New Biologic Agents in Bronchial Asthma

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Definition of asthma

NEW!

- Asthma is a **heterogeneous disease**, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Recognizable clusters of demographic, clinical and/or pathological characteristics are often called **"asthma phenotype"**; however, they do not correlate strongly with specific pathological process or treatment responses.

The 10–20% of asthma patients do not respond to guideline-based therapies ➡ "Unmet need"

Am J Respi Crit Care Med 2004; 170:836–844

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Definition of severe asthma for patients 6 years old and above

Asthma which requires treatment with guidelines suggested medications for **GINA Stages 4-5 asthma** (high dose inhaled CS* and LABA or leukotriene modifier/theophylline) for the previous year or **systemic CS for ≥50% of the previous year** to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.

I. *Uncontrolled* asthma defined as at least one of the following:

1. *Poor symptom control:* ACQ consistently >1.5, ACT ≤19 (or "not well controlled" by NAEPP/GINA guidelines)
2. *Frequent severe exacerbations*: 2 or more bursts of systemic CSs (>3 days each) in the previous year
3. *Serious exacerbations:* at least one hospitalization, ICU stay or mechanical ventilation in the previous year
4. *Airflow limitation:* after appropriate bronchodilator withhold FEV_1< 80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

II. *Controlled* asthma that worsens on tapering of these high doses of inhaled CS or systemic CS (or additional biologics)

New experimental molecular-based treatments for severe asthma

The complexity of chronic severe asthma with different underlying mechanisms (or endotypes) suggests that phenotyping patients with severe asthma and personalised therapy could lead to improved outcomes and fewer side-effects. ated the era of specific therapies for certain to therapy remains problematic. More re hmatic inflammatory pathways have reported positive results and are beginning to help define immuno-inflammatory phenotypes/endotypes (tables 8 and 9).

Phenotyping patients with severe asthma and personalized therapy

Eur Respir J 2014; 43: 343–373

The Classification of Biologic Agents

Therapy	Target	Drugs
Anti-IgE	FcεRI domain of IgE	Omalizumab
Cytokine mediators	Interleukin-5	Mepolizumab, Reslizumab
	Interleukin-5 receptor	Benralizumab
	Interleukin-13	Lebrikizumab, Tralokinumab
	Interleukin-4 receptor α; IL-4/IL-13	Pitrakinra, AMG317, Dupilumab
	Thymic stromal lymphopoietin (TSLP)	AMG 157
	TNF-α	Golimumab
	IL-2 Rα	Daclizumab
Chemokine-receptor antagonists	CXCR2	SCH527123
Mast-cell inhibitors	Tyrosine kinase	Masitinib
Prostaglandin D2 receptor antagonists	CRTH2	AMG 853, OC000459
Toll-like receptor agonists	Toll-like receptor 9	QbG10

Anti-IgE antibody (Omalizumab)

- **International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma**

  Eur Respir J 2014; 43: 343–373

  - Those adults and children aged ≥ 6 years with severe asthma
  - Confirmed IgE dependent allergic asthma
  - Total serum IgE level is **30 to 700 IU/mL** (in 3 studies the range was wider 30 to 1300 IU/mL)

- **If a patient does not respond within 4months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial**

  Eur Respir J 2014; 43: 343–373

- **It stands as the only 'biologic' approved by the FDA, NICE for the treatment of severe asthma**
  - Reduces the rate, severity and duration of exacerbations
  - Improvements in asthma-related symptoms, quality of life, and lung function
  - Reduced emergency room visits, hospital admissions
  - Reduced requirement for both inhaled corticosteroids (ICS) and rescue bronchodilators

J Allergy Clin Immunol 2001; 108:184–190
Allergy 2005; 60:309–316
J Asthma 2012; 49:144–152

CHEST

Original Research

ASTHMA

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

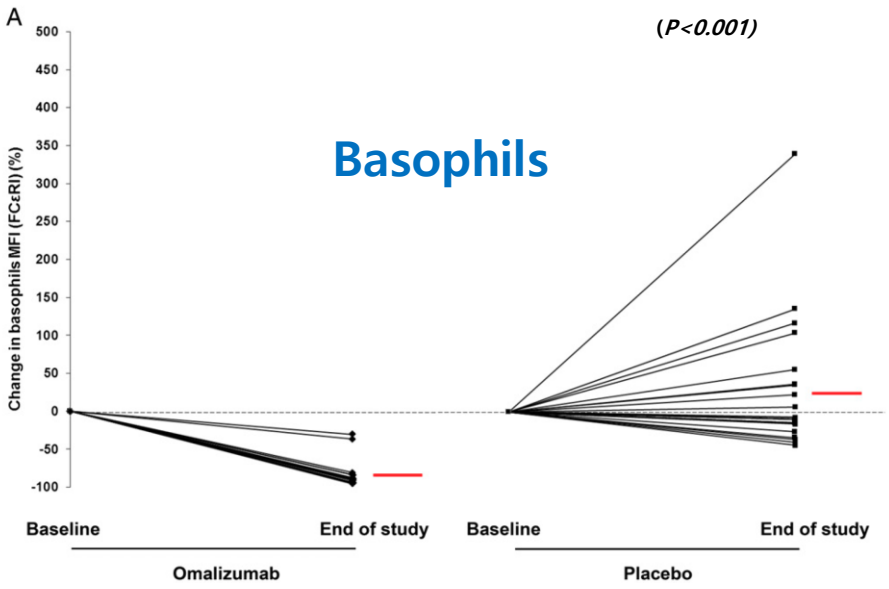
- Ages; 18–70 years (n=41)
- Severe, persistent, nonatopic asthma that was uncontrolled according to GINA step 4 treatment
- Total serum IgE levels ranged from 30 to 700 IU/mL

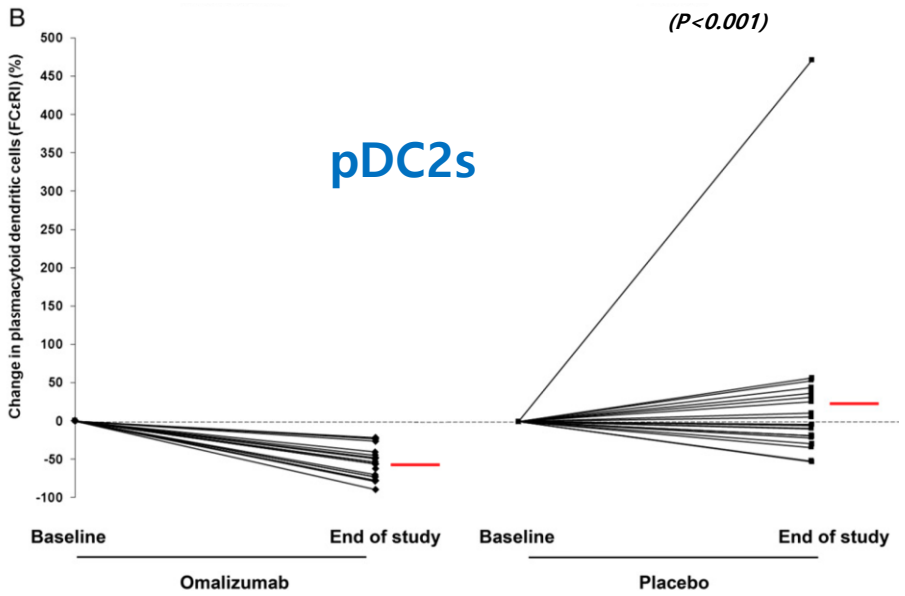
- **The primary end point**
  - The change in expression of high-affinity IgE receptor (FcεRI) on blood basophils and plasmacytoid dendritic cells (pDC2) after 16 weeks

- **Lung function and clinical variables** was also examined

CHEST 2013; 144(2):411–419

Change in FCεRI expression on basophils and plasmacytoid dendritic cells (pDC2s)





Clinical Secondary Efficacy Outcomes at Week 16, According to Treatment Assignment

Outcome	Placebo (n=21)	Omalizumab (n=20)	Difference Between Groups (95% CI)	*P*-Value
FEV_1 (mL)	0±200	250±380	250	**.032**
FEV_1 (% predicted)	- 0.2±7.7	+9.7±16.1	+9.5	**.029**
Responders at visit 10 (no)	5	9	4	.185
Asthma exacerbations	1.43±1.94	0.80±1.47	...	.278
ACQ Score	-0.5±1.43	-0.5±0.98	0	.744
FENO, ppb	0.7±17.6	2.4±18.2	1.7	.766

PHARMACOTHERAPY

Effects of Omalizumab in Non-Atopic Asthma: Results from a Spanish Multicenter Registry

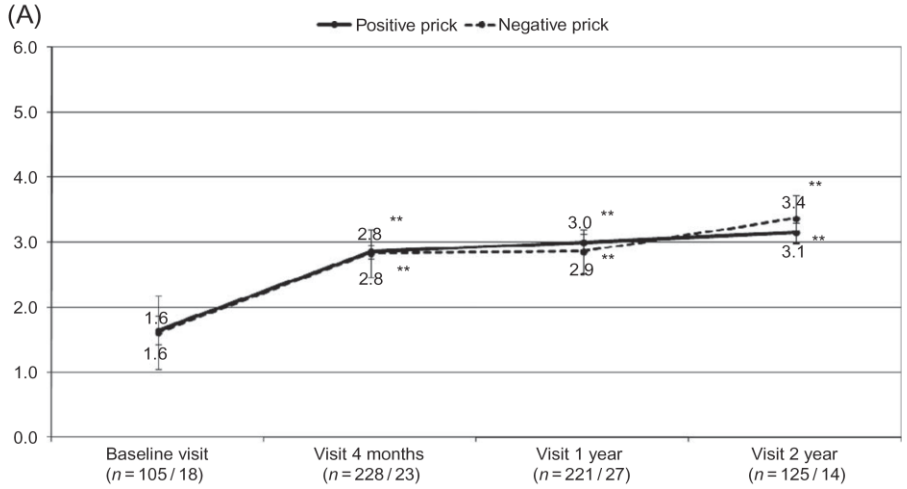
LUIS PÉREZ DE LLANO, M.D., PH.D.,[1] MARÍA DEL CARMEN VENNERA, M.D.,[2,3,4] FRANCISCO J. ÁLVAREZ, M.D.,[5] JUAN F. MEDINA, M.D.,[5] LUIS BORDERÍAS, M.D., PH.D.,[6] CONCHA PELLICER, M.D.,[7] HÉCTOR GONZÁLEZ, M.D., PH.D.,[8] JOSÉ A. GULLÓN, M.D., PH.D.,[8] EVA MARTÍNEZ-MORAGÓN, M.D., PH.D.,[9] CARLOS SABADELL, M.D.,[10] SOLEDAD ZAMARRO, M.D.,[11] AND CÉSAR PICADO, M.D., PH.D.[2,3,4]; on behalf of the Spanish Registry

- To evaluate the effectiveness of omalizumab in non-atopic asthma
- Using data from a multicenter registry of severe asthma, the clinical outcome of severe non-atopic asthmatics vs. severe allergic asthmatics (26 vs. 266)

- Severe exacerbations
- Pulmonary function
- Global Evaluation of Treatment Effectiveness (GETE) scale
- Asthma Control Test (ACT)

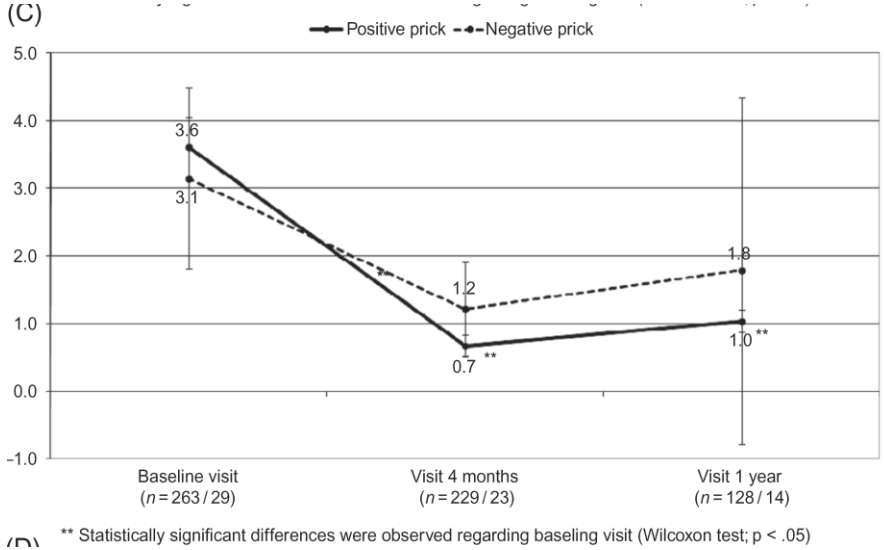
Journal of Asthma, 2013; 50: 296–301

Evolution of GETE



** Statistically significant differences were observed regarding baseling visit (Wilcoxon test; p < .05)

Average of Exacerbations



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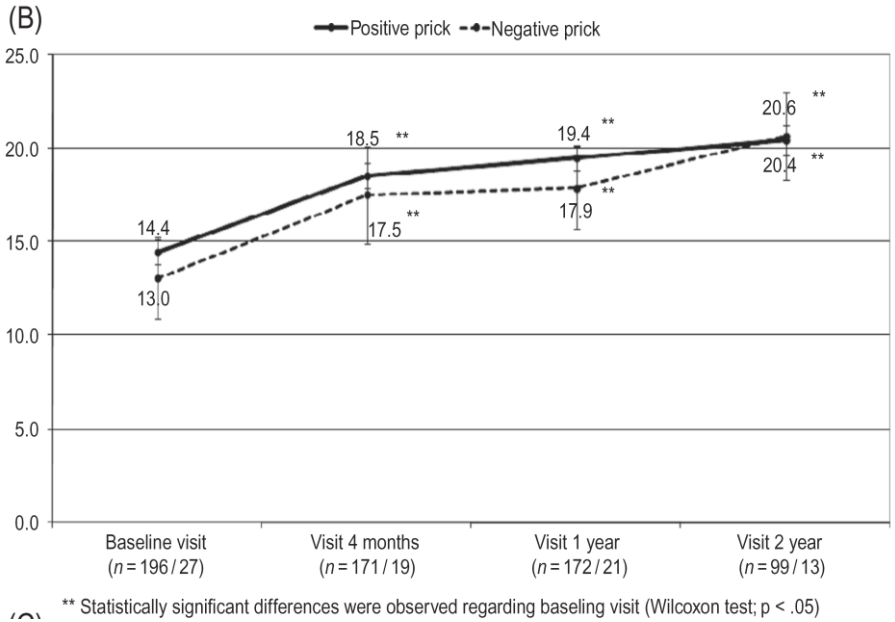
ACT Evolution



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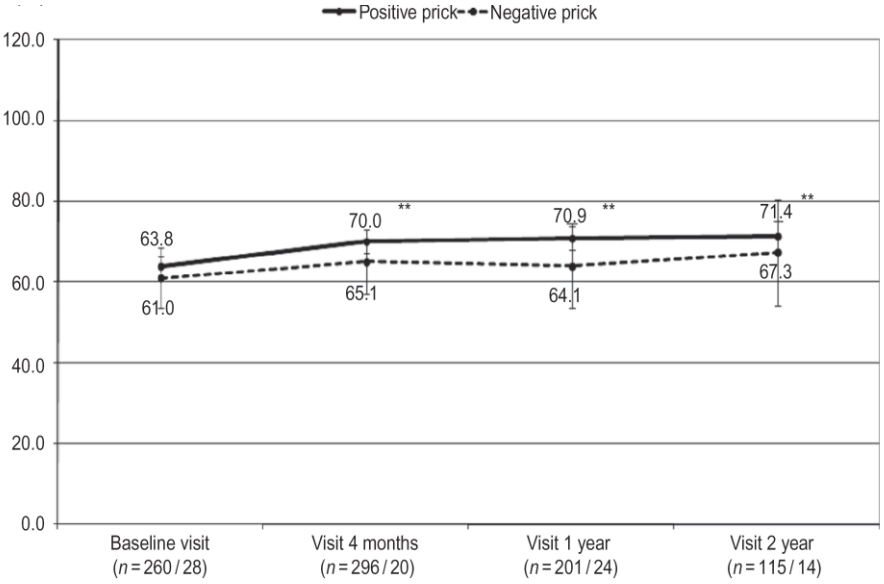
Pulmonary Function



** Statistically significant differences were observed regarding baseling visit (Wilcoxon test; p < .05)

The Effects of Omalizumab to Patients Chronically treated with Oral Corticosteroids

Annals of Internal Medicine | ORIGINAL RESEARCH

Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy

A Randomized Trial

Ann Intern Med. 2011;154:573-582

Nicola A. Hanania, MD, MS; Oral Alpan, MD; Daniel L. Hamilos, MD; John J. Condemi, MD; Irmarie Reyes-Rivera, PhD; Jin Zhu, PhD; Karin E. Rosen, MD, PhD; Mark D. Eisner, MD, MPH; Dennis A. Wong, MD; and William Busse, MD

- **The reduction in asthma exacerbation rate was not important in patients who received long term treatment with OCS**

CHEST | Original Research

ASTHMA

Does Omalizumab Make a Difference to the Real-life Treatment of Asthma Exacerbations?

Results From a Large Cohort of Patients With Severe Uncontrolled Asthma

Chest 2013;143:398–405

- **It seems that patients treated with oral corticosteroids at entry are unlikely to respond as well to omalizumab**

Wiley Online Library

THE COCHRANE LIBRARY
Independent high-quality evidence for health care decision making
from The Cochrane Collaboration

Home > Evidence Based Medicine > Evidence-Based Health Care > The Cochrane Library > Abstract

Omalizumab for Asthma in Adults and Children. Cochrane Database Syst Rev 2014

- **Odds ratio of having one or more exacerbations**

Those who were diagnosed with severe asthma who were receiving background inhaled plus oral steroid therapy (OR: 1.65)

- **Rescue medication use**

No significant difference between subcutaneous omalizumab and placebo was noted for this outcome in participants with severe asthma who were receiving a background therapy of inhaled plus oral corticosteroids.

Not all severe asthma patients may respond to omalizumab treatment
➡ The reflection of tremendous heterogeneity in severe asthma

Exploring the Effects of Omalizumab in Allergic Asthma

An Analysis of Biomarkers in the EXTRA Study

Nicola A. Hanania[1], Sally Wenzel[2], Karin Rosén[3], Hsin-Ju Hsieh[3], Sofia Mosesova[3], David F. Choy[3], Preeti Lal[3], Joseph R. Arron[3], Jeffrey M. Harris[3], and William Busse[4]

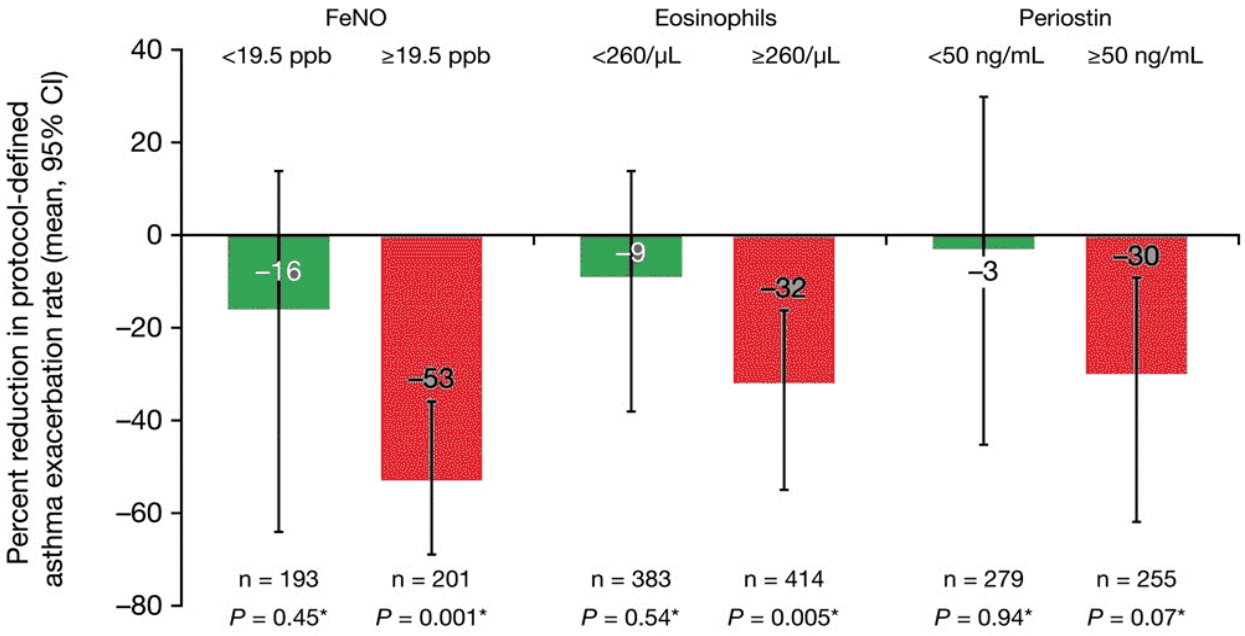
- Ages; 12–75 years (n=850)
- History of severe persistent allergic asthma for more than 1 year
- Asthma remained inadequately controlled despite treatment with high-dose ICS plus long-acting $ß_2$-agonist (LABA)

- **To assess role as a biomarkers of Th2 inflammation and predictors of treatment effects**
  1) FE_{NO}
  2) Blood eosinophil count
  3) Serum periostin

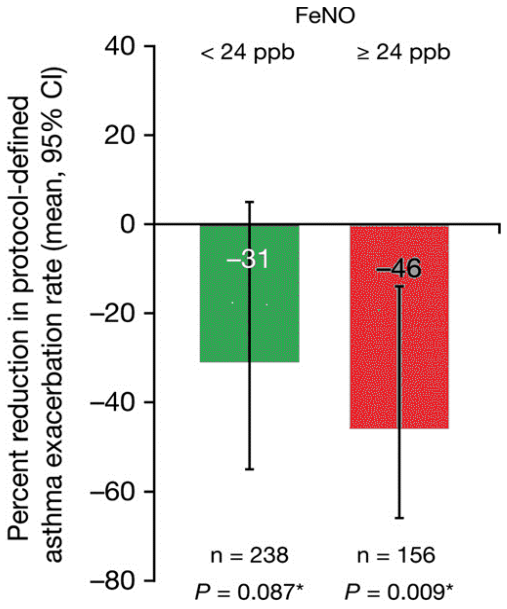
- **Primary endpoint**
  - Number of protocol-defined asthma exacerbations during the 48 wks

AJRCCM. 2013;187:804–811

Mean Percent Reduction in Protocol-defined Asthma Exacerbation Rate in the Low- and High-Biomarker Subgroups

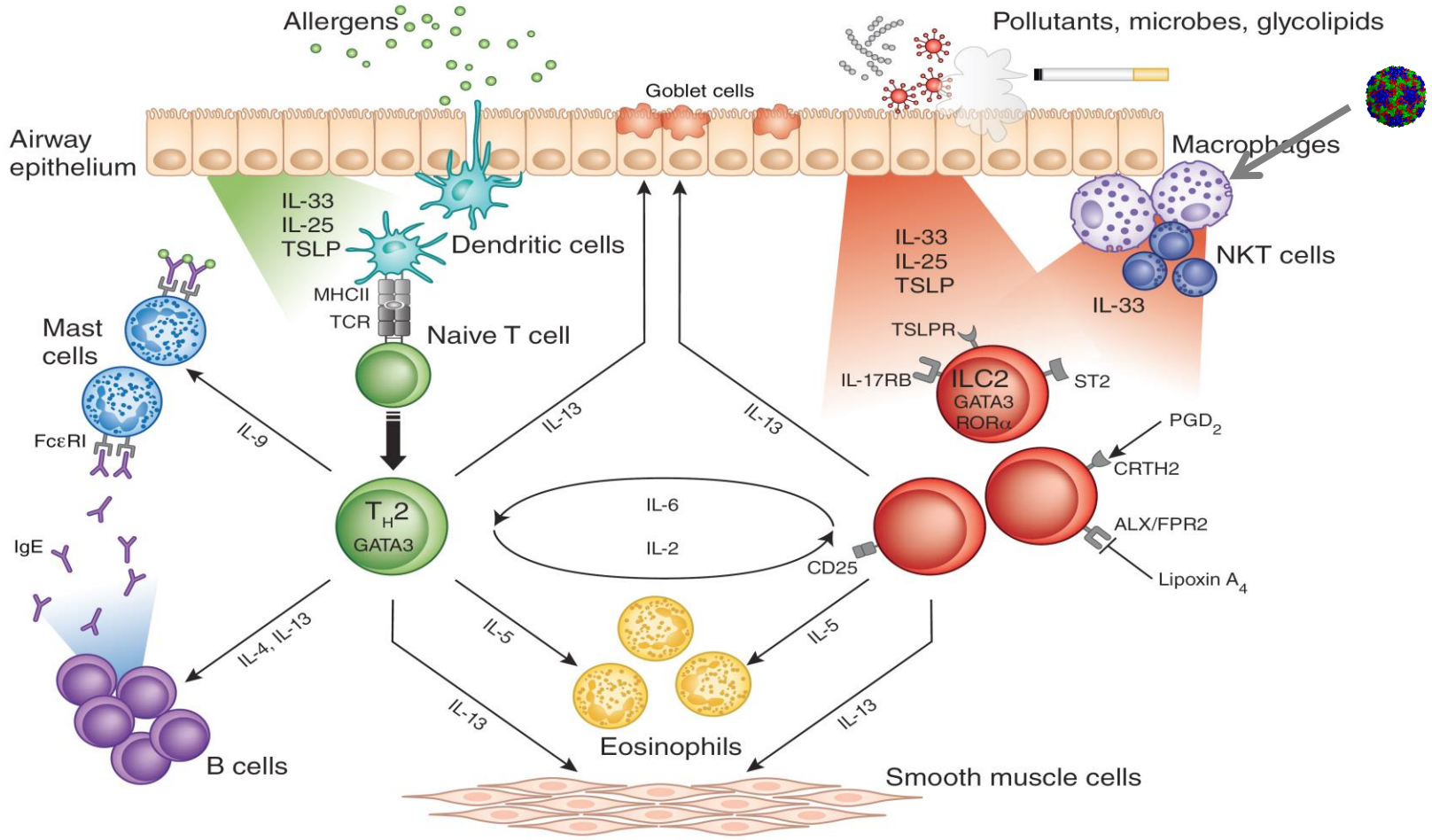


Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93



IL-5-Targeted Antibodies

- **Two Different Pathways lead to Eosinophilic Airway Inflammation in Asthma**



Nat Med 2013;19: 977–979

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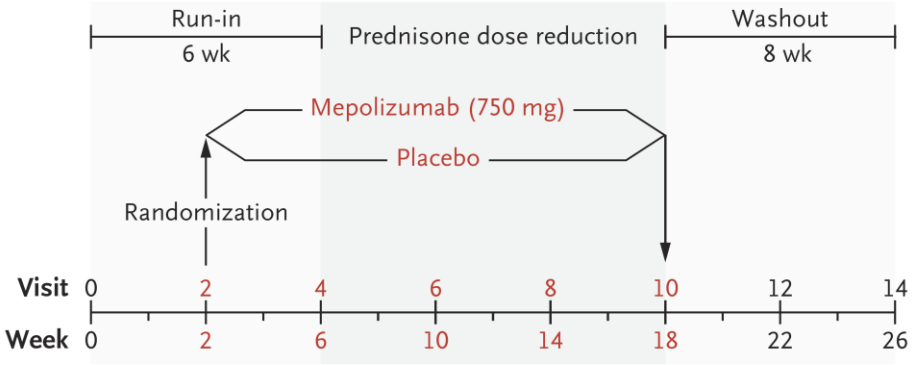
ORIGINAL ARTICLE

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

- Mepolizumab; humanized monoclonal IL-5 antibody
- Persistent sputum eosinophilia (>3%) with oral prednisone. (n=20)
  - Prednisone of 5-25 mg/d, >4 wks & fluticasone; 600-2000 μg
- Mepolizumab (at a dose of 750 mg IV) at 2, 6, 10, 14, and 18 for 26 wks

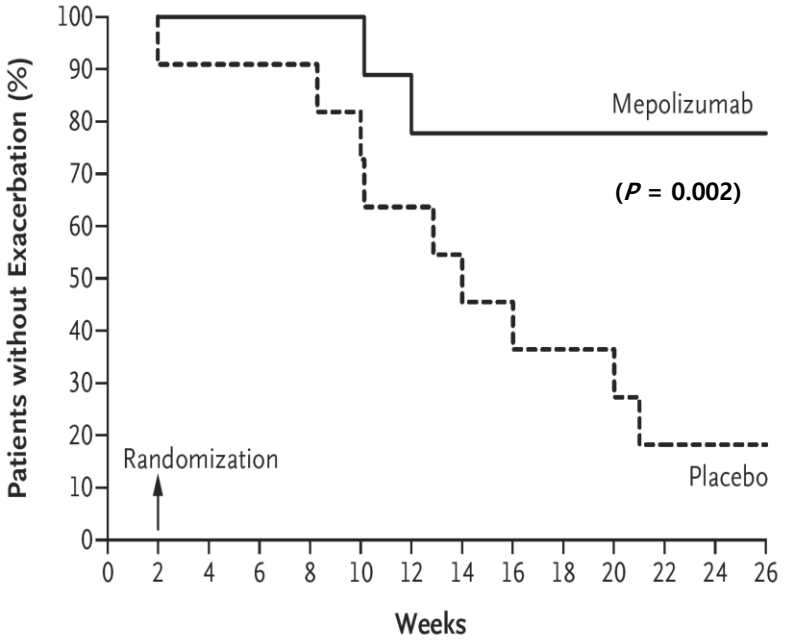
- **The primary outcomes**
  - Prednisone-sparing effect of mepolizumab
  - The proportion of patients with exacerbations
- **Secondary objectives**
  - Effect on the number of eosinophils in sputum and blood
  - Symptoms
  - Airflow limitation

Protocol for Reduction in the Dose of Prednisone



Starting Doses of Prednisone					
25.0	20.0	15.0	10.0	7.5	5.0
20.0	15.0	10.0	7.5	5.0	5.0
17.5	12.5	7.5	5.0	5.0	5.0
15.0	10.0	7.5	5.0	5.0	5.0
12.5	7.5	5.0	2.5	2.5	2.5
10.0	7.5	5.0	2.5	2.5	2.5
7.5	5.0	2.5	0.0	0.0	0.0
5.0	2.5	0.0	0.0	0.0	0.0

The Proportion of Patients without an Asthma Exacerbation



No. at Risk									
Mepolizumab	9	9	8	7	7	7	7	7	
Placebo	10	9	7	7	5	4	3	2	

The Median Time to Exacerbation

- 20 weeks in the mepolizumab group
- 12 weeks in the placebo group

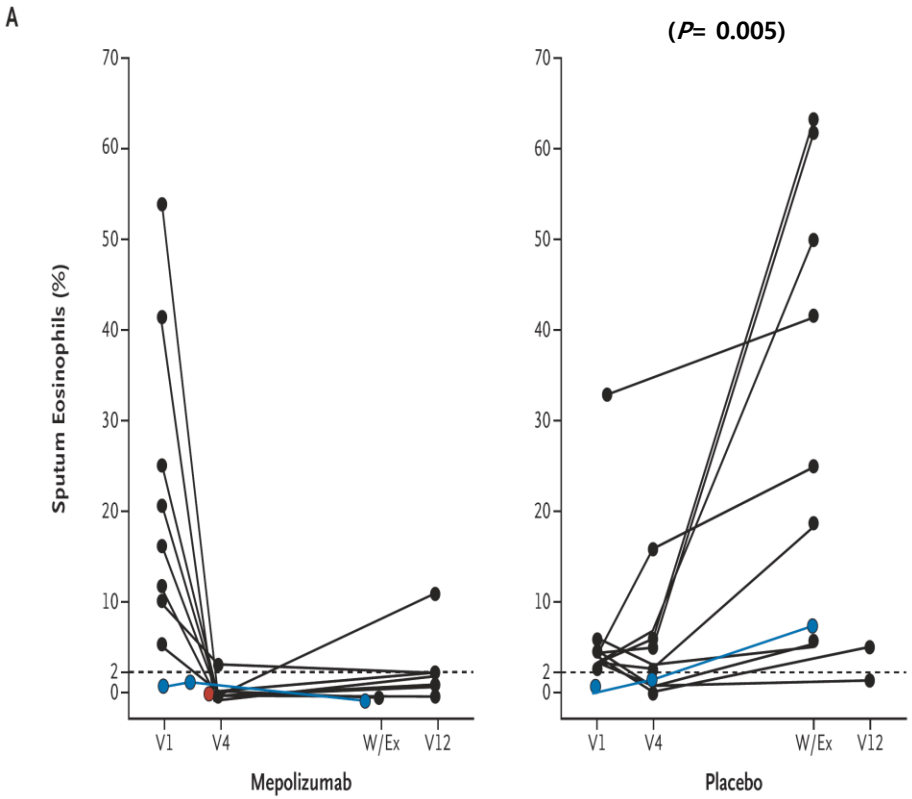
(*P* = 0.003)

Reduction in Prednisone Dose

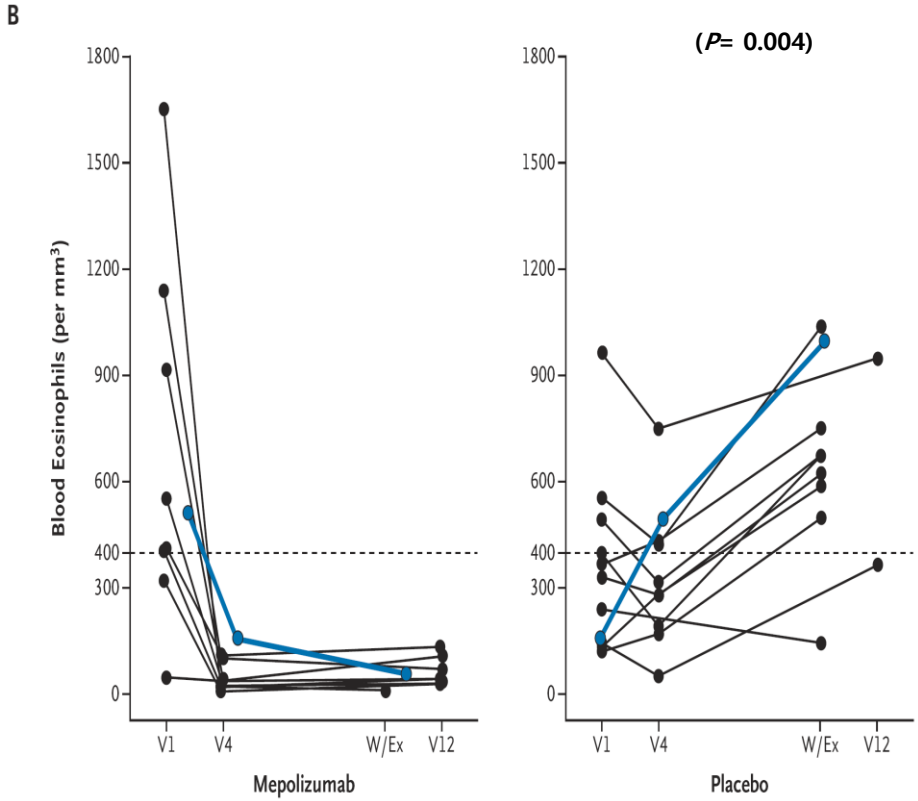
- In the mepolizumab group; 83.8±33.4%
- In the placebo group ; 47.7±40.5%

(*P* = 0.04)

Eosinophils in Sputum



Eosinophils in Blood



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

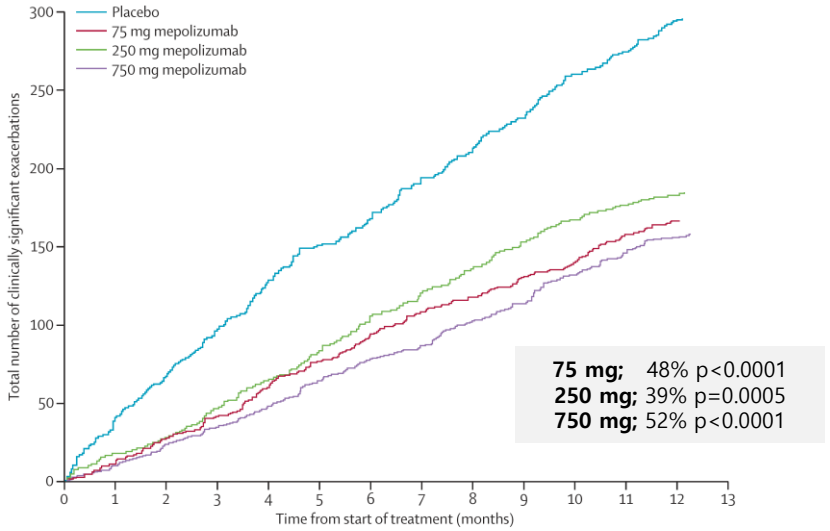
- Ages; 12–74 years (n=621)
- Recurrent severe asthma exacerbations
- Signs of eosinophilic inflammation
  1) sputum eosinophil ≥ 3%, 2) FENO≥50 ppb, 3) blood eosinophil≥300 /mL
  4) deterioration of asthma control after a 25% or less reduction in ICS or oral CS
- One of three doses of I.V. mepolizumab (75, 250, or 750 mg), monthly 13 infusions

- **The primary outcome**
  - The rate of clinically significant asthma exacerbations

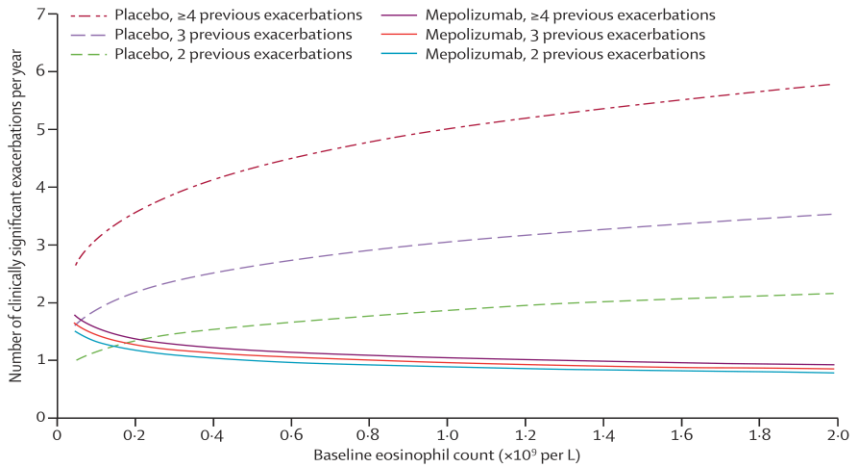
- **Secondary outcomes**
  - Change in blood and sputum eosinophil counts
  - Change in FEV1
  - Change in ACQ score

Lancet 2012; 380: 651–59

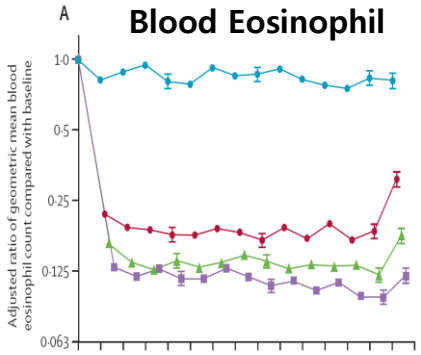
Cumulative Number of Exacerbations with time

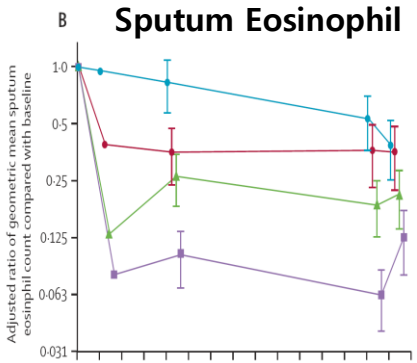


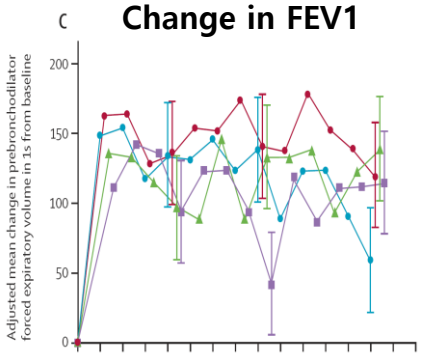
Predictive Modelling of Rate of Exacerbations

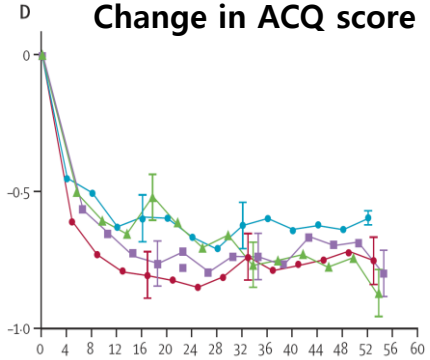


Secondary Outcomes









Blood eosinophil count and number of exacerbations in previous year instead of IgE and Atopy

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

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

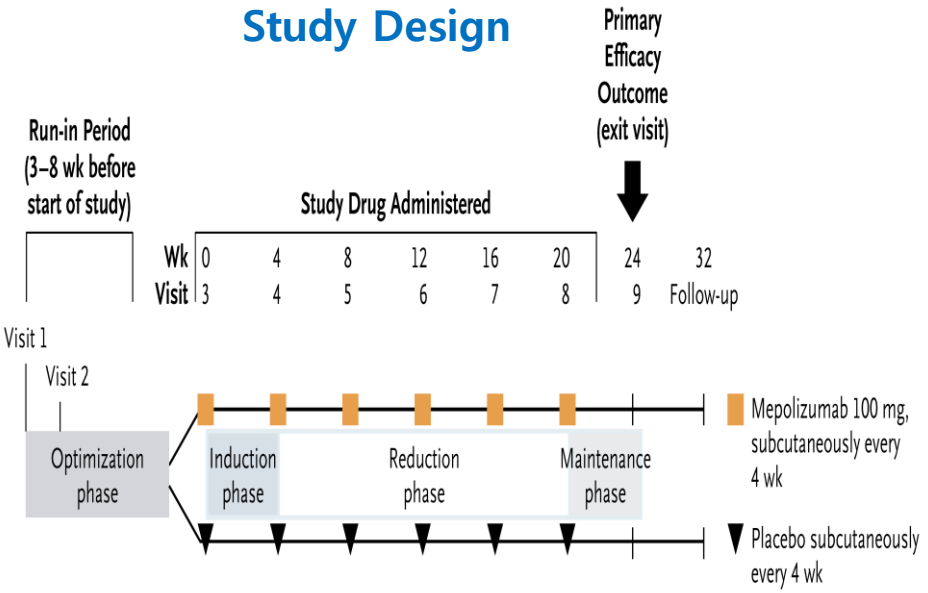
- Ages; 16–74 years (n=135)
- Severe eosinophilic asthma using systemic CS (5-35 mg/D >6mo)
- The presence of eosinophilic inflammation
  1) Blood eosinophil ≥ 300/mL during the 12-month period or
     ≥ 150/mL during the optimization phase
- Mepolizumab (at 100 mg) **SC** every 4 wks for 20 weeks

- **The primary outcome**
  - The degree of reduction in the glucocorticoid dose during 20 to 24 wks

- **Other outcomes**
  - The rate of asthma exacerbations
  - Asthma control
  - Safety

N Engl J Med 2014;371:1189-97

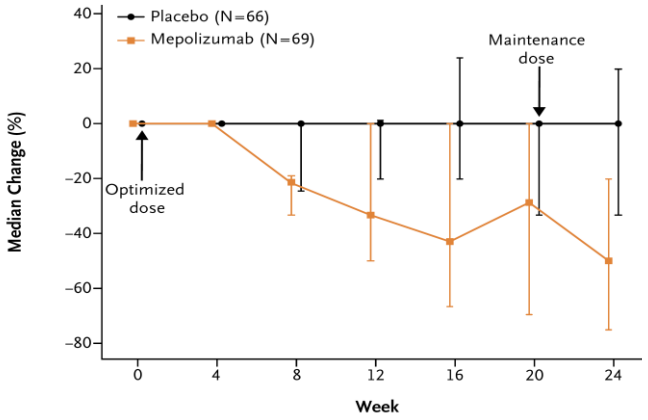
Study Design



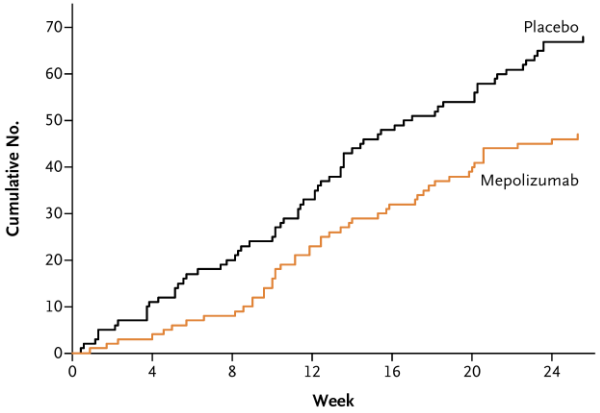
Primary Outcomes

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		

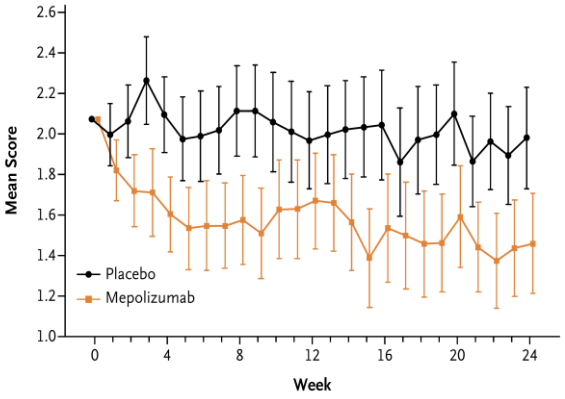
Change from Baseline in Glucocorticoid Dose



Asthma Exacerbations



ACQ-5 Score



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ORIGINAL ARTICLE

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

- Ages; 12-82 years (n=576)
- Asthma exacerbations ≥ 2 in 1 yrs (fluticasone propionate ≥ 880μg with an additional controller)
- Evidence of eosinophilic inflammation
  - Blood Eosinophil count ≥ 150 cells/mL at screening or
    ≥ 300 cells/mL during the previous year
- Mepolizumab; either a **75-mg IV** or
  a **100-mg SC** every 4 weeks for 32 weeks

- **The primary outcome measure**
  - The annualized frequency of clinically significant exacerbations

- **Secondary outcomes**
  - ACQ-5
  - SGRQ
  - FEV1

Summary of Efficacy Outcomes

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	1.75	0.93	47 (29 to 61)†	<0.001	0.81	53 (37 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	138 (43 to 232)	0.004
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±0.07	–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

Conclusions

Mepolizumab administered either intravenously or subcutaneously significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control

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

- Age; 18 to 75 years (n=106)
- Eosinophilic asthma
  - Fluticasone ≥ 880 μg + at least other agents
  - Asthma Control Questionnaire (ACQ) score ≥ 1.5
  - **Induced sputum eosinophils ≥ 3%**
- Reslizumab (3.0 mg/kg, monthly IV for 3months)

- **The primary efficacy measure**
  - Change in ACQ score from baseline to end of therapy

- **Other efficacy measures**
  - Spirometry
  - Blood and induced sputum eosinophil counts
  - The percentage of patients with clinical asthma exacerbations

Am J Respir Crit Care Med. 2011;184:1125–1132

Efficacy Outcomes for Asthma Symptoms and Airway Function

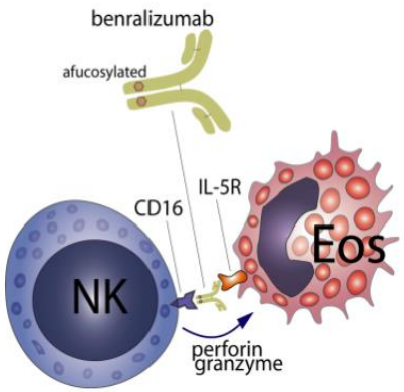
	Reslizumab			Placebo				
	n	Baseline	Change from Baseline	n	Baseline	Change from Baseline	Least-square Mean Difference (95% CI)*	*P* Value*
Asthma control								
ACQ score	53	2.8 (0.79)	−0.7 (1.02)	53	2.5 (0.73)	−0.3 (1.01)	−0.38 (−0.76, 0.01)	0.0541
≤2 at baseline	11	1.8 (0.15)	−0.2 (0.93)	14	1.8 (0.15)	0.0 (0.96)	−0.15 (−0.96, 0.66)	0.7028
>2 at baseline	42	3.0 (0.66)	−0.9 (1.00)	39	2.8 (0.65)	−0.4 (1.03)	−0.45 (−0.90, 0.00)	0.0505
Airway function, prebronchodilator								
FEV_1, L/s	52	2.08 (0.609)	0.18 (0.372)	52	2.26 (0.746)	−0.08 (0.413)	0.240 (0.088, 0.392)	0.0023
% predicted FEV_1	52	66.31 (15.134)	6.19 (11.757)	52	68.90 (16.325)	−2.44 (12.927)	7.978 (3.304, 12.652)	0.0010
FVC, L	52	3.13 (0.830)	0.18 (0.460)	52	3.43 (1.020)	−0.13 (0.521)	0.271 (0.082, 0.460)	0.0054
Eosinophils†								
Induced sputum, median (min, max) percentage	38‡	10.7 (1.7, 67.6)	−95.4 (−100.0, 315.9)	36‡	8.5 (3.0, 77.0)	−38.7 (−96.0, 1,480)	−125.29 (−214.81, −35.77)	0.0068
Blood, median (min, max) × 10^3 cells/μl	52	0.5 (0.10, 1.50)	−0.40 (−1.50, 0.00)	50	0.5 (0.00, 1.20)	0.00 (−0.80, 0.80)	−0.42 (−0.49, −0.35)	<0.0001

Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study

Mario Castro, Sally E Wenzel, Eugene R Bleecker, Emilio Pizzichini, Piotr Kuna, William W Busse, David L Gossage, Christine K Ward, Yanping Wu, Bing Wang, Deepak B Khatry, René van der Merwe, Roland Kolbeck, Nestor A Molfino, Donald G Raible

- Benralizumab, anti-IL-5Rα antibody
- Ages; 18–75 years (n=609)
- 2-6 exacerbations in the past year with medium-high-dose ICS ± LABAs
- Eosinophilic inflammation criteria
  1) ELEN index positive (**an algorithm to predict elevated sputum eosinophils**), 2) FeNO ≥50 ppb
- Eosinophilic groups; benralizumab, 2, 20 or 100 mg **SC** vs. placebo
  Non-eosinophilic groups; benralizumab, 100 mg **SC** vs. placebo

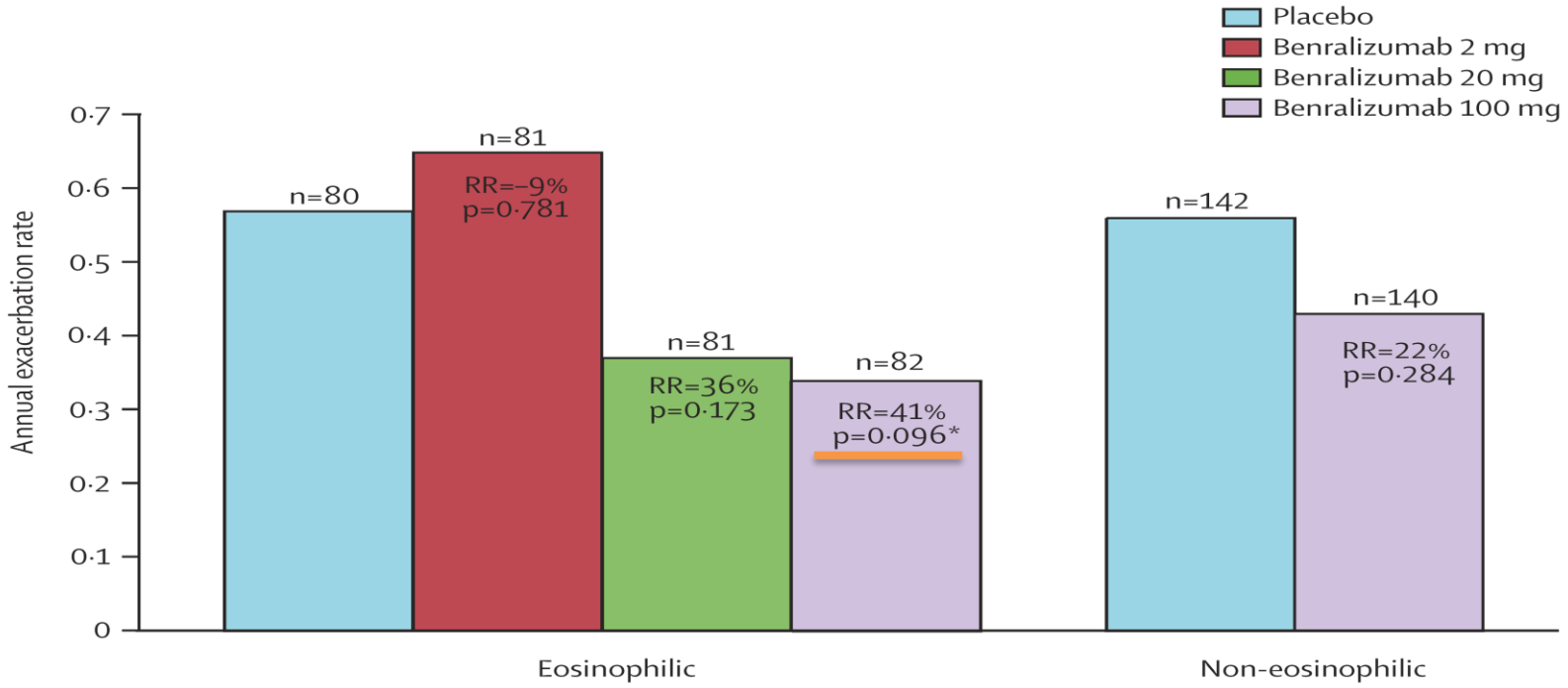
- **The primary efficacy endpoint**
  - The asthma annual exacerbation rate in eosinophilic individuals
- **Secondary efficacy endpoints**
  - Change in FEV1
  - ACQ-6 score
  - Overall symptom score
  - AQLQ score



- Efficient eosinophil depletion through afucosylation
- Eosinophil reduction of bronchial mucosa

Lancet Respir Med 2014; 2: 878–90

Annual exacerbation rate for protocol-defined eosinophilic and non-eosinophilic participants

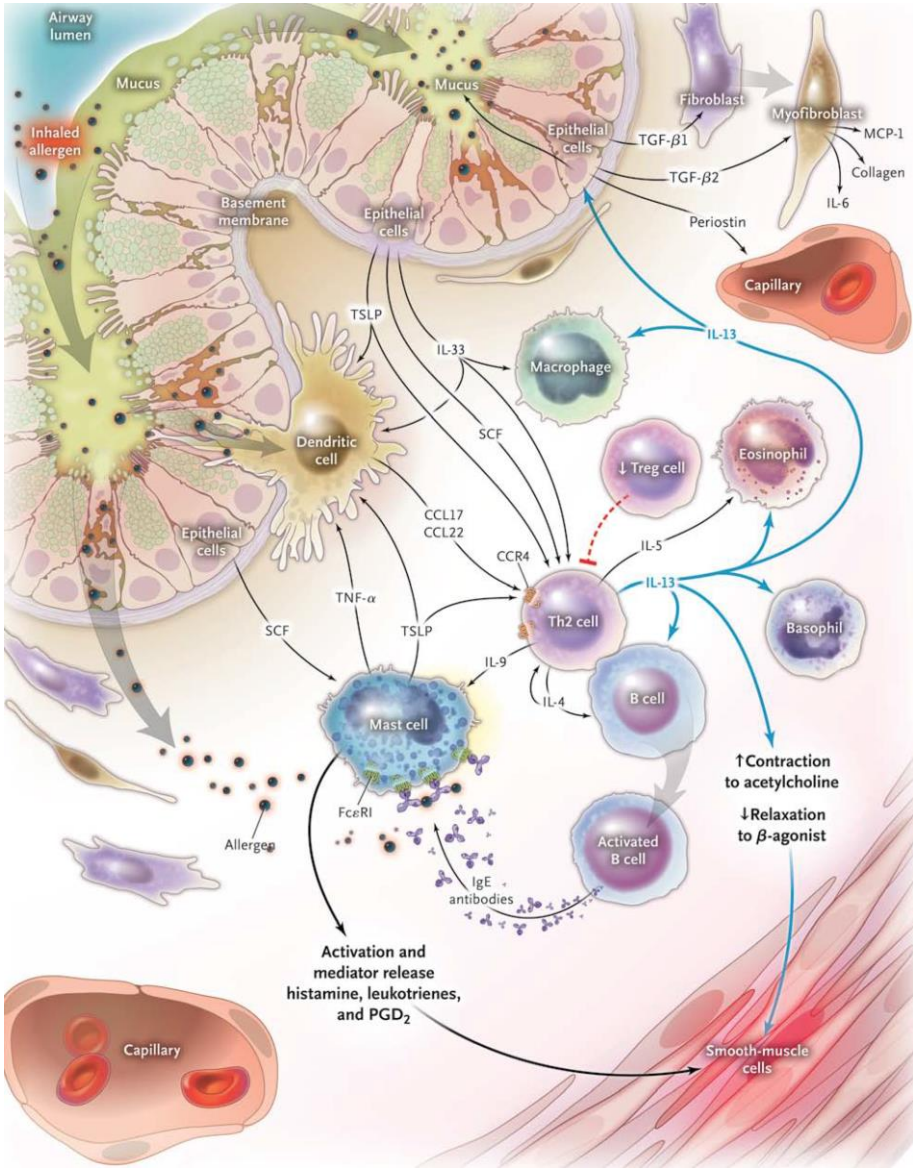


Efficacy endpoints according to baseline blood eosinophil count

statistically significant result p<0.169

	Baseline blood eosinophil count ≥300 cells per µL				Baseline blood eosinophil count <300 cells per µL			
	Placebo (n=83)	Benralizumab 2 mg (n=65)	Benralizumab 20 mg (n=70)	Benralizumab 100 mg (n=97)	Placebo (n=139)	Benralizumab 2 mg (n=16)*	Benralizumab 20 mg (n=11)*	Benralizumab 100 mg (n=124)
Annual exacerbation rate†	0·68 (0·82)	0·75 (0·87)	0·30 (0·55)	0·38 (0·62)	0·49 (0·70)	0·21 (0·46)	0·82 (0·91)	0·42 (0·65)
Rate reduction (80% CI)	..	–7% (–55 to 26)	57% (33 to 72)	43% (18 to 60)	..	57% (NR)	–70% (NR)	16% (–15 to 39)
p value compared with placebo	..	0·822	0·015	0·049	..	0·271	0·265	0·479

IL-13-Targeted Antibodies



NEJM. 2011;365;1142

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

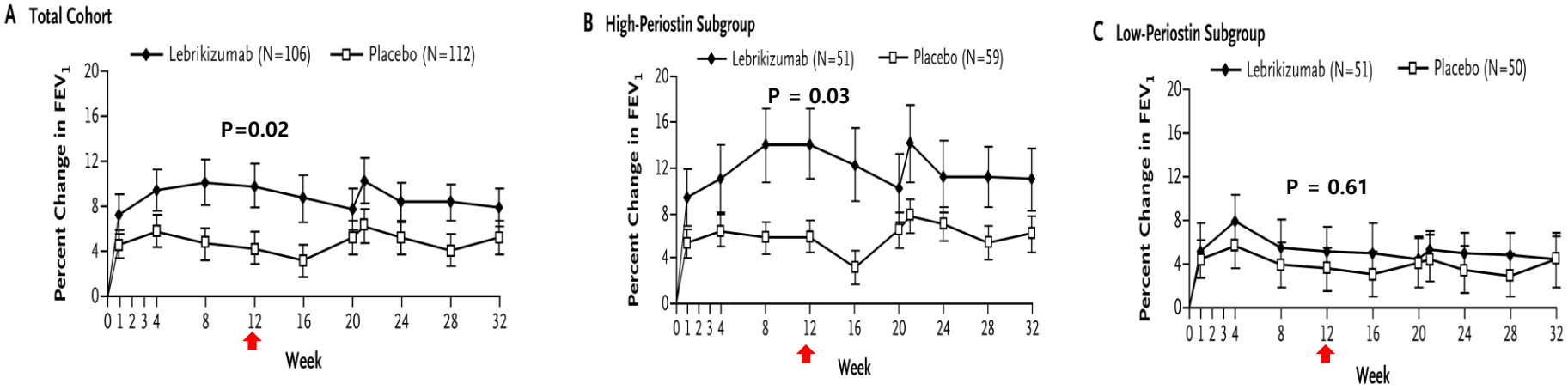
Lebrikizumab Treatment in Adults with Asthma

- 219 adults who had asthma that was inadequately controlled despite ICS (fluticasone; 200-1000 μg)
- Patient subgroups classification
  - Type 2 helper T-cell (Th2) status; total IgE level >100 IU/mL and blood eosinophil count ≥ 140/mL
  - Serum periostin level
- Lebrikizumab (at a dose of 250 mg) **SC monthly** for 6 months

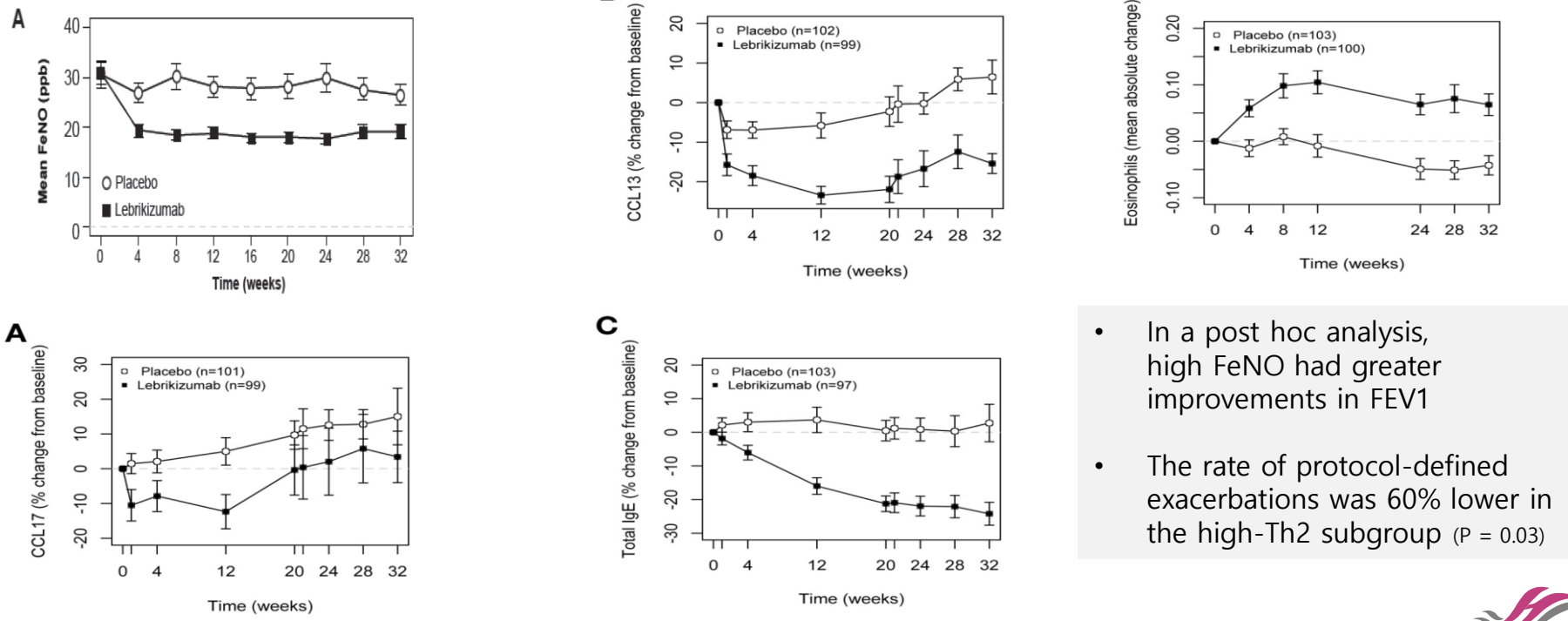
- **The primary efficacy outcome**
  - Change in prebronchodilator FEV1 from baseline to week 12
- **Secondary prespecified outcomes**
  - The rates of exacerbations and severe exacerbations through week 24
  - Peak exploratory flow
  - Change in ACQ5 score
  - Asthma symptom score
  - Use of rescue medication

N Engl J Med 2011;365:1088-98

Primary Outcome; Relative Change in FEV1



Exploratory Efficacy Outcomes



- In a post hoc analysis, high FeNO had greater improvements in FEV1
- The rate of protocol-defined exacerbations was 60% lower in the high-Th2 subgroup (P = 0.03)

A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma

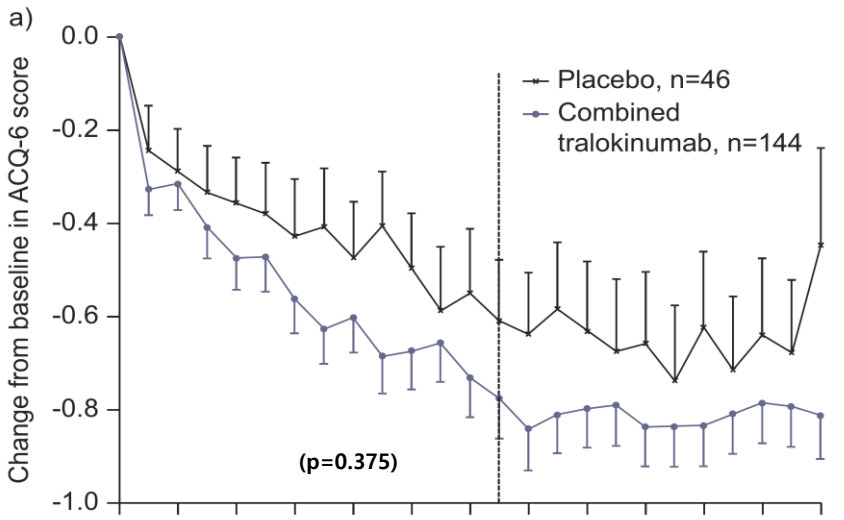
Edward Piper*, Christopher Brightling#, Robert Niven¶, Chad Oh+, Raffaella Faggioni§, Kwai Poon*, Dewei She+, Chris Kell*, Richard D. May*, Gregory P. Geba+ and Nestor A. Molfino+

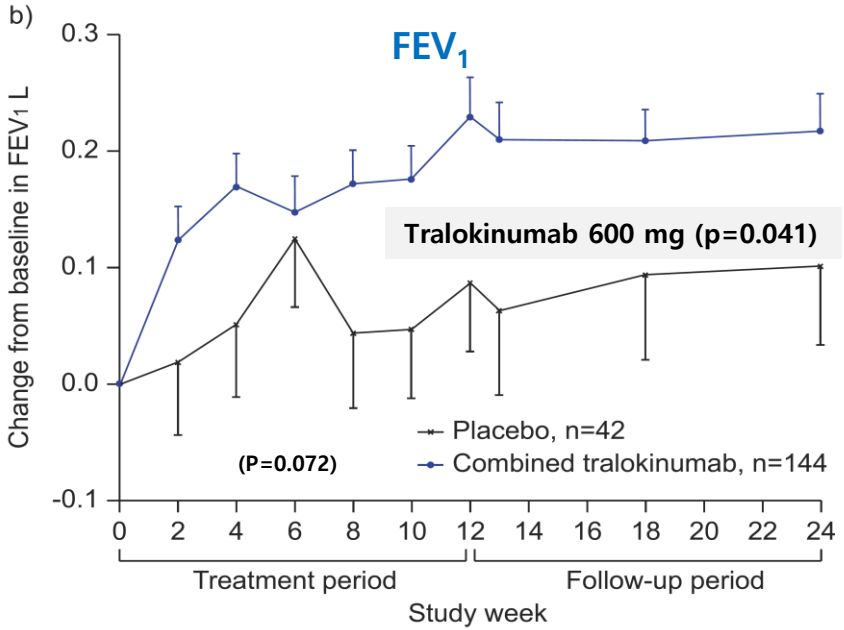
- Ages; 18–65 yrs (n=194)
- Moderate-to-severe uncontrolled asthma
- Tralokinumab 150, 300 or 600 mg **S.C** every 2 weeks for 12 Wks.

- **Primary end-point**
  - Changes in ACQ-6 score
- **Secondary end-points**
  - Pre-bronchodilator lung function
  - Rescue ß2-agonist use
  - Safety

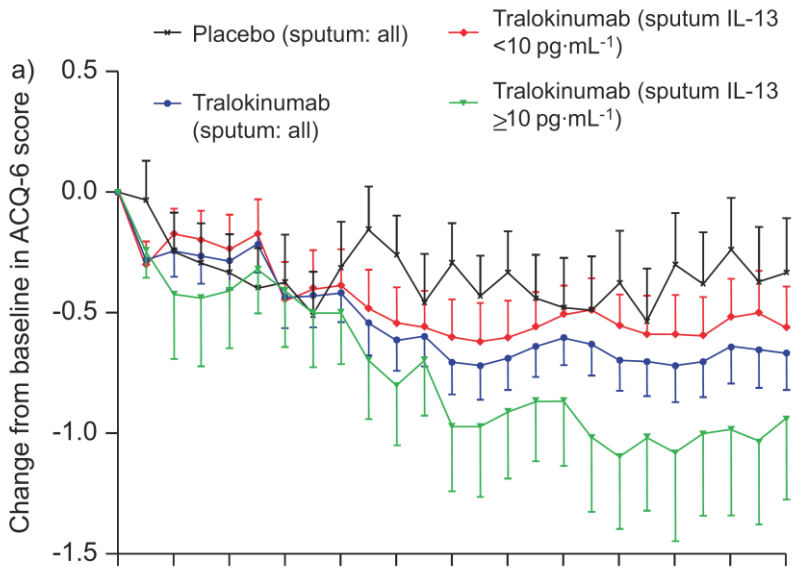
Eur Respir J 2013; 41: 330–338

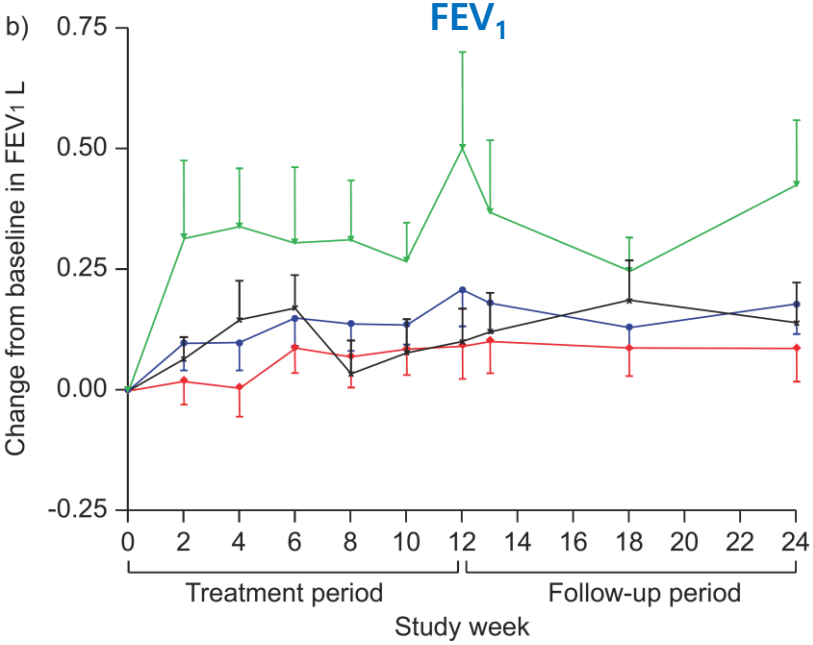
ACQ-6 Score



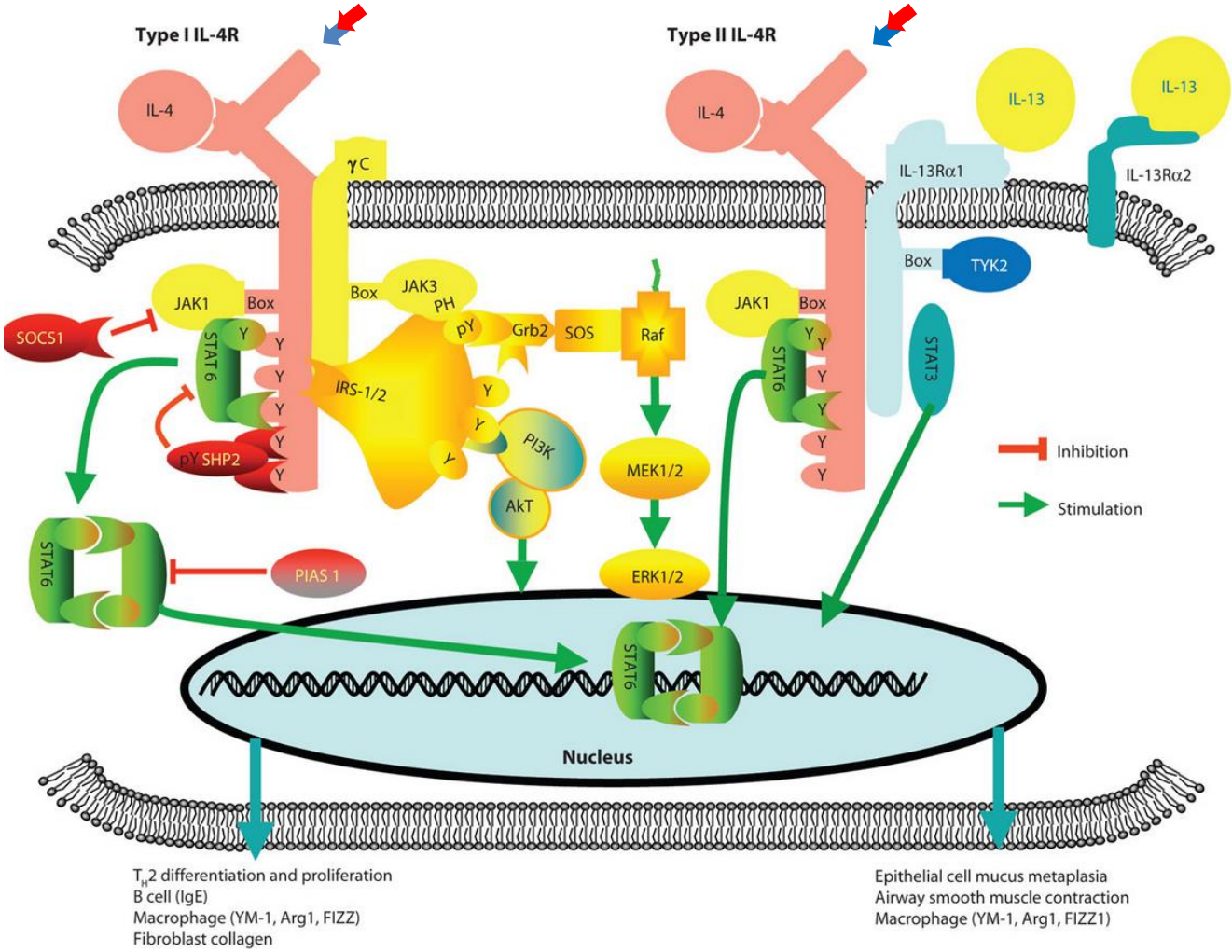


ACQ-6 Score





IL-4/IL-13 Targeted Antibodies



Sci Signal 2008;1(51):pe55.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 27, 2013 VOL. 368 NO. 26

Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

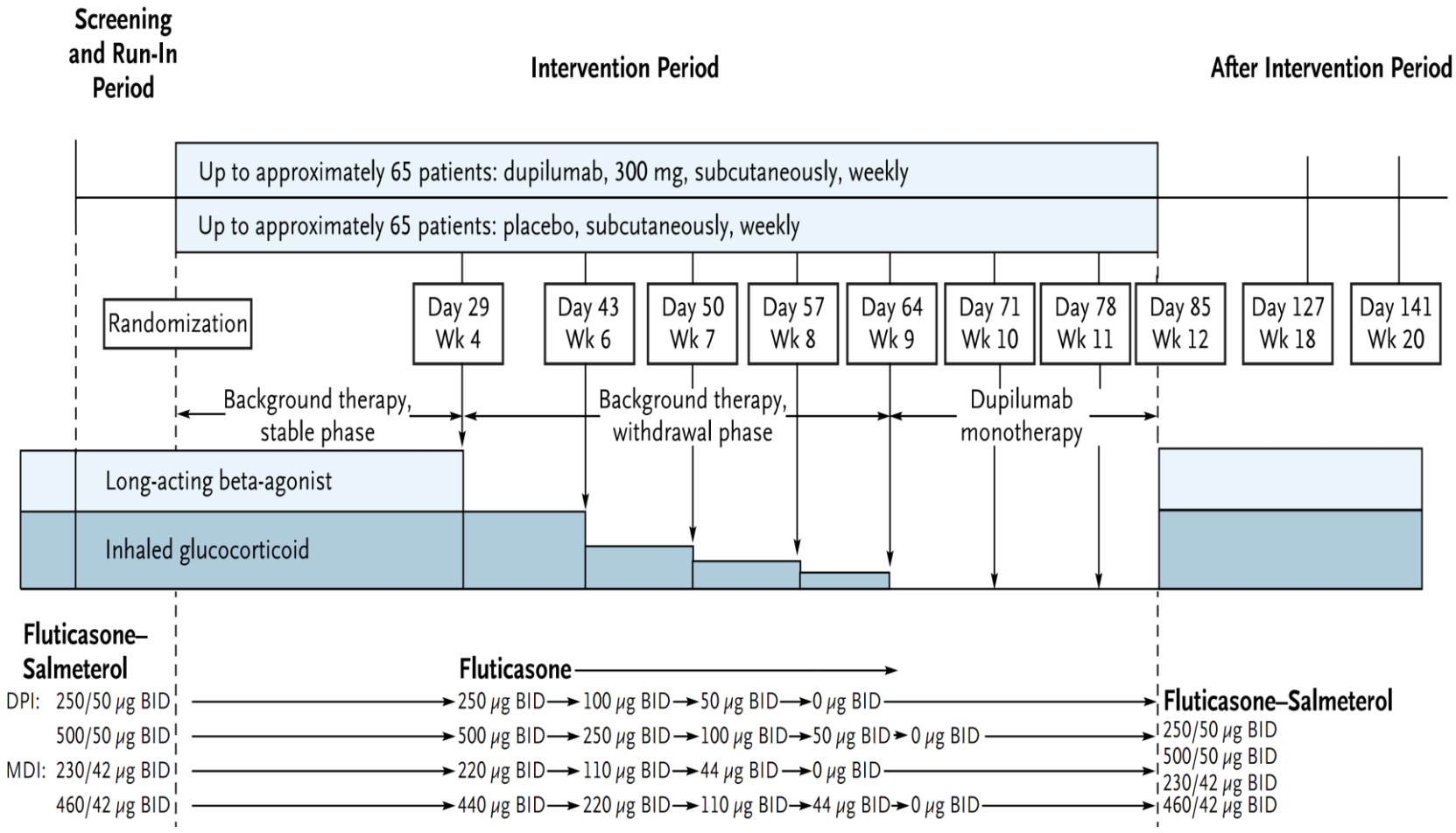
Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

- Dupilumab, anti-IL-4 Rα antibody
- Ages; 18-65 years (n=104)
- Persistent, moderate-to-severe asthma (fluticasone ≥250 μg and salmeterol 50 μg BID)
- Blood eosinophil count ≥ 300 cells/mL or Sputum eosinophil ≥ 3%
- Dupilumab(300 mg); once weekly SC for 12 weeks

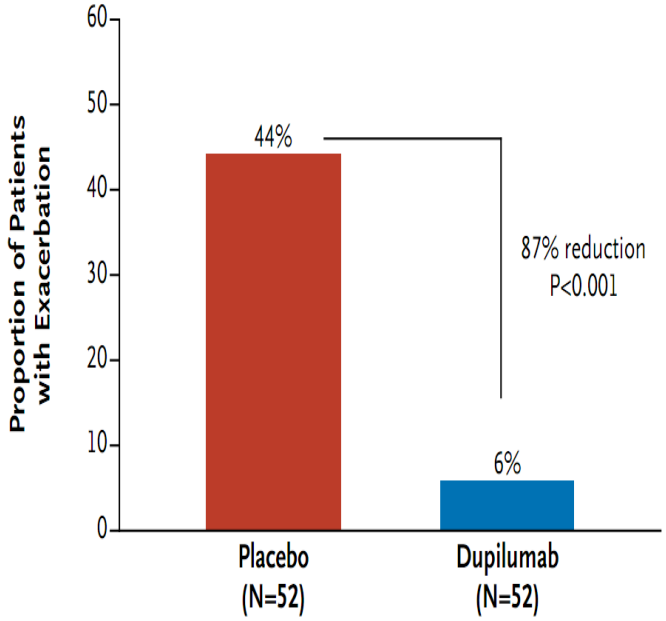
- **The primary efficacy end point**
  - The occurrence of an asthma exacerbation during the 12-week
- **Secondary end points**
  - The time to an asthma exacerbation
  - FEV1
  - PEF
  - ACQ5 score
  - Asthma symptom scores
  - Nocturnal awakenings
  - Rescue ß-agonist use

N Engl J Med 2013;368:2455-66.

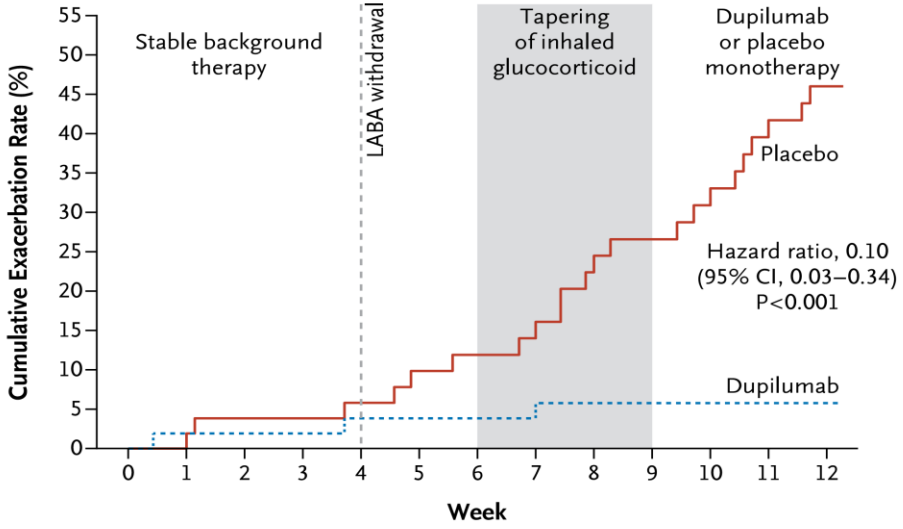
Study Design



A Exacerbations — Primary End Point



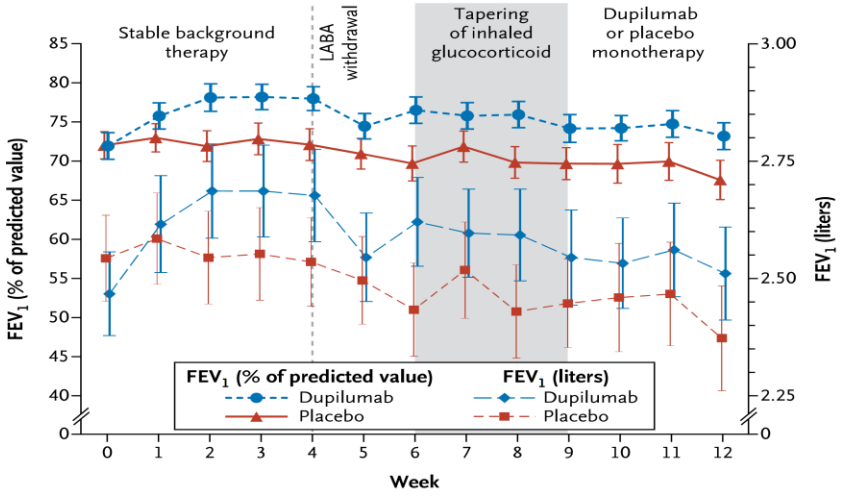
B Time to Exacerbation



No. at Risk

Dupilumab	52	51	51	51	50	50	50	50	47	45	44	43	42
Placebo	52	52	50	50	48	44	43	41	37	35	32	28	24

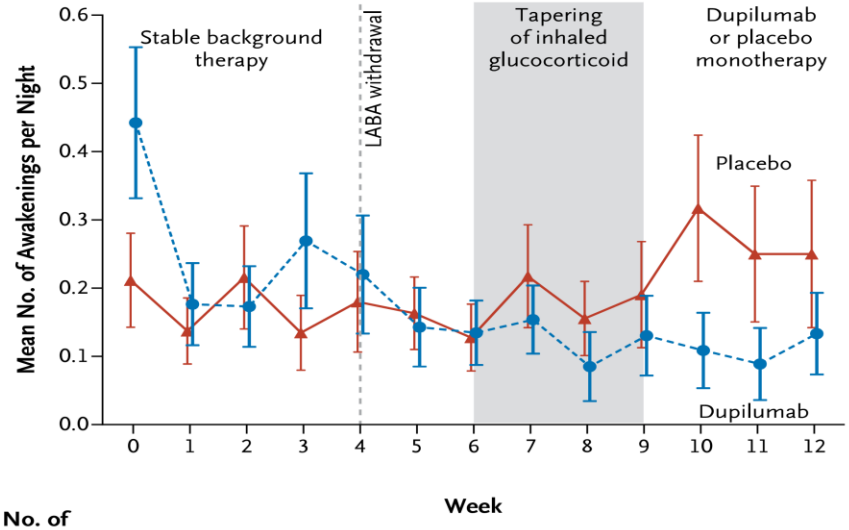
C FEV_1



No. of Patients

FEV_1 (% of predicted value)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36
FEV_1 (liters)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36

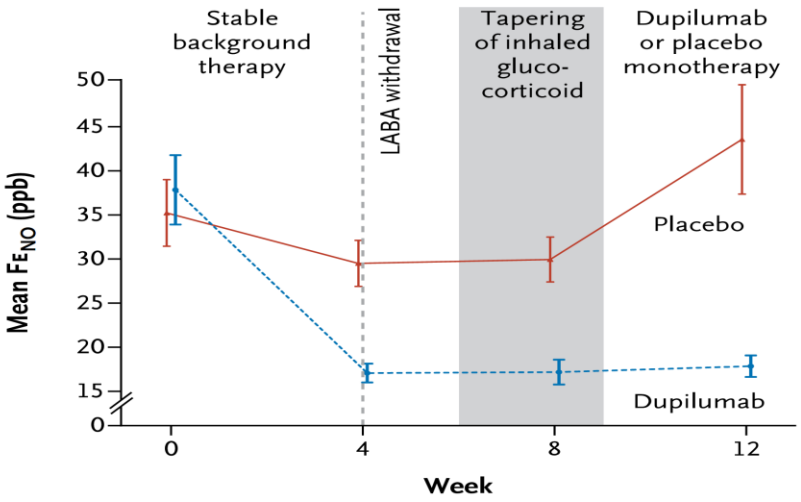
D Nocturnal Awakenings



No. of Patients

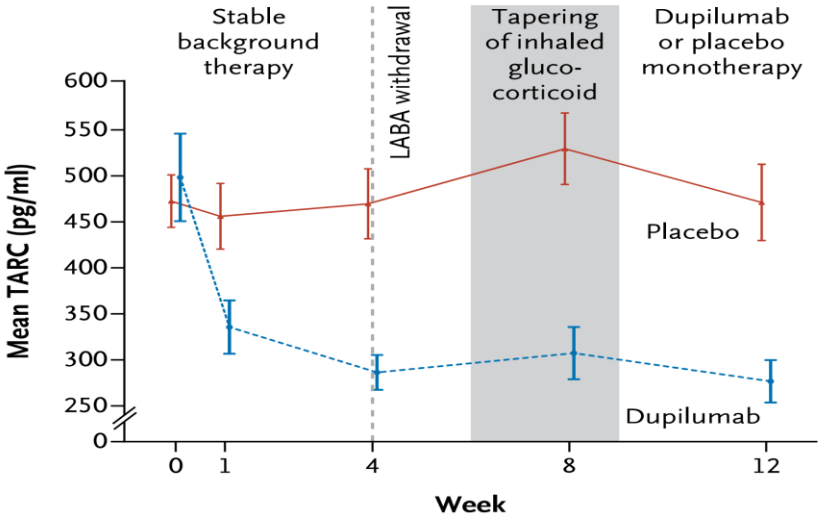
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	51	51	52	50	49	47	46	45	42	41	40	36

A FE_{NO}



No. of Patients				
Dupilumab	51	49	51	41
Placebo	52	51	47	44

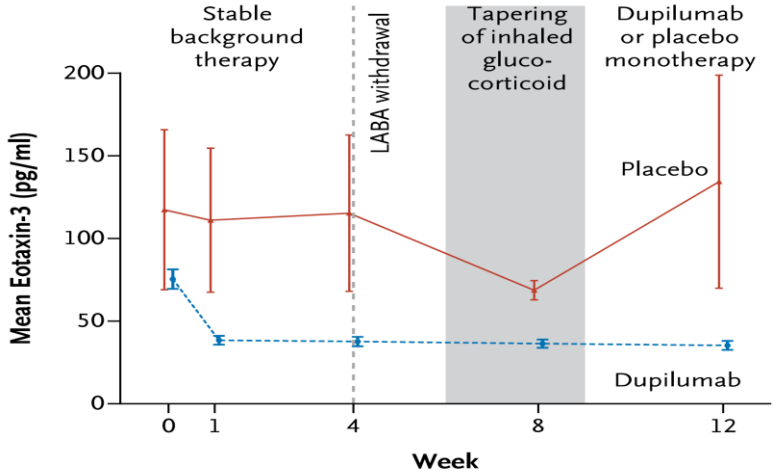
B TARC



No. of Patients					
Dupilumab	52	50	48	52	45
Placebo	52	52	48	48	44

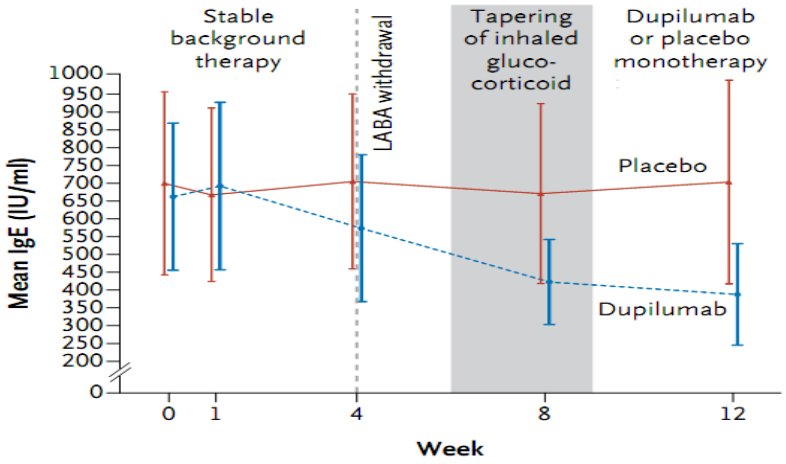
- **Improvement in FEV1 correlated with the reduced FeNO value at week 12 (Pearson's r = −0.408, P = 0.009)**

C Eotaxin-3



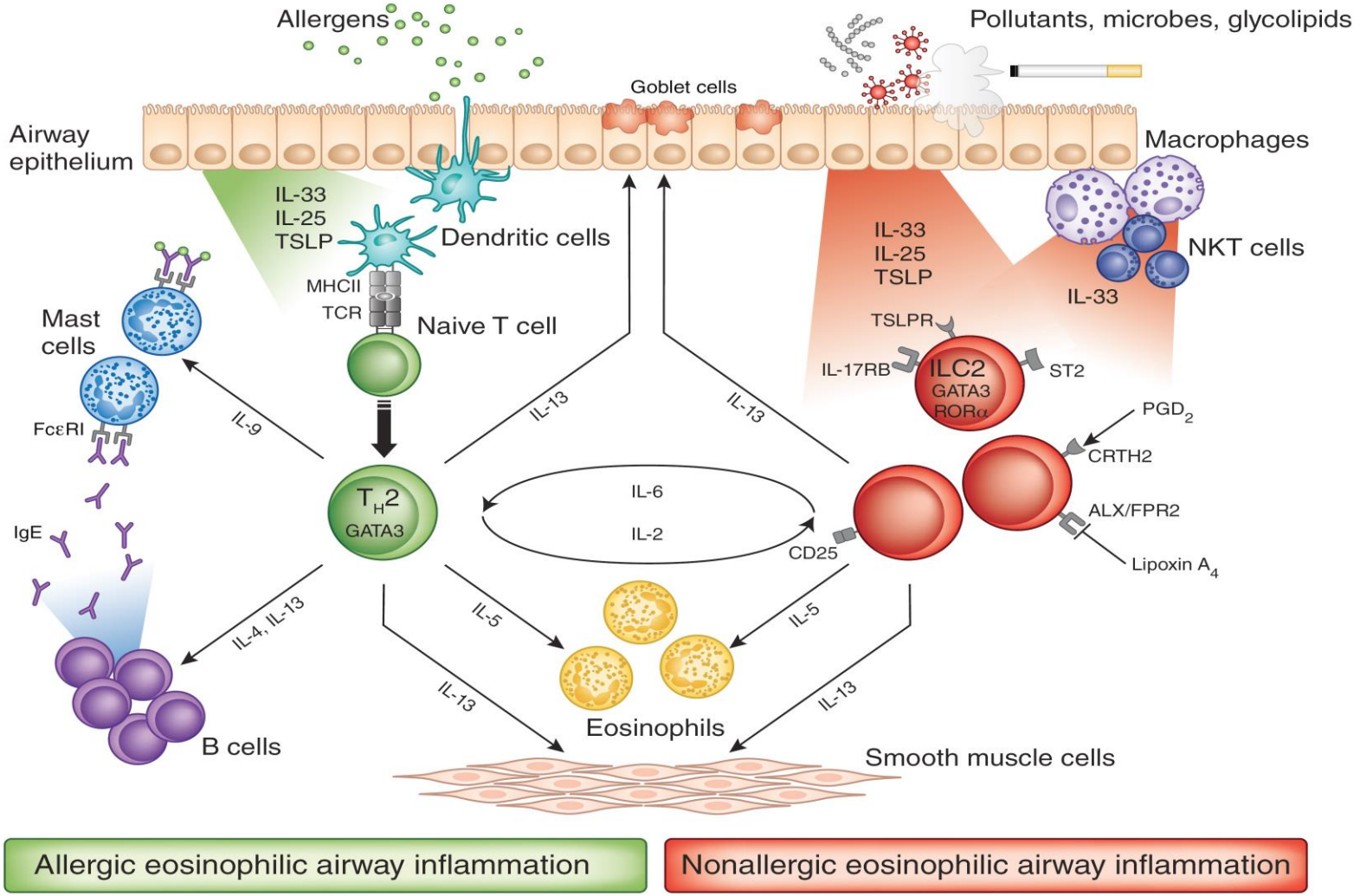
No. of Patients					
Dupilumab	52	50	49	52	44
Placebo	52	52	49	47	44

D IgE



No. of Patients					
Dupilumab	52	50	49	52	45
Placebo	52	52	50	47	44

Thymic stromal lymphopoietin (TSLP) Targeted Antibodies

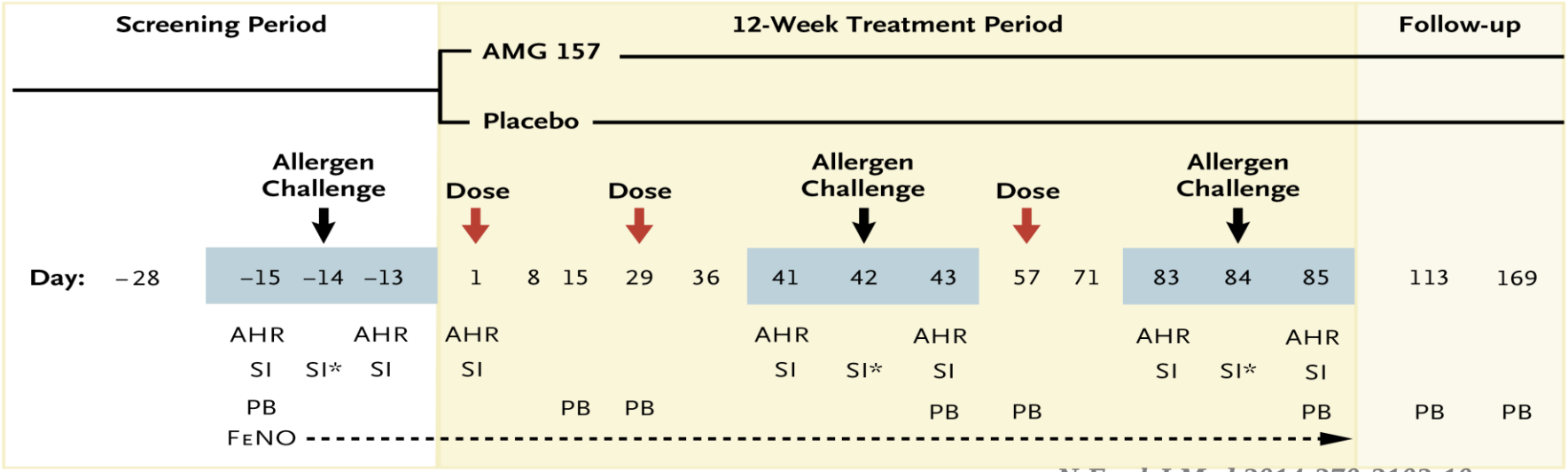


Nat Med 2013;19: 977–979

Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses

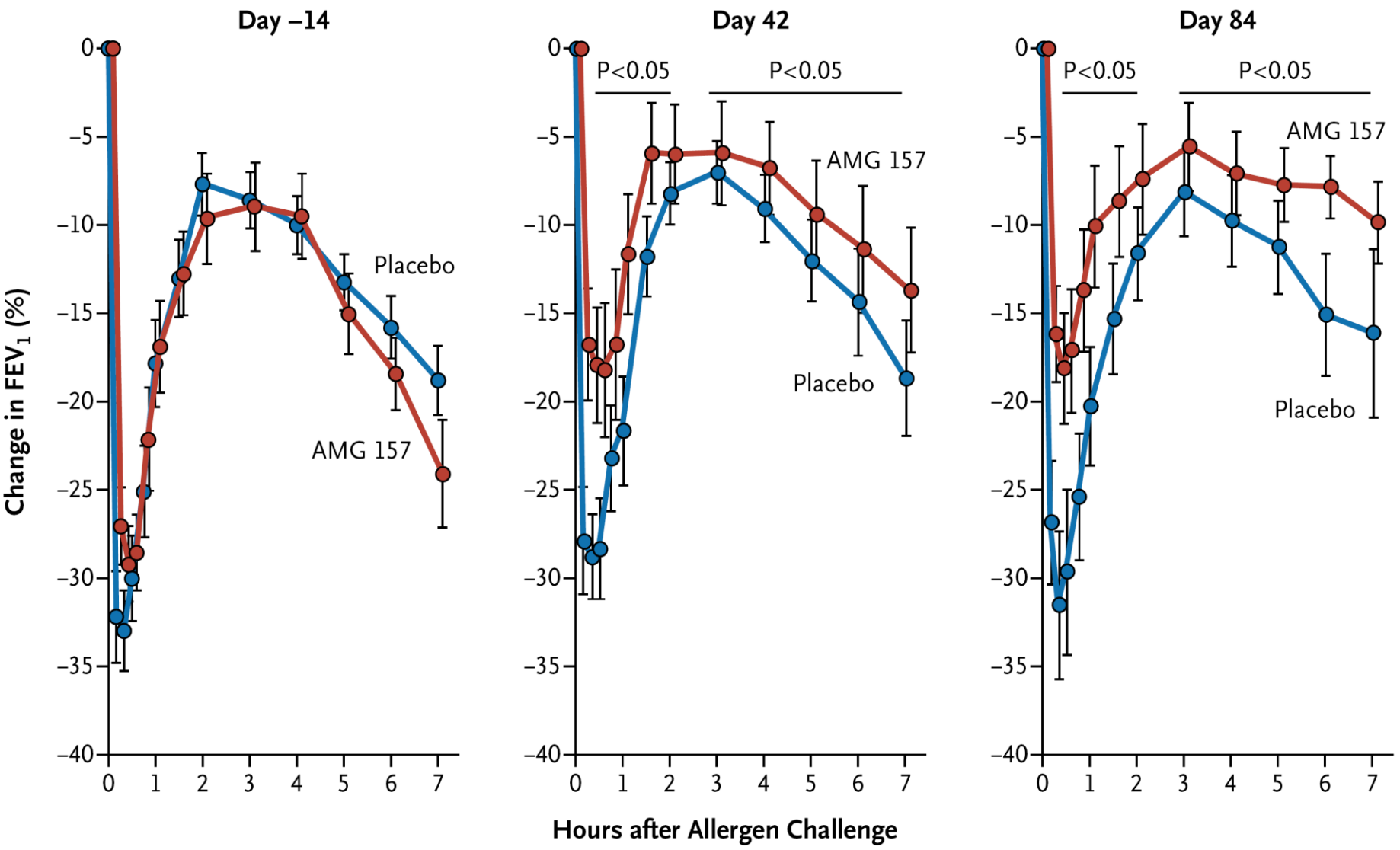
- AMG 157, anti-TSLP antibody
- Ages; 18–60 yrs (n=31)
- Mild, stable atopic asthma
- AMG 157 (700 mg) IV monthly for 3 months

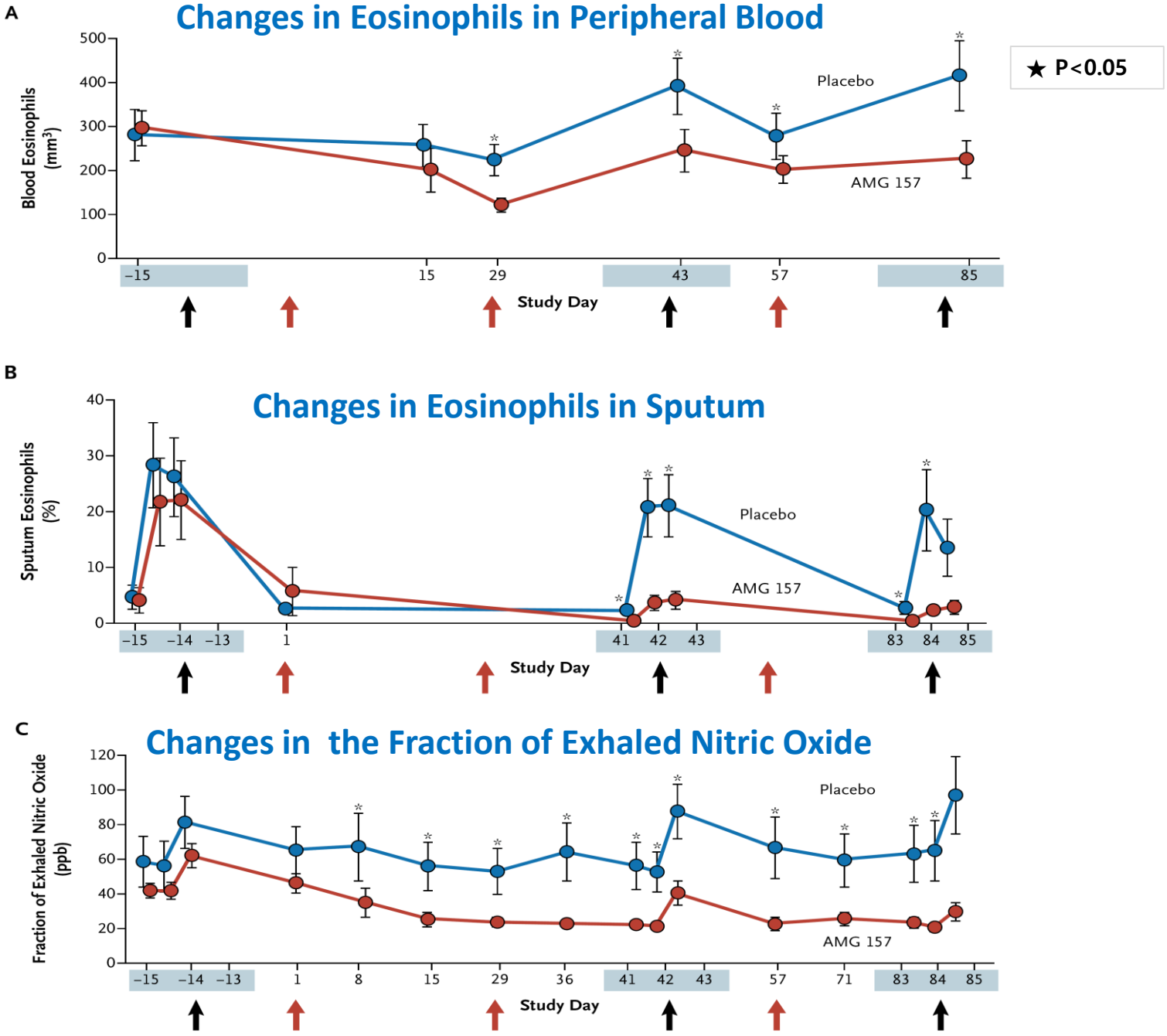
- **The primary end point**
  - The late asthmatic response (3 to 7 hours after the allergen challenge)



N Engl J Med 2014;370:2102-10

Allergen-Induced Percent Reduction in the Forced Expiratory Volume in 1 Second (FEV1).




A
Changes in Eosinophils in Peripheral Blood
Blood Eosinophils (mm³)
500
400
300
200
100
0
Placebo
AMG 157
★ P<0.05
–15
15
29
43
57
85
Study Day
B
Changes in Eosinophils in Sputum
Sputum Eosinophils (%)
40
30
20
10
0
Placebo
AMG 157
–15
–14
–13
1
41
42
43
83
84
85
Study Day
C
Changes in the Fraction of Exhaled Nitric Oxide
Fraction of Exhaled Nitric Oxide (ppb)
120
100
80
60
40
20
0
Placebo
AMG 157
–15
–14
–13
1
8
15
29
36
41
42
43
57
71
83
84
85
Study Day

Others

Author	Severity/n	Treatment	Outcomes	Summary Results
Anti-TNF-α antibody				
Wenzel et al, 2009	Severe asthma uncontrolled with ICS +LABA/309	Golimumab, anti TNFα, 24 w	FEV_1, Exacerbations AQLQ, PEFR	• FEV_1 unchanged • No reduction in exacerbations, AQLQ, PEFR. • SAE; 30.3%
IL- 2 Rα chain antibody				
Busse et al, 2008	Moderate to severe/115	Daclizumab, IL-2Rα chain antibody, 20 weeks	Change in FEV1(%) Asthma Exacerbations	• Improved FEV1 (P= 0.05) • Reduction in daytime asthma scores & use of SABA • Prolonged time to severe exacerbations • Reduction in blood eosinophils
CXCR2 receptor antagonist				
Nair et al, 2012	Severe asthma/34 Sputum neutrophil ≥ 40%	SCH527123, CXCR2 receptor antagonist, 4 Weeks	Changes in sputum and neutrophil activation markers	• Reduction in blood and sputum neutrophil • Reduction in mild exacerbations (p=0.05) • No reduction in ACQ score (p=0.053)
Tyrosine kinase inhibitor targeting stem cell factor receptor (c-kit) and platelet-derived growth factor (PDGF) receptor				
Humbert et al, 2009	Severe, CS dependent/ 44	Masitinib (3, 4.5 and 6 mg/kg/day), 16 w	Oral CS dose ACQ, FEV1	• No difference in OCS dose • ACQ improved (P < 0.001) • No difference in FEV1
TLR-9 agonist				
Beeh et al, 2013	Mild-moderate persistent allergic asthma/63	QbG10; 7 injections of 0.9mg, controlled steroid withdrawal, 12 wks	Asthma symptoms, salbutamol usage, ACQ FEV1, blood eosinophils, FENO,	• All patient-reported parameters improved • At week 12, 2/3 of QbG10; well controlled • Δ FEV1 (p=0.002) • Blood Eosinophil (p=0.01) • FENO (p=0.166)

Proposed guideline for anti-Th2-cytokine therapy in severe refractory asthma

Target	Biomarkers	Expected clinical benefits	Therapeutic limitations	Comments
IgE	• Serum IgE Allergen specific IgE/AST • FENO Blood Eosinophil Periostin	• Reduced exacerbations • Decreased asthma Sx • Improved QOL • Reduced ICS dose • Improved lung function • Reduced ER visits and Hospitalizations	• **Prednisone dose reduction?**	• **Uncertain clinical efficacy in OCS asthma** • Value in non-atopic patients?
IL-5	Peripheral blood and sputum eosinophils	• **Reduced exacerbations** • **Prednisone dose reduction**	• Asthma Sx control (±) • QOL (±) • FEV1 (±)	**Effective in both atopic and non-atopic asthma**
IL-13	Perisotin, FENO	• **Improvement of FEV1**	• Slightly increased blood Eosinophil	
IL-4 /IL-13	Peripheral blood and sputum eosinophils	• **Reductions in exacerbations** • **Improvement in FEV1** • **Reduction in ICS**	• **Prednisone-sparing effects?**	

The suggested surrogated markers of treatments effects

- **Sputum eosinophil counts**
- **Blood eosinophil counts**
- **FeNO**
- **Periostin**

Conclusion

- **New biologic agents are considered as an effective in severe asthma who uncontrolled with standard treatment.**

- **Identification of patients who are most likely to respond to new therapies using phenotyping and biomarkers may be also important in the future.**


Thank You for Your Attention!