NUCALA®
Mepolizumab for Patients with COPD

Introduction

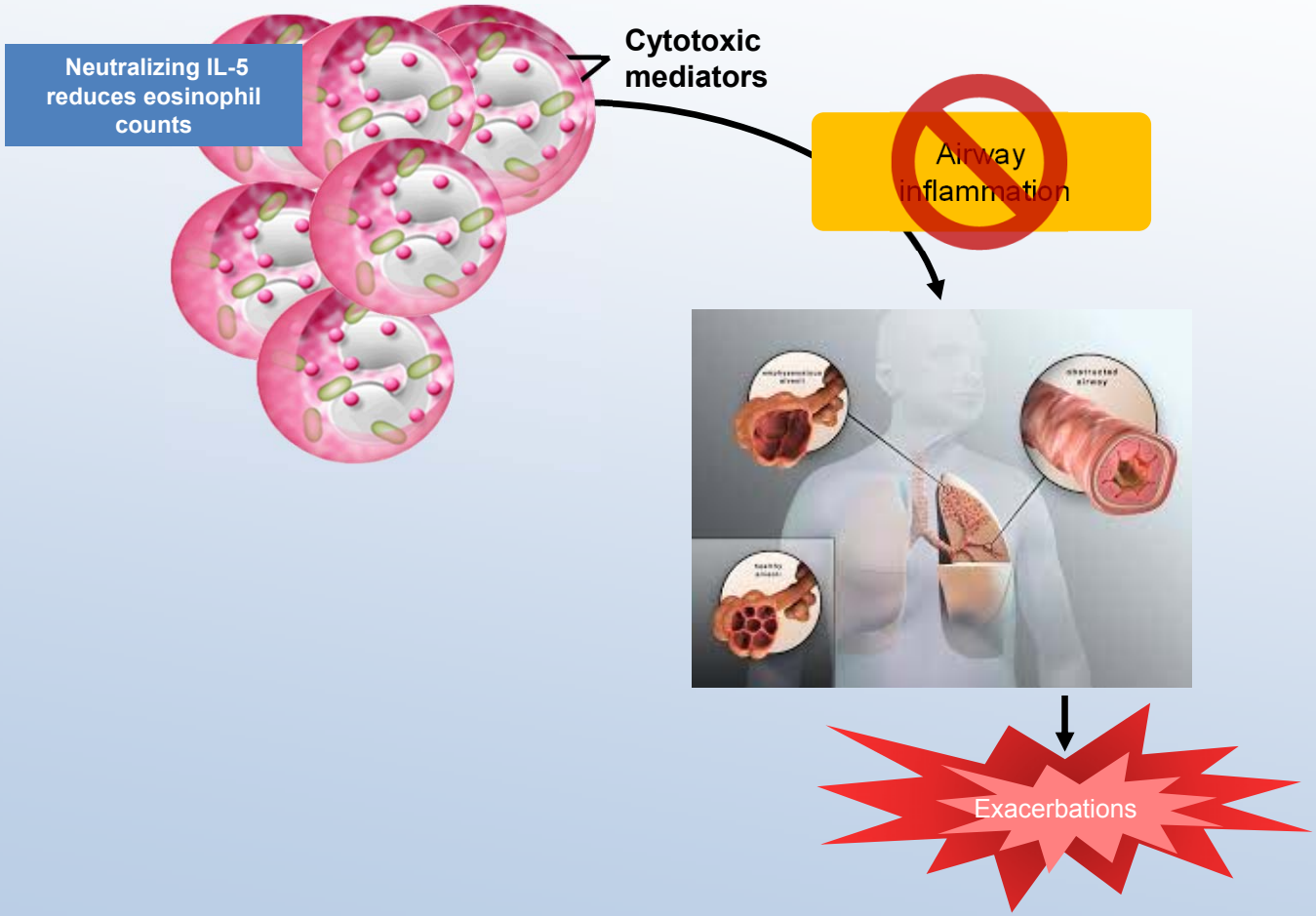
Steven Yancey, MS
Vice President, Medicines Development Leader
GlaxoSmithKline

Chronic Obstructive Pulmonary Disease

- COPD
  - Emphysema
  - Chronic bronchitis
- Treatment Strategies
  - Smoking cessation
  - Medications
  - Avoidance of risk factors
  - Pulmonary Rehab
- Symptoms (frequency and intensity vary by severity)
  - Breathlessness
  - Sputum
  - Chronic cough due to narrowing airways
  - 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.

The Mechanism by Which Mepolizumab Attenuates Eosinophil Inflammation and Exacerbation Frequency

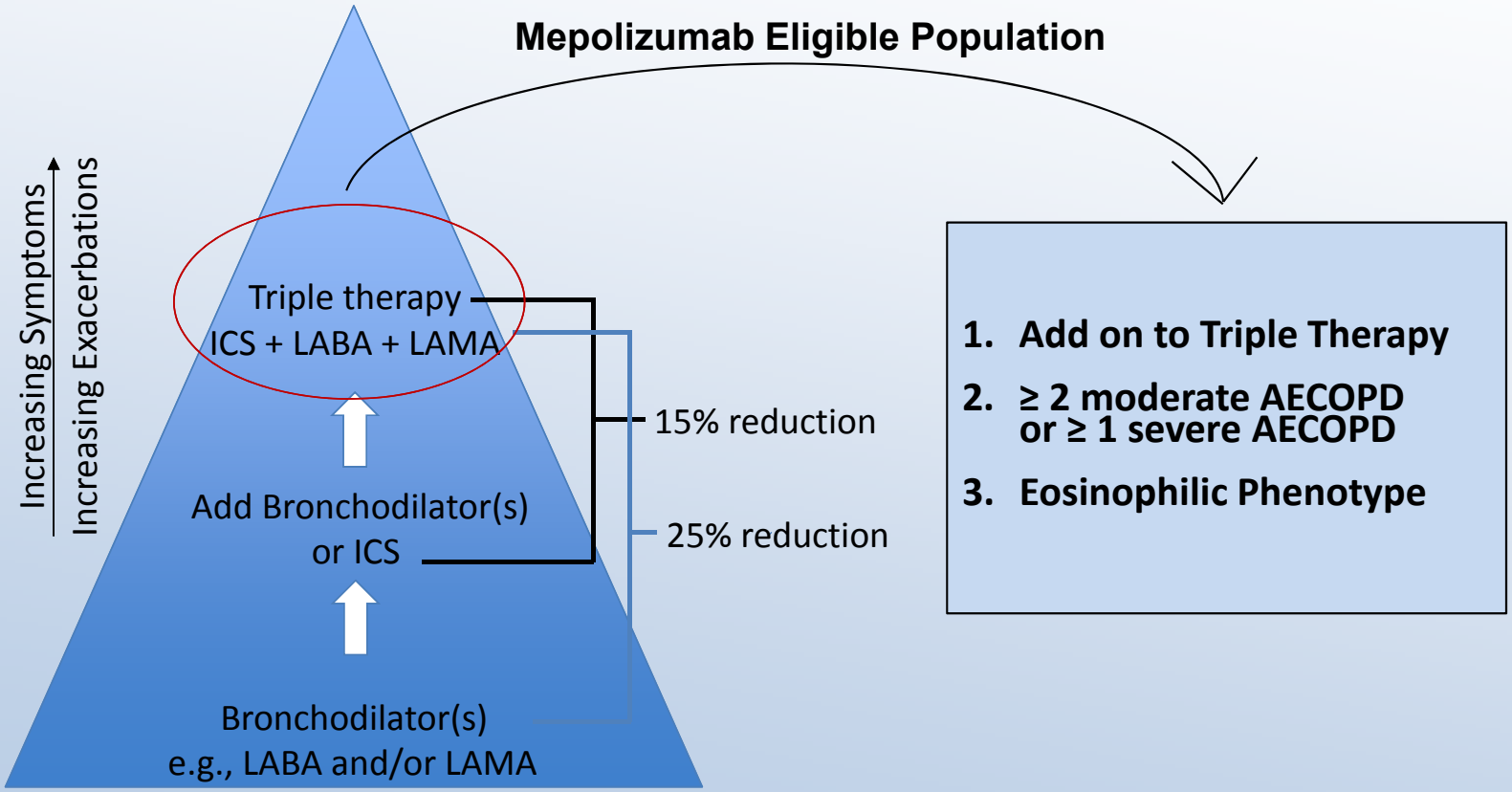


Outcomes Resulting from COPD Exacerbations

Outpatients	**13%-33% require additional intervention within 14d[1]** **71% increased risk of future exacerbation following 1 moderate exacerbation/yr[2]** **10% increased risk of death following 2 moderate exacerbation/yr[2]**
ER patients	**82% readmitted to ER within 30d[3]**
Hospitalized patients	**Up to 6 months to recover** **64% readmitted within 1 year[4]** **26% die within 1 year[5]**
Economic	**15.4 million office visits, 739,000 hospitalizations[5]** **50%-75% COPD costs are for services associated with exacerbations[6]**

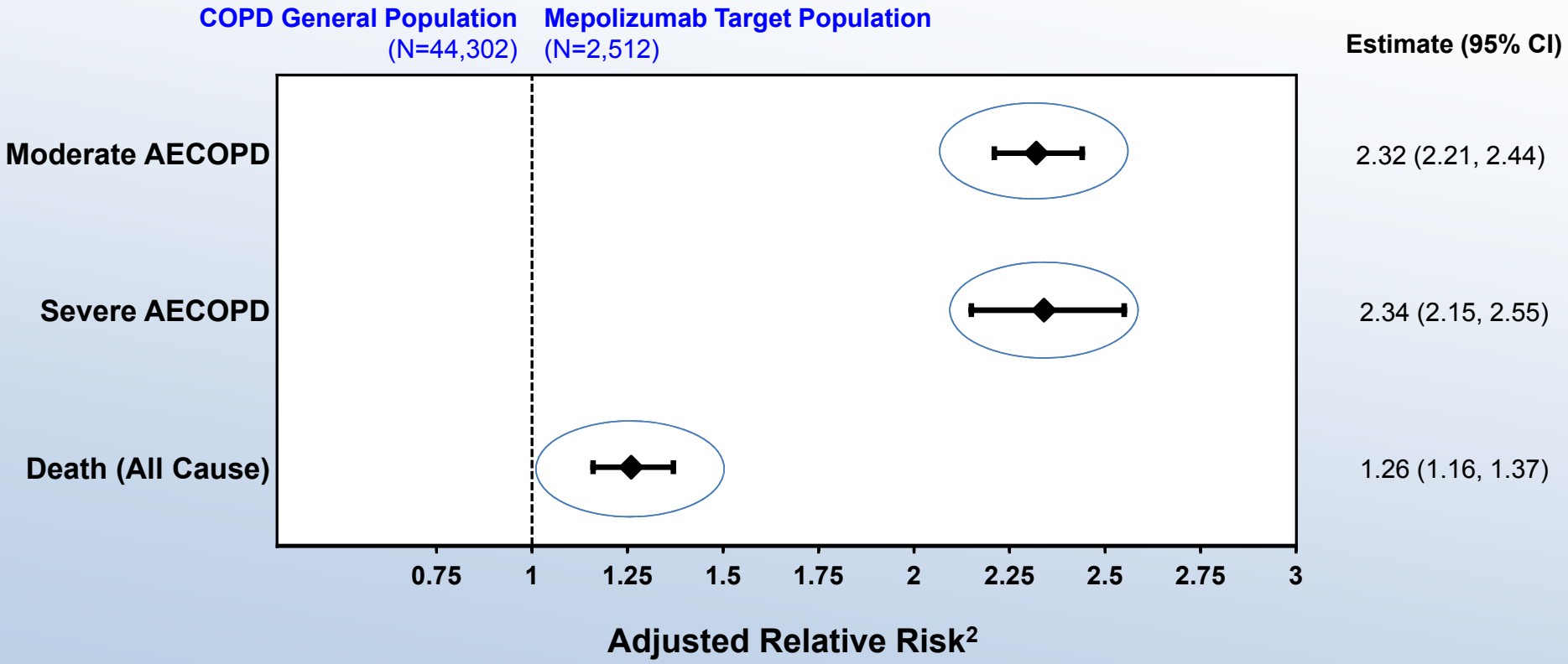
(1) Adams *Chest.* 2000; 117:1345-1352; (2) Rothnie *Am J Respir Crit Care Med*. 2018 Feb 23 [Epub]; (3) Razaee *Int J COPD.* 2018; 13: 109-120; (4) Lindenaeur *Am J Respir Crit Care Med.* 2018; 197(8):1009-1017; (5) www.nhlbi.nih.gov/files/docs/research/2012_ChartBook_508.pdf (6) Celli *Eur Respir J.* 2004 Jun;23(6):932-46

Effectiveness of Current Treatments in Reducing Exacerbation Risk



Lipson et al. *N Engl J Med* 2018; 378:1671-1680, Modified from GOLD 2017

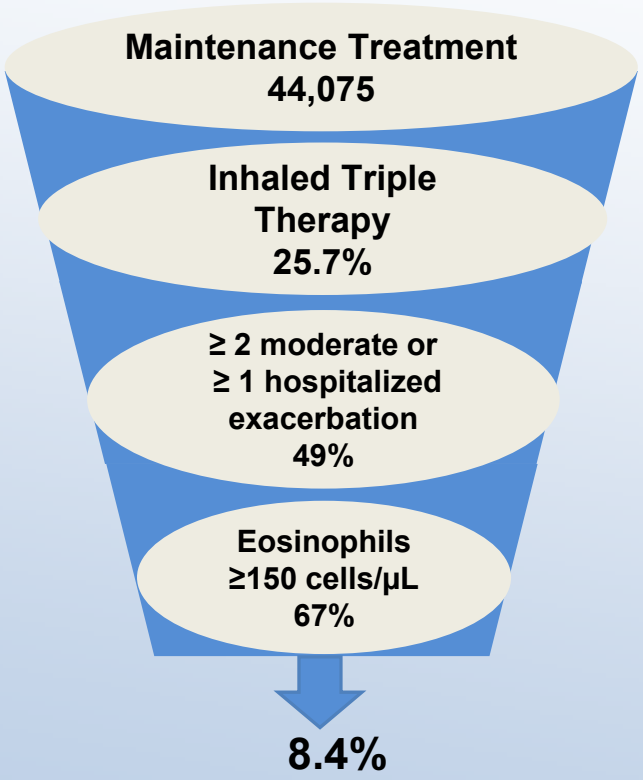
Mepolizumab Eligible Population[1] Experience Significantly Worse Outcomes Compared to the Overall COPD Population



[1] Mepolizumab target population (N=2,512) were patients with COPD, with ≥2mod/≥1sev exacerbation, currently treated with multiple inhaler triple therapy and with current blood eosinophil values ≥150 cells/μL compared with COPD patients identified as not a target for mepolizumab ('not eligible'), N=44,302.

[2] Rate ratios for exacerbations and hazard ratios for mortality adjusted for age, gender, geographical region in England, body mass index, smoking status, comorbidities, index of multiple deprivation, primary care consultations in prior year, and season of index date

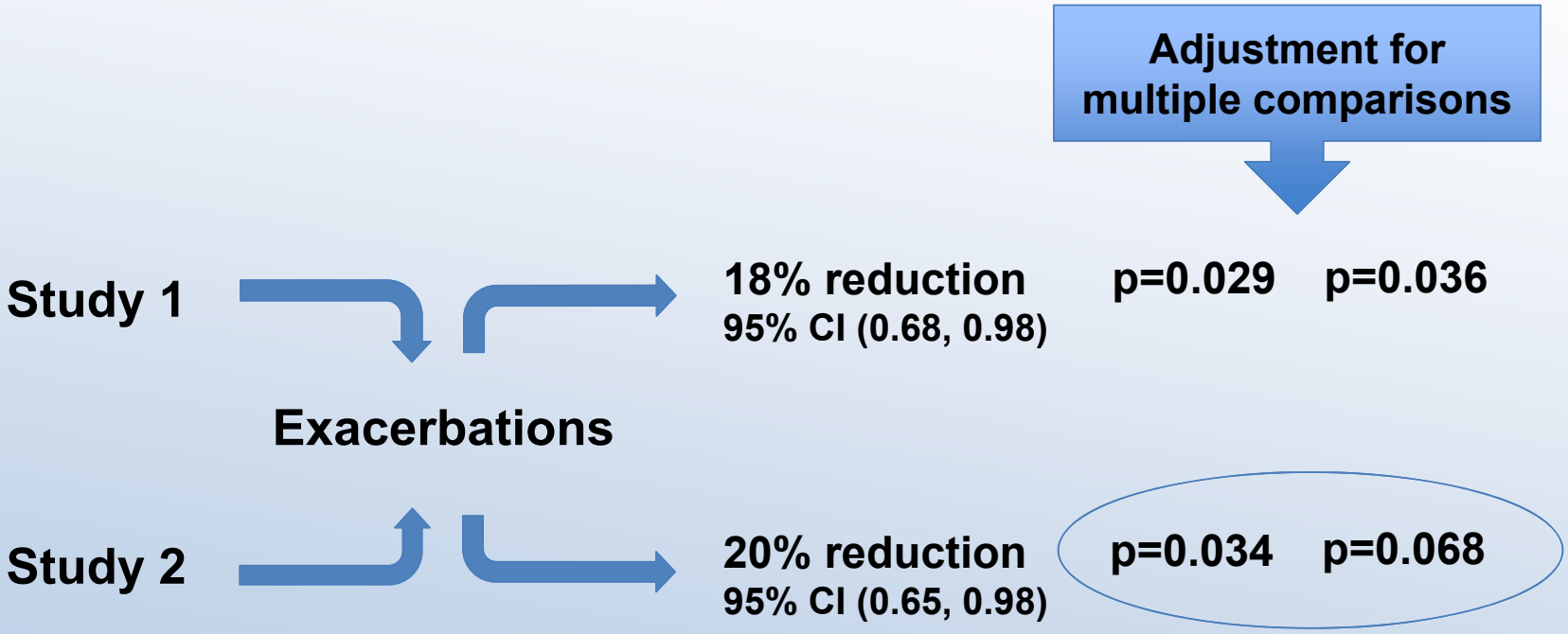
Stratifying Treatment to a Small, Identifiable US COPD Sub-population



COPD population was limited to patients with at least one eosinophil value and the following study inclusion criteria: ≥1 claim for COPD, ≥40 years of age, continuous enrollment for 12 months and ≥1 dispensing/encounter of any inhaled maintenance therapy

Source: DOF #2018N364677_00

High Unmet Need for a Medicine that can Reduce COPD Exacerbations



Pavord et al. *N Engl Med* 2018; 377:1633-1629

Agenda

Eosinophilic COPD	**Ian Pavord, MD** Institute for Lung Health Professor of Respiratory Medicine at Oxford University Oxford, UK
Clinical Efficacy	**Eric Bradford, MD** Director, Project Physician Lead GlaxoSmithKline
Clinical Safety	**Olga Gumieniak, MD, MMSc** Medical Director Global Clinical Safety and Pharmacovigilance GlaxoSmithKline
Physician's Perspective	**Gerard Criner, MD** Professor and Chair, Thoracic Medicine and Surgery Lewis Katz School of Medicine at Temple University Philadelphia, PA
Closing Comments	**Steve Yancey, MS** Vice President, Medicines Development Leader GlaxoSmithKline

Eosinophilic Airway Inflammation as a Treatable Trait in COPD

Ian Pavord

Professor of Respiratory Medicine

University of Oxford

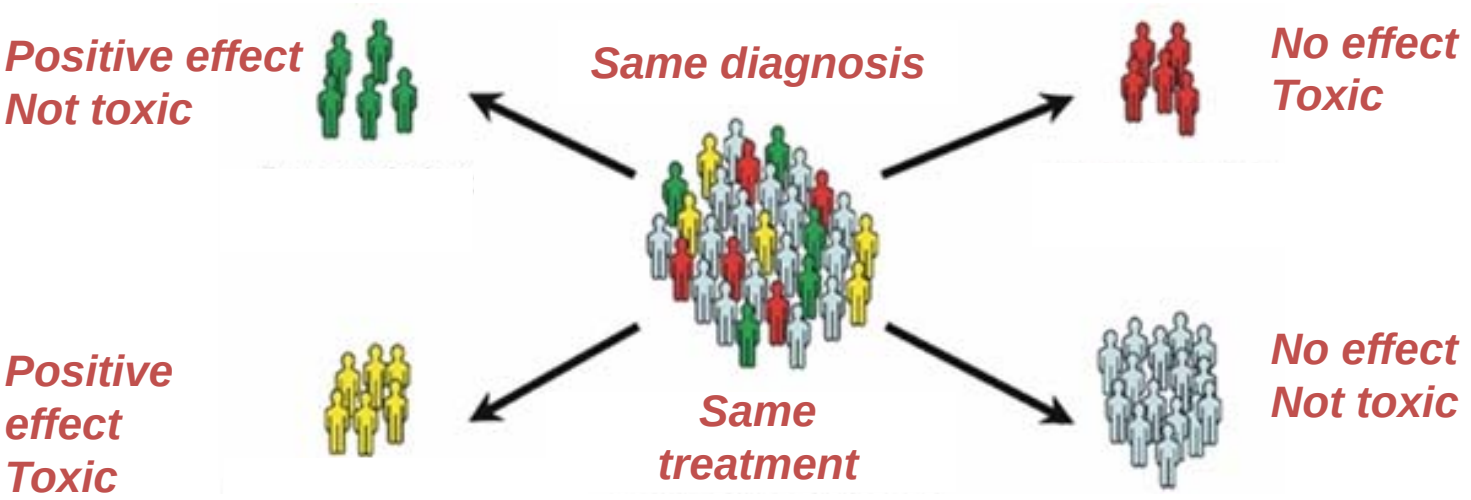
Honorary Consultant Physician

University of Oxford Hospitals NHS Trust

Disclosures

- **Speaker's honoraria:** AstraZeneca, Boehringer Inglehiem, Aerocrine, Chiesi, Novartis and GSK.
- **Advisory panels:** Almirall, AstraZeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp, Regeneron.
- **Sponsorship:** Boehringer Ingelheim, GSK, Astra Zeneca, Chiesi and Napp.

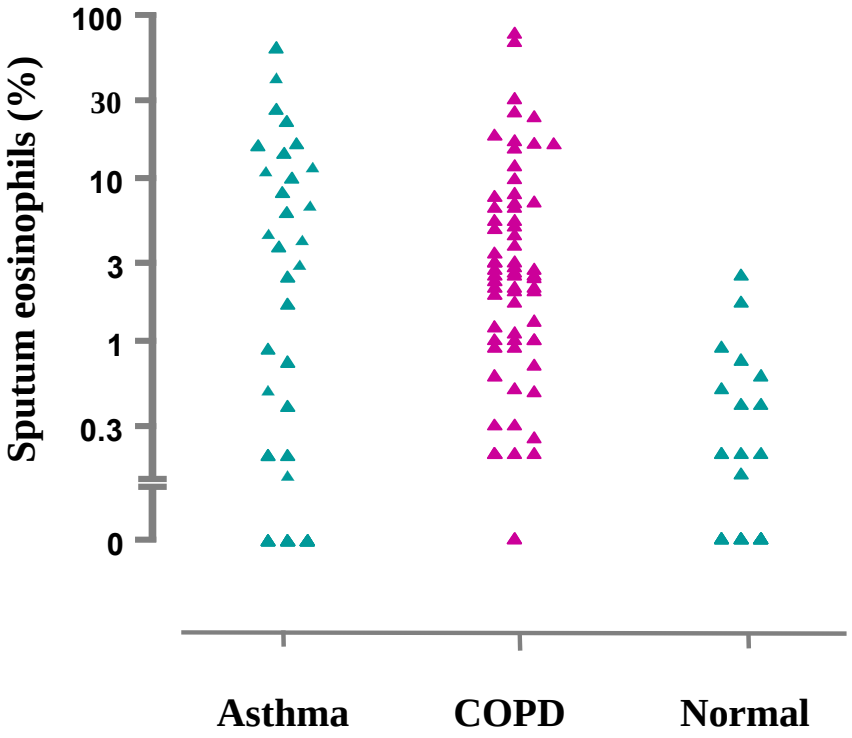
Precision Medicine and Treatable Traits



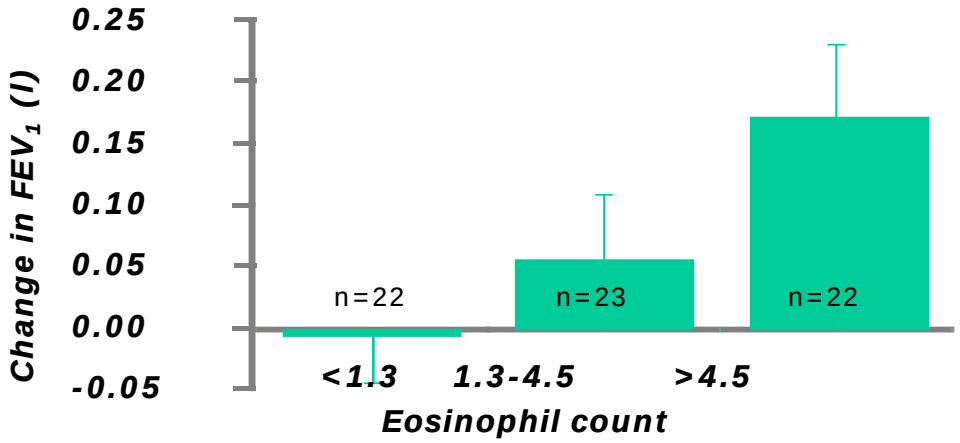
- Treatable trait is a measureable disease characteristic that can be modified, resulting in clinical benefit.

C. Vogelmeier (with permission); Agusti et al. Eur Respir J 2016; 2016;47:410-9

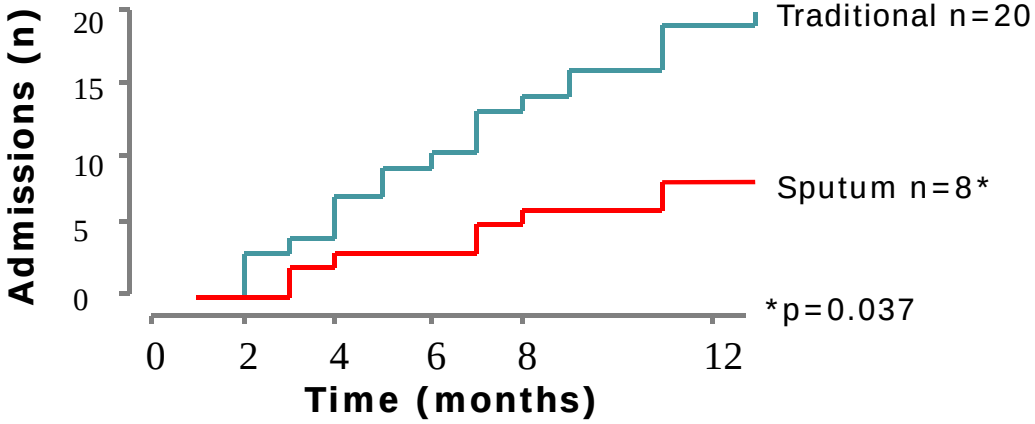
Sputum eosinophil counts in COPD



Brightling et al. Lancet 2000;356:1480-85;
Green et al. Thorax 2002; 57:875-879

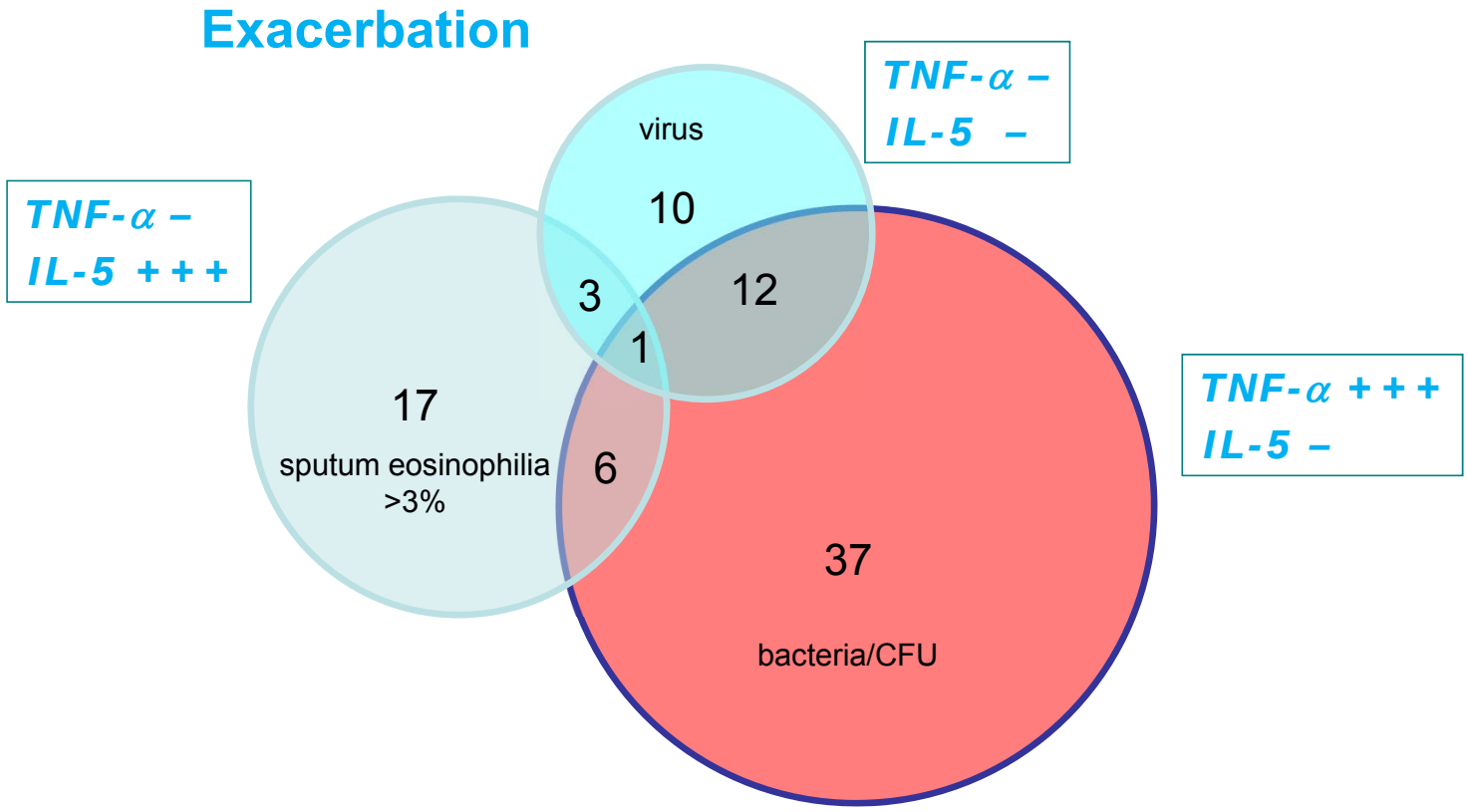


Brightling et al. Lancet 2000;356:1480-85



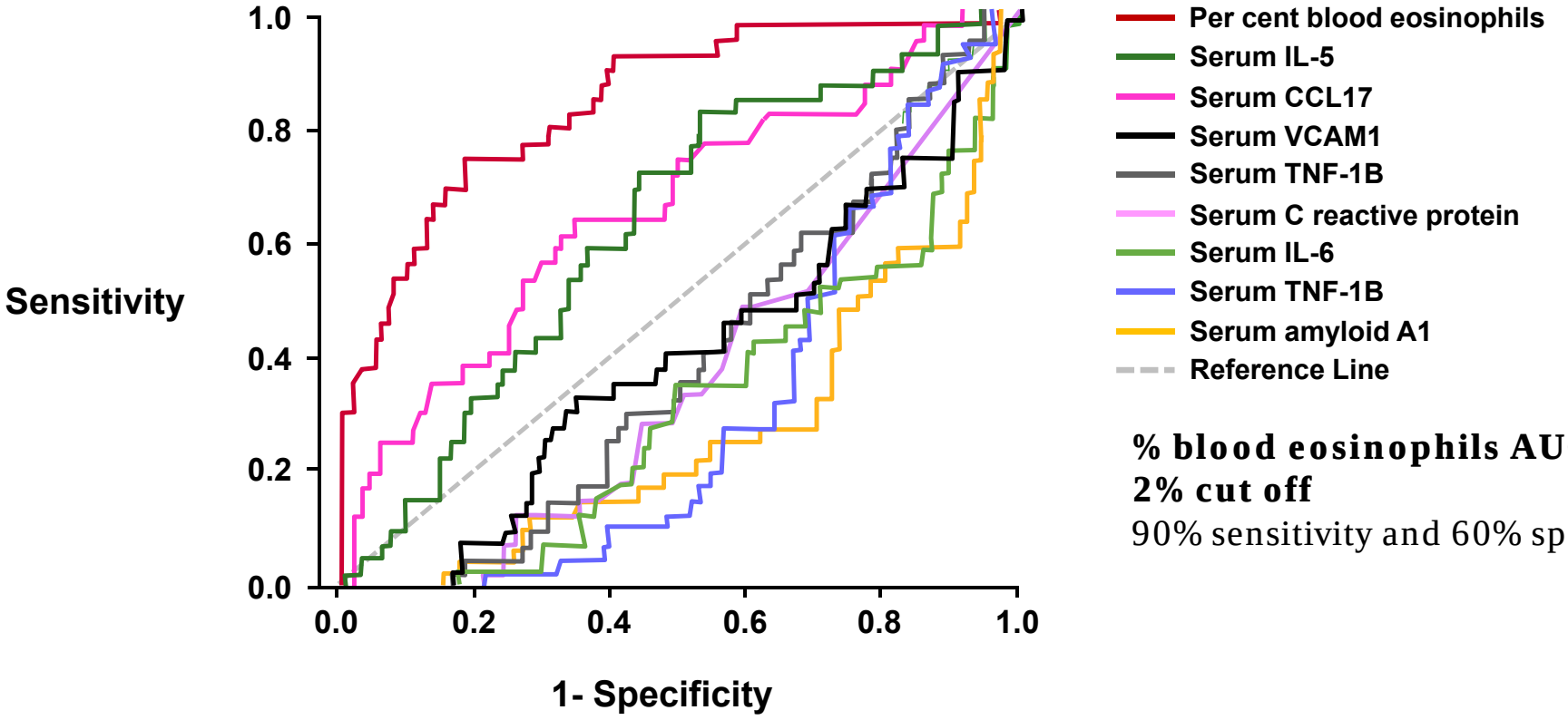
Siva et al. Eur Respir J 2007; 29:906-913

Exacerbations of COPD: they look the same clinically but have distinct biology



Adapted from: Bafadhel et al. Am J Respir Crit Care Med 2011;184:662-71

Blood Eosinophils as a Biomarker of Eosinophilic Exacerbations



% blood eosinophils AUC=0.85
2% cut off
90% sensitivity and 60% specificity

Bafadhel M et al. Am J Respir Crit Care Med 2011;184:662-71

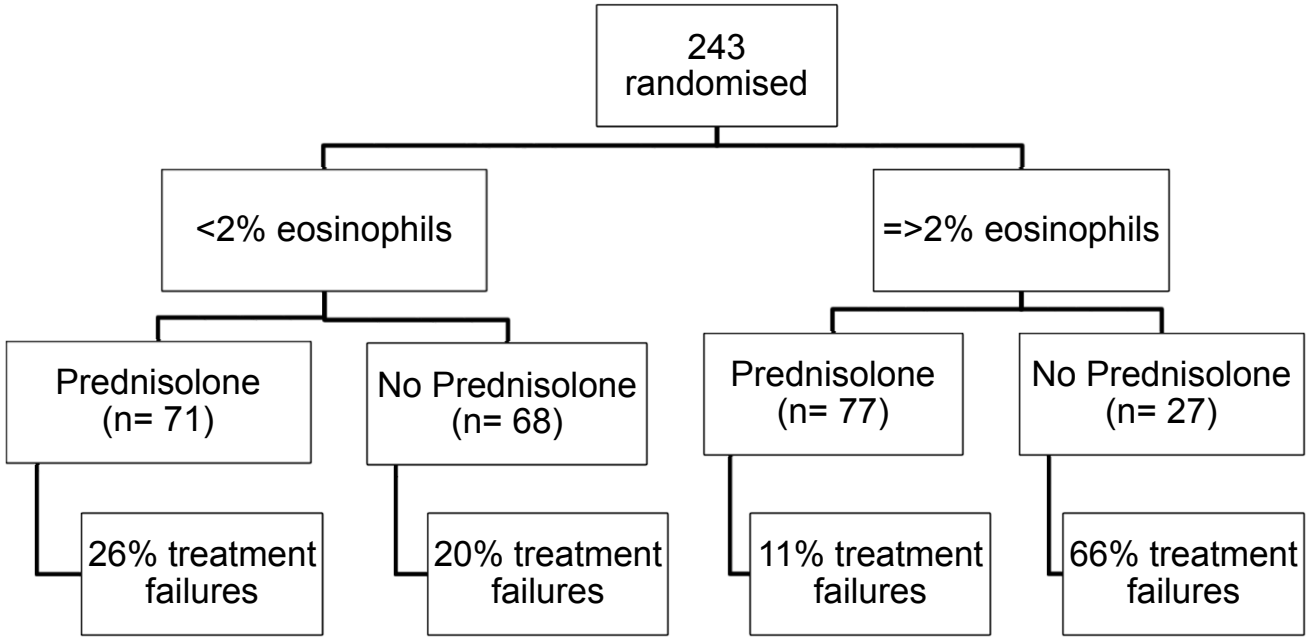
Eosinophilic COPD Exacerbations Are Identifiable and Repeatable: The AERIS Study

- Analysis of 101 patients and 161 exacerbations
- Analysis looked at different COPD exacerbation types* and probability that a prior exacerbation predicted the phenotype of the next exacerbation
- Approximately 24% of all COPD exacerbations in the first year of AERIS were defined as eosinophil-associated events
- Results suggest that if a prior exacerbation in a patient is eosinophil-associated the subsequent exacerbation is more likely to be eosinophil-associated and vice-versa

*Definition of Bacteria-, Virus-, and Sputum Eosinophil–associated Exacerbations of COPD
Bacteria-associated exacerbations were defined as a positive bacterial pathogen on routine culture
A virus-associated exacerbation was defined as one that had a positive sputum viral PCR, whether in isolation or in combination with a positive bacterial pathogen on routine culture.
A sputum eosinophil–associated exacerbation was defined as the presence of more than 3% nonsquamous cells.

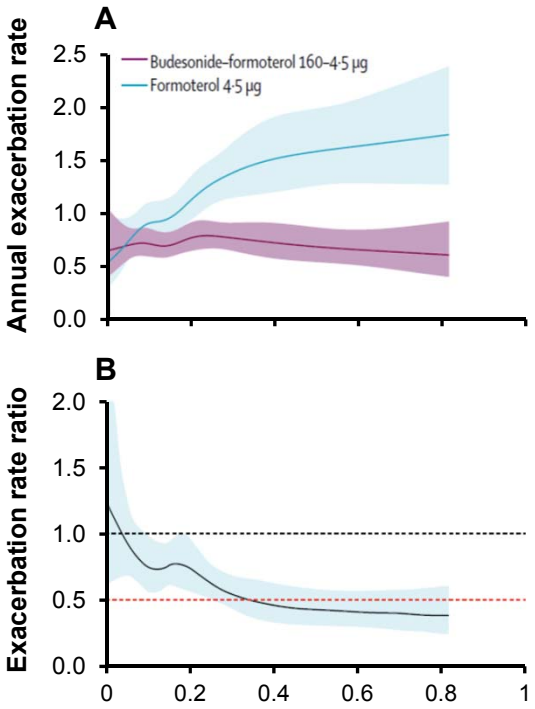
Mayhew et al., Thorax 73:422-430 (2018)

Blood eosinophil directed management of COPD exacerbations: a meta-analysis

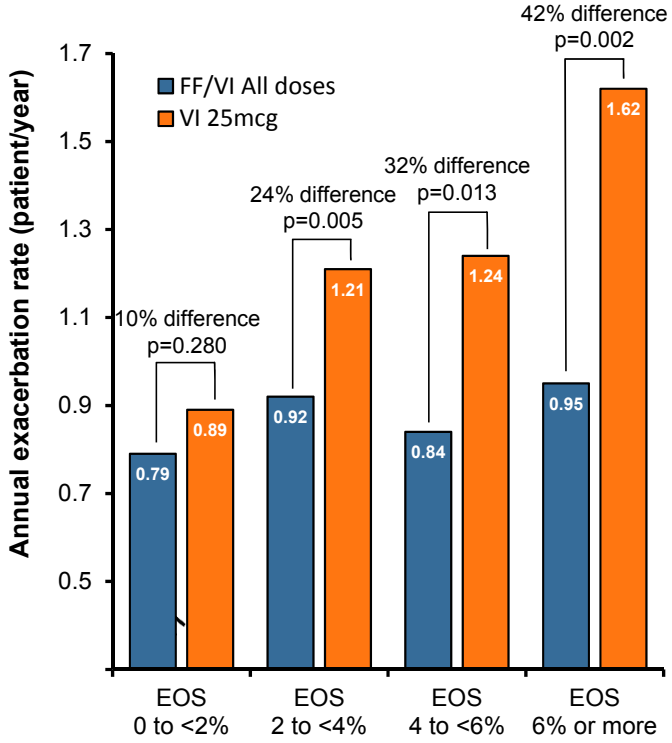


Bafadhel et al. Eur Respir J 2014;44:789-791

Post-hoc analyses of ICS/LABA vs LABA Trials Show Consistent Evidence of Blood Eosinophil Related Risk and Beneficial Effect of ICS



N=4528



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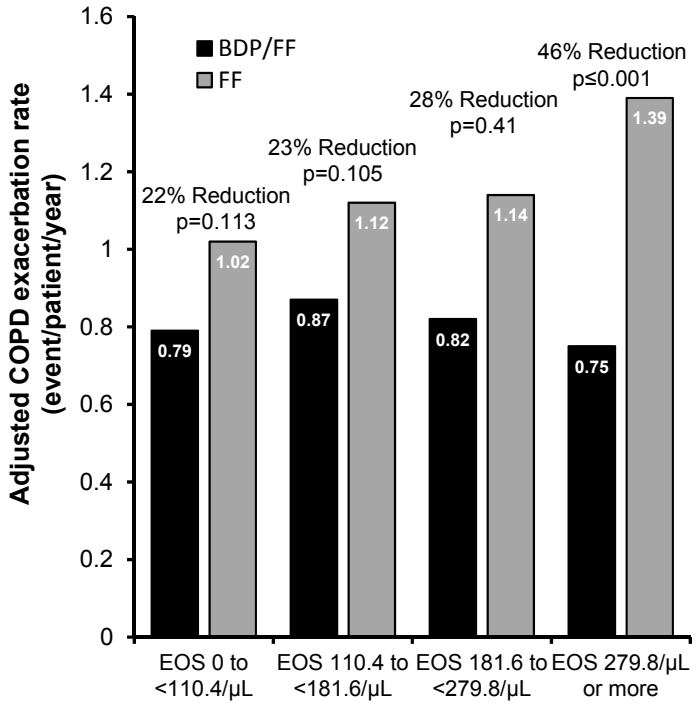
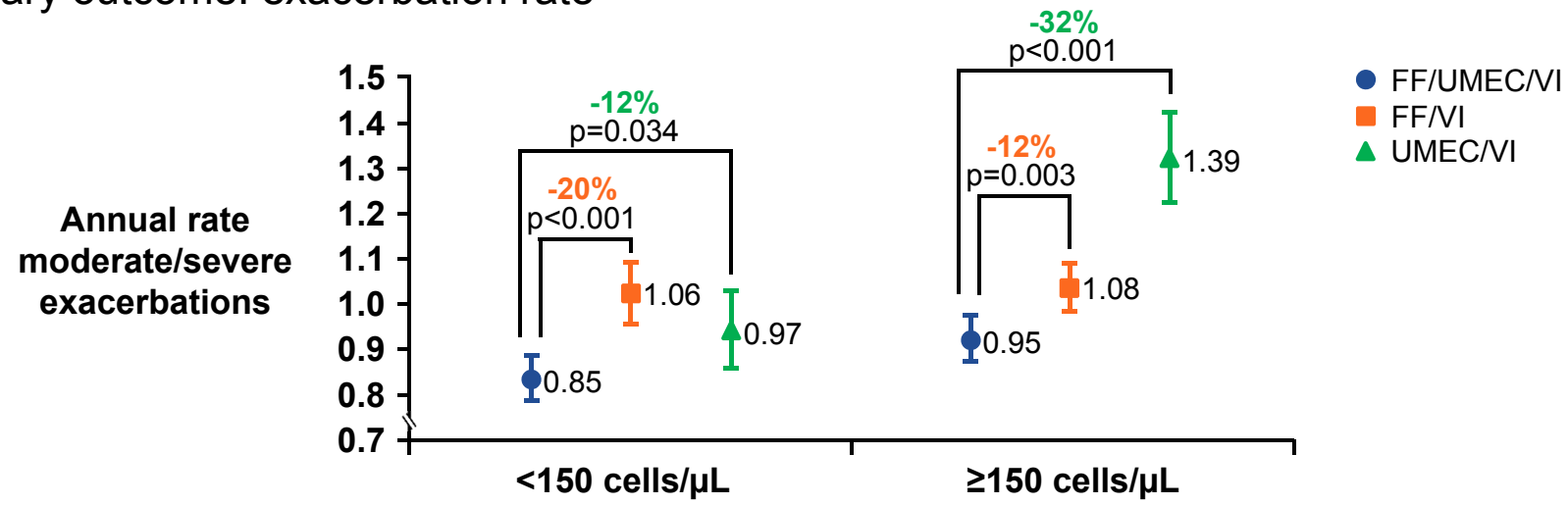


N=1184

Bafadhel et al. Lancet Resp Med 2018;6:117-126; Pascoe et al. Lancet Resp Med 2015;3:435-42; Siddiqui et al. Am J Respir Crit Care Med 2015;192:523-5

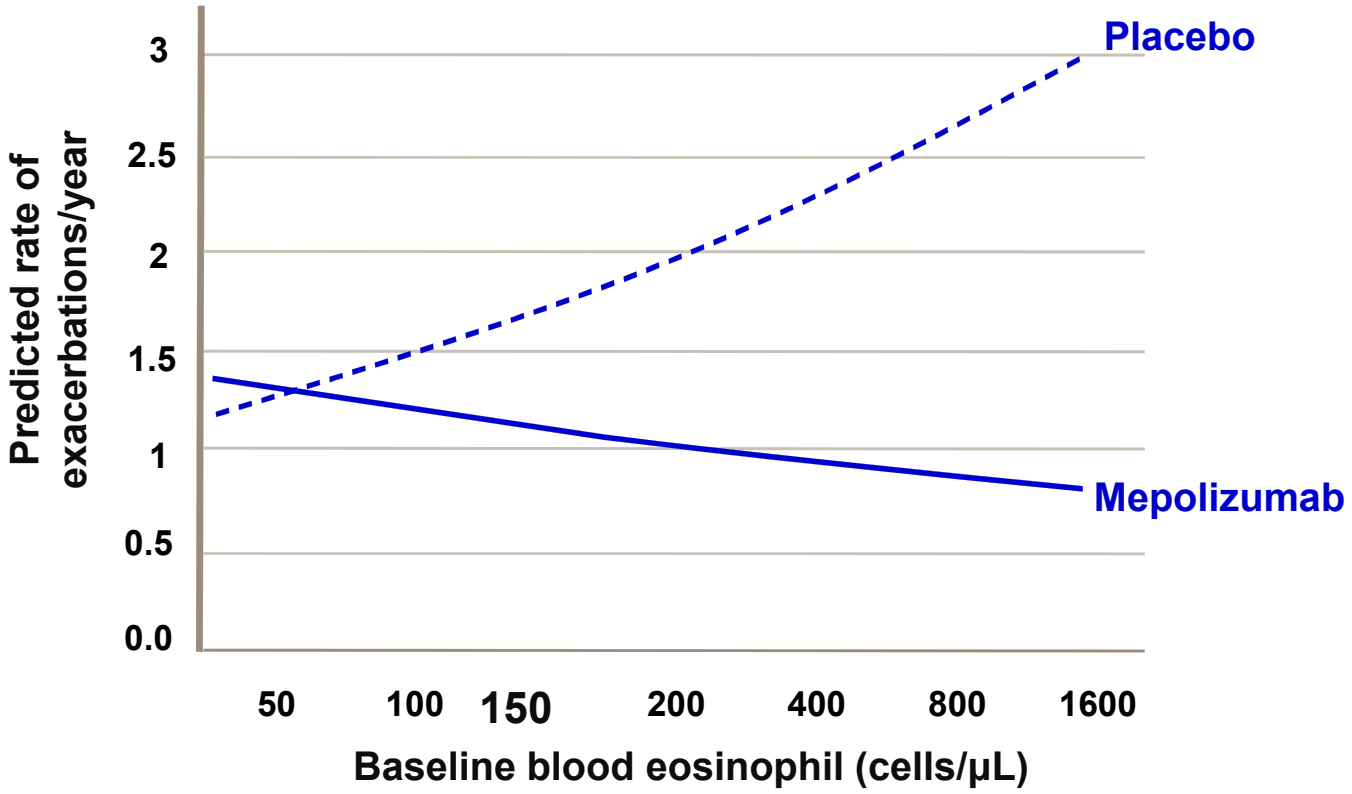
Prospective validation: the IMPACT study

- Once-daily combination of fluticasone furoate (FF,100 µg), umeclidinium (UMEC,62.5 µg), and vilanterol (VI, 25 µg) compared with FF/VI and UMEC/VI
- Parallel group, placebo controlled, double blind, 12 month study
- 10,355 patients with COPD and one or more exacerbations in the last year
- Primary outcome: exacerbation rate



Lipson et al. NEJM 2018;378:1671-80

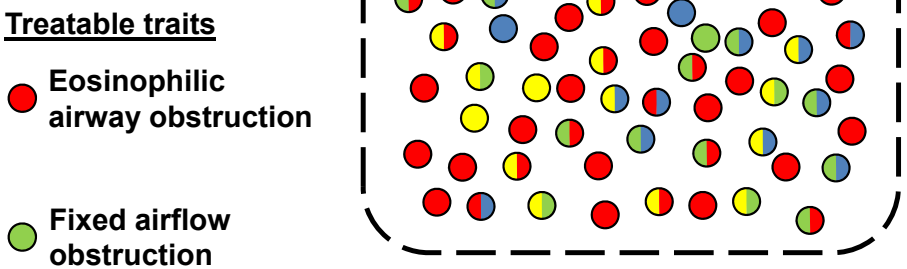
Biomarker directed use of Mepolizumab in severe asthma

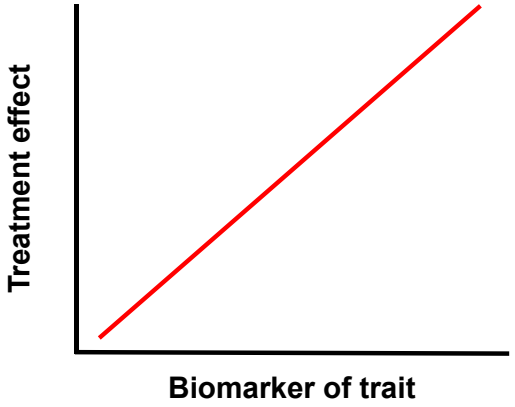


Ortega *et al. Lancet Respir Med* 2016; 4(7): 549-556

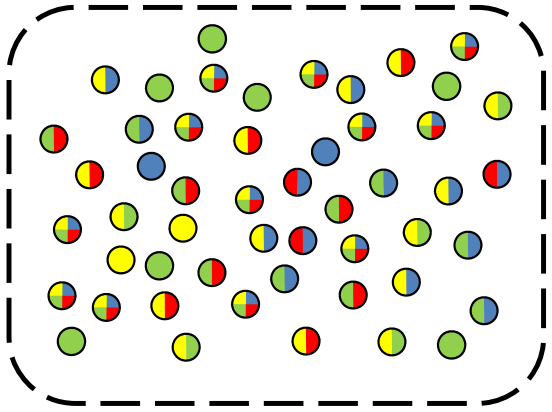
Treatable Traits in Asthma and COPD

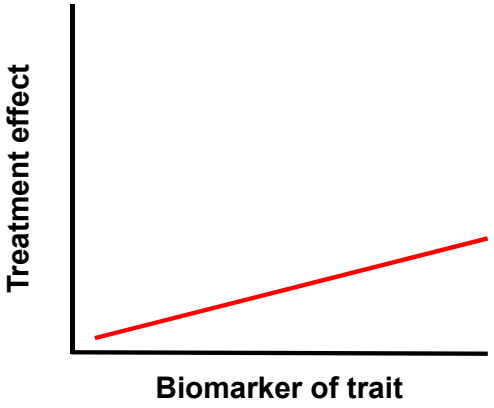
Asthma





COPD





Agusti A. Thorax 2014;69:857–864.

Conclusions

- The blood eosinophil count is a biomarker of an important treatable trait associated with risk of exacerbations
- It is a candidate biomarker for trait specific treatment with anti-IL-5 (Mepolizumab) in patients with COPD

NUCALA®
Mepolizumab for Patients with COPD

Efficacy

Eric Bradford, MD, MSc
Director, Respiratory R&D
GlaxoSmithKline

Overview of Efficacy

- Study design
- Demographics and baseline characteristics
- Results
  - –Treatment discontinuation
  - –Exacerbations
  - –Health related quality of life
  - –Lung function
- Blood eosinophils as predictor of response
- Efficacy Summary

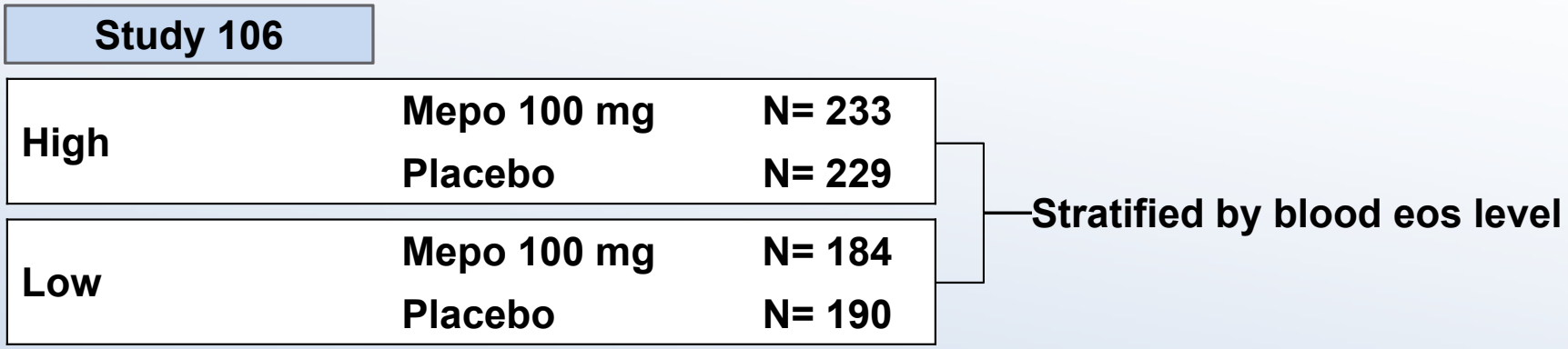
Key Entry Criteria

Key eligibility criteria (Studies MEA117106 and MEA117113)
FEV_1/FVC <0.7
FEV_1 >20% and ≤80% predicted
Current smoker, former smoker, or non-smokers
Excluded current asthma diagnosis (non-smokers, no asthma history)
High dose ICS plus LABA plus LAMA (Inhaled Triple Therapy)
≥2 moderate or ≥1 severe exacerbations in past 12 months*
Blood eosinophil criteria

*** Moderate: requiring use of systemic corticosteroids and/or antibiotics**
Severe: requiring hospitalization

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

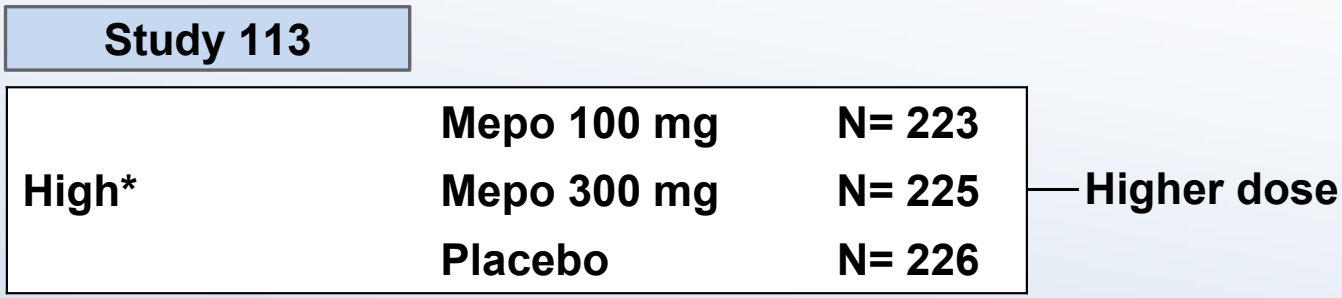
Study 106 Enabled Assessment of Blood Eosinophils as a Predictor of Treatment Response



- High Stratum: ≥150 cells/µL at screening OR ≥300 cells/µL in prior year
- Low Stratum: <150 cells/µL at screening AND no evidence of ≥300 cells/µL in prior year

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Study 113 Enabled Assessment of Higher Dose

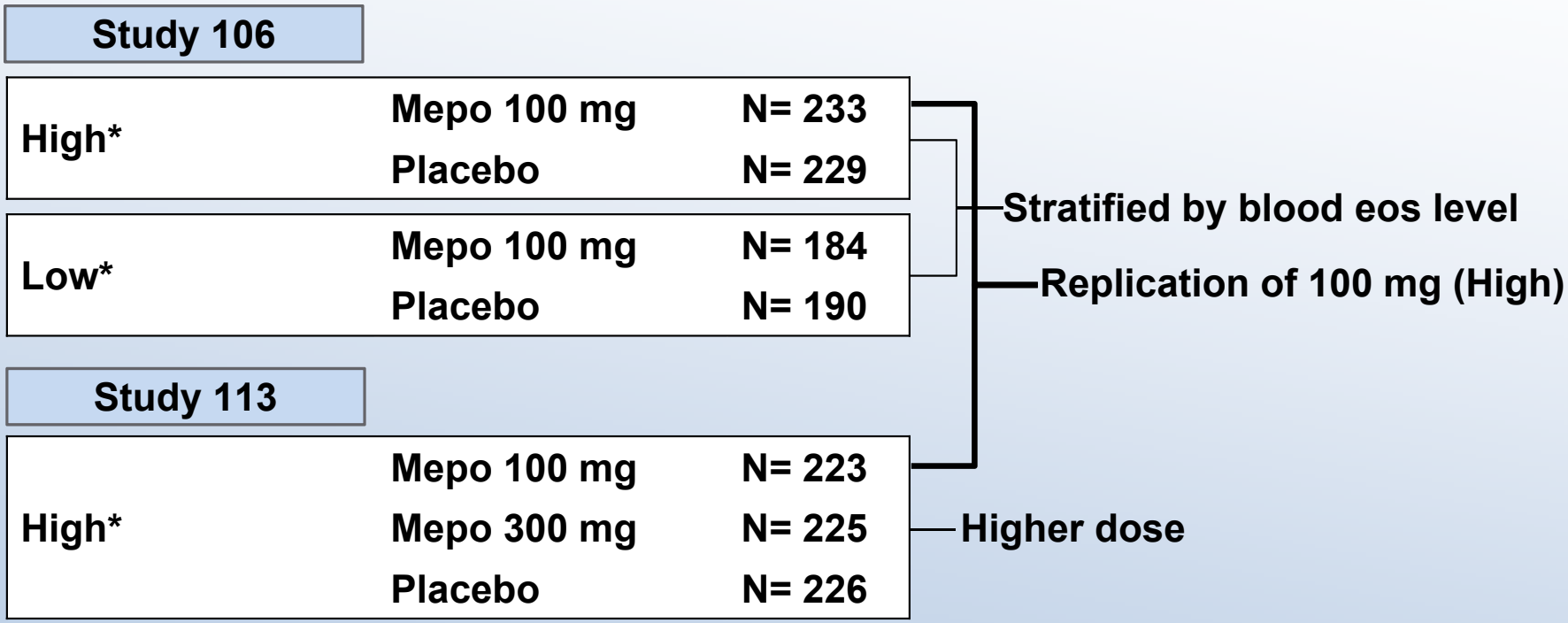


- Patients only included if blood eosinophil counts similar to the High Stratum of Study 106
- Mepolizumab 300 mg included to test for additional benefit at higher dose

*** High: blood eosinophils ≥150 cells/μL at screening OR ≥300 cells/μL in prior year**

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Mepolizumab COPD 52 Week Phase 3 Studies



* High: blood eosinophils ≥150 cells/µL at screening OR ≥300 cells/µL in prior year
Low: blood eosinophils <150 cells/µL at screening AND no evidence ≥300 cells/µL in prior year

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Study Endpoints

Primary Endpoint	
Annual rate of moderate/severe COPD exacerbations	
Study 106 100 mg Mepo vs Placebo (High Stratum) 100 mg Mepo vs Placebo (All Patients)	**Study 113** 100 mg Mepo vs Placebo 300 mg Mepo vs Placebo
Secondary Endpoints	
Time to first moderate/severe COPD exacerbation	
Annual rate of exacerbations requiring Emergency Department (ED) visit and/or hospitalization	
Change from baseline mean total St. George's Respiratory Questionnaire (SGRQ) score	
Change from baseline mean COPD Assessment Test (CAT) score	

Pavord et al. *N Engl Med* 2018; 377:1633-1629

Overview of Efficacy

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Demographic and Baseline Characteristics

	Study 106 N=836	Study 113 N=674
Mean Age, years (SD) ≥65 years	65.4 (8.64) 461 (55)	65.1 (8.89) 359 (53)
Male, n (%)	520 (62)	446 (66)
Race, n (%) White American Indian or Alaskan Native Multiple† Black or African American Asian	 680 (81) 69 (8) 69 (8) 11 (1) 7 (<1)	 542 (80) 0 0 8 (1) 124 (18)
US Patients, n (%) African American, n (%)	88 (11) 10 (11)	79 (12) 8 (10)
Mean Body Mass Index, kg/m^2 (SD)	26.9 (5.7)	26.3 (5.5)
Mean Blood Eosinophils, cells/µL geometric mean (SD logs)	265 (0.57)*	229 (0.85)

***High Stratum only.**

†(American Indian or Alaska Native) & White

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

COPD Baseline Characteristics

	Study 106 N=836	Study 113 N=674
Smoking pack year, Mean (SD)	45.6 (26.5)	44.3 (28.0)
Smoking status, n (%)		
Current smoker	222 (27)	189 (28)
Former smoker	574 (69)	472 (70)
Non-smoker	40 (5)	13 (2)
Exacerbation history in prior year		
Moderate/severe exacerbations, Mean (SD)	2.5 (1.22)	2.7 (1.44)
≥1 severe exacerbation, n (%)	256 (31)	222 (33)
Post-bronchodilator lung function		
FEV_1 (L), Mean (SD)	1.2 (0.5)	1.3 (0.5)
FEV_1 % predicted, Mean (SD)	44.3 (14.9)	46.1 (15.2)
% reversibility, Mean (SD)	9.1 (12.0)	9.8 (11.5)
Patients meeting reversibility criteria, n (%)	121 (14)	108 (16)
FEV_1/FVC, Mean (SD)	0.5 (0.1)	0.5 (0.1)
OCS chronic use, n (%)	38 (4.5)	30 (4.5)
Oxygen use, n (%)	101 (12)	77 (11)
CAT score, Mean (SD)	18.9 (7.7)	19.1 (7.6)
SGRQ Total score, Mean (SD)	54.9 (16.9)	52.7 (16.6)

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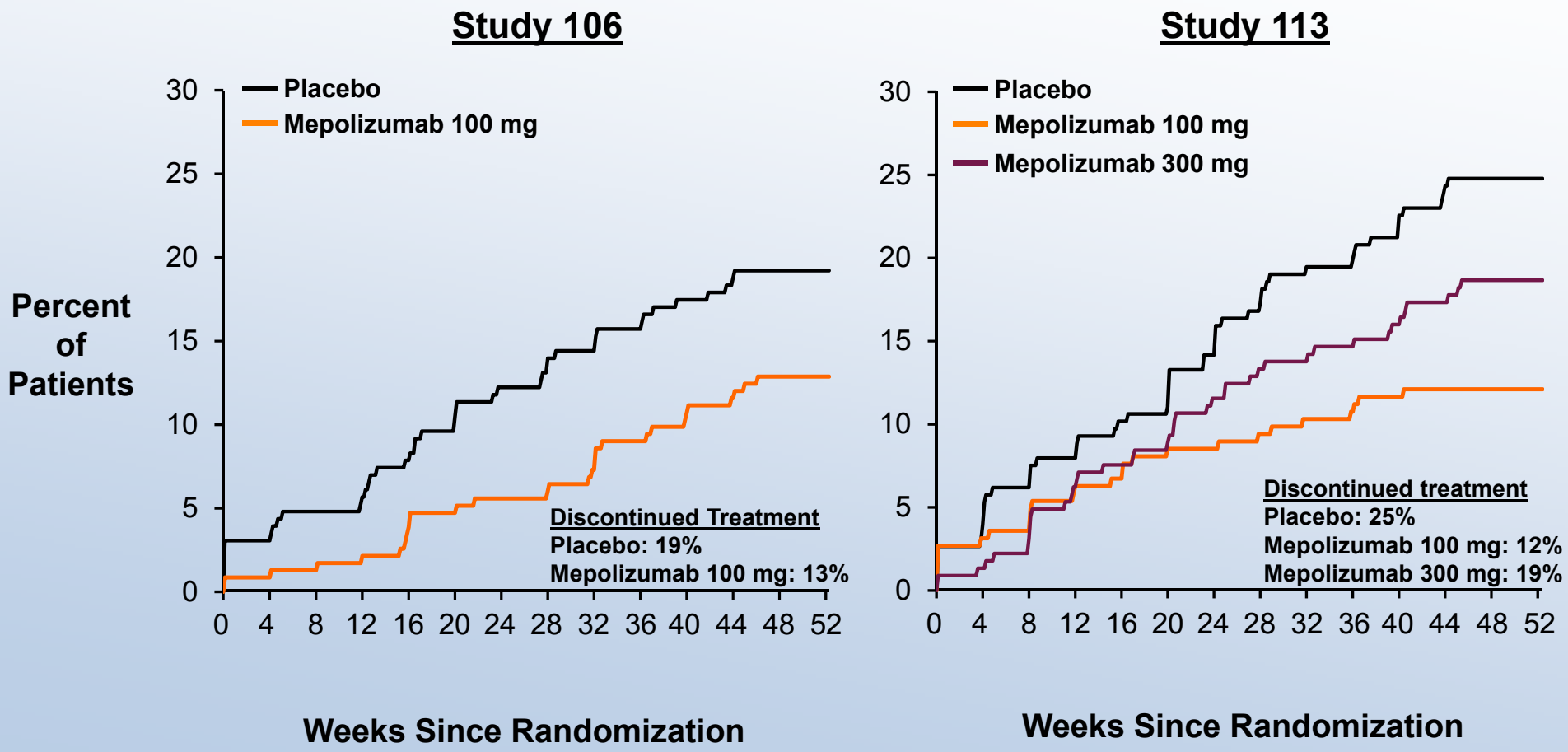
Treatment Discontinuation



Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

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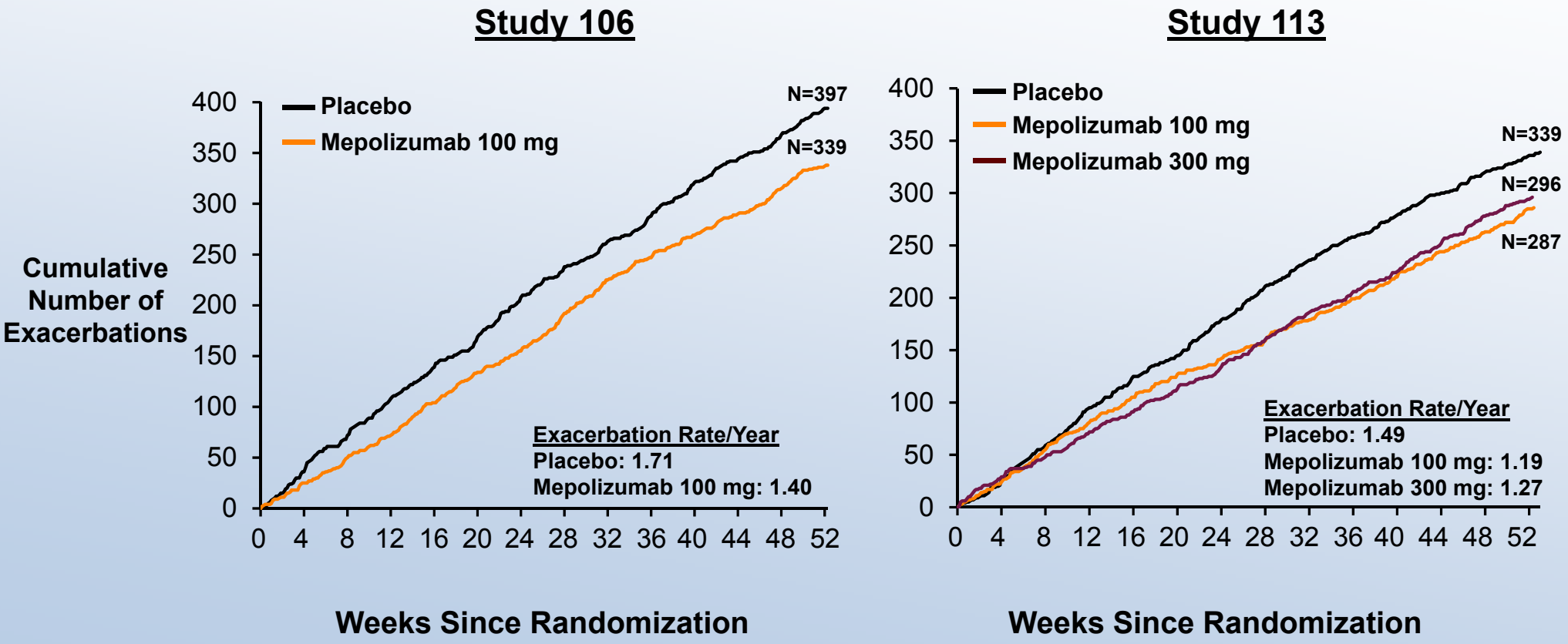
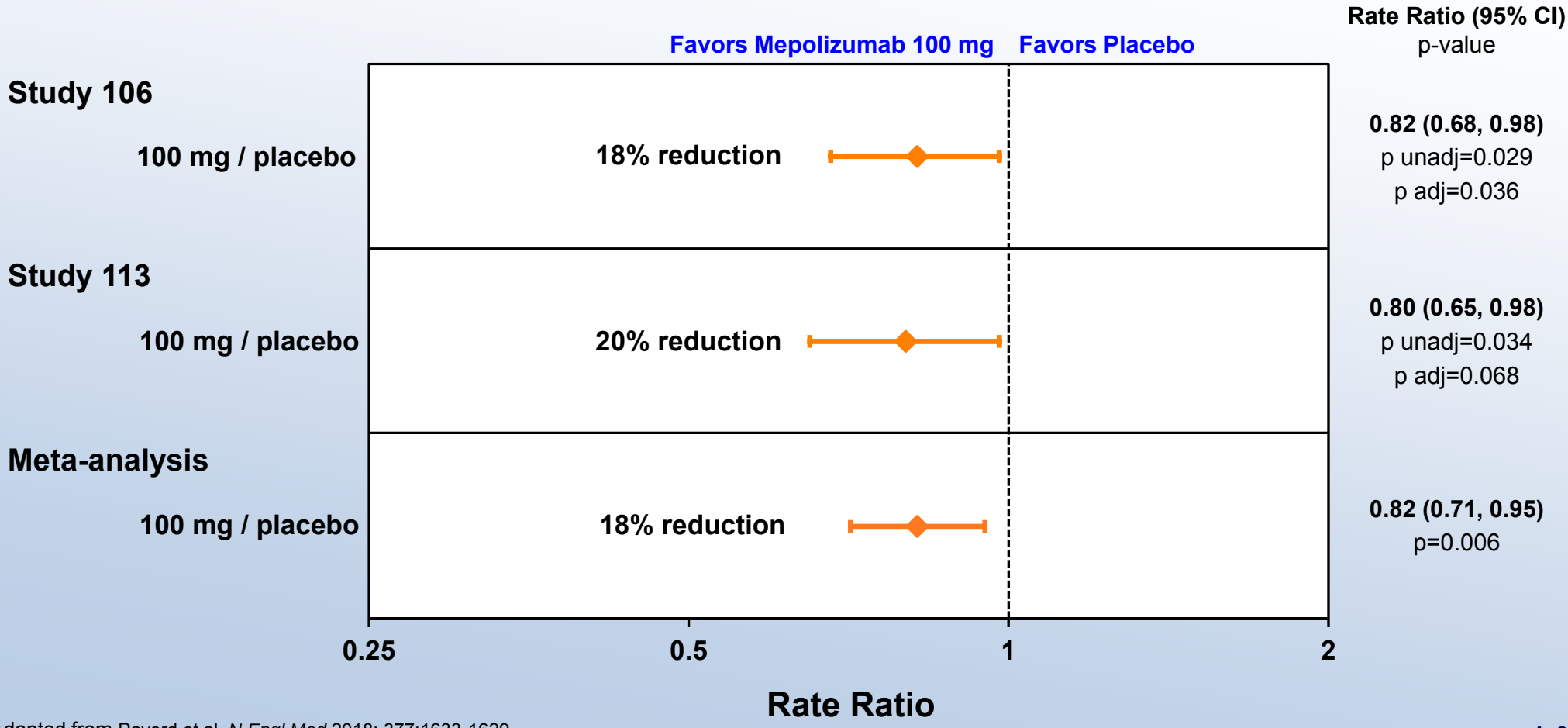
Cumulative Moderate/Severe Exacerbations Over Time On and Off-Treatment



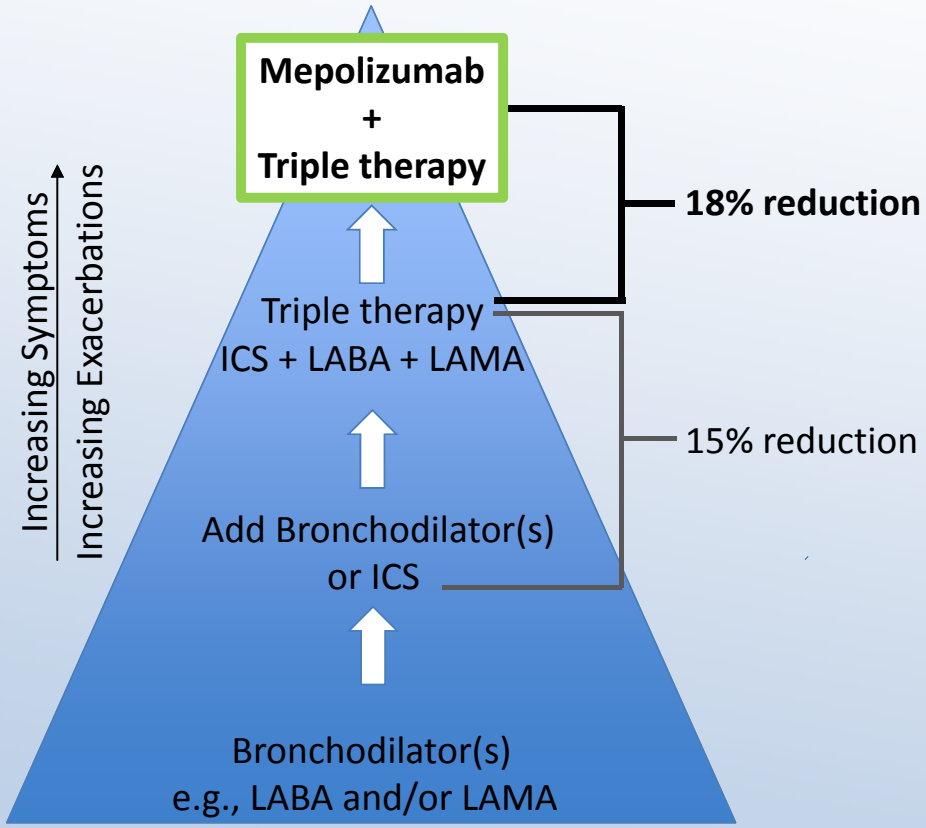
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Moderate/Severe Exacerbations Primary Endpoint



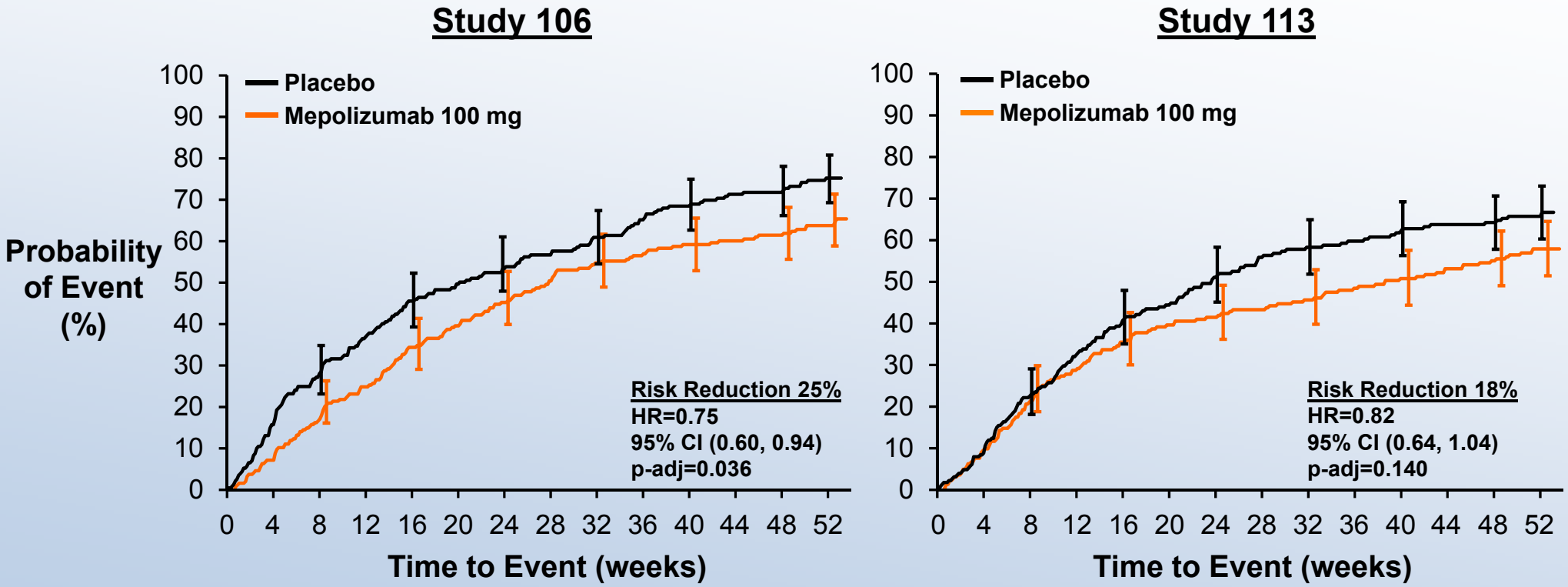
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Putting Mepolizumab Reduction Of Moderate/Severe Exacerbations Into Context



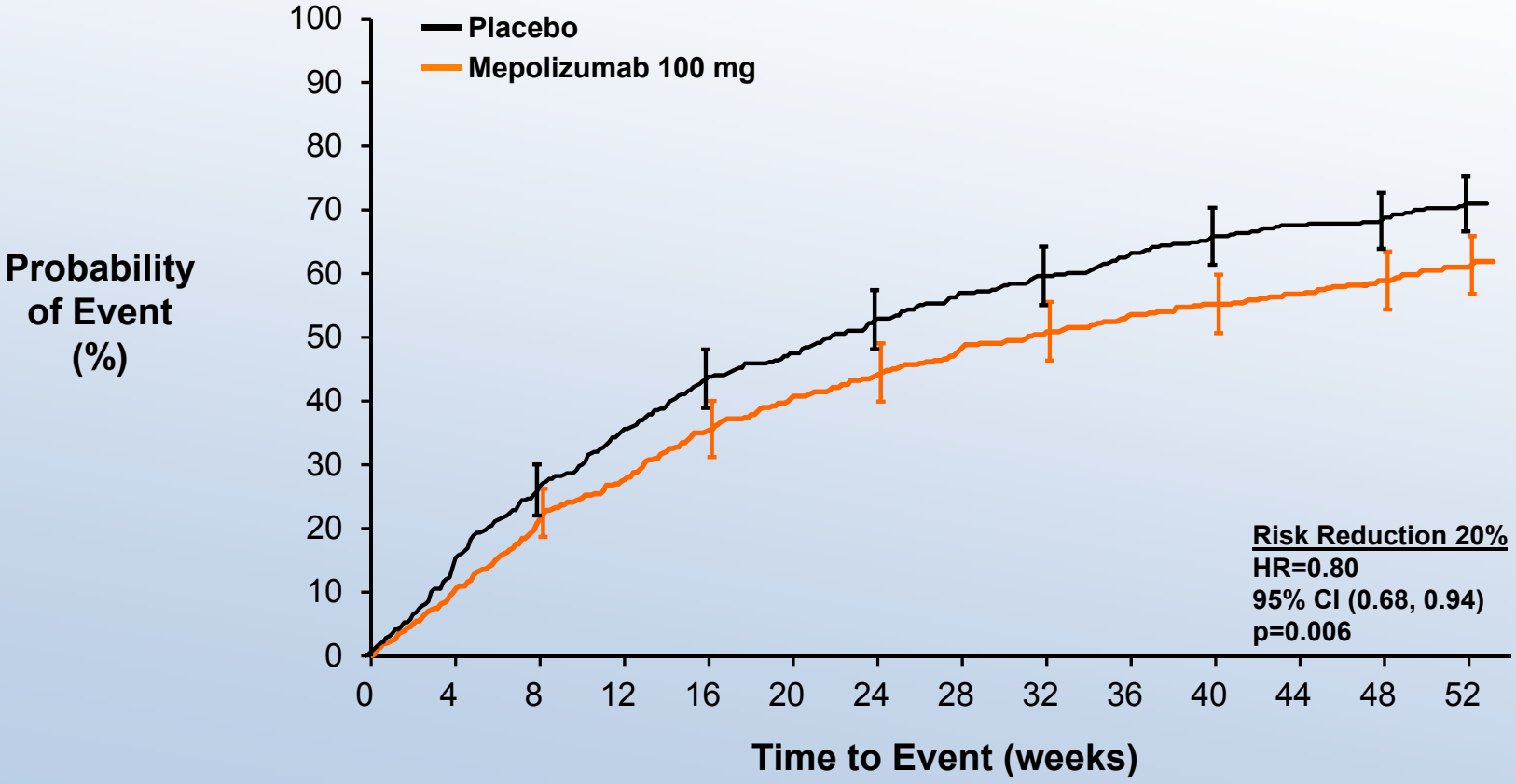
Lipson et al. *N Engl J Med* 2018; 378:1671-1680, Modified from GOLD 2017; Pavord et al. *N Engl Med* 2018; 377:1633-1629

Time to First Moderate/Severe Exacerbation



Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

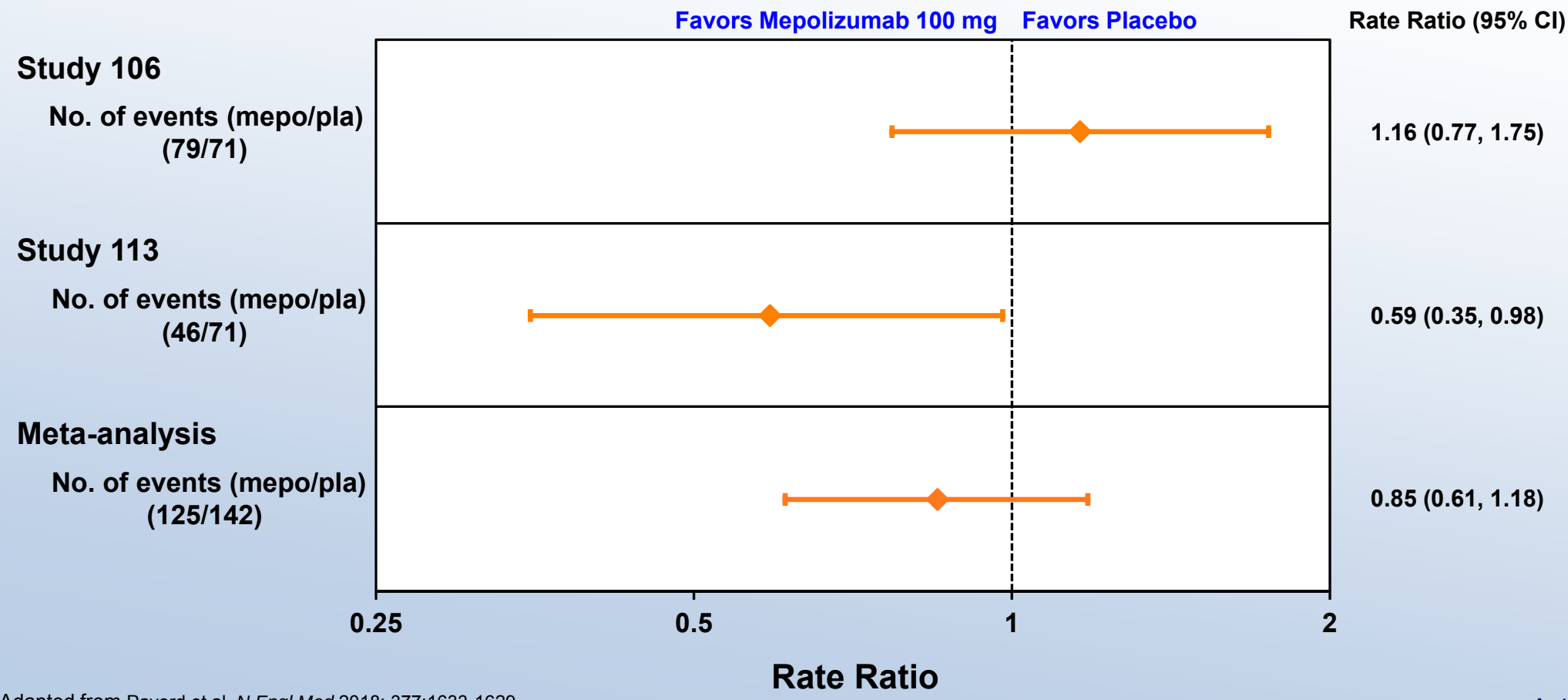
Time to First Moderate/Severe Exacerbation Meta-analysis



Median days until first event, mepolizumab 100mg vs placebo: 63 days longer

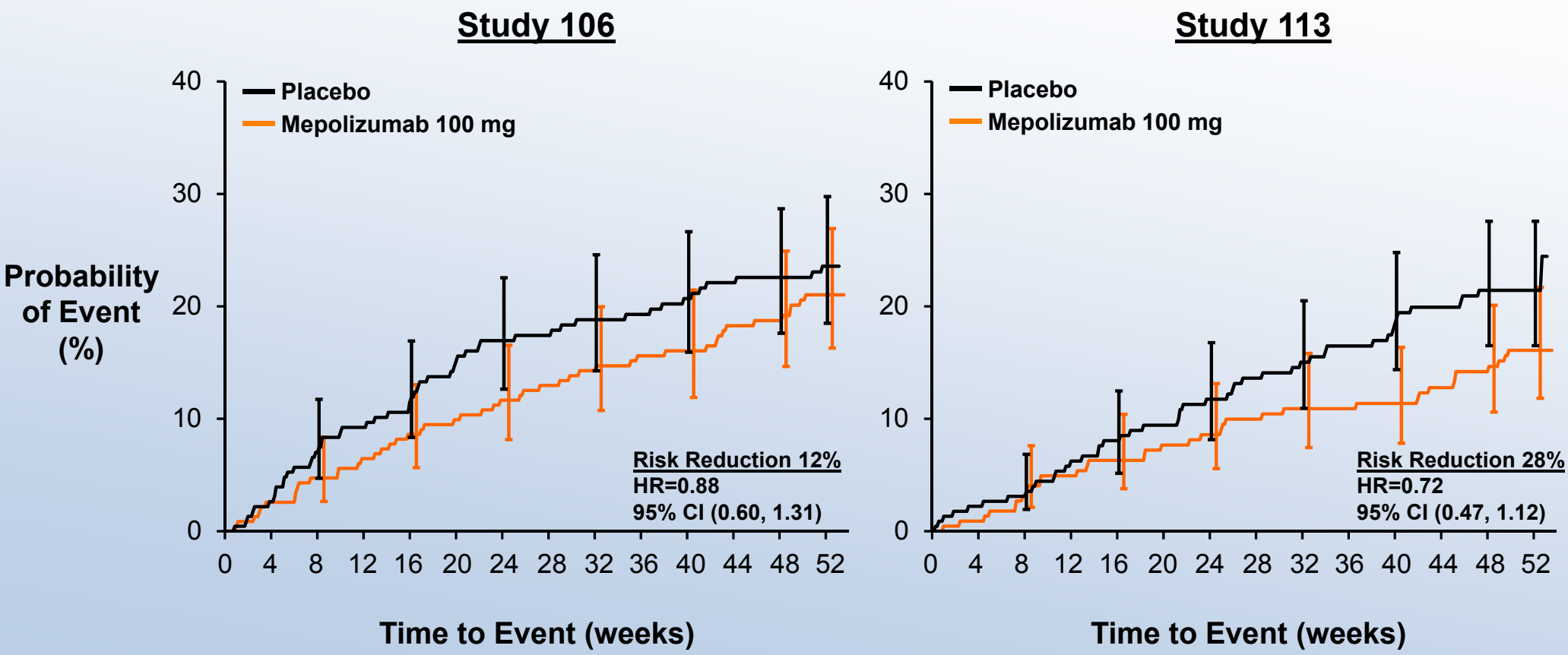
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Exacerbations Leading to ED/Hospitalization



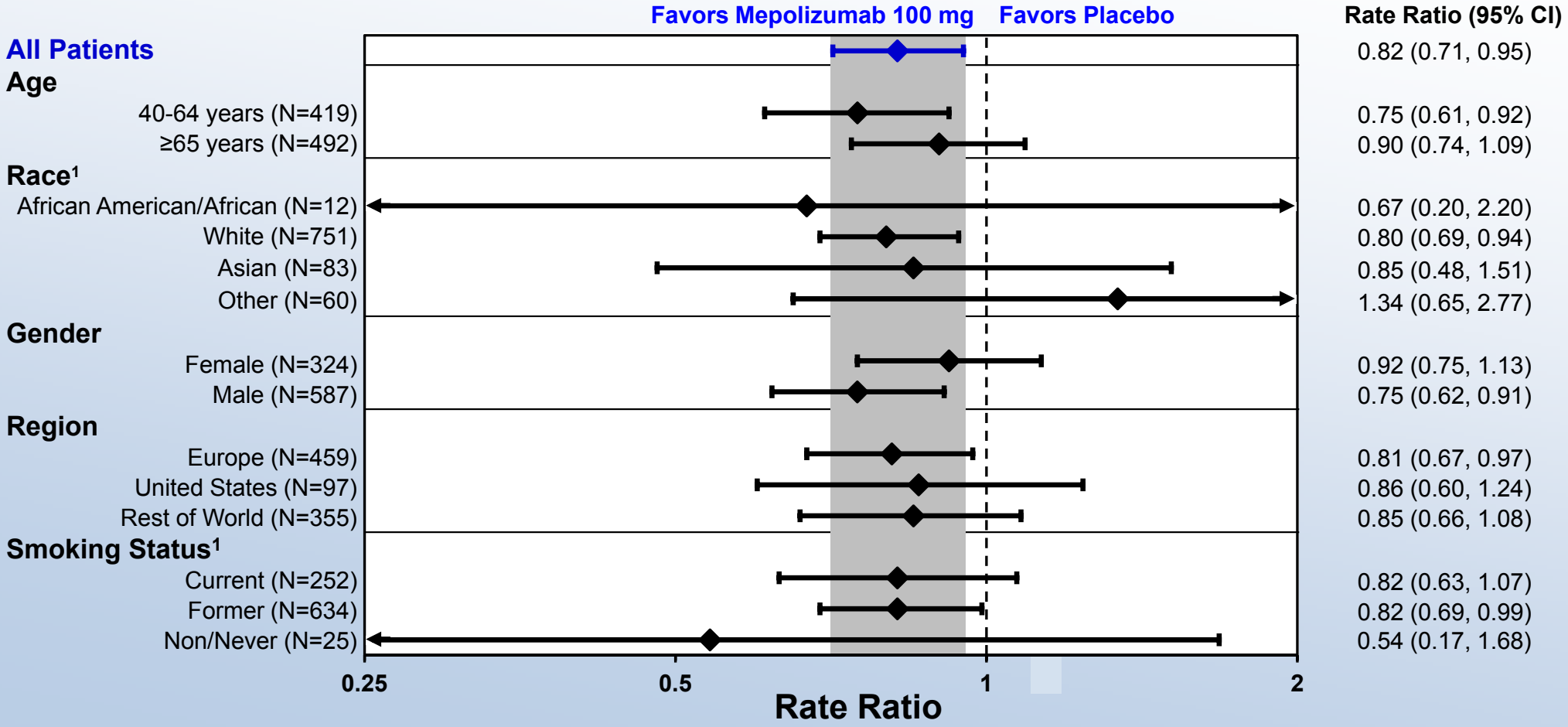
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Time to First Exacerbation Requiring ED/Hospitalization



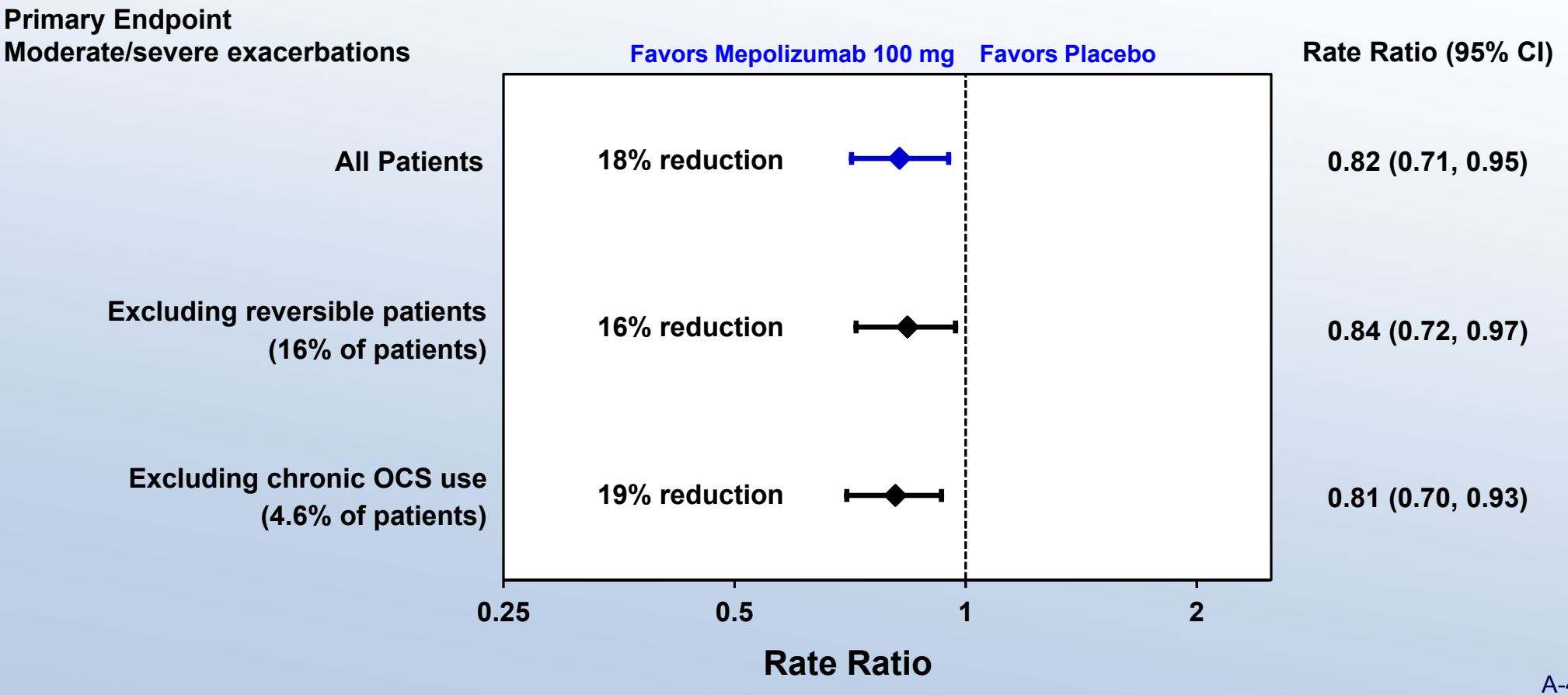
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Rate of Exacerbations by Subgroup Meta-analysis



[1] Model with only study included for covariate adjustment; Asian subgroup from MEA117113

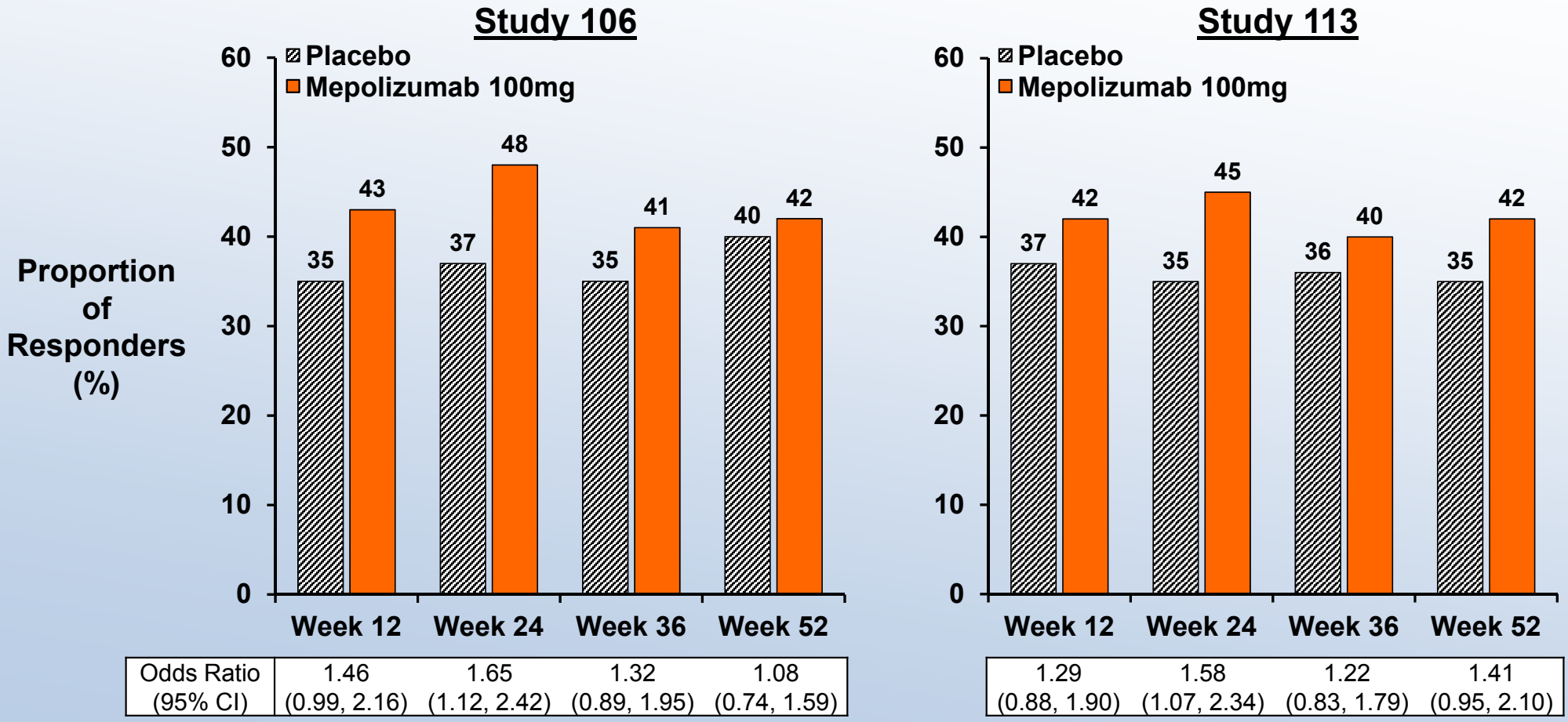
Subgroup Analyses Excluding Patients with Asthma-like Features



Overview of Efficacy

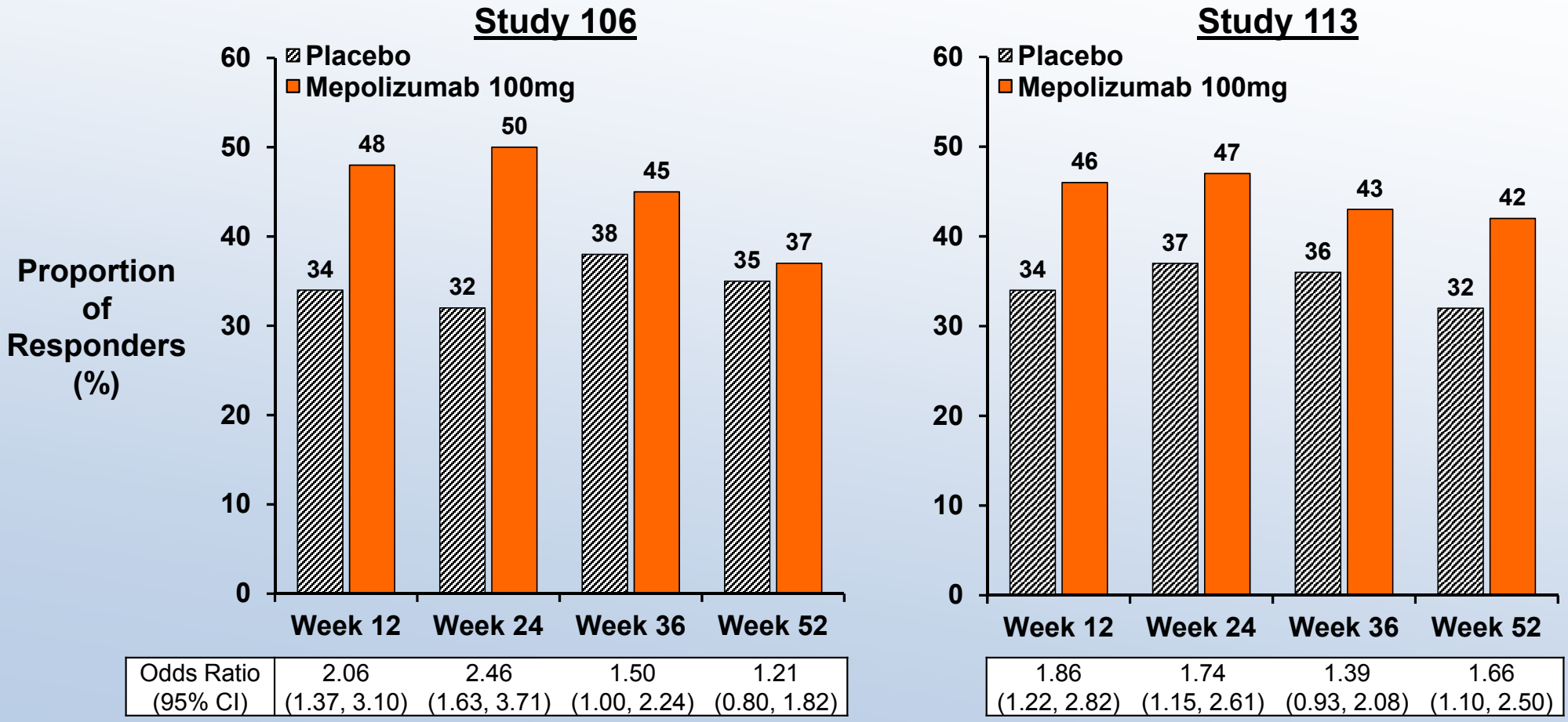
- Study design
- Demographics and baseline characteristics
- Results
  - –Treatment discontinuation
  - –Exacerbations
  - –Health related quality of life
  - –Lung Function
- Blood eosinophils as predictor of response
- Efficacy Summary

SGRQ Responders



Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

CAT Responders*



*** Post-hoc**

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Change from Baseline Trough FEV_1 at Week 52

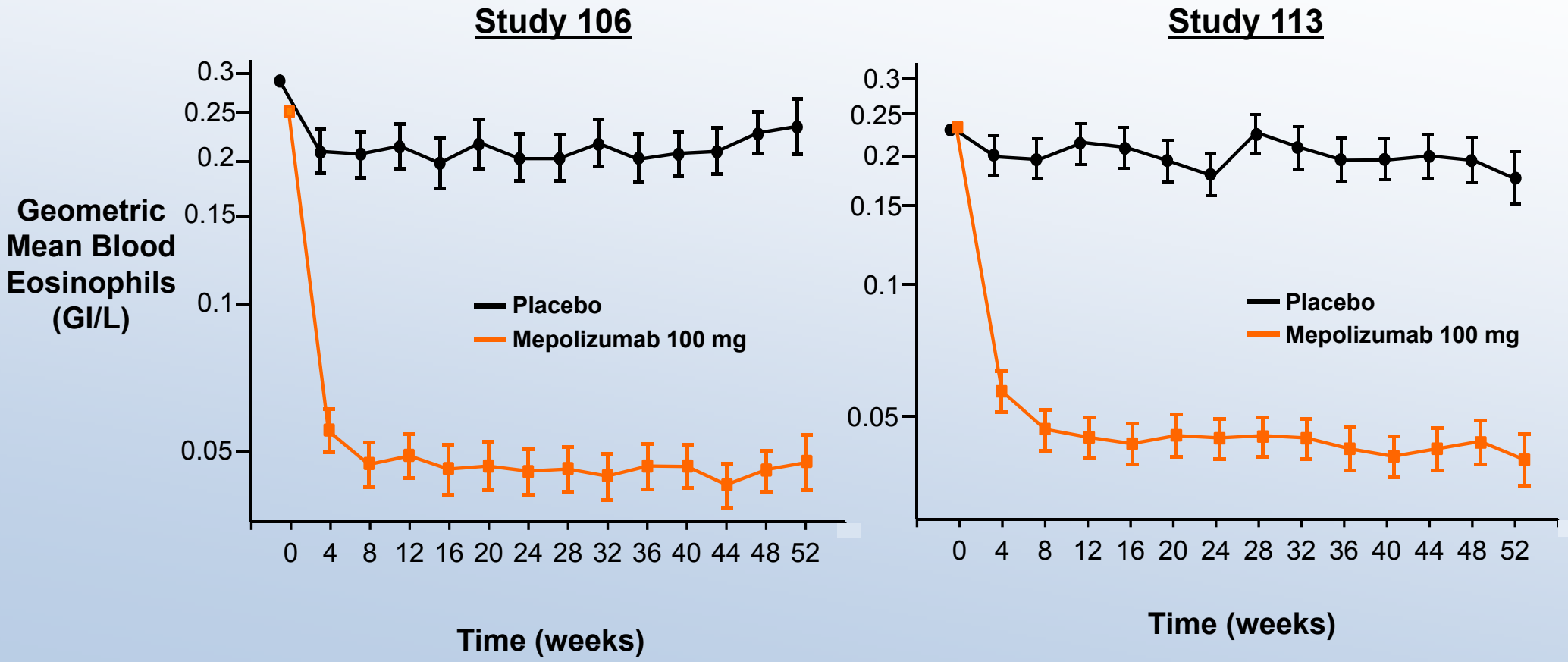
FEV_1 (mL)	Study 106		Study 113	
	Placebo N=229	Mepolizumab 100 mg N=233	Placebo N=226	Mepolizumab 100 mg N=223
Baseline FEV_1, mL (SD)	1145 (468.0)	1140 (461.0)	1225 (507.2)	1223 (491.2)
LS Mean Change, mL (SE)	-7 (15.9)	-17 (15.3)	-13 (17.6)	6 (17.0)

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Overview of Efficacy

- Study design
- Demographics and baseline characteristics
- Results
  - –Treatment discontinuation
  - –Exacerbations
  - –Health related quality of life
  - –Lung Function
- Blood eosinophils as predictor of response
- Efficacy Summary

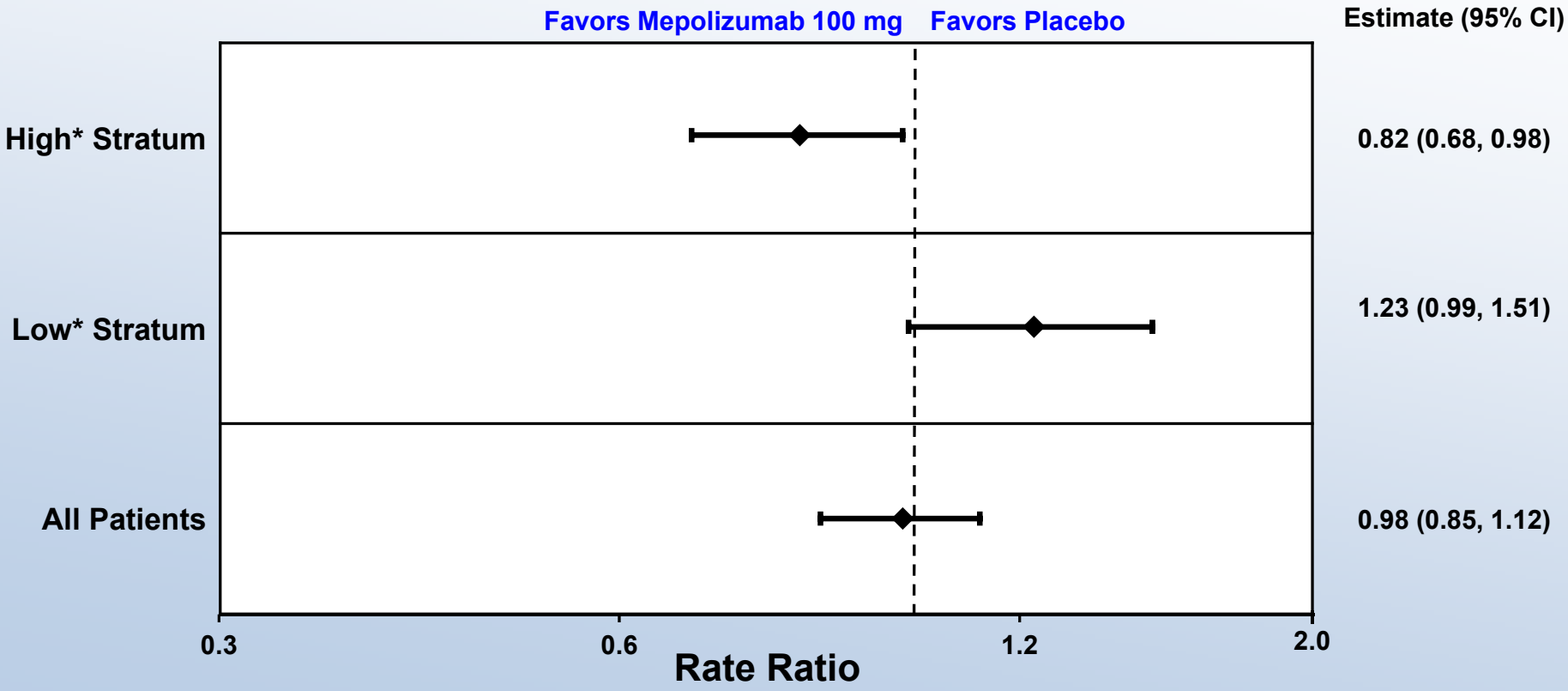
Reduction in Blood Eosinophils with Mepolizumab



Pavord et al. *N Engl Med* 2018; 377:1633-1629

Utility of Blood Eosinophils as a Predictor of Response - Study 106

Rate of Moderate/Severe Exacerbations



* High Stratum: blood eosinophils ≥150 cells/μL at screening OR ≥300 cells/μL in prior year
Low Stratum: blood eosinophils <150 cells/μL at screening AND no evidence ≥300 cells/μL in prior year

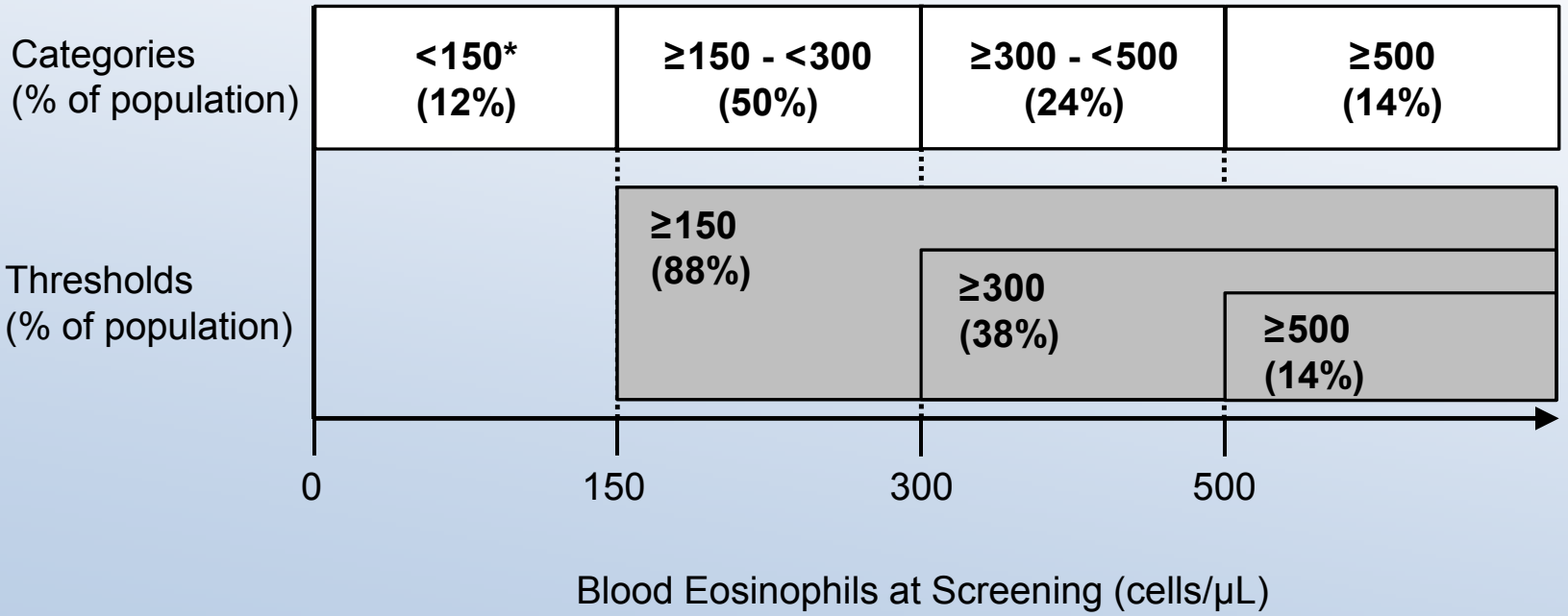
Exacerbation Endpoints in Low Stratum* Study 106

	Mepolizumab 100 mg vs Placebo
Moderate/severe exacerbations, Rate Ratio (95%CI)	1.23 (0.99, 1.51)
Time to first moderate/severe exacerbation, Hazard Ratio (95%CI)	1.07 (0.83, 1.39)
≥1 exacerbation (on- and off-treatment), n (%)	Placebo: 121 (64) Mepolizumab: 117 (64)
Exacerbations requiring ED/hospitalization, Rate Ratio (95%CI)	1.04 (0.66, 1.67)
Severe exacerbations, Rate Ratio (95%CI)	0.89 (0.52, 1.53)

*** Low Stratum: blood eosinophils <150 cells/μL at screening AND no evidence ≥300 cells/μL in prior year**

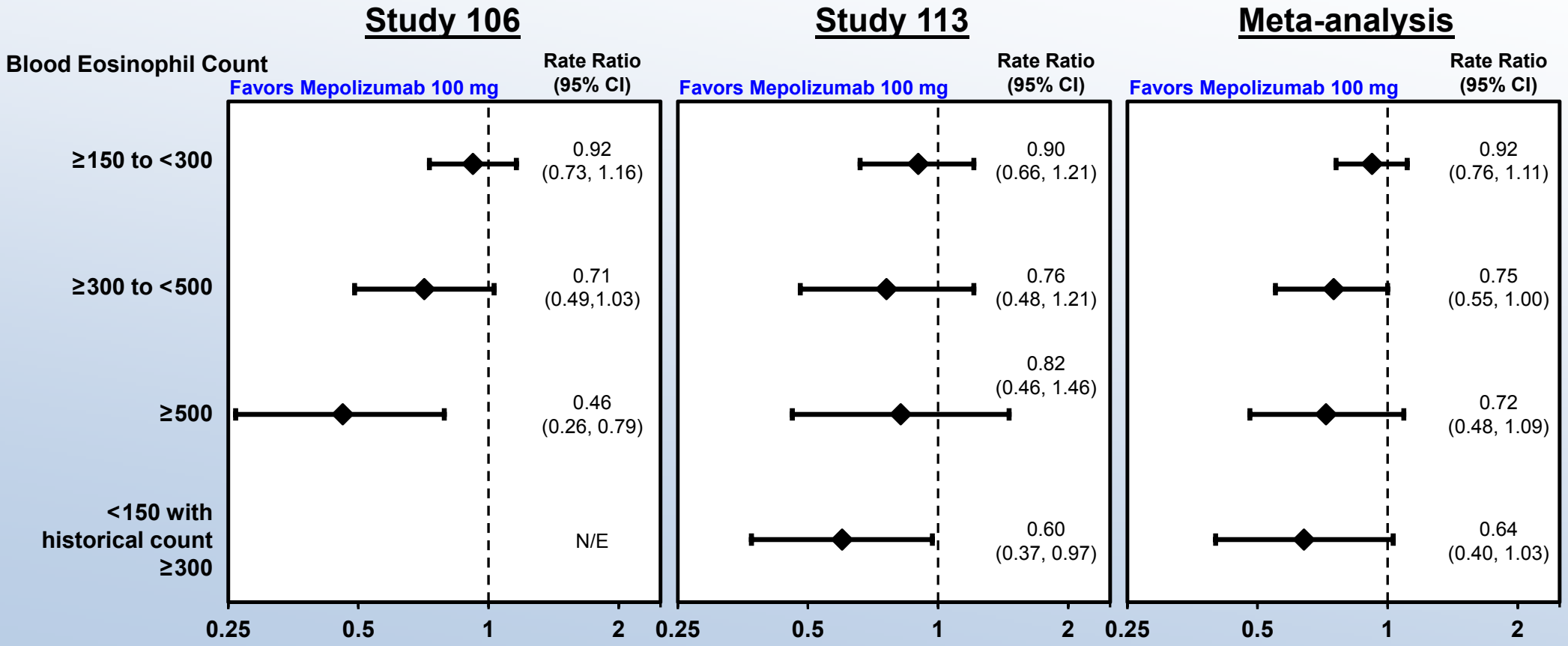
Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Response to Treatment by Blood Eosinophil Categories and Thresholds



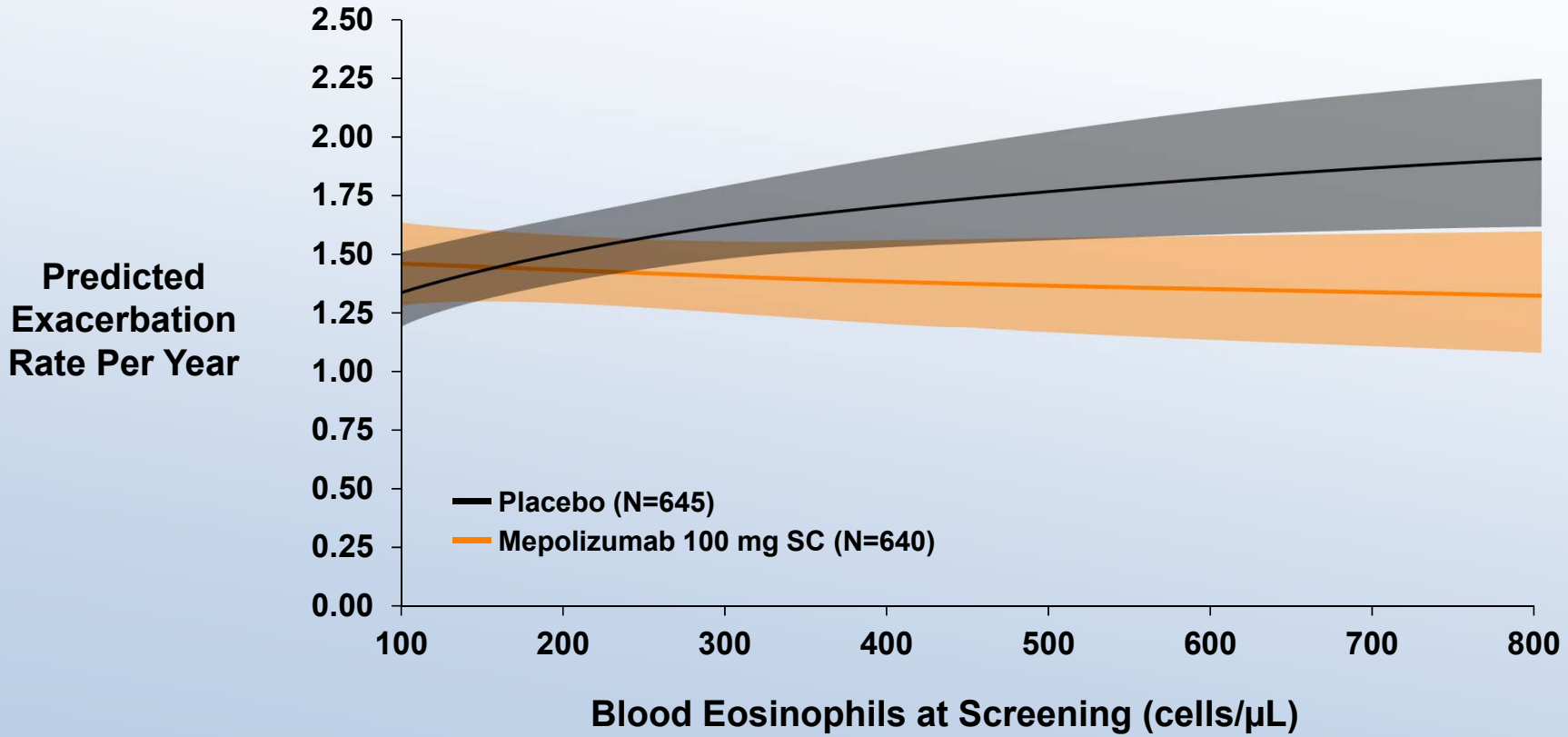
*** Blood eosinophils <150 cells/µL at screening (≥300 cells/µL in prior year)**

Moderate/Severe Exacerbations by Screening Blood Eosinophil Categories



Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Predicted Moderate/Severe Exacerbation Rates by Blood Eosinophils at Screening (COPD) 100 mg vs Placebo



Shaded areas represent 95% CIs for predicted rates from the model of exacerbation rates against screening blood eosinophil count.

Overview of Efficacy

- Study design
- Demographics and baseline characteristics
- Results
  - –Treatment discontinuation
  - –Exacerbations
  - –Health related quality of life
  - –Lung Function
- Blood eosinophils as predictor of response
- Efficacy Summary

Summary of Efficacy
Mepolizumab 100 mg vs Placebo

	Study 106	Study 113	Meta-analysis
Primary Endpoint – Rate of mod/severe exac	18% ↓ *	20% ↓ #	18% ↓ *
Time to First mod/severe exac	25% ↓ *	18% ↓	20% ↓ *
Rate of exac requiring ED/Hospitalization	16% ↑	41% ↓ #	15% ↓
Time to First ED/Hospitalization	12% ↓	28% ↓	19% ↓
SGRQ: Odds of being a responder at Week 52	1.08	1.41	1.23
CAT: Odds of being a responder at Week 52	1.21	1.66	1.39

* Statistically significant
# Statistically significant prior to adjustment for multiplicity

Clinical Conclusions

In patients with COPD who continue to exacerbate despite inhaled triple therapy mepolizumab:

- Reduced rate of moderate/severe exacerbations by 18-20%
- Reduced risk of first moderate/severe exacerbation by 18-25%
- Provided numerical reduction in rate of exacerbations leading to ED/Hospitalization in the meta analysis
- Provided HRQoL improvements that were supportive of treatment benefit
- Established blood eosinophils as predictor of response

NUCALA®
Mepolizumab for Patients with COPD

Safety

Olga Gumieniak, MD, MMSc
Medical Director
Global Clinical Safety and Pharmacovigilance
GlaxoSmithKline

Introduction

- Approved in the US
  - November 2015 for severe eosinophilic asthma (100mg SC every 4 weeks)
  - December 2017 for eosinophilic granulomatosis with polyangiitis (EGPA) (300mg SC every 4 weeks)
- Cumulative clinical trial exposure in all indications: >4000 subjects
- Cumulative post-marketing exposure: ~ 23,343 patient-years

Overview of Safety

- Adverse event overview
- Common adverse events and serious adverse events
- Adverse events of special interest
- Safety Summary

Overview of Adverse Events

Adverse event type n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Any adverse event	**527 (82)**	**523 (82)**	**196 (87)**	**719 (83)**
On-treatment adverse events	521 (81)	516 (81)	191 (85)	707 (82)
Adverse events leading to permanent discontinuation of investigational product	62 (10)	40 (6)	25 (11)	65 (8)
Any serious adverse event	199 (31)	172 (27)	60 (27)	232 (27)
On-treatment serious adverse events	175 (27)	156 (24)	54 (24)	210 (24)
Fatal serious adverse event	26 (4)	20 (3)	8 (4)	28 (3)

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Most Common On-Treatment Adverse Events*

Adverse event n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Any event	**521 (81)**	**516 (81)**	**191 (85)**	**707 (82)**
Nasopharyngitis	111 (17)	103 (16)	40 (18)	143 (17)
COPD	109 (17)	104 (16)	35 (16)	139 (16)
Headache	76 (12)	76 (12)	22 (10)	98 (11)
Pneumonia	59 (9)	53 (8)	20 (9)	73 (8)
URTI	42 (7)	37 (6)	13 (6)	50 (6)
Oropharyngeal pain	22 (3)	39 (6)	11 (5)	50 (6)
Diarrhea	29 (4)	34 (5)	8 (4)	42 (5)
Dyspnea	30 (5)	29 (5)	10 (4)	39 (5)
Influenza	35 (5)	22 (3)	4 (2)	26 (3)
Injection site reaction	22 (3)	18 (3)	11 (5)	29 (3)
Bronchitis	21 (3)	17 (3)	12 (5)	29 (3)
Pyrexia	23 (4)	14 (2)	13 (6)	27 (3)

***Events reported ≥5% in any treatment group**

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Most Common On-Treatment Serious Adverse Events*

Serious adverse event n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Any event	**175 (27)**	**156 (24)**	**54 (24)**	**210 (24)**
COPD	97 (15)	84 (13)	27 (12)	111 (13)
Pneumonia	42 (7)	35 (5)	13 (6)	48 (6)
Respiratory failure	5 (<1)	7 (1)	2 (<1)	9 (1)
Atrial fibrillation	6 (<1)	6 (<1)	0	6 (<1)
Infective COPD exacerbation	4 (<1)	4 (<1)	2 (<1)	6 (<1)
Acute respiratory failure	6 (<1)	5 (<1)	0	5 (<1)
Acute myocardial infarction	4 (<1)	3 (<1)	2 (<1)	5 (<1)
Cardiac failure congestive	3 (<1)	4 (<1)	0	4 (<1)
Sepsis	2 (<1)	4 (<1)	0	4 (<1)
Urinary tract infection	3 (<1)	3 (<1)	1 (<1)	4 (<1)
Diarrhea	0	3 (<1)	1 (<1)	4 (<1)
Bronchitis	3 (<1)	0	1 (<1)	1 (<1)

***Events reported for ≥3 subjects in any treatment group**

Adjudicated Serious Adverse Reports

Adjudicated category n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Adjudicated reports, Total	**199 (31)**	**172 (27)**	**60 (27)**	**232 (27)**
Adjudicated reports, Fatal				
Total	**26 (4.0)**	**20 (3.1)**	**8 (3.6)**	**28 (3.2)**
Respiratory	12 (1.9)	8 (1.3)	4 (1.8)	12 (1.4)
Cardiovascular	7 (1.1)	3 (0.5)	4 (1.8)	7 (0.8)
Cancer	3 (0.5)	4 (0.6)	0	4 (0.5)
Other	3 (0.5)	3 (0.5)	0	3 (0.3)
Unknown (inadequate information)	1 (0.2)	2 (0.3)	0	2 (0.2)
Death associated with COPD	13 (2.0)	10 (1.6)	4 (1.8)	14 (1.6)
Adjudicated reports, Non-fatal				
Total	**181 (28.1)**	**160 (25.0)**	**54 (24.0)**	**214 (24.7)**
Respiratory	131 (20.3)	110 (17.2)	45 (20.0)	155 (17.9)
Cardiovascular	21 (3.3)	26 (4.1)	6 (2.7)	32 (3.7)
Cancer	11 (1.7)	6 (0.9)	4 (1.8)	10 (1.2)
Other	47 (7.3)	40 (6.3)	6 (2.7)	46 (5.3)
Unknown (inadequate information)	2 (0.3)	1 (0.2)	0	1 (0.1)

Overview of Safety

- Adverse event overview
- Common adverse events and serious adverse events
- Adverse events of special interest
- Safety Summary

Systemic and Injection Site Reactions and Immunogenicity

Adverse events of special interest n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Systemic and injection site reactions				
Any systemic reaction event	**13 (2)**	**10 (2)**	**5 (2)**	**15 (2)**
Hypersensitivity (allergic) reactions	3 (<1)	4 (<1)	1 (<1)	5 (<1)
Non-allergic reactions	10 (2)	7 (1)	4 (2)	11 (1)
Anaphylaxis	0	0	1 (<1)*	1 (<1)*
Local injection site reaction	**21 (3)**	**18 (3)**	**11 (5)**	**29 (3)**
Immunogenicity				
Anti-drug antibody assay				
Positive	5 (<1)	27 (4)	4 (2)	31 (4)
Neutralizing antibody assay				
Positive	1	0	0	0

*** Anaphylaxis considered unrelated to mepolizumab and related to diclofenac. Mepolizumab was continued, and patient completed the study**

Adapted from Pavord et al. *N Engl Med* 2018; 377:1633-1629

Infections

Adverse events of special interest n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Infections and Infestations System Organ Class				
Any event	**341 (53)**	**326 (51)**	**113 (50)**	**439 (51)**
SAEs, any event	60 (9)	57 (9)	22 (10)	79 (9)
Potential opportunistic infections				
Any event	**13 (2)**	**18 (3)**	**9 (4)**	**27 (3)**
Herpes zoster	5 (<1)	11 (2)	5 (2)	16 (2)
Candida infection	5 (<1)	5 (<1)	4 (2)	9 (1)
Esophageal candidiasis	1 (<1)	1 (<1)	0	1 (<1)
Gastrointestinal candidiasis	1 (<1)	0	0	0
Herpes simplex	1 (<1)	1 (<1)	0	1 (<1)
Herpes ophthalmic	0	0	1 (<1)	1 (<1)
Pulmonary tuberculosis (reactivation)	0	0	1 (<1)	1 (<1)
Parasitic infections				
Any event	0	0	0	0

Pneumonia

Pneumonia-related adverse events n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Composite of pneumonia-related terms				
Any event	**71 (11)**	**66 (10)**	**26 (12)**	**92 (11)**
SAEs, any event	50 (8)	41 (6)	18 (8)	59 (7)

Malignancies

Adverse events of special interest n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Neoplasms benign, malignant and unspecified				
Any event	**20 (3)**	**20 (3)**	**6 (3)**	**26 (3)**
SAEs, any event	8 (1)	8 (1)	4 (2)	12 (1)
Malignancies				
Any event	**13 (2)**	**13 (2)**	**3 (1)**	**16 (2)**

Serious Cardiac, Vascular and Thromboembolic (CVT) Events

Adverse events of special interest n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Any event	**24 (4)**	**32 (5)**	**10 (4)**	**42 (5)**
Cardiac disorders	21 (3)	26 (4)	8 (4)	34 (4)
Vascular disorders	4 (<1)	5 (<1)	0	5 (<1)
Relevant events from other System Organ Classes				
Nervous system disorders	1 (<1)	3 (<1)	0	3 (<1)
Respiratory disorders	0	1 (<1)	2 (<1)	3 (<1)
General disorders	0	1 (<1)	0	1 (<1)

Supraventricular Tachyarrhythmias SMQ

Supraventricular tachyarrhythmias SMQ events n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Any event	**13 (2)**	**20 (3)**	**10 (4)**	**30 (3)**
Atrial fibrillation	8 (1)	12 (2)	4 (2)	16 (2)
Sinus tachycardia	4 (<1)	1 (<1)	1 (<1)	2 (<1)
Supraventricular tachycardia	0	2 (<1)	3 (1)	5 (<1)
Supraventricular extrasystoles	2 (<1)	1 (<1)	1 (<1)	2 (<1)
Atrial flutter	0	2 (<1)	1 (<1)	3 (<1)
Atrial tachycardia	0	2 (<1)	0	2 (<1)

Adjudicated Serious Adverse Reports - Cardiovascular

Adjudicated subcategory n (%)	Placebo N=645	Mepolizumab 100mg SC N=640	Mepolizumab 300mg SC N=225	Mepolizumab All Doses N=865
Cardiovascular, Total				
Any event	**27 (4)**	**28 (4)**	**10 (4)**	**38 (4)**
Cardiovascular, Fatal				
Any event	**7 (1.1)**	**3 (0.5)**	**4 (1.8)**	**7 (0.8)**
Sudden death	4 (0.6)	1 (0.2)	4 (1.8)	5 (0.6)
MI/ ischemic heart disease	2 (0.3)	0	0	0
Congestive heart failure	0	2 (0.3)	0	2 (0.2)
Stroke	1 (0.2)	0	0	0
Other cardiovascular cause	0	0	0	0
Cardiovascular, Non-fatal				
Any event	**21 (3.3)**	**26 (4.1)**	**6 (2.7)**	**32 (3.7)**
MI/ ischemic heart disease	6 (0.9)	7 (1.1)	2 (0.9)	9 (1.0)
Congestive heart failure	4 (0.6)	7 (1.1)	0	7 (0.8)
Stroke	0	1 (0.2)	0	1 (0.1)
Other cardiovascular cause	13 (2.0)	13 (2.0)	4 (1.8)	17 (2.0)

Gastrointestinal Hemorrhage and Acute Pancreatitis

Gastrointestinal hemorrhage/ Hemorrhages SMQ n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Gastrointestinal hemorrhage SMQ				
Any event	3 (<1)	6 (<1)	2 (<1)	8 (<1)
Hemorrhage SMQ				
Any event	38 (5.9)	44 (6.9)	14 (6.2)	58 (6.7)

Acute Pancreatitis SMQ n (%)	Placebo N=645	Mepolizumab		
		100mg SC N=640	300mg SC N=225	All Doses N=865
Acute pancreatitis SMQ				
Any event	0	3 (<1)	1 (<1)	4 (<1)

Overview of Safety

- Adverse event overview
- Common adverse events and serious adverse events
- Adverse events of special interest
- Safety Summary

Safety Summary

Overall, safety profile similar to placebo:

- No differences in serious adverse events, fatal adverse events or adverse events leading to permanent discontinuation between mepolizumab and placebo
- No differences between 100 mg and 300 mg dose groups
- No new safety concerns identified in review of adverse events of special interest
- Totality of cardiovascular safety information does not support an adverse effect of mepolizumab

No new safety concerns with mepolizumab were identified in this population

A Physician's Perspective of Treating Patients with Advanced COPD and Frequent and Severe Exacerbations

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Presenter Disclosures

Gerard J. Criner, M.D.

Honoraria: None

Grants received: NIH-NHLBI, PA-DOH,GSK, Boehringer- Ingelheim, Novartis, Astra Zeneca, Respironics, MedImmune, Actelion, Forest, Pharmaxis, Pulmonx, Aeris, PneumRx, Pearl

Grants pending: None

Consultation: MedImmune, GSK, Bayer, Dey, Respironics, J&J, Uptake Medical, PortAero, Nuvaira, Eolo, Amirall, CSA Medical, Boehringer-Ingelheim, Astra Zeneca, Celerion, Mereo, Olympus, PneumRX, Spiration, Pulmonx, Broncus, Lungpacer

Equity interest: HGE, Health Care Solutions

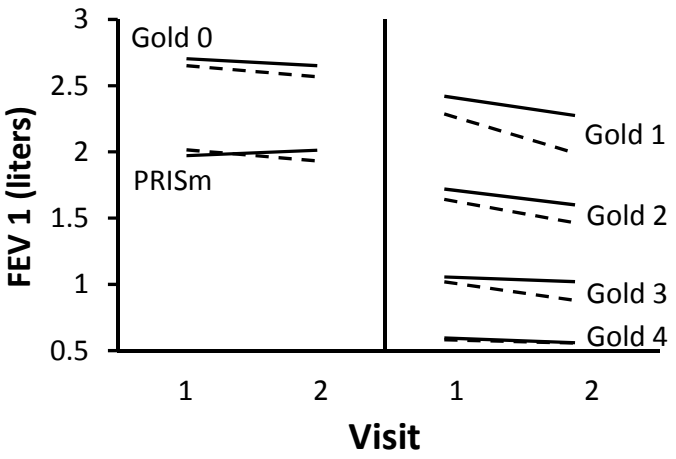
What Do Patients with Advanced COPD and Frequent and Severe Exacerbations Look Like?

- Severely obstructed
- Breathless at rest and with exertion
- Increased cough and mucous production on a frequent basis
- Limited ability to perform activities of daily living
- Reduced exercise tolerance
- Intermittent worsening of respiratory symptoms (exacerbations) requiring frequent treatment or hospitalization

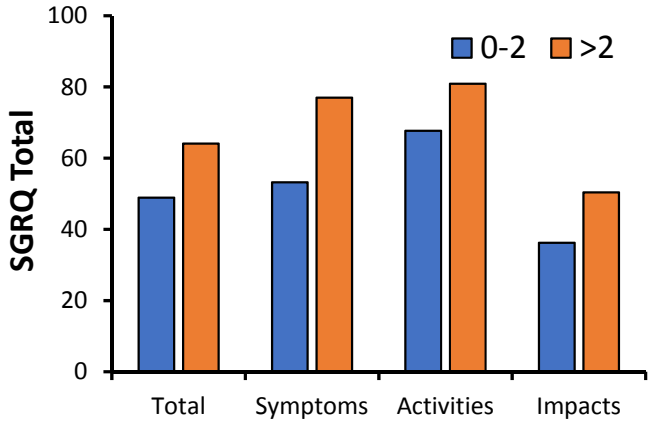
- Frail and fatigued
- Depressed and anxious
- Reduced quality of life
- Limited medical options

Exacerbations Worsen Lung Function, Quality of Life and Reduce Survival

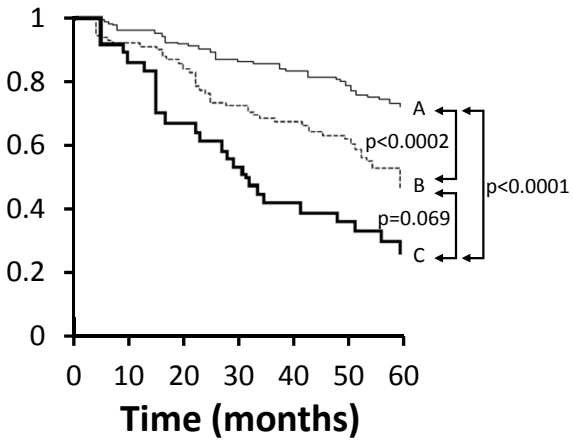
Lung Function Decline [1]



QoL[2]



Mortality[3]

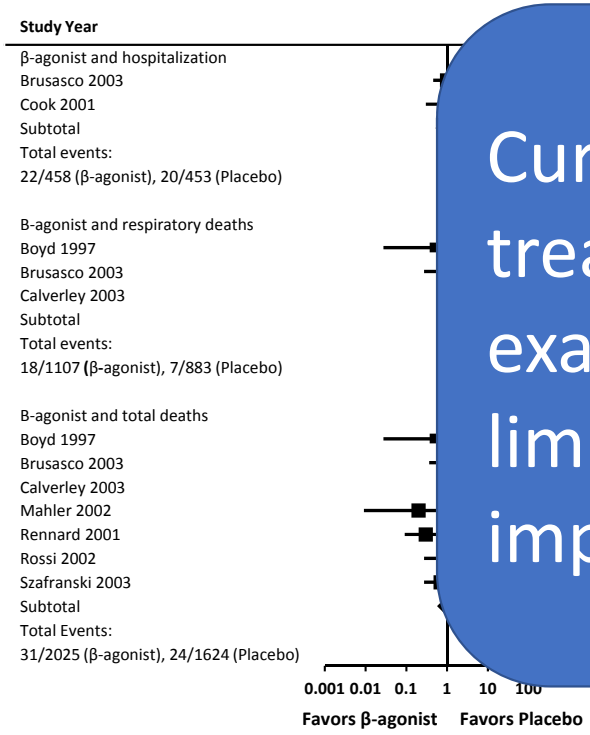


[1] Dransfield, AJRCCM, 2017; [2] Seemungal AJRCCM, 1998; [3] Soler-Cataluna, Thorax, 2005

How Good is Treatment for an Acute Exacerbation?

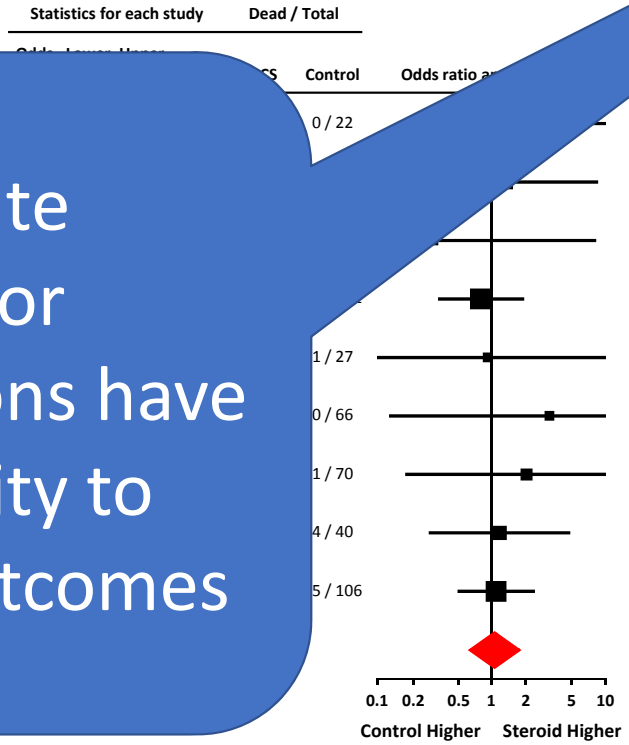
SABA[1]

Hosp & Mortality



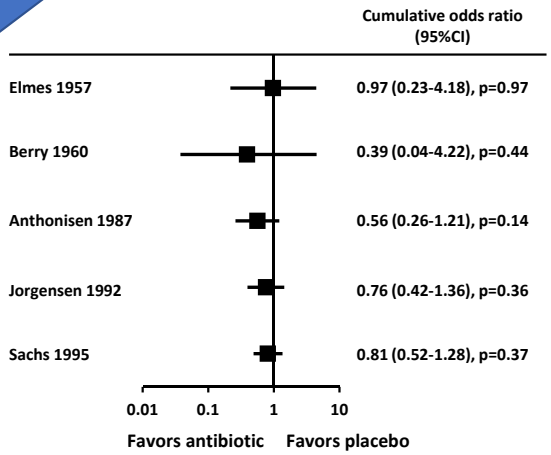
Systemic Steroids[2]

Mortality



Antibiotics[3]

Tx failure



Current acute treatment for exacerbations have limited ability to improve outcomes

[1] Salpeter, Int J COPD, 2007; [2] Abroug, Ann Int Care, 2014; [3] Puhan, BMC, 2008

Significant Complications With Even Short Term Use of Systemic Steroids

COPD population [1,2,4]

- Hyperglycemia
- Hypertension
- Increased re-hospitalization for pneumonia
- Increased Mortality (long-term use)

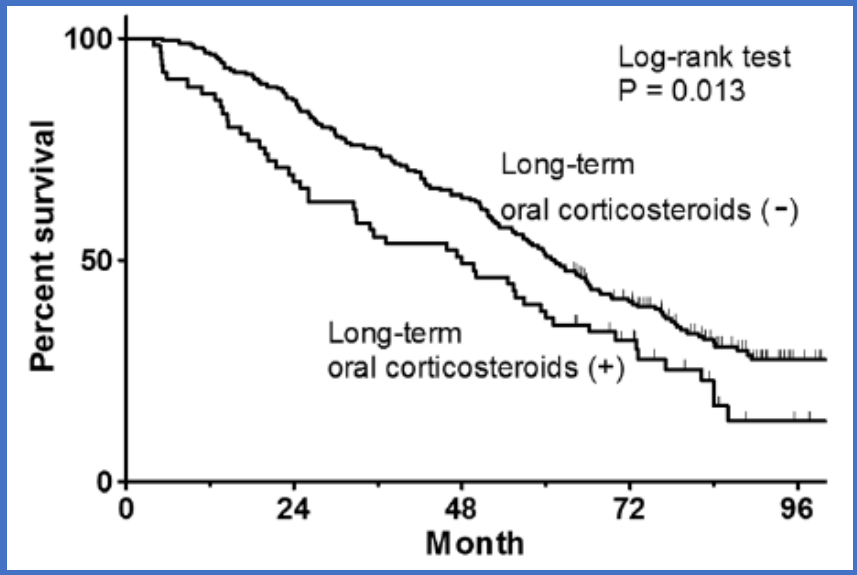


Table 3 | Incider

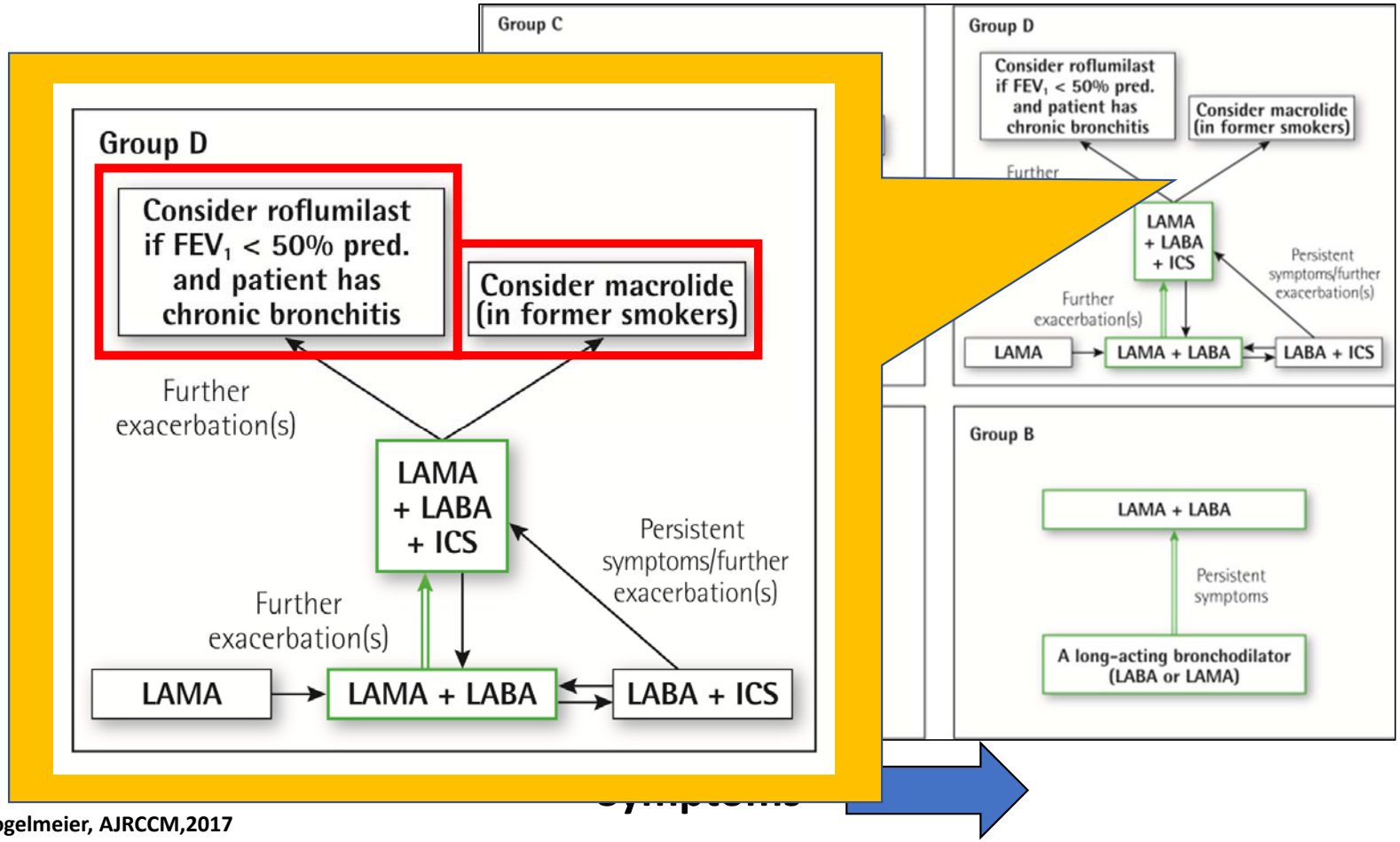
Adverse event							
All doses v no cor							
Sepsis							
Venous thromb							
Fracture							
Dose: <20 mg/da							
Sepsis							
Sepsis							
Venous thromb							
Fracture							
Dose: ≥40 mg/day v 0 m							
Sepsis	196	60	5	4.98 (1.69, 14.72)	<0.001	5.20 (1.77, 15.25)	0.003
Venous thromboembolism	491	60	5	4.15 (2.45, 7.03)	<0.001	2.27 (1.38, 3.74)	0.001
Fracture	2140	60	5	1.77 (1.31, 2.39)	<0.001	1.61 (1.26, 2.05)	<0.001

ays* ratio	P value
14)	<0.001
74)	<0.001
63)	<0.001
34)	<0.001
67)	0.10
69)	<0.001
18)	<0.001
90)	0.03
1.54)	<0.001

*Number of days from data when corticosteroid prescription was filled. Reference period was 5.180 days before prescription date.

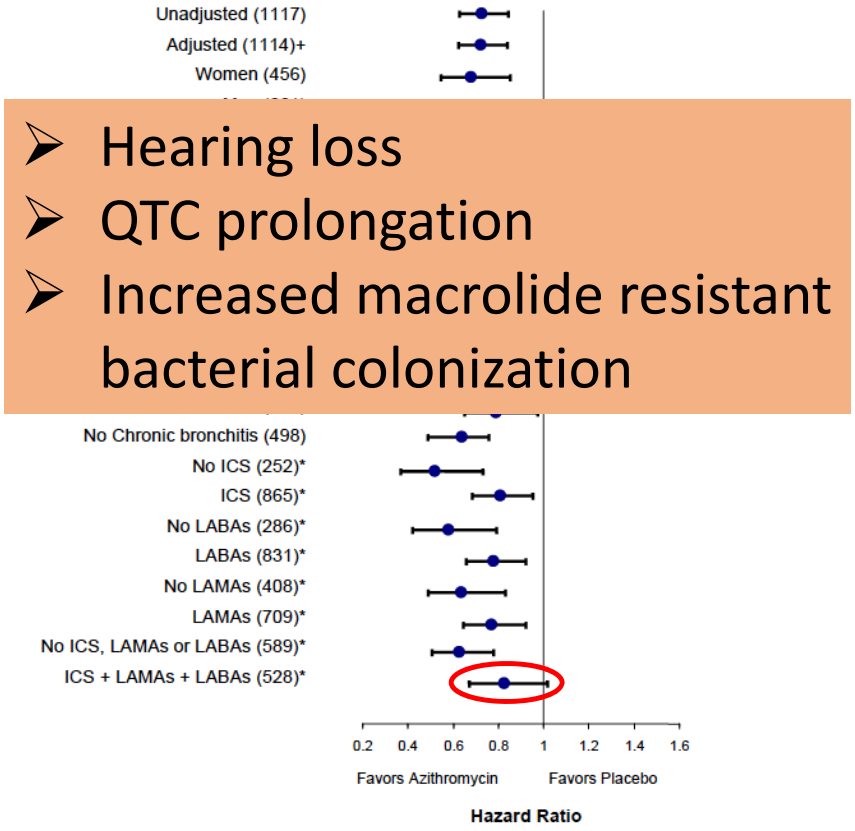
[1] Niewoehner, NEJM, 1999; [2] Leuppi, JAMA, 2013; [3] Walji, BMJ, 2017; [4] Horita, Resp Res, 2014

Recommended Pharmacological Pathway Treatment Algorithms by GOLD Grade



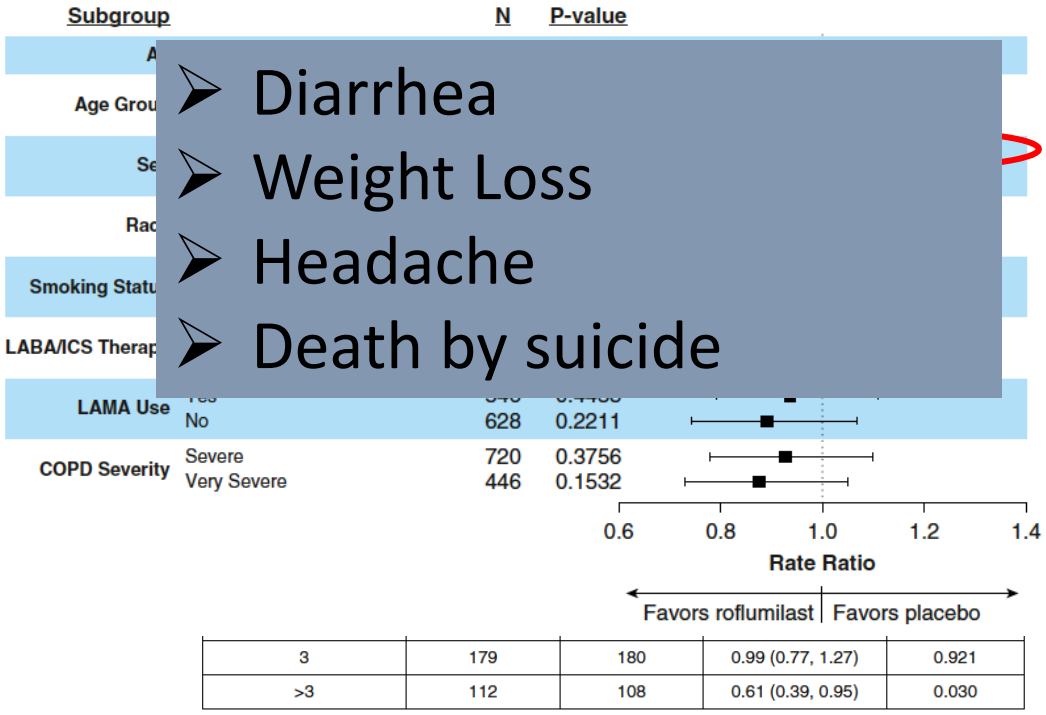
Vogelmeier, AJRCCM,2017

Azithromycin[1]



- Hearing loss
- QTC prolongation
- Increased macrolide resistant bacterial colonization

Roflumilast[2]



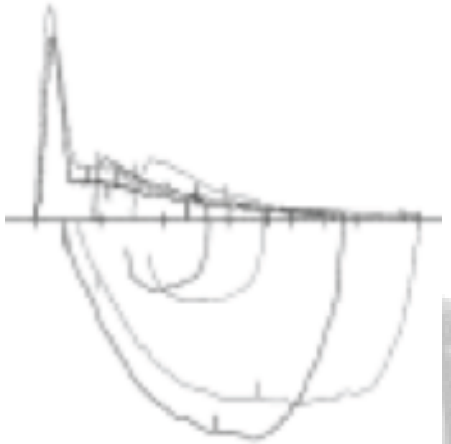
3	179	180	0.99 (0.77, 1.27)	0.921
>3	112	108	0.61 (0.39, 0.95)	0.030

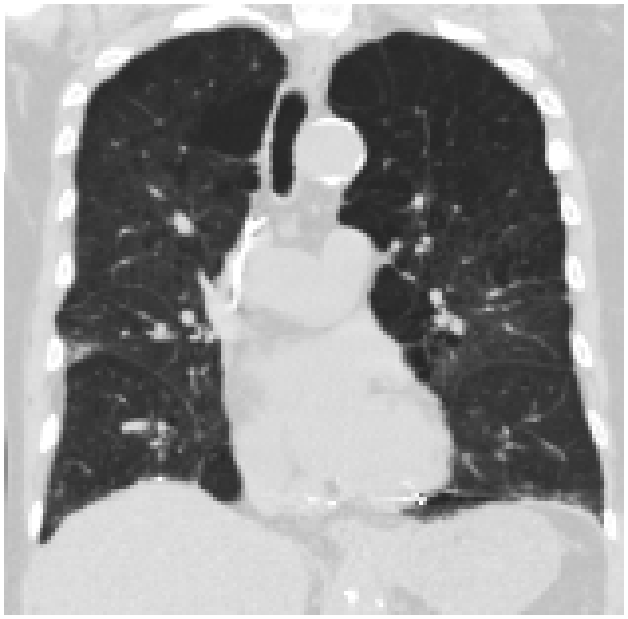
- Diarrhea
- Weight Loss
- Headache
- Death by suicide

[1] Albert, NEJM, 2011; [2] Martinez AJRCCM 2017

Patient Case : Impact of Mepolizumab

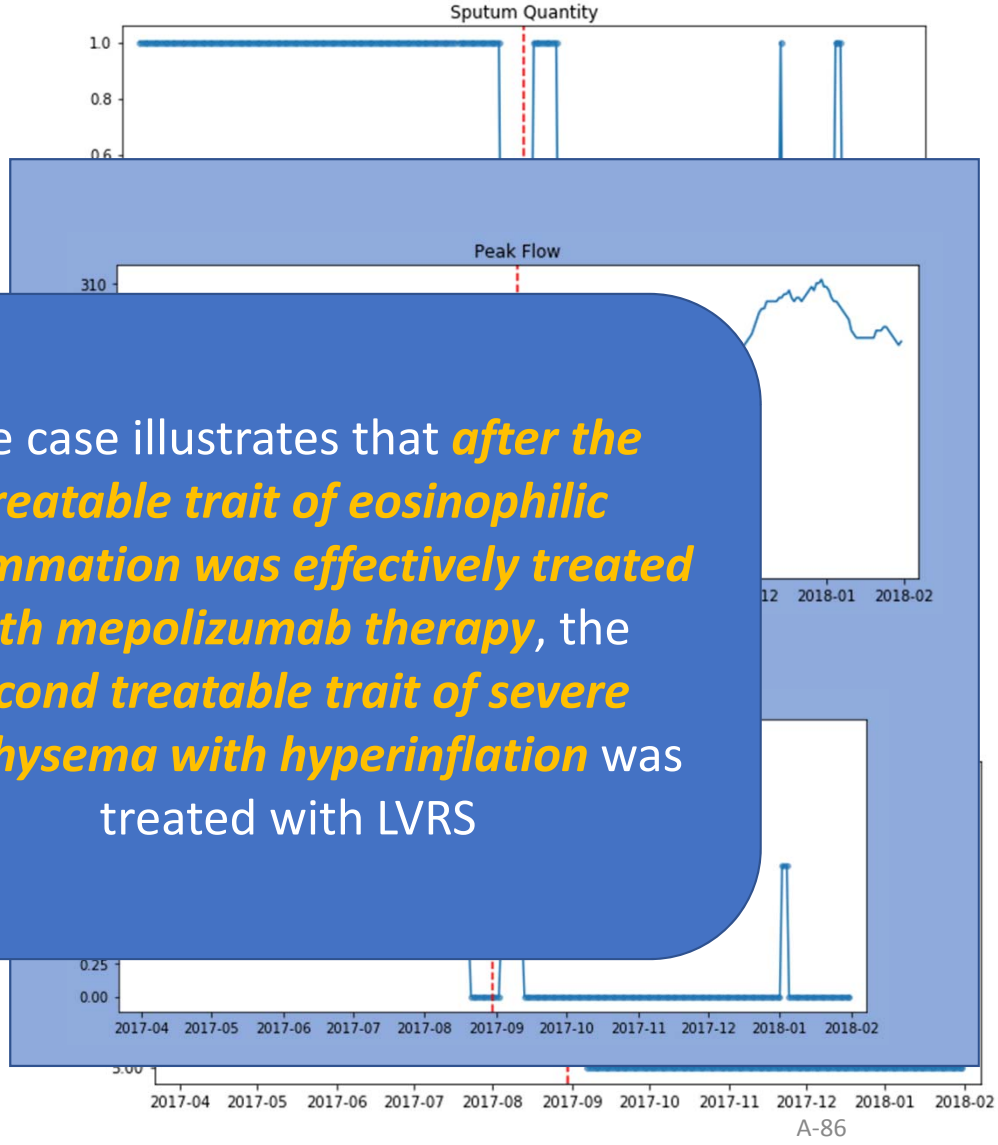
- 70 y.o. male
- COPD x 20 yrs., smoked 60 pack yrs., no history of asthma
- Multiple exacerbations and hospitalizations for COPD
- Nebulized LABA/ICS, LAMA, daily azithromycin, roflumilast, singular, 20 mg prednisone daily for > 12 months
- 2 L oxygen
- FEV_1 0.82 L (29 % pred.), RV 5.25 L (210% pred.), DLCO 36% pred.
- S/P BLVR with EBV in RUL- no effect
- Referred for LVRS- denied secondary to high dose chronic steroids and multiple recent AECOPDs
- Eosinophils 400 cells/uL





Patient Outcome

- Started on Mepolizumab
- Weaned off systemic steroids ov
  6 weeks
- ***No moderate or s***
  exacerbations in the past 8 mo
- Completed rehabilitation
- Underwent successful LVRS 6 months ago
- Improved daily function and markedly reduced dyspnea at rest and with exertion



The case illustrates that ***after the treatable trait of eosinophilic inflammation was effectively treated with mepolizumab therapy***, the ***second treatable trait of severe emphysema with hyperinflation*** was treated with LVRS

Conclusion

- Patients with advanced COPD with moderate and severe exacerbations despite maximal COPD medical therapy have increased symptom burden, poor functional status, and increased mortality
- Mepolizumab fills a void in current medical therapy by providing a clinically relevant reduction in the frequency and severity of exacerbations and avoiding the complications of systemic steroids in the subset of patients with advanced COPD and increased blood eosinophils who remain refractory to maximal medical therapy

NUCALA®
Mepolizumab for Patients with COPD

Closing Remarks

Steven Yancey, MS
Vice President, Medicines Development Leader
GlaxoSmithKline

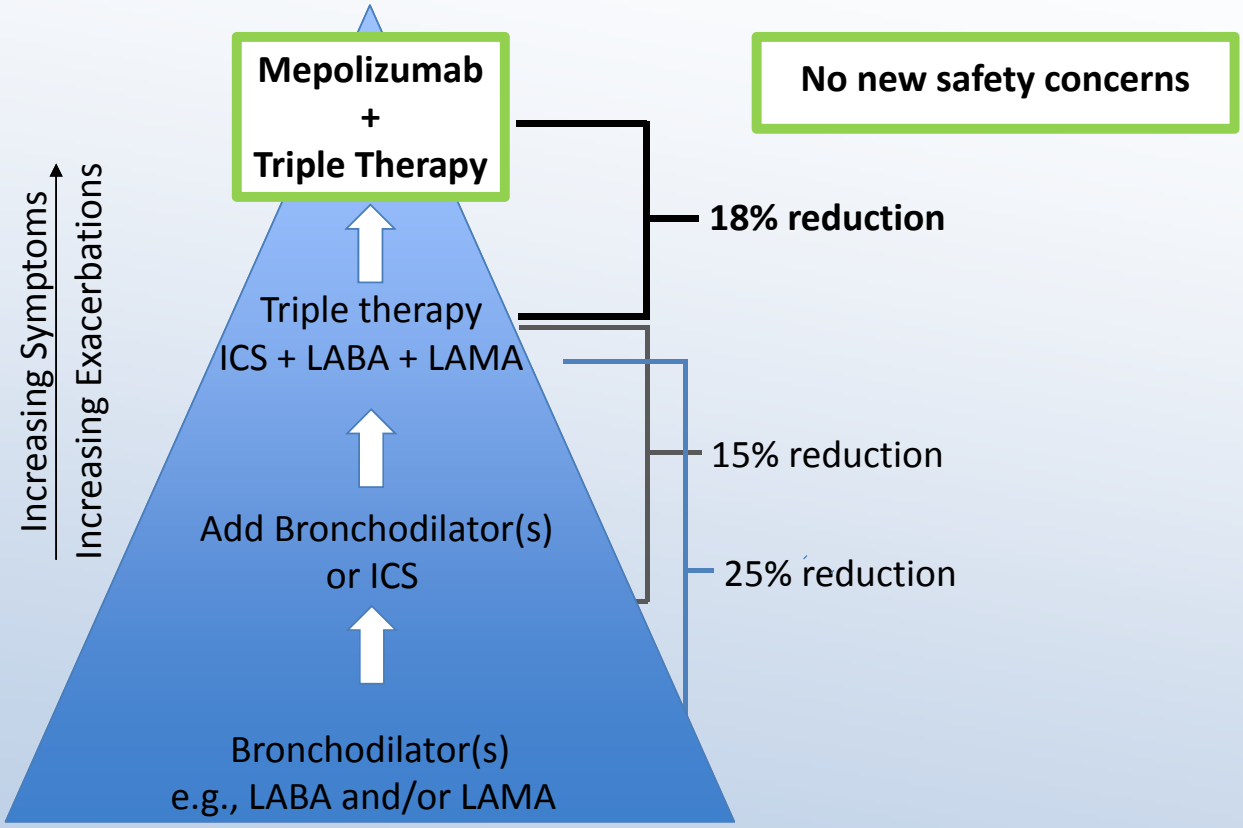
Mepolizumab Addresses Key Unmet Needs in the Care of Patients with COPD

Unmet Need

Exacerbations
- **Perpetuating**
- **Fail to recover**
- **Increase risk of death**
- **Poor QoL**
- **Economic impact**
- **Insidious cycle**

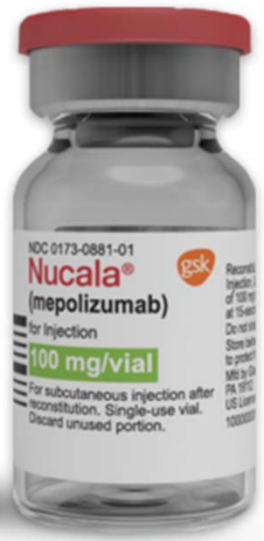
Patients: GOLD D on optimized Triple Therapy

Biomarker to guide treatment



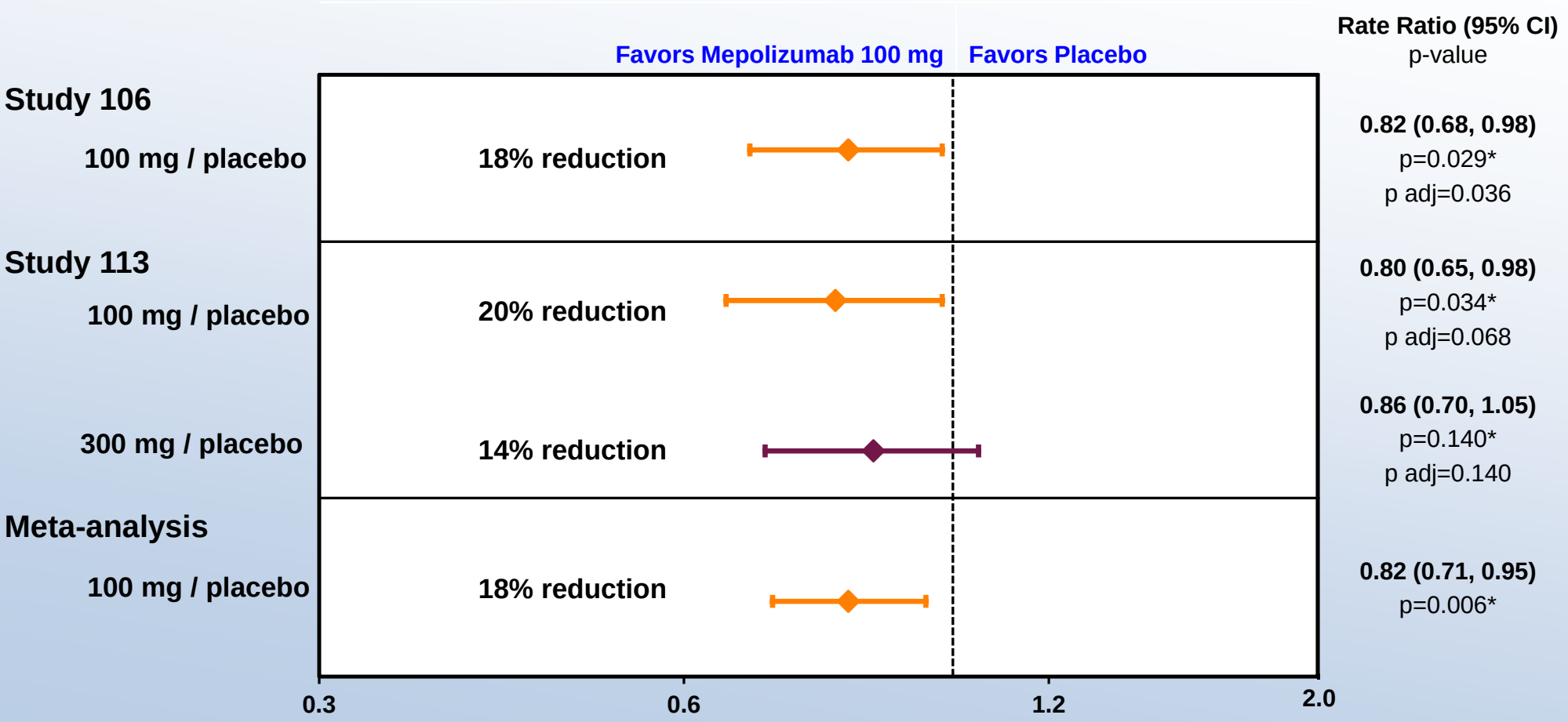
Lipson et al. *N Engl J Med* 2018; 378:1671-1680, Modified from GOLD 2017; Pavord et al. *N Engl Med* 2018; 377:1633-1629

NUCALA Addresses Unmet Needs in Patients with Severe COPD and Eosinophilic Inflammation



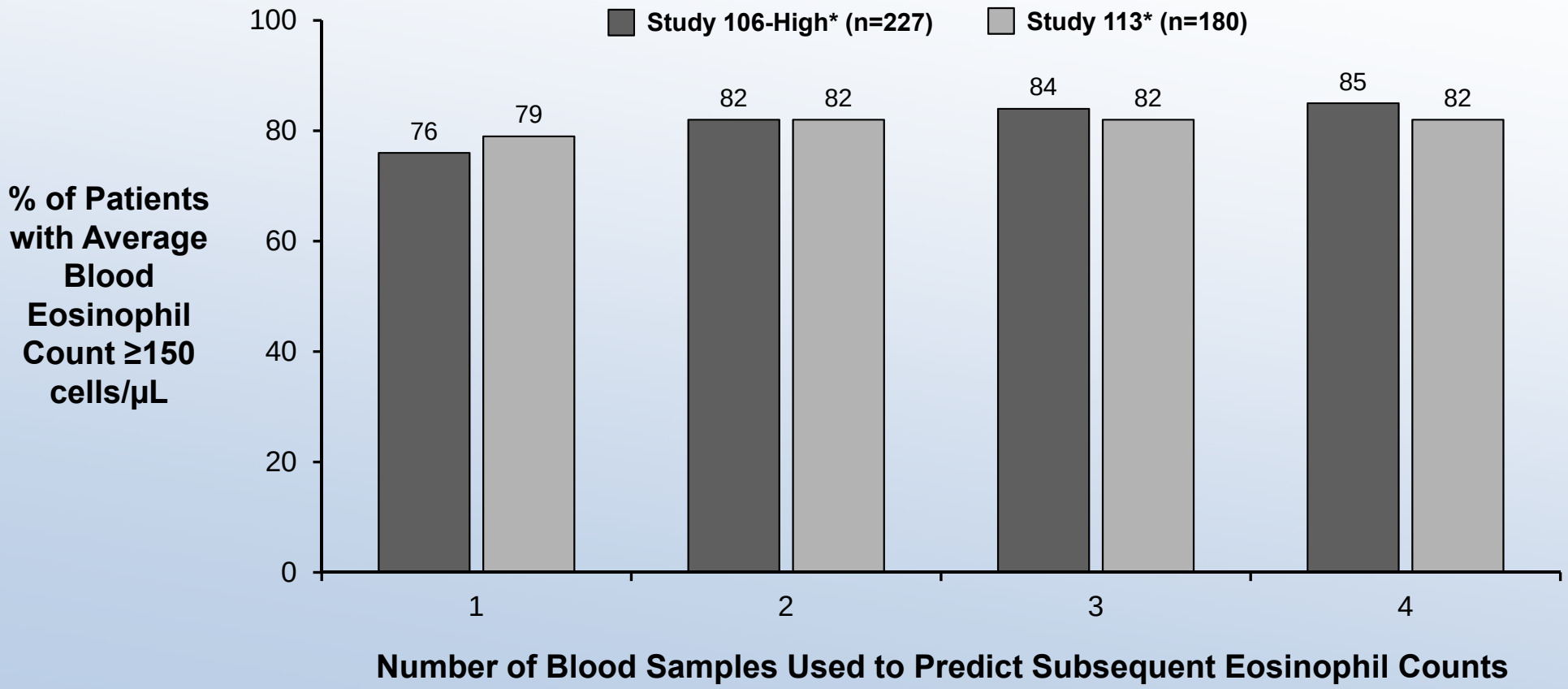
BACKUP SLIDES

Moderate/Severe Exacerbations
Primary Endpoint Including 300mg (BD figure 6)



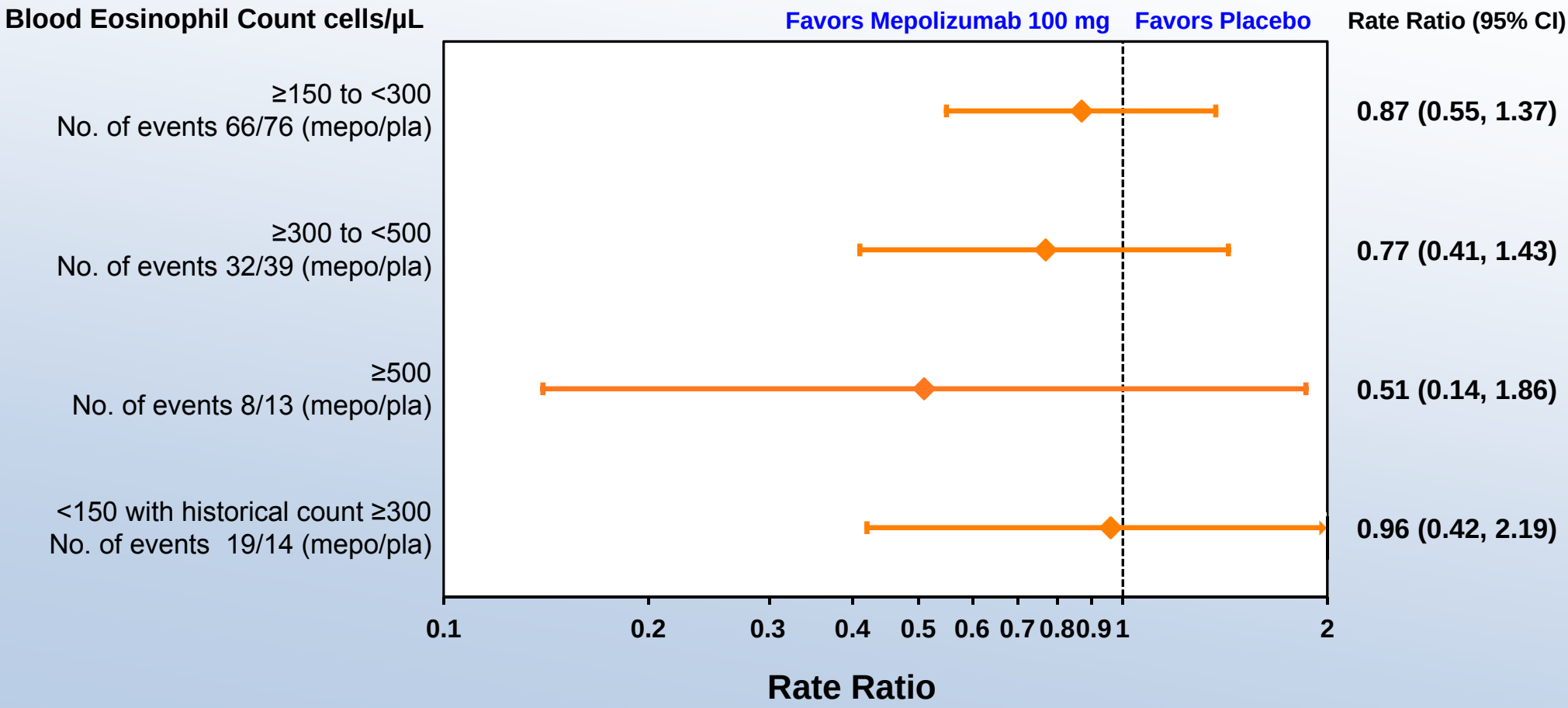
* Unadjusted p-value

Stability of Blood Eosinophils in Placebo Patients



*Placebo patients with blood eosinophils ≥150 cells/µL at the screening visit

Exacerbations Leading to ED/Hospitalization by Screening Blood Eosinophil Categories – Meta analysis 100mg



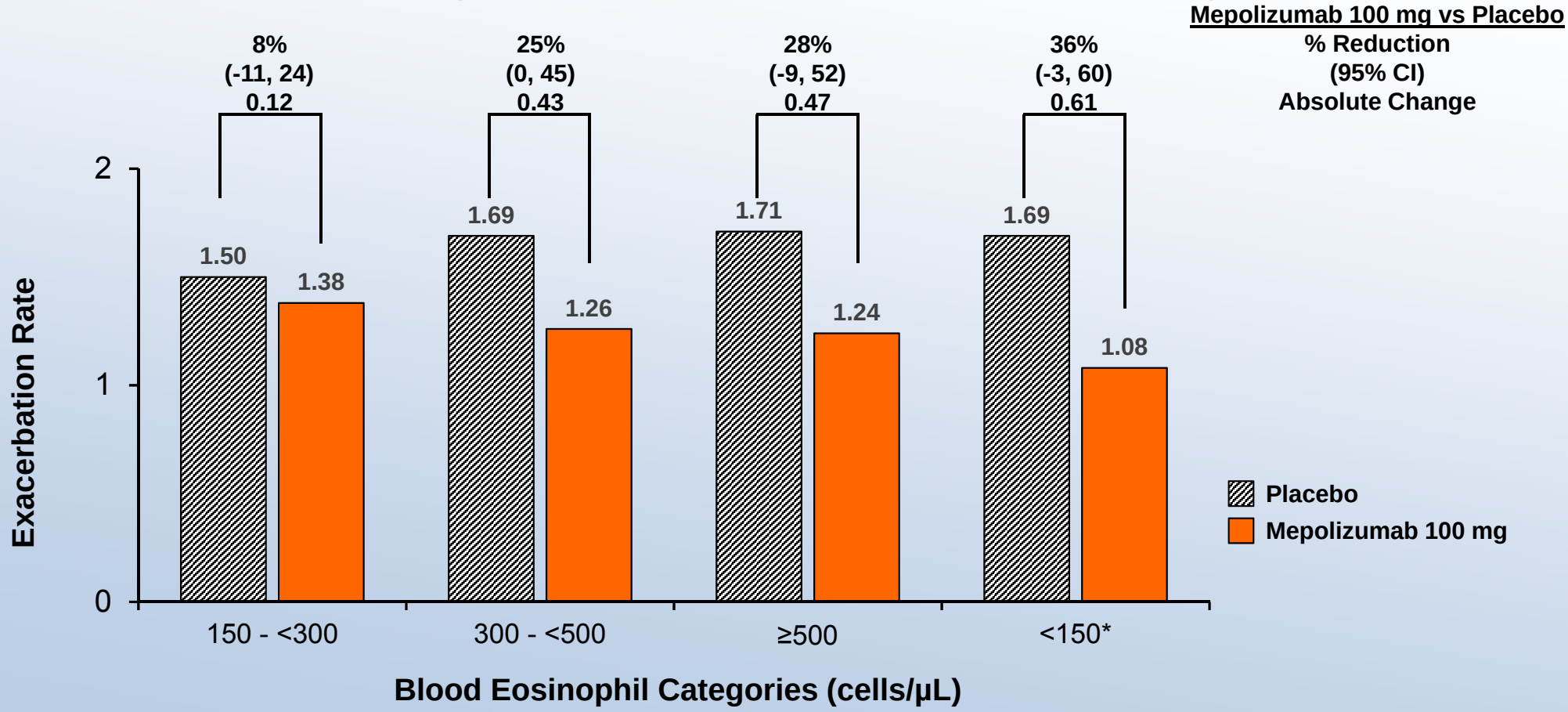
Horizontal bars represent 95% confidence intervals

Comparison of Demography
GSK Mepolizumab COPD and Asthma Studies

	Mepolizumab COPD Study 106 and Study 113	Mepolizumab Severe Asthma Study 588
Mean Age, years	65	50
Percent Male (%)	66%	43%
Mean post-BD FEV_1 (L)	**1.2-1.3**	**2.1**
Mean post-BD %predicted FEV_1	**44-46**	**71**
Percent Reversibility FEV_1 (%)	**9-10**	**28**
Mean post-BD FEV_1/FVC	0.5	0.7
Current Smoker	**28%**	**0%**
Former Smoker	**70%**	**28%***
Non/never Smoker	**2%**	**72%**
Mean pack-years	44	Required <10 for former smokers
IGE U/mL, log transformed geometric mean	78.8	160.05

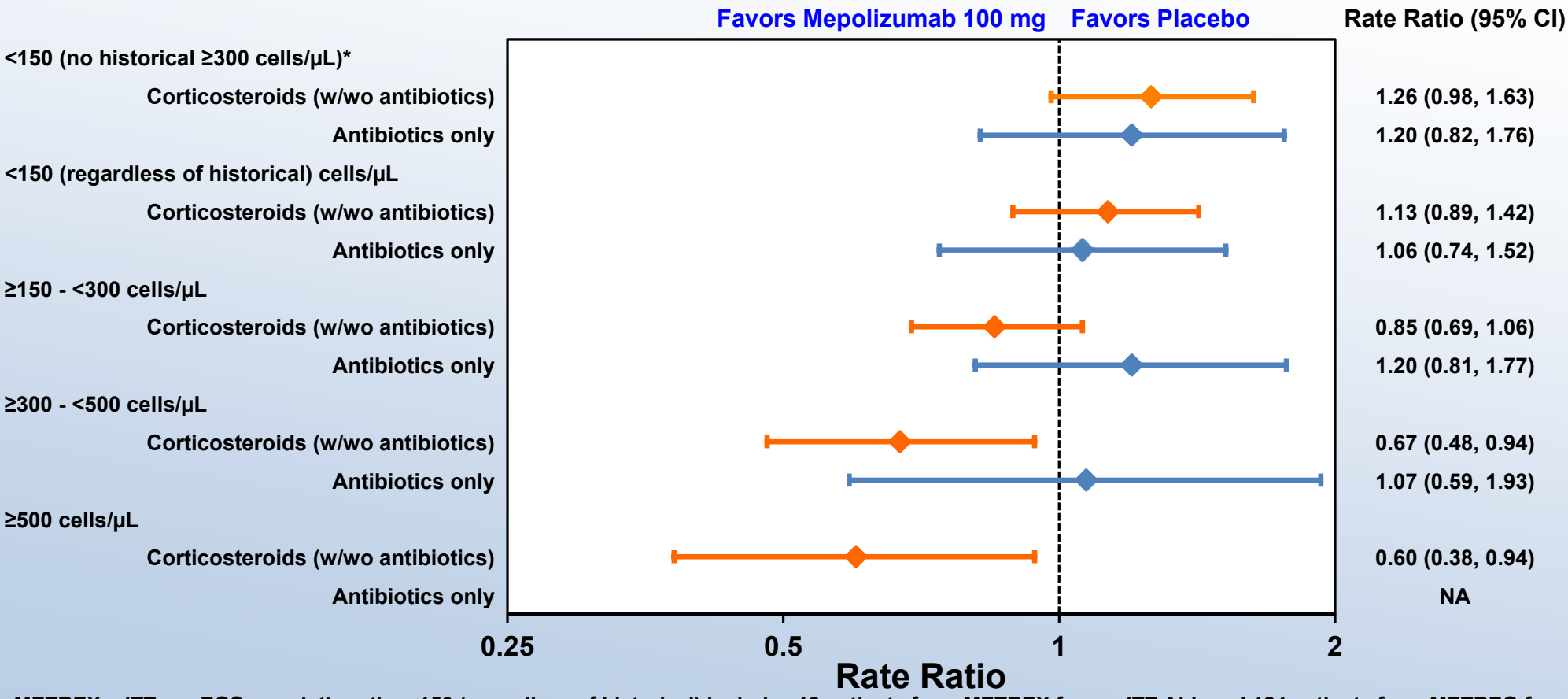
* Former smokers had < 10 pack yr history

Rate of Exacerbation by Screening Eosinophils Category Meta-analysis 100 mg



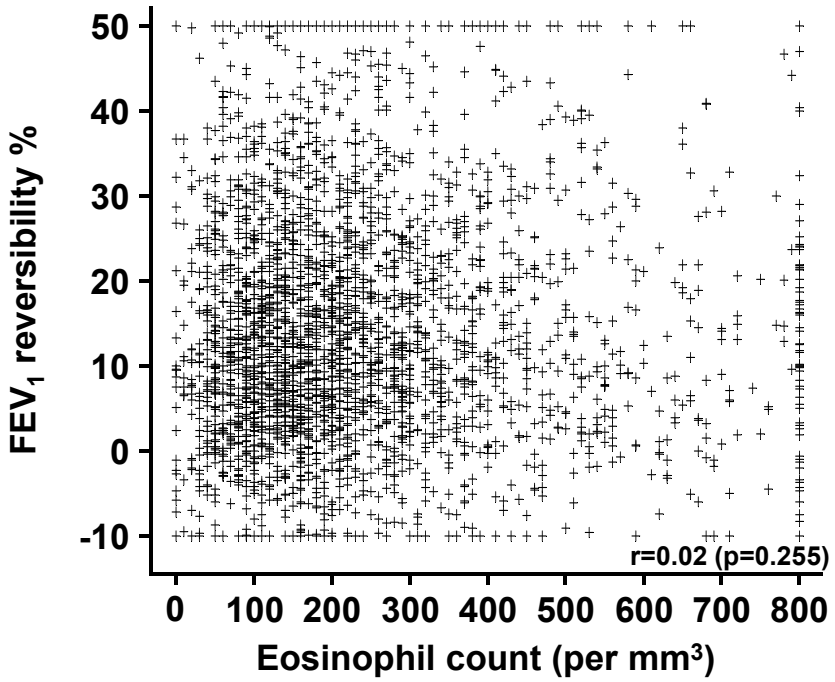
* Blood eosinophil count of <150 cells/uL at screening and ≥ 300 cells/µL in prior year

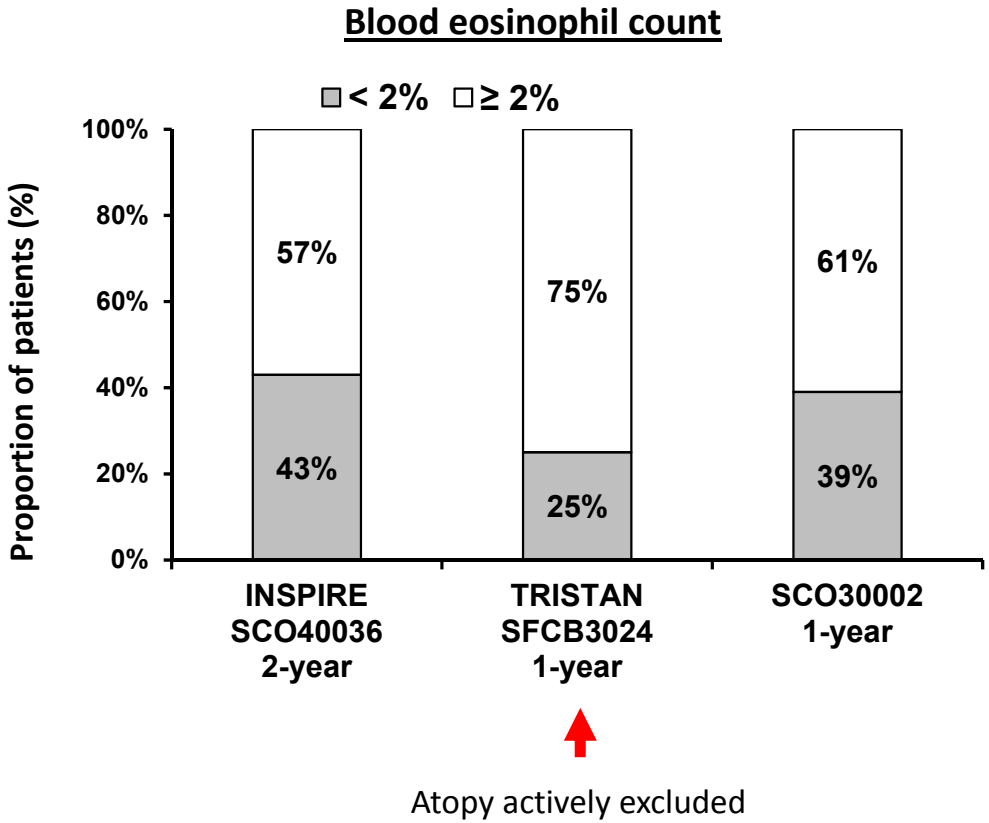
Mod/Sev Exacerbations by Treatment Type Stratified by Screening Blood Eosinophil Categories – Meta Analysis (ABX and SCS)



*From METREX mITT-nonEOS population; the <150 (regardless of historical) includes 13 patients from METREX from mITT-ALL and 124 patients from METREO from mITT with an eosinophil count ≥300 cells/µL in previous year; mITT population: patients receiving ≥1 dose of mepolizumab or placebo. mITT-All population: patients receiving at least one dose of mepolizumab or placebo; mITT-Eos population: patients with ≥150 cells/µL at screening OR ≥300 cells/µL within the previous year

The Relationship Between Blood Eosinophils and Features of Asthma





Pascoe et al. Lancet Resp Med 2015;3:435-42; Pavord et al. Thorax 2016;71:118-125