TREATMENT UPDATES IN CLINICAL IMMUNOLOGY

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DISCLOSURE:

- None
- This lecture is supported by AOA Department of Research and Development

OBJECTIVES

- To be familiar with updated treatment in clinical immunology
- To be able to choose proper treatment for immune disorders

OVERVIEW

- Introduction

  What is New in:

- Allergic Rhinitis
- Asthma
- Immune disorders
- Skin disorders (atopic dermatitis)

INTRODUCTION

- In the last 5 years we have witnessed a tremendous change in understanding immune system and immune disorders.
- This has led us to come up with new recommendations for treating/managing those with immune disorders.
- The result of the research and new findings has led us to formulate new medications targeting a broad spectrum of the immune disorders.

Allergic Rhinitis

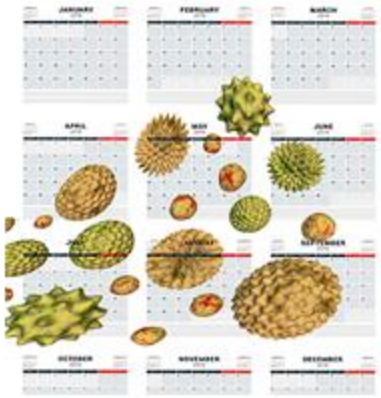
- Immunotherapy-

Sublingual immunotherapy-

April 2014 is considered a milestone in the history of immunotherapy in the United States. It was in this year that after reviewing multiple successful controlled SLIT studies, the US Food and Drug Administration approved the use of several grass and weed allergens for SLIT.

Sublingual products

Health Watch–Jeffrey Stokes



Start 12-16 weeks before start of pollen season

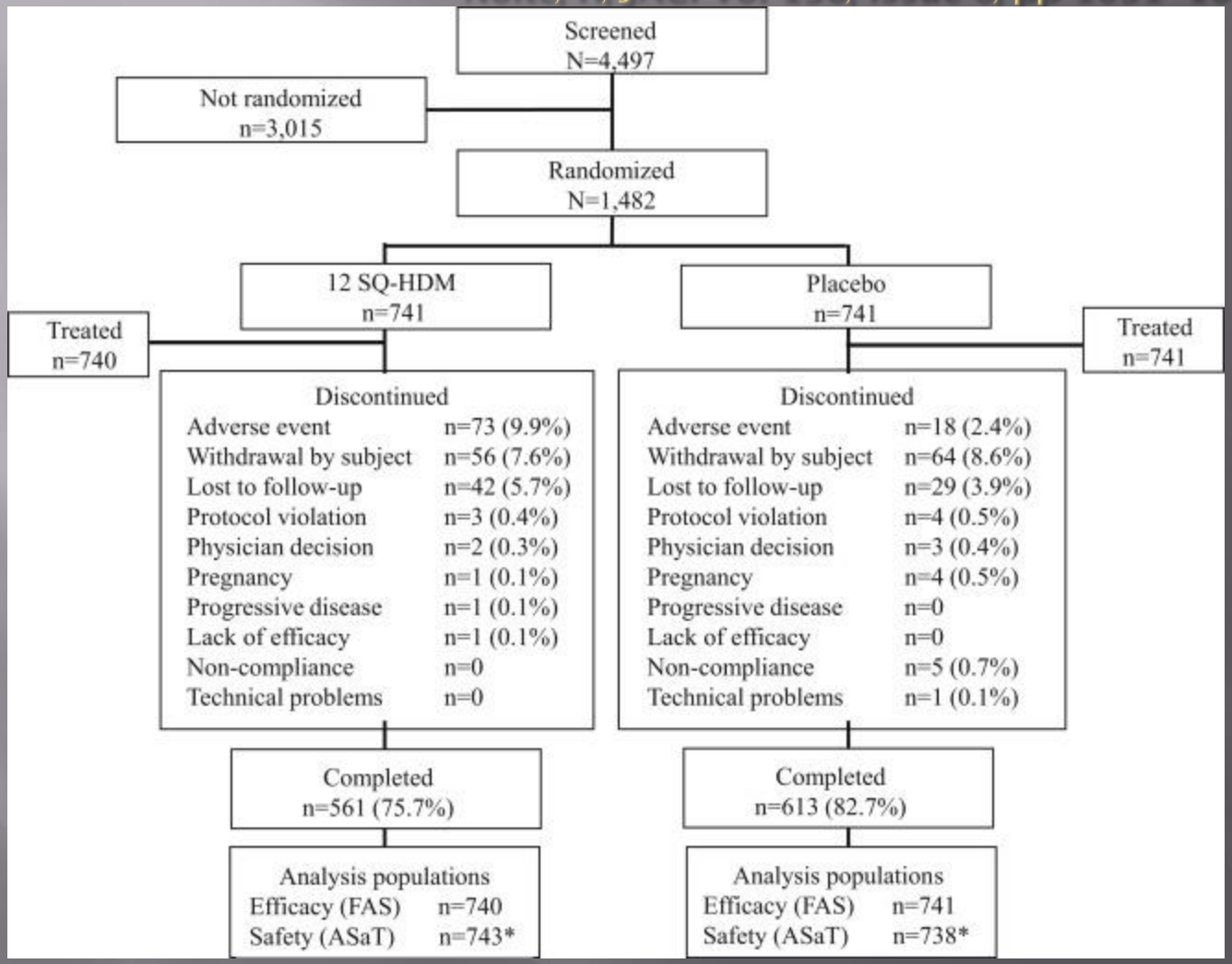
- Administer to children under adult supervision.
- Do not take with food or beverage.

- Place under tongue until dissolved and wait at least 1 minute before swallowing
- Avoid food or beverage for least 5 minutes after dissolution of the table
- * First dose administered in healthcare setting observed for 30 mins

Wash hands after handling the tablet

Sublingual Immunotherapy-House Dusts

Nolte, H; JACI Vol 136; issue 6; pp 1631-1638



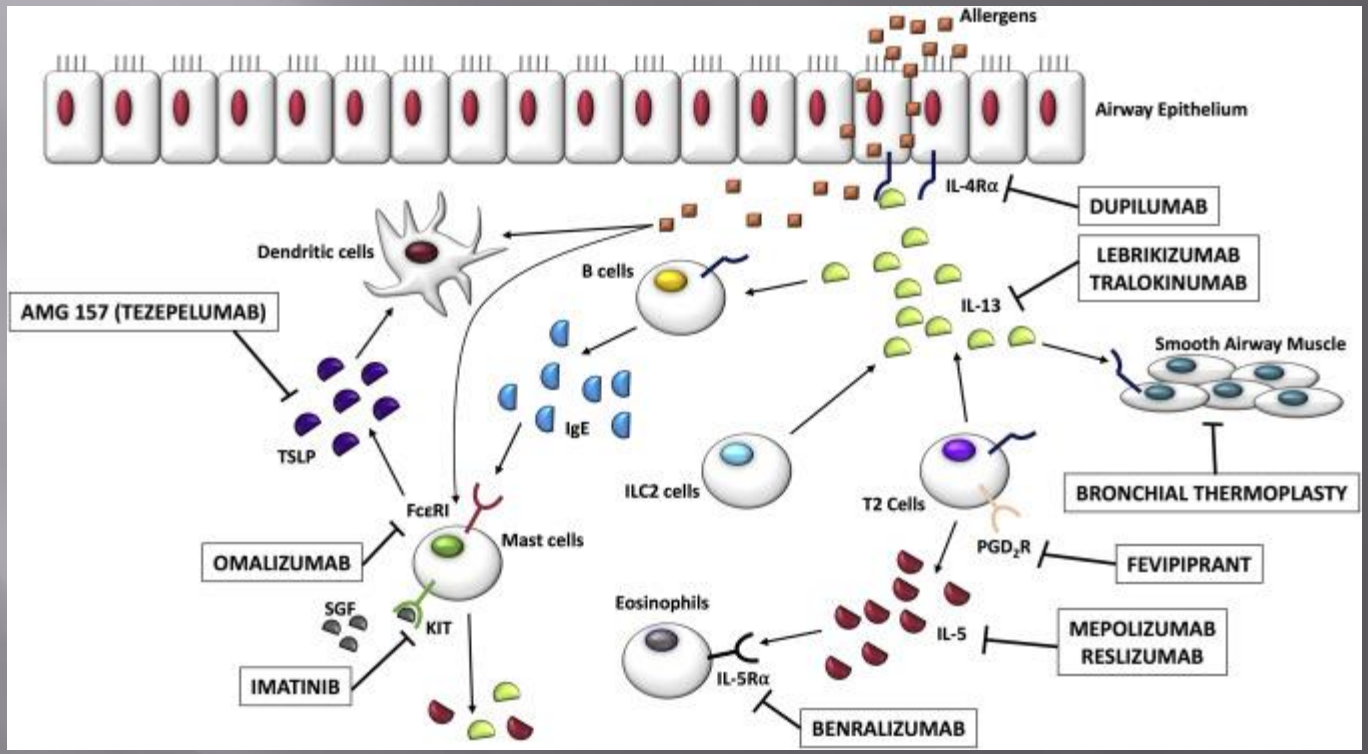
Results:

- In the first North American trial of use of a SLIT-tablet for HDM allergy, 12 SQ-HDM was well tolerated and improved HDM-induced rhinitis symptoms in adults and adolescents.

Bilogical agents with potential for treating patients with severe asthma

S. Peters and W.W. Busse; J Allergy Clin Practice; Sep/Oct 2017

Target	Agent	Mechanism
IgE *	Omalizumab	Prevents IgE from binding to the high-affinity IgE receptor
IL- 5 *	Mepolizumab	Inhibits L- 5
I L-5 *	Reslizumab	Inhibits IL-5
IL-5-R	Benralizumab	Prevents IL- 5 from binding to the IL-5 Ra receptor
IL-13	Tralokinumab	Inhibits I L-13
IL-4/IL-13	Dupilumab	Prevents Il-4 and IL-13 from binding to the Il-4 receptor
TSLP	AMG 157, tezepelumab	Inhibits TSLP


Allergens
Airway Epithelium
IL-4Rα
DUPILUMAB
Dendritic cells
B cells
LEBRIKIZUMAB
TRALOKINUMAB
IL-13
AMG 157 (TEZEPELUMAB)
Smooth Airway Muscle
IgE
TSLP
ILC2 cells
T2 Cells
BRONCHIAL THERMOPLASTY
FcεRI
Mast cells
PGD2R
FEVIPIPRANT
OMALIZUMAB
SGF
KIT
Eosinophils
IL-5
MEPOLIZUMAB
RESLIZUMAB
IMATINIB
IL-5Rα
BENRALIZUMAB

Original Article

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., Mitchell Goldman, M.D., for the ZONDA Trial Investigators

N Engl J Med
Volume 376(25):2448-2458
June 22, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- The use of benralizumab, a monoclonal antibody directed against the alpha subunit of the interleukin-5 receptor, allowed patients with asthma who were dependent on oral glucocorticoids to reduce the glucocorticoid dose to a greater extent than those who received placebo.

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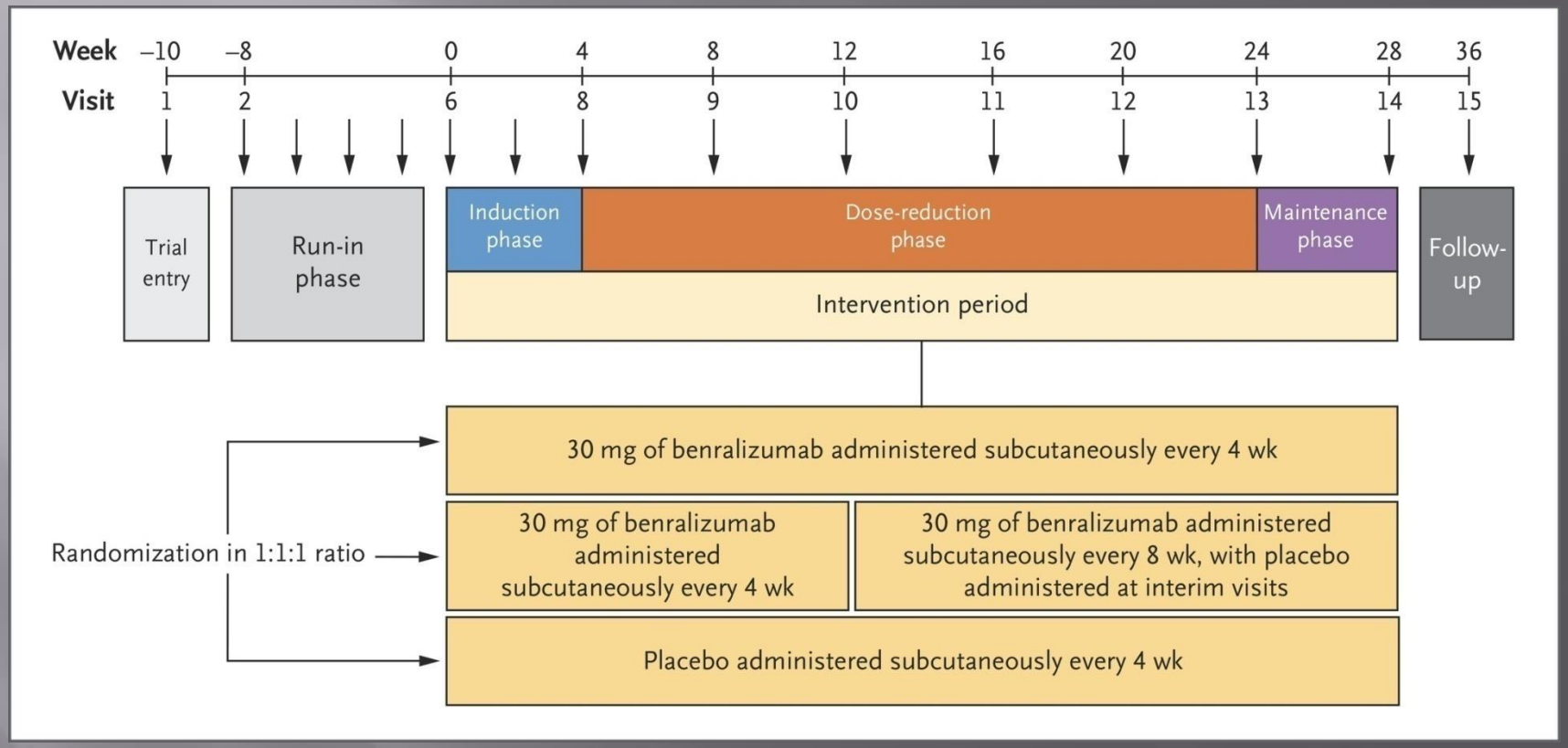
Trial Design.



Nair P et al. N Engl J Med 2017;376:2448-2458

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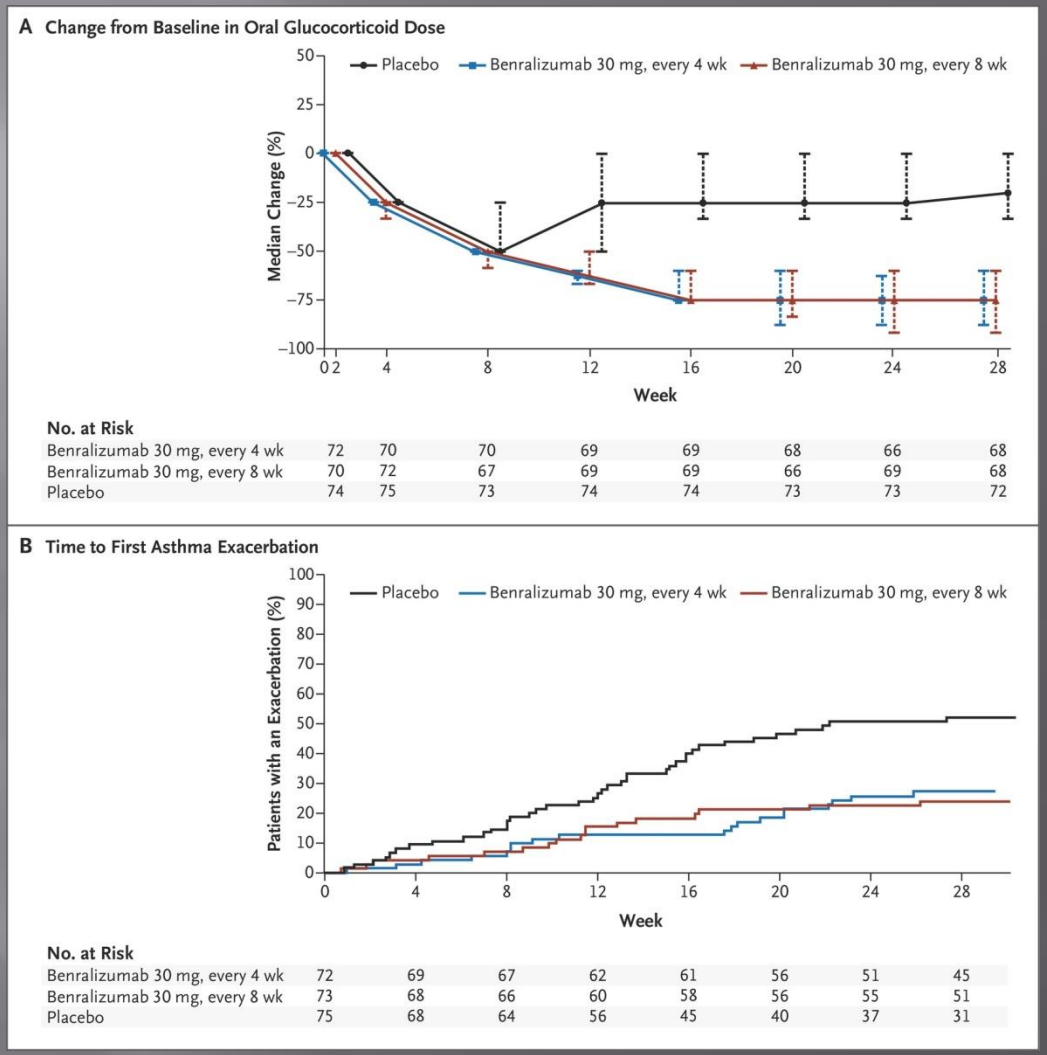
Change from Baseline in the Oral Glucocorticoid Dose and Asthma Exacerbations.



Nair P et al. N Engl J Med 2017;376:2448-2458

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Demographic and Clinical Characteristics of the Patients at Baseline.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=75)	Benralizumab, Every 4 Wk (N=72)	Benralizumab, Every 8 Wk (N=73)
Age — yr	49.9±11.7	50.2±12.0	52.9±10.1
Female sex — no. (%)	48 (64)	40 (56)	47 (64)
Body-mass index†	28.7±5.2	29.8±6.8	30.2±6.5
Median smoking history (range) — pack-yr	6.0 (1 to 9)	5.5 (2 to 9)	5.0 (1 to 8)
Median time since asthma diagnosis (range) — yr	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Median oral glucocorticoid dose (range) — mg/day			
At trial entry‡	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At end of run-in phase	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
Mean inhaled glucocorticoid dose (range) — μg/day	1232 (250 to 5000)	1033 (250 to 3750)	1192 (100 to 3250)
Leukotriene-receptor antagonist — no. (%)	25 (33)	28 (39)	29 (40)
No. of exacerbations in previous 12 mo	2.5±1.8	2.8±2.0	3.1±2.8
FEV_1 before bronchodilation			
Value — liters	1.931±0.662	1.850±0.741	1.754±0.635
Percent of predicted normal value	62.0±16.5	57.4±18.0	59.0±17.9
FEV_1:FVC ratio before bronchodilation — %	62±13	59±13	59±12
Median percent reversibility of FEV_1 (range)§	16.4 (−5.4 to 93.4)	18.2 (−3.0 to 126.0)	22.6 (−3.4 to 88.0)
Total asthma symptom score¶	2.4±1.0	2.5±1.0	2.3±1.1
ACQ-6 score‖	2.7±1.0	2.6±1.1	2.4±1.2
AQLQ(S)+12 score**	4.1±1.1	4.2±1.1	4.4±1.2
Blood eosinophil count			
Median count (range) — cells/mm^3††	535 (160 to 4550)	462 (160 to 1740)	437 (154 to 2140)
Distribution — no. (%)			
≥150 to <300 cells/mm^3	11 (15)	10 (14)	12 (16)
≥300 cells/mm^3	64 (85)	62 (86)	61 (84)

* Plus–minus values are means ±SD. Patients were randomly assigned to receive benralizumab either every 4 weeks or every 4 weeks for the first three doses and then every 8 weeks (with placebo administered at the 4-week interim visits; referred to as the group that received benralizumab every 8 weeks), or placebo. Data on the demographic characteristics of the patients, lung-function variables after bronchodilation, asthma (including smoking) history, and local blood eosinophil counts were collected at visit 1, which occurred 10 weeks before the induction phase began. Data on other clinical characteristics were collected at multiple time points from visit 1 to visit 6 (the start of the induction phase). The last recorded value before randomization served as the baseline measurement. Details about the characteristics at baseline are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients who were taking an oral glucocorticoid other than prednisone or prednisolone at enrollment were switched to an equivalent dose of prednisone or prednisolone at trial entry.

§ The percentage reversibility of the FEV_1 was calculated with the use of FEV_1 values obtained before and after bronchodilation at baseline as follows: ([postbronchodilation FEV_1 − prebronchodilation FEV_1] ÷ prebronchodilation FEV_1) × 100.

¶ The total asthma symptom score is a composite of morning assessments of asthma symptoms, nighttime awakenings, and rescue medication use and an evening assessment of activity impairment. Scores range from 0 to 6, and higher scores indicate a greater symptom burden.

‖ The Asthma Control Questionnaire 6 (ACQ-6)[17] is a six-item questionnaire to assess daytime and nighttime symptoms and rescue use of short-term β_2-agonists. Scores range from 0 to 6, and lower scores indicate better control. Score changes of 0.5 or more points were considered to be clinically meaningful.

** The Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12)[18] is a 32-item questionnaire to assess asthma-related quality of life. Scores range from 1 to 7, and higher scores indicate better asthma-related quality of life. Score changes of 0.5 or more points were considered to be clinically meaningful.

†† Patients were stratified at randomization according to the local laboratory baseline blood eosinophil count that was defined as the result obtained at visit 1.

Nair P et al. N Engl J Med 2017;376:2448-2458

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Primary and Secondary Outcomes.

Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N = 75)	Benralizumab, Every 4 Wk (N = 72)	Benralizumab, Every 8 Wk (N = 73)
Primary outcome			
Median oral glucocorticoid dose (range) — mg/day*			
At baseline	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)	10.0 (7.5 to 40.0)
At final visit	10.0 (0.0 to 40.0)	5.0 (0.0 to 45.0)	5.0 (0.0 to 30.0)
Median reduction from baseline (range) — % of baseline value†	25.0 (−150 to 100)	75.0 (−100 to 100)	75.0 (−50 to 100)
P value†	—	<0.001	<0.001
Reduction from baseline in final oral glucocorticoid dose — no. (%)			
≥90%	9 (12)	24 (33)	27 (37)
≥75%	15 (20)	38 (53)	37 (51)
≥50%	28 (37)	48 (67)	48 (66)
>0%	40 (53)	55 (76)	58 (79)
Any increase or no change in dose	35 (47)	17 (24)	15 (21)
Analysis of percentage reduction from baseline in oral glucocorticoid dose			
Odds ratio (95% CI)	—	4.09 (2.22 to 7.57)	4.12 (2.22 to 7.63)
P value	—	<0.001	<0.001
Secondary outcomes			
Reduction from baseline in final oral glucocorticoid dose, according to percentage reduction			
100% Reduction — no./total no. (%)‡	8/42 (19)	22/39 (56)	22/42 (52)
Odds ratio (95% CI)	—	5.23 (1.92 to 14.21)	4.19 (1.58 to 11.12)
P value	—	<0.001	0.002
≥50% Reduction — no. (%)	28 (37)	48 (67)	48 (66)
Odds ratio (95% CI)	—	3.59 (1.79 to 7.22)	3.03 (1.57 to 5.86)
P value	—	<0.001	<0.001
≥25% Reduction — no. (%)	38 (51)	54 (75)	57 (78)
Odds ratio (95% CI)	—	2.89 (1.45 to 5.79)	3.25 (1.62 to 6.52)
P value	—	0.002	<0.001
Final oral glucocorticoid dose of ≤5.0 mg/day — no. (%)§	25 (33)	44 (61)	43 (59)
Odds ratio (95% CI)	—	3.16 (1.60 to 6.23)	2.74 (1.41 to 5.31)
P value	—	<0.001	0.002

* The baseline oral glucocorticoid dose was the daily dose at which the patient's asthma was stabilized at randomization (after the run-in phase), and the final oral glucocorticoid dose was the final daily dose at week 28.
† Negative values indicate an increase in the final oral glucocorticoid dose from baseline. The P values were calculated with the use of a Wilcoxon rank-sum test.
‡ Patients with a baseline oral glucocorticoid dose of 12.5 mg or less per day at the end of the run-in phase were eligible for a 100% dose reduction (discontinuation of oral glucocorticoid therapy).
§ All the patients with a final oral glucocorticoid dose of 5.0 mg or less per day also had a reduction of at least 25% from baseline in the final oral glucocorticoid dose.

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Summary of Adverse Events.

Table 3. Summary of Adverse Events.*

Event	Placebo (N = 75)	Benralizumab, Every 4 Wk (N = 72)	Benralizumab, Every 8 Wk (N = 73)
		number of patients (percent)	
Adverse event	62 (83)	49 (68)	55 (75)
Adverse event leading to discontinuation of trial regimen	2 (3)	0	3 (4)
Serious adverse event	14 (19)	7 (10)	7 (10)
Serious adverse event unrelated to asthma exacerbation†	11 (15)	6 (8)	6 (8)
Death	0	0	2 (3)
Injection-site reaction	2 (3)	2 (3)	0
Hypersensitivity	1 (1)	1 (1)	2 (3)
Urticaria	1 (1)	0	1 (1)

* Data on adverse events that occurred during the period from the receipt of the first dose of the trial regimen (week 0) to the visit at the end of the trial (week 28) are provided. Complete details of adverse events are provided in Table S8 in the Supplementary Appendix.

† Patients who had only the serious adverse events of worsening asthma or status asthmaticus were excluded from these totals.

Nair P et al. N Engl J Med 2017;376:2448-2458

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Conclusions

- Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates.
- These effects occurred without a sustained effect on the FEV_1.

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Original Article

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

Michael E. Wechsler, M.D., Praveen Akuthota, M.D., David Jayne, F.Med.Sci., Paneez Khoury, M.D., M.H.S., Amy Klion, M.D., Carol A. Langford, M.D., M.H.S., Peter A. Merkel, M.D., M.P.H., Frank Moosig, M.D., Ulrich Specks, M.D., Maria C. Cid, M.D., Raashid Luqmani, D.M., Judith Brown, Ph.D., Stephen Mallett, M.Sc., Richard Philipson, M.D., Steve W. Yancey, M.Sc., Jonathan Steinfeld, M.D., Peter F. Weller, M.D., Gerald J. Gleich, M.D., for the EGPA Mepolizumab Study Team

N Engl J Med
Volume 376(20):1921-1932
May 18, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- Among participants with eosinophilic granulomatosis with polyangiitis, 32% had remission at weeks 36 and 48 when treated with mepolizumab, an anti–interleukin-5 monoclonal antibody, as compared with 3% of the participants in the placebo group.

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Eosinophilic Granulomatosis with Polyangiitis(Churg-Struass)

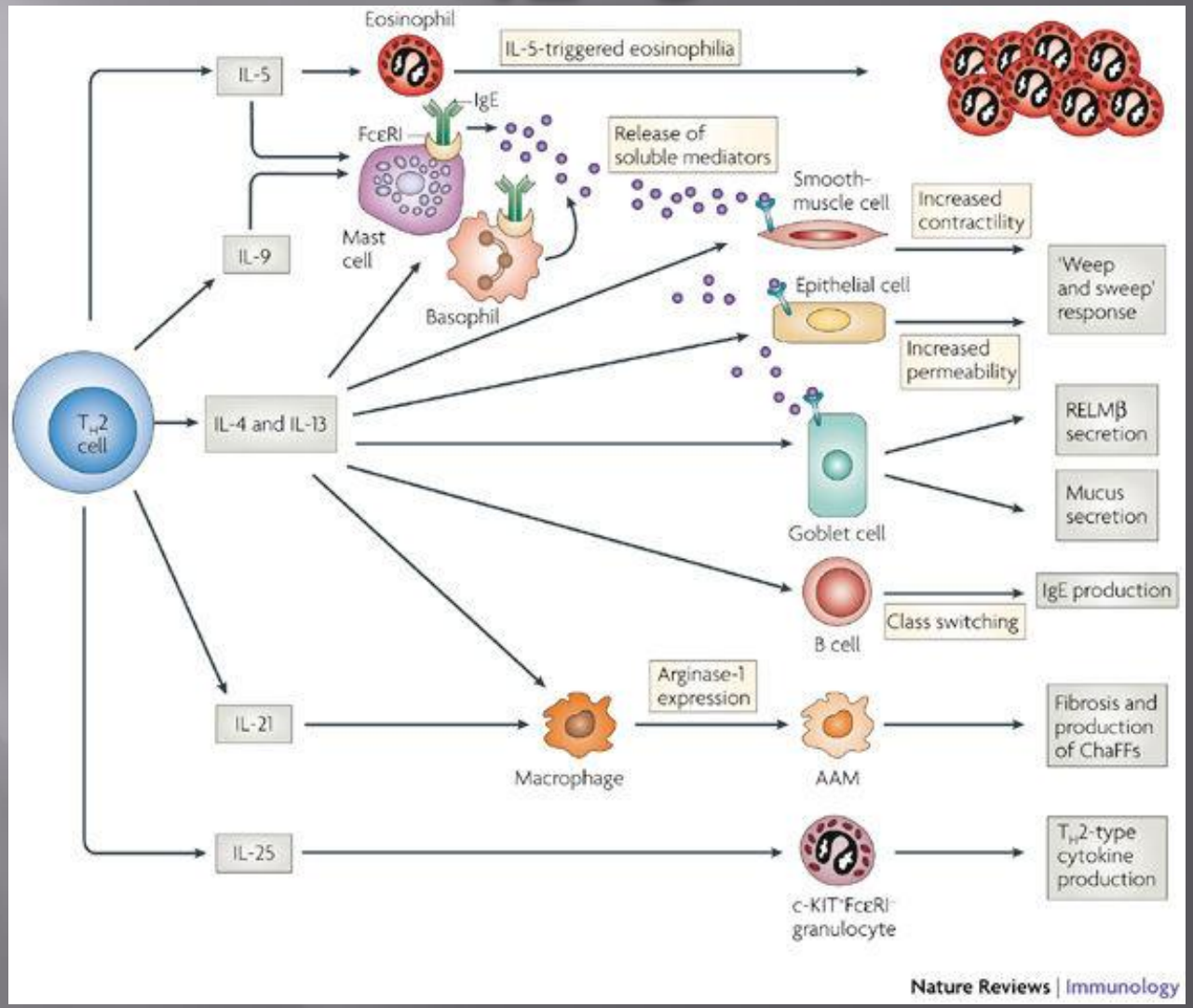
EGPA- is a multisystemic disorder chatacterized by :

- Chronic rhinosinusitis
- Asthma
- Prominent peripheral blood eosinophilia

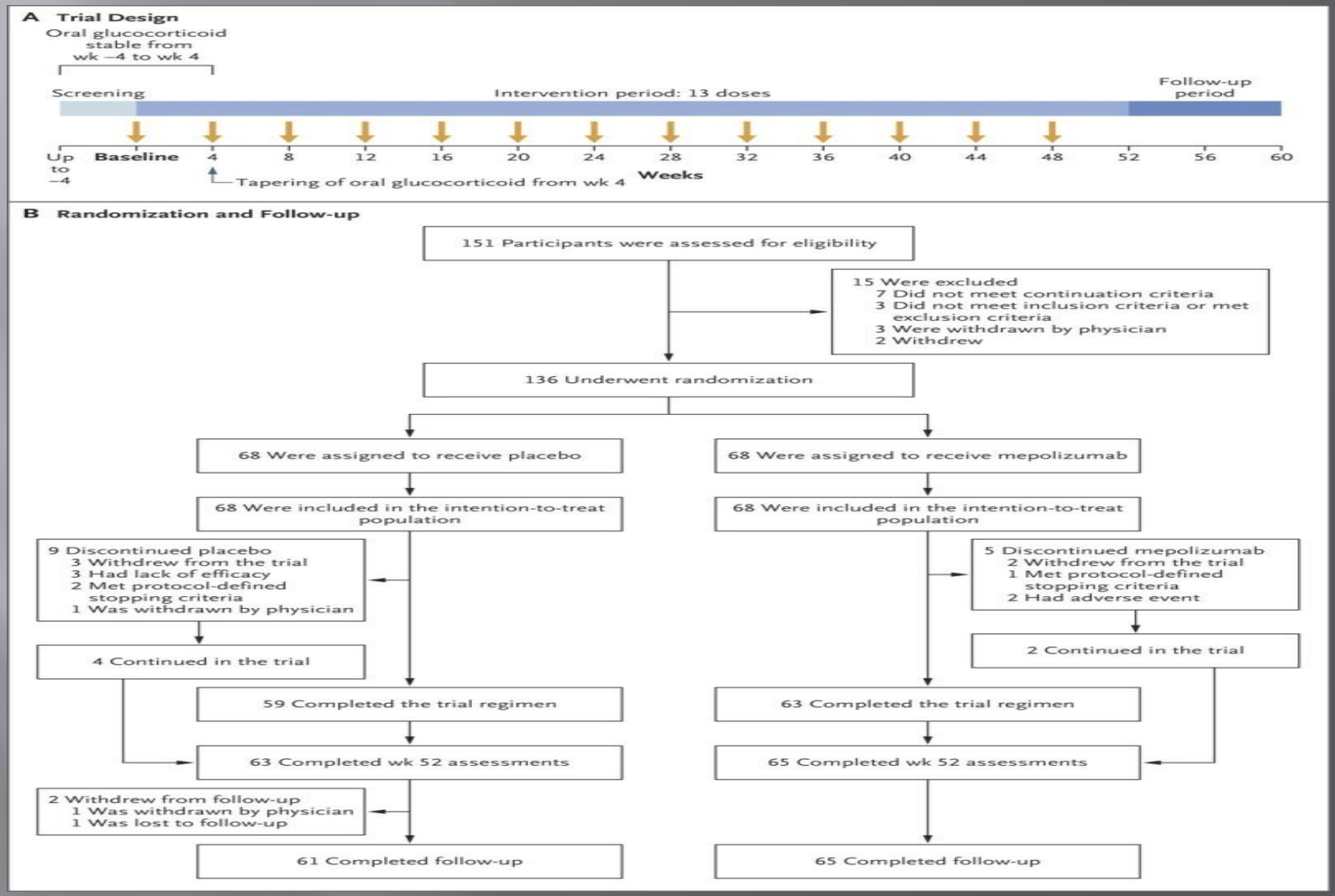
It is classified as vasculitis of the small and medium size arteries.

Asthma is present in more than 90% of the patients.

IL-5


Eosinophil
IL-5-triggered eosinophilia
IL-5
IgE
FcεRI
Release of soluble mediators
Smooth-muscle cell
Increased contractility
Mast cell
IL-9
Basophil
Epithelial cell
'Weep and sweep' response
Increased permeability
T$_H$2 cell
IL-4 and IL-13
RELMβ secretion
Mucus secretion
Goblet cell
IgE production
Class switching
B cell
Arginase-1 expression
IL-21
Macrophage
AAM
Fibrosis and production of ChaFFs
IL-25
T$_H$2-type cytokine production
c-KIT$^+$FcεRI$^-$ granulocyte
Nature Reviews | Immunology

Trial Design and Randomization and Follow-up of the Participants.



Wechsler ME et al. N Engl J Med 2017;376:1921-1932

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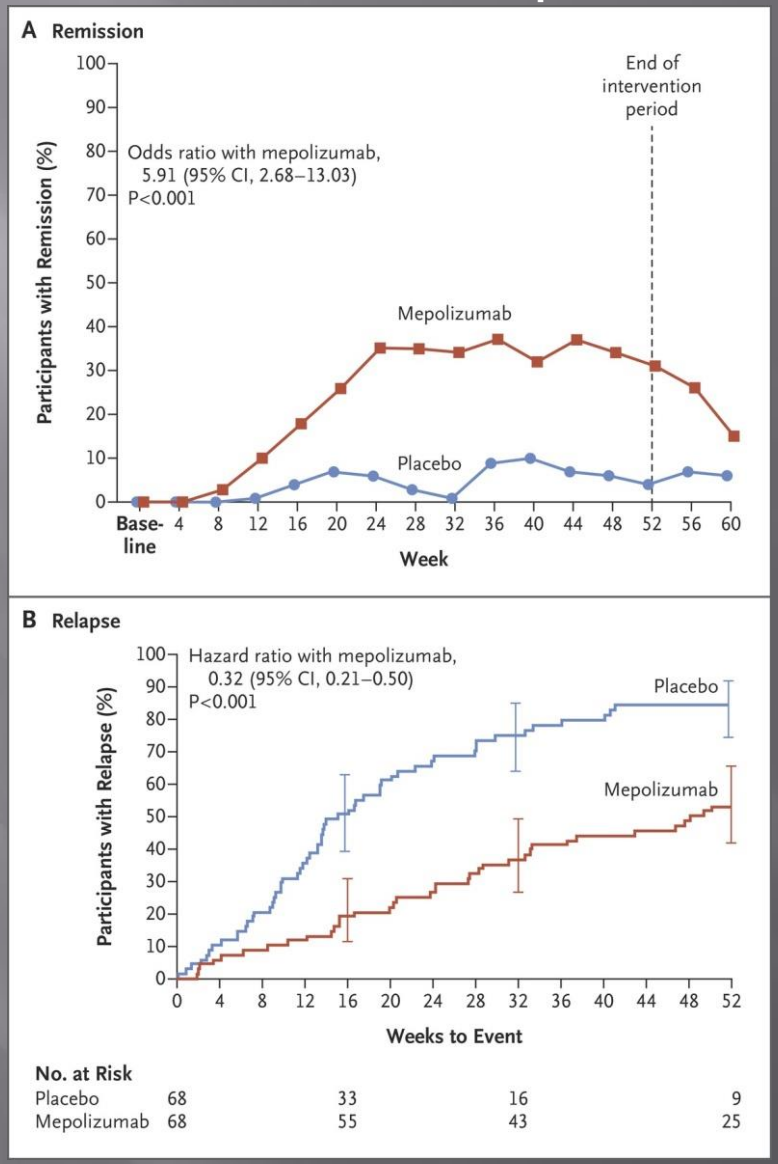
Remission and First Relapse of Eosinophilic Granulomatosis with Polyangiitis in the Intention-to-Treat Population.



Wechsler ME et al. N Engl J Med 2017;376:1921-1932

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Demographic Characteristics and Diagnostic and Baseline Characteristics of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in the Intention-to-Treat Population.

Table 1. Demographic Characteristics and Diagnostic and Baseline Characteristics of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in the Intention-to-Treat Population.*

Characteristic	Mepolizumab (N=68)	Placebo (N=68)
Age — yr	49±12	48±14
Male sex — no. (%)	26 (38)	30 (44)
ANCA-positive status — no. (%)†	7 (10)	6 (9)
Absolute eosinophil count per cubic millimeter‡	177±1.29	172±1.35
BVAS >0 — no. (%)§	37 (54)	48 (71)
Prednisolone or prednisone dose — mg/day		
Median	12.0	11.0
Range	7.5–40.0	7.5–50.0
Immunosuppressive therapy at baseline — no. (%)	41 (60)	31 (46)
EGPA diagnostic disease characteristics — no. (%)		
Asthma with eosinophilia	68 (100)	68 (100)
Biopsy evidence¶	25 (37)	31 (46)
Neuropathy‖	32 (47)	24 (35)
Nonfixed pulmonary infiltrates	50 (74)	48 (71)
Sinonasal abnormality	64 (94)	64 (94)
Cardiomyopathy**	13 (19)	7 (10)
Glomerulonephritis	1 (1)	0
Alveolar hemorrhage	3 (4)	1 (1)
Palpable purpura	9 (13)	8 (12)
ANCA-positive status	13 (19)	13 (19)
Relapsing disease — no. (%)	51 (75)	49 (72)
Refractory disease — no. (%)	34 (50)	40 (59)
Duration since diagnosis of EGPA — yr	5.2±4.4	5.9±4.9
Immunosuppressive therapy since diagnosis — no. (%)	56 (82)	49 (72)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. Demographic characteristics were assessed at visit 2.
† Positive antineutrophil cytoplasmic antibody (ANCA) status for myeloperoxidase or proteinase 3 was assessed by means of immunoassay performed at the Covance laboratory and Q^2 Solutions.
‡ The absolute eosinophil count is presented as geometric means with standard deviation logs.
§ The Birmingham Vasculitis Activity Score (BVAS) was assessed on a scale from 0 to 63, with higher scores indicating greater disease activity.
¶ Biopsy evidence was defined as a biopsy specimen showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation.
‖ Neuropathy was defined as mononeuropathy or polyneuropathy (motor deficit or nerve-conduction abnormality).
** The presence of cardiomyopathy was established by means of echocardiography or magnetic resonance imaging.

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Efficacy End Points in the Intention-to-Treat Population.

Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Mepolizumab (N=68)	Placebo (N=68)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Primary end points				
Accrued weeks of remission over 52-wk period			5.91 (2.68–13.03)	<0.001
0 wk	32 (47)	55 (81)		
>0 to <12 wk	8 (12)	8 (12)		
12 to <24 wk	9 (13)	3 (4)		
24 to <36 wk	10 (15)	0		
≥36 wk	9 (13)	2 (3)		
Remission at wk 36 and wk 48	22 (32)	2 (3)	16.74 (3.61–77.56)	<0.001
Other end points				
Remission within the first 24 wk that was sustained until wk 52	13 (19)	1 (1)	19.65 (2.30–167.93)	0.007
First EGPA relapse	38 (56)	56 (82)	0.32 (0.21–0.50)	<0.001

* Odds ratios are shown for the analyses of the two primary end points and for the secondary analysis of remission within the first 24 weeks that was sustained until week 52. For the analysis of accrued weeks in remission, the odds ratio is for 24 or more weeks of accrued remission. Remission was defined as a BVAS of 0 (on a scale from 0 to 63, with higher scores indicating greater disease activity) and a prednisolone or prednisone dose of 4.0 mg or less per day. For the time-to-event analysis of the first relapse of EPGA, the hazard ratio is shown. Participants with a first EGPA relapse were those who had a relapse before the completion of the planned trial period or who withdrew prematurely from the trial.

Wechsler ME et al. N Engl J Med 2017;376:1921-1932

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Adverse Events and Serious Adverse Events.

Table 3. Adverse Events and Serious Adverse Events.*

Event	Mepolizumab (N=68)	Placebo (N=68)
	no. of participants (%)	
Adverse event		
Any event	66 (97)	64 (94)
Event considered by the investigator to be related to the trial agent	35 (51)	24 (35)
Event leading to trial-agent discontinuation or trial withdrawal	2 (3)	1 (1)
Death	1 (1)†	0
Serious adverse event‡		
Any event	12 (18)	18 (26)
Event considered by the investigator to be related to the trial agent	3 (4)	3 (4)
Systemic or local-site reaction§		
Systemic reaction	4 (6)	1 (1)
Local-site reaction	10 (15)	9 (13)
Anaphylaxis considered by the investigator to be related to the trial agent	0	0
Cardiovascular adverse event¶		
Arrhythmia	2 (3)	3 (4)
Stroke or TIA	1 (1)	0
Congestive heart failure	0	1 (1)
Myocardial infarction or unstable angina	1 (1)	1 (1)

* There were no significant between-group differences. TIA denotes transient ischemic attack.
† The event (cardiac arrest) was not considered by the physician to be related to the trial regimen.
‡ Serious adverse events were defined as any untoward medical occurrence that resulted in death, was life-threatening, resulted in hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, was a congenital anomaly or birth defect, or was indicative of possible drug-induced liver injury with hyperbilirubinemia.
§ Systemic or local-site reactions were identified by means of an electronic case-report form that was designed for the collection of data on systemic reactions.
¶ Cardiovascular adverse events were identified by means of an electronic case-report form that was designed for the collection of data on cardiovascular events.

Wechsler ME et al. N Engl J Med 2017;376:1921-1932

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Conclusions

- In participants with eosinophilic granulomatosis with polyangiitis, mepolizumab resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thus allowing for reduced glucocorticoid use.
- Even so, only approximately half the participants treated with mepolizumab had protocol-defined remission.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article: Brief Report

Interleukin-12 and Interleukin-23 Blockade in Leukocyte Adhesion Deficiency Type 1

Niki M. Moutsopoulos, D.D.S., Ph.D., Christa S. Zerbe, M.D., Teresa Wild, M.S., Nicolas Dutzan, D.D.S., Laurie Brenchley, R.D.H., Giovanni DiPasquale, Ph.D., Gulbu Uzel, M.D., Karen C. Axelrod, R.N., Andrea Lisco, M.D., Lucia D. Notarangelo, M.D., George Hajishengallis, D.D.S., Ph.D., Luigi D. Notarangelo, M.D., and Steven M. Holland, M.D.

N Engl J Med
Volume 376(12):1141-1146
March 23, 2017

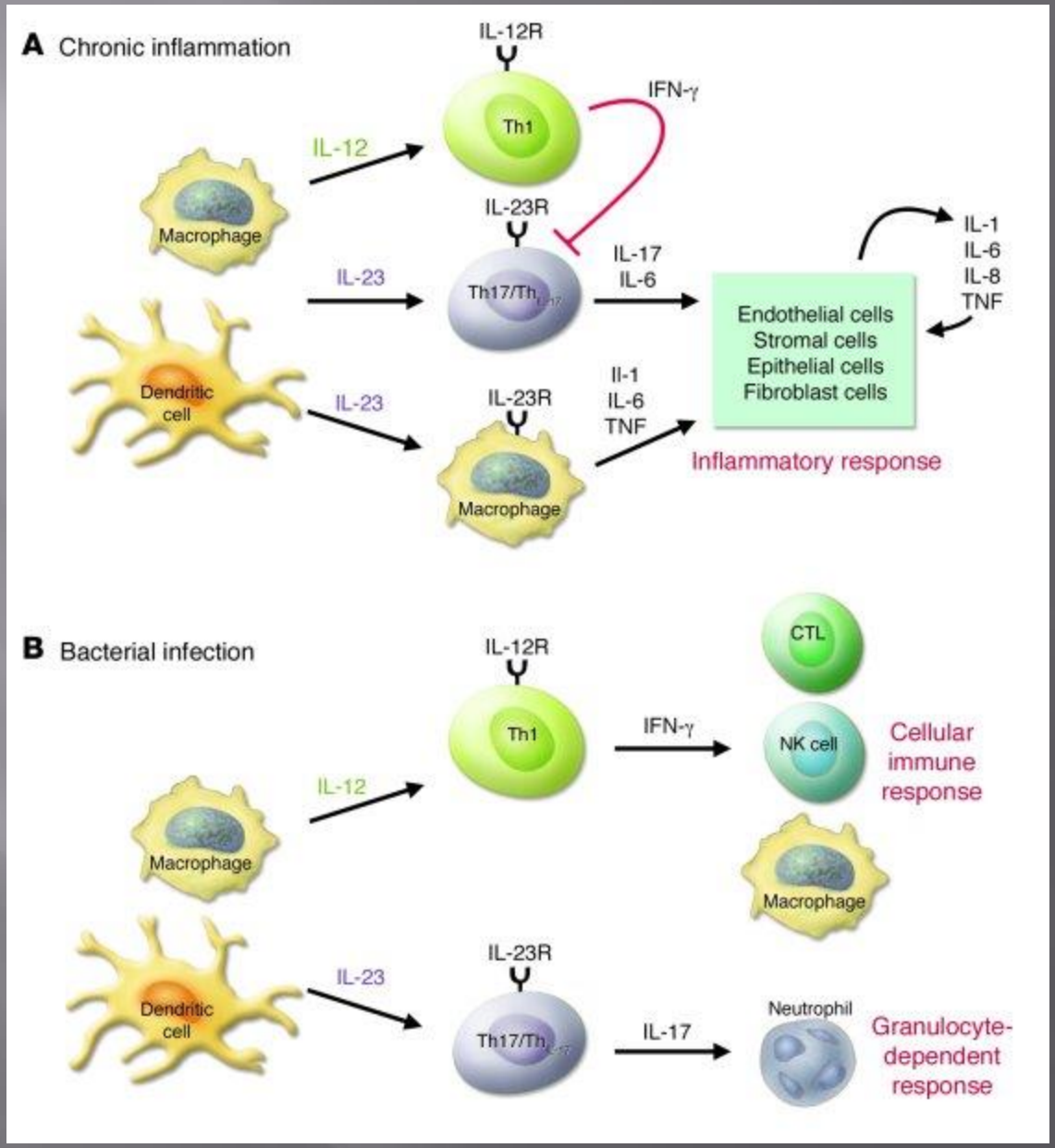
The NEW ENGLAND JOURNAL of MEDICINE

Leukocyte Adhesion Deficiency

- Leukocytes need to get to the site of inflammation. As such they have to get from the bloodstream to the tissues. This involves several steps in the adhesion cascade.
- Adhesion molecules are expressed on endothelial cells and leukocytes.
- There are three leukocyte adhesion molecules designated LAD 1, II, and III

LAD I

- In LAD I the beta-2 integrin is deficient or defective
- Integrins are mainly responsible for adhesion of leukocytes to endothelial cells


A Chronic inflammation
IL-12R
Th1
IFN-γ
IL-12
Macrophage
IL-23R
IL-23
Th17/Th17
IL-17
IL-6
IL-1
IL-6
IL-8
TNF
Endothelial cells
Stromal cells
Epithelial cells
Fibroblast cells
Dendritic cell
IL-23
IL-23R
Il-1
IL-6
TNF
Macrophage
Inflammatory response
B Bacterial infection
IL-12R
Th1
IFN-γ
CTL
NK cell
Cellular immune response
IL-12
Macrophage
Macrophage
IL-23R
IL-23
Dendritic cell
Th17/Th17
IL-17
Neutrophil
Granulocyte-dependent response

Study Overview

- A 19-year-old man with leukocyte adhesion deficiency type 1 had severe periodontitis and a chronic open sacral wound that were corrected by periodic administration of ustekinumab, an antibody to interleukin-12 and interleukin-23 signaling.

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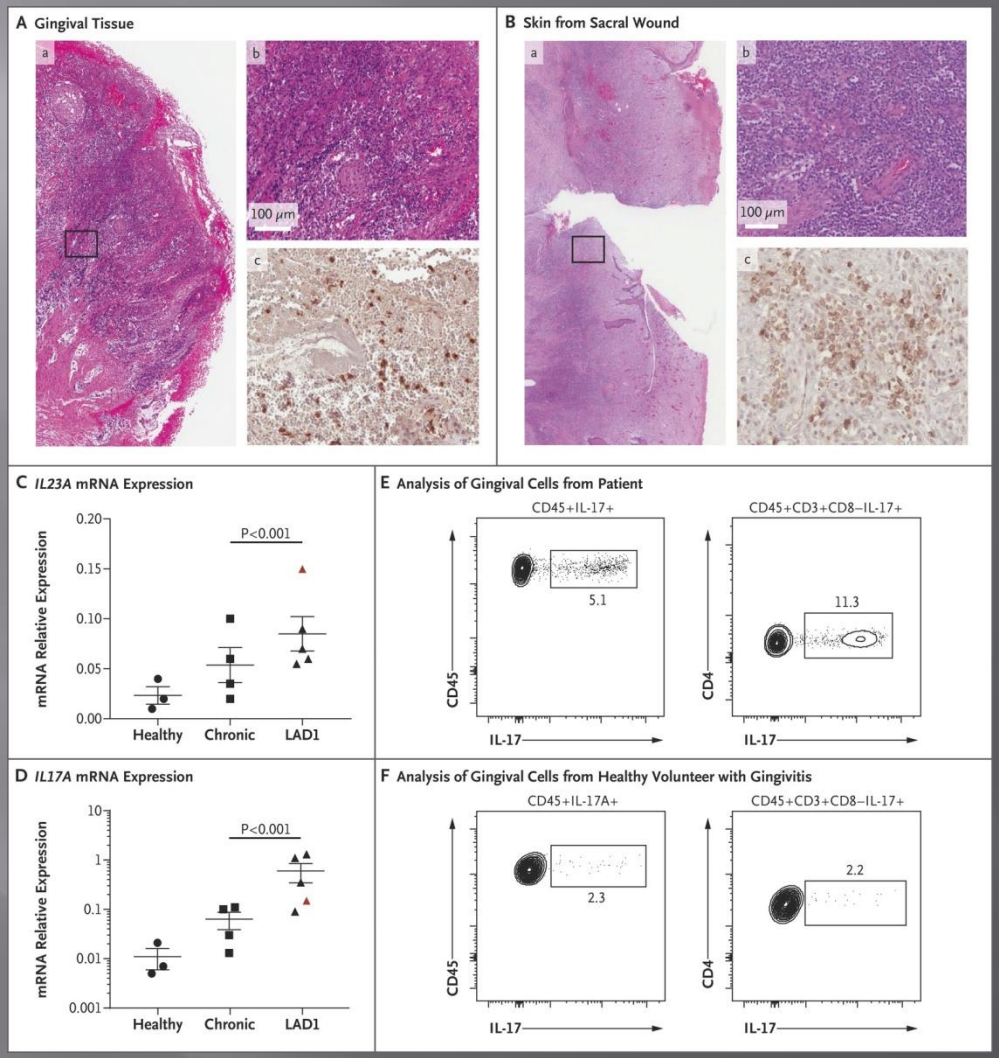
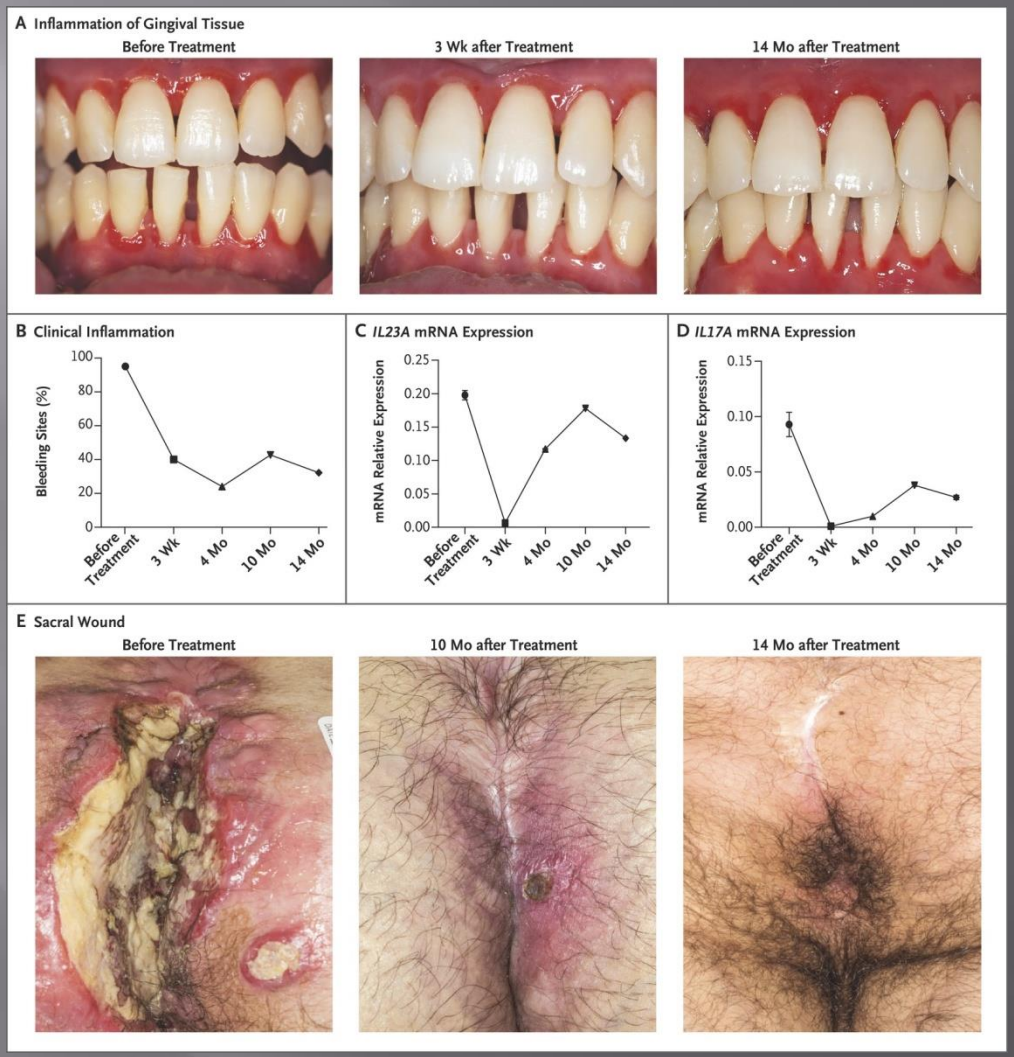
Interleukin-17–Dominated Inflammation in Leukocyte Adhesion Deficiency Type 1 (LAD1).



Moutsopoulos NM et al. N Engl J Med 2017;376:1141-1146

The NEW ENGLAND JOURNAL of MEDICINE

Response to Ustekinumab Treatment.



Moutsopoulos NM et al. N Engl J Med 2017;376:1141-1146

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

Thomas Ruzicka, M.D., Jon M. Hanifin, M.D., Masutaka Furue, M.D., Ph.D., Grazyna Pulka, M.D., Izabela Mlynarczyk, M.D., Andreas Wollenberg, M.D., Ryszard Galus, M.D., Ph.D., Takafumi Etoh, M.D., Ryosuke Mihara, M.S., Hiroki Yoshida, M.S., Jonathan Stewart, M.B., Ch.B., Kenji Kabashima, M.D., Ph.D., for the XCIMA Study Group

N Engl J Med
Volume 376(9):826-835
March 2, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In a phase 2, placebo-controlled trial, nemolizumab, an antibody against interleukin-31 receptor A, reduced pruritus in patients with moderate-to-severe atopic dermatitis.
- These findings support the role of interleukin-31 in the pathophysiology of atopic dermatitis.

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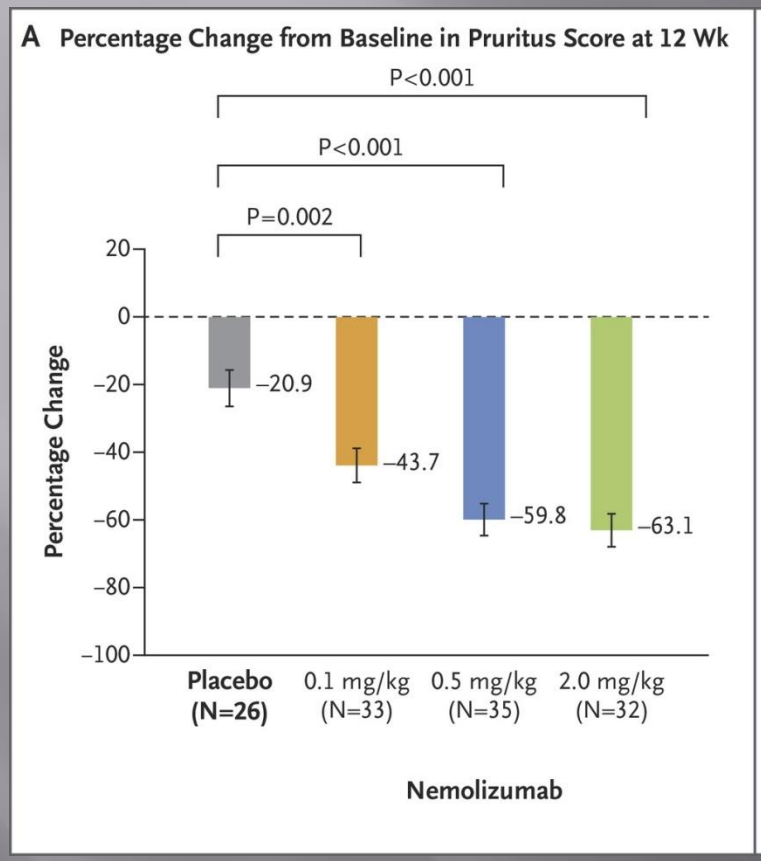
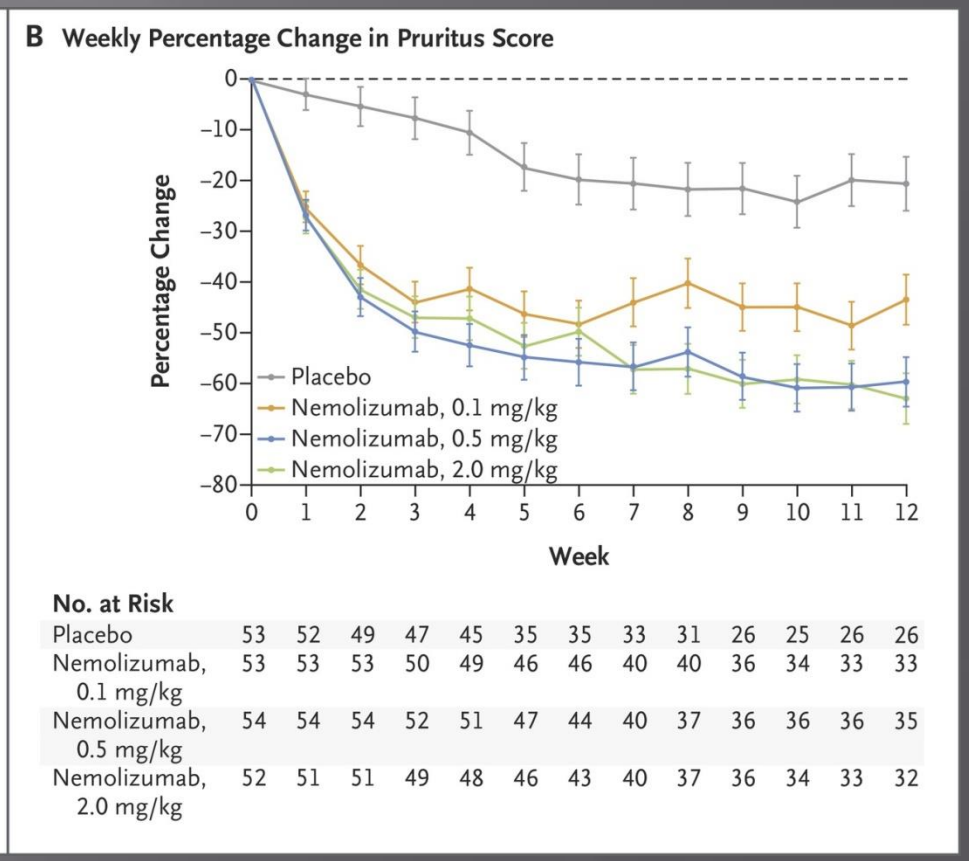
Percentage Change from Baseline in Pruritus Scores.





No. at Risk

Placebo	53	52	49	47	45	35	35	33	31	26	25	26	26
Nemolizumab, 0.1 mg/kg	53	53	53	50	49	46	46	40	40	36	34	33	33
Nemolizumab, 0.5 mg/kg	54	54	54	52	51	47	44	40	37	36	36	36	35
Nemolizumab, 2.0 mg/kg	52	51	51	49	48	46	43	40	37	36	34	33	32

Ruzicka T et al. N Engl J Med 2017;376:826-835

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Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).

Table 1. Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo (N=53)	Nemolizumab			
		0.1 mg/kg (N=53)	0.5 mg/kg (N=54)	2.0 mg/kg (N=52)	2.0 mg/kg Every 8 Wk (N=52)
Male sex — no. (%)	25 (47)	28 (53)	22 (41)	31 (60)	29 (56)
Age — yr	37.0±13.1	33.5±10.3	33.7±11.7	34.4±11.9	35.8±13.6
Region — no. (%)					
United States	12 (23)	12 (23)	12 (22)	11 (21)	12 (23)
Europe	25 (47)	25 (47)	26 (48)	25 (48)	25 (48)
Japan	16 (30)	16 (30)	16 (30)	16 (31)	15 (29)
Weight — kg	74.1±22.2	73.9±22.1	72.3±19.4	71.6±15.9	71.9±19.7
Body-mass index†	26.2±7.0	25.4±6.3	25.6±6.4	24.8±5.1	25.4±6.2
Score on pruritus visual-analogue scale — mm‡	75.1±11.9	75.2±12.0	75.8±12.7	76.2±11.4	78.0±11.8
EASI score§	29.0±14.0	32.4±16.1	28.6±15.0	28.2±12.3	29.0±14.9
Body-surface area affected — %	44.8±26.2	55.9±27.1	45.5±25.2	48.8±25.0	45.8±26.3
Score on static Investigator's Global Assessment — no. (%)¶					
3	27 (51)	22 (42)	24 (44)	24 (46)	25 (48)
4	22 (42)	18 (34)	25 (46)	25 (48)	22 (42)
5	4 (8)	13 (25)	5 (9)	3 (6)	5 (10)
Dermatology Life Quality Index‖	15.6±6.1	15.5±6.2	14.5±6.4	15.7±5.9	16.2±7.5
Sleep measurements**					
Sleep onset latency — min	34.1±35.9	40.8±40.9	35.9±46.8	44.5±44.7	36.7±33.0
Total sleep time — min	330.2±89.0	312.4±80.0	327.2±98.0	323.0±100.2	322.2±77.6
Sleep efficiency — %	71.4±14.3	67.3±13.7	70.0±17.2	68.1±15.5	69.7±15.0
Waking after sleep onset — min	78.8±37.8	86.1±44.9	77.7±44.2	78.7±35.6	78.3±39.2

* Plus–minus values are means ±SD. Nemolizumab or placebo was administered once every 4 weeks, unless otherwise indicated. There were no significant differences between the groups. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡§¶‖ Scores on the pruritus visual-analogue scale range from 0 (no itch) to 100 (worst imaginable itch).
Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating worse disease severity.
Scores on the static Investigator's Global Assessment range from 0 (clear) to 5 (very severe disease).
Scores on the Dermatology Life Quality Index range from 0 to 30, with higher scores indicating a lower quality of life.
** Sleep measurements were recorded by means of actigraphy, which documents whole-body movement and is a validated motion-detection method for recording sleep measurements, including total sleep time, sleep efficiency (total sleeping time divided by the total time in bed), sleep onset latency, and waking after sleep onset.

Ruzicka T et al. N Engl J Med 2017;376:826-835

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Changes from Baseline in Secondary Outcome Measures at 12 Weeks.

Table 2. Changes from Baseline in Secondary Outcome Measures at 12 Weeks.*

Outcome Measure	Placebo (N=53)	Nemolizumab		
		0.1 mg/kg (N=53)	0.5 mg/kg (N=54)	2.0 mg/kg (N=52)
Change in score on pruritus visual-analogue scale				
No. of patients	26	33	35	32
Percent change	−20.9±5.3	−43.7±4.9	−59.8±4.8	−63.1±5.0
Change in EASI score				
No. of patients	26	33	35	32
Percent change	−26.6±8.1	−23.0±7.5	−42.3±7.3	−40.9±7.5
Change in SCORAD score†				
No. of patients	23	27	30	27
Percent change	−18.5±5.2	−27.5±4.9	−37.7±4.8	−39.8±4.9
Improvement of ≥2 points in score on static Investigator's Global Assessment				
No. of patients	26	33	35	32
Patients with improvement — %	11	14	38	25
Change in body-surface area affected by atopic dermatitis				
No. of patients	26	33	35	32
Percent change	−15.7±10.5	−7.5±9.7	−20.0±9.6	−19.4±9.7
Change in sleep-disturbance score on visual-analogue scale‡				
No. of patients	26	33	34	32
Percent change	−31.9±6.3	−52.3±5.8	−59.1±5.8	−62.6±5.9

* Plus–minus values are means ±SE. Nemolizumab or placebo was administered once every 4 weeks in each group.
† Scores on Scoring Atopic Dermatitis (SCORAD) range from 0 to 103, with higher scores indicating greater disease severity. SCORAD assesses the extent and severity of signs of atopic dermatitis through area and intensity assessment by the investigator and subjective symptoms reported by the patient.
‡ Sleep-disturbance scores on the visual-analogue scale range from 0 to 100 mm, with higher scores indicating greater sleep disturbance.

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The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events (Safety Population).

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N=53)	Nemolizumab			
		0.1 mg/kg (N=53)	0.5 mg/kg (N=54)	2.0 mg/kg (N=52)	2.0 mg/kg Every 8 Wk (N=52)
Total no. of adverse events	105	110	80	99	90
Patients with ≥1 adverse event — no. (%)	36 (68)	38 (72)	36 (67)	40 (77)	37 (71)
Patients with ≥1 serious adverse event — no. (%)	1 (2)	1 (2)	0	3 (6)	2 (4)
Related to atopic dermatitis	0	0	0	2 (4)	1 (2)
Not related to atopic dermatitis	1 (2)	1 (2)	0	1 (2)	1 (2)
Patients with adverse event leading to withdrawal from treatment — no. (%)	1 (2)	5 (9)	3 (6)	4 (8)	3 (6)
Related to atopic dermatitis	0	2 (4)	3 (6)	2 (4)	3 (6)
Not related to atopic dermatitis	1 (2)	3 (6)	0	2 (4)	0
Exacerbation of atopic dermatitis — no. (%)†	7 (13)	11 (21)	10 (19)	11 (21)	9 (17)
Nasopharyngitis — no. (%)†	8 (15)	9 (17)	6 (11)	5 (10)	7 (13)
Upper respiratory tract infection — no. (%)†	6 (11)	4 (8)	1 (2)	4 (8)	5 (10)
Peripheral edema — no. (%)†	0	2 (4)	3 (6)	5 (10)	2 (4)
Elevation in blood creatine kinase — no. (%)†	3 (6)	2 (4)	2 (4)	4 (8)	3 (6)

* Nemolizumab or placebo was administered once every 4 weeks, unless otherwise indicated.
† This adverse event was reported in at least 5% of the patients who received nemolizumab.

Ruzicka T et al. N Engl J Med 2017;376:826-835

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Conclusions

- In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A.
- The limited size and length of the trial preclude conclusions regarding adverse events.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

Eric L. Simpson, M.D., Thomas Bieber, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Lisa A. Beck, M.D., Andrew Blauvelt, M.D., Michael J. Cork, M.B., Ph.D., Jonathan I. Silverberg, M.D., Ph.D., M.P.H., Mette Deleuran, M.D., D.M.Sc., Yoko Kataoka, M.D., Jean-Philippe Lacour, M.D., Külli Kingo, M.D., Ph.D., Margitta Worm, M.D., Yves Poulin, M.D., Andreas Wollenberg, M.D., Yuhwen Soo, Ph.D., Neil M.H. Graham, M.B., B.S., M.D., M.P.H., Gianluca Pirozzi, M.D., Ph.D., Bolanle Akinlade, M.D., Heribert Staudinger, M.D., Ph.D., Vera Mastey, M.S., Laurent Eckert, Ph.D., Abhijit Gadkari, Ph.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Marius Ardeleanu, M.D., for the SOLO 1 and SOLO 2 Investigators

N Engl J Med
Volume 375(24):2335-2348
December 15, 2016

Study Overview

- In two 16-week, placebo-controlled trials enrolling adults with moderate-to-severe atopic dermatitis, dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha, was effective in controlling the signs and symptoms of atopic dermatitis.

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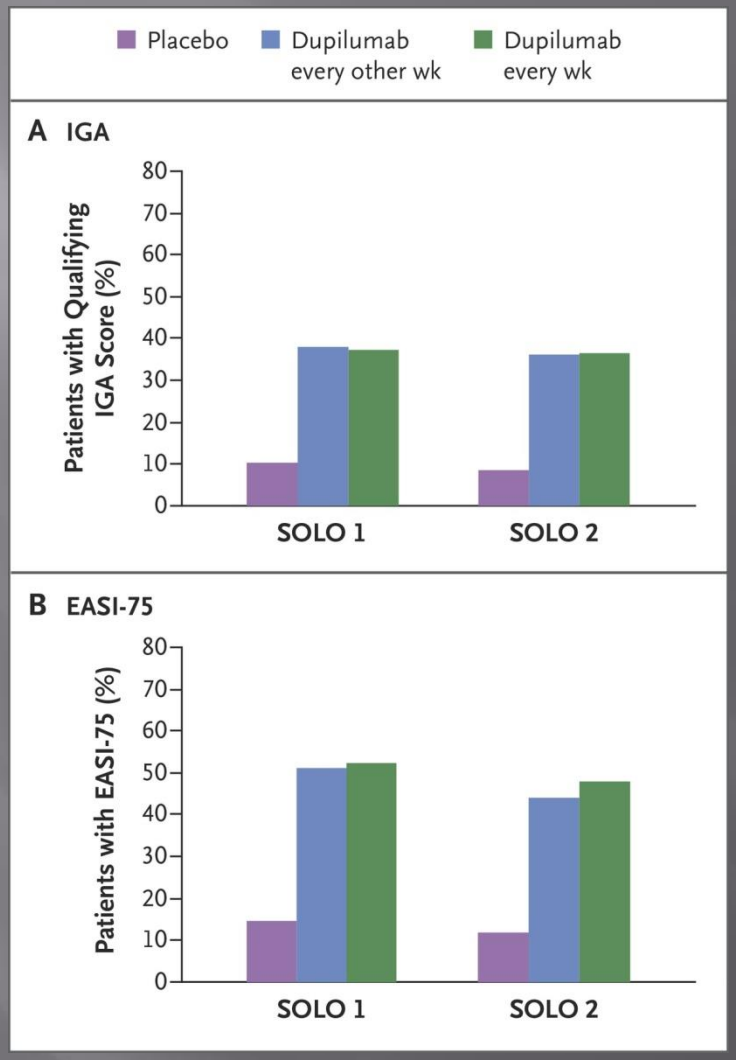
Primary End Point and Key Secondary End Point.



Simpson EL et al. N Engl J Med 2016;375:2335-2348

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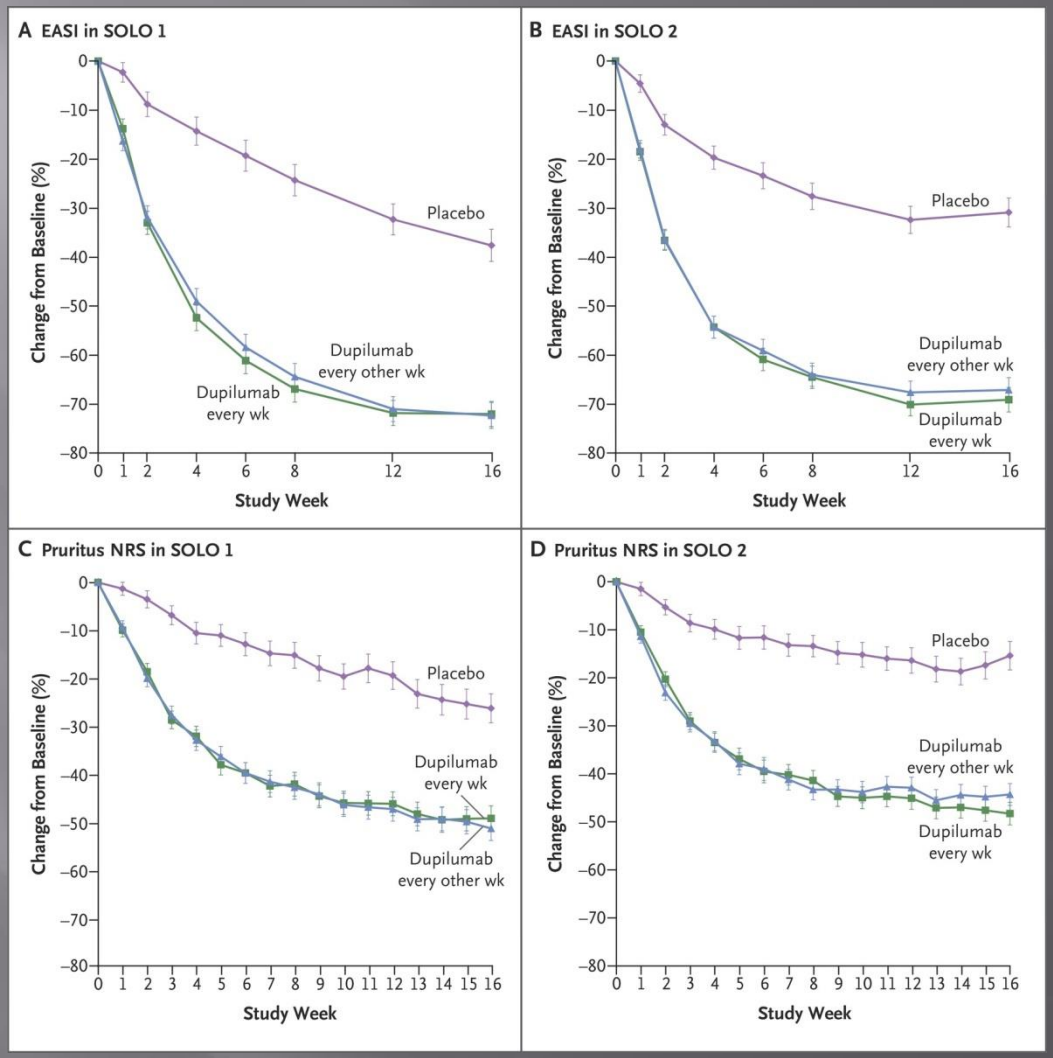
Secondary End Points.



Simpson EL et al. N Engl J Med 2016;375:2335-2348

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Demographic and Clinical Characteristics of the Patients at Baseline.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	SOLO 1			SOLO 2		
	Placebo (N=224)	Dupilumab Every Other Week (N=224)†	Dupilumab Every Week (N=223)	Placebo (N=236)	Dupilumab Every Other Week (N=233)†	Dupilumab Every Week (N=239)
Median age (IQR) — yr	39.0 (27.0–50.5)	38.0 (27.5–48.0)	39.0 (27.0–51.0)	35.0 (25.0–47.0)	34.0 (25.0–46.0)	35.0 (25.0–46.0)
Male sex — no. (%)	118 (53)	130 (58)	142 (64)	132 (56)	137 (59)	139 (58)
Race — no. (%)‡						
White	146 (65)	155 (69)	149 (67)	156 (66)	165 (71)	168 (70)
Black	16 (7)	10 (4)	20 (9)	20 (8)	13 (6)	15 (6)
Asian	56 (25)	54 (24)	51 (23)	50 (21)	44 (19)	45 (19)
Other or missing data	6 (3)	5 (2)	3 (1)	10 (4)	11 (5)	11 (5)
Median disease duration (IQR) — yr	28.0 (19.0–40.0)	26.0 (17.0–40.0)	26.0 (16.0–42.0)	26.0 (18.0–39.0)	24.5 (18.0–36.0)	24.0 (17.0–37.0)
Median affected body-surface area (IQR) — %	57.0 (37.4–77.0)	53.4 (37.4–72.5)	54.5 (39.0–73.0)	53.3 (34.0–72.8)	50.0 (36.0–68.0)	50.0 (34.0–69.0)
Median EASI score (IQR)§	31.8 (22.2–43.8)	30.4 (21.5–40.8)	29.8 (22.0–41.2)	30.5 (22.1–41.7)	28.6 (21.0–40.1)	29.0 (21.2–41.8)
IGA score of 4 — no. (%)¶	110 (49)	108 (48)	106 (48)	115 (49)	115 (49)	112 (47)
Median peak score on numerical rating scale for pruritus (IQR)‖	7.7 (6.2–8.6)	7.6 (5.9–8.7)	7.7 (6.0–8.7)	7.7 (6.5–9.0)	7.8 (6.7–8.9)	7.8 (6.3–8.9)
Median total SCORAD score (IQR)**	67.0 (58.0–77.6)	65.1 (56.5–77.4)	65.9 (57.2–75.8)	68.9 (58.6–78.5)	67.8 (57.3–76.7)	67.4 (58.4–77.9)
Median POEM score (IQR)††	21.0 (16.0–25.0)	21.0 (16.0–25.0)	22.0 (17.0–26.0)	23.0 (17.0–26.0)	21.0 (18.0–25.0)	21.0 (18.0–26.0)
Median DLQI score (IQR)‡‡	14.0 (9.0–20.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)	15.0 (9.0–22.0)	15.0 (10.0–21.0)	16.0 (10.0–22.0)
Median total HADS score (IQR)§§	12.0 (6.0–17.0)	11.0 (6.0–17.0)	12.0 (6.0–17.5)	12.0 (7.0–19.0)	13.0 (8.0–19.0)	14.0 (8.0–20.0)
HADS-A or HADS-D score ≥8 — no. (%)§§	97 (43)	100 (45)	102 (46)	115 (49)	129 (55)	136 (57)
Median GISS score (IQR)¶¶	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–11.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)
Previous history of eczema herpeticum — no. (%)	4 (2)	4 (2)	6 (3)	3 (1)	7 (3)	0

* There were no significant differences between the dupilumab groups and the placebo groups in any of the listed categories. IQR denotes interquartile range. Percentages may not total 100 because of rounding.

† In this regimen, dupilumab was administered every other week and placebo every other week to maintain blinding.

‡ The protocol did not specify how data on race should be collected.

§ Scores on the Eczema Area and Severity Index (EASI) range from 0 to 72, with higher scores indicating greater severity; a change of 6.6 has been estimated as the minimal clinically important difference (MCID).

¶ Scores on the Investigator's Global Assessment (IGA) scale range from 0 to 4, with higher scores indicating greater severity; the MCID for this scale has not been determined.

‖ The peak score on the numerical rating scale for pruritus is a patient-reported measure that assesses the maximum itch intensity in the previous 24 hours on a scale ranging from 0 to 10, with higher values indicating worse itching.

** Scoring Atopic Dermatitis (SCORAD) is a combined score of investigator-reported disease severity and affected body-surface area and patient-reported symptoms of itch and sleep dysfunction; scores range from 0 to 103, with higher scores indicating greater severity; a change of 8.7 has been estimated as the MCID.

†† The Patient-Oriented Eczema Measure (POEM), a composite measure of patient-reported symptoms including the effect of symptoms on sleep, evaluates the frequency of symptoms (including itching) and the effect of atopic dermatitis on sleep on a scale of 0 to 28, with higher scores indicating greater severity; a change of 4 has been estimated as the MCID.

‡‡ The Dermatology Life Quality Index (DLQI) evaluates health-related quality of life on a scale of 0 to 30, with higher scores indicating greater effect on quality of life. A change of 4 has been estimated as the MCID.

§§ The Hospital Anxiety and Depression Scale (HADS) measures patient-reported symptoms of anxiety and depression on a scale from 0 to 42; scores on HADS-A (measuring anxiety) and HADS-D (measuring depression) subscales range from 0 to 21, with higher scores indicating a greater burden of anxiety or depression symptoms; the MCID for this scale has not been determined. The recommended cutoff score for identifying patients with anxiety or depression is 8.

¶¶ The Global Individual Signs Score (GISS) is a cumulative score of ratings for individual components of lesions associated with atopic dermatitis (erythema, infiltration or papulation, excoriations, and lichenification); the cumulative score ranges from 0 to 12, with higher scores indicating greater severity; the MCID for this scale has not been determined.

Simpson EL et al. N Engl J Med 2016;375:2335-2348

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Efficacy Outcomes.

Table 2. Efficacy Outcomes.*

Outcome	SOLO 1†			SOLO 2†		
	Placebo (N=224)	Dupilumab Every Other Week (N=224)	Dupilumab Every Week (N=223)	Placebo (N=236)	Dupilumab Every Other Week (N=233)	Dupilumab Every Week (N=239)
IGA score of 0 or 1 and reduction of ≥2 points from baseline at week 16: primary outcome — no. (%)	23 (10)	85 (38)	83 (37)	20 (8)	84 (36)	87 (36)
Key secondary outcomes						
EASI-75 at wk 16 — no. (%)‡	33 (15)	115 (51)	117 (52)	28 (12)	103 (44)	115 (48)
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 16	−26.1±3.0	−51.0±2.5	−48.9±2.6	−15.4±3.0	−44.3±2.3	−48.3±2.4
Improvement in peak score on numerical rating scale for pruritus — no./total no. (%)						
≥4 points from baseline to wk 16§	26/212 (12)	87/213 (41)	81/201 (40)	21/221 (10)	81/225 (36)	89/228 (39)
≥3 points from baseline to wk 16 ¶	38/221 (17)	103/220 (47)	109/211 (52)	29/226 (13)	117/231 (51)	115/234 (49)
≥4 points from baseline to wk 4§	13/212 (6)	34/213 (16)‖	47/201 (23)	14/221 (6)	51/225 (23)	63/228 (28)
≥4 points from baseline to wk 2§	7/212 (3)	20/213 (9)**	19/201 (9)††	2/221 (1)	24/225 (11)	29/228 (13)
Other secondary outcomes						
Peak least-squares mean change from baseline in peak score on numerical rating scale for pruritus at wk 16	−2.03±0.21	−3.78±0.16	−3.72±0.17	−1.21±0.22	−3.30±0.16	−3.68±0.16
Least-squares mean percent change from baseline in EASI score at wk 16	−37.6±3.3	−72.3±2.6	−72.0±2.6	−30.9±3.0	−67.1±2.5	−69.1±2.5
EASI-50 at wk 16 — no. (%)	55 (25)	154 (69)	136 (61)	52 (22)	152 (65)	146 (61)
EASI-90 at wk 16 — no. (%)	17 (8)	80 (36)	74 (33)	17 (7)	70 (30)	73 (31)
Least-squares mean change from baseline in affected body-surface area at wk 16	−15.4±1.9	−33.4±1.4	−34.3±1.4	−12.6±1.6	−30.6±1.3	−32.1±1.3
Least-squares mean percent change from baseline in SCORAD score at wk 16	−29.0±3.2	−57.7±2.1	−57.0±2.1	−19.7±2.5	−51.1±2.0	−53.5±2.0
Least-squares mean change from baseline in DLQI score at wk 16	−5.3±0.5	−9.3±0.4	−9.0±0.4	−3.6±0.5	−9.3±0.4	−9.5±0.4
Least-squares mean change from baseline in POEM score at wk 16	−5.1±0.7	−11.6±0.5	−11.0±0.5	−3.3±0.6	−10.2±0.5	−11.3±0.5
Least-squares mean change from baseline in HADS total score at wk 16	−3.0±0.7	−5.2±0.5	−5.2±0.5	−0.8±0.4	−5.1±0.4	−5.8±0.4
Least-squares mean percent change from baseline in GISS score at wk 16	−26.4±3.3	−53.4±2.4	−52.0±2.4	−17.9±2.5	−45.6±2.1	−46.8±2.1
Least-squares mean percent change from baseline in peak score on numerical rating scale for pruritus at wk 2	−3.5±1.8	−19.9±1.7	−18.5±1.7	−5.3±1.6	−23.1±1.6	−20.3±1.6

* Plus–minus values are means ±SE. Unless otherwise indicated, efficacy analyses were performed in the full analysis set, which included all patients who underwent randomization. Within each dose regimen, the primary and secondary end points were tested with a hierarchical testing procedure with a prespecified order — in other words, inferential conclusions about successive end points required statistical significance of the previous end point at a 0.025 significance level. Most outcomes were assessed at scheduled trial visits.

† Unless otherwise indicated, P<0.001 for the comparison between each regimen of dupilumab and placebo.

‡ The EASI-75 at week 16 was the coprimary outcome in the European Union and Japan.

§ Included in this analysis were patients with a baseline peak score of at least 4 on the numerical rating scale for pruritus.

¶ Included in this analysis were patients with a baseline peak score of at least 3 on the numerical rating scale for pruritus.

‖ P=0.001 versus placebo.

** P=0.010 versus placebo.

†† P=0.009 versus placebo.

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Adverse Events.

Table 3. Adverse Events.*

Event	SOLO 1			SOLO 2		
	Placebo (N=222)	Dupilumab Every Other Week (N=229)	Dupilumab Every Week (N=218)	Placebo (N=234)	Dupilumab Every Other Week (N=236)	Dupilumab Every Week (N=237)
	number of patients (percent)					
Adverse or serious adverse event						
At least 1 adverse event	145 (65)	167 (73)	150 (69)	168 (72)	154 (65)	157 (66)
At least 1 serious adverse event	11 (5)	7 (3)	2 (1)	13 (6)	4 (2)	8 (3)
Death†	0	0	0	0	1 (<1)	1 (<1)
Adverse event leading to treatment discontinuation	2 (1)	4 (2)	4 (2)	5 (2)	2 (1)	3 (1)
Noninfectious adverse event‡						
Injection-site reaction	13 (6)	19 (8)	41 (19)	15 (6)	32 (14)	31 (13)
Exacerbation of atopic dermatitis	67 (30)	30 (13)	21 (10)	81 (35)	32 (14)	38 (16)
Headache	13 (6)	21 (9)	11 (5)	11 (5)	19 (8)	22 (9)
Allergic conjunctivitis	2 (1)	12 (5)	7 (3)	2 (1)	2 (1)	3 (1)
Infectious adverse event‡						
Infections and infestations§	63 (28)	80 (35)	74 (34)	76 (32)	65 (28)	68 (29)
Nasopharyngitis	17 (8)	22 (10)	25 (11)	22 (9)	20 (8)	20 (8)
Upper respiratory tract infection	5 (2)	6 (3)	11 (5)	5 (2)	7 (3)	9 (4)
Conjunctivitis¶	2 (1)	11 (5)	7 (3)	1 (<1)	9 (4)	9 (4)
Any herpes viral infection‖	9 (4)	15 (7)	9 (4)	8 (3)	10 (4)	12 (5)
Oral herpes	4 (2)	9 (4)	4 (2)	4 (2)	8 (3)	9 (4)
Herpes simplex	3 (1)	7 (3)	2 (1)	1 (<1)	0	1 (<1)
Eczema herpeticum	2 (1)	1 (<1)	1 (<1)	1 (<1)	2 (1)	0
Herpes virus infection	0	0	1 (<1)	1 (<1)	0	0
Herpes zoster	1 (<1)	1 (<1)	0	1 (<1)	0	0
Ophthalmic herpes simplex	0	0	1 (<1)	0	0	0
Genital herpes	1 (<1)	0	0	0	0	1 (<1)
Herpes ophthalmic	0	0	0	1 (<1)	0	1 (<1)
Herpes simplex otitis externa	0	0	0	0	1 (<1)	0
Adjudicated skin infection	18 (8)	13 (6)	14 (6)	26 (11)	13 (6)	15 (6)
Non-skin infection	49 (22)	69 (30)	67 (31)	57 (24)	58 (25)	61 (26)

* Patients are listed according to the study drug received, which may differ from the randomized group. Adverse events that were reported at the level of preferred terms occurred in at least 5% of the patients in any randomized group, with the exception that all adverse events with preferred terms related to herpes virus infection are reported here. Included in the safety analysis were all the patients who underwent randomization and received at least one dose of dupilumab or placebo.
† Details regarding the two deaths are provided in the Supplementary Appendix.
‡ Adverse events are reported at the preferred term level of the *Medical Dictionary for Regulatory Activities* (MedDRA) hierarchy, unless otherwise indicated.
§ This adverse event is reported at the system organ class level in the MedDRA hierarchy.
¶ This MedDRA preferred term includes conjunctivitis of unspecified cause.
‖ This adverse event is reported at the high-level term in the MedDRA hierarchy.

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Conclusions

- In two phase 3 trials of identical design involving patients with atopic dermatitis, dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo.
- Trials of longer duration are needed to assess the long-term effectiveness and safety of dupilumab.

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Questions?

Thank You