCRF
‡ There was one fatal post-treatment pneumonia on VI 25 in HZC102871

Pneumonia Event Rates with FF/VI 100/25 vs. FP/SAL 250/50

FF/VI 100/25

	FF/VI 100/25 N = 806	VI 25 N = 818
Pneumonia events per 1000 treatment years	85.7	42.3
Serious pneumonia events per 1000 treatment years	42.9	12.1
Number of fatal events*	1	0

Fluticasone propionate/salmeterol (FP/SAL 250/50)[1,2]

	FP/SAL 250/50 N = 788	SAL 50 N = 791
Pneumonia events per 1000 treatment years	91.9	48.8
Serious pneumonia events per 1000 treatment years	53.0	33.1
Number of fatal events*	1	0

*Number of fatal events during treatment

1. Adapted from Ferguson, et al. Respir Med 2008;102:1099-1108
2. Adapted from Anzueto, et al. COPD 2009;6:320-329

NNH Pneumonia: 1-Year Exacerbation Studies

	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	FP/SAL 250/50[1,2]
Subject based NNH (NNH to have 1 additional subject with a pneumonia per year)	39.2	33.0	28.7	26.2
Event based NNH (NNH to have 1 additional pneumonia occur per year)	27.5	23.0	19.1	25.0

1. Adapted from Ferguson, et al. Respir Med 2008;102:1099-1108.
2. Adapted from Anzueto, et al. COPD 2009;6:320-29.

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
  - 1 year exacerbation studies
- ICS safety
  - Pneumonia
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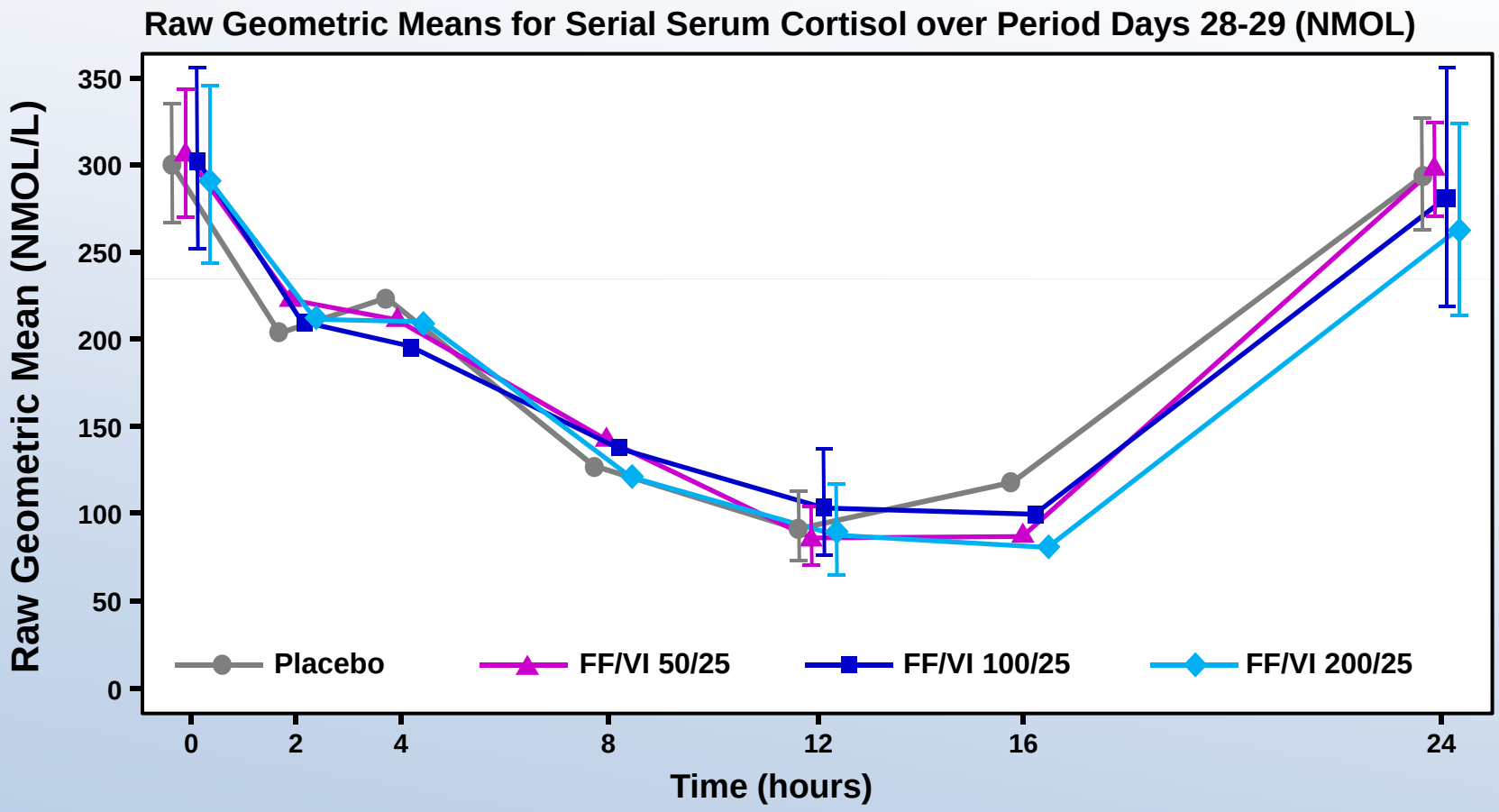
- LABA safety
  - Cardiovascular effects
- Risk management

HPA-Axis Assessment
COPD Study (HZC110946) Serum Cortisol Production (0 – 24h)



- HPA axis not adversely affected by FF/VI as assessed by 24-hour serum cortisol production
- No effect on 24h urinary cortisol excretion for active treatment groups in 6 month studies

Fractures
1-year Exacerbation Studies
(HZC102970 and HZC102871)

	FF/VI 50/25 N = 820	FF/VI 100/25 N = 806	FF/VI 200/25 N = 811	VI 25 N = 818
Patients with fractures	14 (1.7%)	19 (2.4%)	13 (1.6%)	8 (1.0%)
Total fracture events	15	19	14	8
Upper extremities*	2	6	3	2
Lower extremities†	6	3	3	1
Rib and chest	3	6	3	2
Pelvis and hip	2	1	1	1
Lumbar and thoracic spine	1	2	3	1
Other	1	1	1	1

*Upper Extremities: Shoulder, Arm, Wrist, Hand
† Lower Extremities: Leg, Ankle, Foot/Metatarsal, Toe

Fractures
FF/VI and FP/SAL in 1-year Exacerbation Studies

FF/VI

	FF/VI 100/25 N = 806	VI 25 N = 818
Patients with fractures	19 (2.4%)	8 (1.0%)

Fluticasone propionate/salmeterol (FP/SAL)[1,2]

	FP/SAL 250/50 N = 788	SAL 50 N = 791
Patients with fractures	21 (2.7%)	16 (2.0%)

1. Data on file; GlaxoSmithKline study SCO100250
2. Data on file; GlaxoSmithKline study SCO40043

Ocular Associated Adverse Events
6-month Lung Function and 1-year Exacerbation Studies (HZC112206 and HZC112207, HZC102970 and HZC102871)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N = 203
Subjects (%)	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	3 (<1%)	0
Cataract	1 (<1%)	1 (<1%)	0	0	1 (<1%)	3 (<1%)	0
Glaucoma	0	0	1 (<1%)	0	0	0	0

	FF/VI 50/25 N = 820	FF/VI 100/25 N = 806	FF/VI 200/25 N = 811	VI 25 N = 818
Subjects (%)	7 (<1%)	12 (1%)	7 (<1%)	9 (1%)
Cataract	5 (<1%)	5 (<1%)	2 (<1%)	5 (<1%)
Cataract operation	1 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)
Glaucoma	0	4 (<1%)	1 (<1%)	2 (<1%)
Eye pain	0	1 (<1%)	2 (<1%)	0
Cataract subcapsular	1 (<1%)	0	0	0
Intraocular pressure increased	0	1 (<1%)	0	0
Ocular hypertension	0	0	1 (<1%)	0

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
  - 1 year exacerbation studies
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- LABA safety
  - Cardiovascular effects
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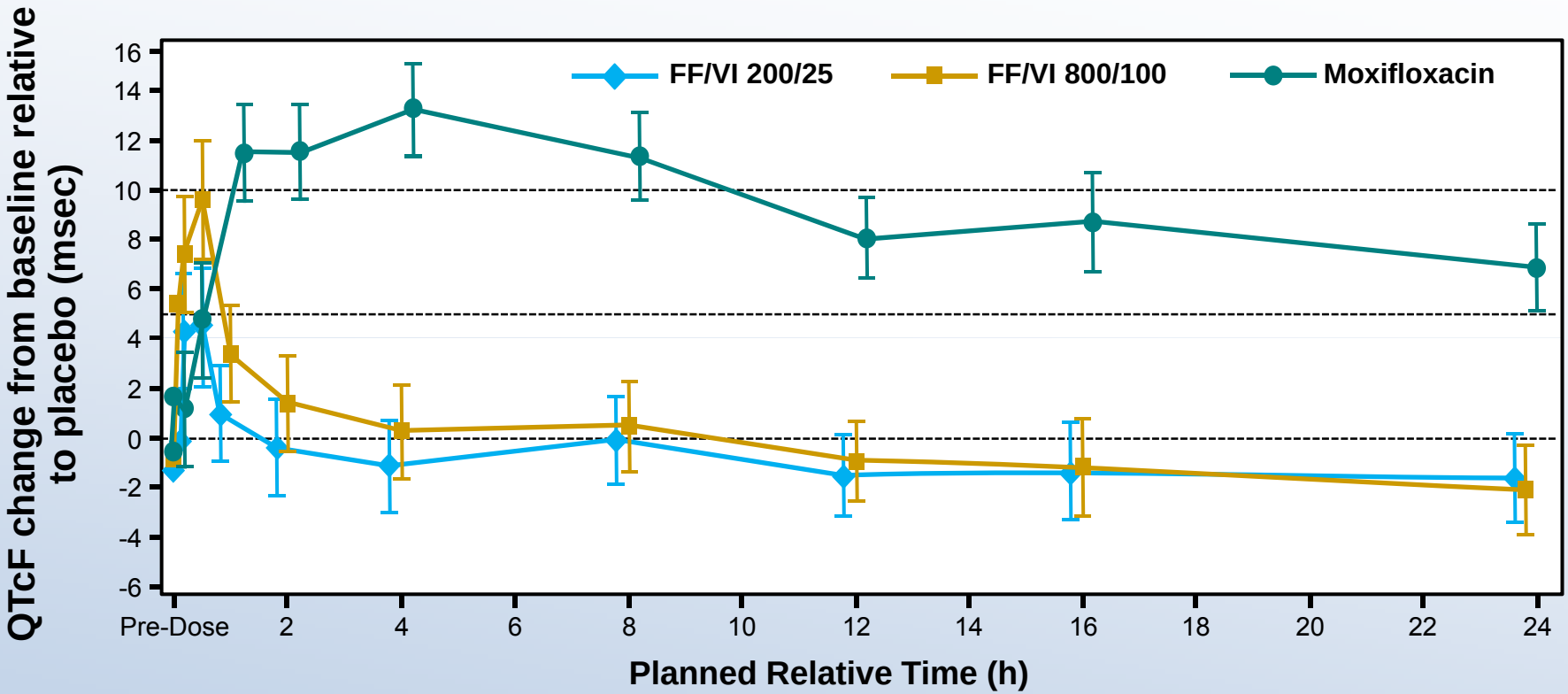
QTcF
Thorough QT Study FF/VI (HZA102936)



- FF/VI 200/25mcg: mean difference versus placebo <5 msec and upper 90% CI <10 msec
- FF/VI 800/100mcg: largest mean difference 9.6 msec and upper 90% CI 12.0 msec

Arrhythmias with Potential Clinical Consequences 24-hour Holter Data from 6-month Lung Function Studies* (HZC112206 and HZC112207)

	Placebo N = 168	FF/VI 50/25 N = 98	FF/VI 100/25 N = 188	FF/VI 200/25 N = 98	VI 25 N = 191	FF 100 N = 184	FF 200 N = 89
Ventricular arrhythmias all	**10 (6%)**	**7 (7%)**	**12 (6%)**	**8 (8%)**	**15 (8%)**	**13 (7%)**	**3 (3%)**
Sustained VT >100bpm	0	0	0	0	0	0	1 (1%)
Non sustained VT	9 (5%)	6 (6%)	12 (6%)	7 (7%)	15 (8%)	13 (7%)	1 (1%)
Supraventricular arrhythmias all	**1 (<1%)**	**1 (1%)**	**6 (3%)**	**2 (2%)**	**5 (3%)**	**5 (3%)**	**1 (1%)**
Sustained supraventricular tachycardia	0	0	3 (2%)	1 (1%)	1 (<1%)	3 (2%)	1 (1%)
Atrial fibrillation	1 (<1%)	0	3 (2%)	1 (1%)	4 (2%)	4 (2%)	0
Atrial flutter	0	1 (1%)	0	0	0	1 (<1%)	0

* Integrated data from 1016 of the 2254 subjects in 6 month placebo controlled studies HZC112206 and HZC112207

Cardiovascular Events*
6-month Lung Function Studies
(HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N = 203
Cardiac arrhythmias	30 (7%)	11 (5%)	22 (5%)	10 (5%)	20 (5%)	23 (6%)	16 (8%)
Ischemic heart disease	4 (<1%)	3 (1%)	4 (<1%)	1 (<1%)	3 (<1%)	4 (<1%)	2 (<1%)
Cardiac failure	3 (<1%)	1 (<1%)	3 (<1%)	4 (2%)	3 (<1%)	4 (<1%)	0
Cerebrovascular disorders	0	2 (<1%)	4 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	0

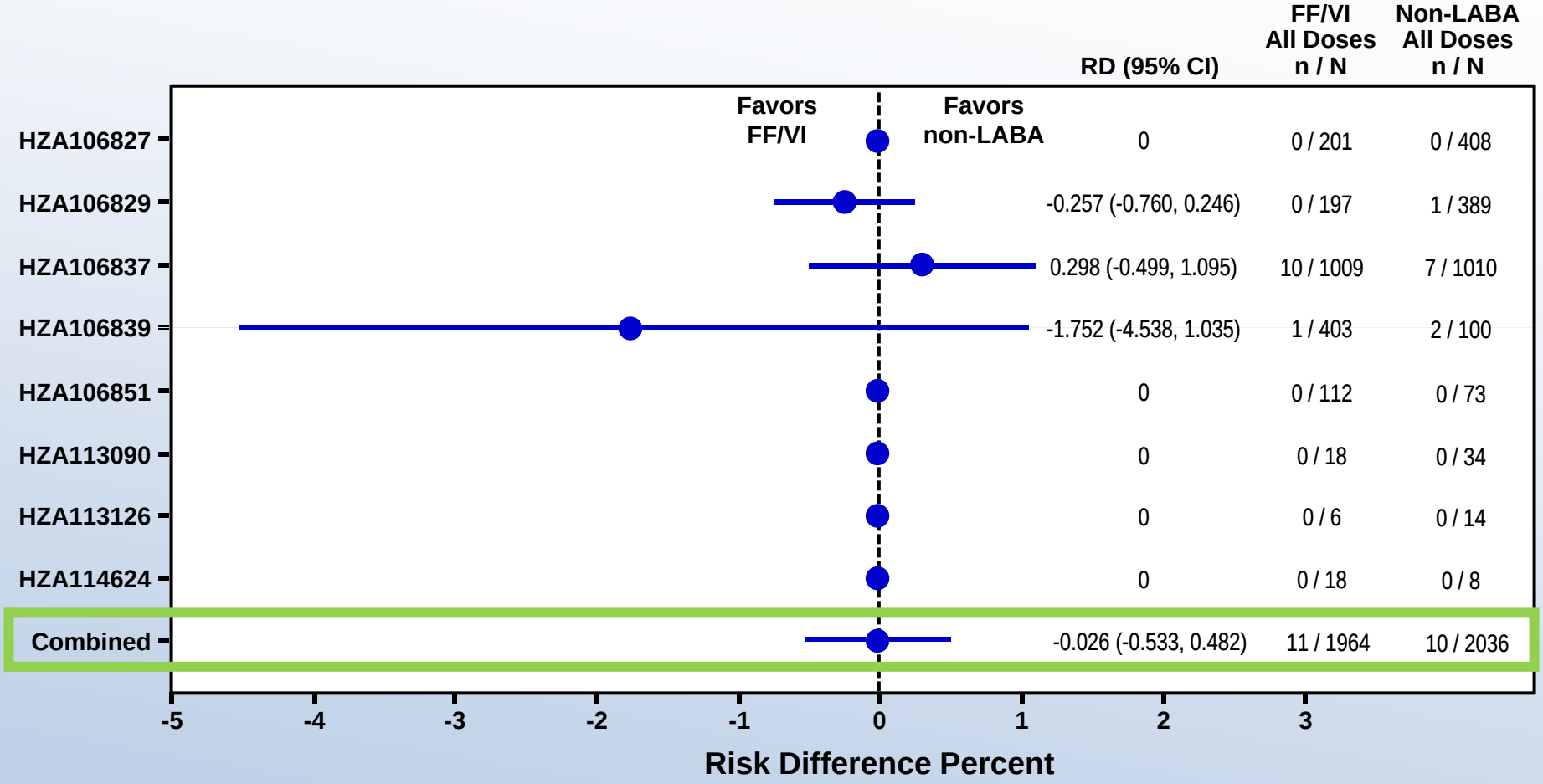
* Cardiac Standardized MedDRA Queries (SMQ)

Other Tolerability: Adverse Events of Special Interest 6-month Lung Function Studies (HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N=203
LABA-associated							
Tremor	1 (<1%)	0	1 (<1%)	0	0	1 (<1%)	0
Hypertension	10 (2%)	5 (2%)	4 (<1%)	1 (<1%)	3 (<1%)	8 (2%)	7 (3%)
Effects on potassium	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	0
ICS-associated							
Systemic steroid effects	2 (<1%)	2 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Local steroid effects	15 (4%)	24 (12%)	27 (7%)	13 (6%)	14 (3%)	18 (4%)	17 (8%)
Effects on glucose*	3 (<1%)	3 (1%)	7 (2%)	3 (1%)	6 (1%)	5 (1%)	3 (1%)

* Both ICS and LABA have potential effects on glucose

Asthma Composite Endpoint
FF/VI All Doses vs. Non-LABA All Doses



- No asthma-related deaths or intubations
- 21 asthma-related hospitalizations: 11 with FF/VI and 10 with non-LABA

Safety Fluticasone furoate / Vilanterol

- Adverse events, serious adverse events and deaths
  - 6 month lung function studies
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- LABA safety
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- Risk management

Safety Summary

- Pneumonia
  - Increased risk for FF/VI versus VI alone
  - Consistent with the ICS class
- HPA axis
  - No clinically relevant suppression and effects
- Bone
  - Increase in fractures
  - Consistent with the ICS class
- Cardiac effects
  - No increase in cardiovascular events
- Overall safety and tolerability profile
  - Consistent with the LABA/ICS combination class

Clinical Perspective

Stephen I. Rennard, MD
Larson Professor of Medicine
Division of Pulmonary, Critical Care, Sleep and Allergy
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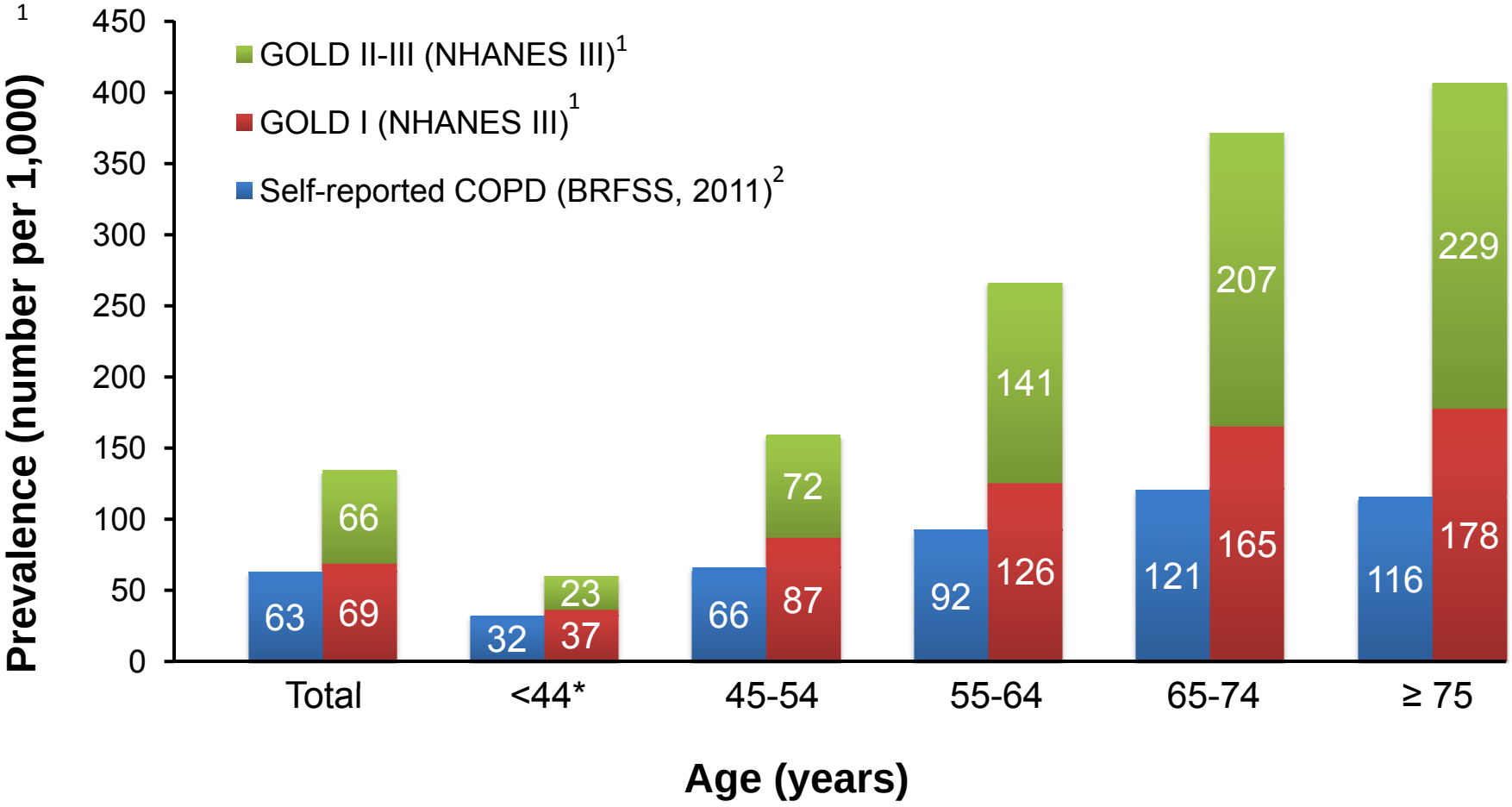
Prevalence of COPD in the United States



*** 18-44 (BRFSS); 25-44 (NHANES III)**

[1] Data from the Third National Health and Nutrition Examination Survey, 1988-1994. Presented in Mannino et al. Chronic Obstructive Pulmonary Disease Surveillance- United States, 1971–2000. In: Surveillance Summaries, August 2, 2002. MMWR 2002;51(No. SS-6):1-16.

[2] Data from the Behavioral Risk Factor Surveillance System, United States, 2011. Not age adjusted. US civilian adult population aged ≥18 years responding yes to "Have you ever been told by a doctor or health professional that you have COPD, emphysema, or chronic bronchitis?". Presented in Centers for Disease Control and Prevention. Chronic Obstructive Pulmonary Disease Among Adults - United States, 2011. MMWR 2012;61: 938-943.

Global Strategy for Diagnosis, Management and Prevention of COPD

Manage Stable COPD: Pharmacologic Therapy

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

Patient	Recommended First choice	Alternative choice	Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA	Theophylline
B	LAMA *or* LABA	LAMA and LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.	SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.	Carbocysteine *SABA and/or* SAMA Theophylline

From the Global Strategy for Diagnosis, Management and Prevention of COPD 2013, Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.org

Global Strategy for Diagnosis, Management and Prevention of COPD

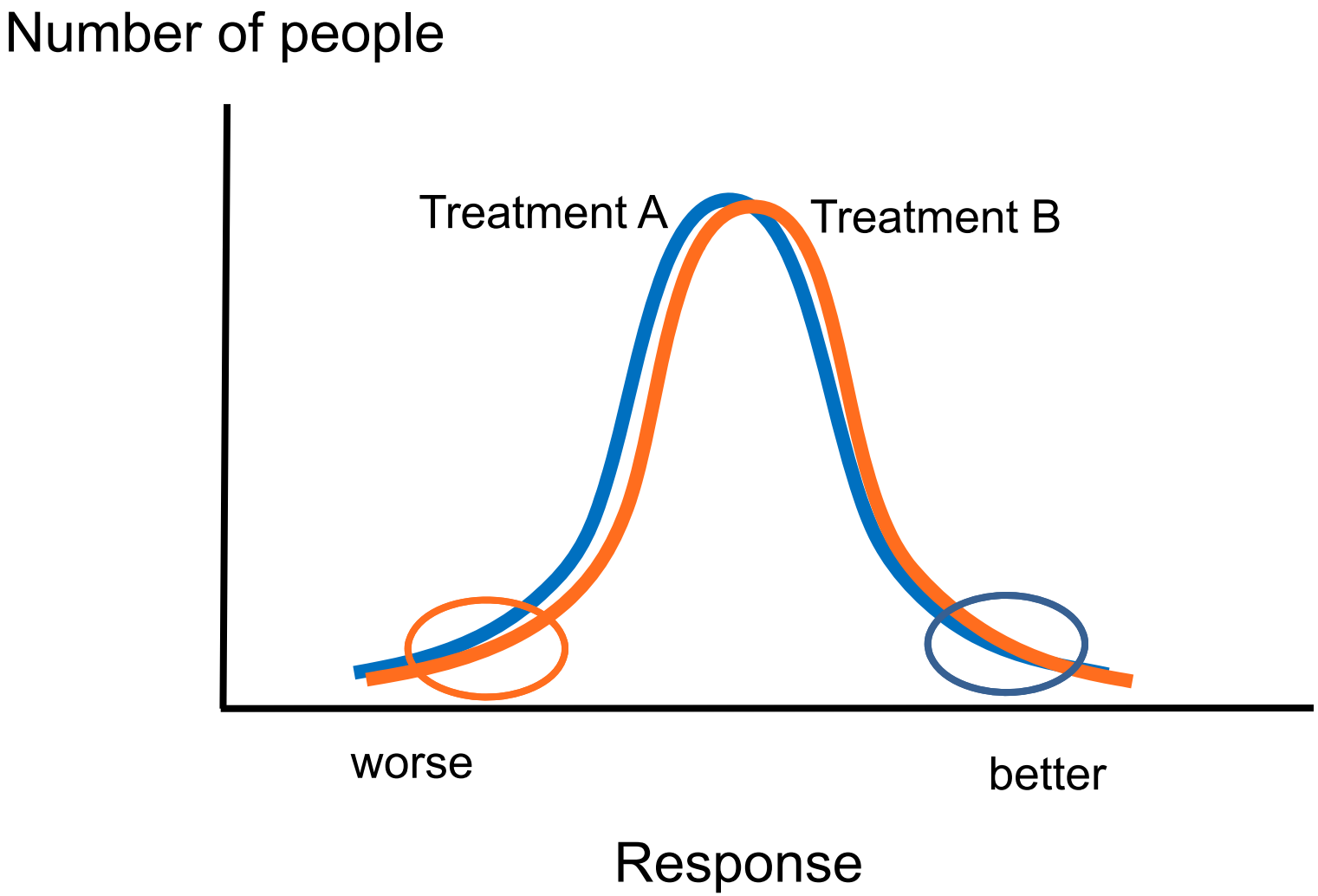
Manage Stable COPD: Pharmacologic Therapy

(Medications in each box are mentioned in alphabetical order, and therefore not necessarily in order of preference.)

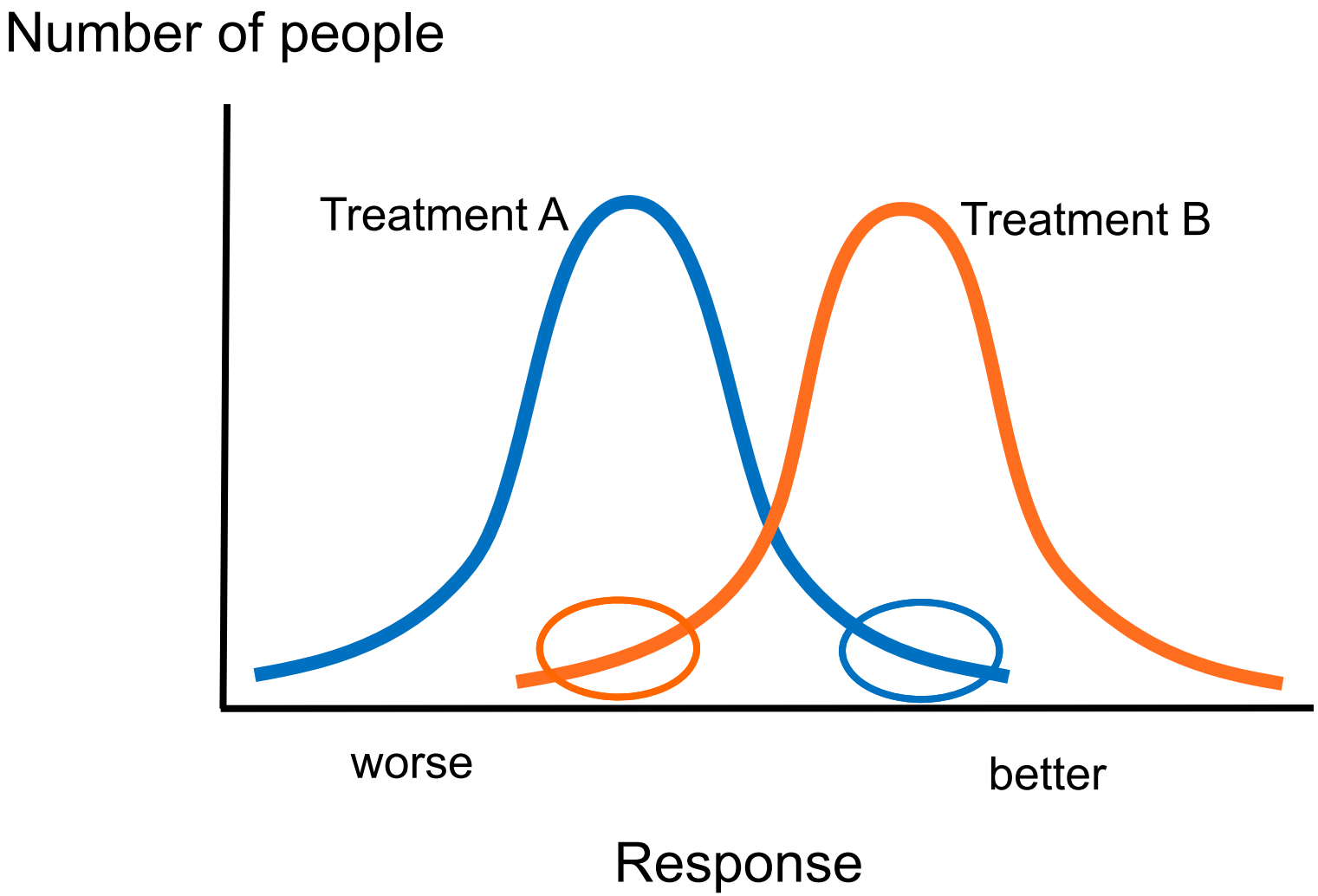
Patient	Recommended First choice	Alternative choice	Other Possible Treatments
A	SAMA prn *or* SABA prn	LAMA *or* LABA *or* SABA and SAMA	Theophylline
B	LAMA *or* LABA	LAMA and LABA	SABA *and/or* SAMA Theophylline
C	ICS + LABA *or* LAMA	LAMA and LABA *or* LAMA and PDE4-inh. *or* LABA and PDE4-inh.	SABA *and/or* SAMA Theophylline
D	ICS + LABA *and/or* LAMA	ICS + LABA and LAMA *or* ICS+LABA and PDE4-inh. *or* LAMA and LABA *or* LAMA and PDE4-inh.	Carbocysteine *SABA and/or* SAMA Theophylline

From the Global Strategy for Diagnosis, Management and Prevention of COPD 2013, Global Initiative for Chronic Obstructive Lung Disease (GOLD), www.goldcopd.org

Difference: Clinical Trials and Clinical Care



Difference: Clinical Trials and Clinical Care



“COPD HETEROGENEITY”

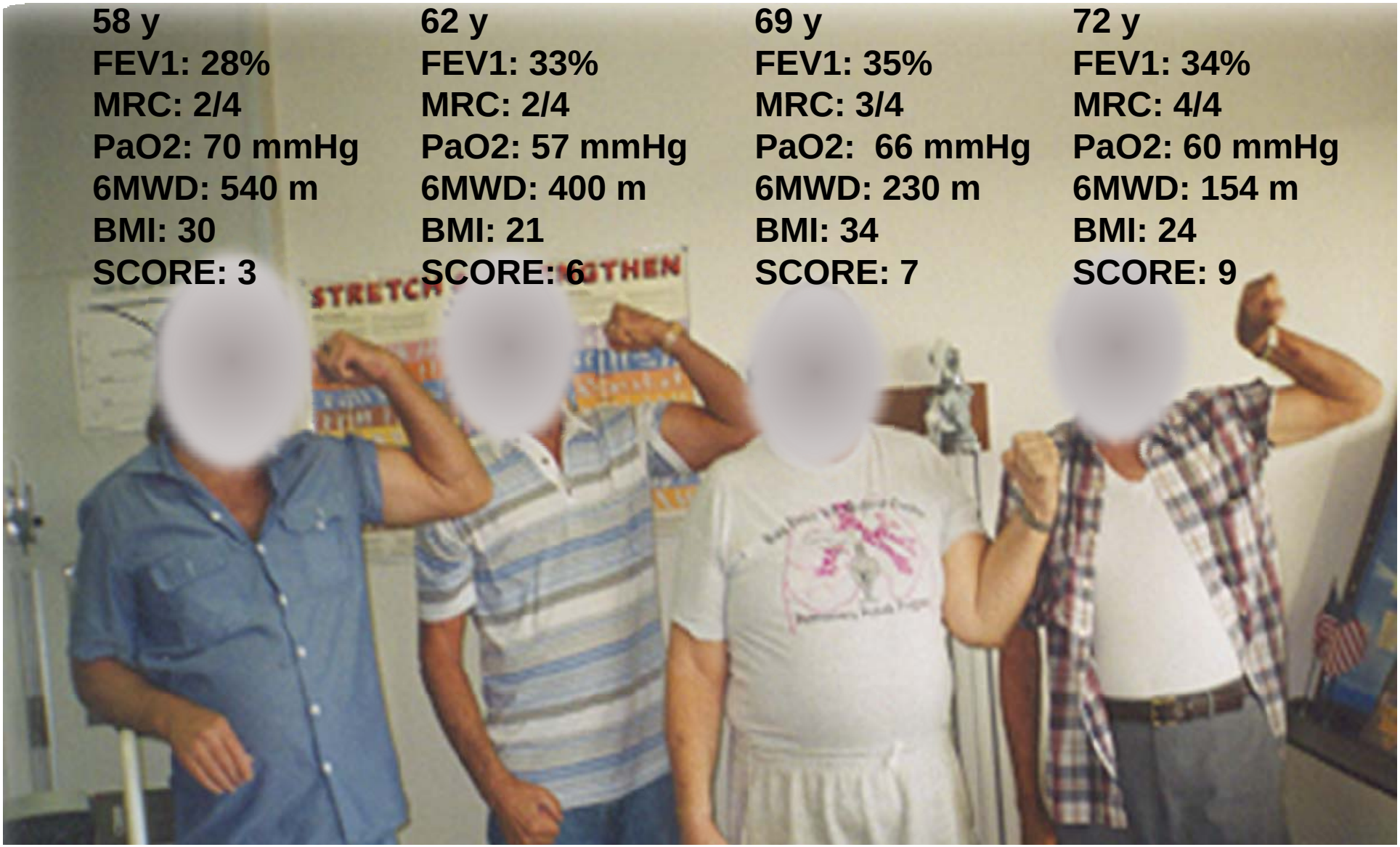
Cote & Celli

PT # 1	PT # 2	PT # 3	PT # 4
58 y	62 y	69 y	72 y
FEV1: 28%	FEV1: 33%	FEV1: 35%	FEV1: 34%

“COPD HETEROGENEITY”

Cote & Celli

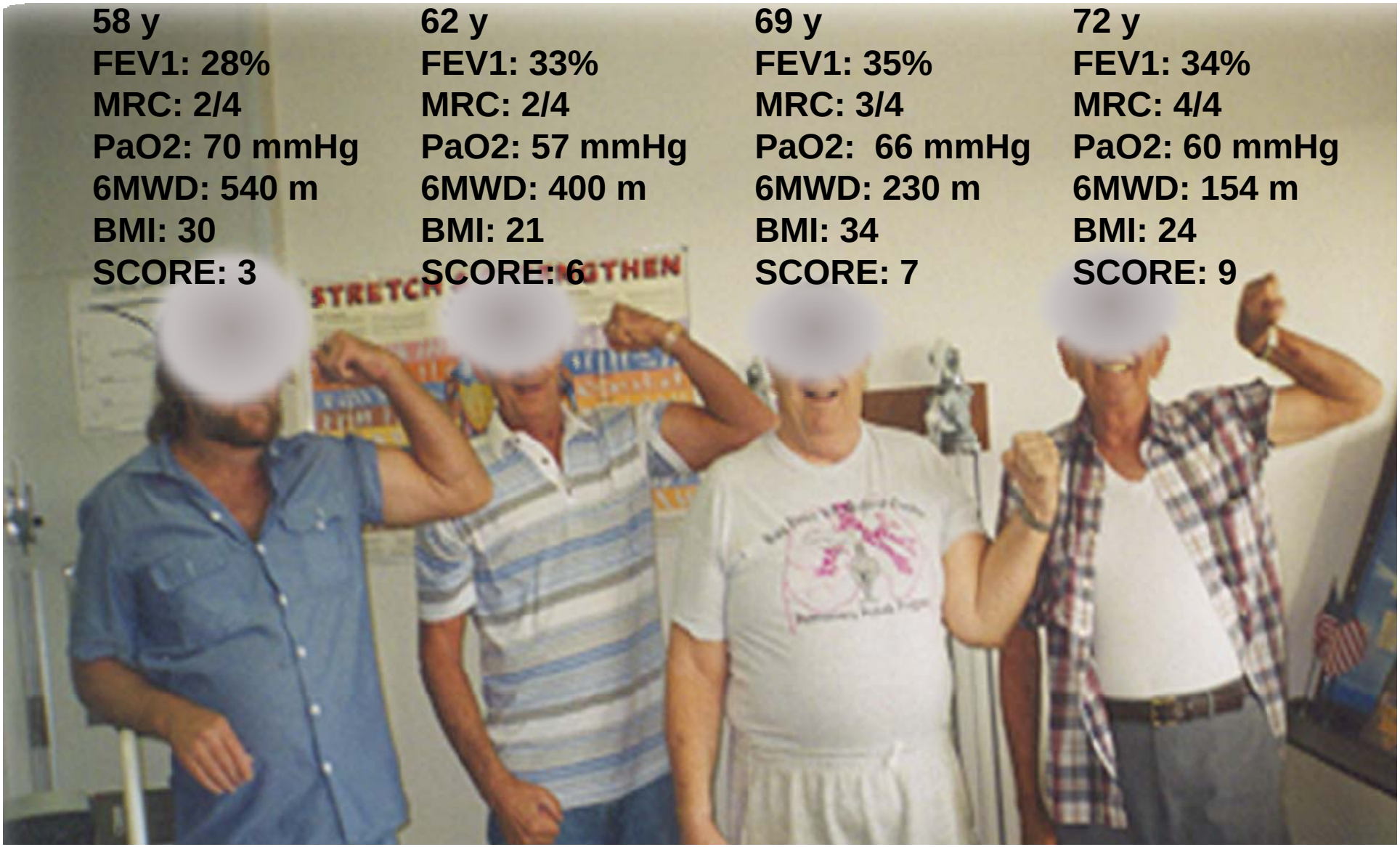
PT # 1	PT # 2	PT # 3	PT # 4
58 y	62 y	69 y	72 y
FEV1: 28%	FEV1: 33%	FEV1: 35%	FEV1: 34%
MRC: 2/4	MRC: 2/4	MRC: 3/4	MRC: 4/4
PaO2: 70 mmHg	PaO2: 57 mmHg	PaO2: 66 mmHg	PaO2: 60 mmHg
6MWD: 540 m	6MWD: 400 m	6MWD: 230 m	6MWD: 154 m
BMI: 30	BMI: 21	BMI: 34	BMI: 24
SCORE: 3	SCORE: 6	SCORE: 7	SCORE: 9



“COPD HETEROGENEITY”

Cote & Celli

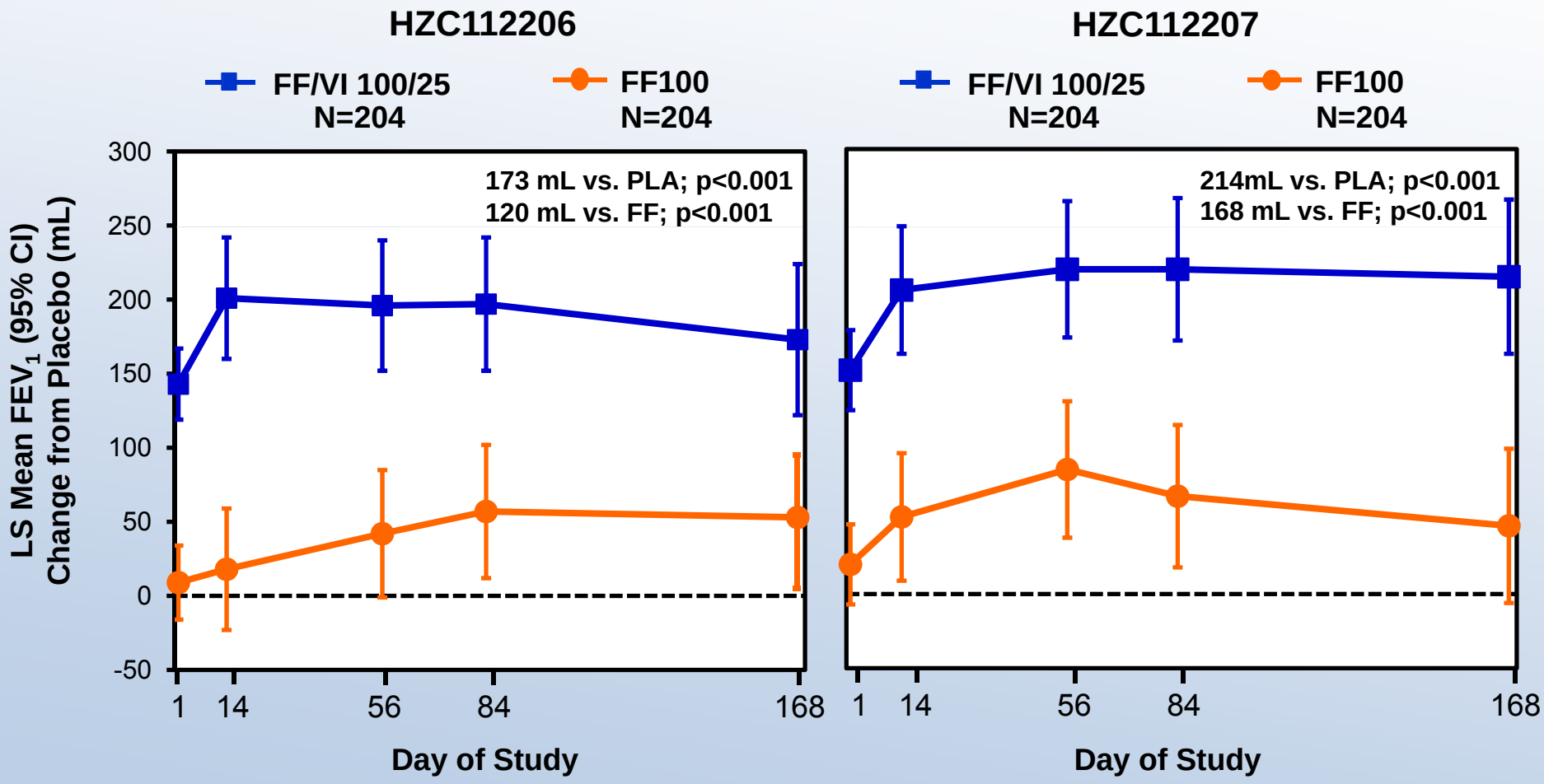
PT # 1	PT # 2	PT # 3	PT # 4
58 y	62 y	69 y	72 y
FEV1: 28%	FEV1: 33%	FEV1: 35%	FEV1: 34%
MRC: 2/4	MRC: 2/4	MRC: 3/4	MRC: 4/4
PaO2: 70 mmHg	PaO2: 57 mmHg	PaO2: 66 mmHg	PaO2: 60 mmHg
6MWD: 540 m	6MWD: 400 m	6MWD: 230 m	6MWD: 154 m
BMI: 30	BMI: 21	BMI: 34	BMI: 24
SCORE: 3	SCORE: 6	SCORE: 7	SCORE: 9



Closing Remarks

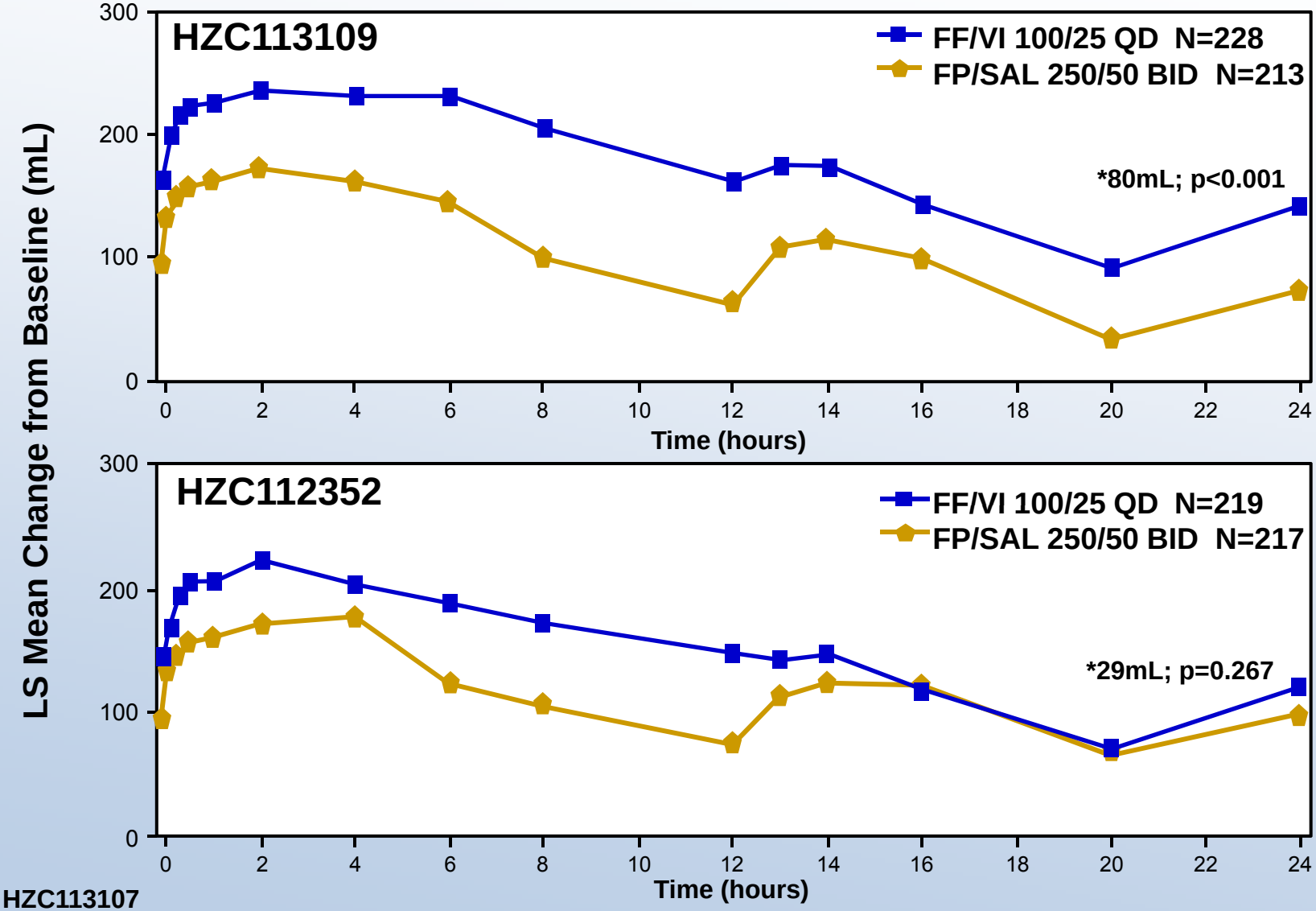
Katharine Knobil, MD

Effect of BREO ELLIPTA 100/25 Difference in 0-4hr Weighted Mean FEV_1 6-Month Lung Function Studies



Martinez et al. Resp Med 2013;107:550-59.
Kerwin et al. Resp Med 2013 ;107:560-69.

24-Hour Serial FEV_1 on Day 84
FF/VI 100/25 vs. FP/SAL 250/50

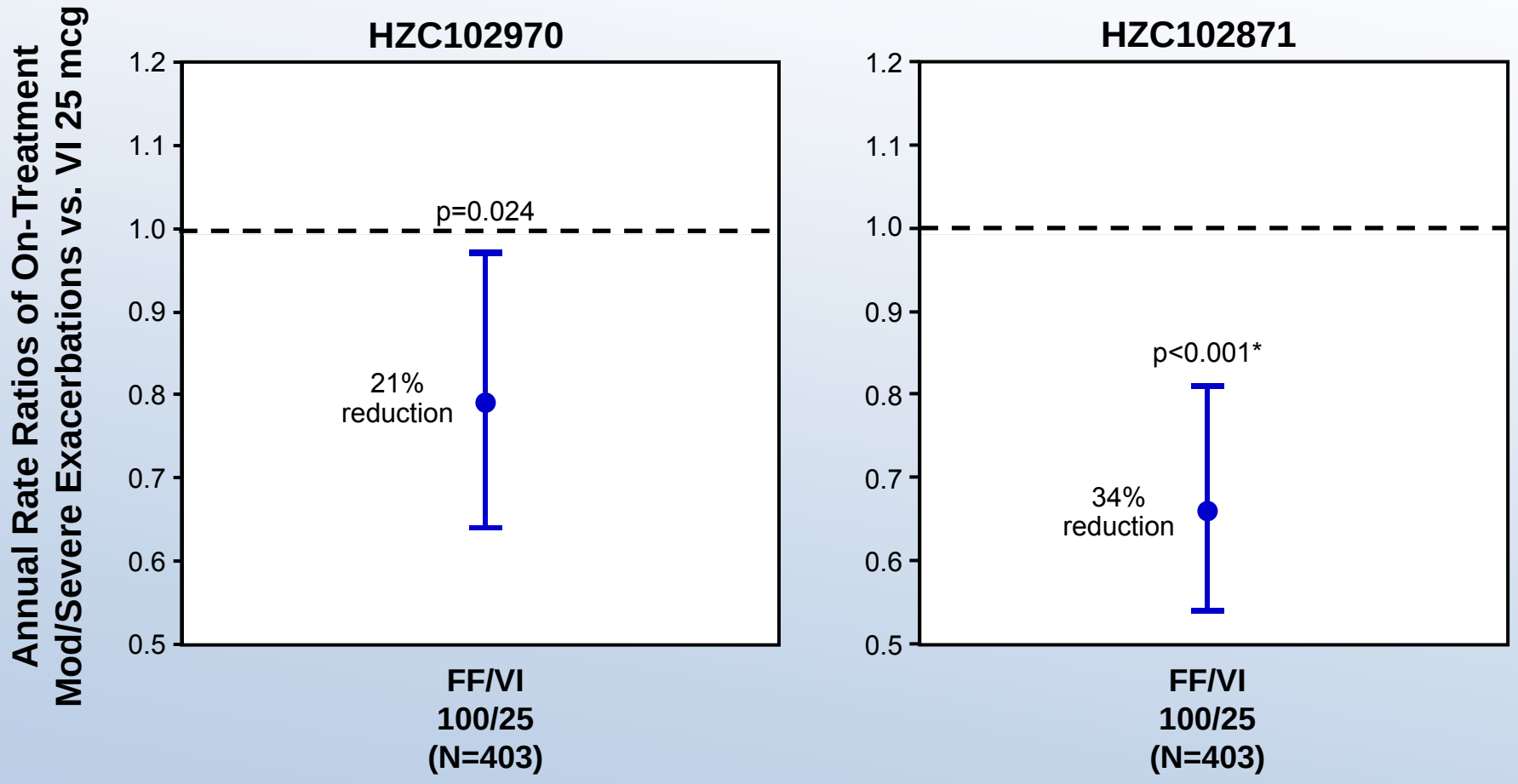


HZC113107

FF/VI 100/25 (N=224) vs. FP/SAL 500/50 (N=233) difference=*22mL; p=0.282

* 24-hour weighted mean FF/VI vs. FP/SAL

Primary Endpoint: Moderate and Severe Exacerbations Annual Rate Ratios FF/VI 100/25 vs. VI 25mcg 1-Year Exacerbation Studies



***nominal p-value**

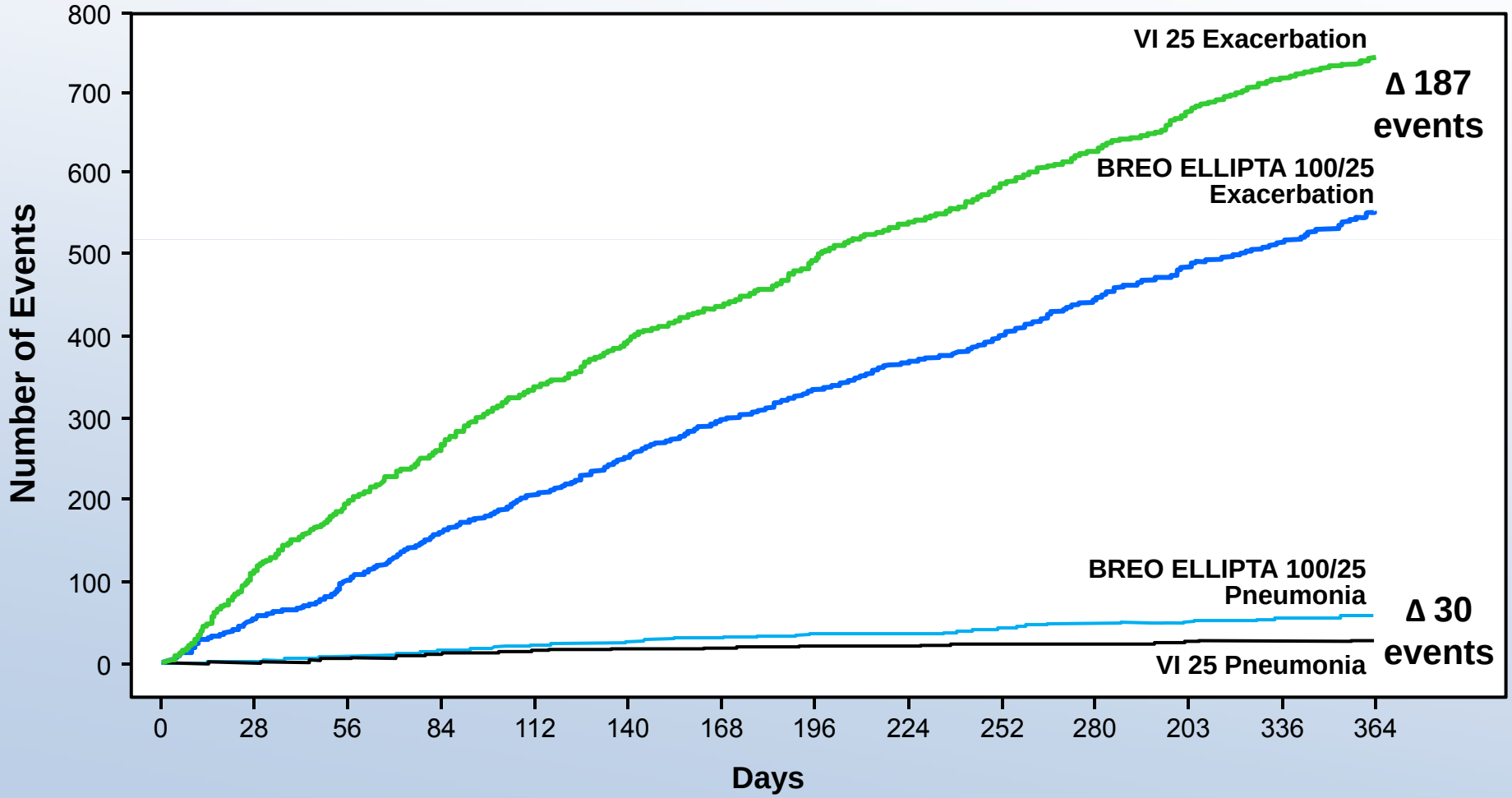
Annual Rate Reduction FF/VI 100/25 vs. VI 25mcg Integrated 1-Year Exacerbation Studies = 27%

Safety Profile Well Characterized

- Large safety database
- No evidence of tremor, hypertension, or effects on potassium
- No increase in ocular effects, effect on HPA axis, or serum glucose
- No evidence of an increase in cardiovascular events
- Increase in oral candidiasis
- Increase in fractures and pneumonias
  - generally consistent with the safety profile of established ICS/LABA combinations

Need to weigh the benefits, including reducing exacerbations, with the risks, including pneumonia

Benefit and Risk
Cumulative On-treatment Pneumonia and Exacerbation Events for BREO ELLIPTA 100/25 and VI 25



Studies HZC102871 & HZC102970

BREO ELLIPTA 100/25
Proposed Indication

"BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) ***indicated for the long-term once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD),*** *including chronic bronchitis and/or emphysema. BREO ELLIPTA is also indicated* ***to reduce exacerbations of COPD in patients with a history of exacerbations.***

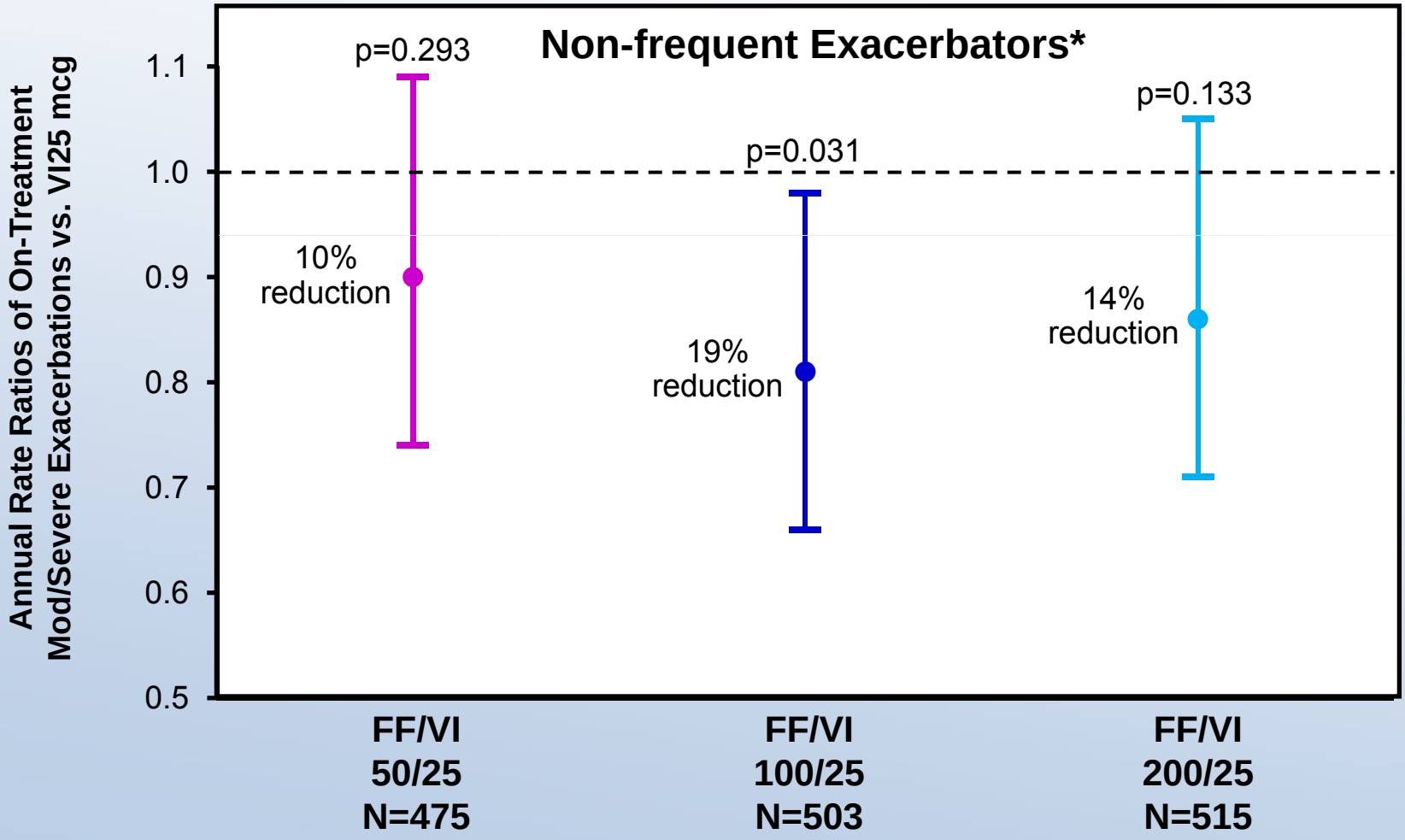
Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

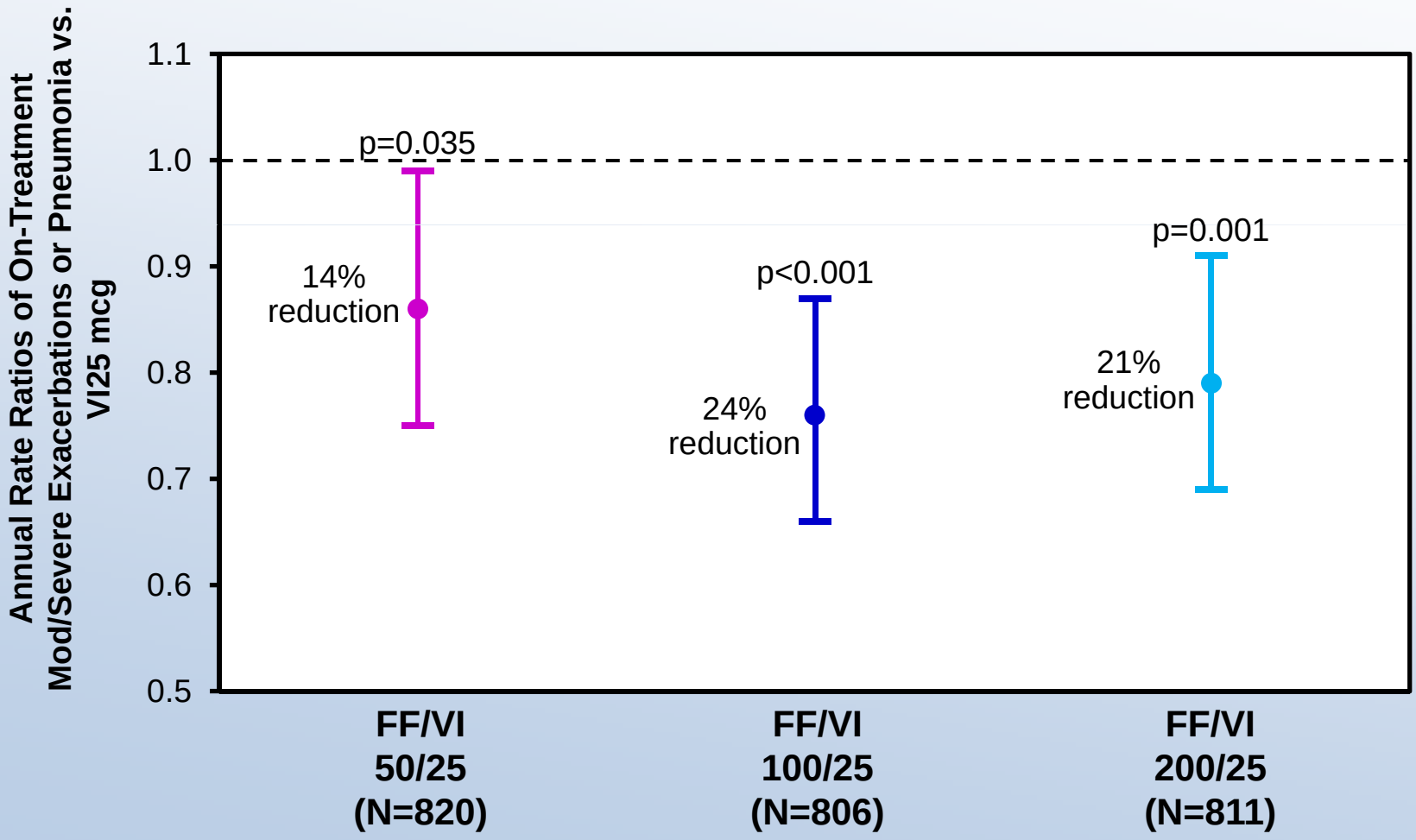
BACK UP SLIDES

Overlap of AE Pneumonia and COPD Exacerbation Events (HZC102970 & HZC102871)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818	Total N=3255
Either moderate/severe COPD exacerbation or AE/SAE pneumonia	677	584	629	751	2641
Either severe COPD exacerbation or SAE pneumonia	88	93	78	87	346
Either fatal COPD exacerbation or fatal pneumonia	3	2	9	3	17

Moderate and Severe Exacerbations vs. VI 25mcg Non-frequent Exacerbators (HZC102970 and HZC102871)



*39% of subjects were frequent exacerbators (≥2 exacerbations/prior year)

Analysis of On-treatment Moderate or Severe COPD Exacerbations or Pneumonia (HZC102970 and HZC102871)