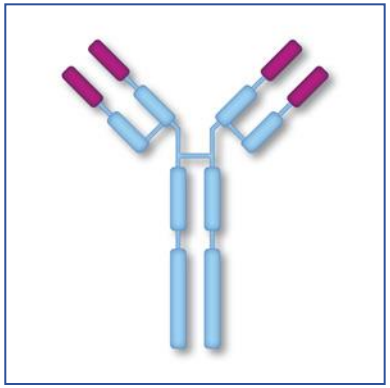
Pneumo Update Europe 2017

9-10 June, Vienna

Allergy



Stephen Durham, UK

Allergy: Outline

1. How does sublingual immunotherapy compare with pharmacotherapy for allergic rhinitis?

2. Is 2 years allergen immunotherapy sufficient for long-term tolerance?

3. Atopic dermatitis – novel biologic approaches.

4. Nasal polyps – novel biologic approaches.

5. Food allergy – is there a role for allergen immunotherapy?

Allergen Immunotherapy: State of the Art

Indications

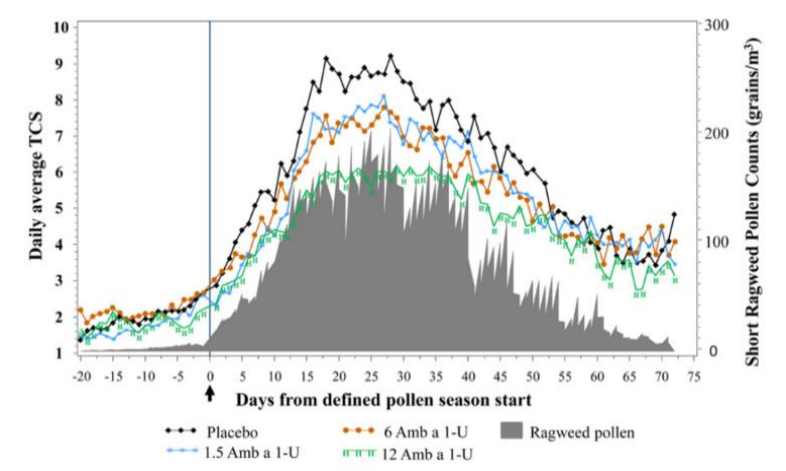
- Rhinoconjunctivitis with/without mild asthma
- *Symptoms on exposure* to relevant allergen
- *IgE sensitisation* to relevant allergen (SPT and /or Sp-IgE)
- Inadequate response to anti-allergic drugs
- Unacceptable drug side effects
- Polysensitisation not a contra-indication

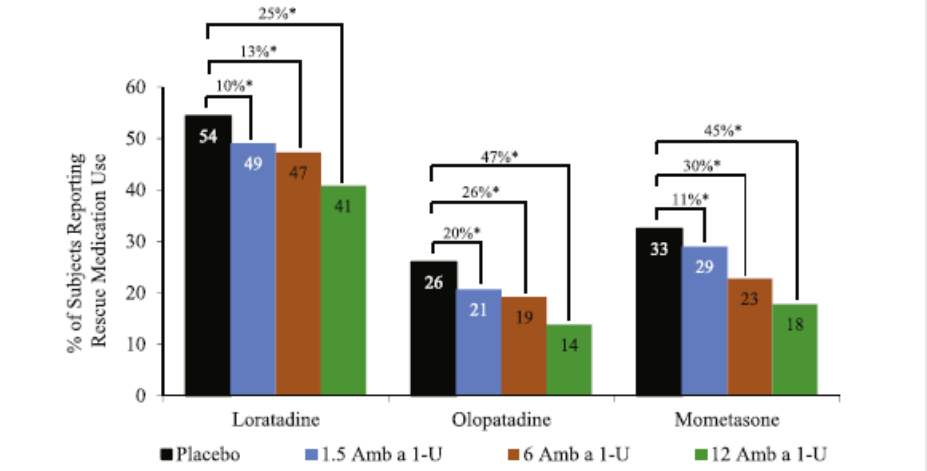
Contra-indications

- *Moderate-severe* asthma
- *Multiple* allergies
- Severe side effects with SCIT
- Autoimmune/Immunodeficiency disorders
- Malignancy
- Pregnancy (*continue maintenance SLIT OK*)
- Lack of understanding, poor adherence to treatment

Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults

Peter S. Creticos, MD,[a] Jennifer Maloney, MD,[b] David I. Bernstein, MD,[c] Thomas Casale, MD,[d] Amarjot Kaur, PhD,[b] Robert Fisher, MD,[e] Nancy Liu, PhD,[b] Kevin Murphy, MD,[f] Kristóf Nékám, MD,[g] and Hendrik Nolte, MD, PhD[b] *Baltimore, Md, Whitehouse Station, NJ, Cincinnati, Ohio, Omaha and Boys Town, Neb, Milwaukee, Wis, and Budapest, Hungary*

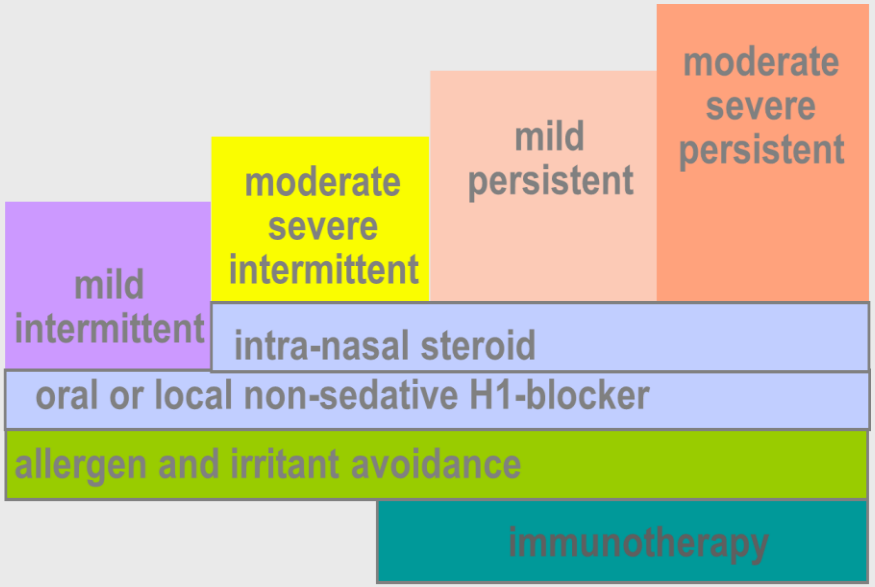




N= 784, 12 months treatment

J Allergy Clin Immunol 2013; 131: 1342-9

Treatment for Allergic Rhinitis



	SLIT SMD (95%CI)
	39*, n = 2,746
Symptoms	-0.49 (-0.64, -0.34)
Medication	-0.41 (-0.55, -0.28)

ARIA. Bousqet J et al JACI 2001; 108Suppl 5S147
ARIA Update Brozek et al JACI 2010;126: 466-76

Radulovic S et al, Allergy. 2011 Jun;66(6):740-52
Cochrane Database Syst Rev. 2011

1. How does sublingual immunotherapy compare with pharmacotherapy for allergic rhinitis

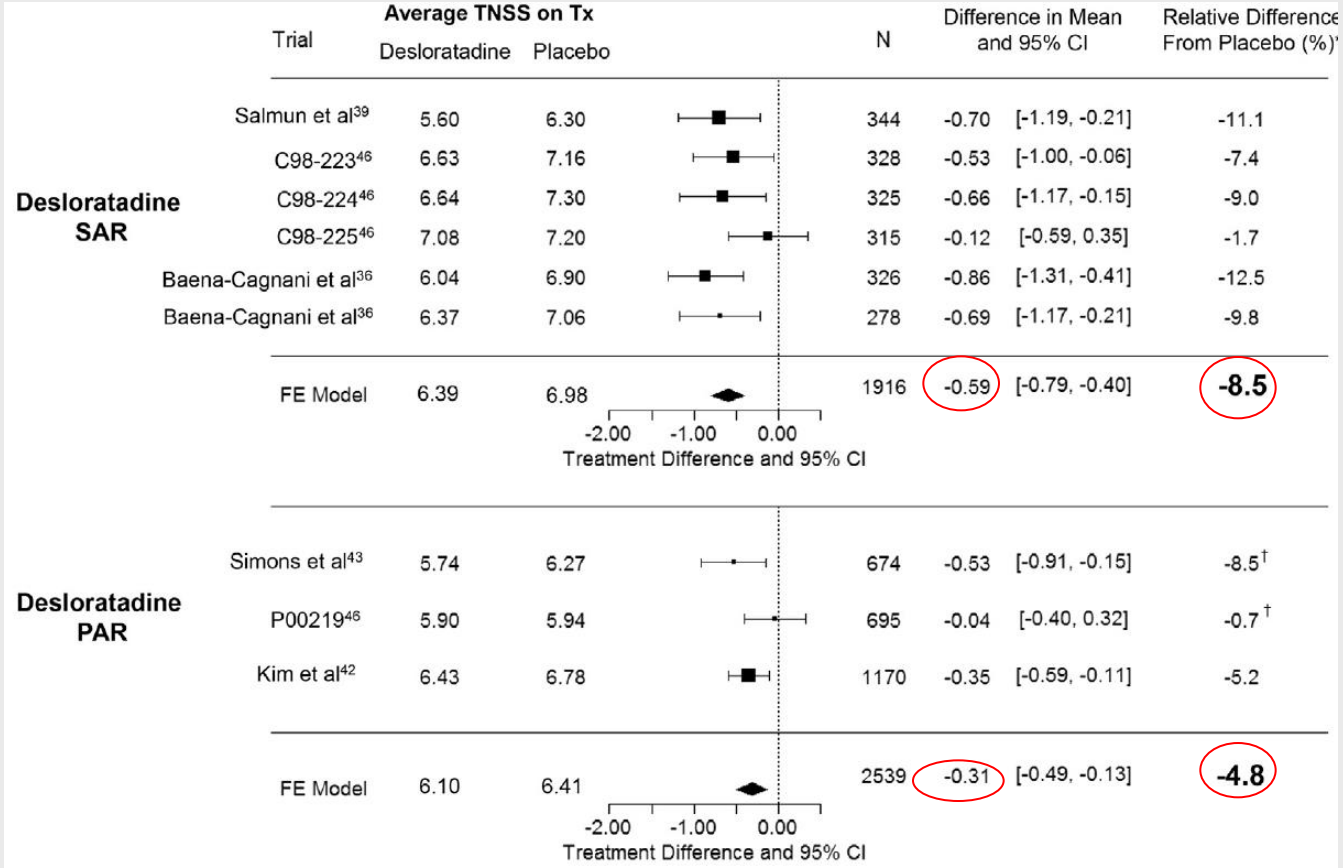
Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses

Durham SR, Creticos PS, Nelson HS, Li Z, Kaur A, Meltzer EO, Nolte H.
J Allergy Clin Immunol. 2016;138:1081-1088.

6 timothy grass SLIT-tablet trials	n=3094
2 ragweed SLIT-tablet trials	n=658
2 house dust mite SLIT-tablet trials	n=1768
7 montelukast 10mg trials	n=6799
9 desloratidine 5 mg trials	n=4455
8 mometasone furoate 200mcg trials	n=2140

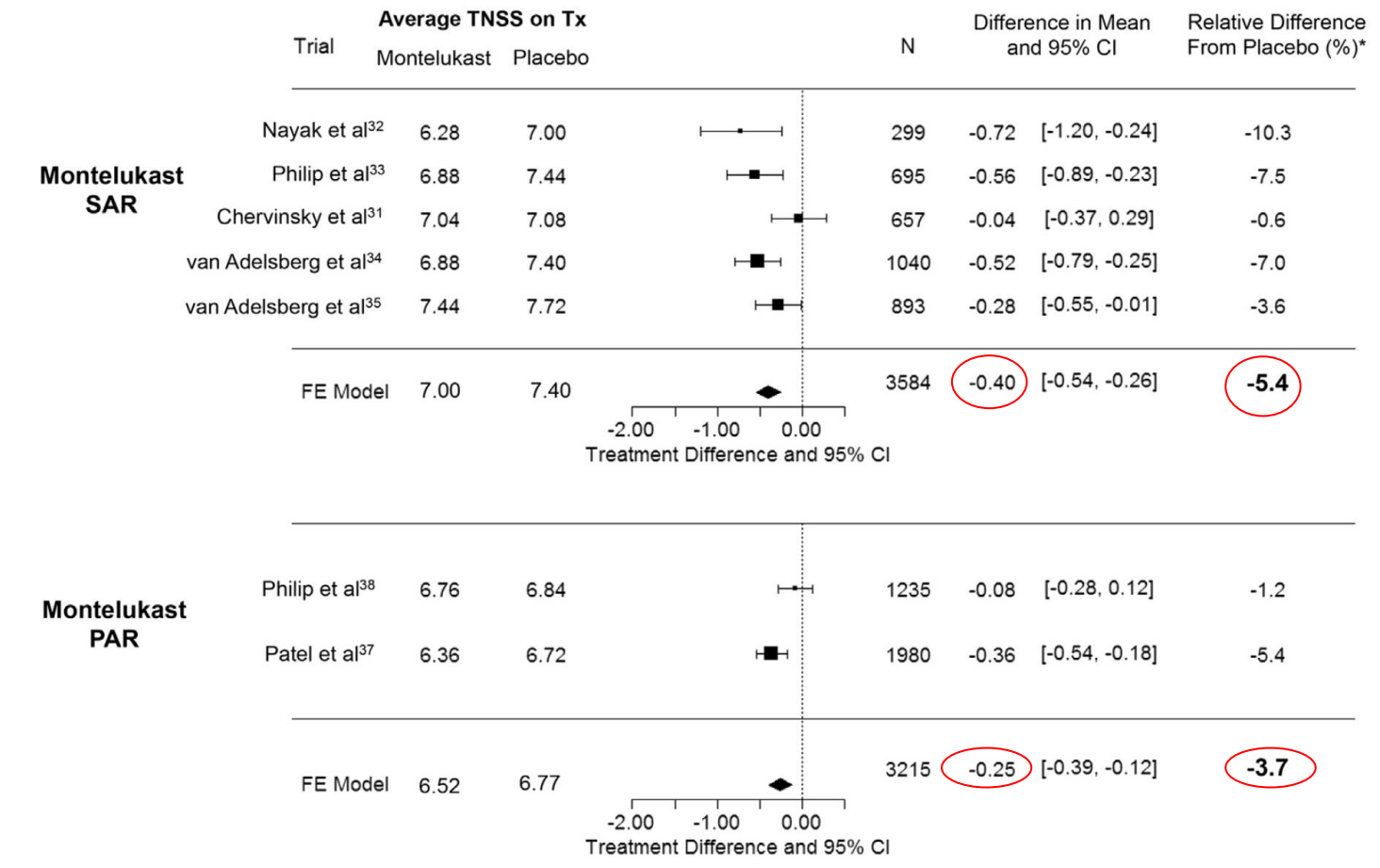
Primary endpoint: total nasal symptom score (TNSS, scale 0-12)
Fixed effects model

Antihistamine treatment in seasonal (SAR)and perennial (PAR) rhinitis



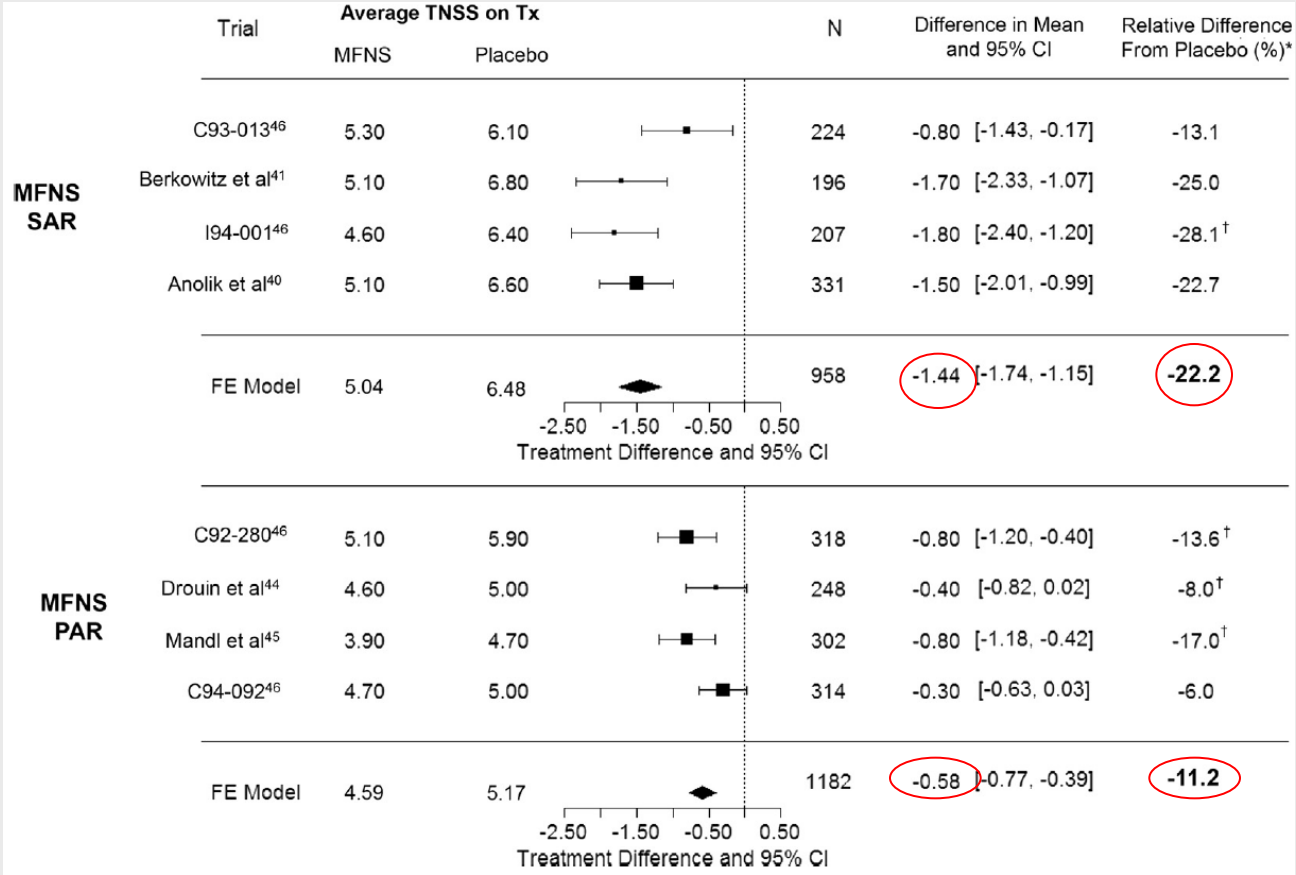
Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Montelukast treatment in allergic rhinitis SAR and PAR



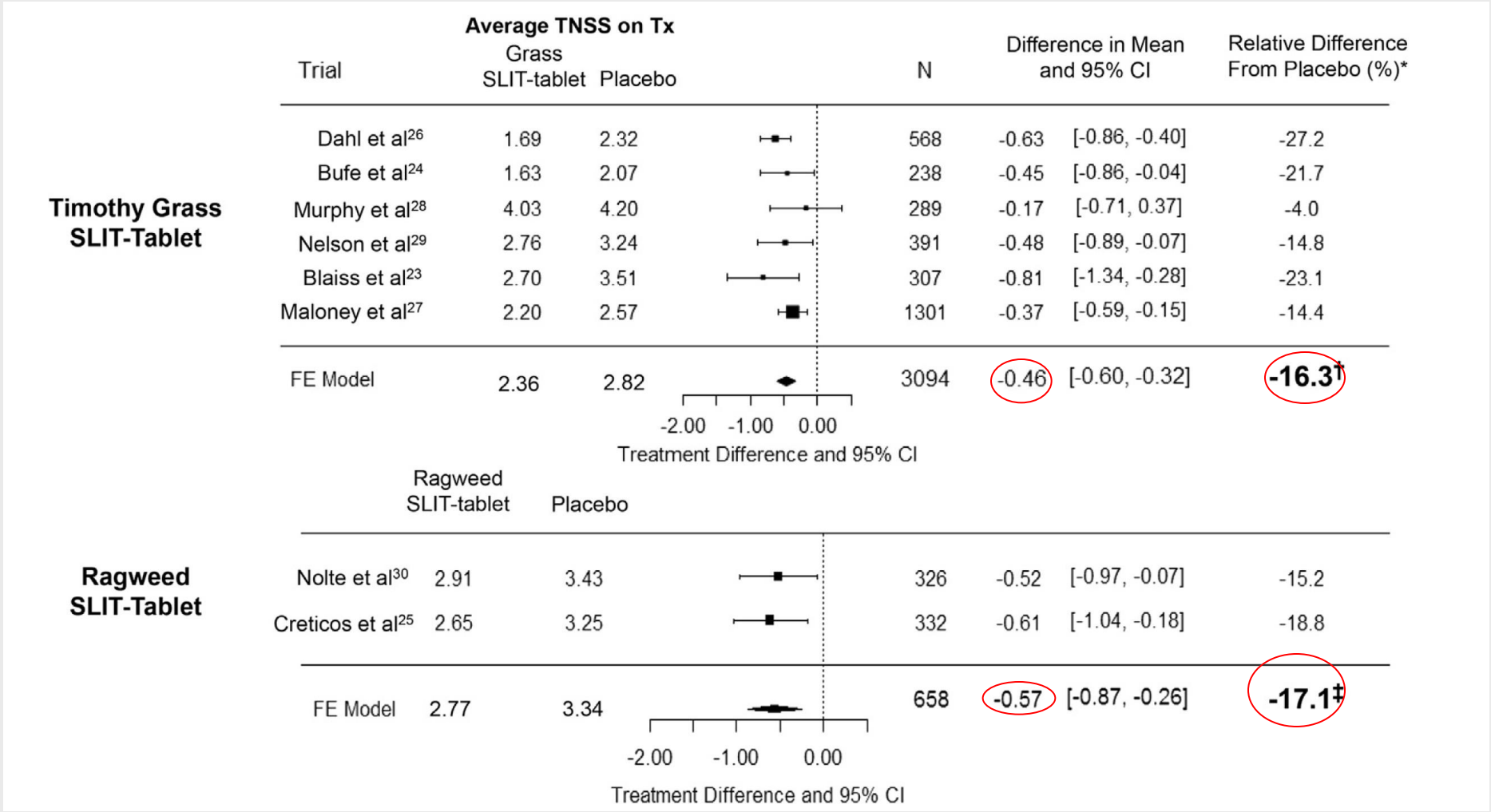
Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Nasal steroid treatment in allergic rhinitis (SAR and PAR)



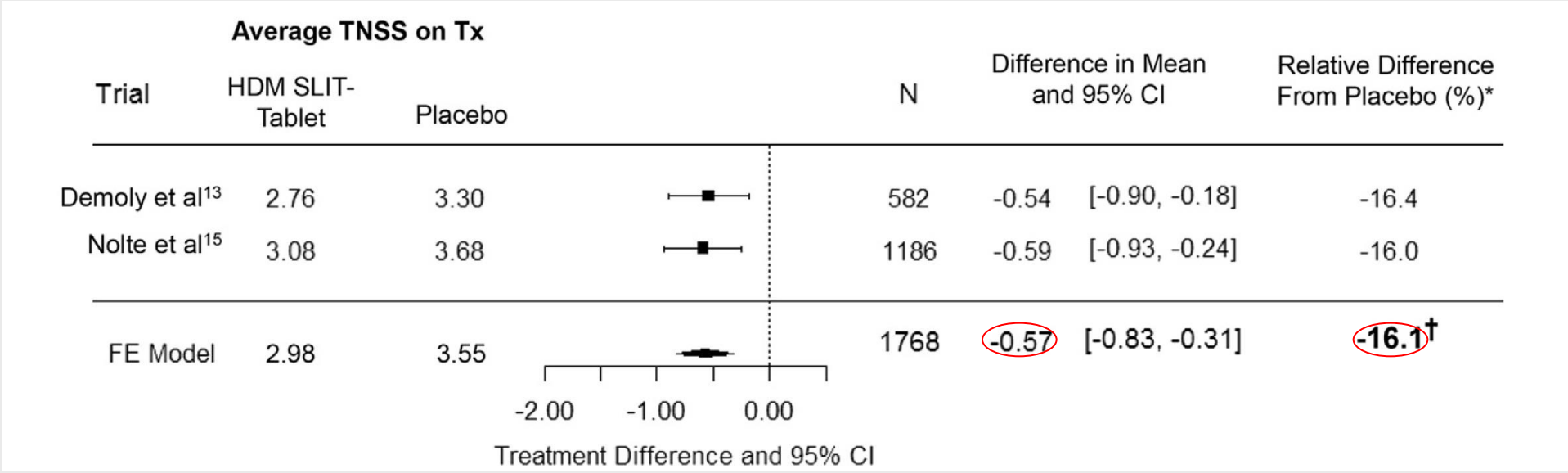
Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Sublingual tablet immunotherapy in seasonal allergic rhinitis (SAR)



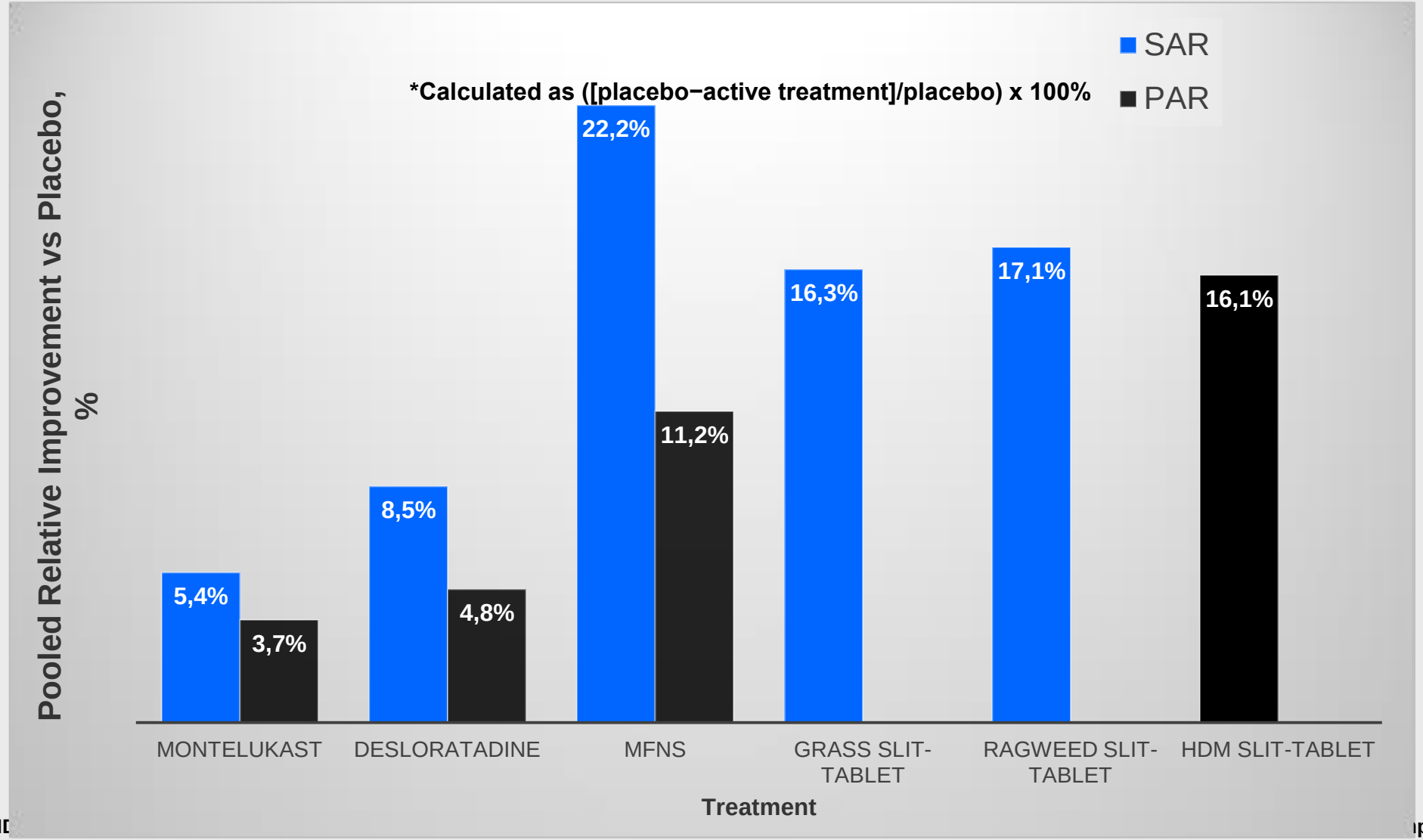
Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Sublingual tablet immunotherapy in HDM perennial allergic rhinitis (PAR)



Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses



Durham et al. J Allergy Clin Immunol. 2016;138:1081-1088.

Summary and Take-Home Message

- Indirect comparisons show that effect sizes with sublingual tablet IT compared to placebo were numerically higher than with an antihistamine, and a leukotriene antagonist and were comparable to an intranasal corticosteroid

- Treatment effect sizes with allergen immunotherapy (in contrast to anti-allergic drugs) compared to placebo have to be viewed on background use of rescue medication.

- These data support the complementary use of sublingual tablet immunotherapy in treatment of allergic rhinitis

- An additional benefit of sublingual IT is long-term effects after stopping treatment

Rhinitis, sinusitis, and upper airway disease

SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial

Stephen R. Durham, MD,[a] Waltraud Emminger, MD,[b] Alexander Kapp, MD, PhD,[c] Jan G. R. de Monchy, MD,[d] Sabina Rak, MD,[e] Glenis K. Scadding, MD, FRCP,[f] Peter A. Wurtzen, PhD,[g] Jens S. Andersen, PhD,[g] Bente Tholstrup, MSc,[g] Bente Riis, PhD,[g] and Ronald Dahl, MD[h] *London, United Kingdom, Vienna, Austria, Hannover, Germany, Groningen, The Netherlands, Gothenburg, Sweden, and Hørsholm and Aarhus, Denmark*

Adult male and female participants aged 18-65 yrs
(Year 1, n=634, Years 2-5, n=351 participants)

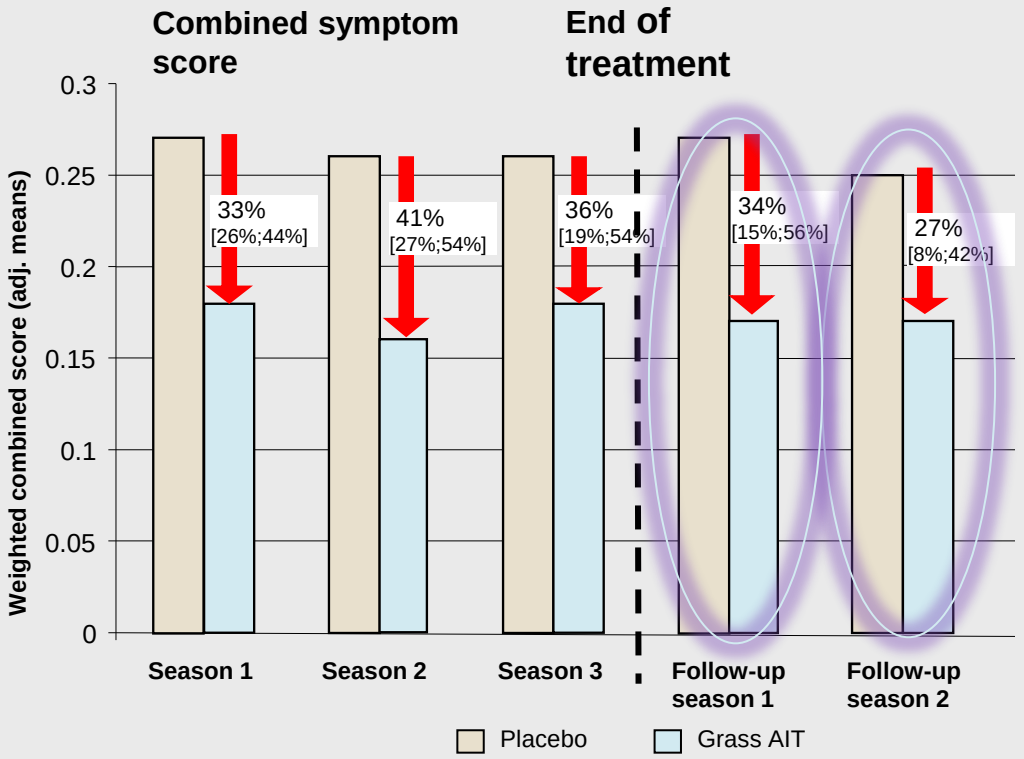
≥2 years of seasonal rhinoconjunctivitis

Severe symptoms, despite treatment with anti-allergic drugs during the grass pollen season

Positive *Phleum pratense* SPT (≥3mm,)
Specific IgE (≥ class 2)

FEV_1 ≥ 70% of predicted value

No symptoms due to adjacent or overlapping tree/weed pollen seasons or active perennial rhinitis



Durham et al. J Allergy Clin Immunol 2012;129: 717-725

2. Is two years allergen immunotherapy sufficient for long-term tolerance

Research

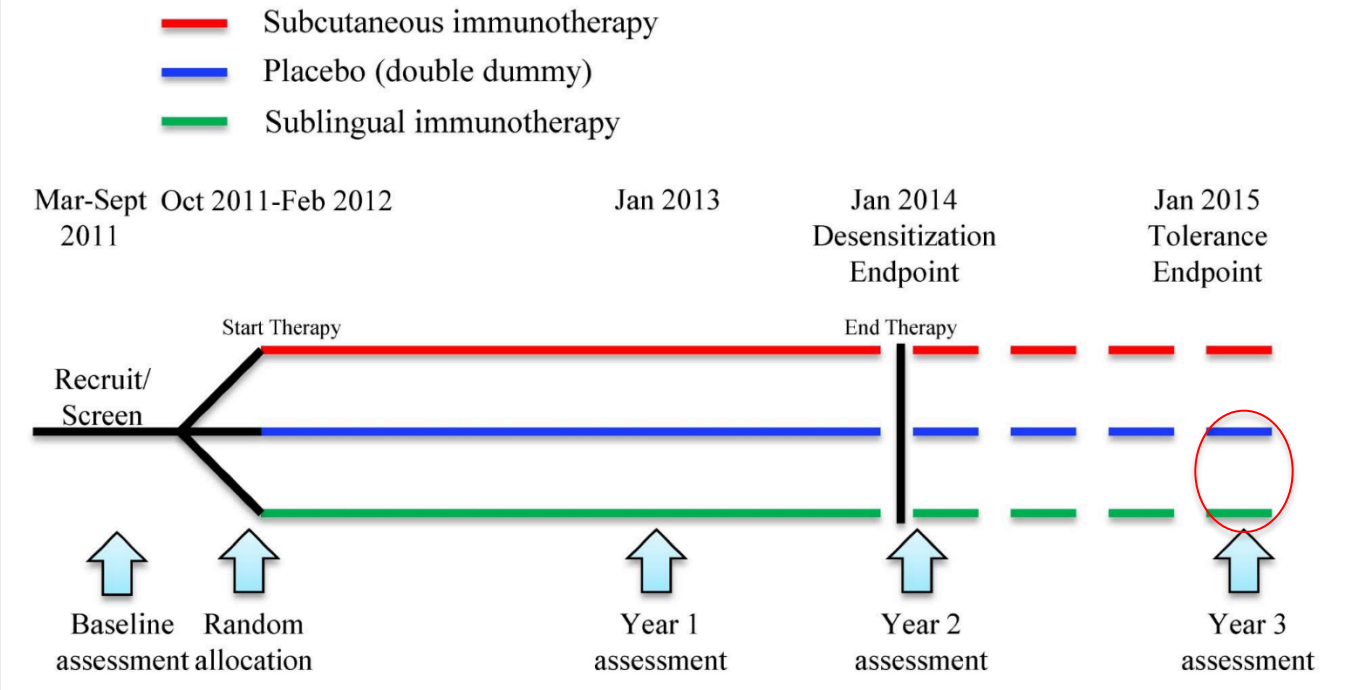
JAMA | Original Investigation

Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis

The GRASS Randomized Clinical Trial

Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

GRASS TRIAL - Study Flow



Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

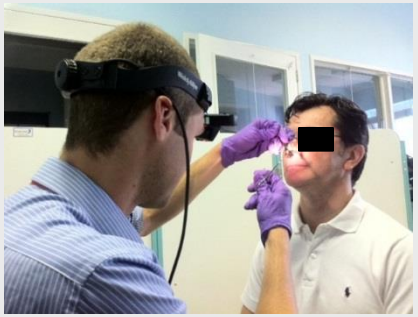
Participant Demographics

	SLIT (n=34)	Placebo (n=36)	SCIT (n=36)	p value
Age, yrs Mean (SD),	**34.1** (9.9)	**32.8** (8.1)	**33.7** (9.5)	0.957
Gender (M/F %)	**72/28**	**67/33**	**64/36**	0.750
Ethnicity (White/Other %)	**67/33**	**71/29**	**83/17**	0.560
Grass SPT Mean (SD), mm	**10.4** (3.3)	**8.9** (3.3)	**8.6** (3.6)	0.024
Grass Sp IgE Mean (SD), KU/L	**38.2** (58.9)	**28.2** (33.4)	**36.7** (53.9)	0.644

Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

NASAL CHALLENGE DEVICE

NASAL FLUID COLLECTION



SYMPTOM SCORE (TNSS)

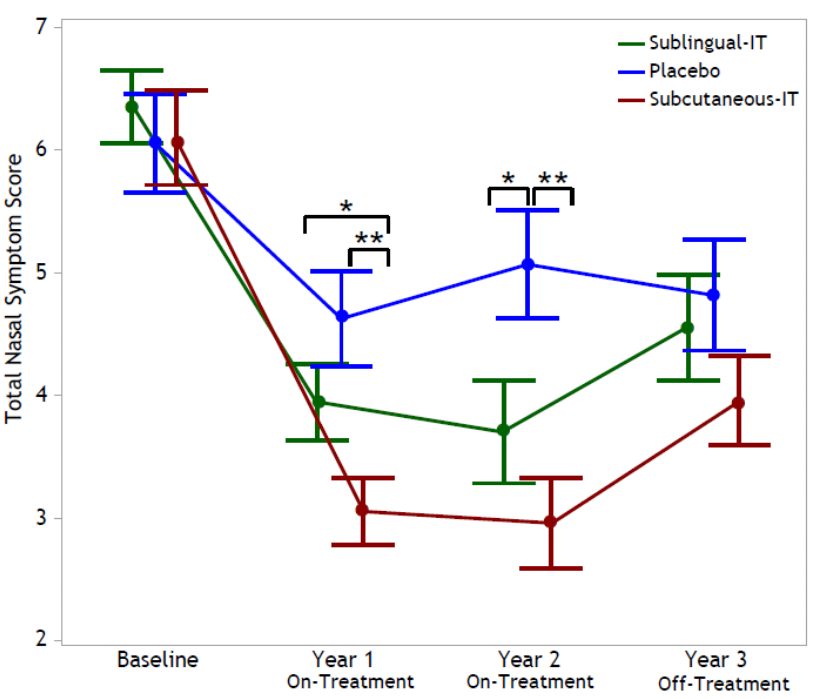
Sneezing	0-3
Nose running	0-3
Blockage	0-3
Itch	0-3
TOTAL	0-12

Modified from Bousquet et al 1987 and Lent et al 2006

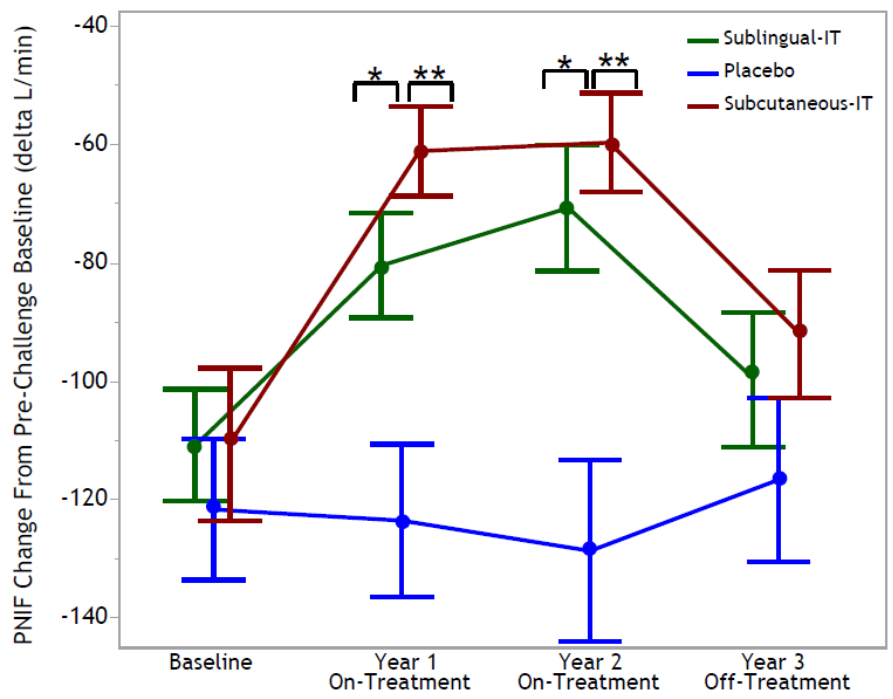
PEAK NASAL INSPIRATORY FLOW (PNIF)

Scadding GW et al. J Immunol Methods 2012;384: 25-32.

TNSS (Scale 0-12)



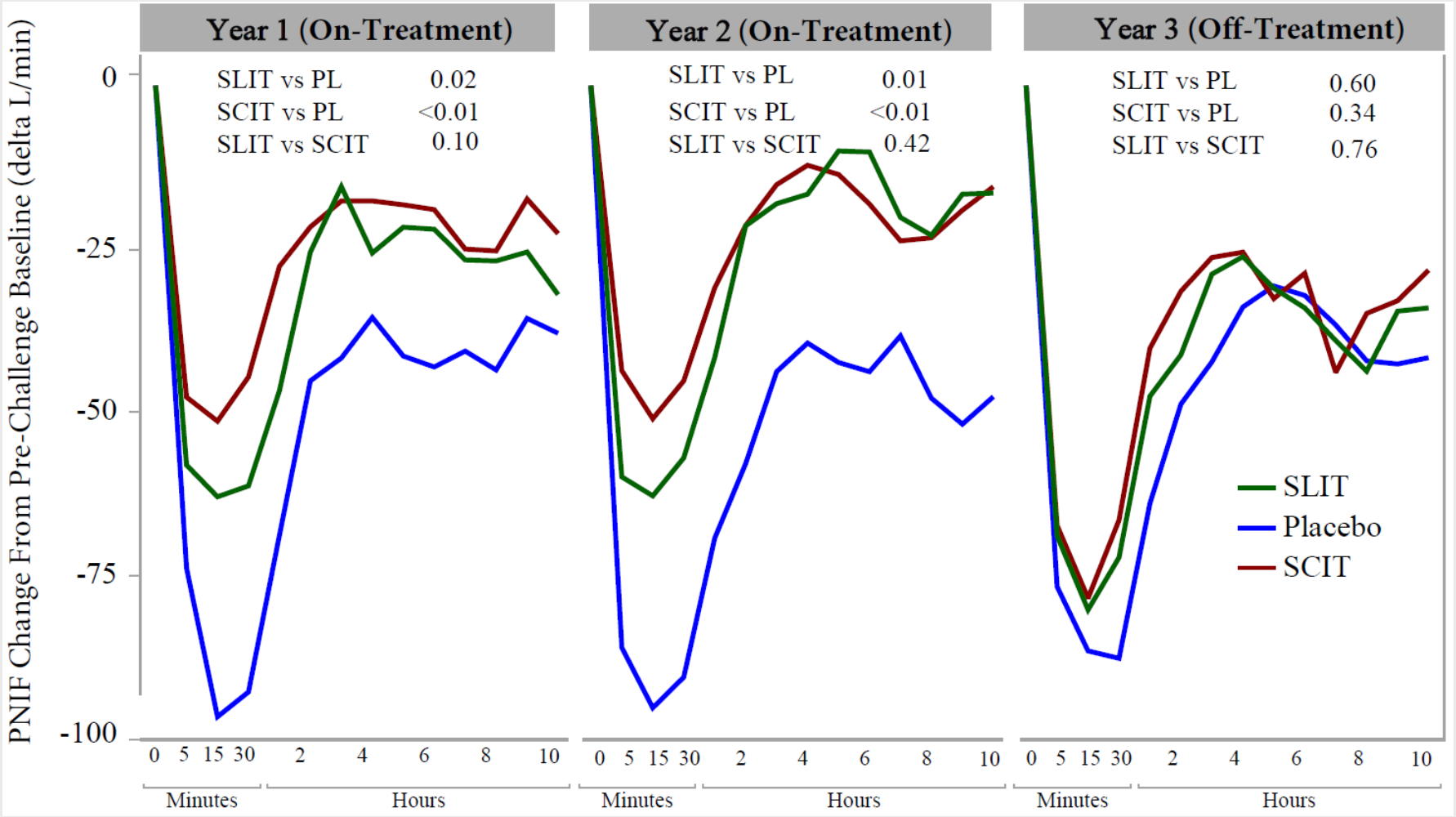
PNIF (Litres/min)



Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

Peak Nasal Inspiratory Flow (PNIF)

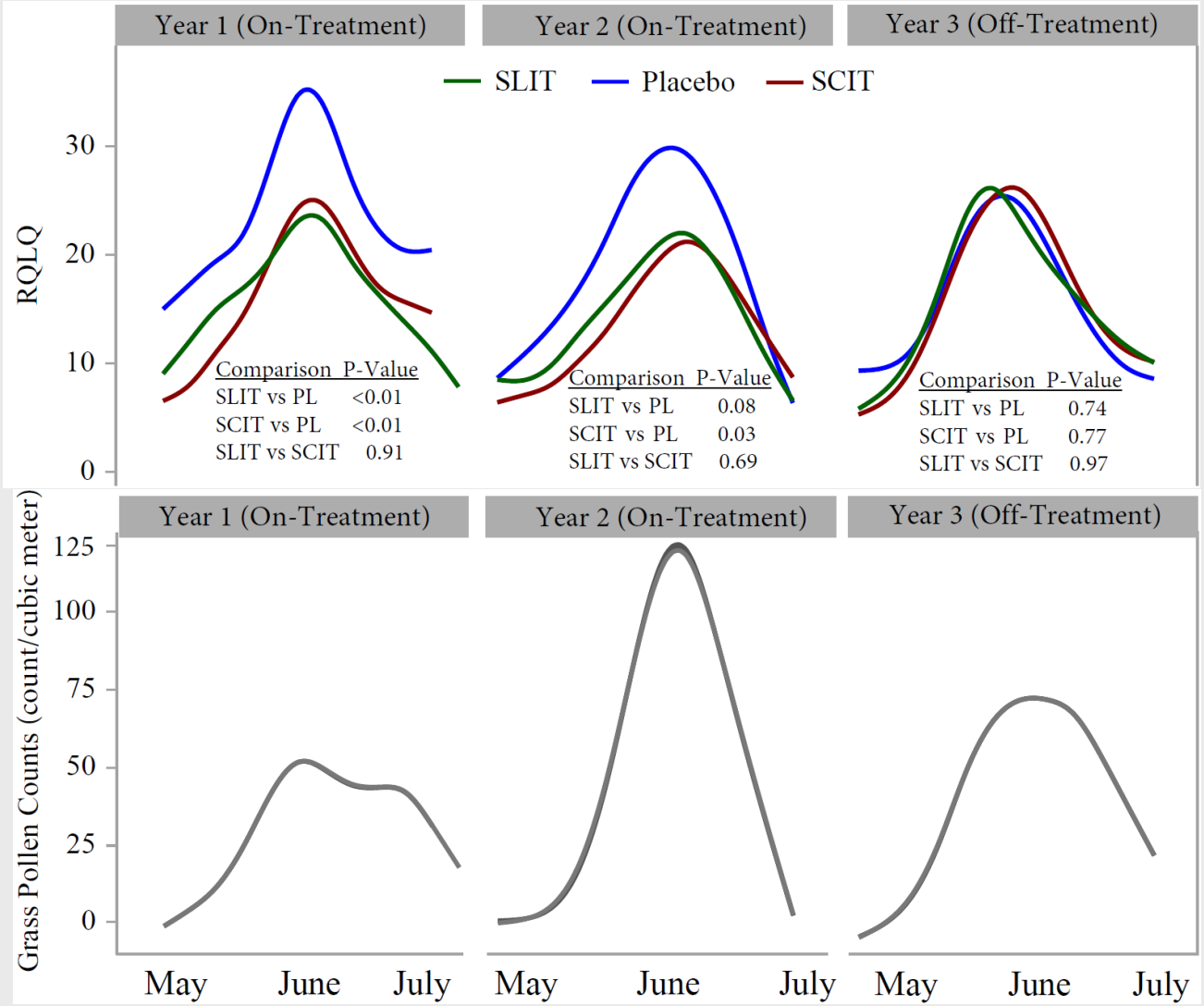
Time-course of changes after nasal allergen challenge



Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

Quality Of Life Scores (RQLQ)

Time-course of weekly changes during May-July



Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

Adverse Events

According to international MedDRA classification

System Organ Class Preferred Term	SLIT (N=36)	Placebo (N=34)	SCIT (N=36)	Total (N=106)
Total # Adverse Events	163	174	216	553
Total # Related AEs	34	18	64	116
# Subjects with ≥ 1 AE	34 (94.4%)	33 (97.1%)	35 (97.2%)	102 (96.2%)
Immune System Disorders	5 (13.9%)	9 (26.5%)	20 (55.6%)*^	34 (32.1%)
Hypersensitivity	1 (2.8%)	4 (11.8%)	17 (47.2%)*^	22 (20.8%)
Gastrointestinal Disorders	13 (36.1%)	8 (23.5%)	8 (22.2%)	29 (27.4%)
Dyspepsia	8 (22.2%)†^	1 (2.9%)	0	9 (8.5%)

***P<0.05, SCIT vs. Placebo**
^P<0.05, SLIT vs. SCIT
†P<0.05, SLIT vs. Placebo

Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

Summary

- Two years treatment with sublingual (or subcutaneous) immunotherapy was not significantly different from placebo in improving the nasal response to allergen challenge at 3 year follow up

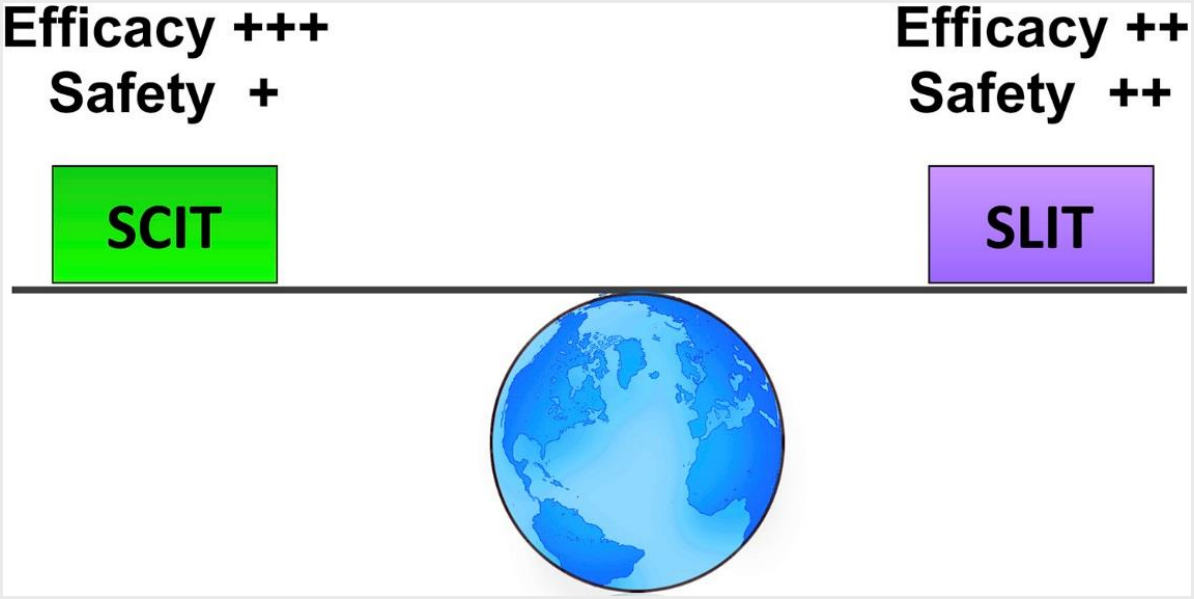
- Two years treatment with SLIT or SCIT *were* effective:

  - inhibited allergen-induced nasal responses
  - improved seasonal outcomes
  - suppressed Th2 immunity

- SLIT had a better safety profile

- Allergen immunotherapy should be continued for at least 3 years for long-term tolerance, as per internat. guidelines

Take-Home Message

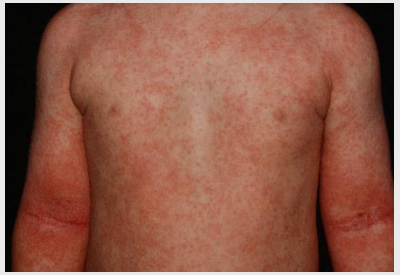


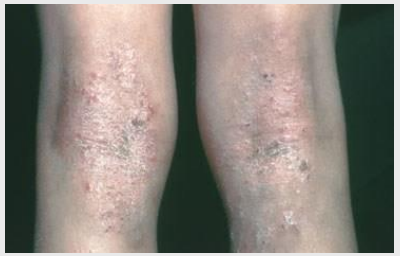
SLIT v SCIT:
Patients' choice and treat for at least 3 years

Durham SR, Penagos M. J Allergy Clin Immunol 2016; 137: 339-349.

3. Atopic Dermatitis (AD) – novel biologic approaches

- Affects 2–10% of adults worldwide
- Severe cases associated with
  - substantial psychosocial distress
- Co-morbidities include asthma, rhinitis and food allergy



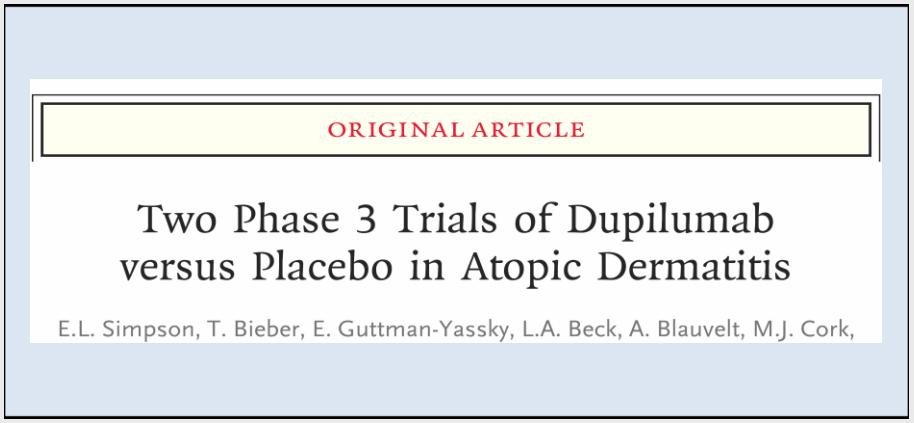


Silverberg JI, Hanifin JM. JACI 2013; 1132.
Silverberg JI, et al. J Dermatolog Treat 2016; 27: 568–76.

State of the Art – treatment of severe atopic dermatitis

- Long-term treatment with topical steroids, tacrolimus and emollients
- Systemic corticosteroids and associated complications
- Immunosuppressants: Cyclosporin, Azathioprine
- (serious toxicity)
- Monoclonal antibody therapy (Dupilumab) as steroid/immunosuppresent sparing agent?

Dupilumab anti-(IL4R-α)


ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork,

Two DBPCT, Phase 3 trials of identical design (SOLO 1 and SOLO 2)

- **Inclusion: Adults; moderate- severe atopic dermatitis**
  No response to topical corticosteroids

- **Randomised (1:1:1) for 16 weeks, SC dupilumab**
  - (300 mg) or placebo weekly or 2 weekly (with alternate week placebo)

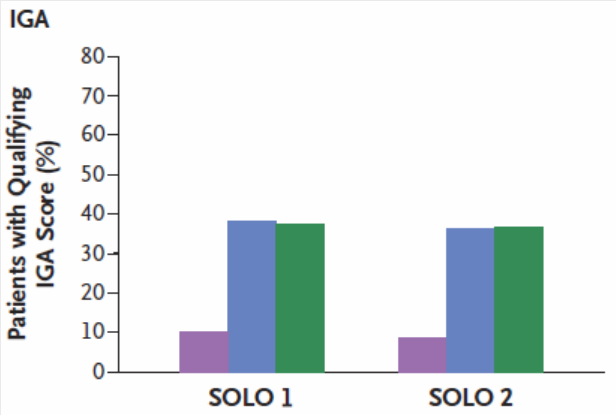
- **All groups were on topical corticosteroids +/- topical calcineurin inhibitors PRN**

- **Primary endpoints: Patients (%) (IGA) 0/1 and 2-point or higher @ week 16.**

Simpson et al. N Engl J Med 2016;375:2335-48.

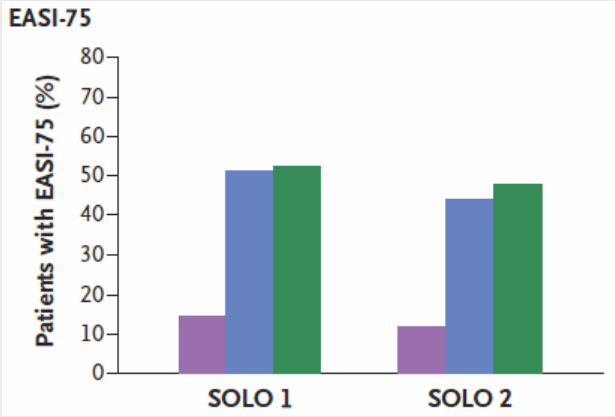
Dupilumab (IL4R-α): IGA & EASI-75 score

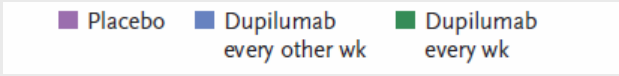
Reduction from baseline >2 points on the IGA at week 16



Investigator's Global Assessment (IGA). Proportion of patients with IGA 0-1 Scores. Ranges 0-4, higher scores=severe disease

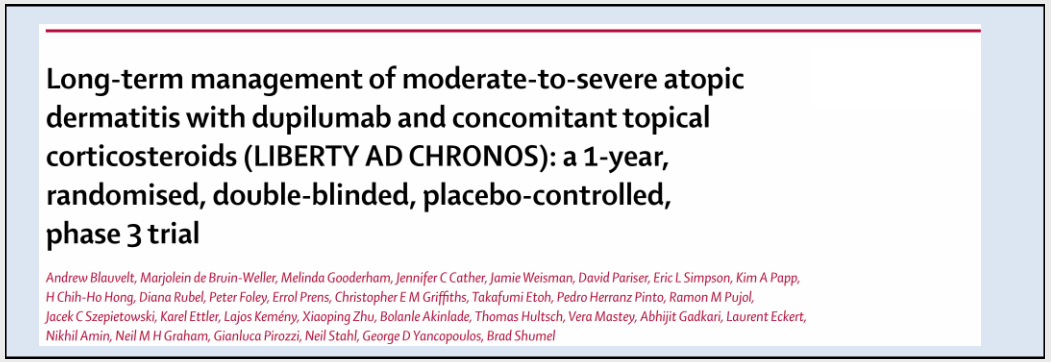
Improvement from baseline of at least 75% on the Eczema Area and Severity Index (EASI-75) at week 16





Simpson et al. N Engl J Med 2016;375:2335-48.

Dupilumab (anti-IL-4R-α)



Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial

Andrew Blauvelt, Marjolein de Bruin-Weller, Melinda Gooderham, Jennifer C Cather, Jamie Weisman, David Pariser, Eric L Simpson, Kim A Papp, H Chih-Ho Hong, Diana Rubel, Peter Foley, Errol Prens, Christopher E M Griffiths, Takafumi Etoh, Pedro Herranz Pinto, Ramon M Pujol, Jacek C Szepietowski, Karel Ettler, Lajos Kemény, Xiaoping Zhu, Bolanle Akinlade, Thomas Hultsch, Vera Mastey, Abhijit Gadkari, Laurent Eckert, Nikhil Amin, Neil M H Graham, Gianluca Pirozzi, Neil Stahl, George D Yancopoulos, Brad Shumel

- **Inclusion: Adults; moderate- severe atopic dermatitis**
  Poor response to topical corticosteroids

- **Randomised to (3:1:3): SC dupilumab 300 mg once weekly (qw), dupilumab 300 mg every 2 weeks (q2w), or placebo.**

- **All groups were on topical corticosteroids with/without topical calcineurin inhibitors PRN**

- **Co-primary endpoints:**

  1) (%) achieving Investigator's Global Assessment (IGA) 0/1 and 2-point or higher @ 16 wks

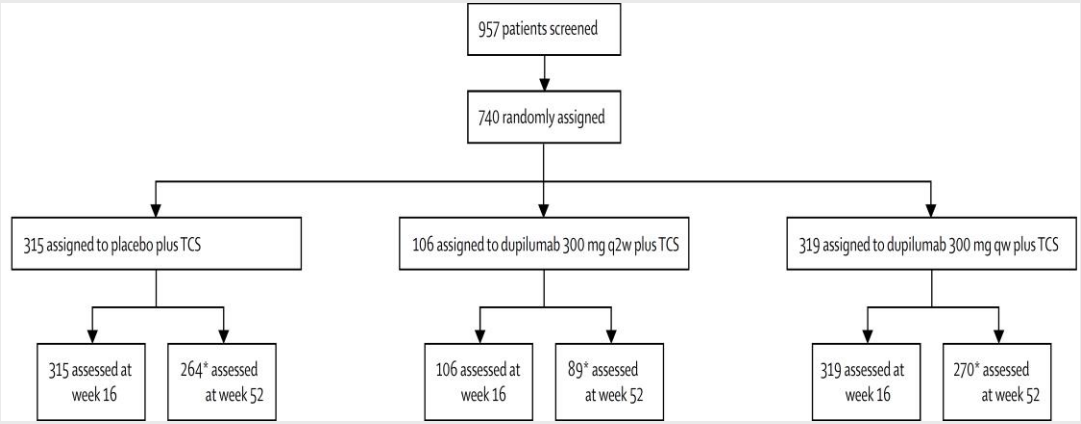
  2) Eczema Area and Severity Index 75% improvement from baseline (EASI-75) @ week 16.

Blauvelt a et al. Lancet 2017; May epub **PMID: 28478972**

Dupilumab

Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial

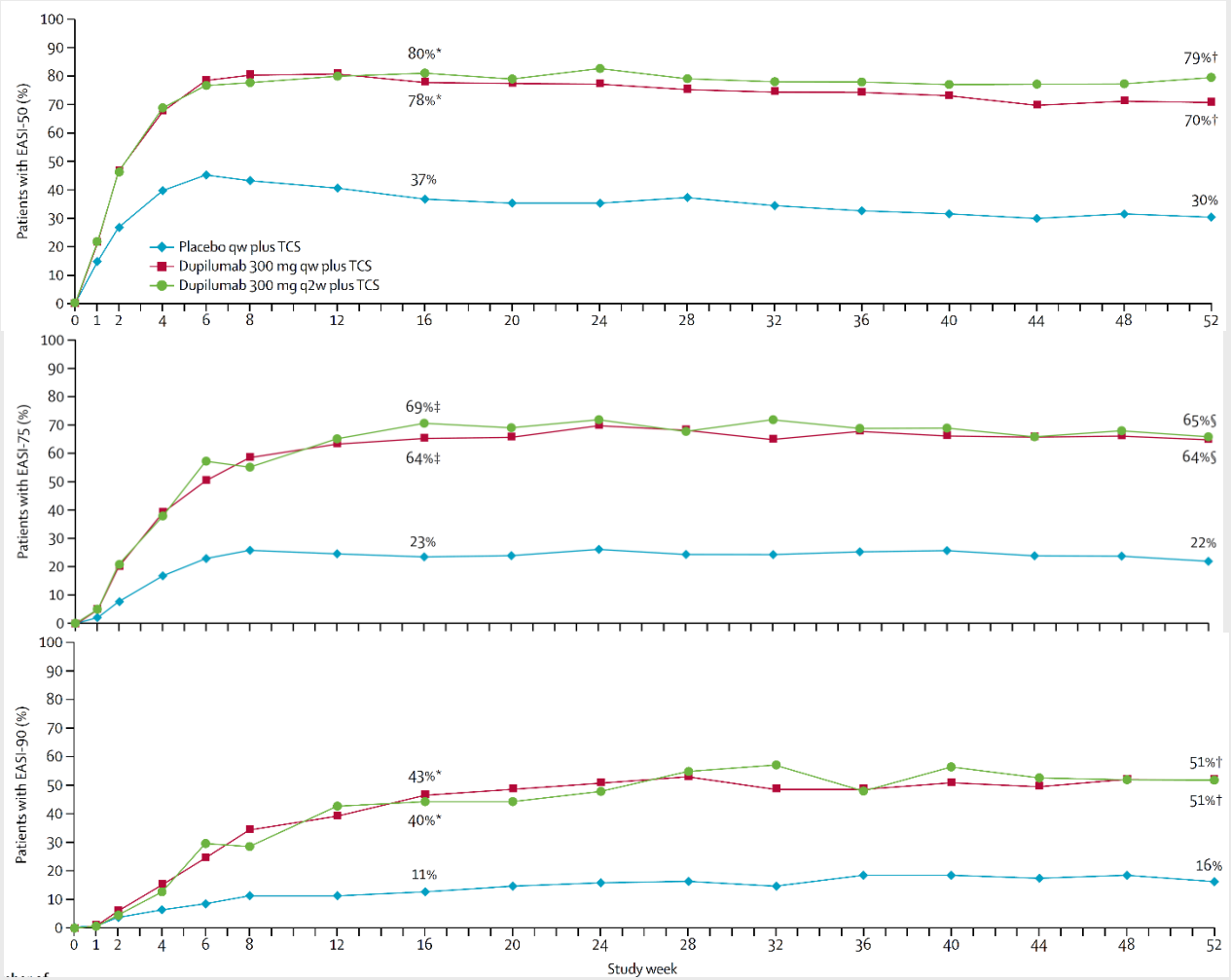
Andrew Blauvelt, Marjolein de Bruin-Weller, Melinda Gooderham, Jennifer C Cather, Jamie Weisman, David Pariser, Eric L Simpson, Kim A Papp, H Chih-Ho Hong, Diana Rubel, Peter Foley, Errol Prens, Christopher E M Griffiths, Takafumi Etoh, Pedro Herranz Pinto, Ramon M Pujol, Jacek C Szepietowski, Karel Ettler, Lajos Kemény, Xiaoping Zhu, Bolanle Akinlade, Thomas Hultsch, Vera Mastey, Abhijit Gadkari, Laurent Eckert, Nikhil Amin, Neil M H Graham, Gianluca Pirozzi, Neil Stahl, George D Yancopoulos, Brad Shumel



	Placebo qw plus TCS (n=315)	Dupilumab 300 mg q2w plus TCS (n=106)	Dupilumab 300 mg qw plus TCS (n=319)
Age (years)	34·0 (25·0–45·0)	40·5 (28·0–49·0)	34·0 (26·0–45·0)
Sex			
Men	193 (61%)	62 (58%)	191 (60%)
Women	122 (39%)	44 (42%)	128 (40%)
Race			
White	208 (66%)	74 (70%)	208 (65%)
Black or African American	19 (6%)	2 (2%)	13 (4%)
Asian	83 (26%)	29 (27%)	89 (28%)
Other	5 (2%)	1 (1%)	9 (3%)
Atopic dermatitis disease duration (years)	26·0 (17·0–38·0)	28·0 (20·0–44·0)	26·0 (18·0–39·0)
BSA (%)	55·0% (40·0–75·0)	58·8% (43·5–78·5)	52·0% (36·0–71·5)
EASI score	29·6 (22·2–40·8)	30·9 (22·3–41·6)	29·0 (21·6–40·7)
IGA score*			
4	147 (47%)	53 (50%)	147 (46%)
3	168 (53%)	53 (50%)	172 (54%)
Comorbid type 2 immune diseases at baseline†			
Allergies (other than food allergy)	63% (200/315)	62% (68/110)	67% (211/315)
Allergic rhinitis	43% (134/315)	48% (53/110)	41% (130/315)
Asthma	41% (130/315)	41% (45/110)	37% (116/315)
Food allergy	30% (96/315)	35% (39/110)	36% (112/315)

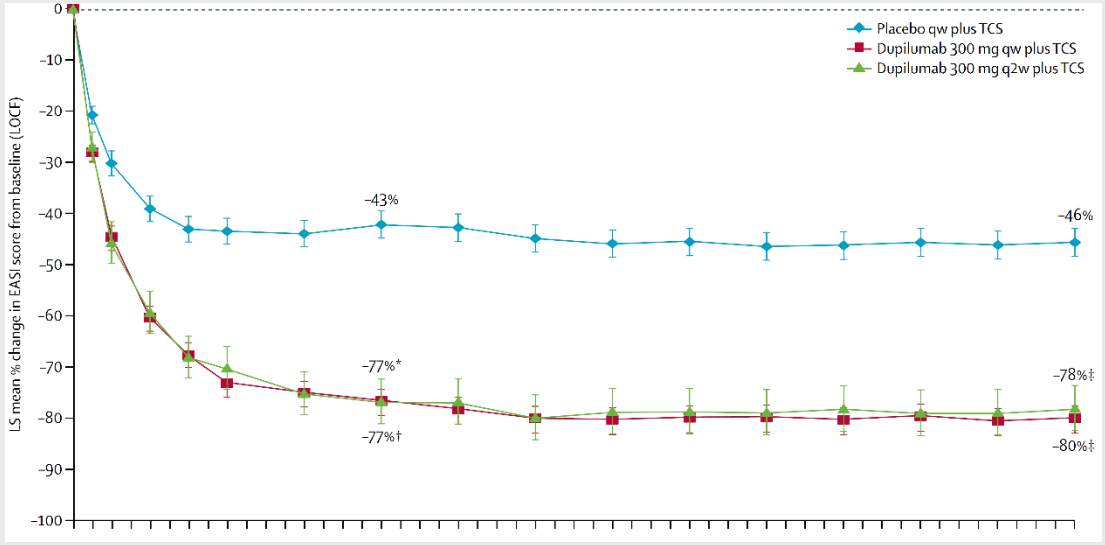
***Blauvelt a et al. Lancet 2017; May epub* PMID: 28478972**

Dupilumab – Eczema area and severity index score (EASI)

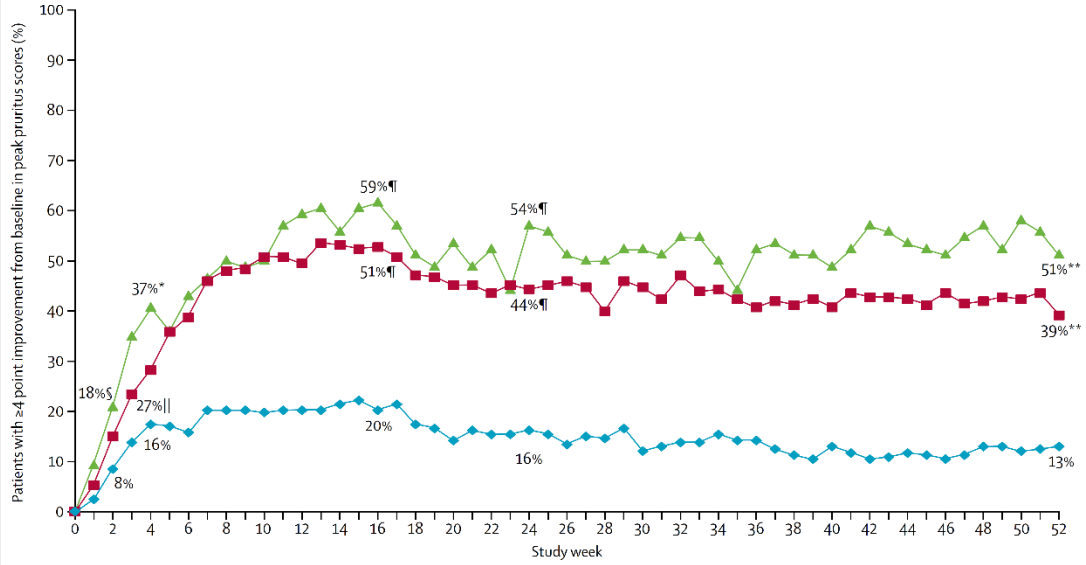


Blauvelt a et al. Lancet 2017; May epub **PMID: 28478972**

Dupilumab (IL4R-α)- EASI score



Least squares mean percent change in EASI score over time



Proportion of patients who achieved ≥4-point improvement from baseline in peak pruritus NRS scores

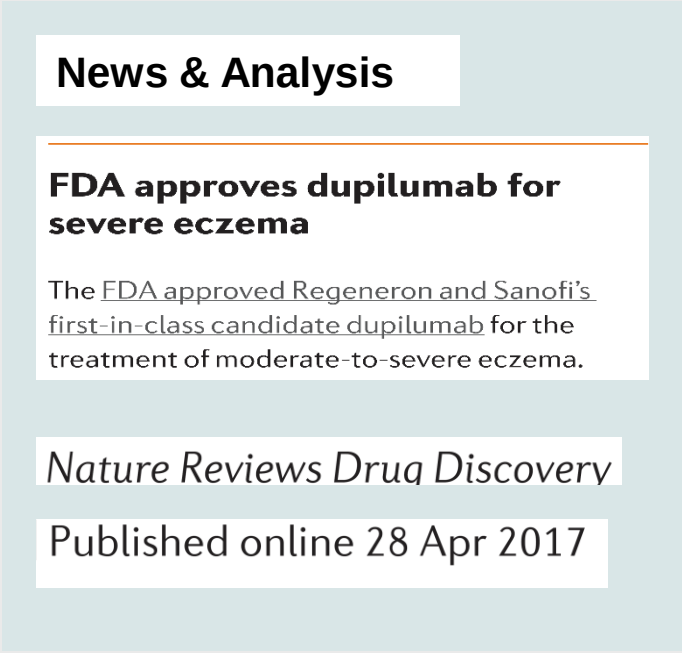
Blauvelt a et al. Lancet 2017; May epub **PMID: 28478972**

Summary- Take-Home Message

Dupilumab added to standard corticosteroid treatment in Mod-severe atopic dermatitis:

– *Improves atopic dermatitis signs and symptoms*

– *Acceptable safety profile*


News & Analysis

FDA approves dupilumab for severe eczema

The FDA approved Regeneron and Sanofi's first-in-class candidate dupilumab for the treatment of moderate-to-severe eczema.

Nature Reviews Drug Discovery

Published online 28 Apr 2017

4. Nasal polyps and novel biologic approaches: State of the Art

- Medical management of chronic sinusitis with nasal polyposis:

  intranasal corticosteroids
  nasal saline irrigation
  antibiotics
  +/- short-course oral steroids

- Repeat (revision) surgery is associated with less success and a higher potential for adverse effects

- Alternative treatment options are needed for this patient group

- Eosinophils are the most common infiltrating inflammatory cells and Th2 cytokines are predominant in eosinophilic polyps

Mepolizumab and nasal polyps

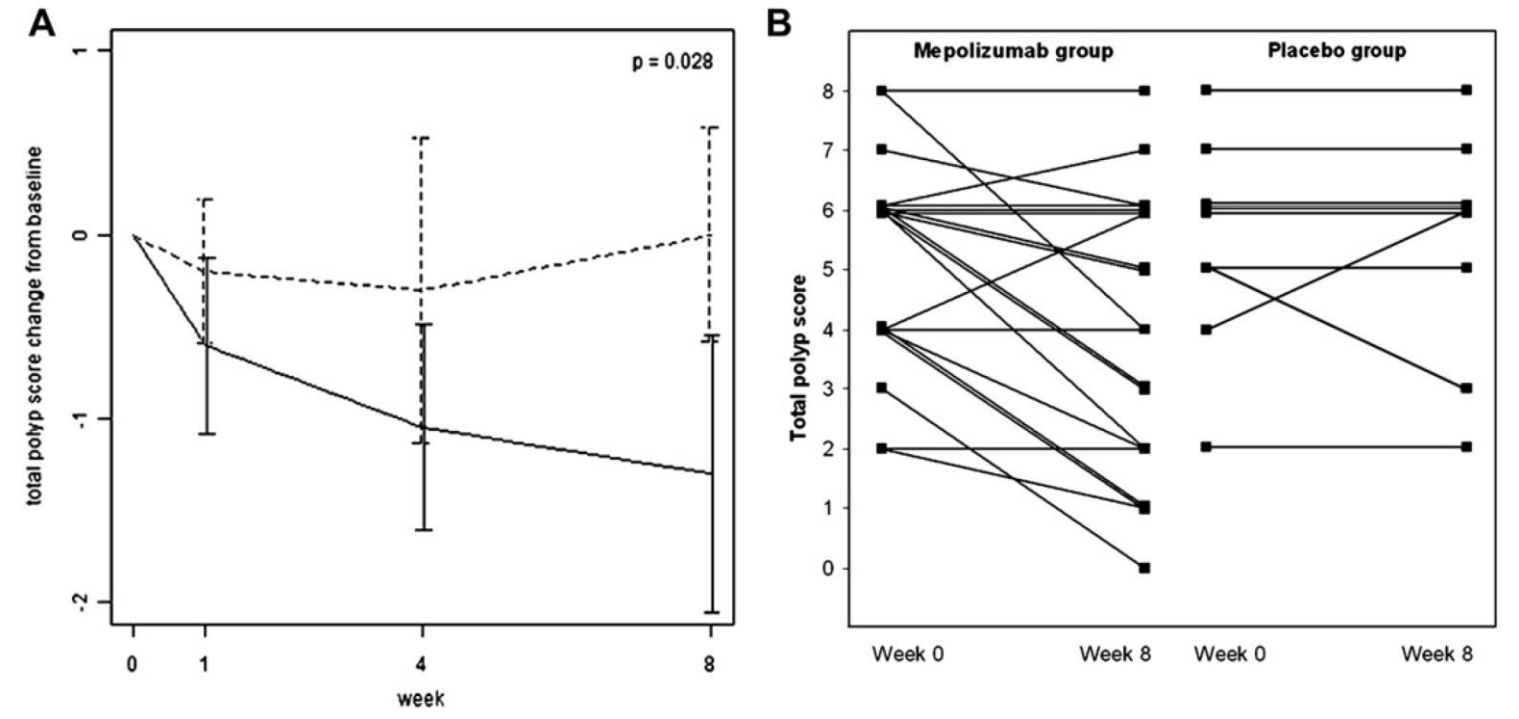
Mepolizumab, a humanized anti–IL-5 mAb, as a treatment option for severe nasal polyposis

Philippe Gevaert, MD, PhD,[a]* Nicholas Van Bruaene, MD,[a]* Tom Cattaert, PhD,[b,c] Kristel Van Steen, PhD,[b,c] Thibaut Van Zele, MD, PhD,[a] Frederic Acke, MD,[a] Natalie De Ruyck, MSc,[a] Katrien Blomme, MSc,[a] Ana R. Sousa, PhD,[d] Richard P. Marshall, MD, PhD,[d] and Claus Bachert, MD, PhD[a] *Ghent and Liège, Belgium, and Stevenage, United Kingdom*

- 30 polyps patients grade>3 included and ~ 50% had previous surgery.
- Randomised to Mepolizumab (n=20) vs placebo (n=10): 2 single doses of 750mg i.v 28 days apart.
- Primary endpoint = change in Nasal Polyp Score at 12weeks

Gevaert et al. J Allergy Clin Immunol 2011; 2011:989-95

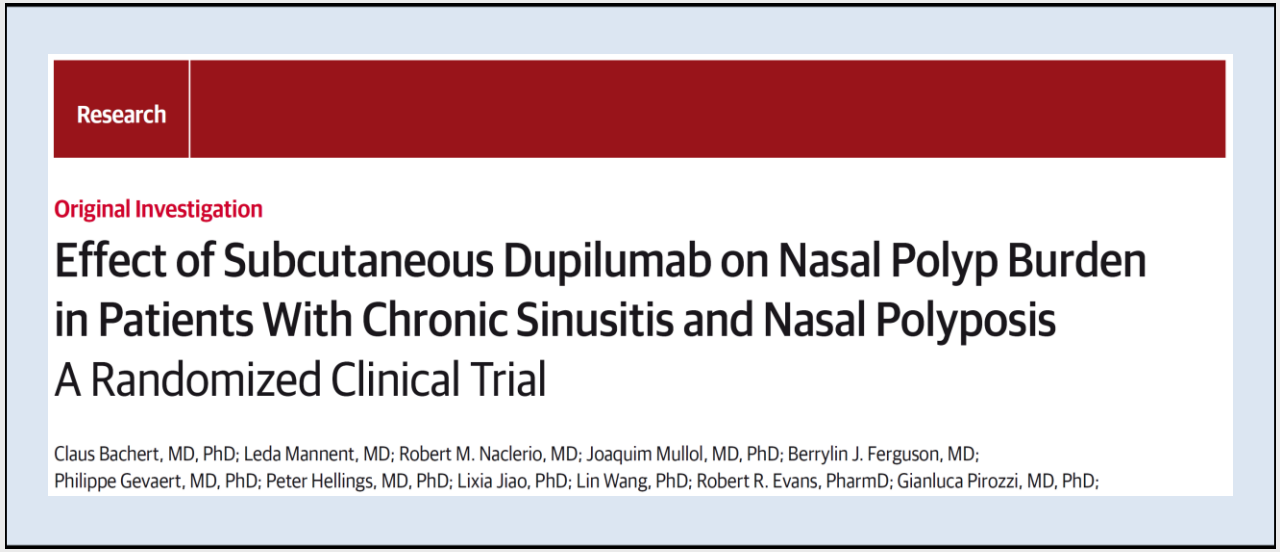
Mepolizumab and nasal polyps



- **Reduction of NP score of at least 1 point: 60% Mepo vs 10% placebo**
- **Efficacy maintained for at least 3-6 mths in all subjects**
- **By 3mths 50% of PL group had progressed to surgery vs 15% on Mepo**

Gevaert et al. J Allergy Clin Immunol 2011; 2011:989-95

Dupilumab and nasal polyps



Research

Original Investigation

Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis
A Randomized Clinical Trial

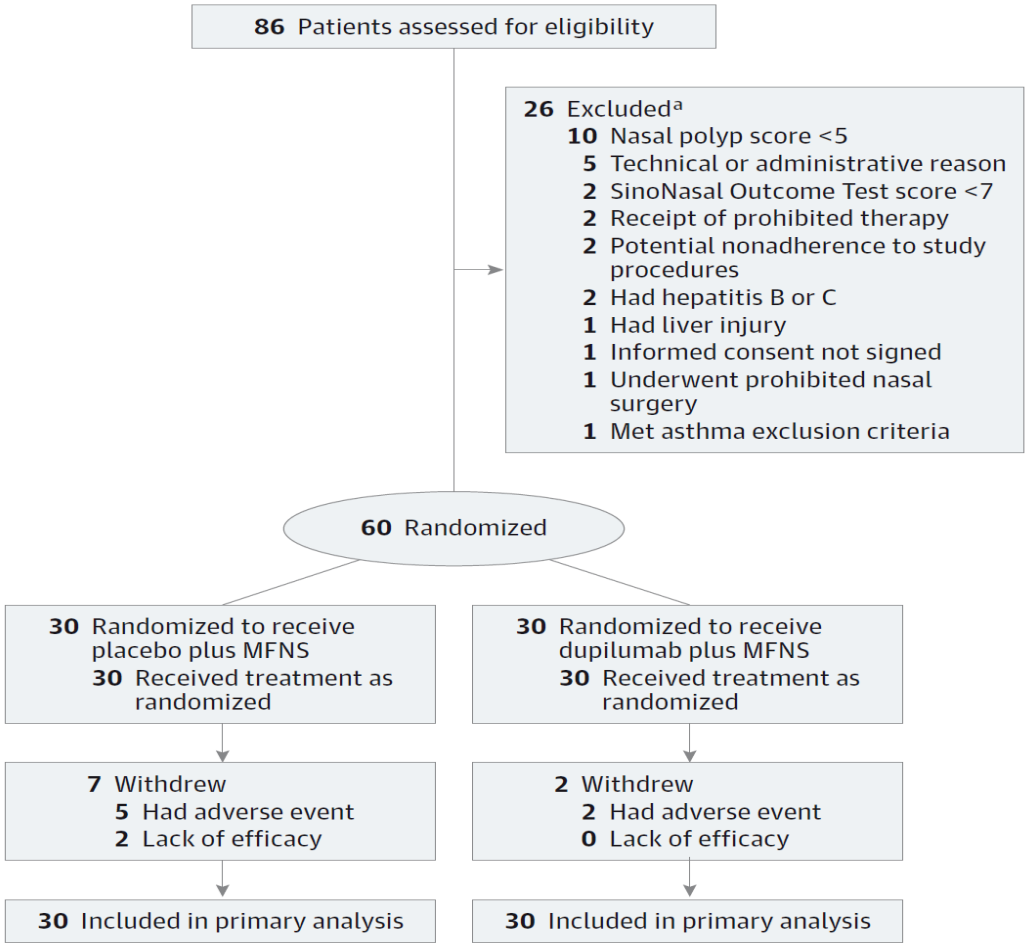
Claus Bachert, MD, PhD; Leda Mannent, MD; Robert M. Naclerio, MD; Joaquim Mullol, MD, PhD; Berrylin J. Ferguson, MD; Philippe Gevaert, MD, PhD; Peter Hellings, MD, PhD; Lixia Jiao, PhD; Lin Wang, PhD; Robert R. Evans, PharmD; Gianluca Pirozzi, MD, PhD;

- **Double-blind, placebo-controlled randomized study of dupilumab (inhibits binding of IL-4 and IL-13 to IL-4Ra).**
- **Primary outcome: Change in endoscopic nasal polyp score (range, 0-8) at 16 weeks**

Bachert C et al., JAMA 2016;315:469-479

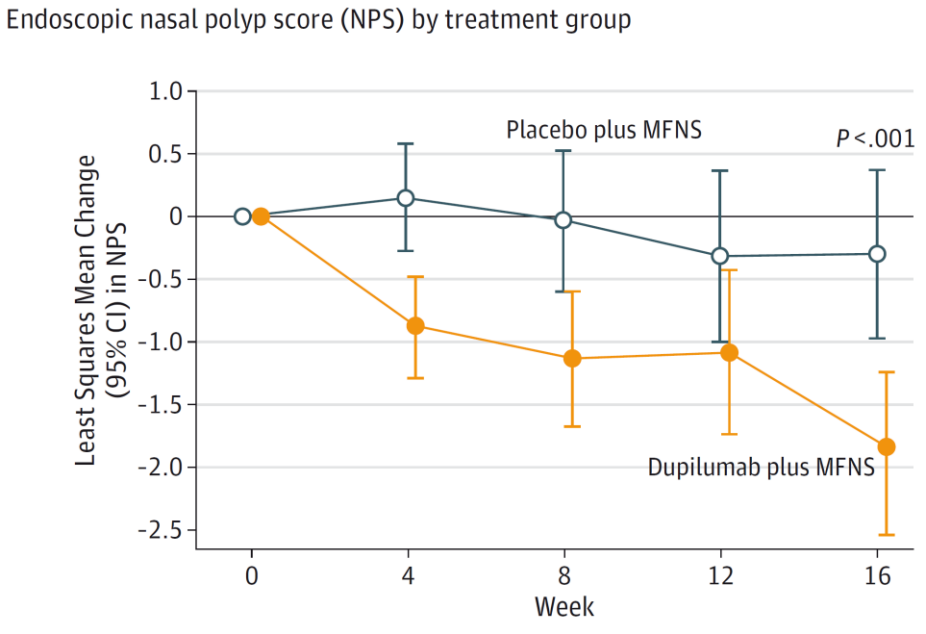
Dupilumab and nasal polyps

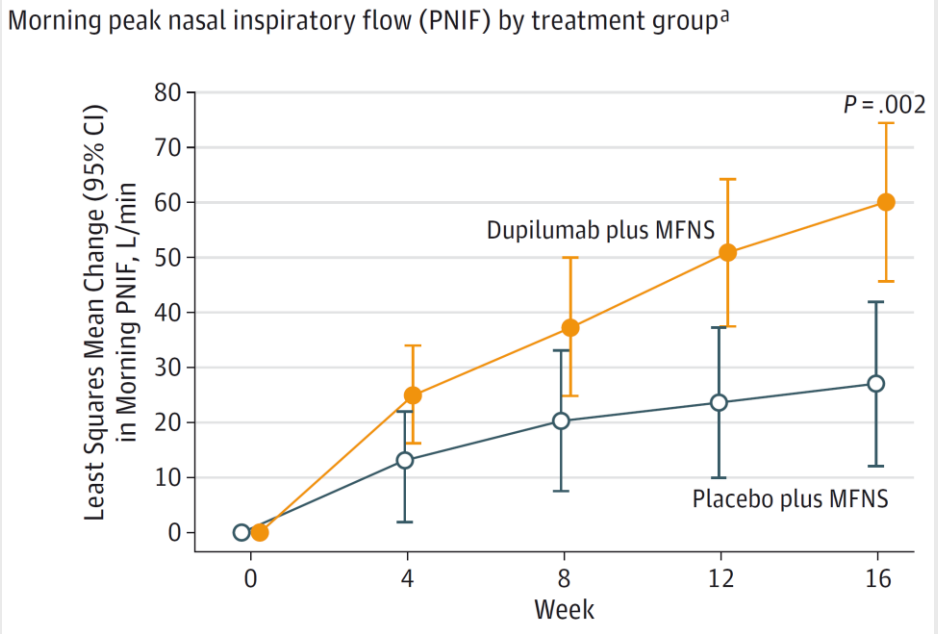
Figure 1. Patients Enrolled and Included in the Analysis



Bachert C et al., JAMA 2016;315:469-479

Dupilumab and nasal polyps





Bachert C et al., JAMA 2016;315:469-479

Summary and Take-Home Message

- Nasal polyposis refractory to intranasal corticosteroids, addition of mepolizumab or dupilumab to INCS compared with INCS alone reduces endoscopic nasal polyp burden.

- Further studies are needed to assess longer treatment duration, larger samples, and direct comparison with other medications.

5. Food Allergy – is there a role for allergen Immunotherapy?

Food allergy: State of the Art

- Food allergy may result in considerable morbidity and mortality.
- Peanut allergy has become a global public health problem affecting now 1.5% to 3% of children.
- Epidemiological studies have demonstrated an increasing prevalence and severity of food allergy, particularly in children

Kotz D, et al. JACI 2011:623–30.
Sicherer SH, et al. JACI 2010:1322-6.

Food Allergy-Treatment

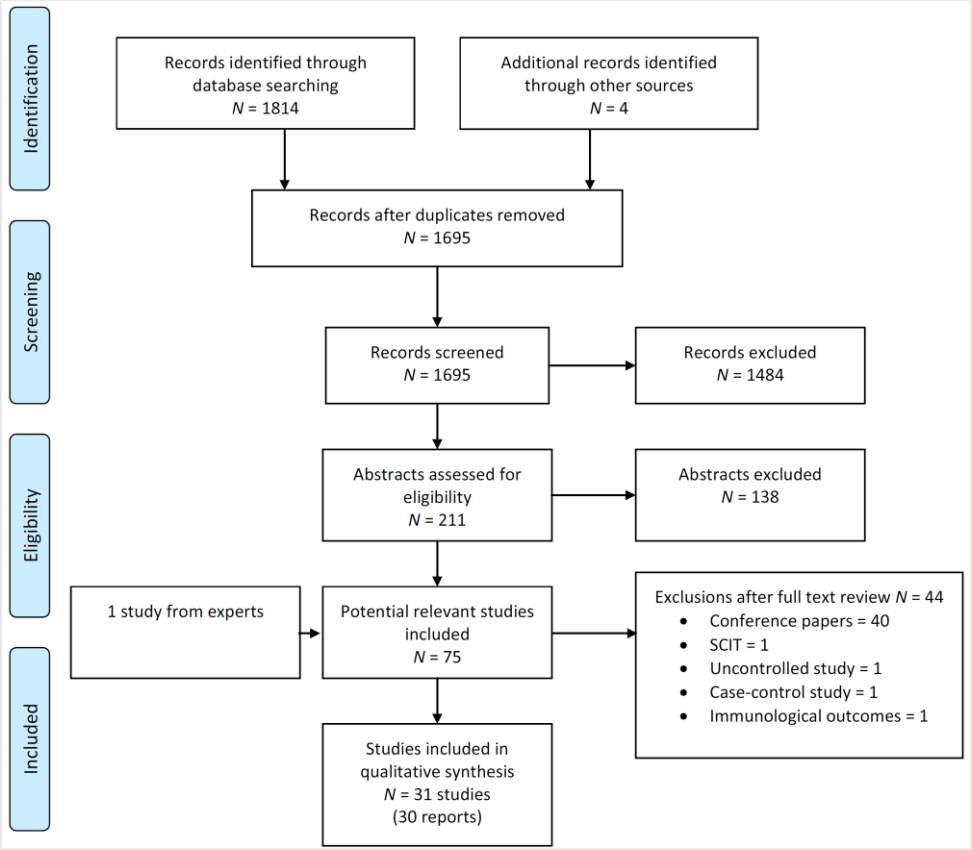
- Current treatment approach for food allergy is allergen avoidance and access to self-injectable epinephrine.
- But despite of active avoidance, the risk of an adverse reaction from exposure is ongoing.
- Recent efforts have focused on development of allergen-specific immunotherapeutic approaches to treat peanut allergy- ? SLIT/ORAL

NIAID-Sponsored Expert Panel, JACI 2010;126(suppl):S1-58.
Fleischer DM, et al. Pediatrics 2012;e25-32.
Yu JW, et al.JACI 2006:466-72.

REVIEW ARTICLE

Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis

U. Nurmatov[1], S. Dhami[2], S. Arasi[3,4], G. B. Pajno[3], M. Fernandez-Rivas[5], A. Muraro[6], G. Roberts[7,8], C. Akdis[9], M. Alvaro-Lozano[10], K. Beyer[11,12], C. Bindslev-Jensen[13], W. Burks[14],



Nurmatov et al. Allergy. 2017 May 11. doi: 10.1111/all.13201.

Systemic review of AIT for food allergy

Table 1 Description of the included studies (n = 31)

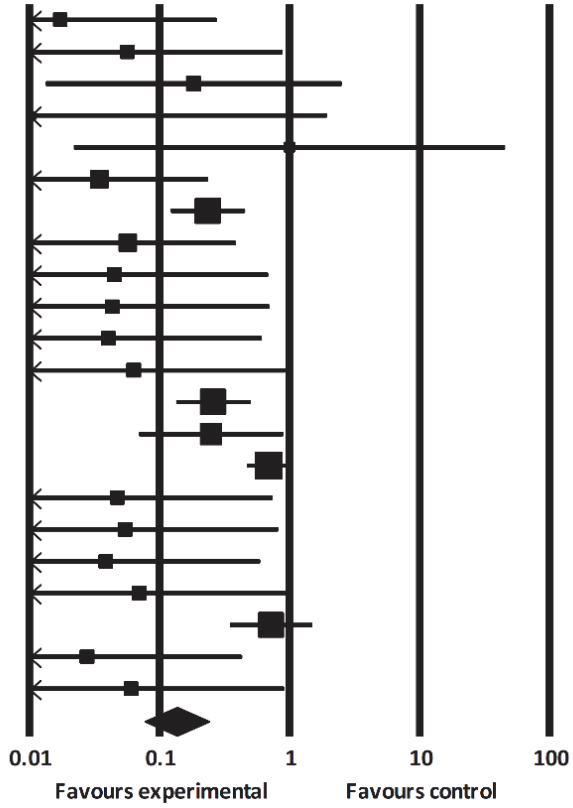
	Food allergen (s)								Route AIT		
Study (first author, year, country)	Cow's milk	Hen's egg	Peanut	Hazelnut	Peach	Apple	Fish	Other(s)	OIT	SLIT	EPIT
RCT (n = 25)											
Anagnostou, 2014, UK			X						X		
Burks, 2012, USA		X							X		
Caminiti, 2009, Italy	X								X		
Caminiti, 2015; Italy		X							X		
Dello Iacono, 2013, Italy		X							X		
Dupont, 2010, France	X										X
Enrique, 2005, Spain				X						X[†]	
Escudero, 2015, Spain		X							X		
Fernandez-Rivas, 2009, Spain					X					X[‡]	
Fleischer, 2012, USA			X							X	
Fuentes-Aparicio, 2013, Spain		X							X		
Kim, 2011, USA			X							X	
Lee, 2013, Korea	X								X		
Longo, 2008, Italy	X								X		
Martorell, 2011, Spain	X								X		
Meglio, 2013, Italy		X							X		
Morisset, 2007, France[‡‡]	X	X							X		
Pajno, 2010, Italy	X								X		
Patriarca, 1998, Italy	X	X				X	X		X		
Salmivesi, 2012, Finland	X								X		
Skripak, 2008, USA	X								X		
Staden, 2007, Germany	X	X							X		
Tang, 2015, Australia			X						X[†*]		
Varshney, 2011, USA			X						X		
CCT (n = 6)											
García-Ara, 2013, Spain	X								X		
Martınez-Botas, 2015, Spain	X								X		
Mansouri, 2007, Iran	X								X		
Patriarca, 2003, Italy	X	X	X		X	X	X	X[§]	X		
Patriarca, 2007, Italy	X	X				X	X	X[¶]		X[‡]	
Syed, 2014, USA			X						X		

Nurmatov et al. Allergy. 2017 May 11. doi: 10.1111/all.13201.

Systematic review of Oral-AIT for food allergy

Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in OIT v. controls

Study name	Statistics for each study			Events / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Anagnostou 2014	0.017	0.001	0.277	0 / 46	24 / 39	3.04
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	3.08
Caminiti 2009	0.183	0.013	2.528	0 / 3	7 / 10	3.28
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	1.06
Dello Lacono 2013	1.000	0.022	45.635	1 / 10	1 / 10	1.83
Escudero 2015	0.035	0.005	0.238	1 / 31	28 / 30	4.86
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	9.77
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	4.92
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	3.11
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	3.01
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	3.11
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	3.18
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	9.78
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	7.15
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	10.70
Pajno 2010	0.048	0.003	0.746	0 / 15	10 / 15	3.07
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	3.12
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	3.09
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	3.17
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	9.48
Syed 2014	0.028	0.002	0.433	0 / 20	20 / 23	3.08
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	3.13
	0.135	0.076	0.237	44 / 409	432 / 573	



Heterogeneity: $I^2 = 62\%$; ($P < 0.0001$);
Test for overall effect: $Z = -6.967$ ($P < 0.0001$).

Nurmatov et al. Allergy. 2017 May 11. doi: 10.1111/all.13201.

Oral-AIT for Peanut allergy

Food, drug, insect sting allergy, and anaphylaxis

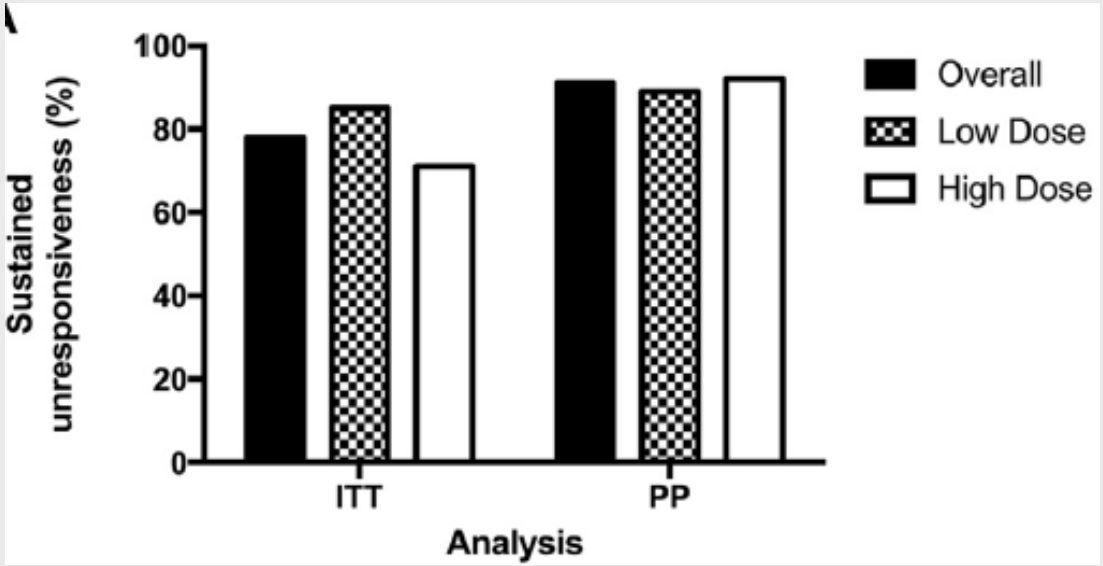
Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective

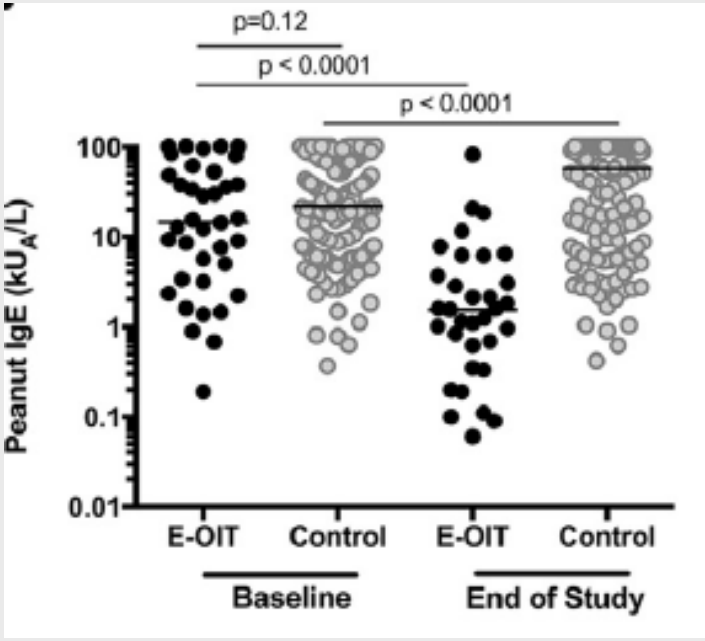
Brian P. Vickery, MD,[a] Jelena P. Berglund, PhD,[b] Caitlin M. Burk, BA,[a] Jason P. Fine, PhD,[a] Edwin H. Kim, MD, MHS,[a] Jung In Kim, MS,[a] Corinne A. Keet, MD, PhD,[c] Michael Kulis, PhD,[a] Kelly G. Orgel, BS,[a] Rishu Guo, MD, PhD,[a] Pamela H. Steele, CPNP,[a] Yamini V. Virkud, MD, MPH,[d] Ping Ye, PhD,[a] Benjamin L. Wright, MD,[e] Robert A. Wood, MD,[c] and A. Wesley Burks, MD[a] *Chapel Hill and Durham, NC, Baltimore, Md, Boston, Mass, and Scottsdale, Ariz*

- To test the safety, effectiveness, and feasibility of early OIT (E-OIT) in the treatment of newly diagnosed peanut allergic children.
- Inclusion: 37 children (9 – 36 months) with peanut allergy randomized 1:1 to receive E-OIT at goal maintenance doses of 300 or 3000 mg/d in a double-blinded fashion for 3 years.
- Primary endpoint: Sustained unresponsiveness at 4 weeks after stopping early intervention oral immunotherapy (4-SU), assessed by DBPCFC
- Outcomes were compared with 154 matched standard-care controls.

Vickery BP et al., JACI;139:173-81

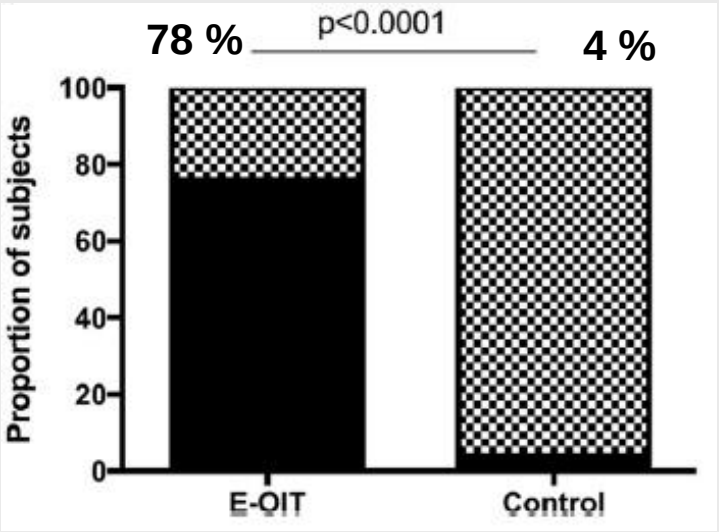
Oral-AIT for Peanut allergy



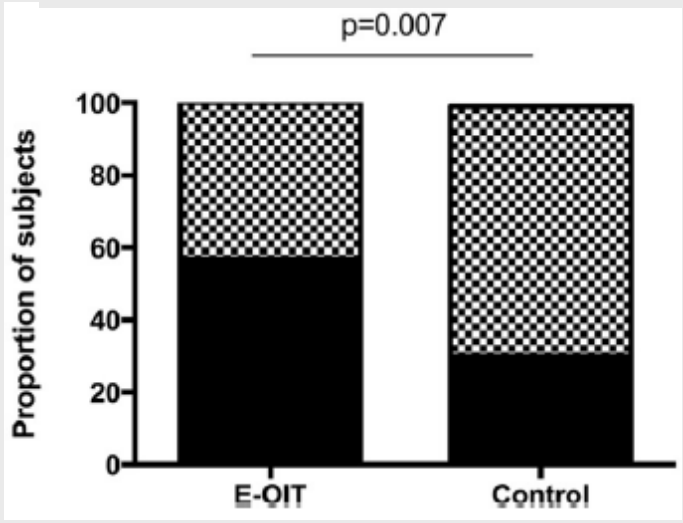


Nurmatov et al. Allergy. 2017 May 11. doi: 10.1111/all.13201.

Oral-AIT for Peanut allergy



Worst-case analysis of predictive sIgE>15:



E-OIT and control participants able to reintroduce peanut-containing foods

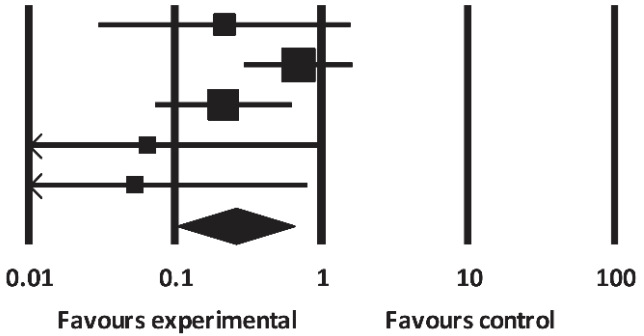
Imputed proportions able to reintroduce peanut-containing foods with evidence-based worst-case assumptions.

Vickery BP et al., JACI;139:173-81

Systematic review of SLIT-AIT for food allergy

Risk ratios (RR) of desensitization as assessed by double-blind placebo-controlled food challenge in SLIT v. controls

Study name	Statistics for each study			Events / Total		Risk ratio and 95% CI	Relative weight
	Risk ratio	Lower limit	Upper limit	Control	Experimental		
Enrique 2005	0.218	0.030	1.588	1 / 11	5 / 12		15.08
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37		35.88
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20		30.23
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11		9.47
Patriarca 2007	0.054	0.004	0.806	0 / 10	36 / 42		9.33
	0.257	0.103	0.641	9 / 67	80 / 122		



Heterogeneity: $I^2 = 41\%$; ($P < 0.147$);
Test for overall effect: $Z = 2.91$ ($P < 0.004$).

Nurmatov et al. Allergy. 2017 May 11. doi: 10.1111/all.13201.

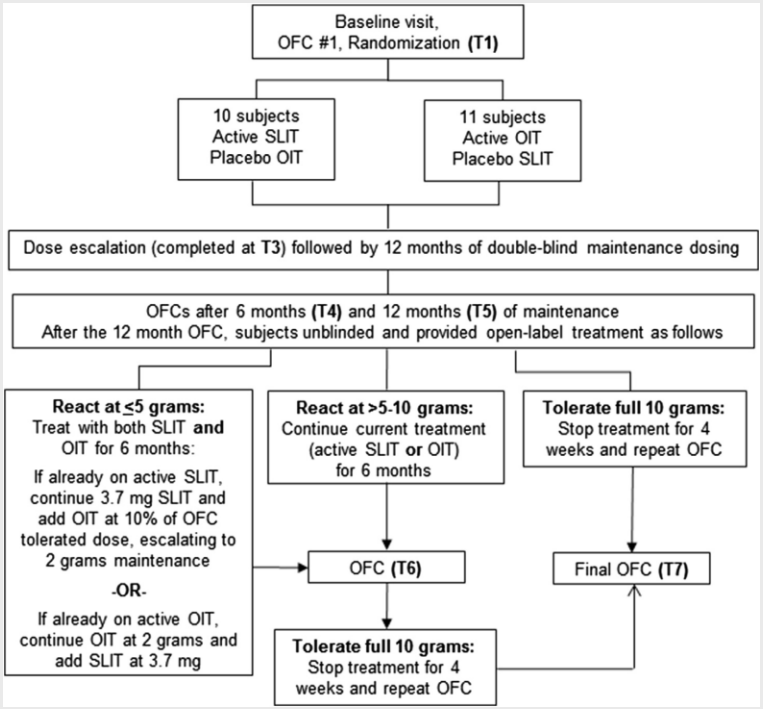
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Sublingual versus Oral Immunotherapy for the Treatment of Peanut Allergy

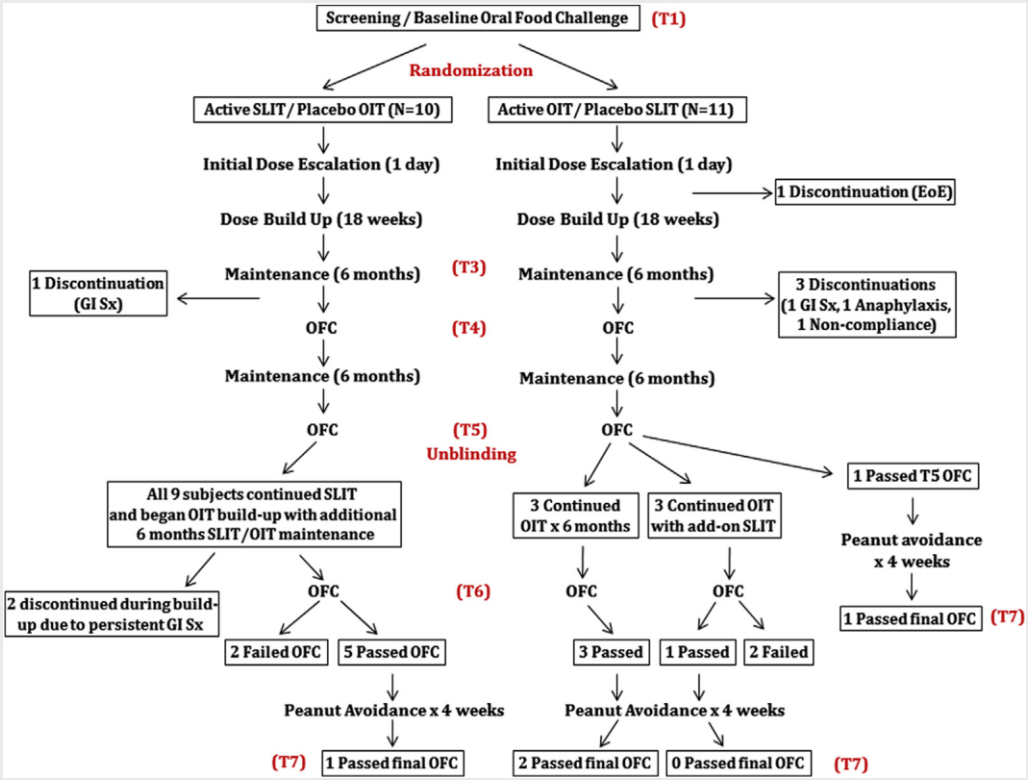
Satya D. Narisety[1], Pamela A. Frischmeyer-Guerrerio[2,*], Corinne A. Keet[2], Mark Gorelik[2], John Schroeder[3], Robert G. Hamilton[3], and Robert A. Wood[2]

- To compare head to head Oral and SLIT for peanut allergy in children (6-21yrs).
- Double-blind study, randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT.
- Doses escalated to 3.7mg/day (SLIT) or 2000mg/day (OIT).
- Subjects re-challenged after 6 and 12 months of maintenance.
- Primary endpoint: Peanut desensitization, defined as a 10-fold increase in the oral food challenge (OFC) threshold after 12 months of therapy.

Narisety et al. J Allergy Clin Immunol 2015; 135:1275-82

SLIT or Oral-AIT for Peanut allergy

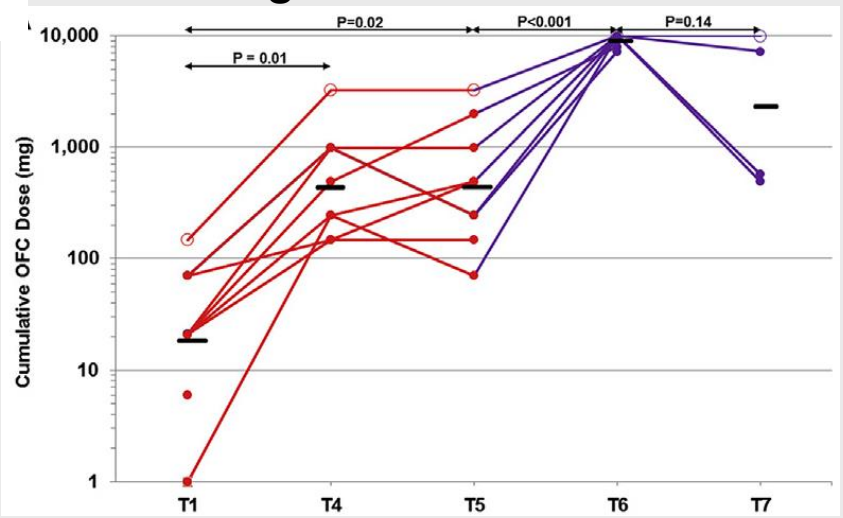




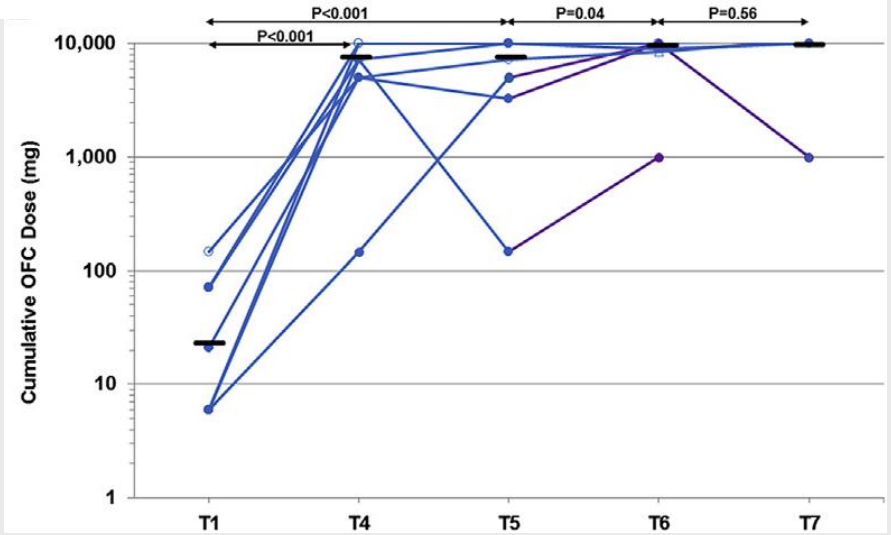
Narisety et al. J Allergy Clin Immunol 2015; 135:1275-82

SLIT or Oral-AIT for Peanut allergy

Change in cumulative OFC dose after SLIT



Change in cumulative OFC dose af



- **Safety : The proportion of doses with adverse reactions was significantly higher in the OIT group (43% vs 9% of doses, P <.001).**

Narisety et al. J Allergy Clin Immunol 2015; 135:1275-82

Summary and Take-Home Message

- **OIT appeared far more effective than SLIT for the treatment of Peanut Allergy**
- **OIT is associated with significantly more adverse reactions than SLIT**
- **Sustained unresponsiveness is demonstrated in only a minority of subjects**

List of References

1. Silverberg JI, et al. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013; 1132.
2. Silverberg JI, et al. Addressing treatment challenges in atopic dermatitis with novel topical therapies. J Dermatolog Treat 2016; 27: 568–76.
3. Ring J, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012; 26: 1045–60.
4. Blauvelt A, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017 May 4. Ahead of print.
5. Simpson EL, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis.. N Engl J Med. 2016 Dec 15;375(24):2335-2348
6. Mullard A, et al. FDA approves dupilumab for severe eczema.. Nat Rev Drug Discov. 2017 Apr 28;16(5):305.
7. Bousquet J, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001 Nov;108(5 Suppl):S147-334.
8. Calderon M et al. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007; (1):CD001936
9. Frew AJ, et al. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006 Feb;117(2):319-25.
10. Radulovic S et al, Systematic reviews of sublingual immunotherapy (SLIT). CochraneDatabase Syst Rev. 2011
11. Creticos PS, et al. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol. 2013 May;131(5):1342-9.

List of References (continued)

12. Durham SR, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. J Allergy Clin Immunol 2016;138:1081-8
13. Nurmatov et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy 2017; accepted
14. Vickery BP, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017 Jan;139(1):173-181
15. Narisety SD, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015 May;135(5):1275-82.
16. Gevaert P, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011 Nov;128(5):989-95.
17. Bachert C, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. JAMA. 2016 Feb 2;315(5):469-79.
18. Durham SR, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999 Aug 12;341(7):468-75.
19. Durham SR, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol. 2012 Mar;129(3):717-725.
20. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis?. JACI 2016; 137: 339-349
21. Scadding GW, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. JAMA 2017; 317, 615-625.