ANTI-IL-5 FOR THE TREATMENT OF SEVERE ASTHMA

AAIFNC | November 1, 2017

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OUTLINE

- Severe Asthma Definition and Epidemiology
- Anti-IL-5 Biology
- Mepolizumab Studies
- Resilizumab Studies
- Omalizumab versus anti-IL-5 Therapy

OUTLINE

- **Severe Asthma Definition and Epidemiology**
- Anti-IL-5 Biology
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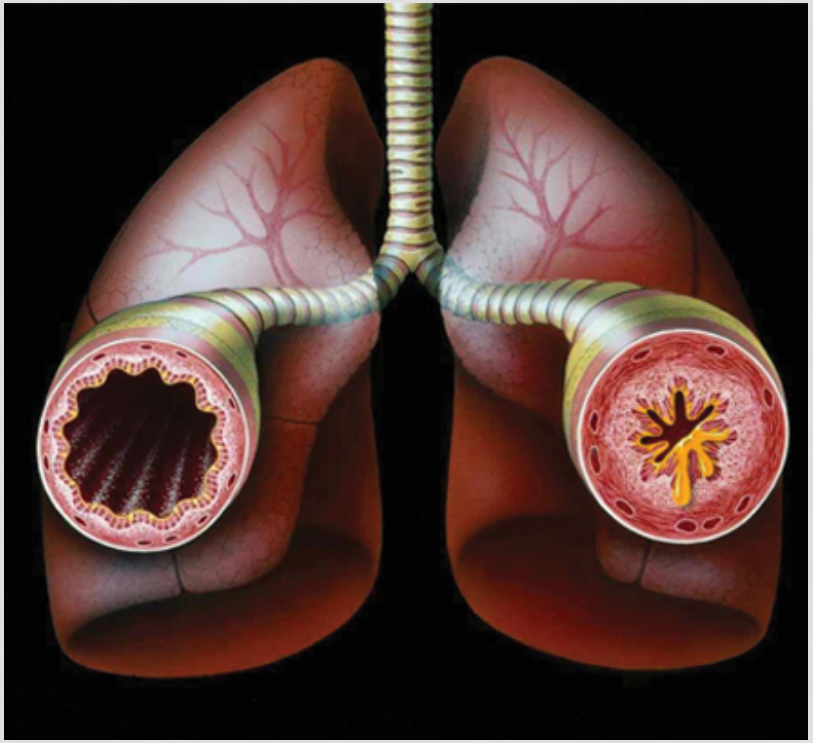
HEALTH CONSEQUENCES



- 300 million suffer globally
- 56 billion spent in USA annually
  - Medications
  - 5-10% with Severe Asthma

SEVERE ASTHMA

- According to recent ERS/ATS consensus, severe asthma is defined as:

"asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic CS) to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy."

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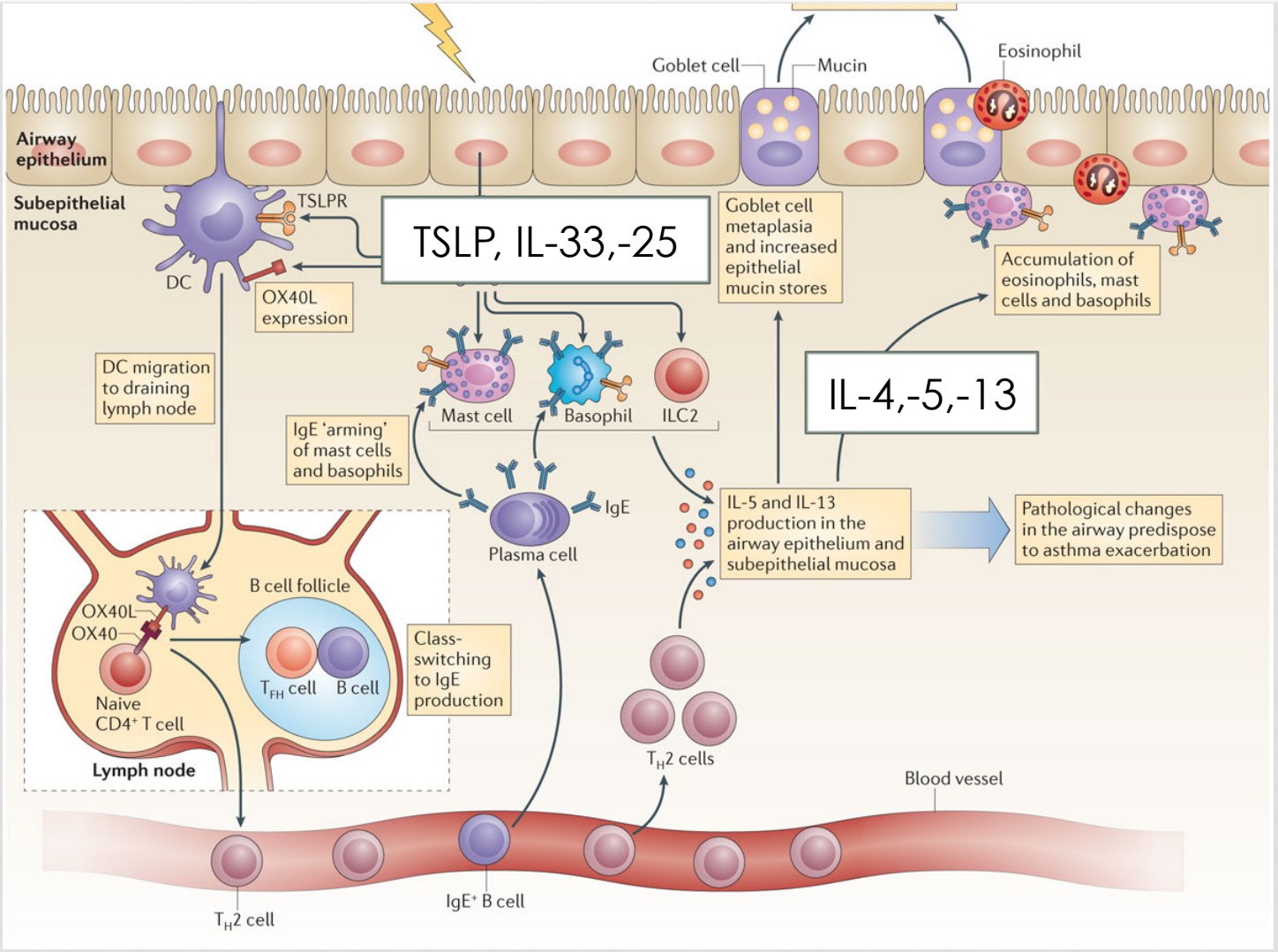
THE BIOLOGIC MECHANISM



ANTI-IL-5

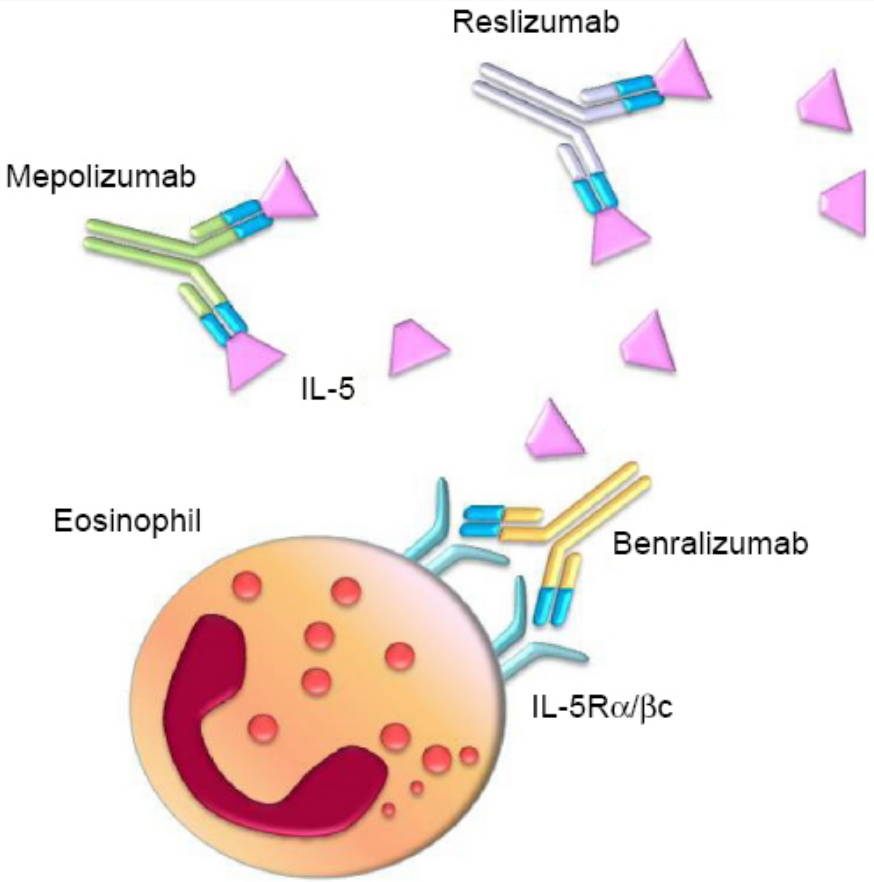


Figure 2 Anti-IL-5/IL-5R biologic therapies.
Notes: Monoclonal antibodies aimed to inhibit eosinophil functions include mepolizumab and reslizumab, which bind to and neutralize IL-5, as well as benralizumab, which targets and blocks IL-5Rα.
Abbreviation: IL-5, interleukin-5.

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INDICATIONS FOR MEPOLIZUMAB

- For add-on, maintenance treatment of severe asthma in patients who are age 12 or older and have an eosinophilic phenotype
- NICE recommends a threshold of an absolute blood eosinophil >/= 300/microL
- Clinical trial data suggest that efficacy requires an absolute blood eosinophil count >/= 150/microL
- This threshold is less clear in patients on daily systemic glucocorticoids

The NEW ENGLAND JOURNAL of MEDICINE

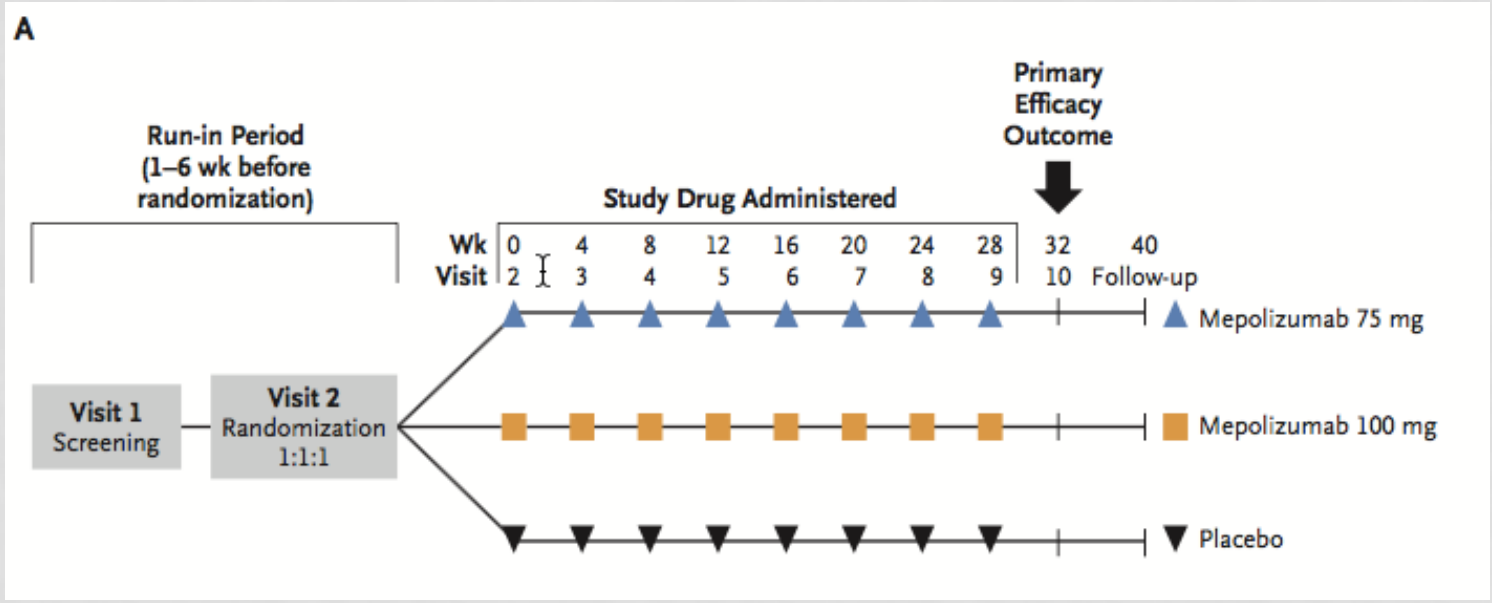
ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

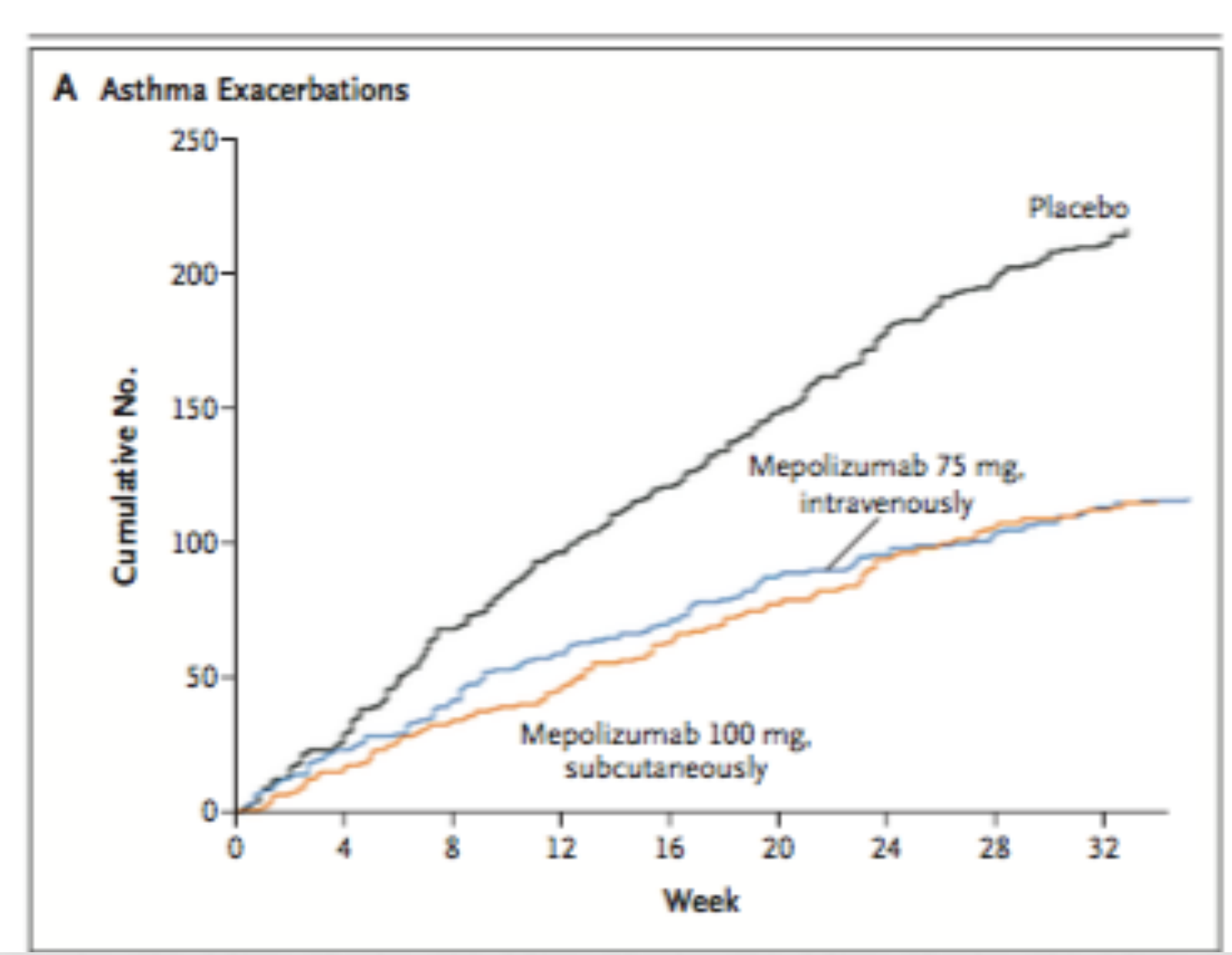
Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*

2014

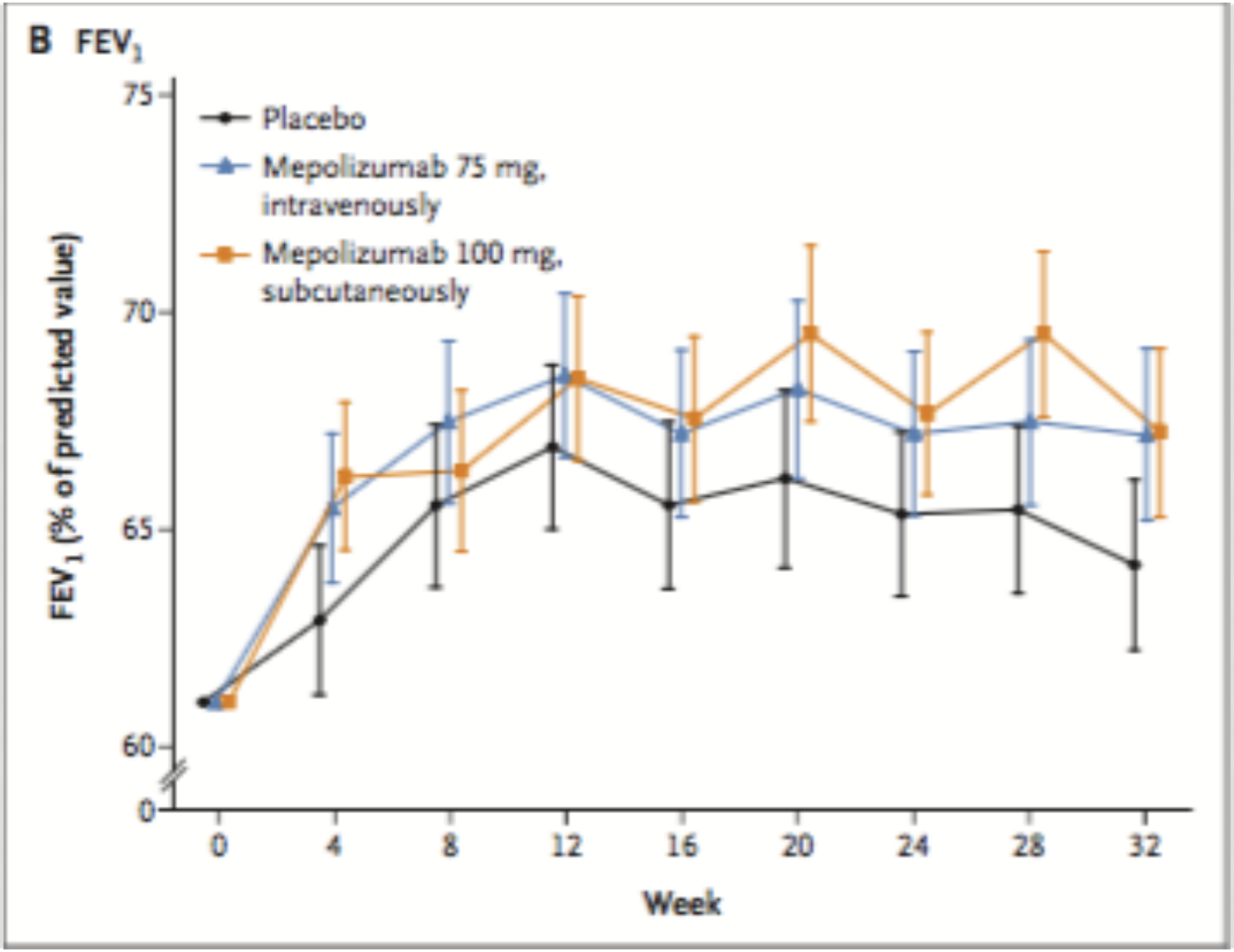
N=576, eosinophils >150, high dose ICS



Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma



Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma



Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.74	0.93	47 (28 to 60)†	<0.001	0.83	53 (36 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (–41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (–66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33		
Change from baseline in score on Asthma Control Questionnaire	–0.50±0.07	–0.92±0.07	–0.42 (–0.61 to –0.23)	<0.001	–0.94±0.0	–0.44 (–0.63 to –0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	–9.0±1.2	–15.4±1.2	–6.4 (–9.7 to –3.2)	<0.001	–16.0±1.1	–7.0 (–10.2 to –3.8)	<0.001

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

- Quality of life scores (SGRQ score) improved by 7 points!
- Asthma Control Questionaire-5 score improved by 0.44 points as early as week 4!

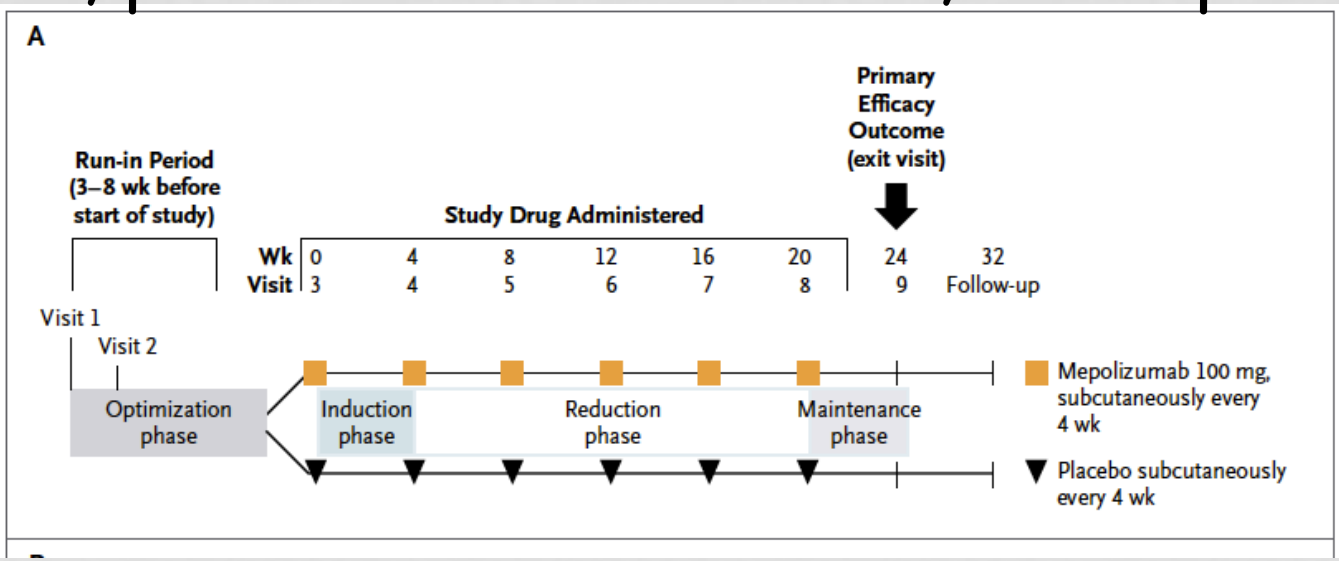
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2014 VOL. 371 NO. 13

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma 2014

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*

- N=135, prednisone x ≥6 months, eosinophils >150



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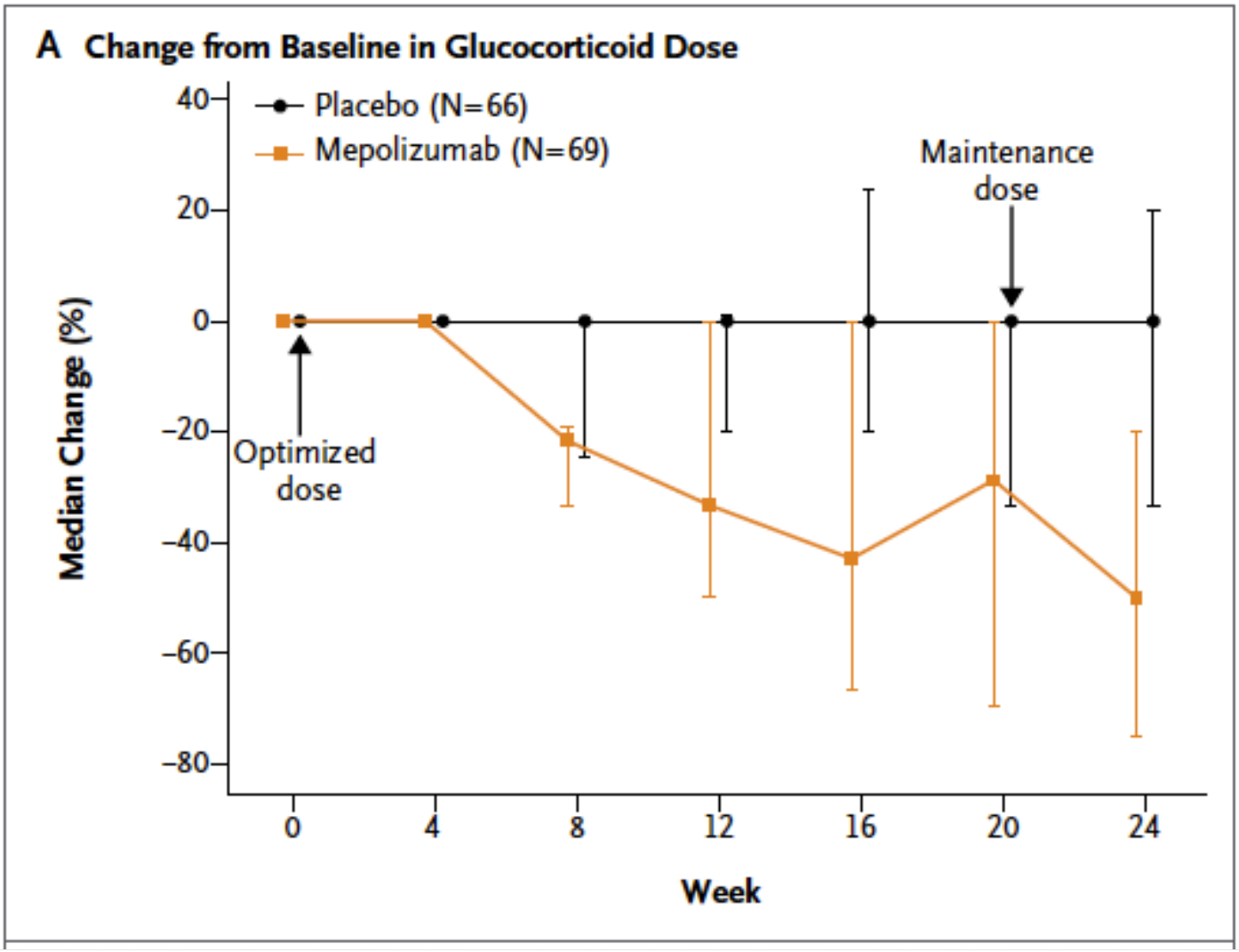

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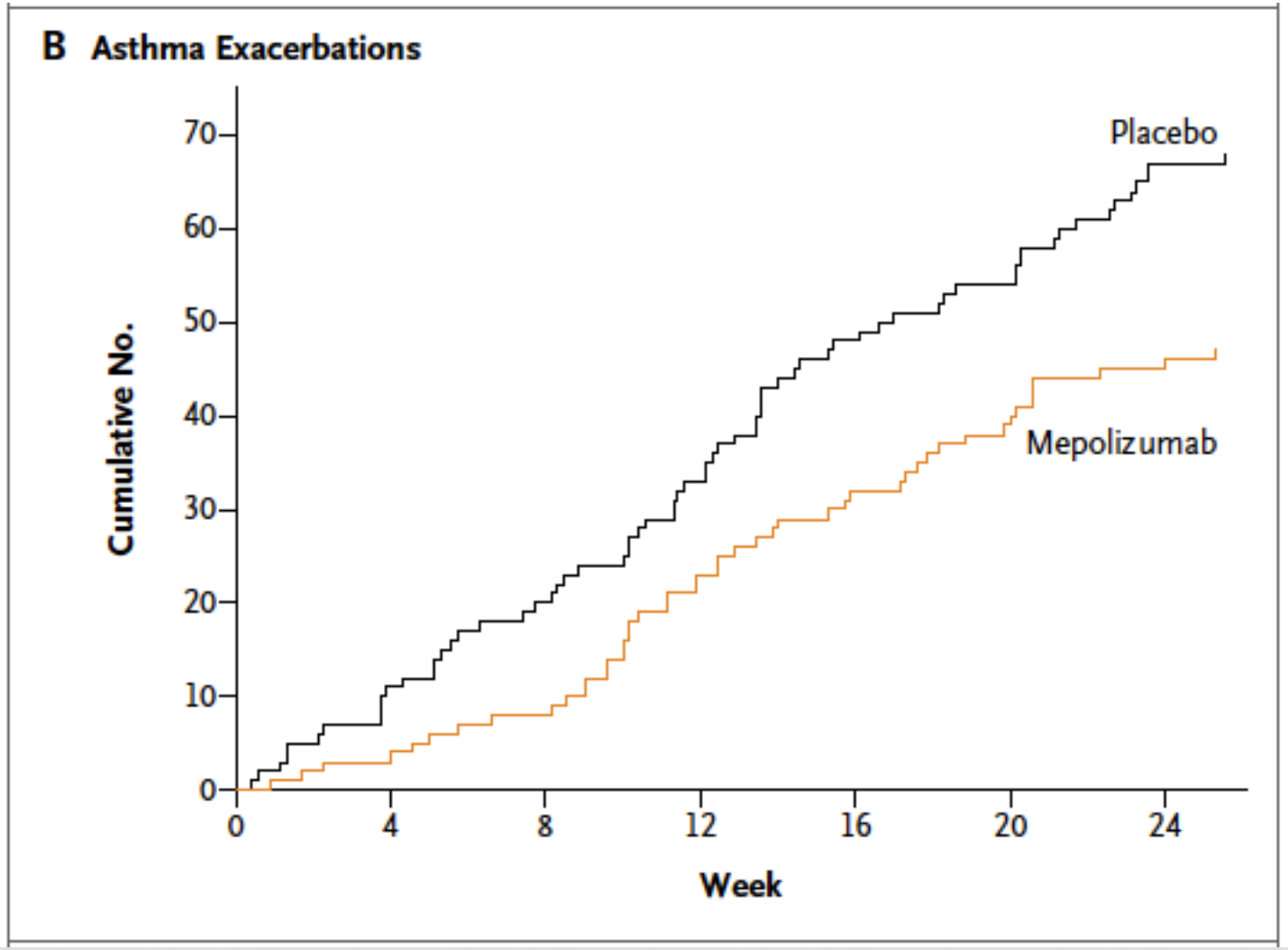

Table 3. Summary of Adverse Events.*

Variable	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
	number of patients (percent)		
All adverse events	158 (83)	161 (84)	152 (78)
Nonasthma event	157 (82)	161 (84)	152 (78)
Worsening of asthma	29 (15)	18 (9)	13 (7)
Drug-related event, per investigator assessment†	30 (16)	33 (17)	39 (20)
Leading to study withdrawal	4 (2)	0	1 (1)
Serious adverse events			
During treatment	27 (14)	14 (7)	16 (8)
Drug-related event, per investigator assessment†	1 (1)	0	1 (1)
Fatal	1 (1)	0	0
Most common adverse events‡			
Nasopharyngitis	46 (24)	45 (24)	33 (17)
Headache	33 (17)	46 (24)	39 (20)
Upper respiratory tract infection	27 (14)	22 (12)	24 (12)
Sinusitis	18 (9)	11 (6)	18 (9)
Bronchitis	18 (9)	14 (7)	9 (5)
Oropharyngeal pain	15 (8)	12 (6)	7 (4)
Injection-site reaction	6 (3)	5 (3)	17 (9)

Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study

Njira Lugogo, MD[1]; Christian Domingo, MD[2]; Pascal Chanez, MD, PhD[3]; Richard Leigh, MBChB[4]; Martyn J. Gilson, MSc[5]; Robert G. Price, MSc[6]; Steven W. Yancey, MSc[7]; and Hector G. Ortega, MD[7,*]

ABSTRACT

Purpose: Patients with severe eosinophilic asthma often experience recurrent asthma exacerbations despite intensive inhaled corticosteroid therapy. In 2 previous double-blind studies (MENSA [NCT01691521] and SIRIUS [NCT01691508]), treatment with intravenous or subcutaneous mepolizumab was associated with significantly reduced annualized exacerbation rates and oral corticosteroid (OCS) requirements compared with placebo. The purpose of this study was to assess the long-term safety and efficacy of subcutaneous mepolizumab treatment in patients with severe eosinophilic asthma.

Methods: COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received subcutaneous mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. The primary objective was to assess the long-term safety of mepolizumab; end points included adverse events (AEs) and serious AEs (SAEs). Efficacy assessments included the annualized exacerbation rate and durability of response (defined as the exacerbation rate and OCS dose reduction when combined with MENSA and SIRIUS data, respectively).

Findings: In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58, previous placebo: 36) patients experienced on-treatment AEs and SAEs, respectively. No fatal AEs were reported. Totals of 13 (2%) and 29 (4%) patients experienced systemic and local site reactions, respectively. There were no reports of mepolizumab-related anaphylaxis. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and OCS dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these end points following treatment with mepolizumab in COSMOS.

Implications: These data demonstrate a favorable safety profile of mepolizumab and indicate a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma.

Accepted for publication July 20, 2016.

ADVERSE EVENTS

- No significant increase in serious adverse events
- Headache and nasopharyngitis were commonly reported side effects

Mepolizumab versus placebo for asthma (Review)

Powell C, Milan SJ, Dwan K, Bax L, Walters N

BENEFITS OF MEPOLIZUMAB

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- **50% reduction in asthma exacerbations!**

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- **50% reduction in asthma exacerbations!**
- **Decreases in ER visits and hospitalizations!**

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- **Clinically important improvements in asthma control and quality of life QUICKLY after initiation of therapy!**

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- **Improvements in lung function!**

BENEFITS OF MEPOLIZUMAB

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- **Decreases in ER visits and hospitalizations!**
- **Clinically important improvements in asthma control and quality of life QUICKLY after initiation of therapy!**
- **Improvements in lung function!**
- **Significant reduction in oral steroids**

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- **Decreases in ER visits and hospitalizations!**
- **Clinically important improvements in asthma control and quality of life QUICKLY after initiation of therapy!**
- **Improvements in lung function!**
- **Significant reduction in oral steroids**
- **No anaphylaxis!**

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INDICATIONS FOR RESLIZUMAB

- Add-on, maintenance therapy of severe asthma in patients who are age 18 or older and have an eosinophilic phenotype
- In pivotal trials, an eosinophilic phenotype was defined as a peripheral blood absolute eosinophil count of 400/microL or greater, although the threshold required for patients on systemic glucocorticoids is not clear

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

Mario Castro, James Zangrilli, Michael E Wechsler, Eric D Bateman, Guy G Brusselle, Philip Bardin, Kevin Murphy, Jorge F Maspero, Christopher O'Brien, Stephanie Korn

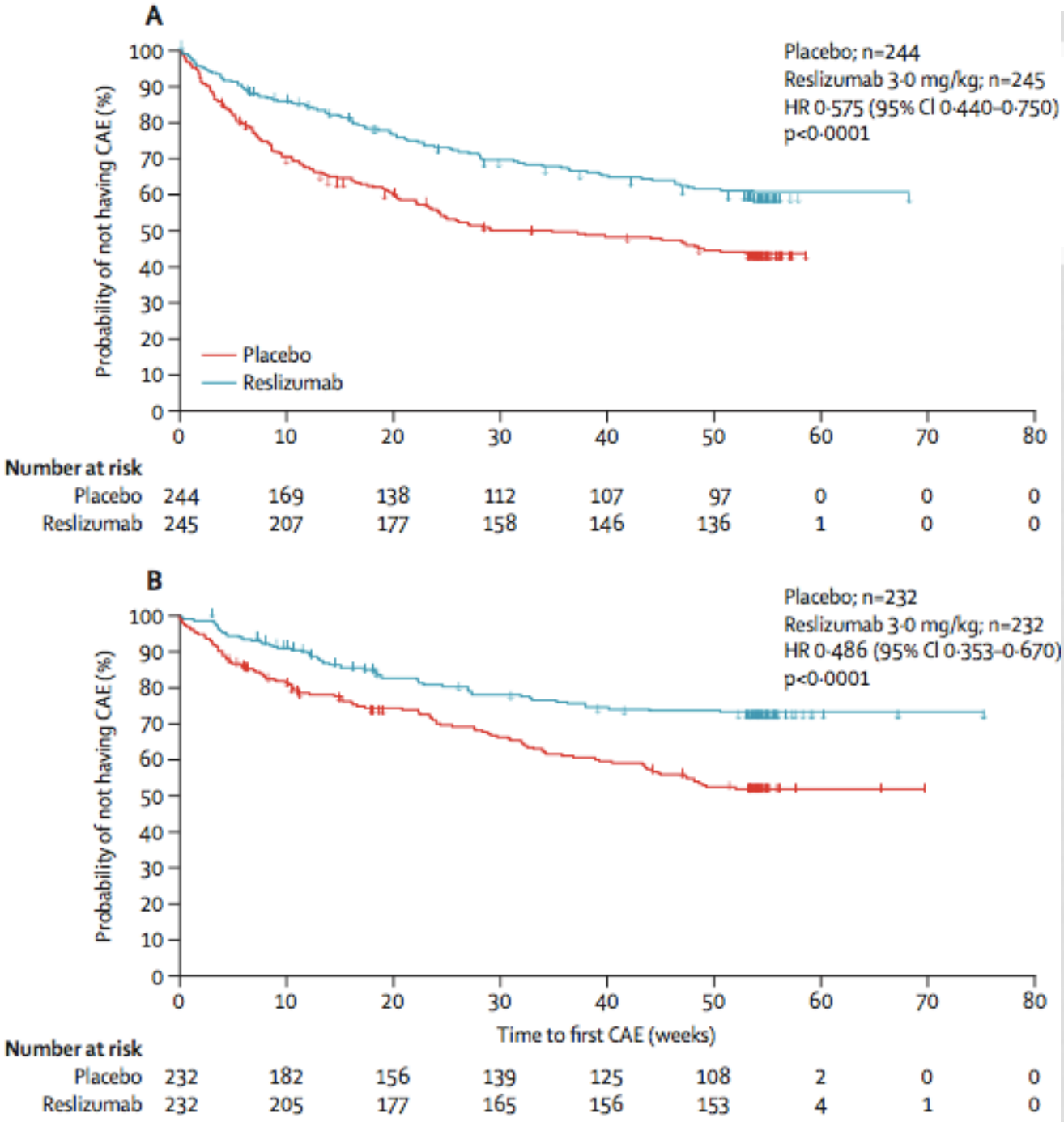
Summary

Background Elevated numbers of blood eosinophils are a risk factor for asthma exacerbations. Reslizumab is a humanised anti-interleukin 5 monoclonal antibody that disrupts eosinophil maturation and promotes programmed cell death. We aimed to assess the efficacy and safety of reslizumab in patients with inadequately controlled, moderate-to-severe asthma.

Lancet Respir Med 2015; 3: 355–66

Published Online February 23, 2015 http://dx.doi.org/10.1016/

- N=953, eosinophils >400, recurrent exacerbations


A
Placebo; n=244
Reslizumab 3·0 mg/kg; n=245
HR 0·575 (95% CI 0·440–0·750)
p<0·0001
Probability of not having CAE (%)
Placebo
Reslizumab
Number at risk
Placebo 244 169 138 112 107 97 0 0 0
Reslizumab 245 207 177 158 146 136 1 0 0
B
Placebo; n=232
Reslizumab 3·0 mg/kg; n=232
HR 0·486 (95% CI 0·353–0·670)
p<0·0001
Probability of not having CAE (%)
Time to first CAE (weeks)
Number at risk
Placebo 232 182 156 139 125 108 2 0 0
Reslizumab 232 205 177 165 156 153 4 1 0

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

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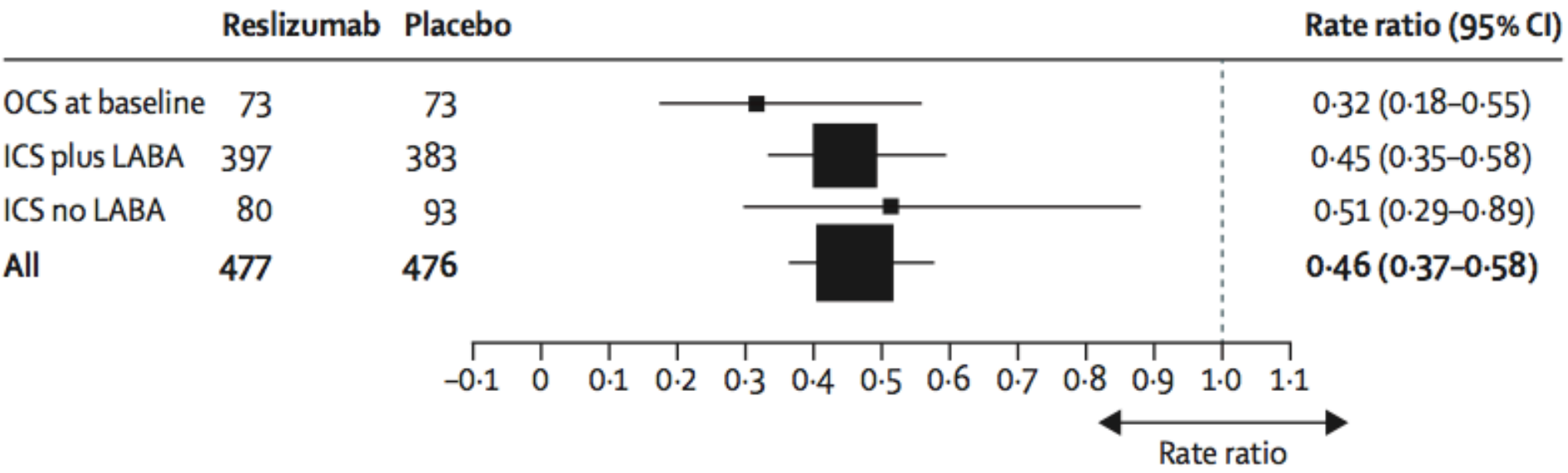

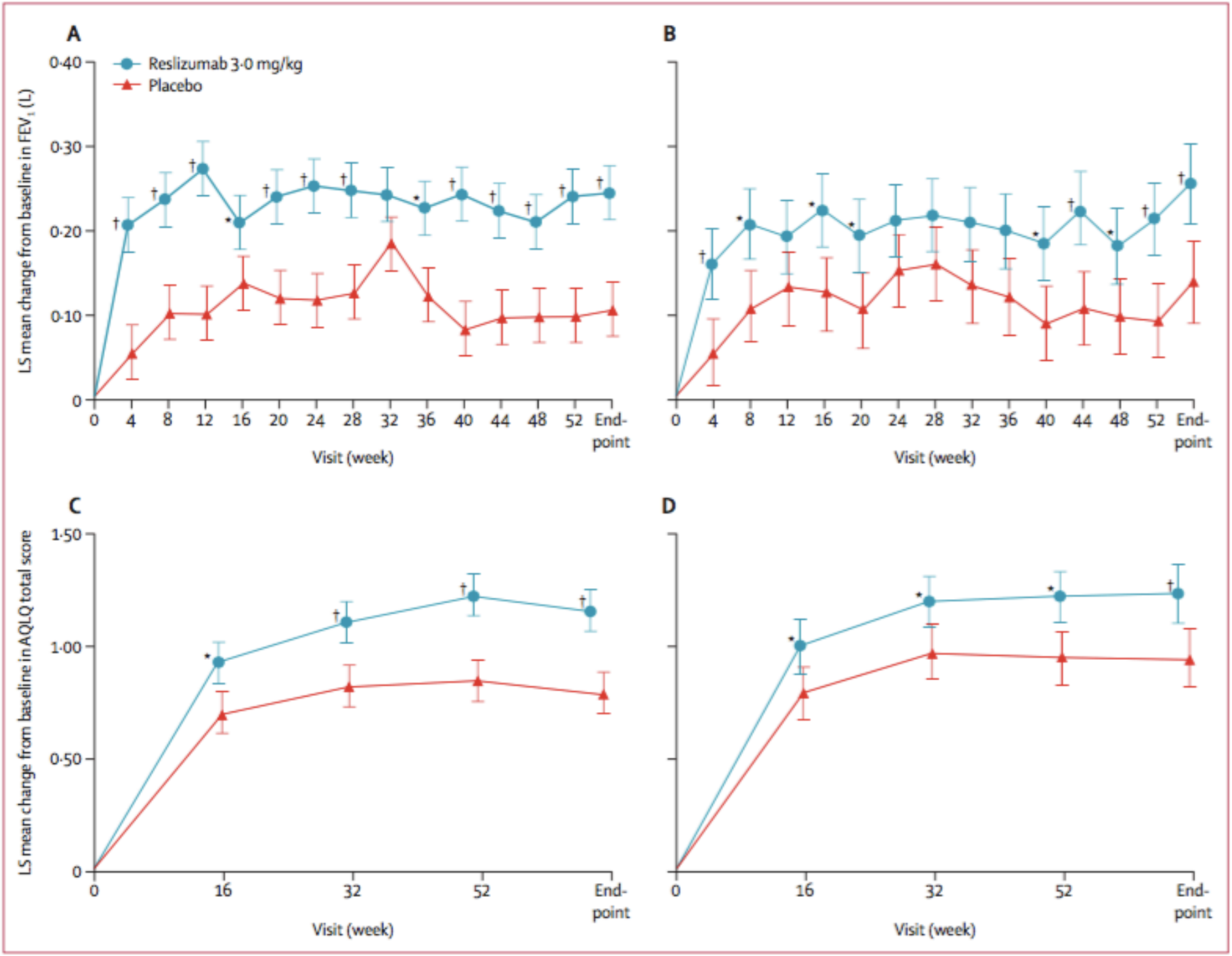
A
Reslizumab 3·0 mg/kg
Placebo
LS mean change from baseline in FEV1 (L)
0·40
0·30
0·20
0·10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 End-point
Visit (week)
B
0 4 8 12 16 20 24 28 32 36 40 44 48 52 End-point
Visit (week)
C
LS mean change from baseline in AQLQ total score
1·50
1·00
0·50
0
0 16 32 52 End-point
Visit (week)
D
0 16 32 52 End-point
Visit (week)

	Study 1		Study 2	
	Placebo (n=243)	Reslizumab (n=245)	Placebo (n=232)	Reslizumab (n=232)
All-grade adverse events	206 (85%)	197 (80%)	201 (87%)	177 (76%)
Asthma worsening	127 (52%)	97 (40%)	119 (51%)	67 (29%)
Upper respiratory tract infection	32 (13%)	39 (16%)	16 (7%)	8 (3%)
Nasopharyngitis	33 (14%)	28 (11%)	56 (24%)	45 (19%)
Sinusitis	29 (12%)	21 (9%)	10 (4%)	9 (4%)
Headache	30 (12%)	19 (8%)	17 (7%)	33 (14%)
Influenza	23 (9%)	18 (7%)	7 (3%)	6 (3%)
Nausea	10 (4%)	12 (5%)	3 (1%)	2 (<1%)
Bronchitis	24 (10%)	13 (5%)	14 (6%)	2 (<1%)
Urinary tract infection	11 (5%)	13 (5%)	1 (<1%)	0
Allergic rhinitis	6 (2%)	13 (5%)	10 (4%)	6 (3%)
Oropharyngeal pain	8 (3%)	13 (5%)	3 (1%)	5 (2%)
Back pain	13 (5%)	13 (5%)	8 (3%)	12 (5%)
Pharyngitis	13 (5%)	10 (4%)	8 (3%)	7 (3%)
Cough	13 (5%)	11 (4%)	7 (3%)	3 (1%)
Dyspnoea	12 (5%)	10 (4%)	5 (2%)	2 (<1%)
Respiratory tract infection	5 (2%)	6 (2%)	8 (3%)	9 (4%)
Dizziness	13 (5%)	5 (2%)	4 (2%)	6 (3%)
Serious adverse events	34 (14%)	24 (10%)	23 (10%)	18 (8%)
Asthma	13 (5%)	11 (4%)	6 (3%)	3 (1%)
Pneumonia	0	2 (<1%)	6 (3%)	2 (<1%)
Road traffic accident	0	0	3 (1%)	1 (<1%)
Adverse events leading to discontinuation	8 (3%)	4 (2%)	9 (4%)	8 (3%)
Deaths	1 (<1%)	0	0	0

Data are n (%), based on the number of patients who had at least one adverse event of a particular classification. Adverse events that occurred in at least 5% of patients in any group during the study treatment period are shown, as are serious adverse events that occurred in at least 1% of patients in any group. *The safety population included all randomly assigned patients who received at least one dose of any study drug.

***Table 3*: Most common adverse events (safety population*)**

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- Resilizumab Studies
- **Omalizumab versus anti-IL-5 Therapy**

OMALIZUMAB VERSUS ANTI-IL-5 THERAPY

- Currently, no head to head studies have been performed to compare the effect difference of these two antibodies on severe asthma

DIFFERENT PATIENT POPULATIONS

- Omalizumab indicated for allergic asthma (sensitization to perennial allergens)
  - Severe adult asthmatics are less likely to be atopic (34% vs. 52% in mild to moderate asthmatics)
- Anti-IL-5 antagonists indicated for eosinophilic asthma
  - Severe asthmatics are more likely to have eosinophilic inflammation compared to non-severe asthmatics

Amelink M et al. Severe adult-onset asthma: A distinct phenotype. J Allergy Clin Immunol 2013.

SEVERE ASTHMATICS

- A larger subset of severe asthmatics have an eosinophilic phenotype than they are atopic

Original Article

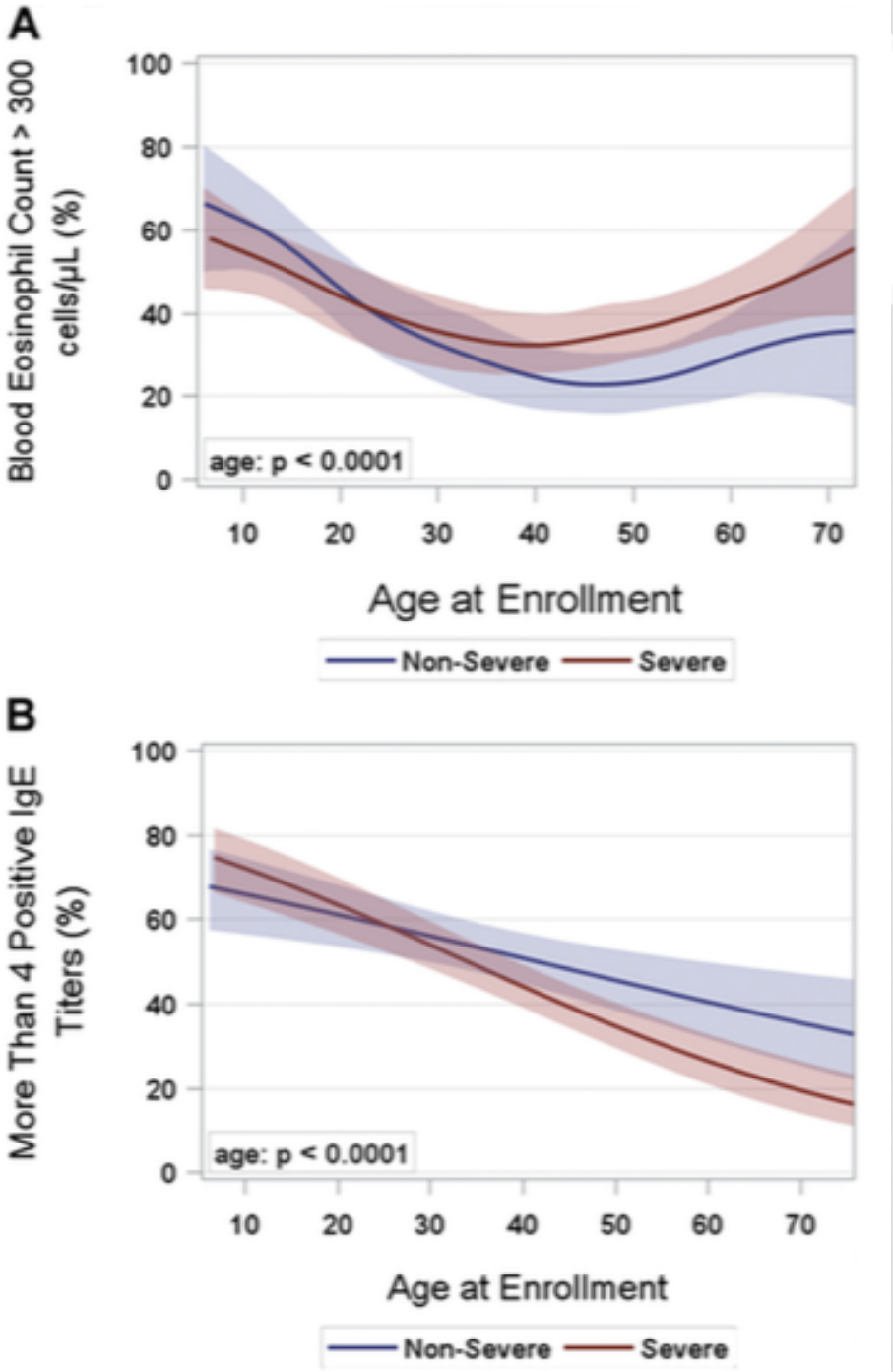
Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age

TABLE III. Features of the SARP III cohort by age and asthma severity: markers of inflammation

	Children (<18 y)		Adults	
	Severe	Nonsevere	Severe	Nonsevere
Sample, n	111	77	313	213
Sputum differential, n	27	17	241	166
Sputum cell count (cells × 10^4/μL), median (min, max)	77.4 (23.7, 153.1)	61.9 (9.5, 199.8)	97.6 (0.0, 195.3)	82.4 (34.9, 187.0)
Sputum eosinophil %, median (min, max)	1.6 (0.0, 53.7)	1.1 (0.0, 61.4)	0.8 (0.0, 63.9)	0.7 (0.0, 59.4)
Sputum neutrophil %, median (min, max)	53.8 (9.4, 90.1)	40.8 (8.3, 80.3)	51.7 (1.5, 99.8)	55.8 (0.5, 99.3)
FeNO (ppb), median (quartiles)	23.0 (12.0, 46.0)	28.0 (12.0, 49.0)	21.0* (13.0, 37.0)	24.0 (16.0, 43.0)
Expired NO > 30 ppb, n (%)†	40 (36.7)	33 (44.0)	96 (31.1)*	87 (40.8)
Serum IgE, median (quartiles)	465 (164, 1207)	490 (151, 834)	163 (45, 384)	141 (46, 374)
At least 1 of 15 positive blood IgE tests, n (%)	104 (94.5)	67 (89.3)	234 (75.2)	173 (82.0)
Number of positive (of 15) allergen-specific IgE tests, median (min, max)	6.0 (3.0, 11.0)	7.0 (3.0, 11.0)	3.0* (0.5, 7.0)	4.0 (2.0, 7.0)
Highly sensitized ≥ 4/15 positive allergen tests, n (%)	74 (67.3)	50 (66.7)	115 (37.0)*	101 (47.9)
Total blood eosinophils (cells/μL), median (quartiles)	324 (162, 514)	359 (208, 575)	228* (134, 399)	189 (111, 320)
Blood eosinophilia ≥300 cells/μL, n (%)	60 (54.1)	49 (63.6)	120 (38.5)*	60 (28.2)

*$P < .05$, severe vs nonsevere.

†% expressed per column.


A
Blood Eosinophil Count > 300 cells/µL (%)
100
80
60
40
20
0
age: p < 0.0001
10
20
30
40
50
60
70
Age at Enrollment
Non-Severe
Severe
B
More Than 4 Positive IgE Titers (%)
100
80
60
40
20
0
age: p < 0.0001
10
20
30
40
50
60
70
Age at Enrollment
Non-Severe
Severe

OMALIZUMAB AND ASTHMA EXACERBATIONS

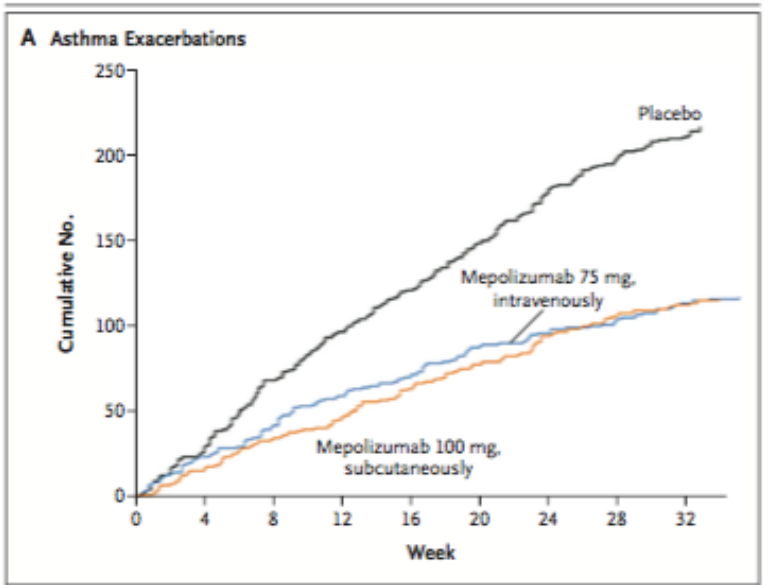
- In an analysis of 10 studies (3261 participants), there was an absolute reduction of only 10% compared to placebo

Cochrane Library

Cochrane Database of Systematic Reviews

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P



OMALIZUMAB AND ASTHMA EXACERBATIONS IN SEVERE COHORT

- Omalizumab versus placebo in participants receiving background inhaled plus oral steroid therapy (OR 1.65, 95% CI 0.66 to 4.13; one study, 95 participants)

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

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OMALIZUMAB AND ASTHMA EXACERBATIONS IN SEVERE COHORT

- Omalizumab versus placebo in participants receiving background inhaled plus oral steroid therapy **(OR 1.65, 95% CI 0.66 to 4.13; one study, 95 participants)**

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

2014

ASTHMA EXACERBATIONS IN SEVERE ASTHMA

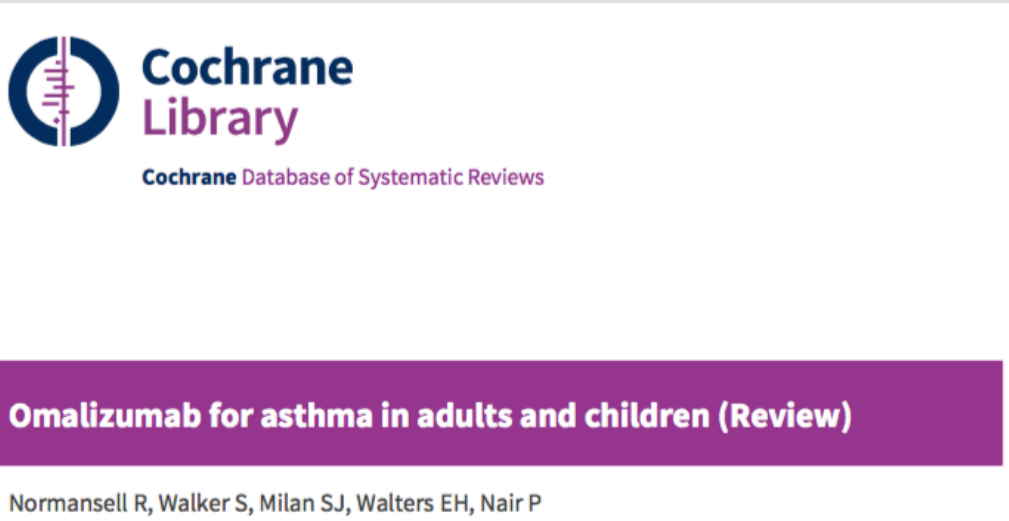
- Clearest benefit observed in participants with moderate asthma
- Uncertainty surrounds those receiving a background therapy of inhaled plus oral corticosteroids.

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

DIRECT QUOTE FROM COCHRANE REVIEW

"We are much less certain of any positive impact of omalizumab on exacerbations in patients with more severe asthma"



NO EFFECT ON FEV1

Table 4—*Analysis of Secondary Outcomes (Omalizumab vs Placebo)*

Outcome	No.	Omalizumb vs Placebo	Measure (95% CI)	*P* Value	I^2, %
Rescue medication (stable phase),[11,23,25-27]	2,285	2.27 vs 2.76[a]	WMD = −0.52 (−0.79 to 0.25)	.0002	40
Final pulmonary function (FEV_1 or PEF) (stable phase)[23-26,a]	1,651	3.82 vs 3.63[ab]	SMD = 0.07 (−0.03 to 017)[ab]	.15	0
(stable phase),[12,23,27] L/m					
Asthma symptom score (stable phase)[11,23,25-27]	1,893	1.53 vs 1.71[a]	WMD = −0.30 (−0.40 to 0.20)	.0001	13
Change in AQLQ score (stable phase)[23,25-28]	2,131	0.37 vs 0.06[a]	WMD = 0.33 (0.28-0.37)	.0001	53
Rescue medication (steroid-reduction phase),[23,25-26] puffs/d	1,291	2.27 vs 2.76[a]	WMD = −0.73 (−1.04 to 0.42)	.0001	0
Prematurely discontinued patients[11-12,23-28]	3,429	9.6% vs 12.5%	RR = 0.69 (0.50-0.97)	.03	60
Withdrawals due to adverse events[11-12,23-28]	3,429	1.3% vs 1.5%	RR = 0.97 (0.43-2.20)	.95	26
Any adverse effect[11-12,23-28]	3,429	84.9% vs 82.4%	RR = 1.01 (0.97-1.05)	.80	53
Serious adverse effects[11-12,23-28]	3,429	3.8% vs 5.3%	RR = 0.75 (0.52-1.10)	.14	17
Treatment-related adverse effects[11-12,24,27-28]	2,112	5.0% vs 3.2%	RR = 1.61 (1.05-2.47)	.03	0
Urticaria[12,23-28]	2,853	2.5% vs 2.1%	RR = 1.11 (0.53-2.32)	.79	34
Injection site reactions[12,23-28]	2,853	19.9% vs 13.2%	RR = 1.43 (1.15-1.79)	.002	37
Anaphylactic reactions[11,28]	995	0.33% vs 0.24%	RR = 1.08 (0.13-8.74)	.94	0

AQLQ = Asthma Quality of Life Questionnaire; PEF = peak expiratory flow; SMD = standardized mean difference; WMD = weighted mean difference. See Table 3 for expansion of other abbreviation.

[a]Mean value.

[b]Expressed in SD units.

Rodrigo GJ et. al. *Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review.* Chest 2011

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Asthma symptom score (stable phase)[11,23,25-27]	1,893	1.53 vs 1.71[a]	WMD = −0.30 (−0.40 to 0.20)	.0001	13
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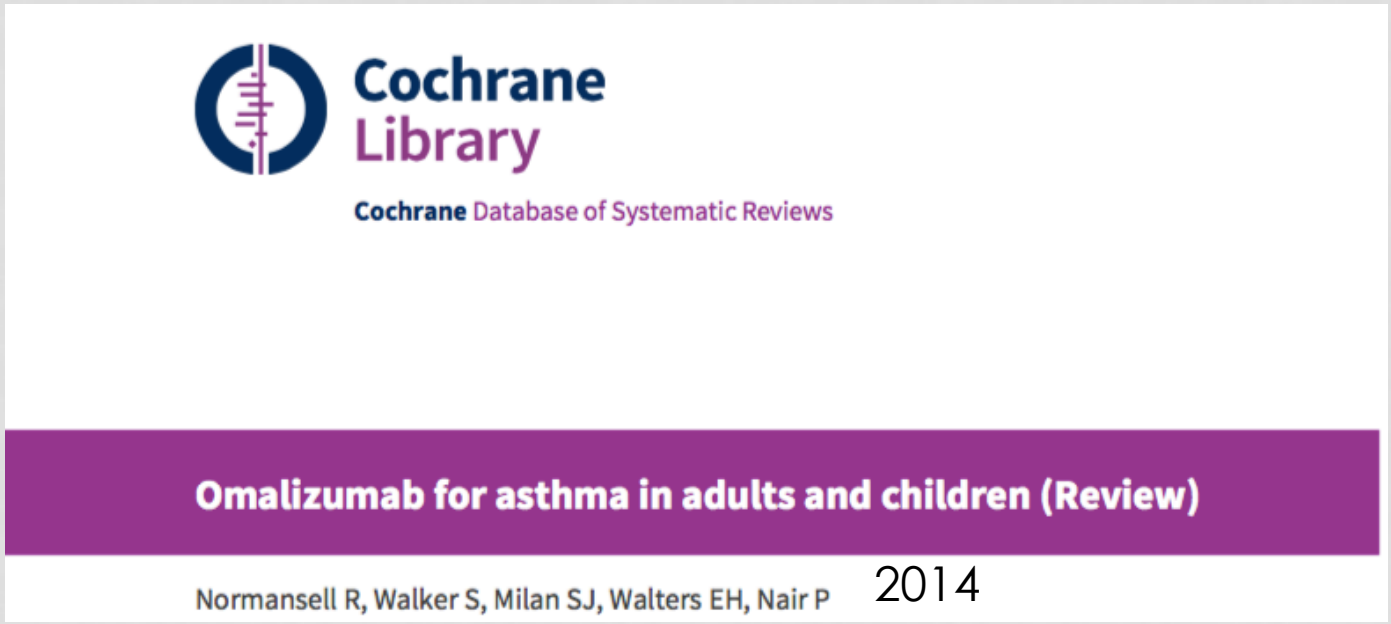
LUNG FUNCTION

- Cochrane recommends **"background adherence to inhaled therapy as superior than adding omalizumab to achieve such small improvements in lung function"**

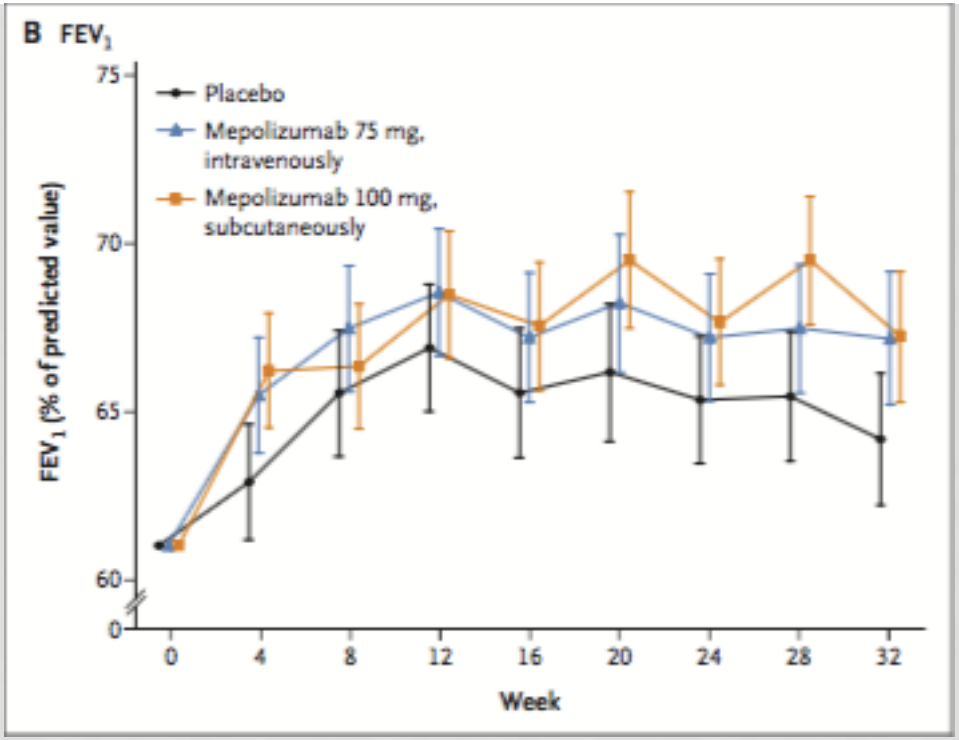


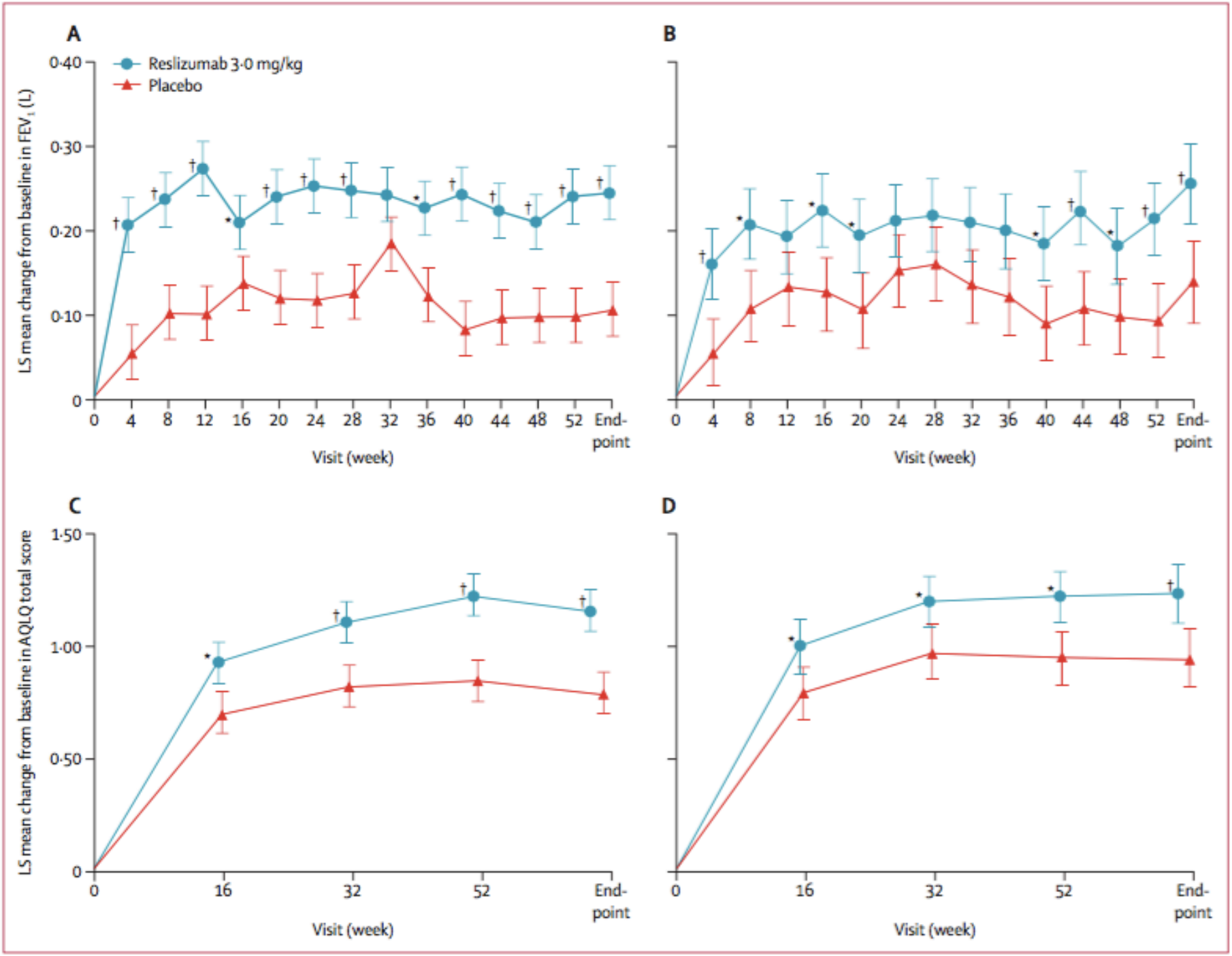
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., and Pascal Chanez M.D., Ph.D., for the MENSA Investigators*




A
Reslizumab 3·0 mg/kg
Placebo
LS mean change from baseline in FEV1 (L)
0·40
0·30
0·20
0·10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 End-point
Visit (week)
B
0 4 8 12 16 20 24 28 32 36 40 44 48 52 End-point
Visit (week)
C
LS mean change from baseline in AQLQ total score
1·50
1·00
0·50
0
0 16 32 52 End-point
Visit (week)
D
0 16 32 52 End-point
Visit (week)

STEROID SPARING EFFECTS

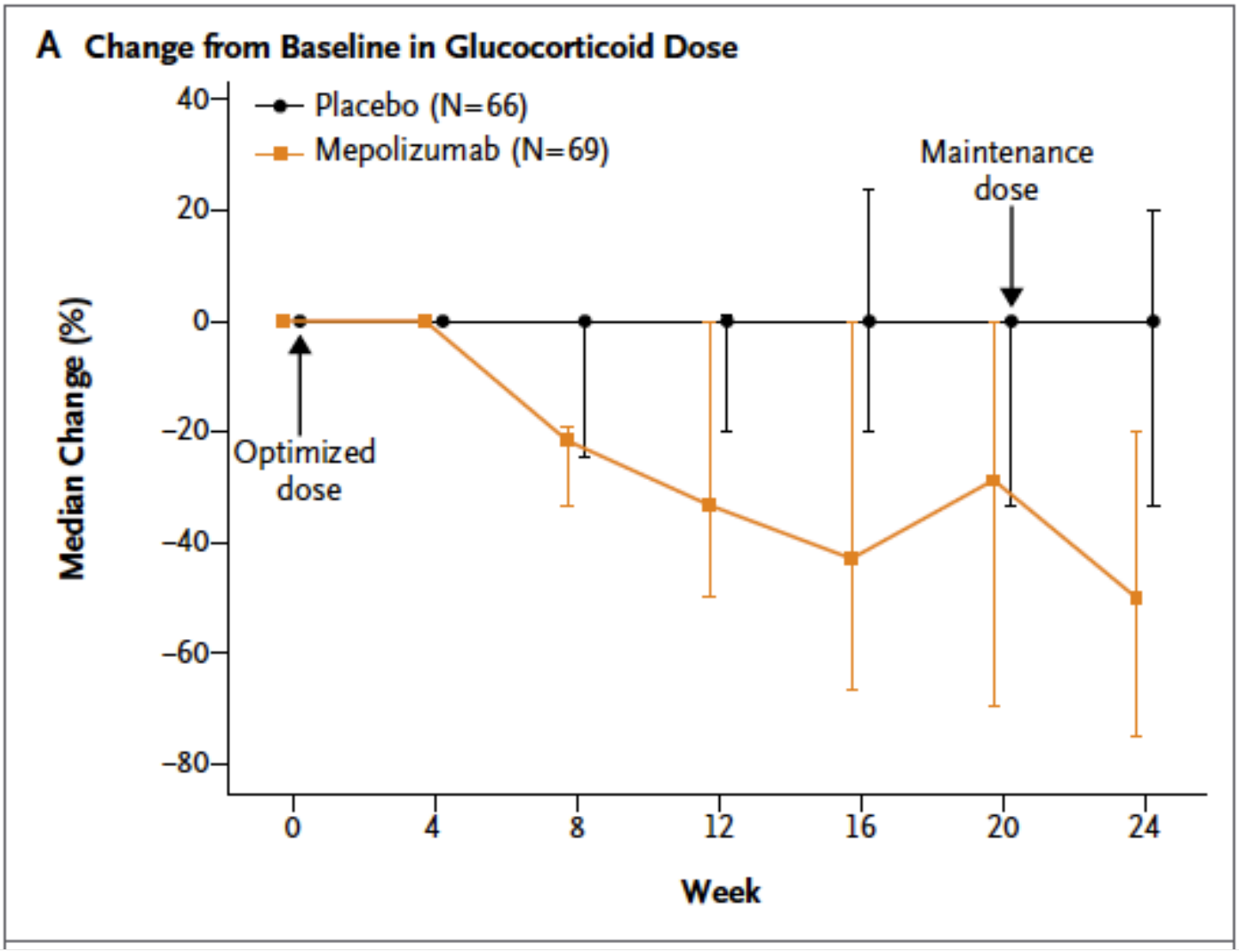
- Reduction in daily ICS dose with omalizumab was clinically modest
- Noteworthy that participants treated with placebo also able to reduce their intake of ICS by a significant amount

DIRECT QUOTE FROM COCHRANE

“The modest mean outcome difference in steroid consumption between treatment and placebo groups bring into question the true size of the steroid sparing effect of omalizumab”

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*



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  - Reported cases of anaphylaxis beginning as late as 4 days after the injection, and protracted anaphylaxis occurring over the course of 1-2 days
- Possible elevated risk for CV and cerebrovascular events requires further study

SAFETY

Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma

Carlos Iribarren, MD, MPH, PhD,[a] Abdelkader Rahmaoui, MD,[b] Aidan A. Long, MD,[c] Stanley J. Szefler, MD,[d] Mary S. Bradley, MS,[b] Gillis Carrigan, PhD, MSc,[b] Mark D. Eisner, MD, MPH,[b] Hubert Chen, MD, MPH,[b] Theodore A. Omachi, MD, MBA,[b] Michael E. Farkouh, MD, MSc,[e] and Kenneth J. Rothman, DrPH[f] *Oakland and South San Francisco, Calif; Boston and Cambridge, Mass; Aurora, Colo; Toronto, Ontario, Canada; and Research Triangle Park, NC*

ANTI-IL-5 SUPERIOR TO OMALIZUMAB FOR SEVERE ASTHMA

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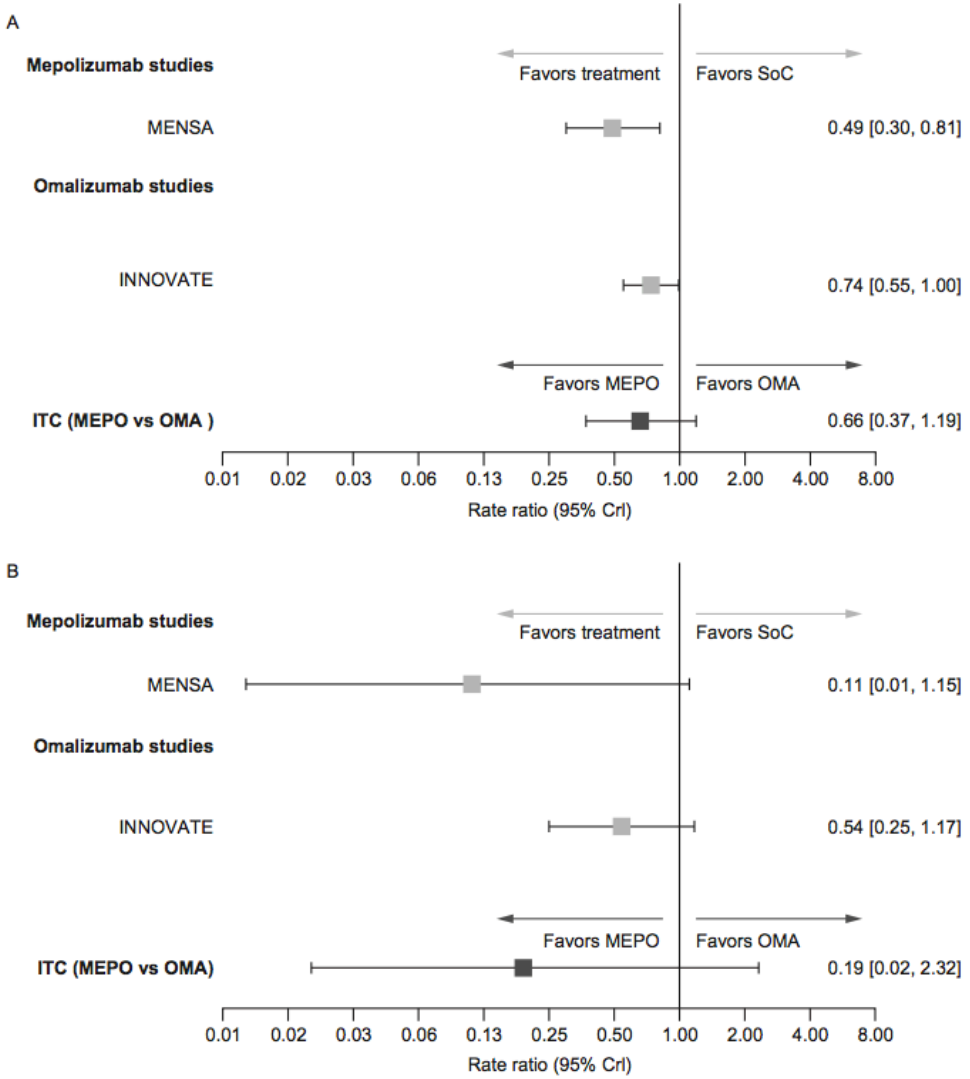
- Anti-IL-5 agents may target a larger subset of severe asthmatics
- IV and SC routes available
- No weight limitations
- Works much faster than omalizumab (< 4 weeks versus 3-4 months)

Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison

Sarah M. Cockle [a], Gillian Stynes [a,1], Necdet B. Gunsoy [b], Daniel Parks [c], Rafael Alfonso-Cristancho [c], Jaro Wex [d], Eric S. Bradford [e], Frank C. Albers [e], Jenny Willson [a,*]



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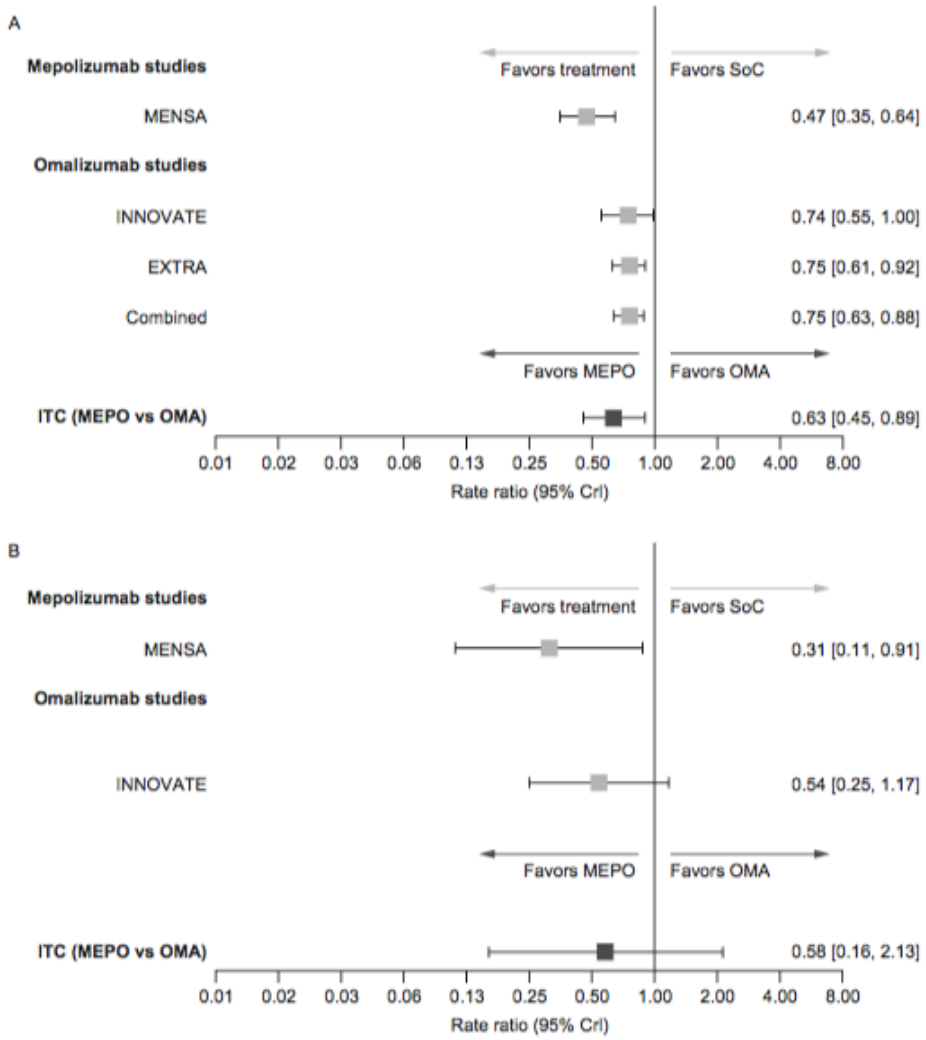

Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma

T. B. Casale[1] | B. E. Chipps[2] | K. Rosén[3] | B. Trzaskoma[3] | T. Haselkorn[4] | T. A. Omachi[3] | S. Greenberg[5,6] | N. A. Hanania[7]

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[5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

[6]Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, NY, USA

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Email: tbcasale@health.usf.edu

Funding information
The pivotal studies were designed and funded by Genentech, Inc., South San Francisco, CA, USA, and Novartis Pharma AG, Basel, Switzerland. The current analysis also was funded by Genentech, Inc., and Novartis Pharma AG

Edited by: Marek Sanak

Abstract

Background: Recent efficacy studies of asthma biologics have included highly enriched patient populations. Using a similar approach, we examined factors that predict response to omalizumab to facilitate selection of patients most likely to derive the greatest clinical benefit from therapy.

Methods: Data from two phase III clinical trials of omalizumab in patients with allergic asthma were examined. Differences in rates of asthma exacerbations between omalizumab and placebo groups during the 16-week inhaled corticosteroid (ICS) dose-stable phase were evaluated with respect to baseline blood eosinophil counts (eosinophils <300/μL [low] vs ≥300/μL [high]) and baseline markers of asthma severity (emergency asthma treatment in prior year, asthma hospitalization in prior year, forced expiratory volume in 1 second [FEV_1; FEV_1 <65% vs ≥65% predicted], inhaled beclomethasone dipropionate dose [<600 vs ≥600 μg/day], and long-acting beta-agonist [LABA] use [yes/no]).

Results: Adults/adolescents (N = 1071) were randomized to receive either omalizumab (n = 542) or placebo (n = 529). In the 16-week ICS dose-stable phase, rates of exacerbations requiring ≥3 days of systemic corticosteroid treatment were 0.066 and 0.147 with omalizumab and placebo, respectively, representing a relative rate reduction in omalizumab-treated patients of 55% (95% CI, 32%-70%; P = .002). For patients with eosinophils ≥300/μL or with more severe asthma, this rate reduction was significantly more pronounced.

Conclusion: In patients with allergic asthma, baseline blood eosinophil levels and/or clinical markers of asthma severity predict response to omalizumab.

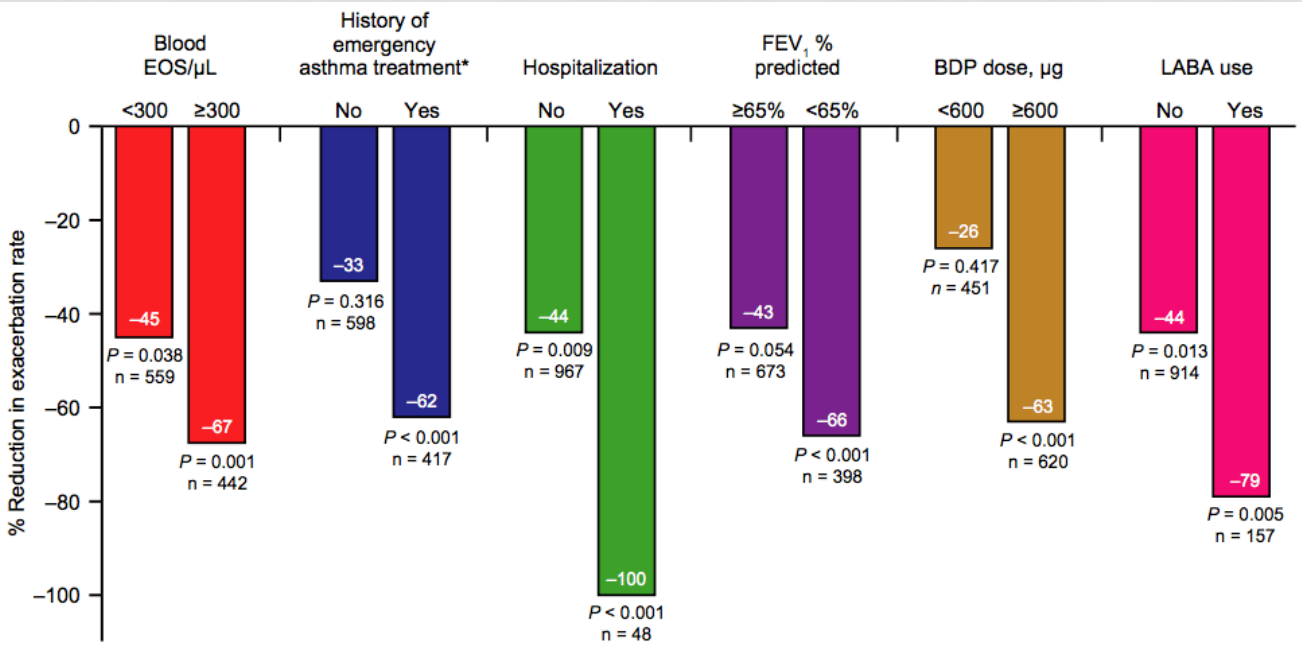
KEYWORDS
asthma, biologic therapy, biomarkers, eosinophils, omalizumab

TABLE 1 Baseline demographic and clinical characteristics

Characteristic[a]	Pooled pivotal trials N = 1071	
	Omalizumab n = 542	Placebo n = 529
Age, years, mean (SD)	39.7 (13.8)	39.0 (13.7)
Female, %	55	55
Duration of asthma, years, mean (SD)	20.5 (13.6)	20.8 (14.0)
Prebronchodilator % predicted FEV_1, mean (SD)	65 (12.04)	65 (11.13)
Blood eosinophil count, per μL, geometric mean (SE)	253 (7.0)	274 (7.7)
Serum IgE, IU/mL, geometric mean (SE)	143 (5.29)	144 (5.28)
Inhaled BDP dose, μg, mean (SD)	670.4 (222.2)	672.8 (238.3)
Treated with LABAs at baseline, %	14.0	15.3
Emergency asthma treatment in preceding year, %	41.4	40.8
Hospital admission for exacerbation in preceding year, %	3.3	6.3

BDP, beclomethasone dipropionate; FEV_1, forced expiratory volume at 1 s; IgE, immunoglobulin E; LABA, long-acting beta-agonist.

[a]Percentages based on nonmissing data.



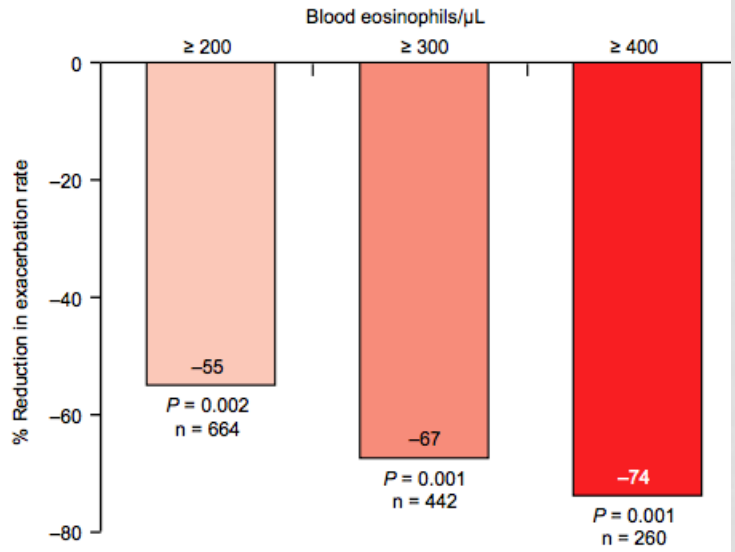


FIGURE 2 Relative percentage change in exacerbation rate by blood eosinophil levels

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COST COMPARISON

- Omalizumab 300 mg $2453.98
- Mepolizumab 100 mg $3342.14
- Reslizumab 100 mg/10 mL $1032.00

COST COMPARISON

- What is the cost of osteoporosis?
- What is the cost of cataract surgery?
- What is the cost of recurrent hospitalizations and ER visits?
- What is the cost of developing diabetes?

BENEFITS OF OMALIZUMAB VERUS ANTI-IL-5

OMALIZUMAB

- 10% reduction in asthma exacerbation rates
- Limited data in severe asthmatics!
- Minimal if any improvement in lung function
- Data is mixed on reducing ICS dosing. No DATA to support reduction in OCS
- Takes at least 3-4 months to see any effect
- SC ONLY

ANTI-IL-5

- 50% reduction in asthma exacerbation rates
- Robust data with severe asthmatics on OCS
- Significant improvement in lung function (up to 220mL!)
- SIRIUS study with 50% reduction in oral steroid dosing!
- Benefits in ALL outcomes seen before 4 weeks
- OPTIONS!!!

RISKS OF OMALIZUMAB VERUS ANTI-IL-5

OMALIZUMAB

- Higher rates of adverse events compared to placebo
- Anaphylaxis 0.2%

ANTI-IL-5

- No significant adverse events compared to placebo for both agents
- No anaphylaxis with mepolizumab!

REFERENCES

- Ortega HG et. al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. N Eng J Med. 2014
- Bel EH et. al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. N Eng J Med. 2014
- Lugogo N et. al. Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study. 2016
- Powell C et. al. Mepolizumab versus placebo for asthma (Review). Cochrane Library. 2014
- Castro et. al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomized, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015
- Amelink M et al. Severe adult-onset asthma: A distinct phenotype. J Allergy Clin Immunol 2013.
- Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age.
- Normansell R et. al. Omalizumab for asthma in adults and children (Review). Cochrane Database of Systematic Reviews. 2014
- Rodrigo GJ et. al. *Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review.* Chest 2011
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CHEST

Original Research

ASTHMA

A Proof-of-Concept, Randomized, Controlled Trial of Omalizumab in Patients With Severe, Difficult-to-Control, Nonatopic Asthma

Gilles Garcia, MD, PhD; Antoine Magnan, MD, PhD; Raphaël Chiron, MD; Cécile Contin-Bordes, MD, PhD; Patrick Berger, MD, PhD; Camille Taillé, MD, PhD; Gilles Devouassoux, MD, PhD; Frédéric de Blay, MD, PhD; Louis-Jean Couderc, MD, PhD; Alain Didier, MD, PhD; Dermot S. O'Callaghan, MD; Pierre-Olivier Girodet, MD, PhD; Isabelle Bourdeix, PhD; Vincent Le Gros, MD; and Marc Humbert, MD, PhD

Background: **While up to 50% of patients with severe asthma have no evidence of allergy, IgE has been linked to asthma, irrespective of atopic status. Omalizumab, an anti-IgE monoclonal antibody, is reported to significantly benefit a subset of patients with severe, persistent, allergic asthma. Therefore, we investigated whether omalizumab has biologic and clinical effects in patients with refractory nonatopic asthma.**

Methods: **Forty-one adult patients who, despite daily treatment with or without maintenance oral corticosteroids, had severe, nonatopic, refractory asthma according to GINA (Global Initiative for Asthma) step 4, were randomized to receive omalizumab or placebo in a 1:1 ratio. The primary end point was the change in expression of high-affinity IgE receptor (FcεRI) on blood basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks. The impact of omalizumab on lung function and clinical variables was also examined.**

Results: **Compared with placebo, omalizumab resulted in a statistically significant reduction in FcεRI expression on basophils and pDC2 ($P < .001$). The omalizumab group also showed an overall increase in FEV_1 compared with baseline (+250 mL, $P = .032$; +9.9%, $P = .029$). A trend toward improvement in global evaluation of treatment effectiveness and asthma exacerbation rate was also observed.**

Conclusions: **Omalizumab negatively regulates FcεRI expression in patients with severe nonatopic asthma, as it does in severe atopic asthma. Omalizumab may have a therapeutic role in severe nonatopic asthma. Nonetheless, our preliminary findings support further investigation to better assess the clinical efficacy of omalizumab.**

Trial registry: **ClinicalTrials.gov; No.: NCT01007149; URL: www.clinicaltrials.gov and European Clinical Trials Database, EudraCT; No.: 2009-010937-38; URL: https://www.clinicaltrialsregister.eu**

CHEST 2013; 144(2):411–419

Abbreviations: FcεRI = high-affinity receptor for IgE; GETE = global evaluation of treatment effectiveness; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; ITT = intent to treat; LABA = long-acting β_2-agonist; MFI = mean fluorescence intensity; pDC2 = plasmacytoid dendritic cell

Table 3—*Summary of Predictive Covariates, According to Definition of Response***

Covariates	Reduced Symptoms	Reduced Usage of Rescue Medication	Improved Lung Function	Improved QoL	Composite Definition	Direction of Greatest Benefit with Omalizumab‡
Age					0.16	Older
Gender						
BDP dose	0.025†	0.045†			0.037†	Higher
Total IgE level				0.20		Higher
Active dermatitis						
No. positive allergens				0.066		Higher
Duration of asthma						
Total symptom score					0.12	Higher§
Overall QoL score	0.062	0.14	0.18			Lower‖
In the past year:						
No. of visits to a doctor's office for urgent asthma treatment		0.085	0.082		0.027†	Higher
Overnight hospital admission for asthma		0.055			0.12	Yes
Number of emergency department visits for asthma treatment						
Treatment for asthma in an ICU						
History of emergency asthma treatment¶	0.092	0.083	0.057		0.015†	Yes
FEV_1						
Absolute value	0.086	0.011†	0.071		0.072	Lower
% predicted	0.13	0.057	0.14			Lower
≤ 65% predicted or > 65% predicted					0.019†	≤ 65%
FVC		0.096	0.043†		0.14	Lower
$FEF_{25-75\%}$	0.015†	0.005†			0.092	Lower
Morning PEF		0.074			0.17	Lower

*Values shown are p values for the significance of the treatment-by-predictive covariate interaction. A small p value means that the graph of probability of response against the value of the baseline covariate gives lines for omalizumab and placebo groups that are very nonparallel. See Table 1 for expansion of abbreviation.

†Covariates that were significantly predictive of response ($p < 0.05$); absence of stated value indicates $p > 0.2$. For definitions of response, see Table 2.

‡Indicates the trend associated with the greatest benefit from omalizumab relative to placebo, in terms of the composite definition of response.

§A high total symptom score indicates a patient with severe symptoms.

‖Lower score indicates greater impairment of QoL.

¶A composite variable based on history in the last year of at least one of the following events: overnight hospital admission or treatment in an ICU for asthma, or at least one emergency department or doctor's office visit for urgent asthma treatment.

Bousquet J et. al. *Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma.* Chest 2004

PREDICTORS OF RESPONSE

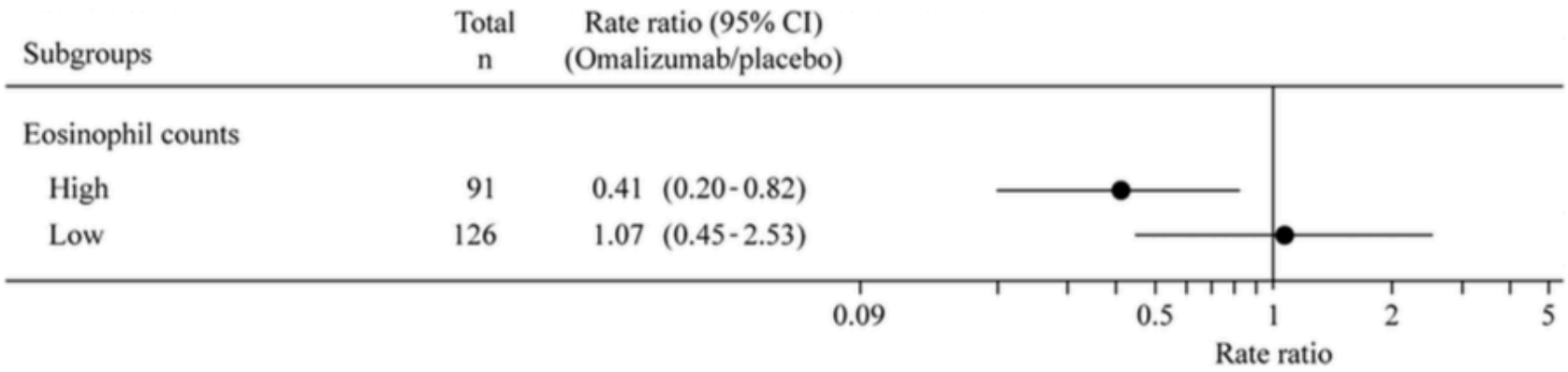

FIG 1. Rate ratio (95% CI) of protocol-defined asthma exacerbation by subgroup.

Busse W et. al. *High eosinophil count: A potential biomarker for assessing successful omalizumab treatment effects*. JACI 2013

DURATION OF TREATMENT

Original article

Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations

Raymond G. Slavin, MD,[a] Caterina Ferioli, BSc,[b] Stacey J. Tannenbaum, PhD,[c] Carmen Martin, PhD,[d] Martin Blogg, BSc,[d] and Philip J. Lowe, PhD[b] *St Louis, Mo, Basel, Switzerland, East Hanover, NJ, and Horsham, United Kingdom*

Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control

M. Molimard [a,*], L. Mala [b], I. Bourdeix [b], V. Le Gros [b]

ORIGINAL ARTICLE AIRWAY DISEASES

After 6 years with Xolair; a 3-year withdrawal follow-up

A. Nopp[1], S. G. O. Johansson[1,2], J. Adédoyin[1], J. Ankerst[3], M. Palmqvist[4] & H. Öman[5]

[1]Department of Medicine, Clinical Immunology and Allergy Unit, Karolinska Institute, Stockholm; [2]Department of Clinical Immunology and Transfusion Medicine, Karolinska University Hospital, Stockholm; [3]Clinical Sciences, Department of Medicine, Lund; [4]Department of Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Göteborg; [5]MIAB, Uppsala, Sweden

STEROID REDUCTION

The oral corticosteroid-sparing effect of omalizumab in children with severe asthma

Malcolm Brodlie,[1,2] Michael C McKean,[2] Samantha Moss,[2]
David A Spencer[2]

2012

Reslizumab for Poorly Controlled, Eosinophilic Asthma

A Randomized, Placebo-controlled Study

Mario Castro[1], Sameer Mathur[2], Frederick Hargreave[3†], Louis-Philippe Boulet[4], Fang Xie[5], James Young[6], H. Jeffrey Wilkins[5], Timothy Henkel[5], and Parameswaran Nair[3]; for the Res-5-0010 Study Group

[1]Washington University School of Medicine, St. Louis, Missouri; [2]University of Wisconsin, Madison, Madison, Wisconsin; [3]McMaster University, Hamilton, Ontario, Canada; [4]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada; [5]Cephalon, Inc., Frazer, Pennsylvania; and [6]United BioSource Corporation, Ann Arbor, Michigan

Phase 3 Study of Reslizumab in Patients With Poorly Controlled Asthma

Effects Across a Broad Range of Eosinophil Counts

Jonathan Corren, MD; Steven Weinstein, MD; Lindsay Janka, MS; James Zangrilli, MD; and Margaret Garin, MD

TABLE 2] Change From Baseline to Week 16 for Efficacy Variables by Baseline Eosinophil Count

	Overall Population		Baseline Eosinophils < 400 cells/μL		Baseline Eosinophils ≥ 400 cells/μL	
Efficacy Variable	Placebo	Reslizumab, 3.0 mg/kg	Placebo	Reslizumab, 3.0 mg/kg	Placebo	Reslizumab, 3.0 mg/kg
FEV_1, L						
No.	97	394	76	316	19	77
Baseline mean ± SE	2.172 ± 0.0643	2.098 ± 0.0350	2.182 ± 0.0746	2.068 ± 0.0372	2.153 ± 0.1392	2.224 ± 0.0928
Mean change from baseline ± SE	0.187 ± 0.0446	0.255 ± 0.0232	0.215 ± 0.0484	0.247 ± 0.0255	0.002 ± 0.1216	0.272 ± 0.0557
Treatment effect change ± SE	0.068 ± 0.0495		0.033 ± 0.0539		0.270 ± 0.1320	
95% CI	−0.030 to 0.165		−0.073 to 0.139		0.008 to 0.532	
P value	.1719		.5422		.0436	
FVC, L						
No.	97	394	76	316	19	77
Baseline mean ± SE	3.209 ± 0.0924	3.041 ± 0.0481	3.217 ± 0.1095	2.973 ± 0.0513	3.206 ± 0.1757	3.321 ± 0.1234
Mean change from baseline ± SE	0.236 ± 0.0506	0.247 ± 0.0263	0.256 ± 0.0537	0.248 ± 0.0283	0.055 ± 0.1449	0.230 ± 0.0681
Treatment effect change ± SE	0.012 ± 0.0560		−0.009 ± 0.0598		0.175 ± 0.1571	
95% CI	−0.098 to 0.122		−0.126 to 0.109		−0.137 to 0.487	
P value	.8361		.8853		.2675	
ACQ–7[a]						
No.	97	394	76	316	19	77
Baseline mean ± SE	2.574 ± 0.0698	2.559 ± 0.0353	2.564 ± 0.0778	2.574 ± 0.0390	2.677 ± 0.1692	2.501 ± 0.0839
Mean change from baseline ± SE	−0.648 ± 0.0878	−0.844 ± 0.0453	−0.714 ± 0.0954	−0.836 ± 0.0499	−0.368 ± 0.2407	−0.858 ± 0.1105
Treatment effect change ± SE	−0.195 ± 0.0974		−0.122 ± 0.1065		−0.490 ± 0.2616	
95% CI	−0.387 to −0.004		−0.332 to 0.087		−1.010 to 0.030	
P value	.0457		.2511		.0643	
SABA use, puffs/day						
No.	96	392	76	315	18	76
Baseline mean ± SE	2.0 ± 0.19	1.9 ± 0.09	2.0 ± 0.21	1.9 ± 0.10	2.2 ± 0.44	1.9 ± 0.21
Mean change from baseline ± SE	−0.4 ± 0.19	−0.3 ± 0.10	−0.4 ± 0.21	−0.2 ± 0.11	−0.1 ± 0.43	−0.8 ± 0.19
Treatment effect change ± SE	0.063 ± 0.2050		0.216 ± 0.2300		−0.708 ± 0.4587	
95% CI	−0.340 to 0.466		−0.236 to 0.668		−1.619 to 0.204	
P value	.7589		.3484		.1264	

Mean change from baseline expressed as least squares mean with associated SE. SABA = short-acting β-agonist. See Table 1 legend for expansion of other abbreviation.
[a]Negative changes in ACQ indicate improved asthma control. The minimal clinically important difference for ACQ is 0.5 units.

Table 1
Study and population inclusion criteria for the ITC.

ITC population	Disease criteria		Treatment eligibility criteria[a, b]			
			MEPO eligibility		OMA eligibility	
	Disease and current treatment	Exacerbation history	MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)	MEPO RCTs (IPD available)	OMA RCTs (aggregate RCT data only)
Overlap population Patient population that is eligible for both MEPO and OMA	Severe asthma patients aged ≥12 years taking ≥1000 μg/day BDP-equivalent ICS plus	≥2 exacerbations (requiring SCS) OR ≥1 severe exacerbation (requiring hospitalization) in previous 12 months	Required Based on blood eosinophil count inclusion criteria in MEPO RCTs: blood eosinophil count ≥150 cells/μL at treatment initiation or ≥300 cells/μL in prior 12 months	Required Based on OMA RCTs that included patients meeting disease criteria	Required Sub-group of MEPO patients that met EU OMA license criteria: based on weight, IgE levels and positive RAST	Required OMA RCTs that included patients meeting EU OMA license
Trial population Patient population eligible for either MEPO or OMA	≥1 additional controller	≥1 exacerbation (requiring SCS or asthma hospitalization or asthma ED visit) in the previous 12 months	Required (As per Overlap population)	Not required in this scenario	Not required in this scenario	Required (As per Overlap population)

BDP, beclomethasone dipropionate; ED, emergency department; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IPD, individual patient-level data; ITC, indirect treatment comparison; MEPO, mepolizumab; OMA, Omalizumab; RAST, radioallergosorbent test; RCT, randomized controlled trial; SCS, systemic corticosteroids.

[a] Criteria additional to disease criteria.

[b] Definition of treatment eligibility differs for MEPO and OMA studies, due to data availability. MEPO eligibility in OMA studies was proxied using exacerbation history requirements at enrollment as imposed by the disease severity criteria.

Table 2
Key characteristics of double-blind, randomized controlled trials included in the ITC.

	Study duration (weeks)	Treatment arms[a]	Key inclusion criteria	Number of patients	Included in Overlap population[b] analysis	Included in Trial population[c] analysis
Mepolizumab-included studies						
MENSA [12],[d]	32	• Mepolizumab 100 mg SC every 4 weeks (n = 194) • Placebo (n = 191)	• Blood eosinophil counts≥150 cells/μL at initiation of treatment or≥300 cells/μL in previous 12 months • ≥2 asthma exacerbation in previous 12 months	527	✓	✓
Omalizumab-included studies						
INNOVATE [16],[d]	28	• Omalizumab administered every 2 or 4 weeks to provide dose of ≥0.016 mg/kg per IU/mL of IgE (n = 209) • Placebo (n = 210)	• Persistent allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥2 asthma exacerbation (or 1 severe exacerbation) in previous 12 months	419	✓	✓
Chanez et al., 2010 [9],[e]	16	• Omalizumab administered every 2 or 4 weeks as per EU prescribing information [9] (n = 20) • Placebo (n = 11)	• Persistent allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥2 severe asthma exacerbations in previous 12 months	31	✓	✓
EXTRA [18],[f]	48	• Omalizumab ≥0.008 mg/kg per IU/mL of IgE every 2 weeks or ≥0.016 mg/kg of IgE every 4 weeks (n = 427) • Placebo (n = 421)	• Severe allergic asthma despite high doses of corticosteroids and long-acting β_2 agonists • ≥1 asthma exacerbation in previous 12 months	848	–	✓

- Mouse data shows that eosinophils and IgE and B cells are not needed for animal models of asthma
- Benralizumab can kill eosinophils, cytotoxicity
- Reslizumab is a humanized monoclonal antibody that targets IL-5. Occupies the region ERRR corresponding to AA 89-92 on IL-5
- Mepolizumab is a humanized monoclonal antibody that prevents binding of IL-5 to the alpha chain of the IL-5 receptor

BENRALIZUMAB

- Fully human afucosylated monoclonal antibody to the alpha subunit of the IL-5 receptor
- Currently under investigation
- Prelim studies in humans showed an adequate safety profile with significant reduction in peripheral eosinophilia and rates of exacerbations.
- Only one study found significant benefit in favor of omalizumab in patients with severe asthma who were receiving background therapy of both inhaled corticosteroids and long-acting beta agonists.

MEPOLIZUMAB VS RESLIZUMAB

- No head-to-head trials
- Age may impact which therapy to administer
- Mepolizumab is administered SC, while reslizumab requires an IV infusion
- Patients with obesity may require larger doses of reslizumab
- Cutoffs of blood eosinophils

DREAM STUDY

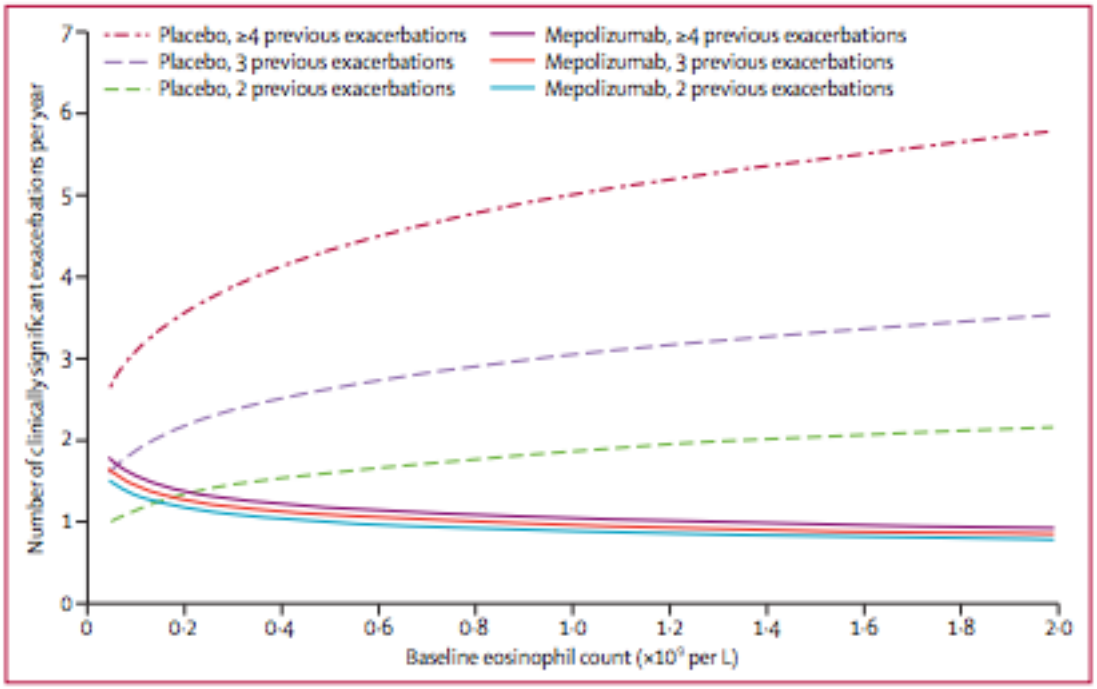

***Figure 4*: Predictive modelling of rate of exacerbations**
Done on the basis of blood eosinophil count at baseline, history of exacerbations, and treatment with mepolizumab or placebo.