

WITH THE ENDORSEMENT OF:



Network
Respiratory Diseases
(ER-NET)



Milan, Italy
March 3-4, 2023

10th

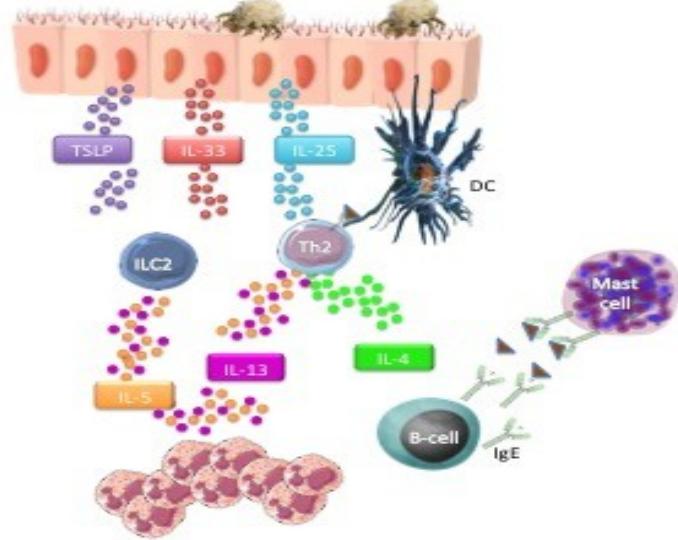
International Meeting on
PULMONARY RARE DISEASES AND ORPHAN DRUGS

Biological therapies in type 2 asthma

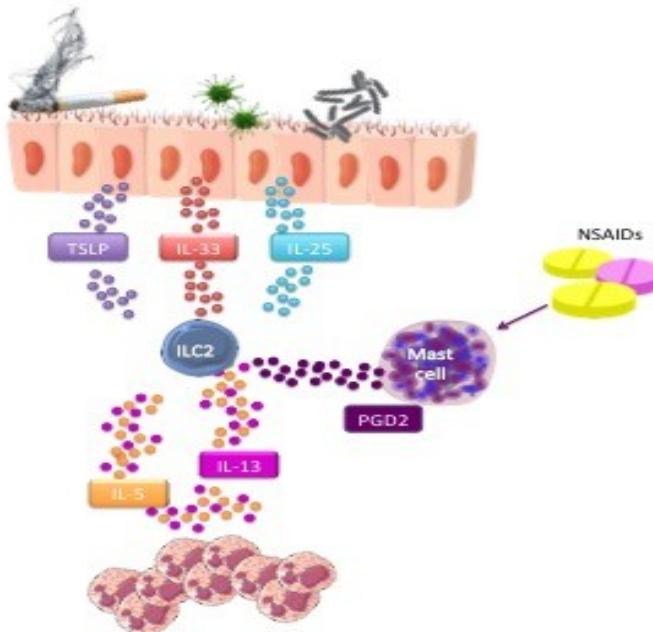
Prof. Enrico Heffler, MD, PhD
Associate Professor of Internal Medicine
Director of Postgraduate Residency Programme
in Allergy and Clinical Immunology
Humanitas University – Milano (Italy)

Severe asthma: a type-2 disease

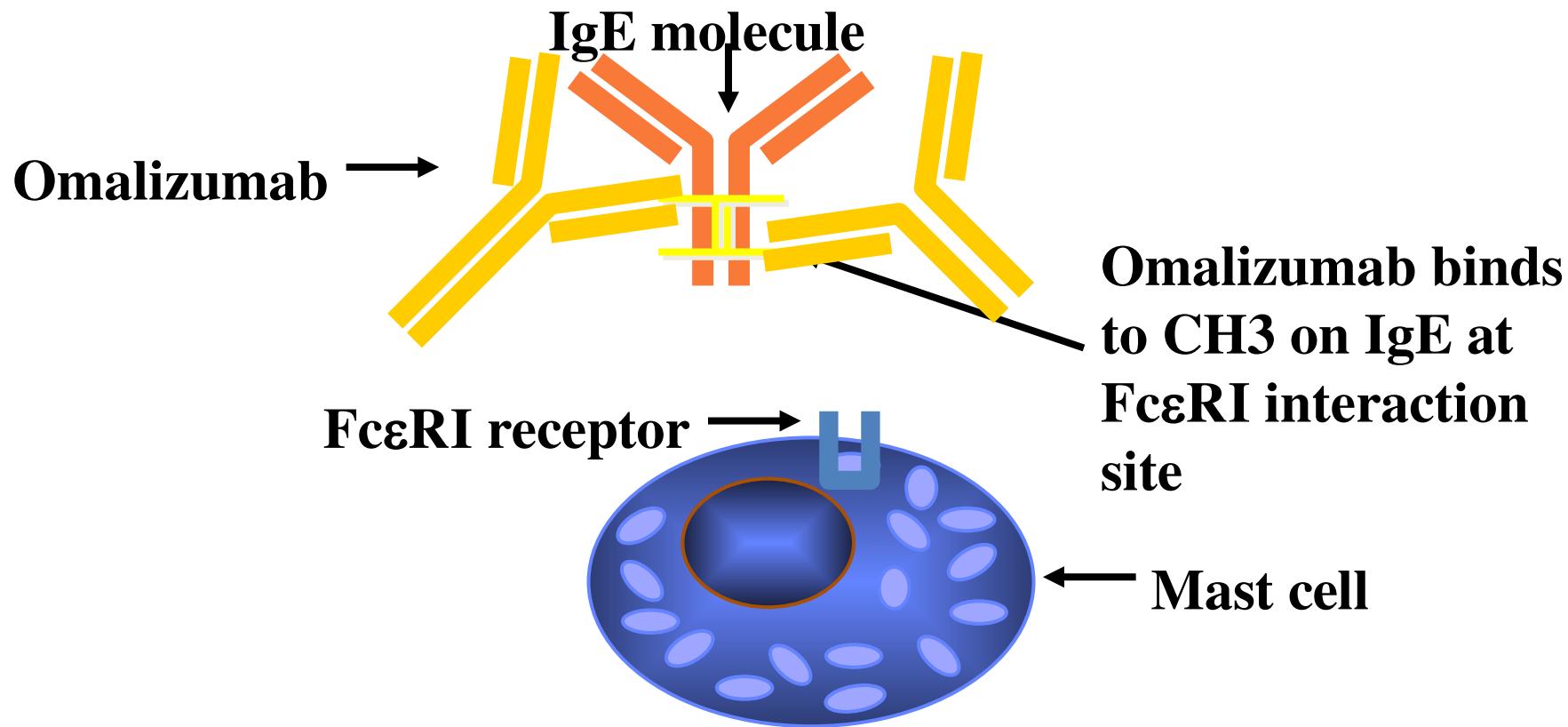
ALLERGIC EOSINOPHILIC AIRWAY INFLAMMATION



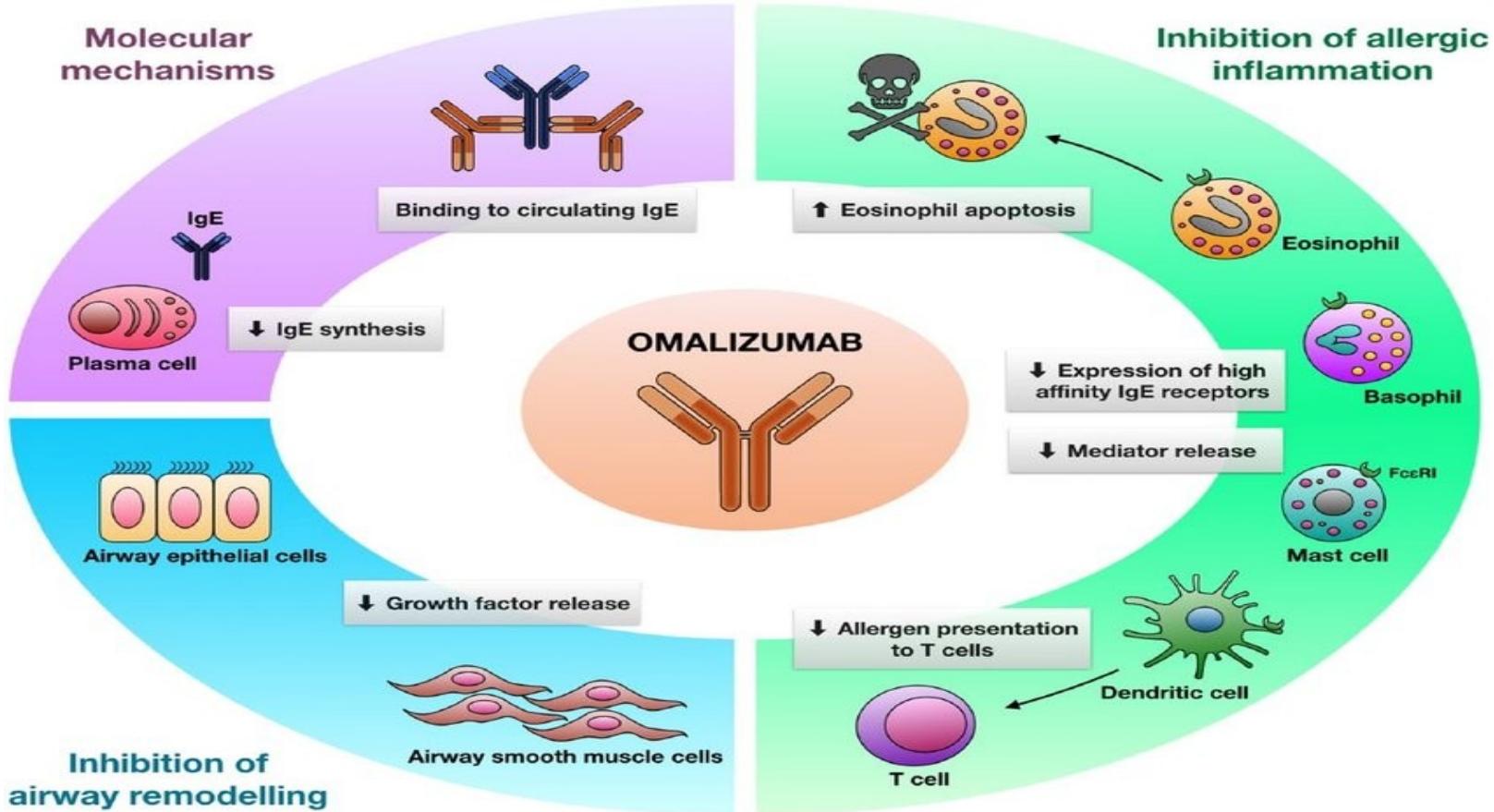
NON-ALLERGIC EOSINOPHILIC AIRWAY INFLAMMATION



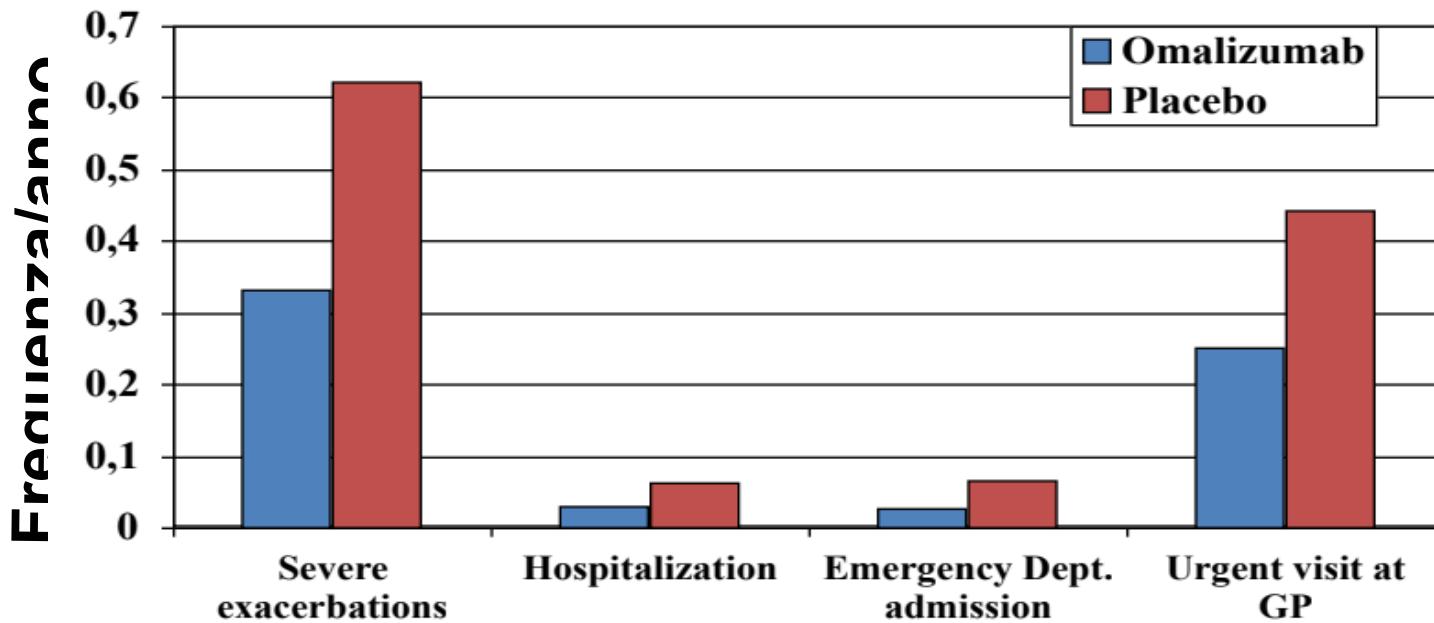
Omalizumab



Omalizumab



Omalizumab



Omalizumab

	Annual exacerbation rate treatment difference	Percent reduction	p-value
INNOVATE study ¹	0.69	26.2%	0.043
ETOPA study ²	1.49	60.4%	<0.001
SOLAR study ³	0.29	37.5%	0.027
Busse study ⁴	0.40	40.3%	<0.001
Solèr study ⁵	0.70	57.6%	<0.001
Holgate study ⁶	0.42	26.5%	0.165
ALTO study	0.18	15.3%	0.077
Pooled⁷	0.56	38.3%	<0.0001

1. Humbert M, et al. Allergy 2005; 2. Ayres JG, et al. Allergy 2004; 3. Vignola AM, et al. Allergy 2004;
4. Busse W, et al. J Allergy Clin Immunol 2001; 5. Solèr M, et al. Eur Respir J 2001;
6. Holgate ST, et al. Clin Exp Allergy 2004; 7. Bousquet J, et al. Allergy 2005

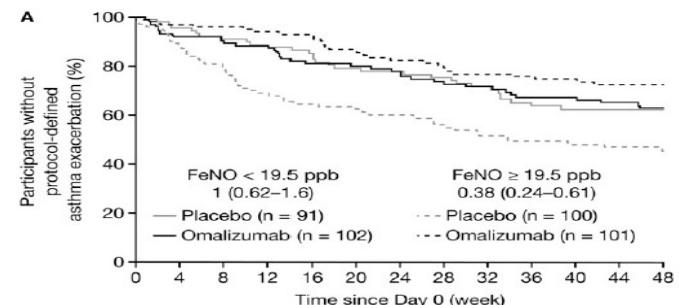
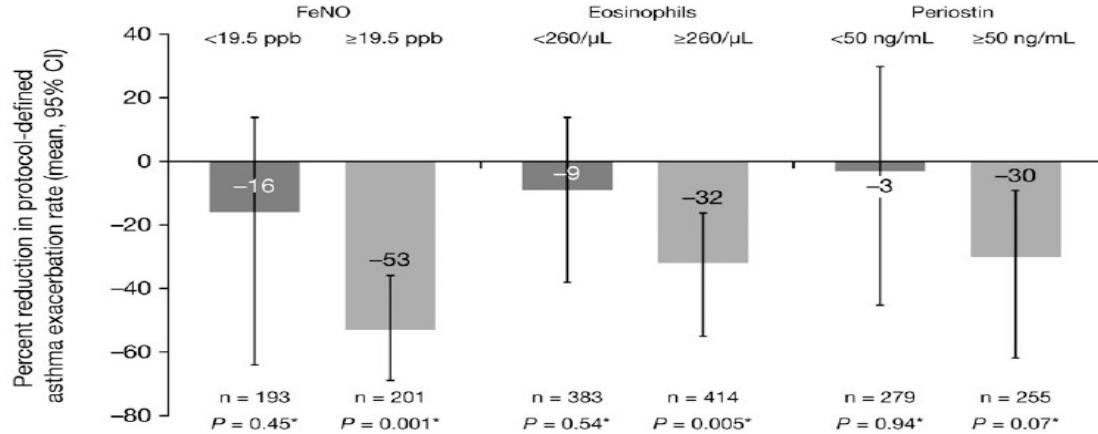
Omalizumab

Exploring the Effects of Omalizumab in Allergic Asthma An Analysis of Biomarkers in the EXTRA Study

Nicola A. Hanania¹, Sally Wenzel², Karin Rosén³, Hsin-Ju Hsieh³, Sofia Mosesova³,
David F. Choy³, Preeti Lal³, Joseph R. Arron³, Jeffrey M. Harris³, and William Busse⁴



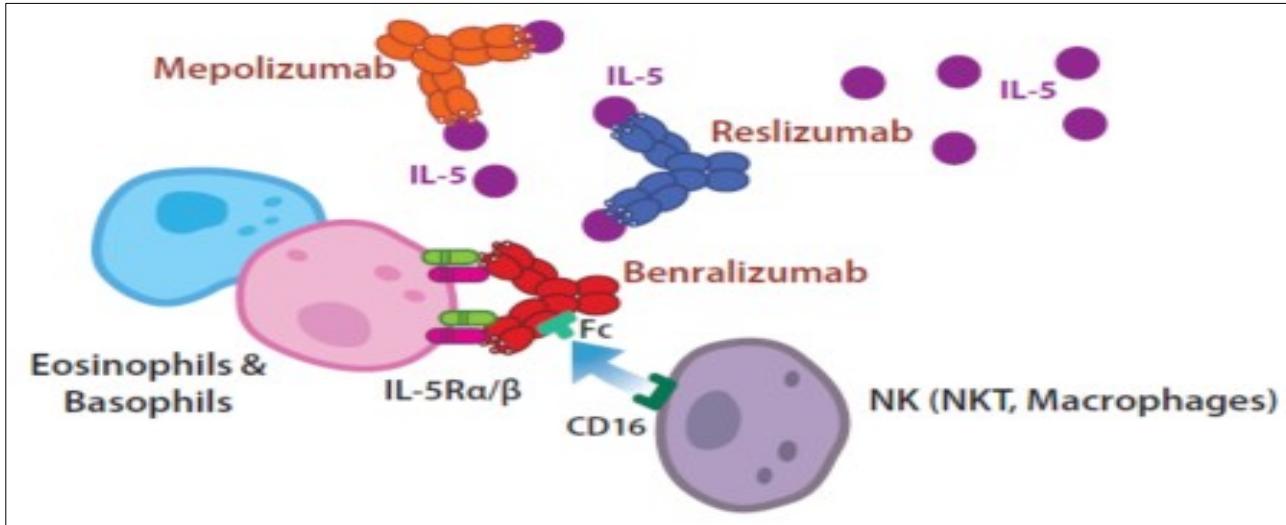
Am J Respir Crit Care Med 2013



Omalizumab: Long-term efficacy

	All patients	RAO+ patients	RAO- patients	RAO+ vs RAO- P value
Number	32	18	14	
Women (%)	22 (69)	13 (72)	9 (64)	NS
AGE, yrs , mean (SD)	57 ± 12	59 ± 12	56 ± 12	NS
BMI , mean (SD)	25.5 ± 4.0	25.6 ± 4.4	25.3 ± 3.6	NS
Smokers , n (%)	7 (22)	3 (17)	4 (29)	NS
Country residence n (%)	14 (44)	9 (50)	9 (64)	NS
Polisensitization, n (%)	22 (69)	13 (72)	9 (64)	NS
Rhinitis, n (%)	21 (66)	15 (83)	6 (43)	0.027
Rhinosinusitis, n (%)	21 (66)	14 (78)	7 (50)	NS
Nasal Polyps , n (%)	17 (53)	13 (72)	4 (29)	0.031
Nasal Polyps score, mean (SD)	13.3 ± 1.7	13.2 ± 1.7	14.0 ± 1.4	NS
Systemic arterial hypertension,n(%)	17 (53)	7 (39)	10 (71)	NS
Cardiovascular disease, n (%)	4 (13)	1 (6)	3 (21)	NS
Depression, n (%)	15 (47)	8 (44)	7 (47)	NS
Osteoporosis, n (%)	11 (34)	5 (28)	6 (43)	NS
Gastroesophageal reflux dis., n (%)	18 (56)	11 (61)	7 (50)	NS
Oral corticosteroids, n (%)	24 (75)	16 (89)	8 (57)	0.05
Asthma duration, yrs, , mean (SD)	22 ± 10	19 ± 10	27 ± 10	0.026
Age at asthma onset, yrs,mean (SD)	35 ± 15	38 ± 15	32 ± 17	NS
Total IgE UI , mean (SD)	429 ± 369	473 ± 425	346 ± 245	NS
Eosinophils cells/μL , mean (SD)	592 ± 389	754 ± 379	351 ± 284	0.002
Eosinophils ≥300 cells/μL, n (%)	23 (72)	18 (100)	5 (36)	0.0001
F_eNO, ppb, mean (SD)	47.4 ± 45.2	66.8 ± 50	23.9 ± 22.8	0.007
F_eNO ≥ 30 ppb, n (%)	15 (47)	13 (72)	2 (14)	0.0016
Asthma Control Test , mean (SD)	16.0 ± 4.0	16.3 ± 4.3	15.5 ± 3.7	NS
Asthma exacerbations, n,mean (SD)	4.34 ± 1.6	4.6 ± 1.6	4.1 ± 1.5	NS
FEV₁, % pred, mean (SD)	60.5 ± 12.5	64.5 ± 11.8	55.3 ± 11.6	0.035
D-FEV₁ PB*, % baseline , mean (SD)	17.3 ± 11.1	22.7 ± 11.5	10.4 ± 5.5	0.001
Positive Albuterol test, n (%)	19 (59)	16 (89)	3 (21)	0.0002

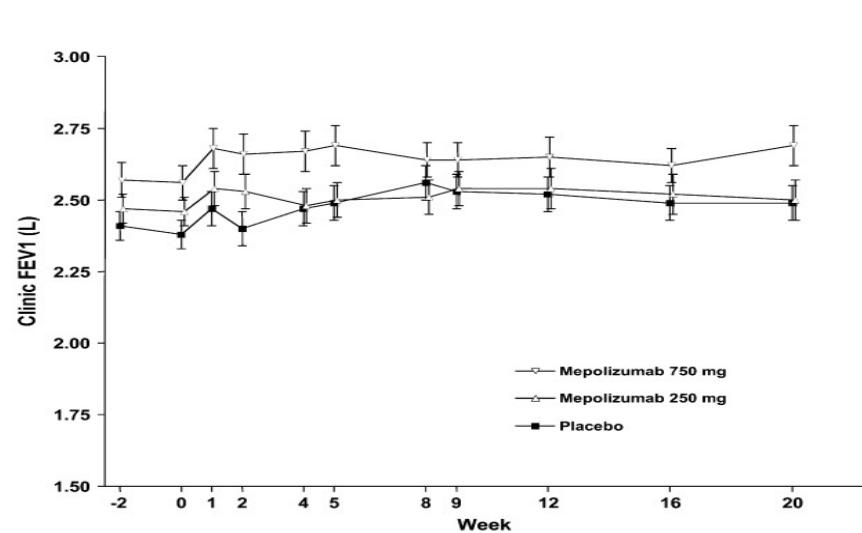
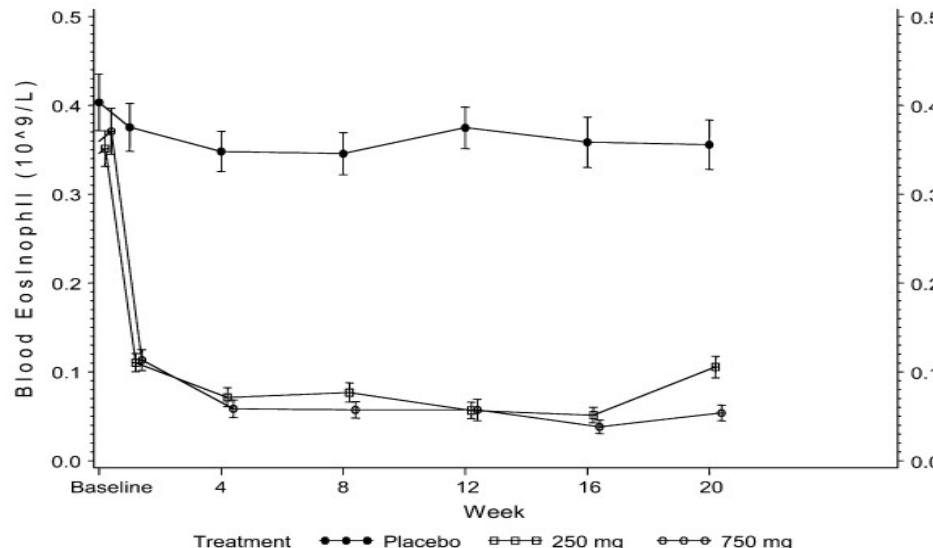
Anti-IL5 strategies



A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page¹, Cheri Swenson², Isidore Faiferman³, John Matthews³, Michael Williams³, Lesley Brannick³, Douglas Robinson⁴, Sally Wenzel⁵, William Busse², Trevor T. Hansel⁴, and Neil C. Barnes⁶, on behalf of the International Mepolizumab Study Group*

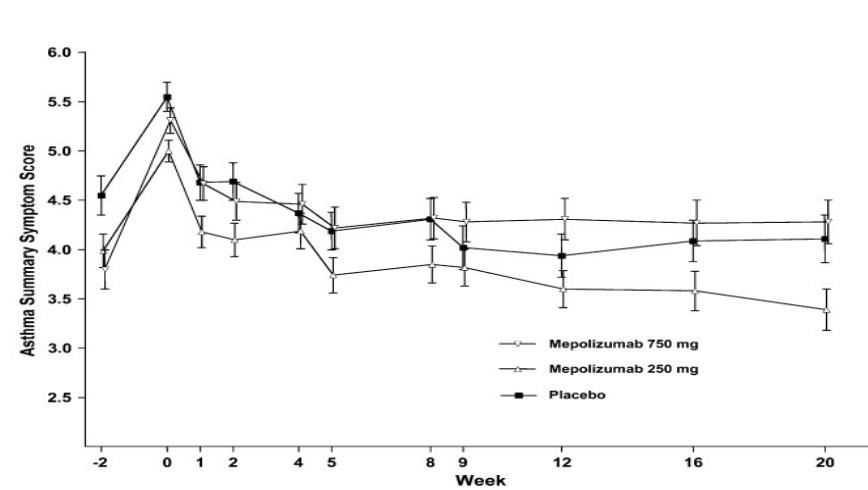
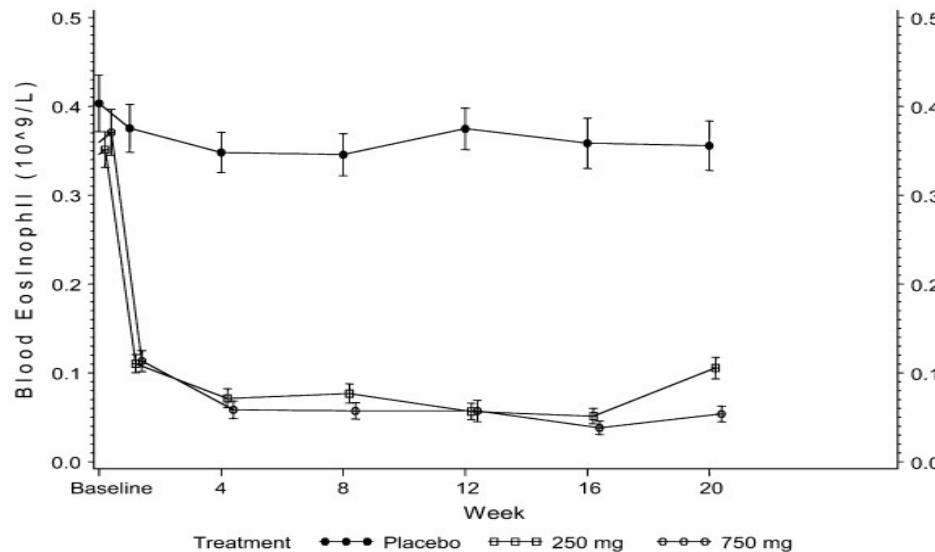
AJRCCM 2007



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AJRCCM 2007



ORIGINAL ARTICLE

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P.,
Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc.,
Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P.,
Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P.,
Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

■ INCLUSION CRITERIA:

- Refractory asthma
- **Sputum eosinophils > 3% DCC, despite high dose of inhaled corticosteroids**
- At least 2 exacerbations in the last 2 years, with the need to make a short course of systemic corticosteroids

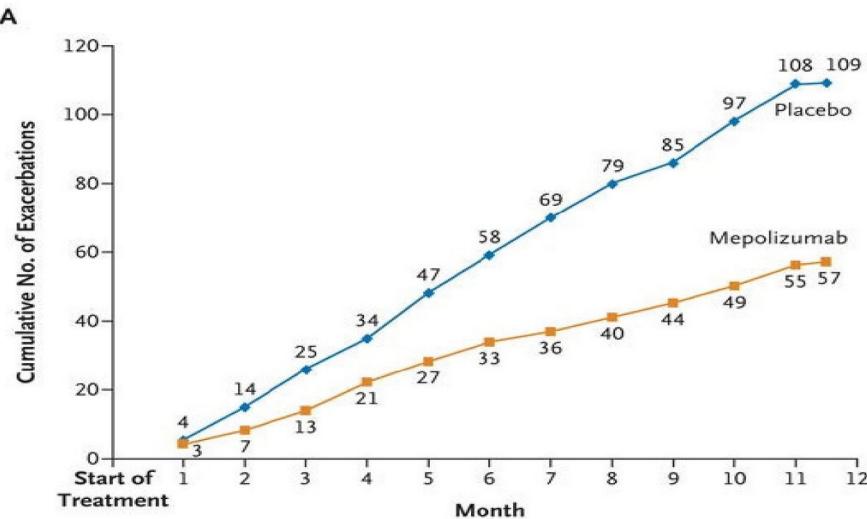
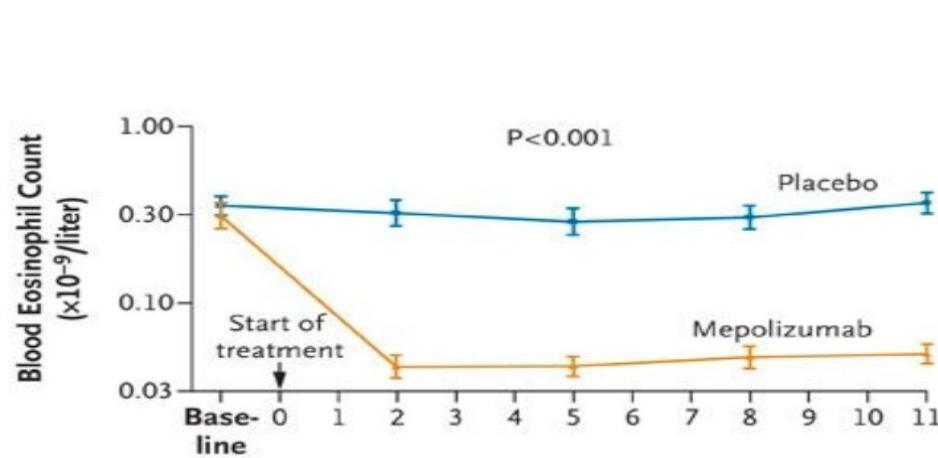
■ THERAPY:

- Mepolizumab 750 mg i.v./month (n=209) for a total of 12 months vs placebo (n=32)

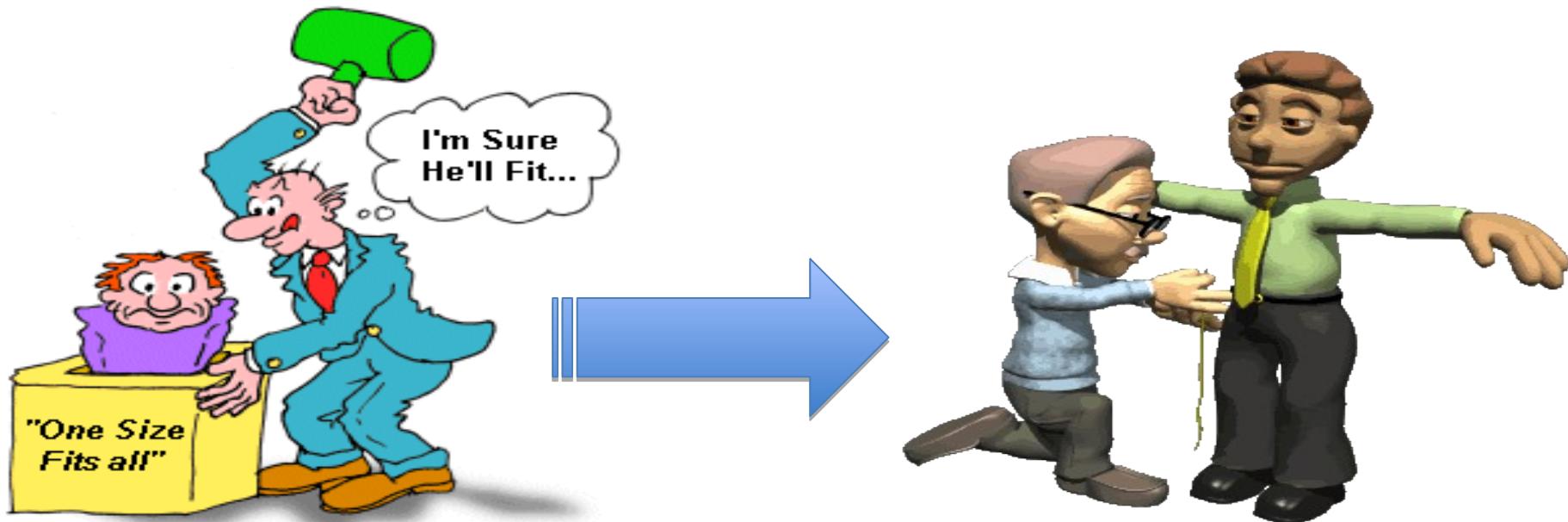
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PHENOTYPE-DRIVEN THERAPY

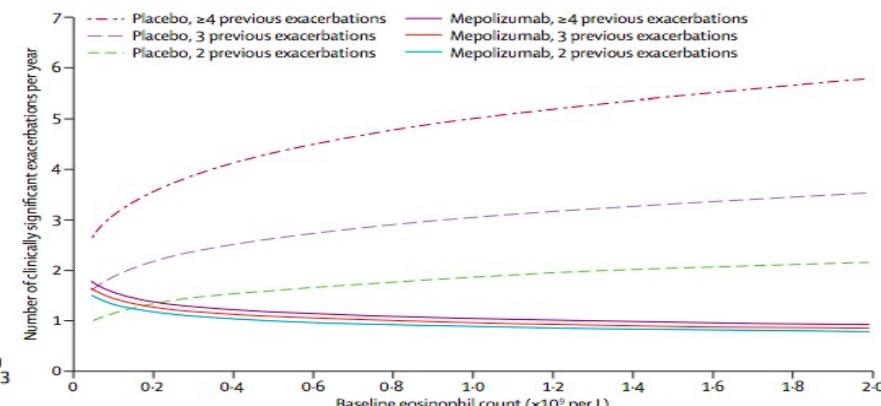
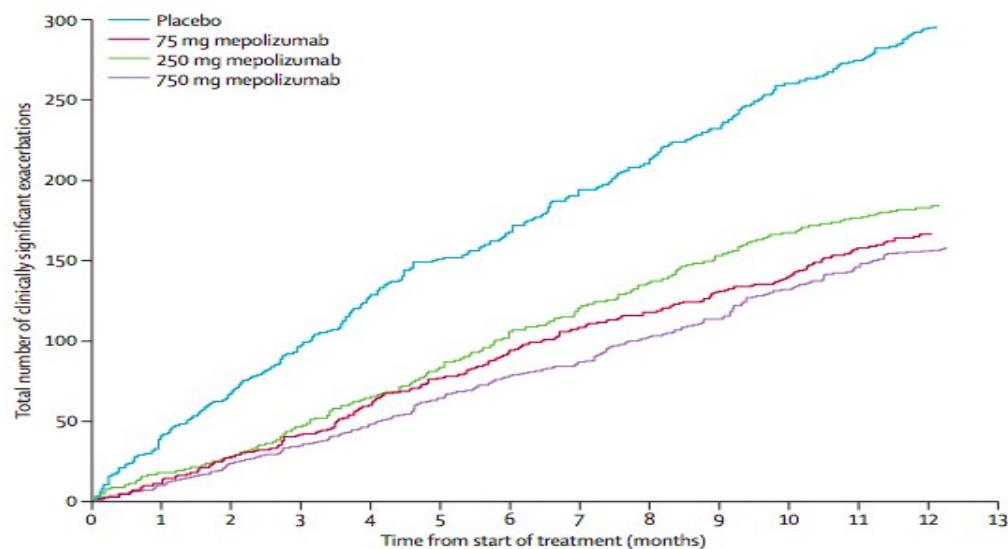


Tailored-therapy

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

Lancet 2012



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

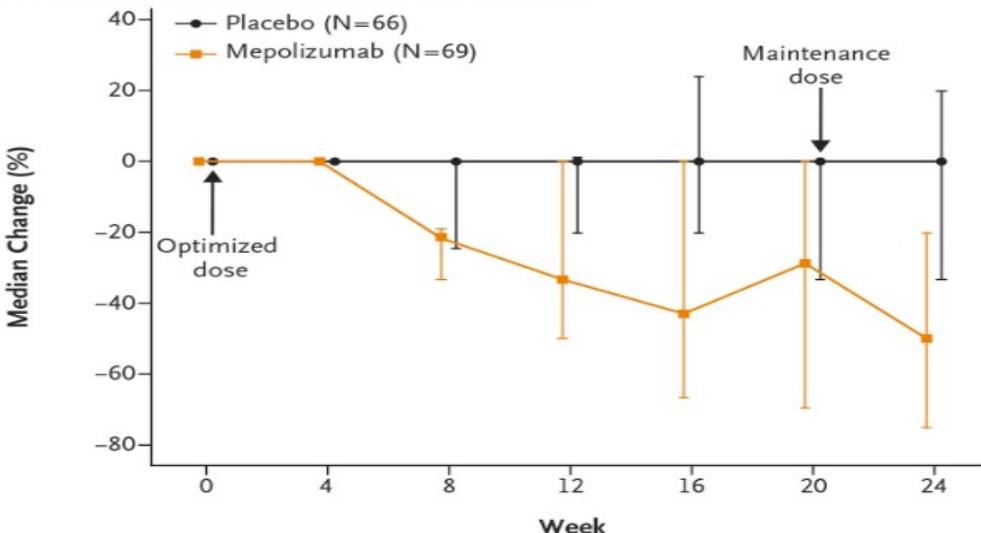
SEPTEMBER 25, 2014

VOL. 371 NO. 13

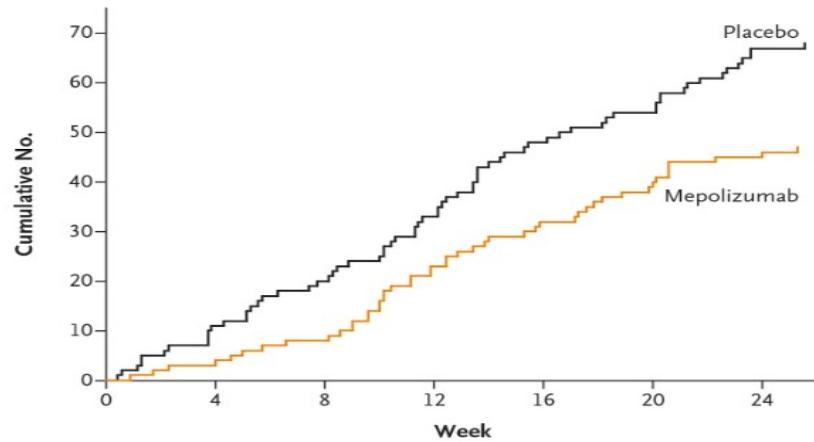
Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

A Change from Baseline in Glucocorticoid Dose

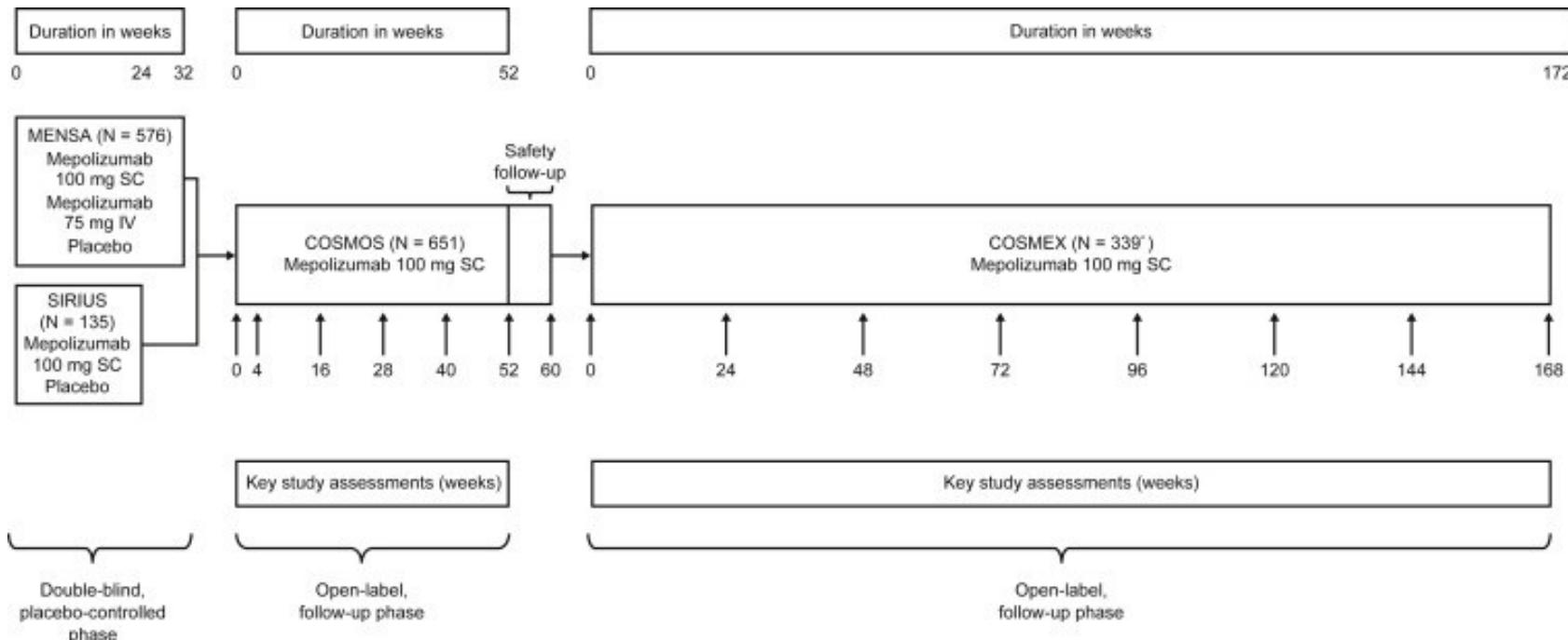


B Asthma Exacerbations



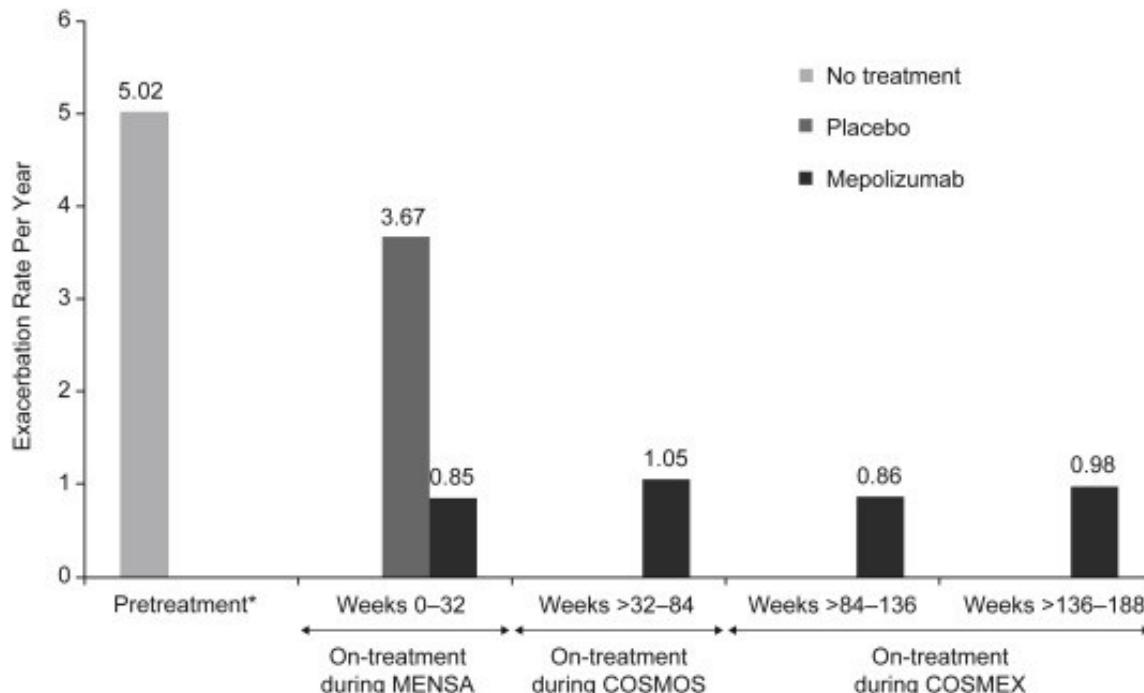
Mepolizumab: Long-term efficacy

COSMOS + COSMEX studies: ≥ 3 years of Mepolizumab



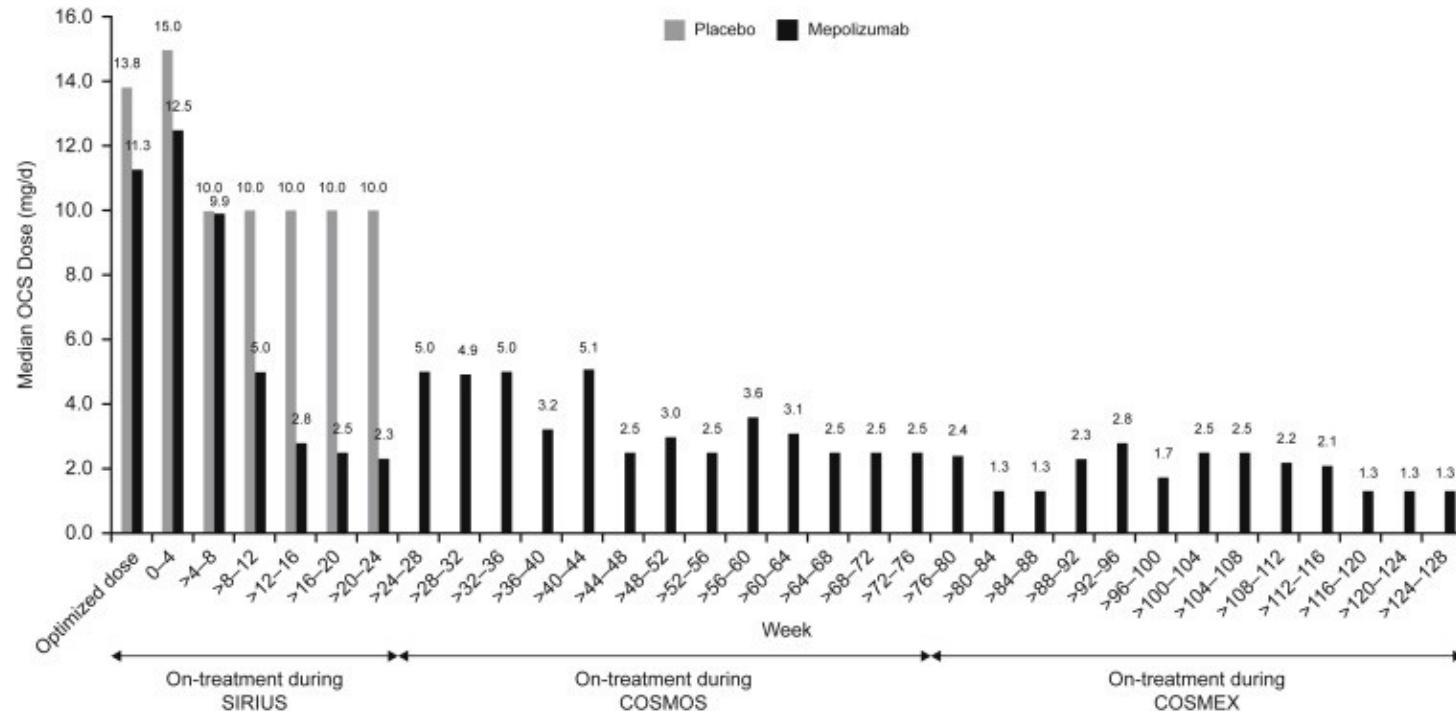
Mepolizumab: Long-term efficacy

COSMOS + COSMEX studies: \geq 3 years of Mepolizumab



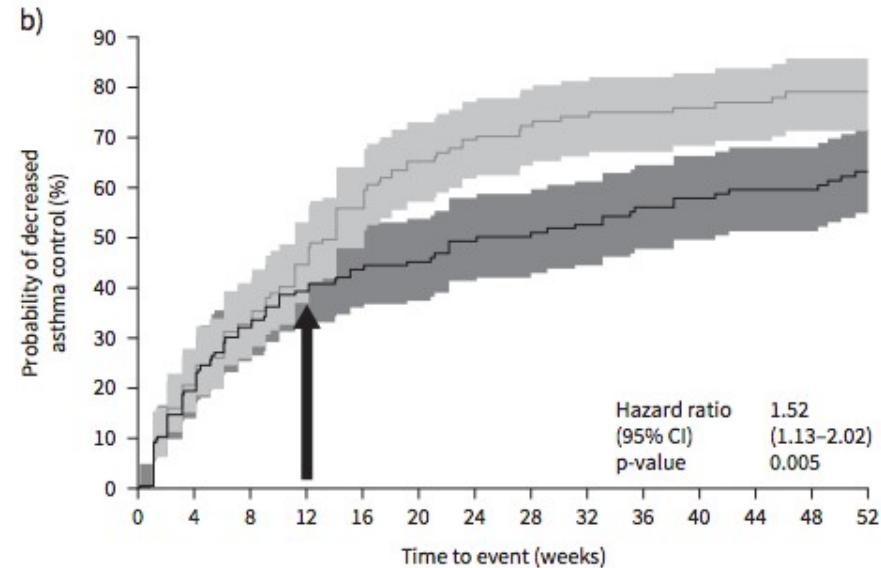
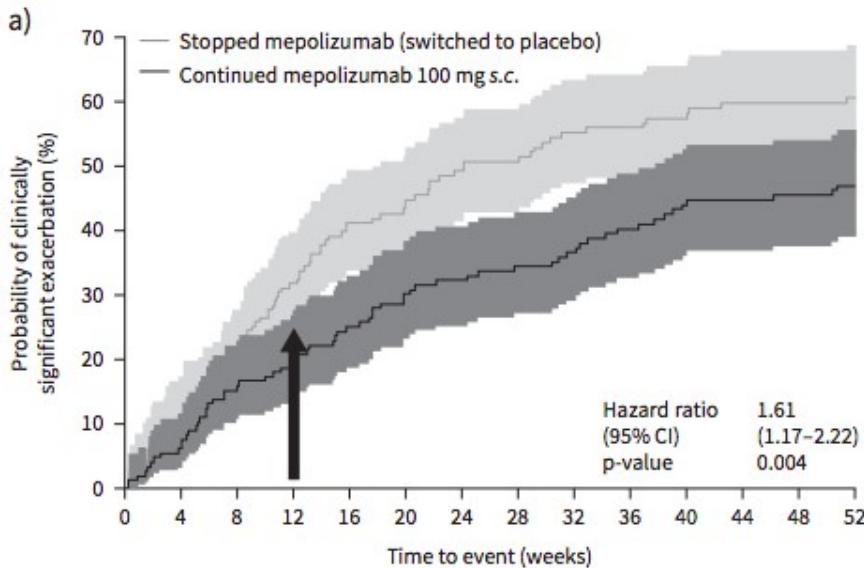
Mepolizumab: Long-term efficacy

COSMOS + COSMEX studies: \geq 3 years of Mepolizumab

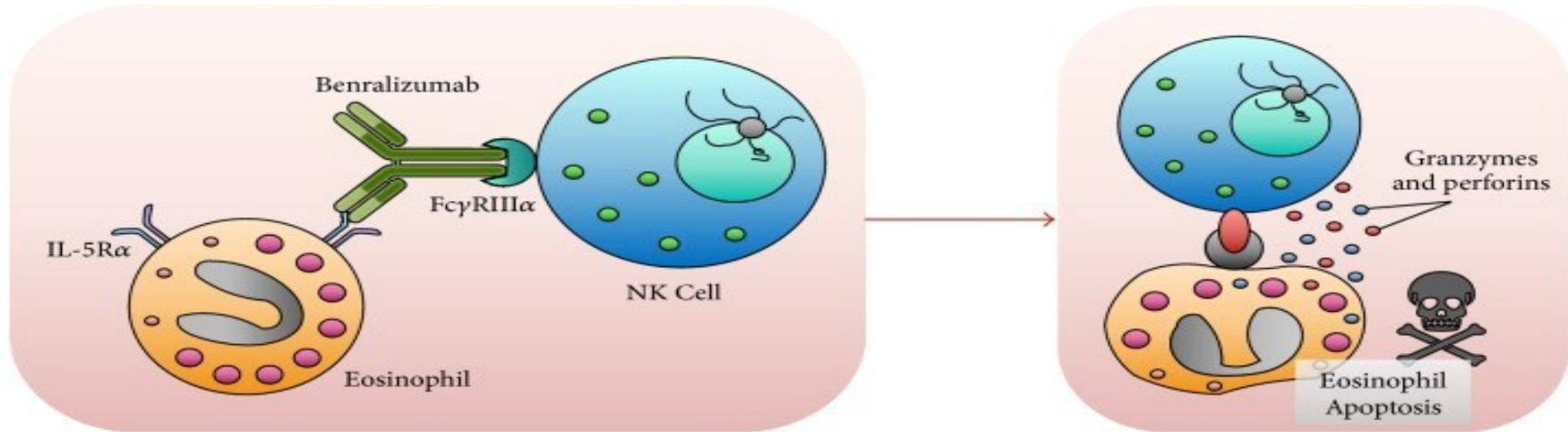


Mepolizumab: Long-term efficacy

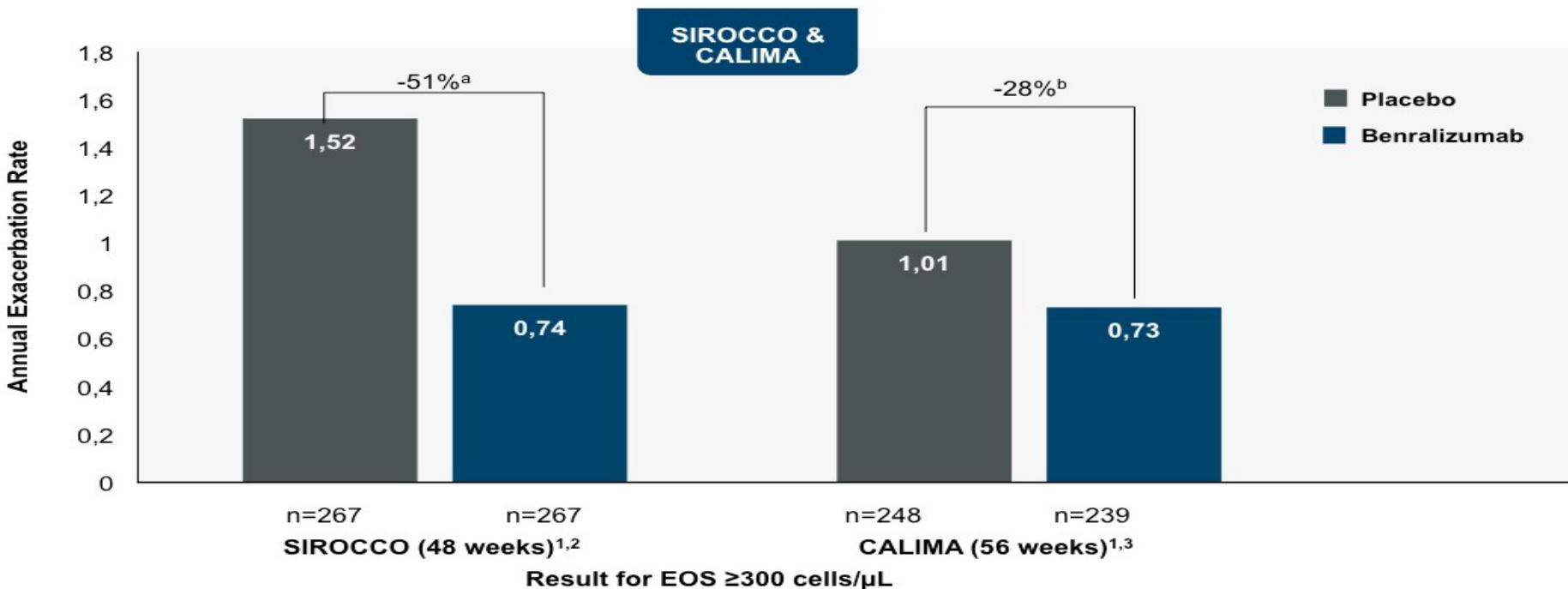
Stopping vs Continuing Mepolizumab in patients treated for ≥ 3 years (COMET Study)



Anti-IL5 receptor (Benralizumab)



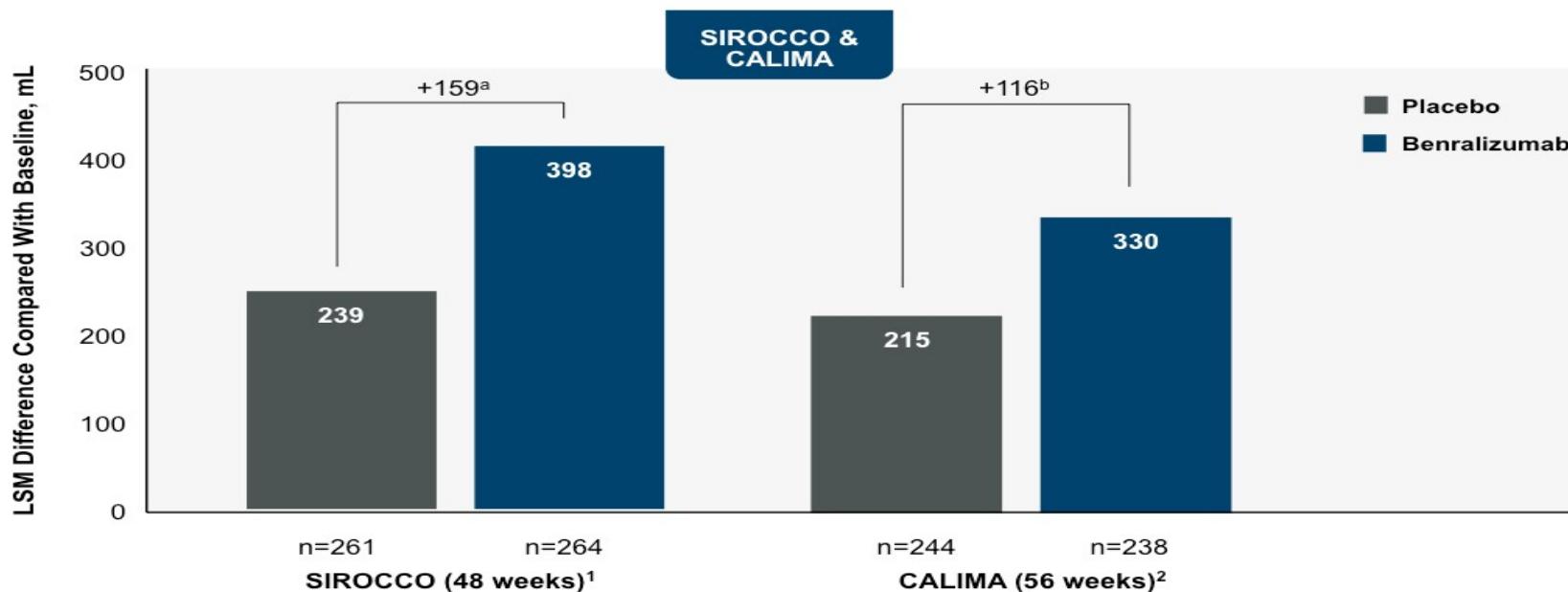
Benralizumab reduces annual exacerbation rate



Bleecker ER et al. *Lancet*. 2016

FitzGerald JM et al. *Lancet*. 2016

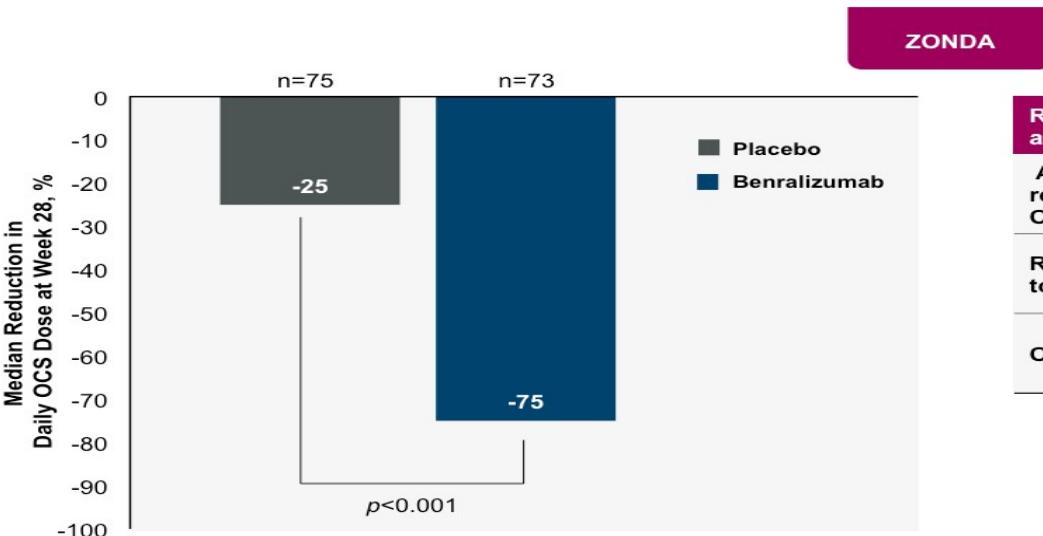
Benralizumab improves prebronchodilator FEV₁



Secondary Endpoint: Benralizumab led to a significant improvement in lung function (prebronchodilator FEV₁) compared to placebo in the SIROCCO and CALIMA trials

Bleecker ER et al. *Lancet*. 2016
FitzGerald JM et al. *Lancet*. 2016

Benralizumab significantly reduces OCS dose ...while maintaining asthma control

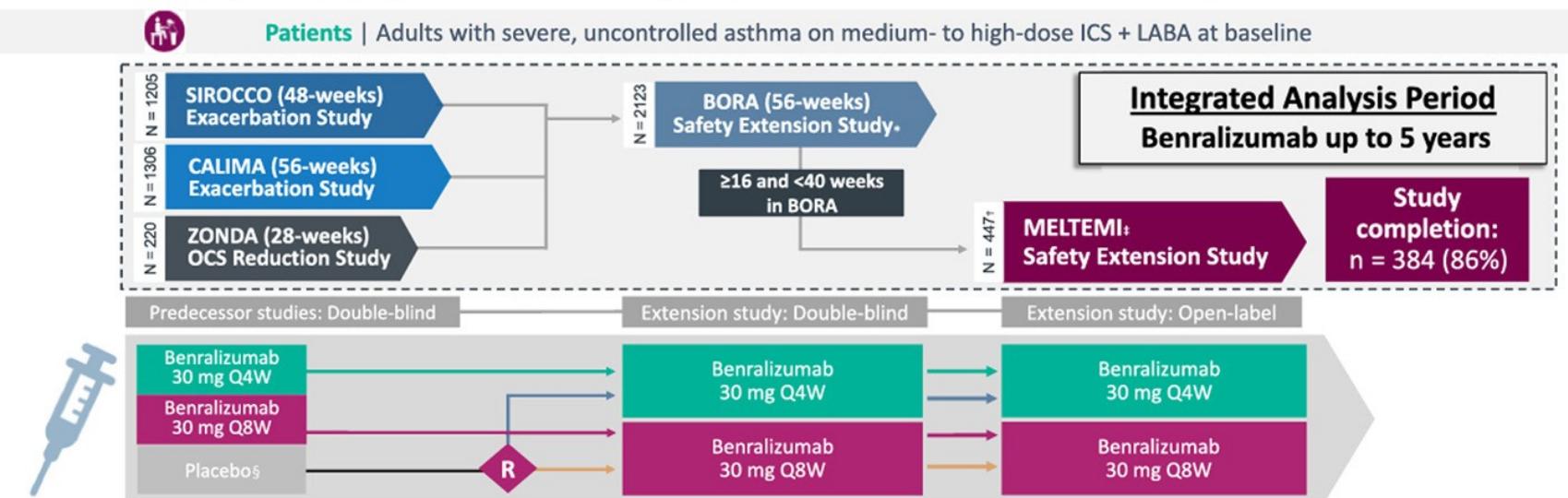


Reduction in Final OCS Dose at Week 28	Benralizumab n=73	Placebo n=75
Analysis of percentage reduction from baseline in OCS dose, OR (95% CI)	4.12 (2.22–7.63)	—
Reduction in daily OCS dose to 0 mg/day, n (%) ^a	22 (52%)	8 (19%)
OR (95% CI)	4.19 (1.58–11.12)	

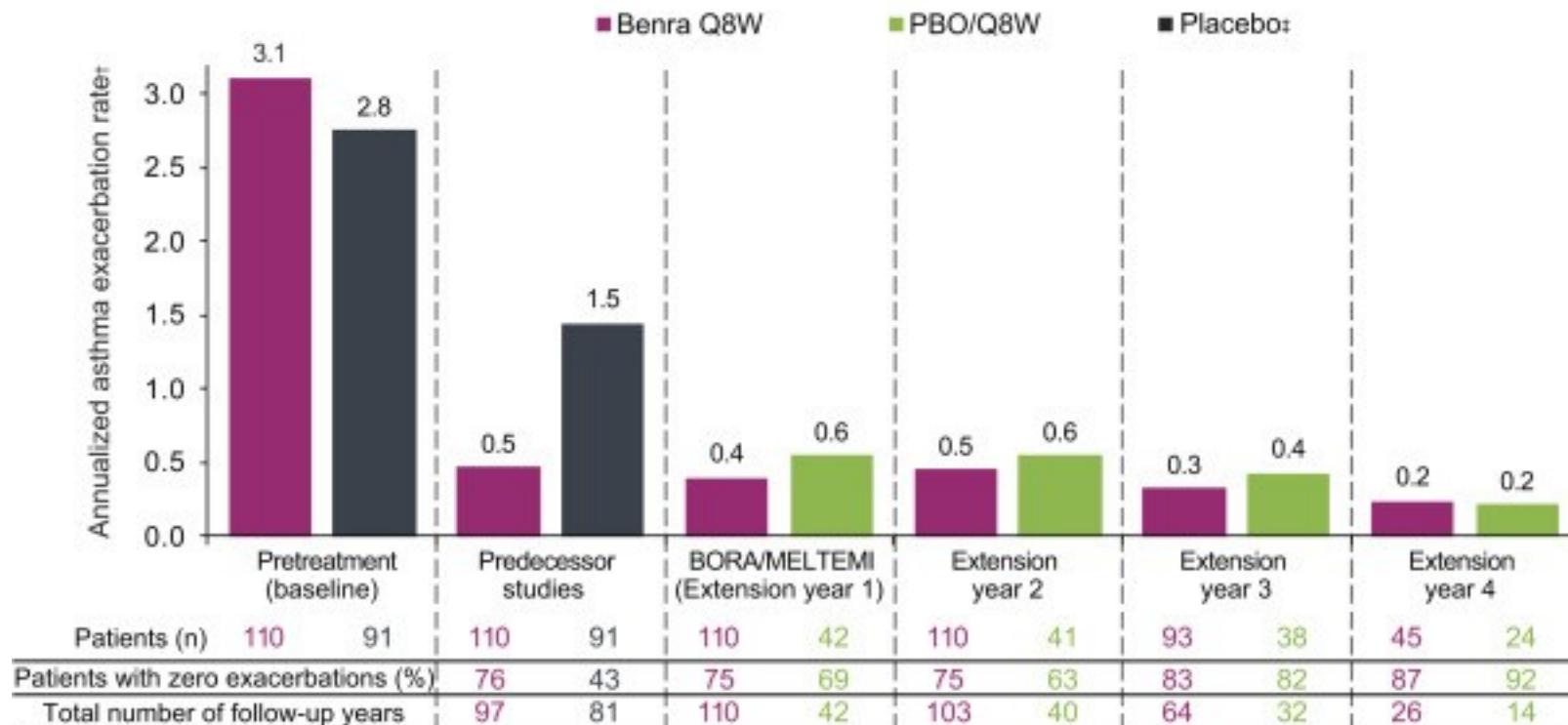
Benralizumab: Long-term efficacy

Phase III MELTEMI Integrated Analysis Study

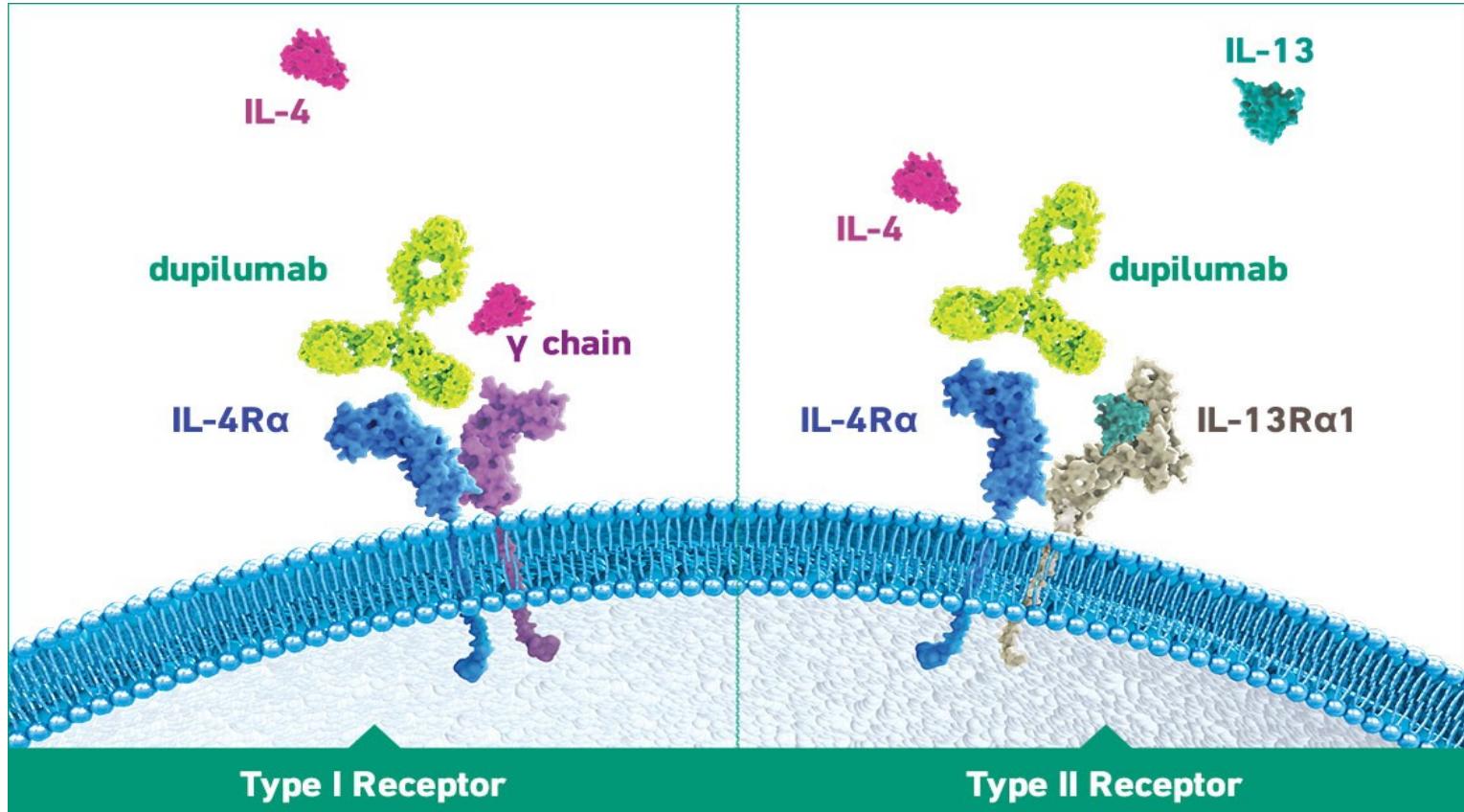
Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to Five Years



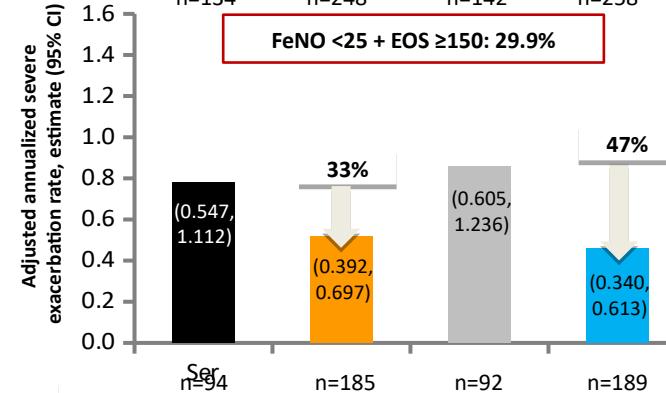
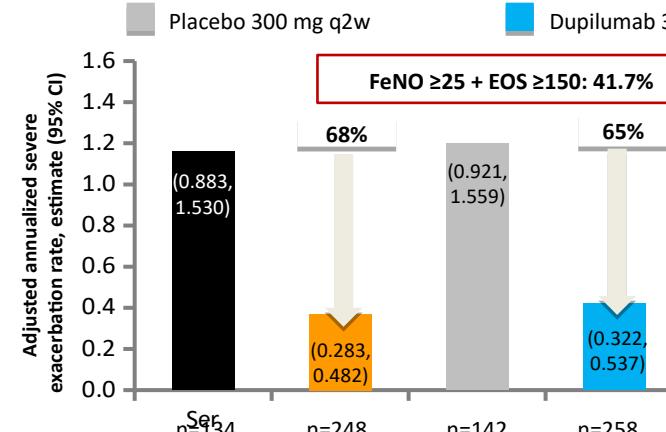
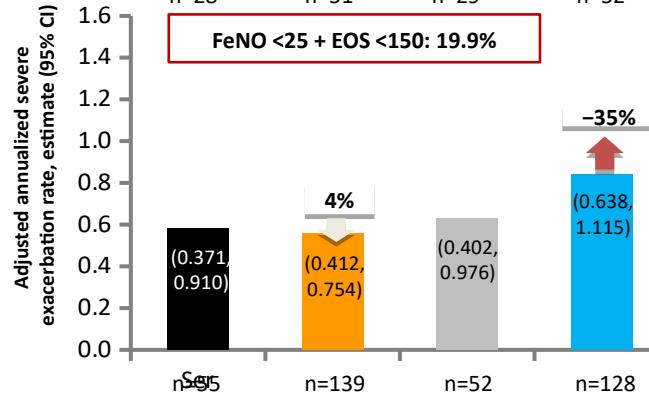
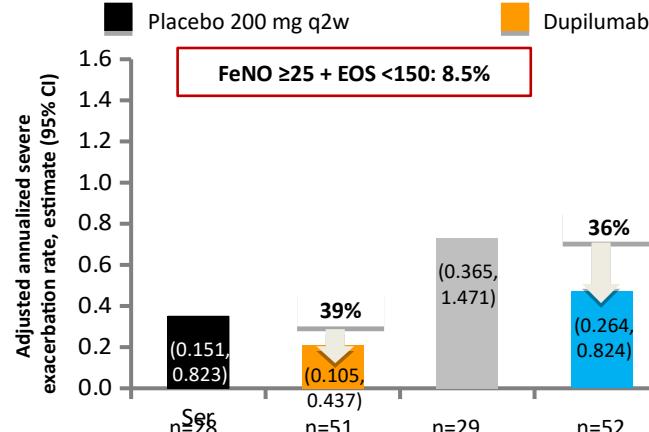
Benralizumab: Long-term efficacy



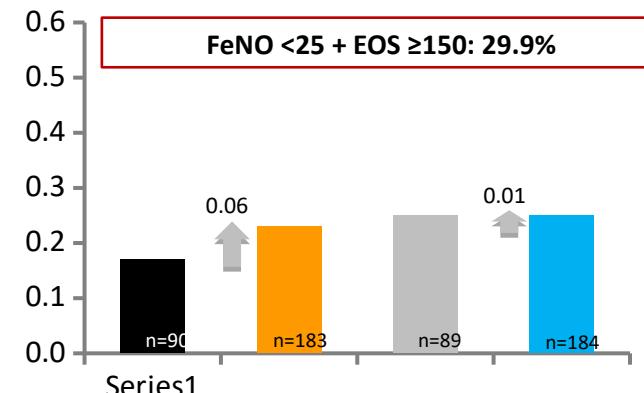
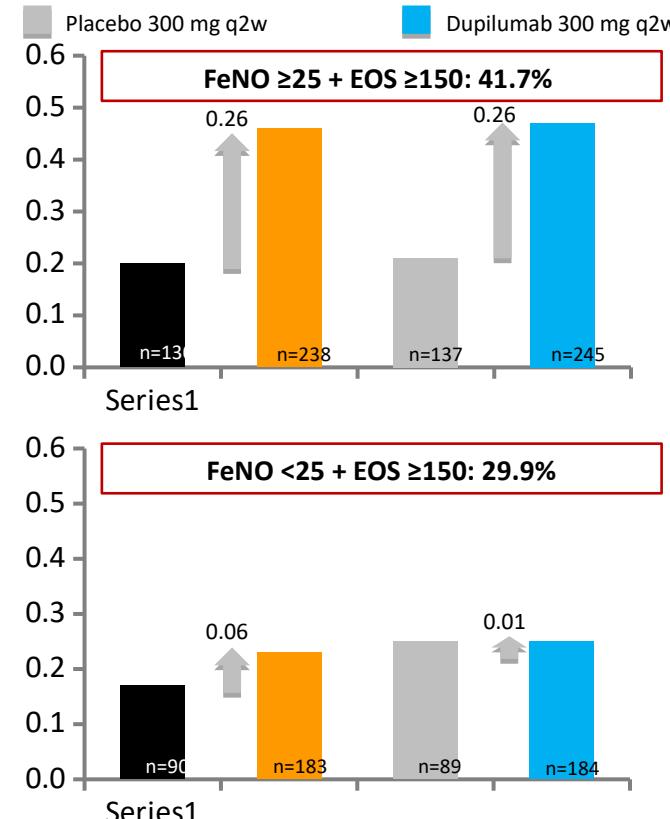
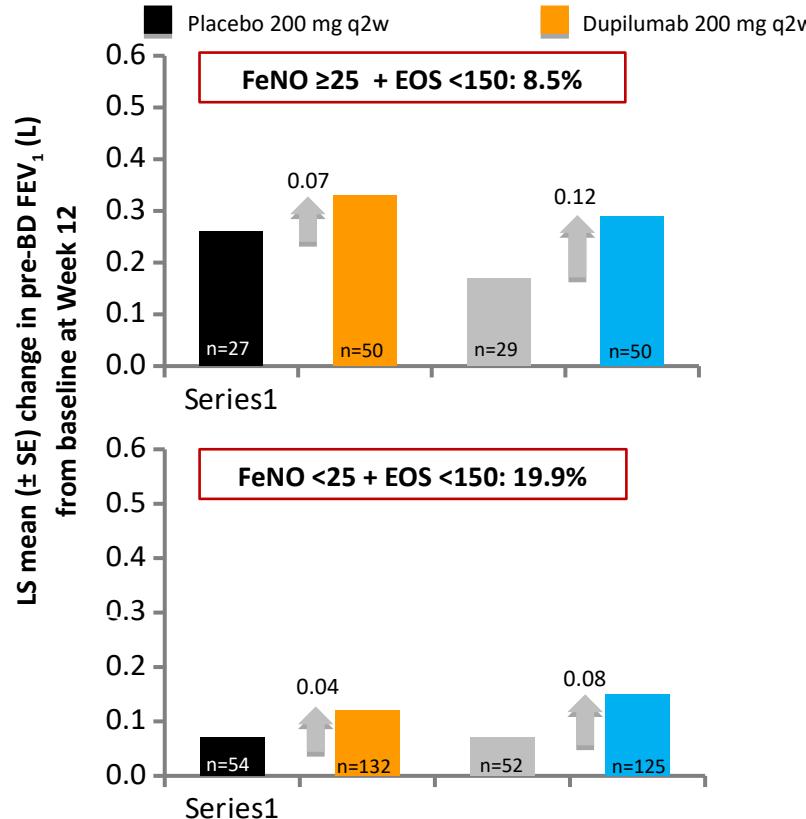
DUPILUMAB



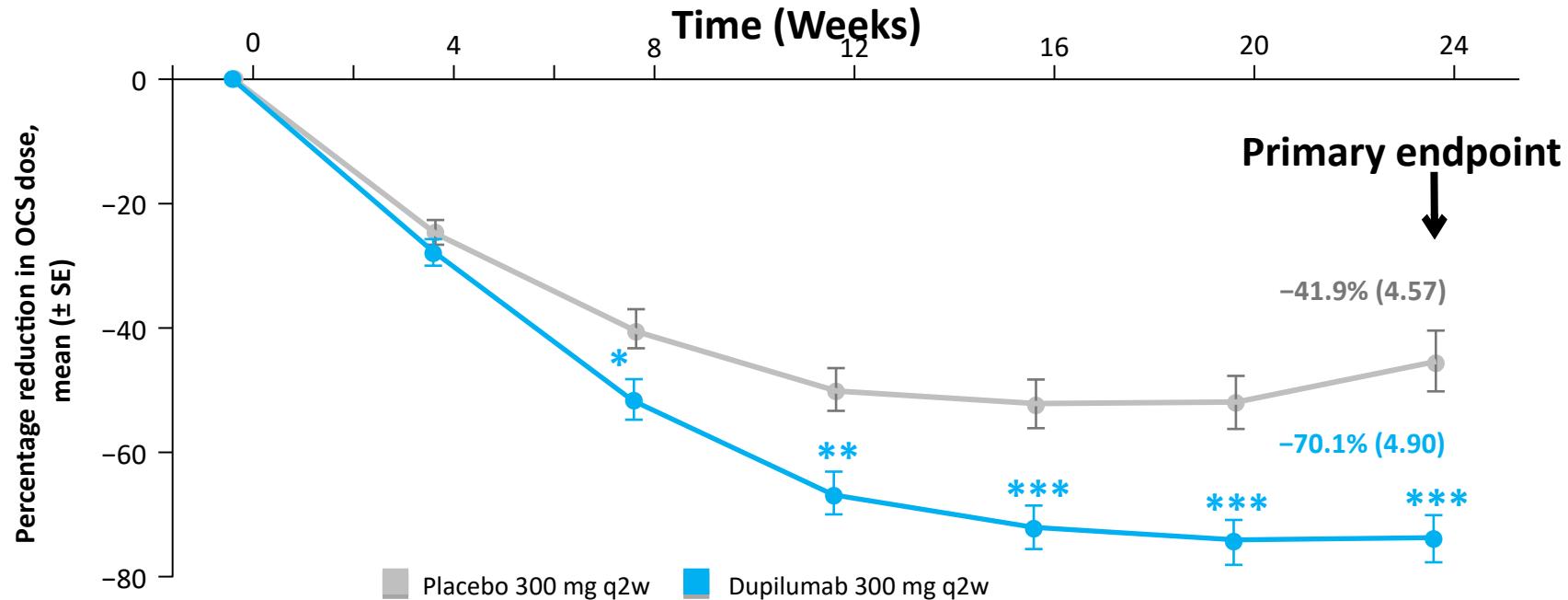
Phase 3 (QUEST): Dupilumab Elicited the Greatest Reduction in Severe Exacerbation Rate in Patients with Elevated Type 2 Biomarkers



Phase 3 (QUEST): Dupilumab Elicited the Greatest Improvement in Lung Function in Patients with Elevated Type 2 Biomarkers



Steroid-Sparing Study (VENTURE): Dupilumab Significantly Reduced OCS Use vs Placebo at Week 24 in the Overall Population



Dupilumab: Long-term efficacy

TRAVERSE: Open-Label Extension Study

- Patients entered the extension trial after finishing active treatment or placebo in a previous Dupilumab asthma clinical study, including the three pivotal trials that lasted between 24 and 52 weeks^{1,2}

Pivotal Trials	Phase 2b	DRI	24 weeks
	Phase 3	QUEST	52 weeks
	Phase 3	VENTURE	24 weeks

n=2282

of these patients were enrolled
into the TRAVERSE open-label
extension study

Primary Endpoint¹

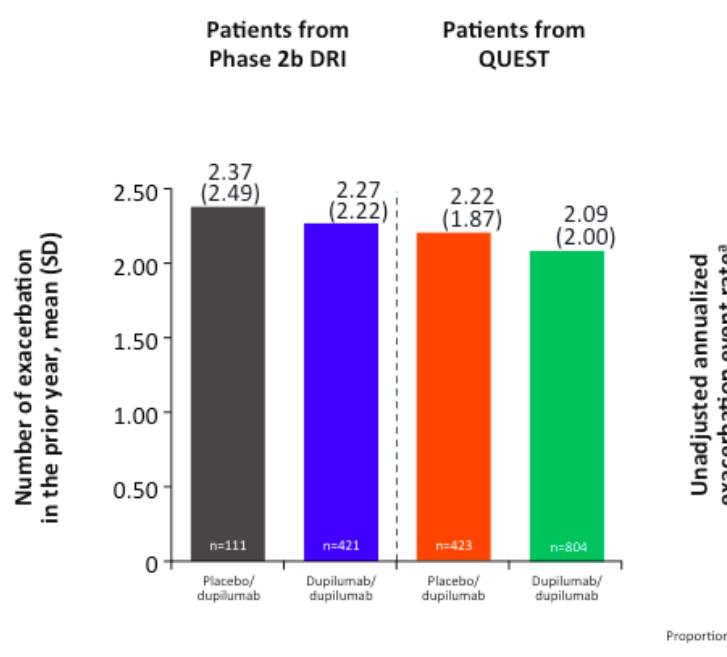
- Proportion of patients experiencing any TEAEs up to Week 96

Key Secondary Endpoint

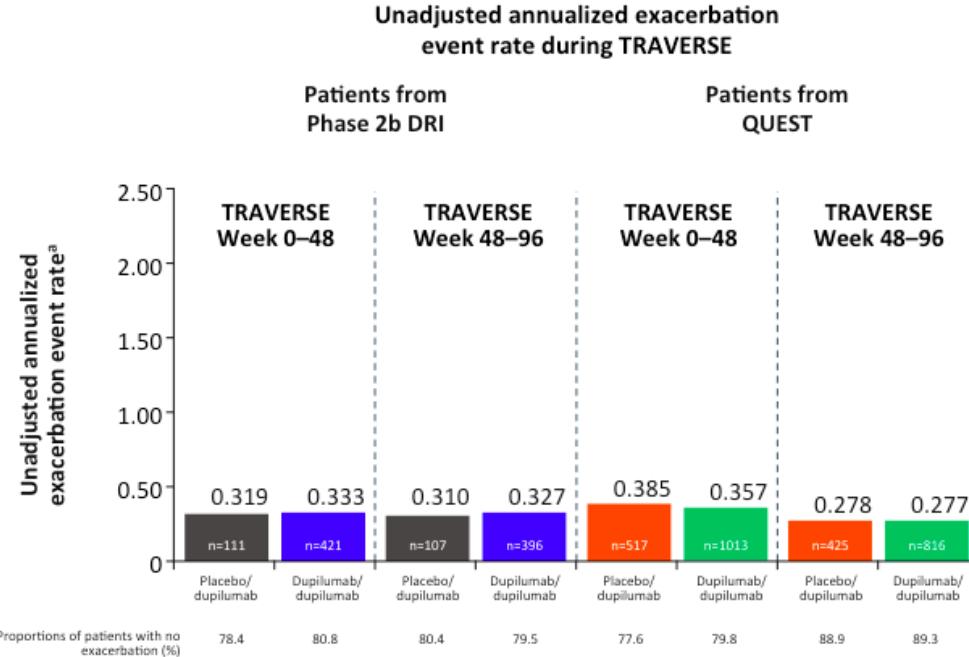
- Annualised severe exacerbation rate up to Week 96
- FEV₁ to Week 96
- Blood eosinophils and serum total IgE levels up to Week 96

Dupilumab: Long-term efficacy

Number of exacerbations in the year prior to the parent study



Unadjusted annualized exacerbation event rate during TRAVERSE

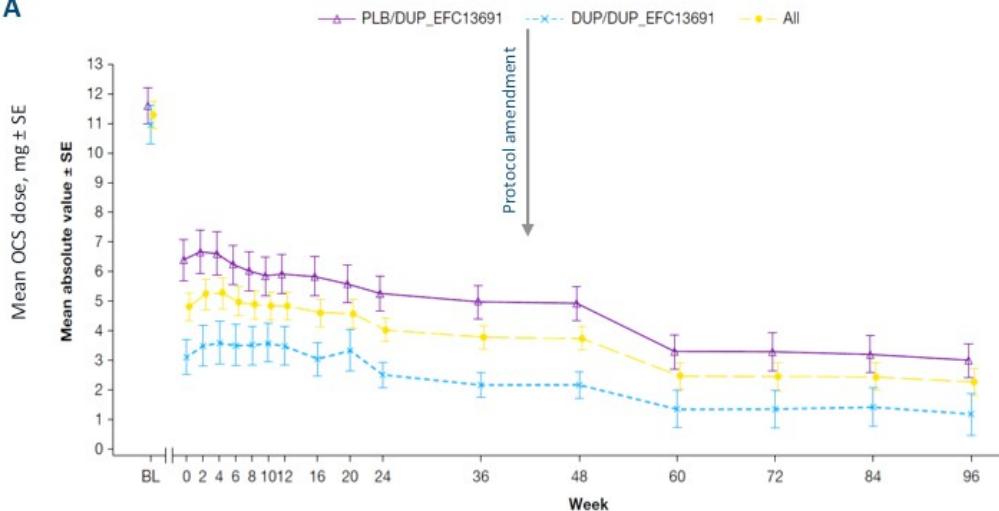


- Among non-OCS-dependent patients,^a the reductions in AER seen with dupilumab during the parent studies were sustained and showed additional reductions during TRAVERSE

Dupilumab: Long-term efficacy

Dupilumab reduced OCS use from parent study baseline in patients rolled over from VENTURE into TRAVERSE

A

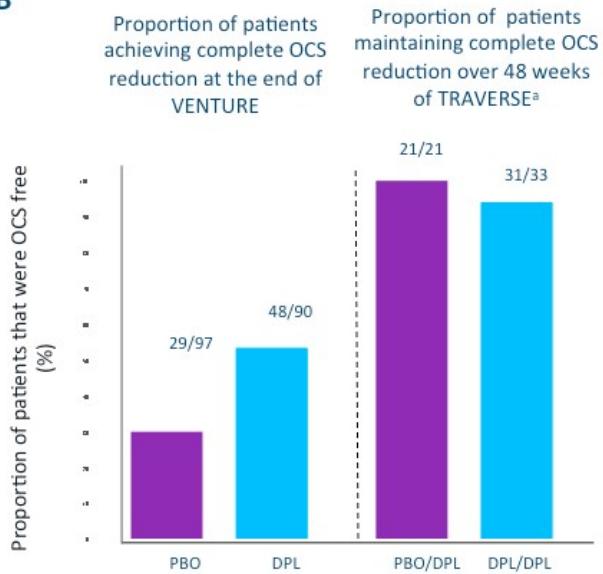


#Subjects

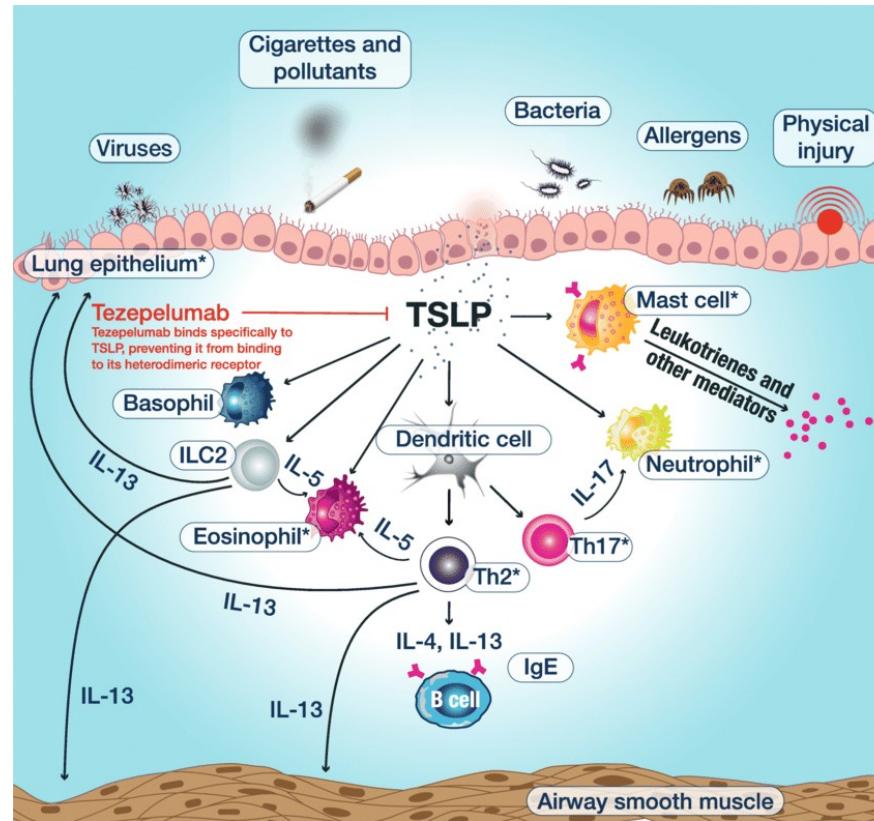
PLB/DUP_EFC13691	97	97	90	88	86	86	84	83	82	81	79	77	30	28	28	28	
DUP/DUP_EFC13691	90	90	74	71	69	71	70	68	66	66	64	60	57	22	22	21	19
All	187	187	164	159	155	157	156	152	149	145	139	134	52	50	49	47	

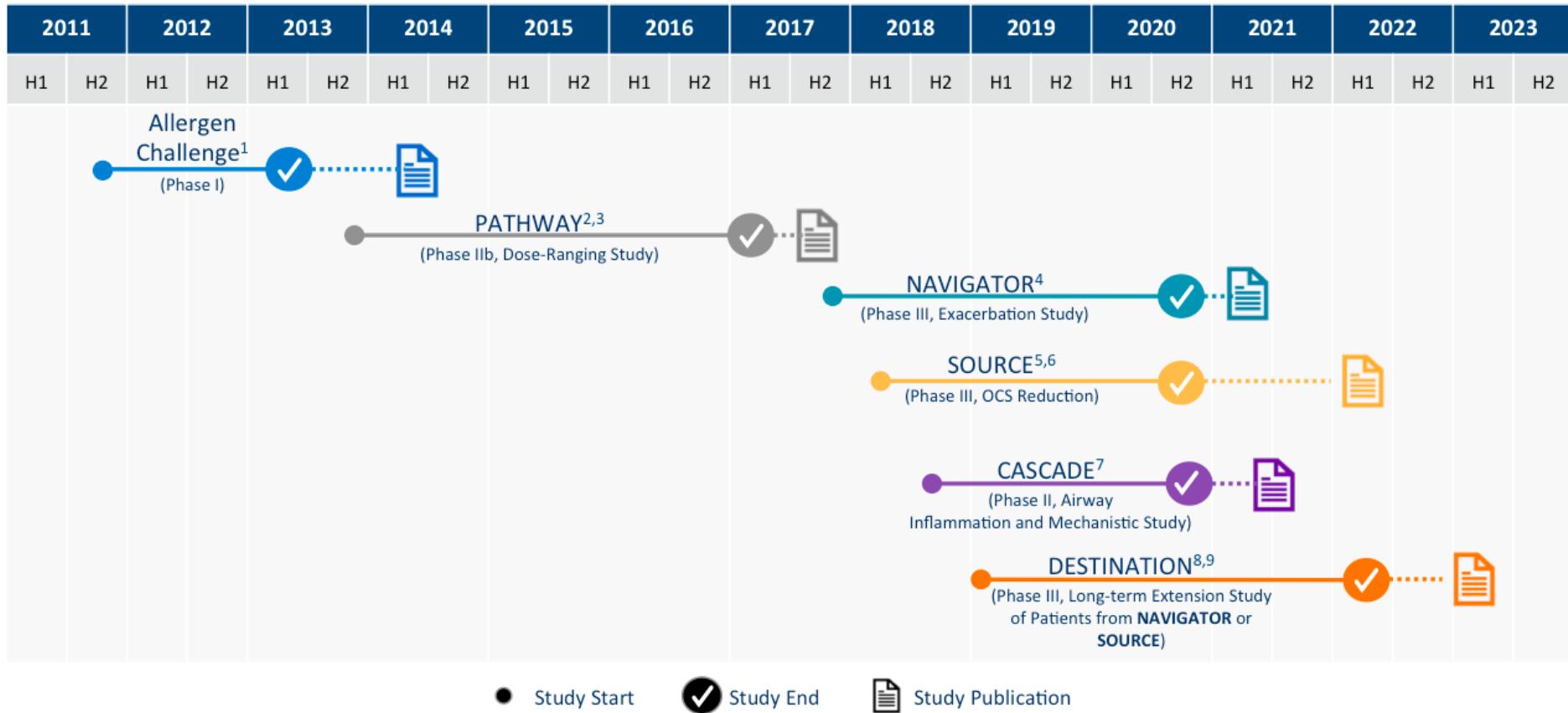
The majority of patients who were OCS free during VENTURE, were able to remain OCS free during TRAVERSE

B



Tezepelumab: a humanized monoclonal antibody against TSLP





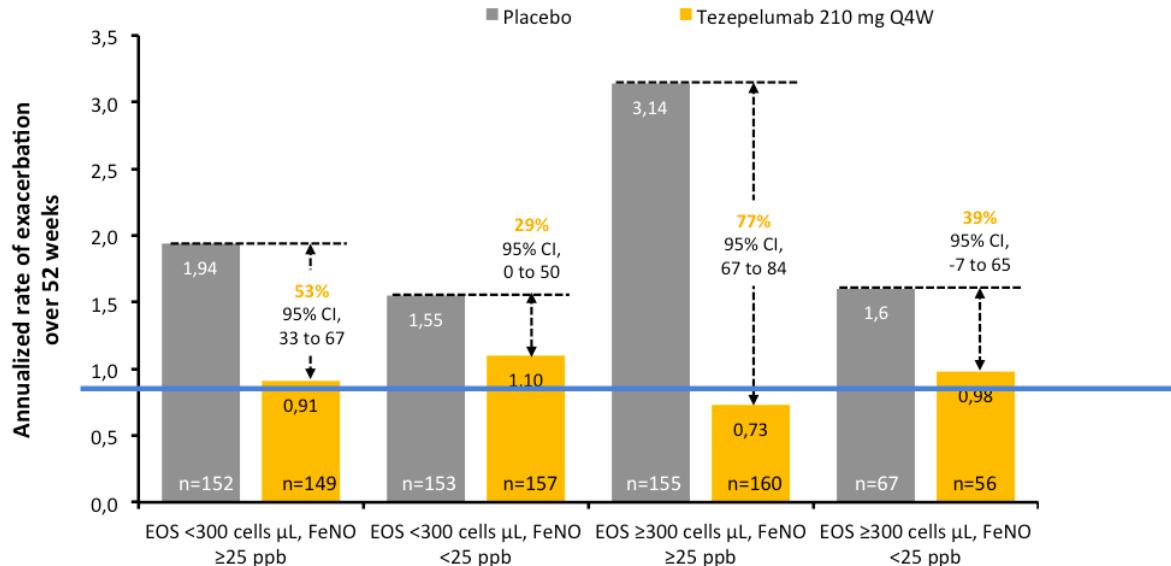
H = half; OCS = oral corticosteroid.

1. Gauvreau GM et al. *N Engl J Med.* 2014;370:2102–2110; 2. Corren J et al. *N Engl J Med.* 2017;377:936–946; 3. Study NCT02054130. ClinicalTrials.gov website;
4. Menzies-Gow A et al. *N Engl J Med.* 2021;384:1800–1809; 5. Wechsler M et al. *Lancet Respir Med.* 2022;10(7):650–660; 6. Study NCT03406078. ClinicalTrials.gov website;
7. Diver S et al. *Lancet Respir Med.* 2021;9:1299–1312; 8. Study NCT03706079. ClinicalTrials.gov website; 9. Menzies-Gow A et al. Online ahead of print. *Lancet Respir Med.* 2023.

Tezepelumab

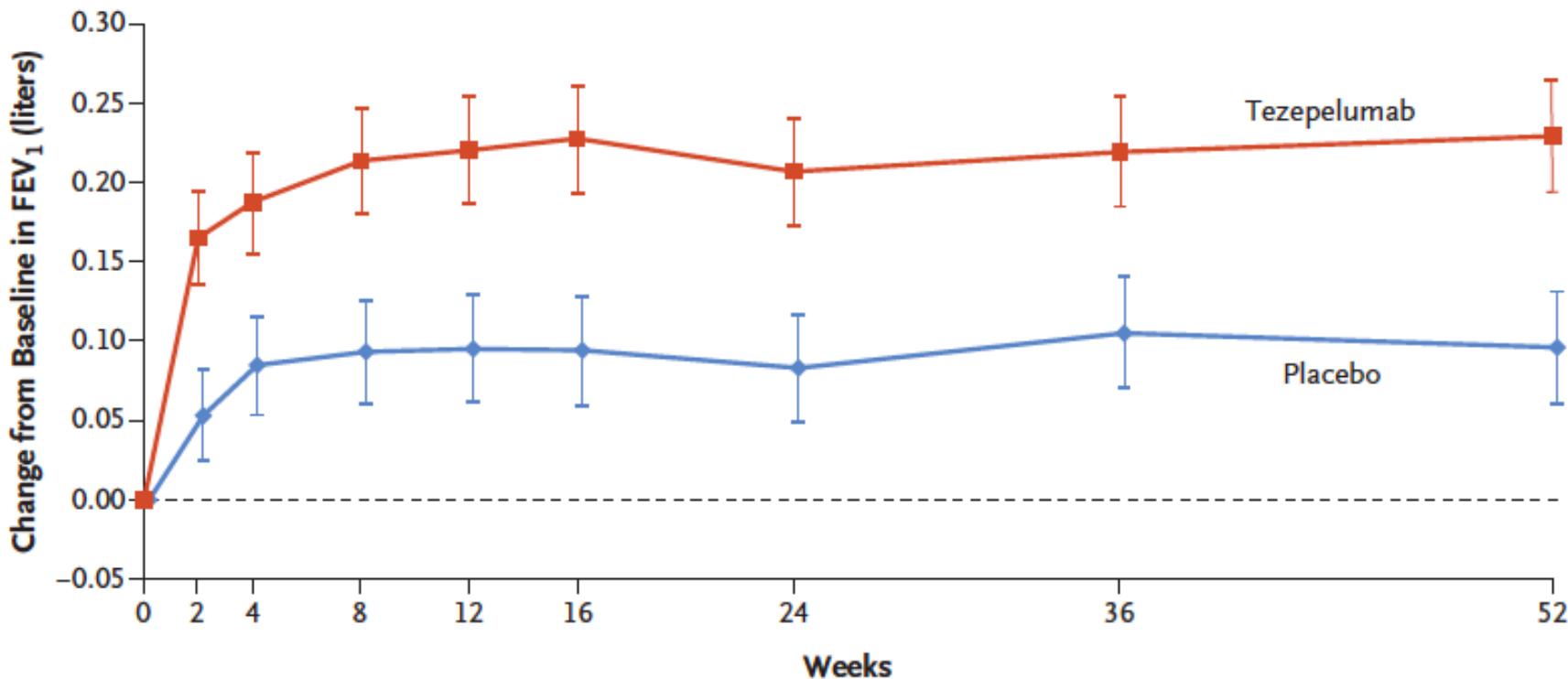


NAVIGATOR: AAER Over 52 weeks by Baseline EOS count and FeNO levels



Treatment with tezepelumab reduced AAER compared to placebo in patients across a wide range of baseline EOS counts and FeNO levels

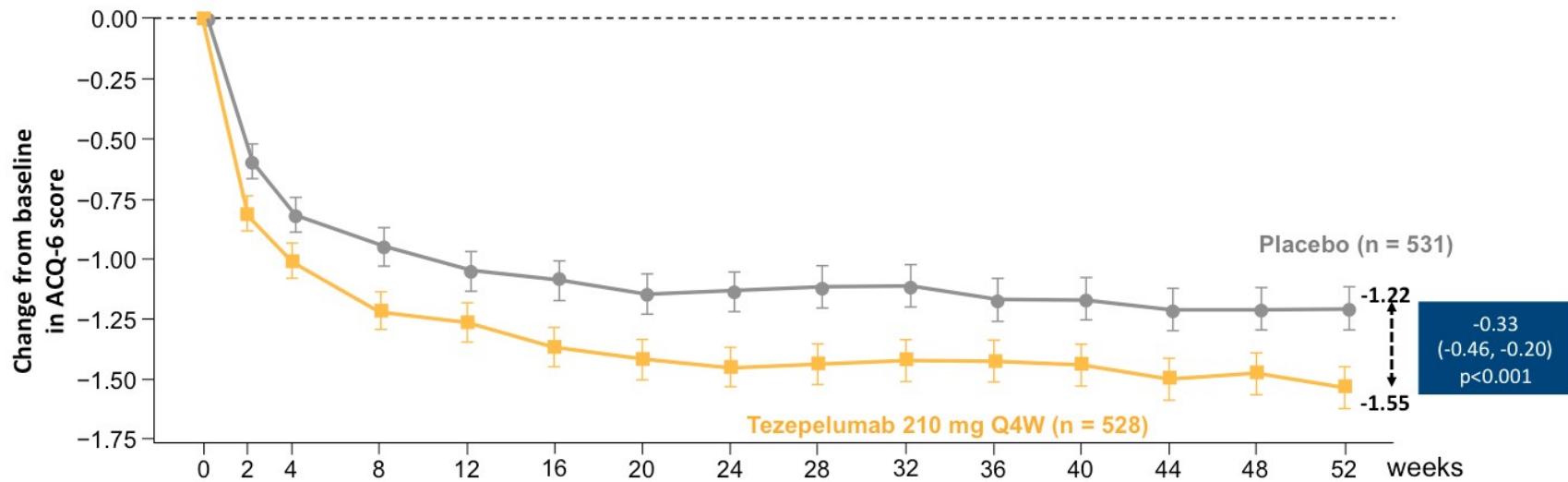
Tezepelumab



Tezepelumab

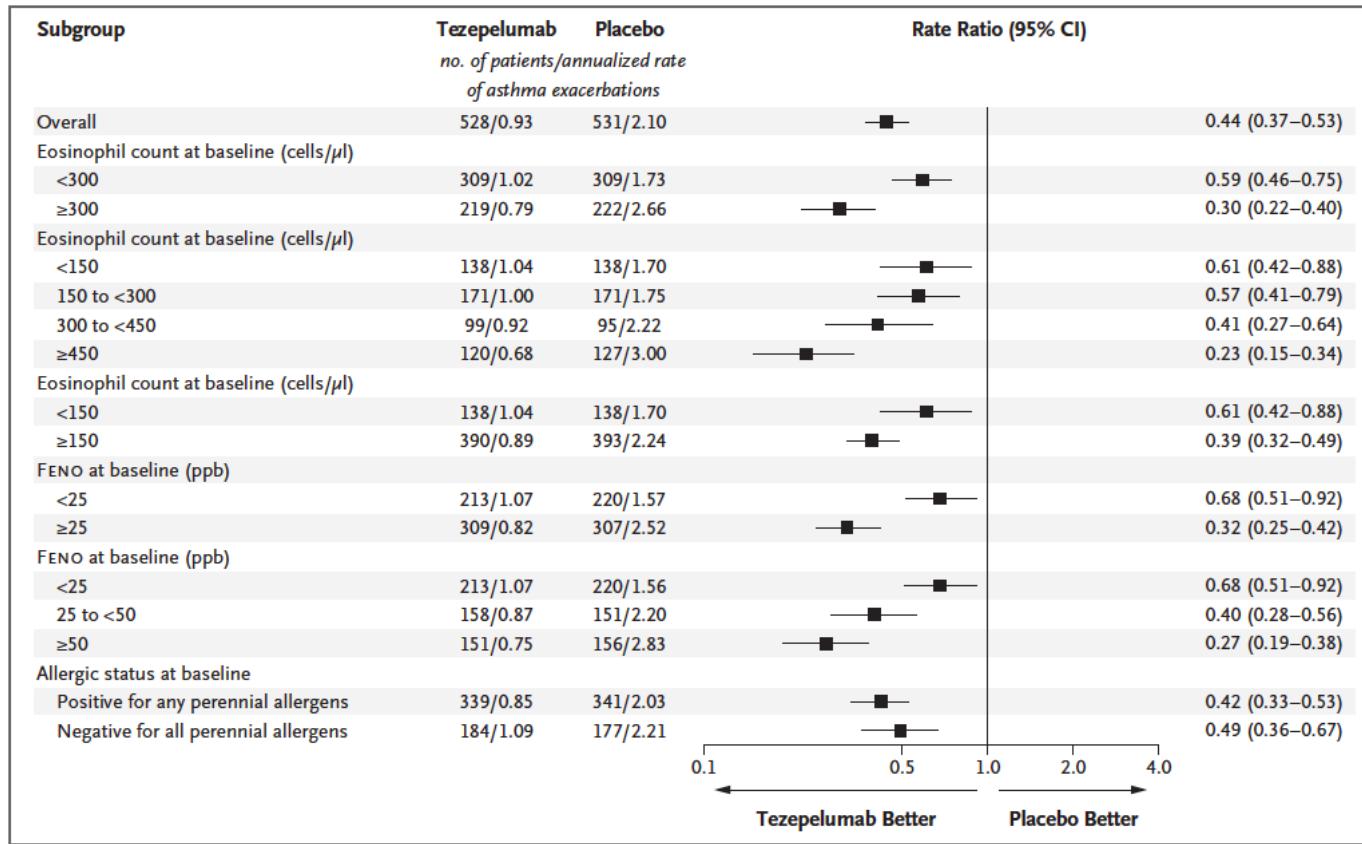


NAVIGATOR: Effect on Asthma Control (ACQ-6)



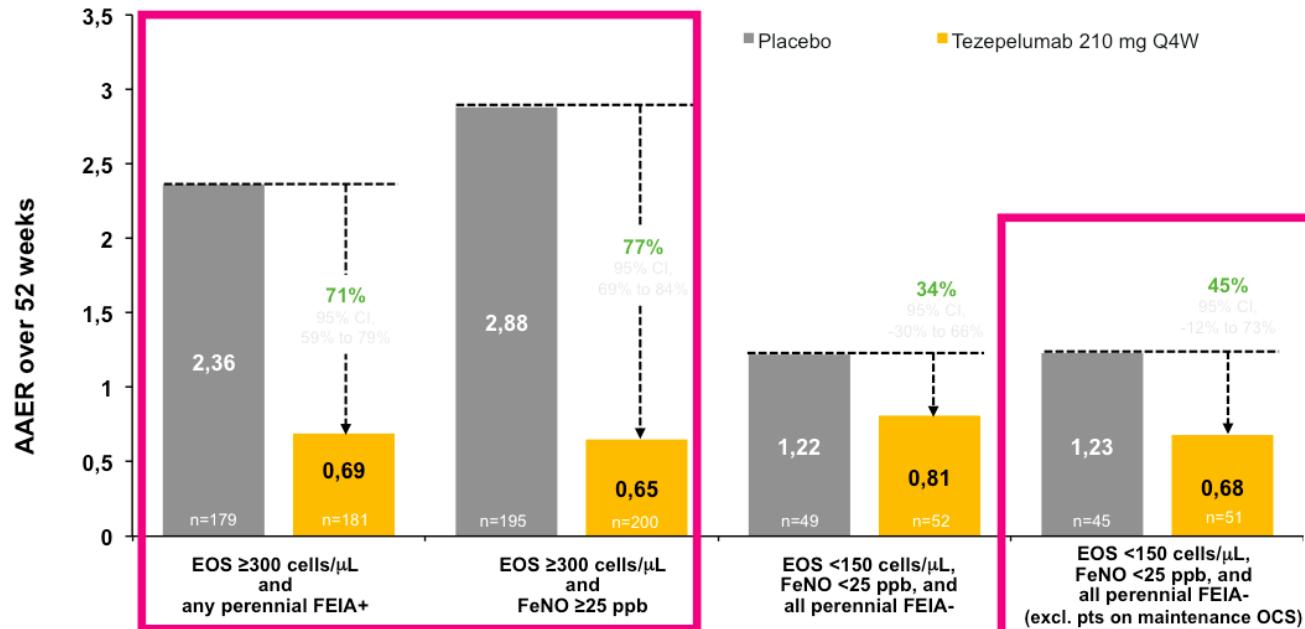
Tezepelumab improved the ACQ-6 score versus placebo as early as Week 2 and throughout the treatment period

Tezepelumab



Tezepelumab

NAVIGATOR & PATHWAY Pooled Analysis Effect on Asthma Exacerbations across Combined Subgroups



In a post-hoc analysis of pooled PATHWAY and NAVIGATOR data, tezepelumab reduced exacerbations for patients with multiple elevated biomarker and multiple low biomarker levels

Menzies-Gow A et al. – NEJM 2021

Tezepelumab

DESTINATION is a Long-term Extension of the **NAVIGATOR** and **SOURCE** Phase III Studies



NAVIGATOR¹

Phase III

Efficacy and safety of tezepelumab in
**adults and adolescents with severe,
uncontrolled asthma**

N=1061

Age range = 12–80 years

Tezepelumab dose: 210 mg Q4W
52 weeks



SOURCE²

Phase III

Efficacy and safety of tezepelumab
in reducing **OCS use in adults**
with severe **OCS-dependent asthma**

N=150

Age range = 18–80 years

Tezepelumab dose: 210 mg Q4W
48 weeks

n=827

n=124

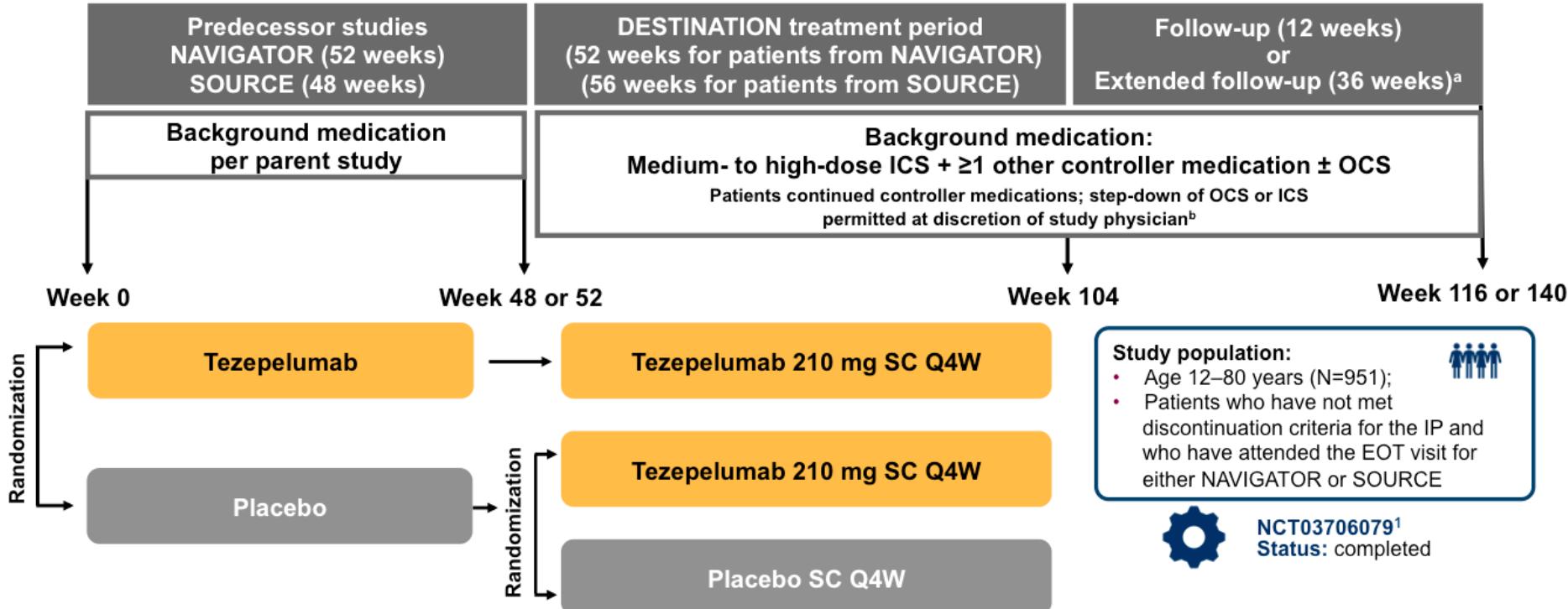


DESTINATION³

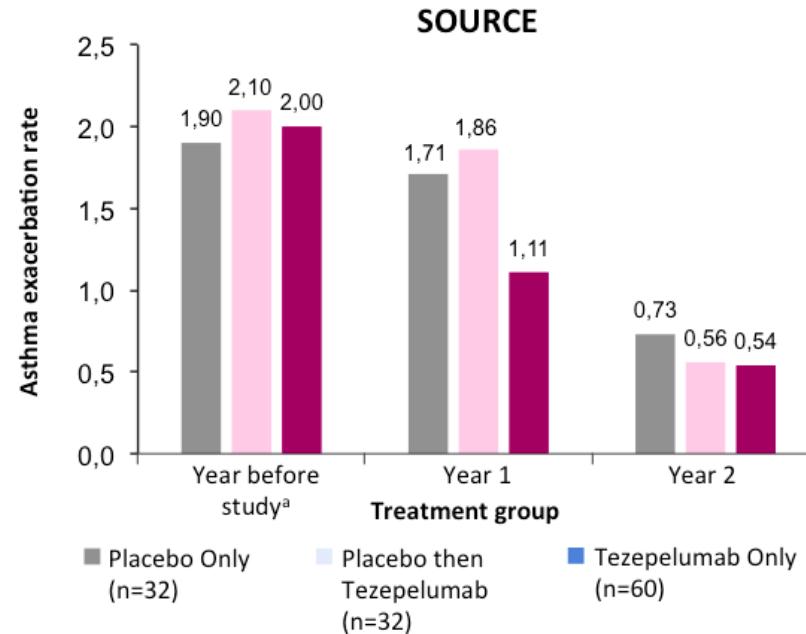
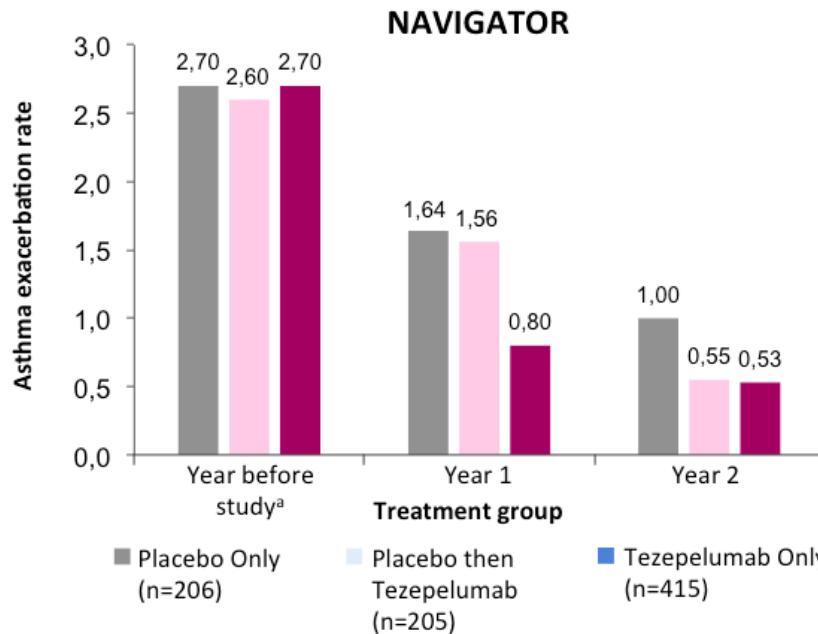
Phase III, long-term extension study

Safety and efficacy of tezepelumab in **adults and adolescents with severe, uncontrolled asthma** who
completed treatment in **NAVIGATOR** or **SOURCE**

Tezepelumab



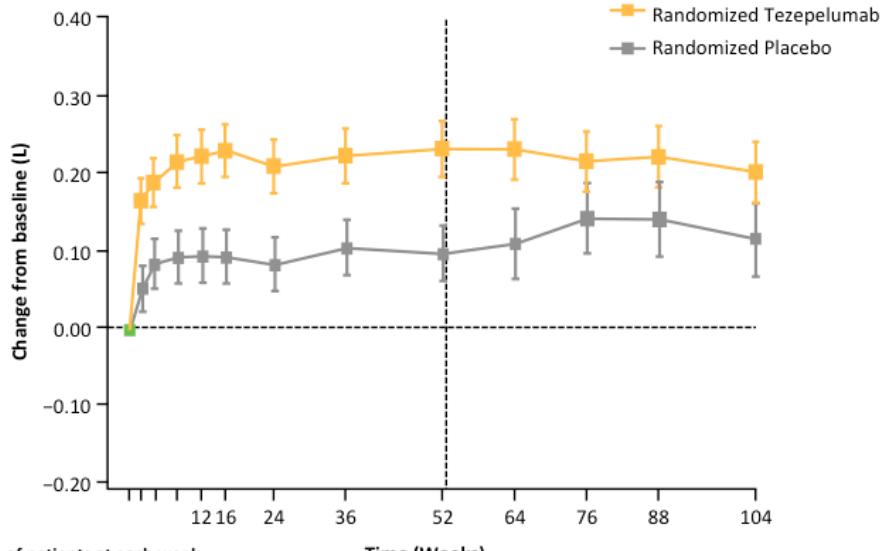
Tezepelumab



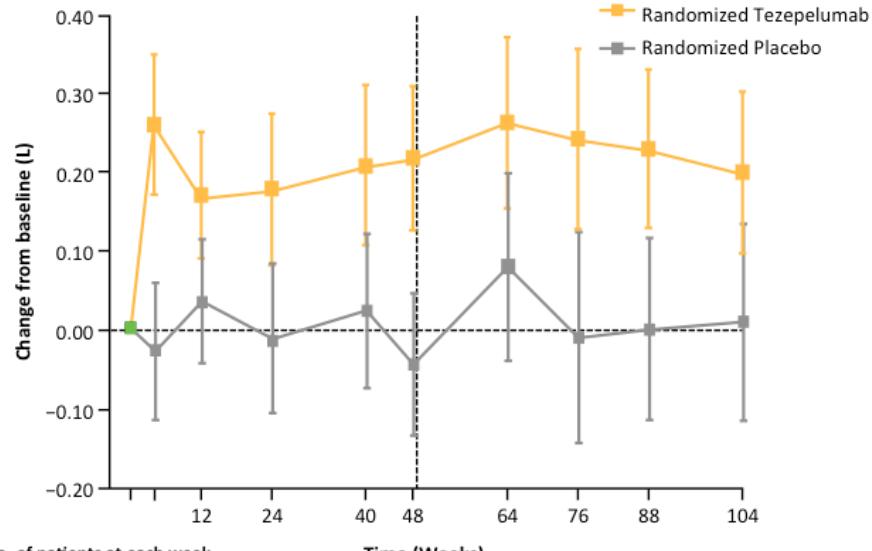
- Asthma exacerbations were lower in Year 1 than in the year before study entry for both treatment groups^{1,2}
- A greater reduction in asthma exacerbations was observed for the tezepelumab group compared with the placebo group over 2 years^{1,2}

Tezepelumab

Pre-BD FEV₁ – NAVIGATOR

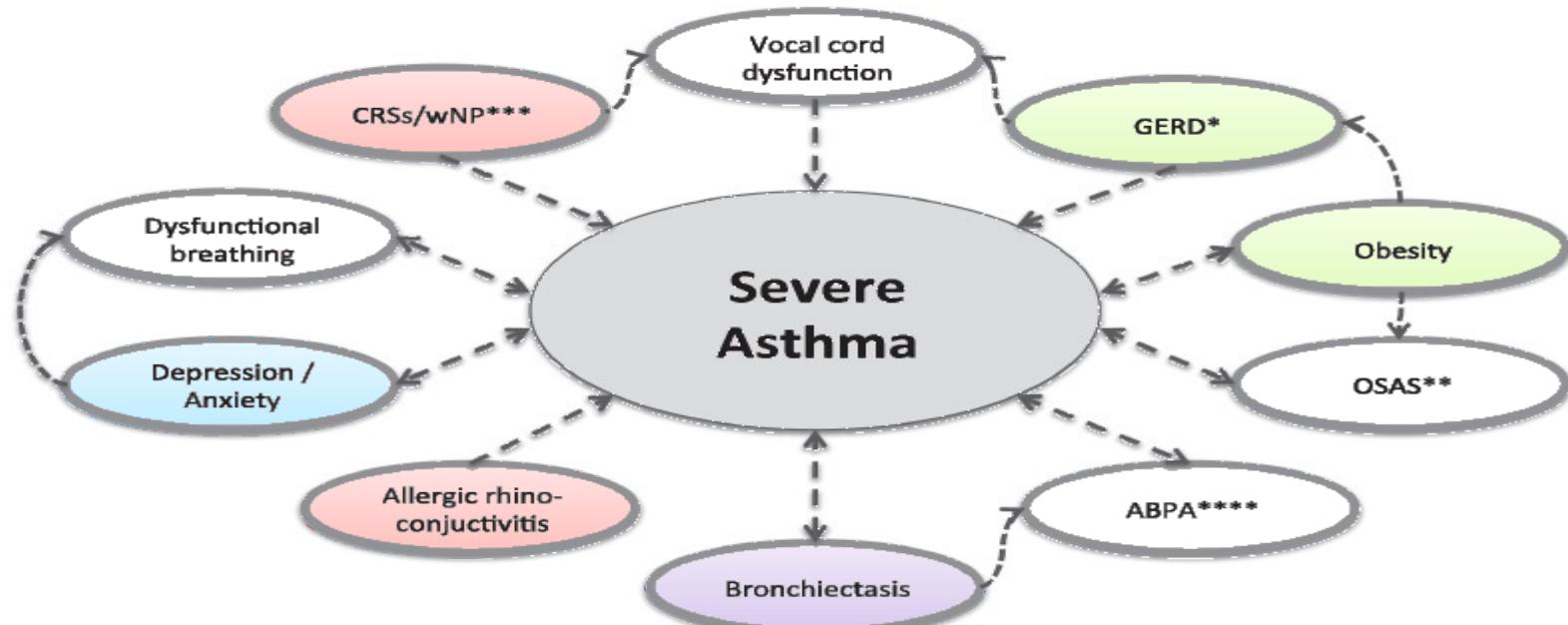


Pre-BD FEV₁ – SOURCE

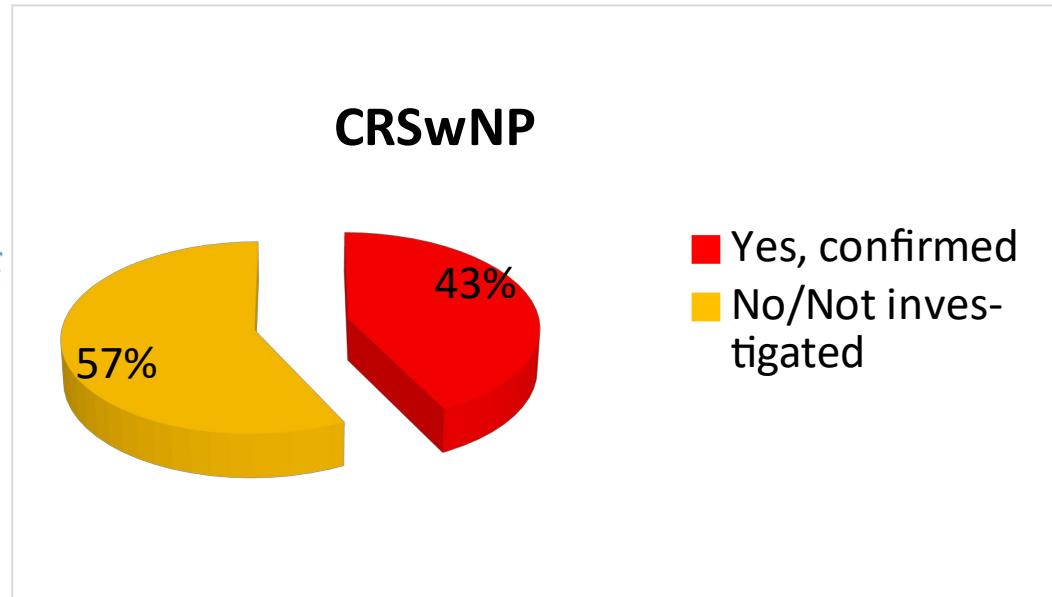


- Across both parent studies, improvements in pre-bronchodilator FEV₁ were sustained across the treatment period for patients treated with tezepelumab compared with placebo

Severe asthma comorbidities

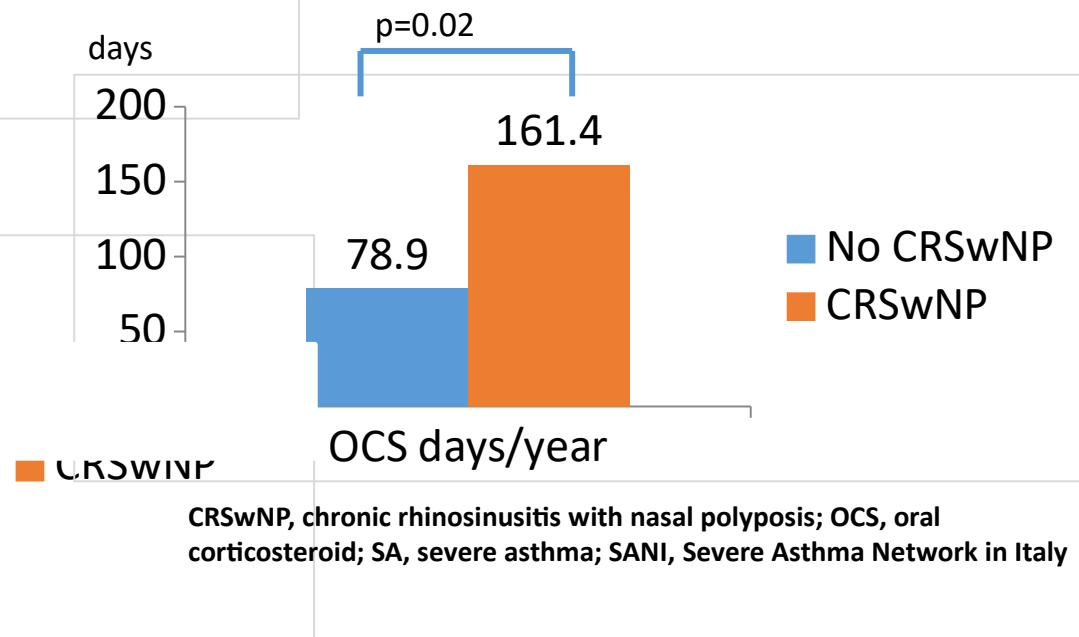
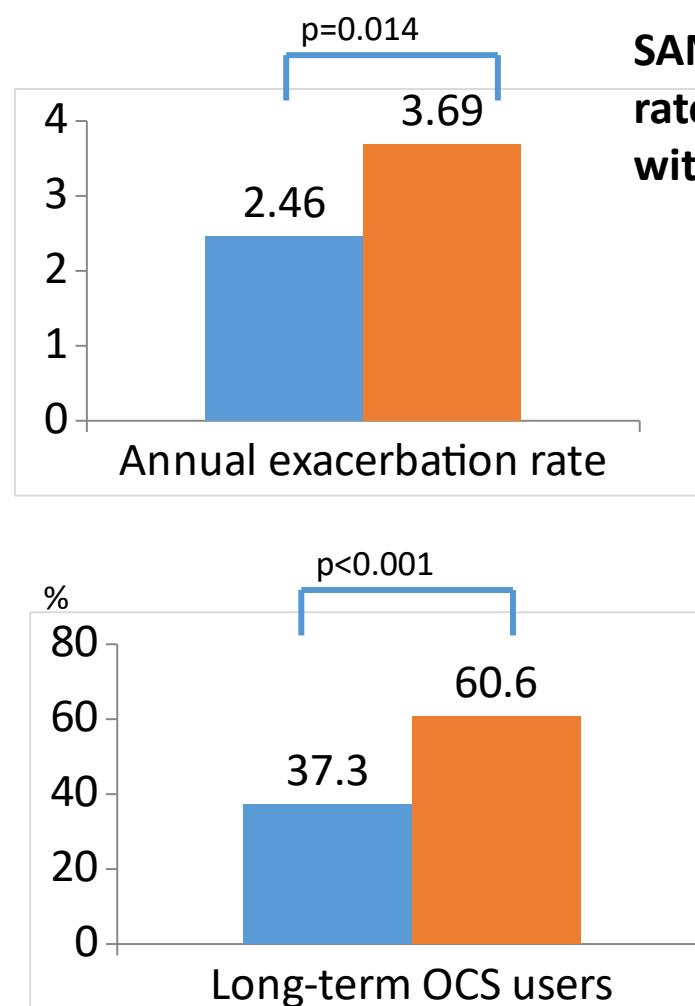


CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP) IN SEVERE ASTHMA



Heffler E et al. – JACI in Pract 2019

SANI registry: annual exacerbation rate and OCS use in SA patients with or without CRSwNP

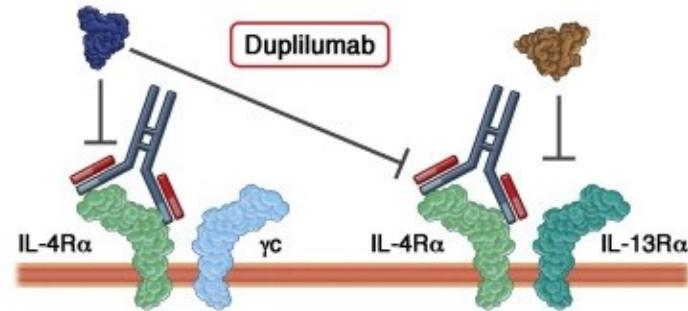
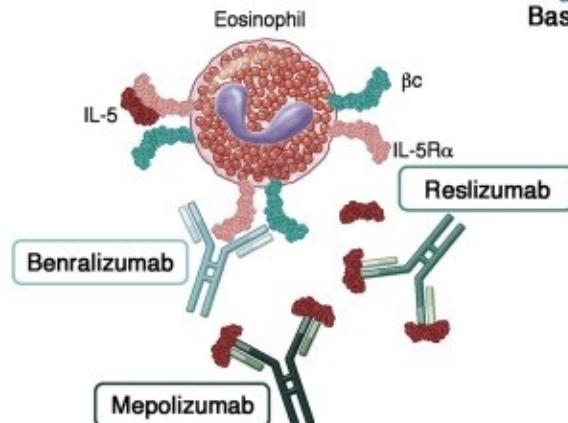
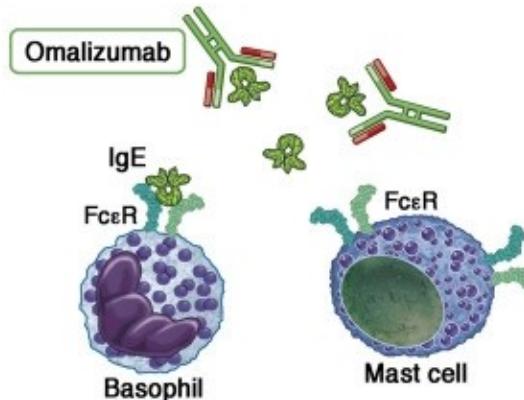
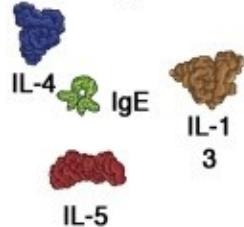


Biologicals for CRSwNP

B

Cells and mediators of Type 2 Inflammation

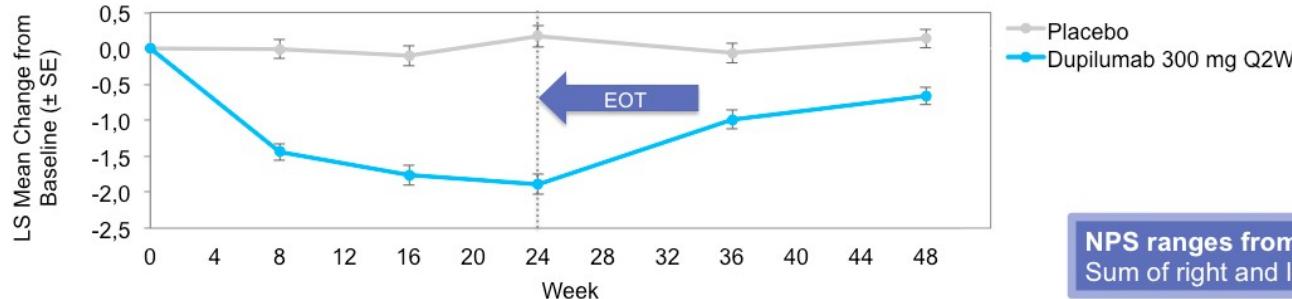
ILC2s
Th2 cells
B cells
Tfh cells
Eosinophils
Mast cells
Basophils



B-cells, Monocytes, Fibroblasts, T-cells, Eosinophils, Epithelial cells

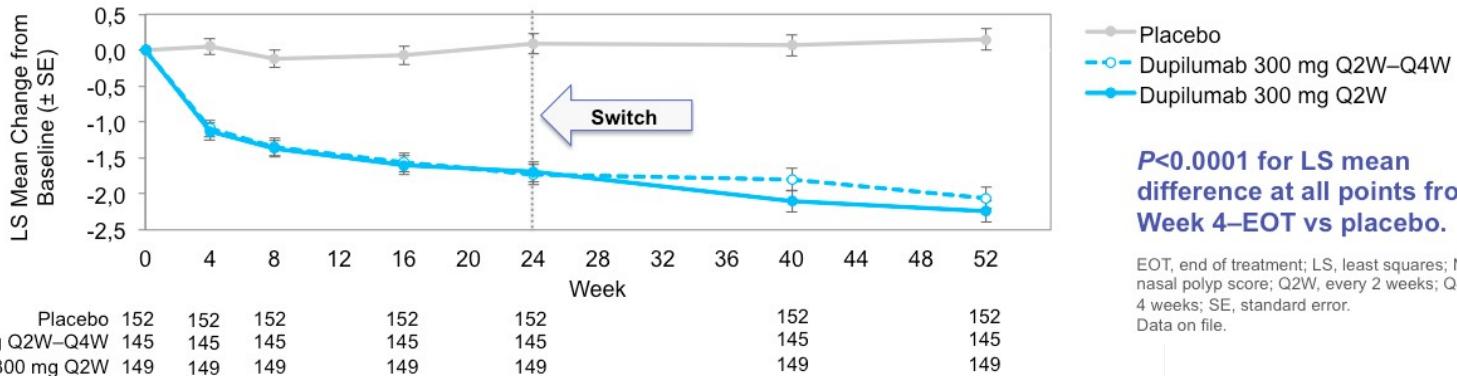
Anti-IL4/IL13 strategies: Dupilumab

SINUS-24



NPS ranges from 0 to 8 points
Sum of right and left scores (0–4)

SINUS-52

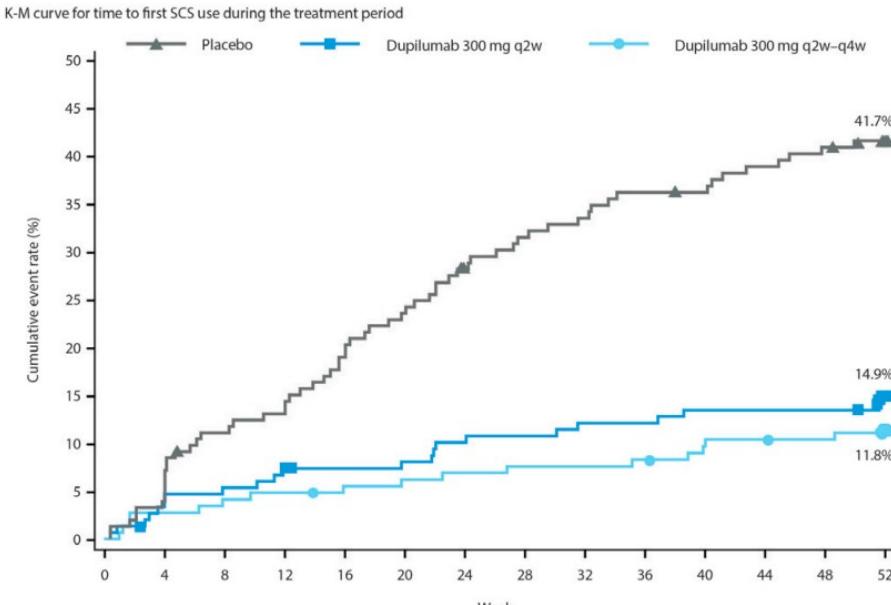


$P<0.0001$ for LS mean difference at all points from Week 4–EOT vs placebo.

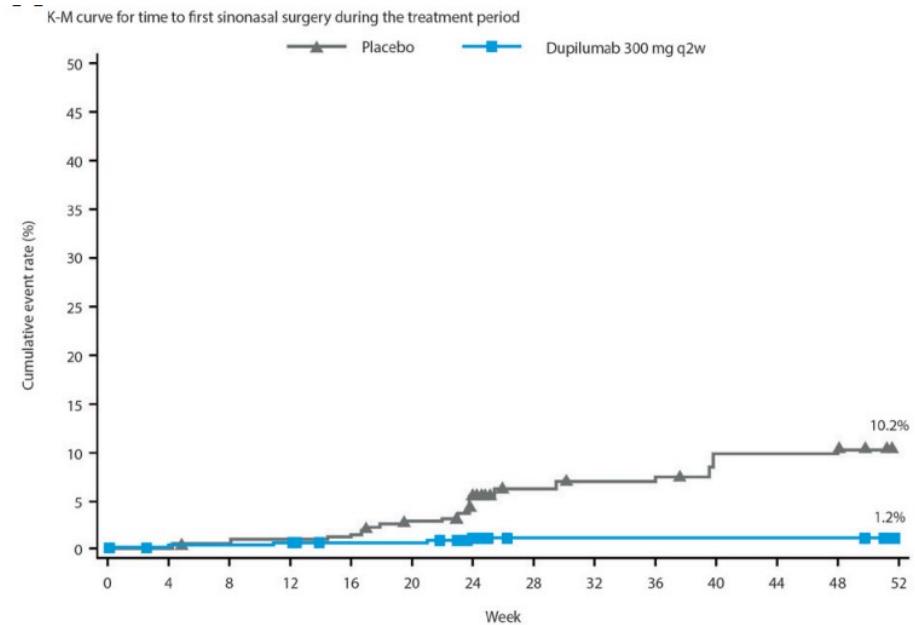
EOT, end of treatment; LS, least squares; NPS, nasal polyp score; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.
Data on file.

Anti-IL4/IL13 strategies: Dupilumab

Systemic corticosteroids

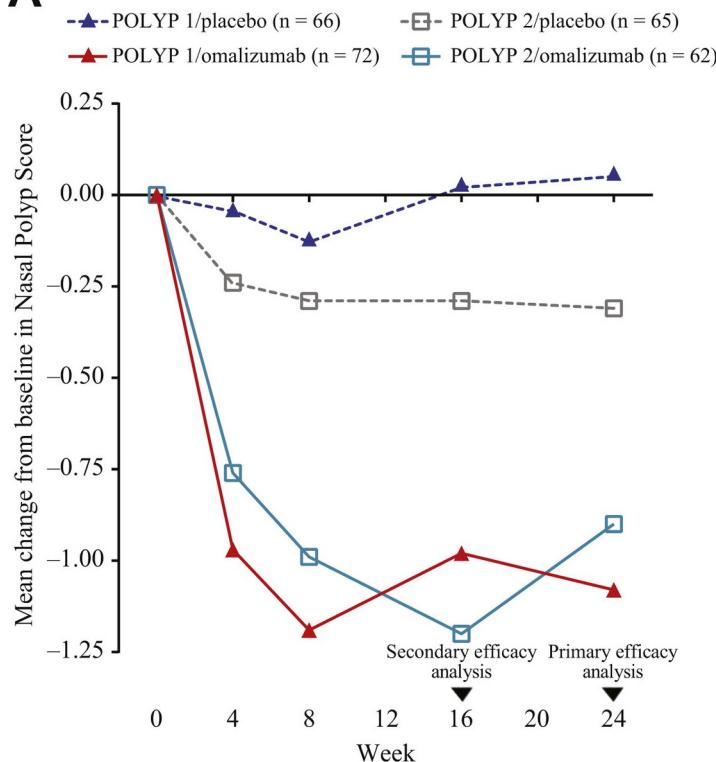


Surgery

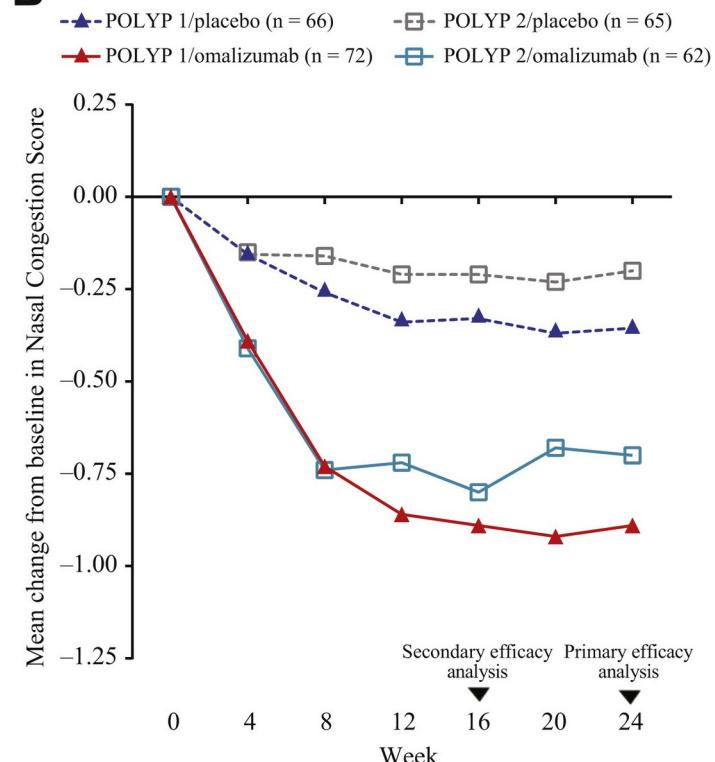


Anti-IgE strategies: Omalizumab

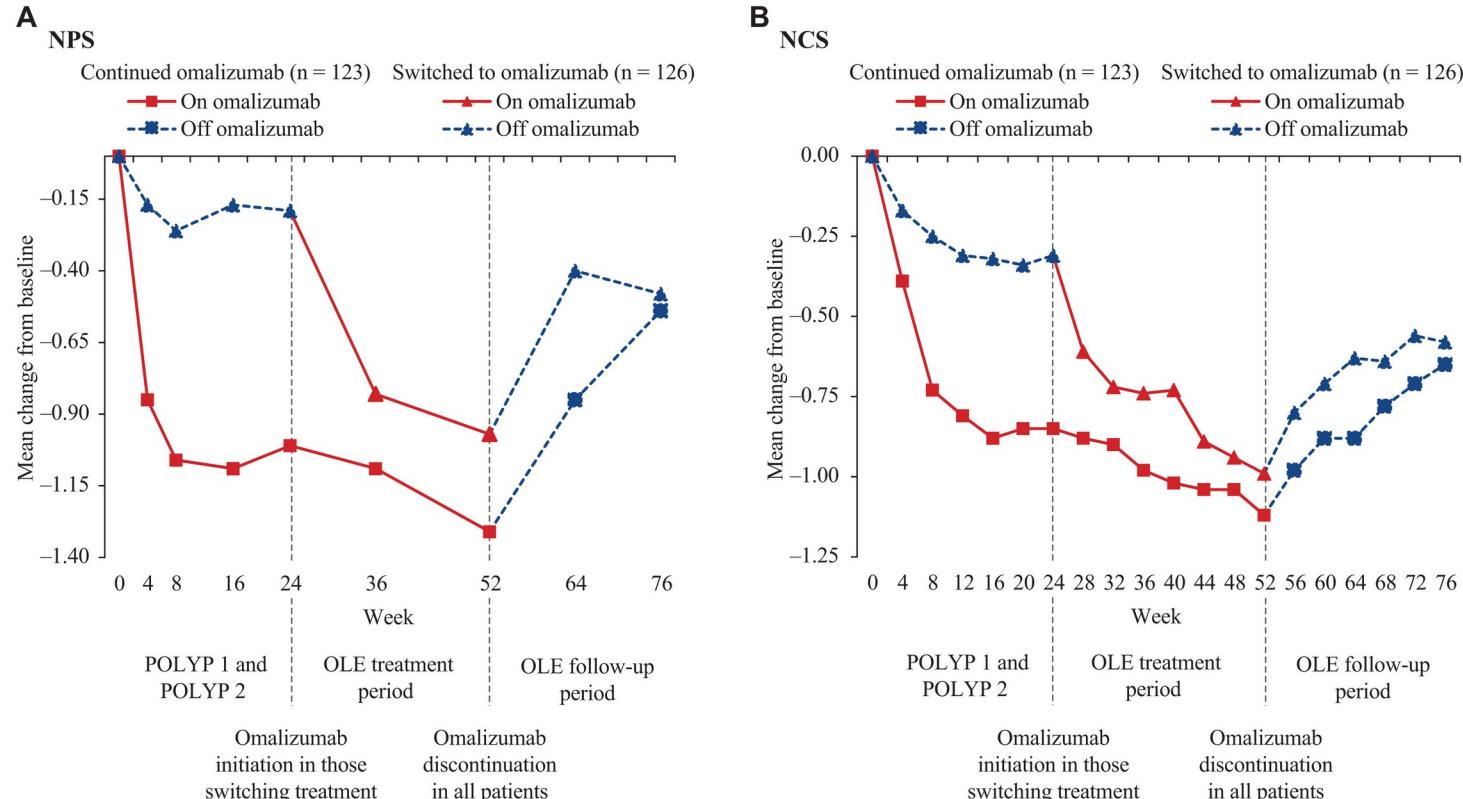
A



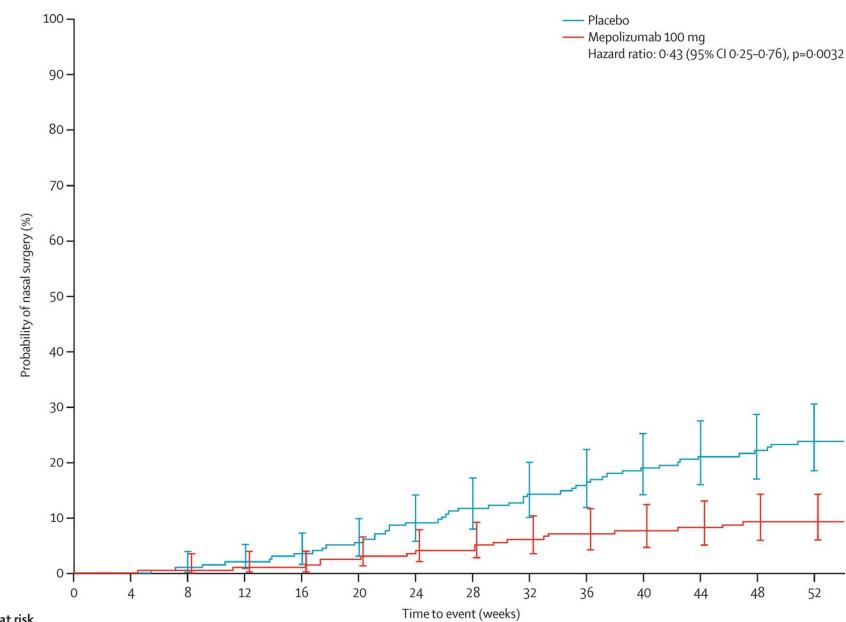
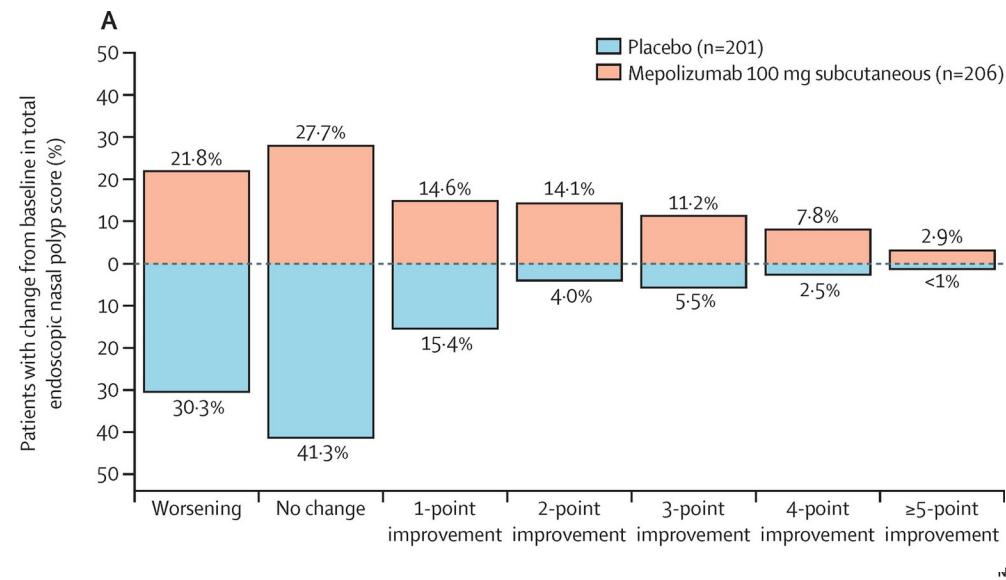
B



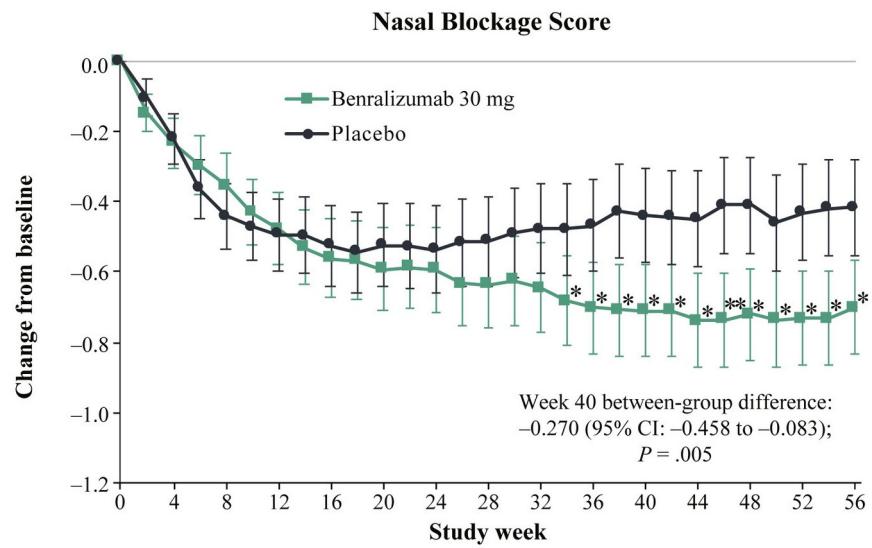
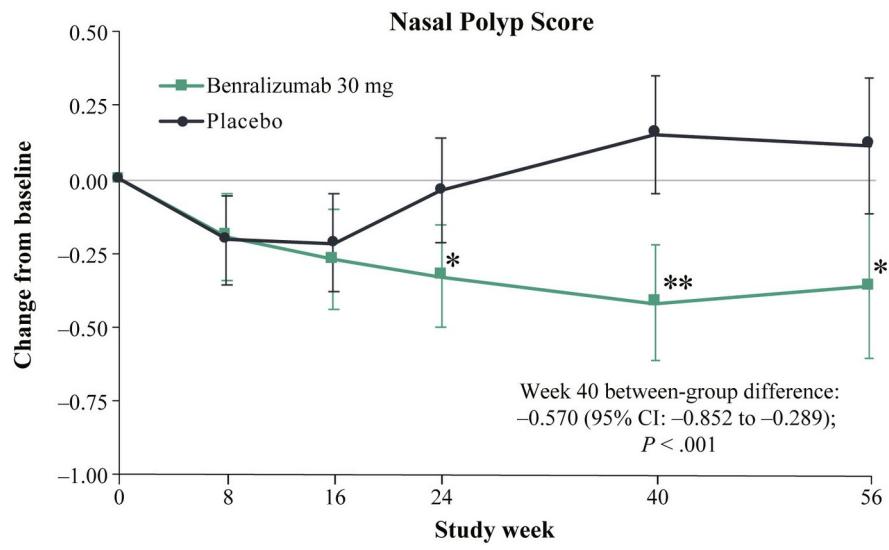
Anti-IgE strategies: Omalizumab



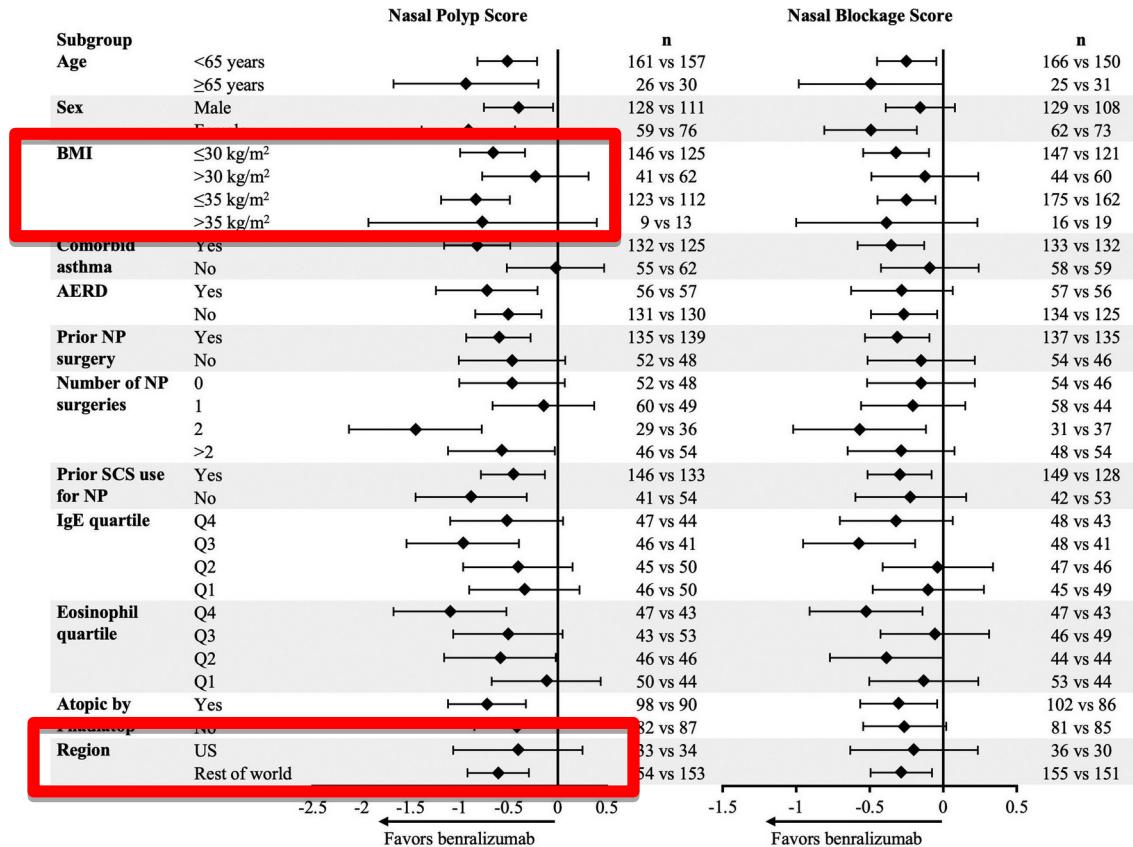
Anti-IL5 strategies: Mepolizumab



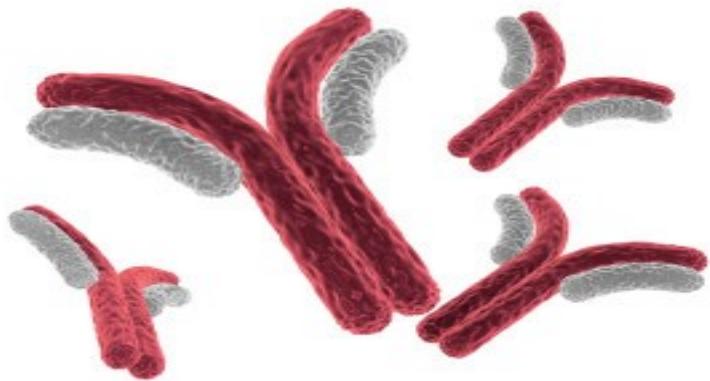
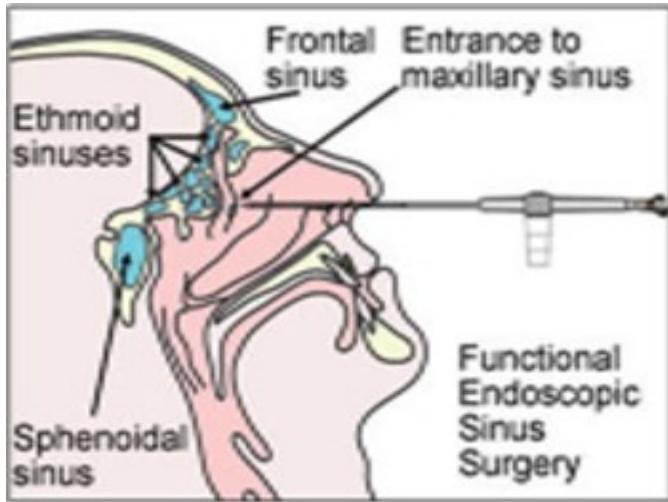
Anti-IL5 strategies: Benralizumab



Anti-IL5 strategies: Benralizumab



Surgery and/or Biologics?



NEED OF REAL-LIFE STUDIES



Project by Centri di Riferimento Asma Grave GINA SIAAC SIP/IRS

FOUNDERS:



Società Italiana di
Allergologia, Asma ed
Immunologia Clinica



Promotori



Endorsement by



Personalized Medicine, Asthma and Allergy



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