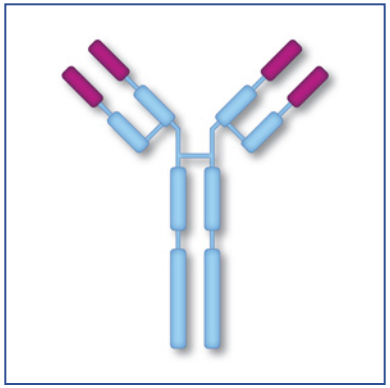
Pneumo Update Europe 2018

15 - 16th June, Budapest

Allergy



Stephen R Durham, UK

Allergy: Outline

1. **Allergen immunotherapy – what's new?**

2. Allergen avoidance strategies – new evidence in children

3. Allergy prevention - update on the LEAP and GAP trials

4. Upper airway disease – nasal polyps

5. Monoclonal Abs directed against *Fel d 1* for cat allergy

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 AIT OK)
- Lack of understanding, poor adherence to treatment

Allergen Immunotherapy – what's new?

- EAACI Systematic review and meta-analysis
- EAACI Guide on AIT for rhinoconjunctivitis
- Update on GRASS trial – mechanisms

Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis

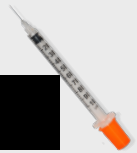
S. Dhami[1] | U. Nurmatov[2] | S. Arasi[3,4] | T. Khan[5] | M. Asaria[6] | H. Zaman[7] | A. Agarwal[8] | G. Netuveli[9] | G. Roberts[10,11,12] | O. Pfaar[13,14] | A. Muraro[15] | I. J. Ansotegui[16] | M. Calderon[17] | C. Cingi[18] | S. Durham[17] | R. Gerth van Wijk[19] | S. Halken[20] | E. Hamelmann[21,22] | P. Hellings[23] | L. Jacobsen[24] | E. Knol[25] | D. Larenas-Linnemann[26] | S. Lin[27] | P. Maggina[28] | R. Mösges[29] | H. Oude Elberink[30] | G. Pajno[31] | R. Pawankar[32] | E. Pastorello[33] | M. Penagos[17] | C. Pitsios[34] | G. Rotiroti[35] | F. Timmermans[36] | O. Tsilochristou[37] | E.-M. Varga[38] | C. Schmidt-Weber[39] | J. Wilkinson[39] | A. Williams[40] | M. Worm[41] | L. Zhang[42] | A. Sheikh[43]

Dhami S et al. Allergy 2017; 72: 1597-1631.

5932 studies, 160 eligible for systematic review

Allergen immunotherapy for allergic rhinitis

5932 studies reviewed, 160 elegible for systematic review



Subcutaneous immunotherapy

Symptom scores
SCIT 632; **PLACEBO** 499
n = 16; I^2: 62%; p <0.0001

- 0.65
- 0.86 - 0.43

Medication scores
SCIT 602; **PLACEBO** 464
n = 16; I^2: 64%; p <0.0001

- 0.52
- 0.75 - 0.29

Combined scores
SCIT 364; **PLACEBO** 338
n = 11; I^2: 58%; p <0.0001

- 0.51
- 0.77 - 0.26

- 1 0

FAVORS **SCIT**

Sublingual immunotherapy

Symptom scores
SLIT 2285; **PLACEBO** 2187
n = 41; I^2: 69%; p <0.0001

- 0.48
- 0.61 - 0.36

Medication scores
SLIT 1496; **PLACEBO** 1390
n = 29; I^2: 57%; p <0.0001

- 0.31
- 0.44 - 0.18

Combined scores
SLIT 375; **PLACEBO** 301
n = 4; I^2: 65%; p <0.008

- 0.47
- **0.81** - 0.12

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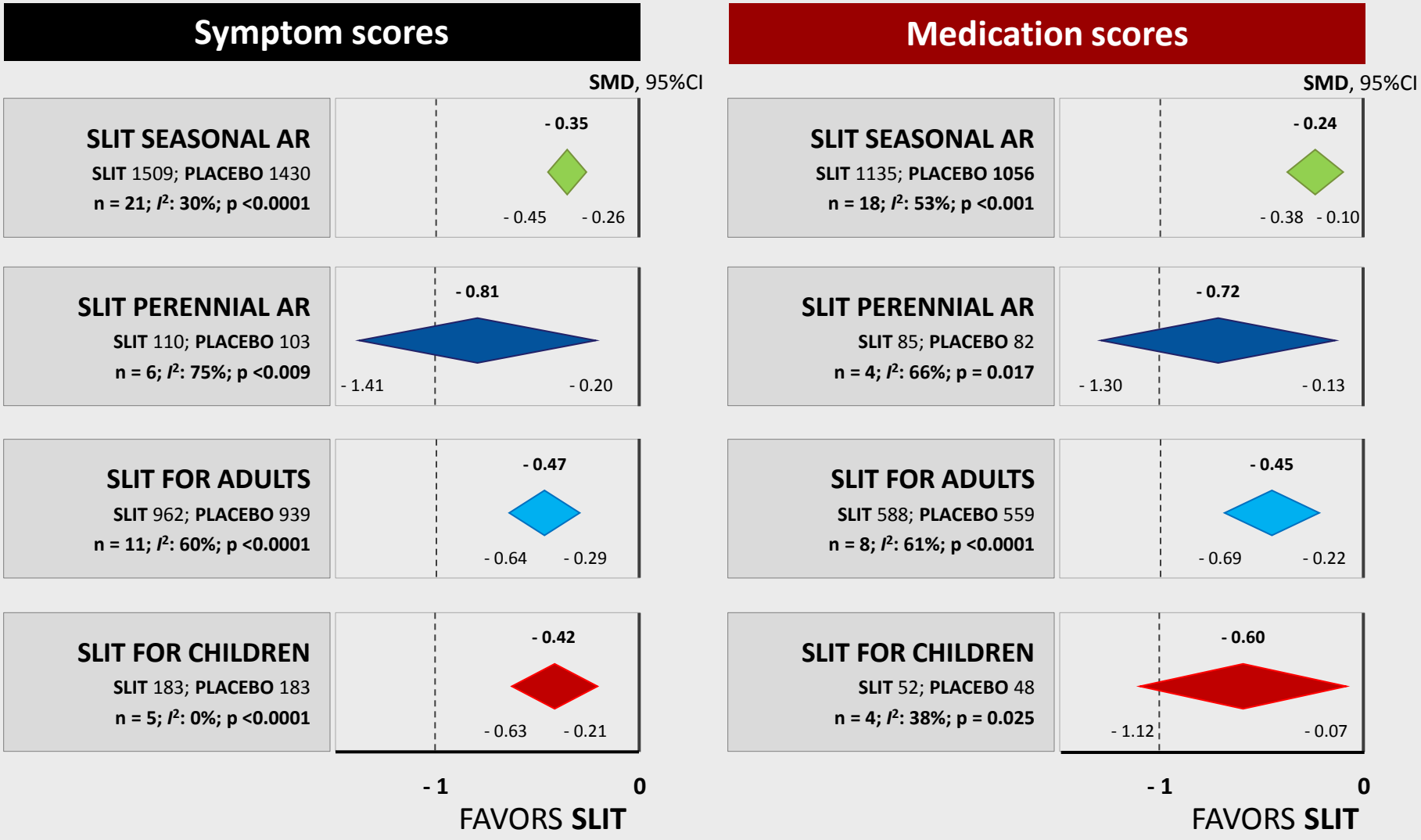
FAVORS **SLIT**

Dhami S, et al. Allergy 2017; 72: 1597-1631.

SLIT for allergic rhinitis (subgroup analyses)



Dhami S, et al. Allergy 2017; 72: 1597-1631.

EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis

G. Roberts[1,2,3*] | O. Pfaar[4,5*] | C. A. Akdis[6,7] | I. J. Ansotegui[8] | S. R. Durham[9] | R. Gerth van Wijk[10] | S. Halken[11] | D. Larenas-Linnemann[12] | R. Pawankar[13] | C. Pitsios[14] | A. Sheikh[15] | M. Worm[16] | S. Arasi[17,18] | M. A. Calderon[9] | C. Cingi[19] S. Dhami[20] | J. L. Fauquert[21] | E. Hamelmann[22] | P. Hellings[23,24] | L. Jacobsen[25] | E. F. Knol[26] | S. Y. Lin[27] | P. Maggina[28] | R. Mösges[29] | J. N. G. Oude Elberink[30,31] | G. B. Pajno[17] | E. A. Pastorello[32] | M. Penagos[9] | G. Rotiroti[33] | C. B. Schmidt-Weber[34] | F. Timmermans[35] | O. Tsilochristou[36] | E.-M. Varga[37] | J. N. Wilkinson[38] | A. Williams[39] L. Zhang[40] | I. Agache[41] | E. Angier[42] | M. Fernandez-Rivas[43] | M. Jutel[44,45] | S. Lau[46] | R. van Ree[47] | D. Ryan[48] | G. J. Sturm[49,50] | A. Muraro[51]

Roberts G et al. Allergy 2018; 73:765-798.

EAACI Guidelines on Allergen Immunotherapy: Executive Statement

Authors: Muraro A[1]*, Roberts G[2-4]*, Halken S[5], Agache A[6], Angier L[7], Fernandez–Rivas M[8], Gerth van Wijk R[9], Jutel M[10], Lau S[11], Pajno G[12], Pfaar O[13,14], Ryan D[15], Sturm GJ[16], van Ree R[17], Varga E-M[18], Bachert C[19], Calderon M[20], Canonica GW[21], Durham SR[20], Malling HJ[22], Wahn U[23], Sheikh A[24].

Muraro A et al. Allergy 2018; 73: 739-743

EAACI guidelines on allergen immunotherapy

Executive statement

- **The following can be recommended for AR for short-term benefit:**

	Adults			Children		
RECOMMENDATION	**A**	**B**	**C**	**A**	**B**	**C**
Continuous grass pollen SCIT	☑				☑	
Continuous grass pollen SLIT tablets	☑				☑	
HDM SLIT tablet (but not aqueous solution)	☑				☑	
Continuous SCIT for perennial allergens		☑				☑
Pre- and pre-/co-seasonal SCIT	☑				☑	
Modified (allergoids) and unmodified allergen SCIT extracts	☑				☑	
SLIT aqueous solutions for grass and tree pollens		☑		☑		

Muraro A et al. Allergy 2018; 73: 739-743

EAACI guidelines on allergen immunotherapy

Executive statement

- The following can be recommended for AR for **long-term benefit:**

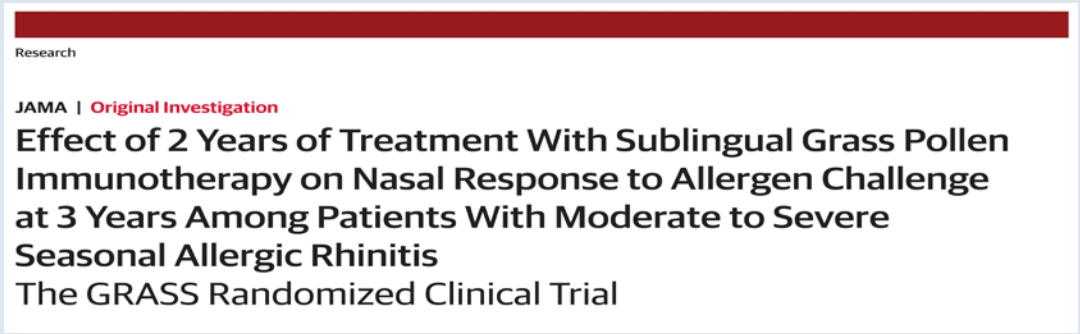
	Adults			Children		
RECOMMENDATION	**A**	**B**	**C**	**A**	**B**	**C**
Continuous grass pollen SCIT	☑				☑	
Continuous grass pollen SLIT	☑				☑	
HDM SLIT tablets (single DBPC study)	☑					

Muraro A et al. Allergy 2018; 73: 739-743

EAACI guidelines on allergen immunotherapy Summary

- An individual product-based evaluation of evidence for efficacy is recommended before treatment with a specific product is initiated
- To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used (Grade A).
- SCIT and initial SLIT dosage should be administered by competent staff with patients waiting in the clinic for at least 30 minutes after dose (Grade C).

Muraro A et al. Allergy 2018; 73: 739-743



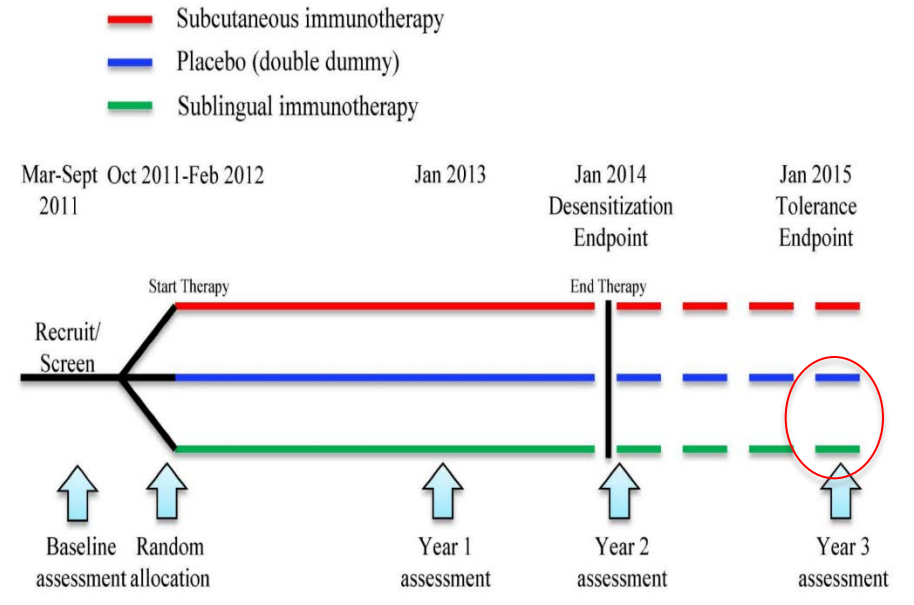
Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

SCIT (Alutard SQ® *Phleum Pratense*) containing 20 mcg Phl p 5 subcutaneous injections weekly updosing, monthly for 2 years

SLIT (Grazax® *Phleum Pratense*) containing 15 mcg Phl p 5 daily sublingual tablets for 2 years

GRASS TRIAL

Study Design

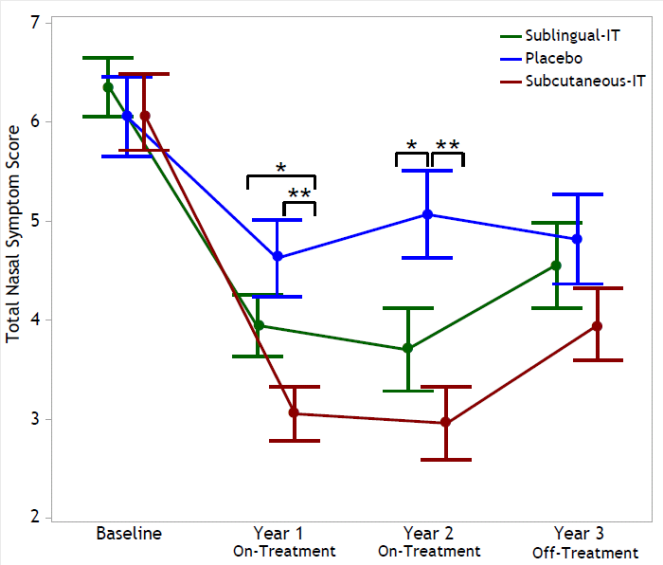


Participant Demographics

	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

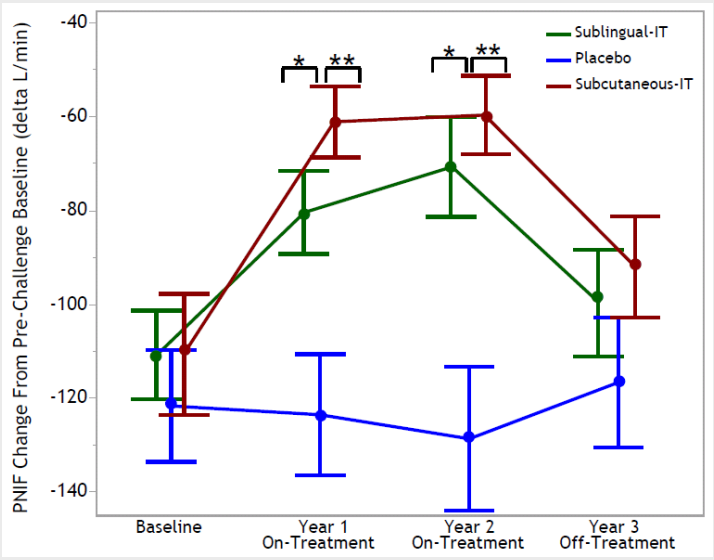
Scadding GW, Calderon M, Shamji M et al JAMA 2017;317:615-625

Primary endpoint: nasal allergen challenge (TNSS)



TOTAL NASAL SYMPTOM SCORE (TNSS)

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

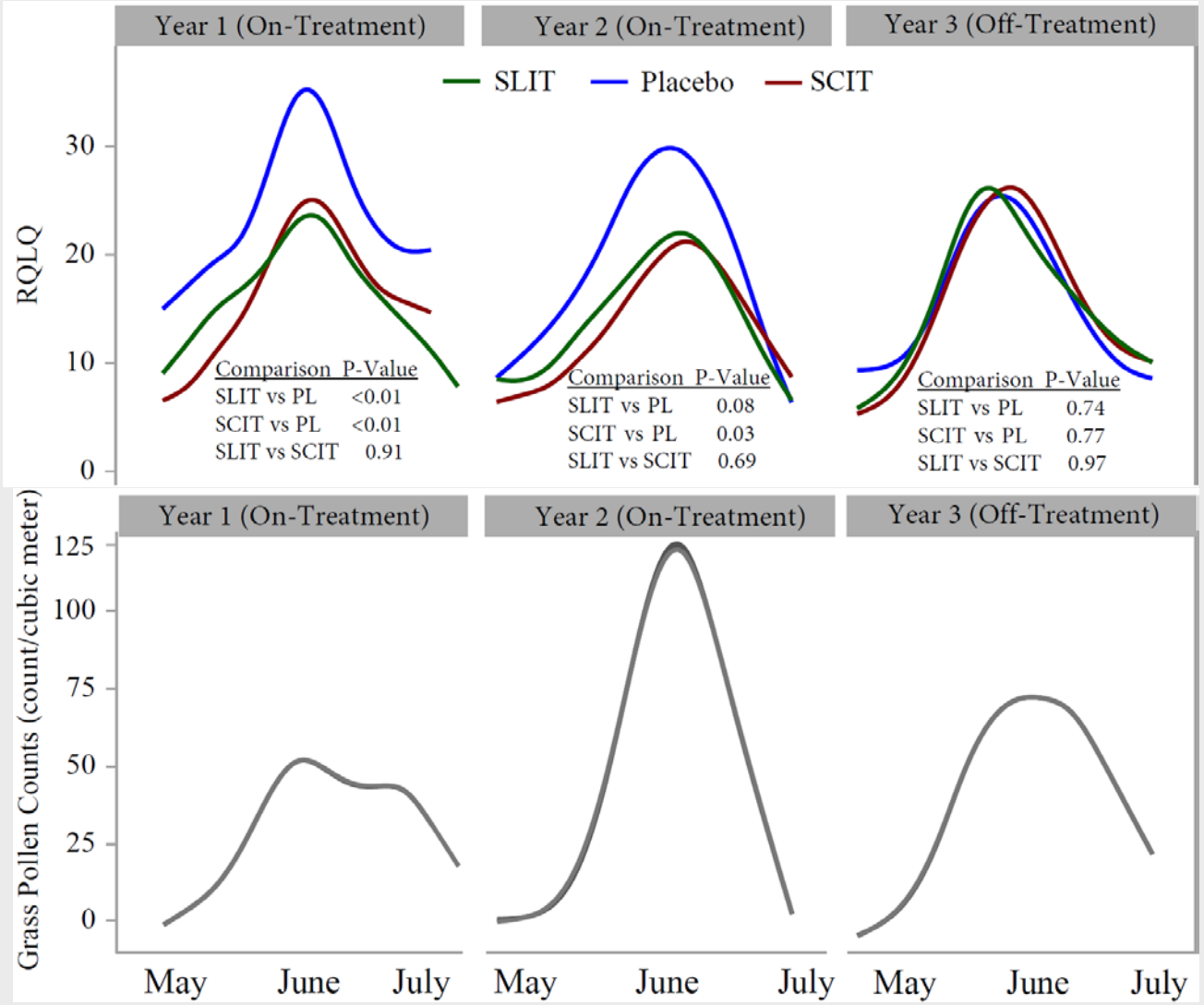


PEAK NASAL INSPIRATORY FLOW (PNIF)

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, et al JAMA 2017; 317: 615-625

GRASS: clinical conclusion

Two years treatment with sublingual or subcutaneous immunotherapy was highly effective (desensitisation) but insufficient for long-term clinical benefit (tolerance)

Mechanisms of allergic diseases

Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers

Mohamed H. Shamji, PhD, FAAAI, and Stephen R. Durham, MD, FRCP *London, United Kingdom*

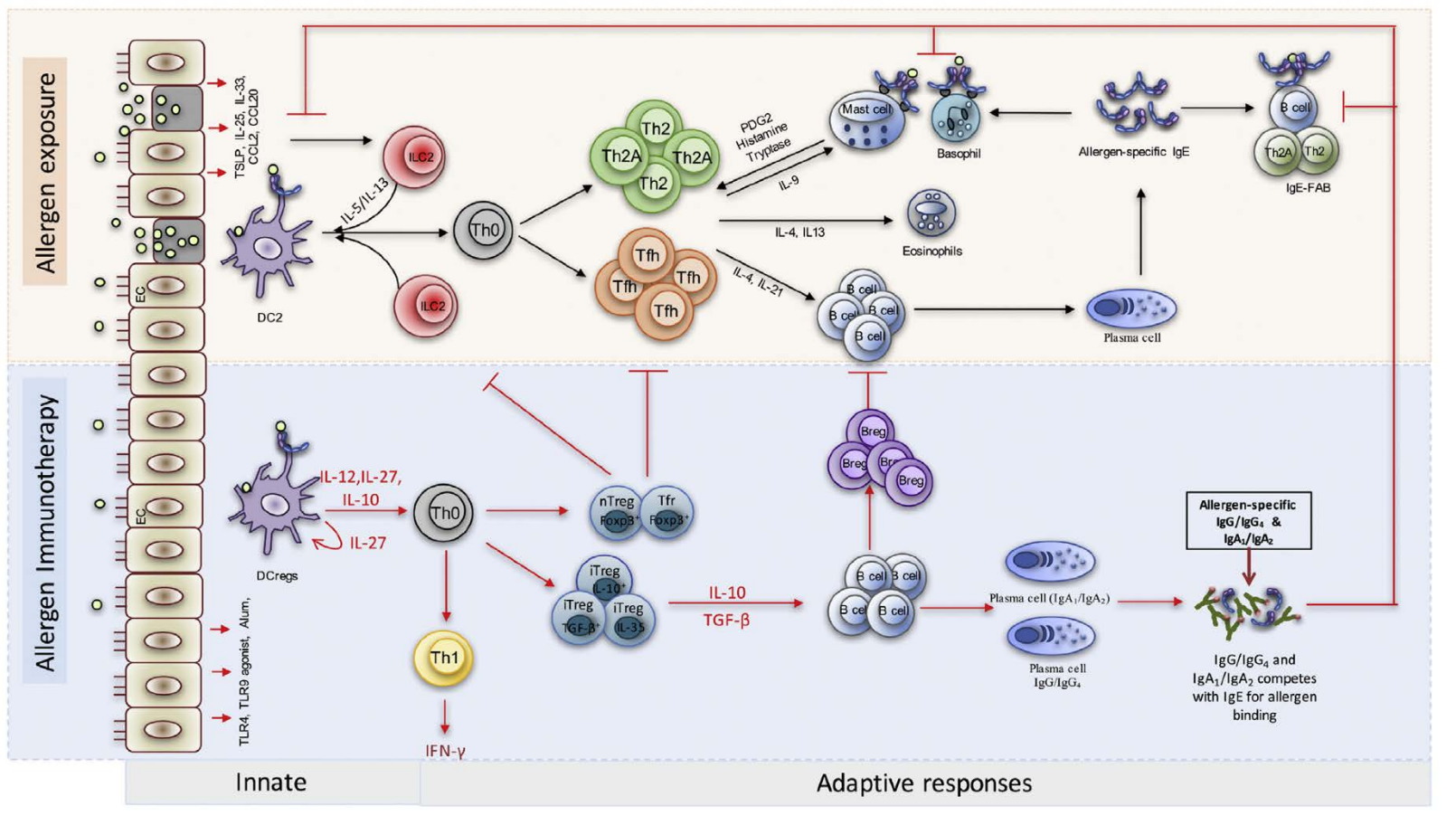
J Allergy Clin Immunol 2017 Dec;140:1485-1498

Synchronous immune alterations mirror clinical response during allergen immunotherapy

Amedee Renand, PhD,[a]* Mohamed H. Shamji, PhD,[b,f]* Kristina M. Harris, PhD,[c] Tielin Qin, PhD,[c] Erik Wambre, PhD,[a] Guy W. Scadding, MD,[b] Peter A. Wurtzen, PhD,[d] Stephen J. Till, PhD,[e,f] Alkis Togias, MD,[g] Gerald T. Nepom, MD, PhD,[a,c] William W. Kwok, PhD,[a] and Stephen R. Durham, MD[b,f] *Seattle, Wash, London, United Kingdom, Bethesda, Md, and Hørsholm, Denmark*

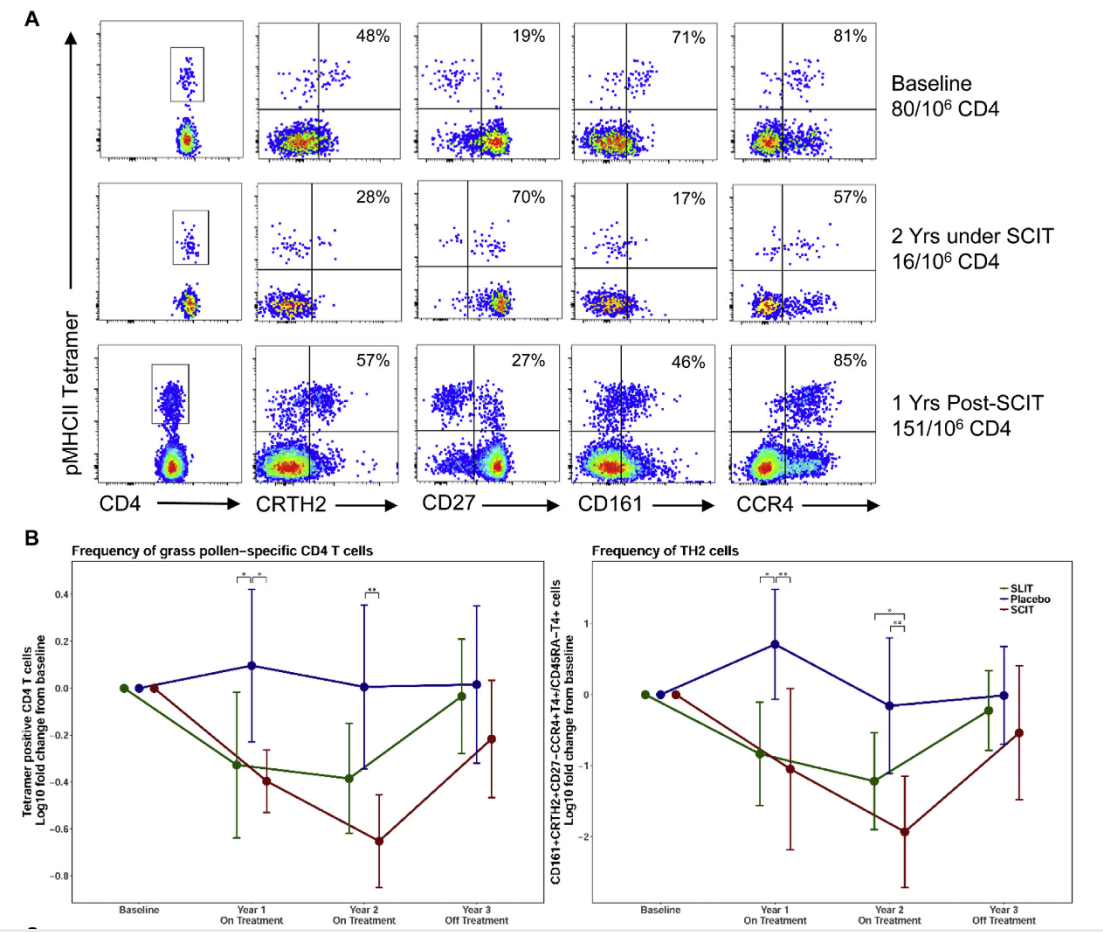
J Allergy Clin Immunol 2018;141:1750-60

Mechanisms of allergen immunotherapy



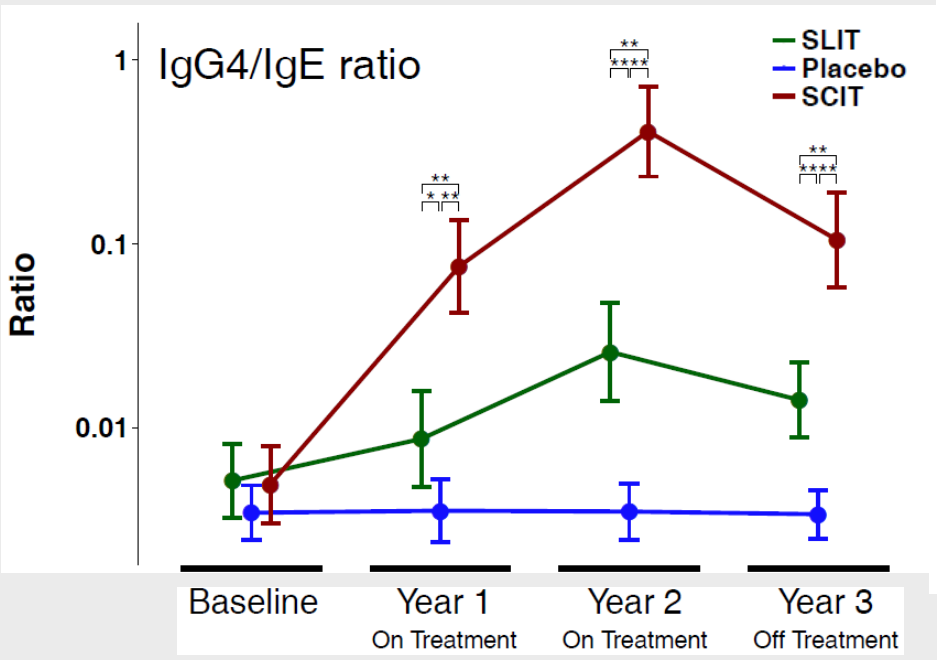
Shamji M and Durham S J Allergy Clin Immunol 2017 Dec;140:1485-1498

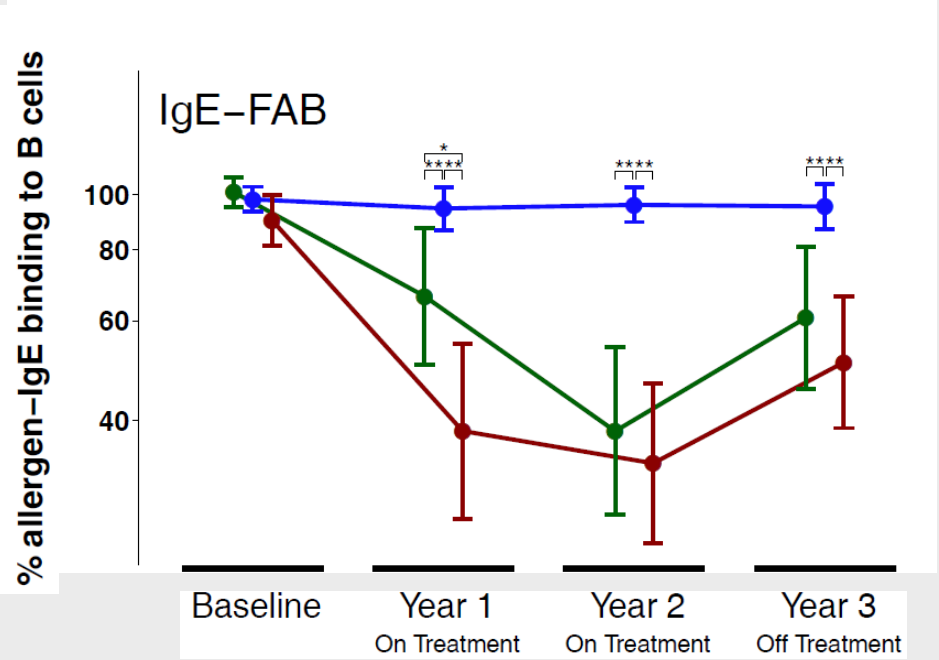
Allergen-specific CD4+Th2 cells



Renand A, Shamji M et al J Allergy Clin Immunol 2018;141:1750-60

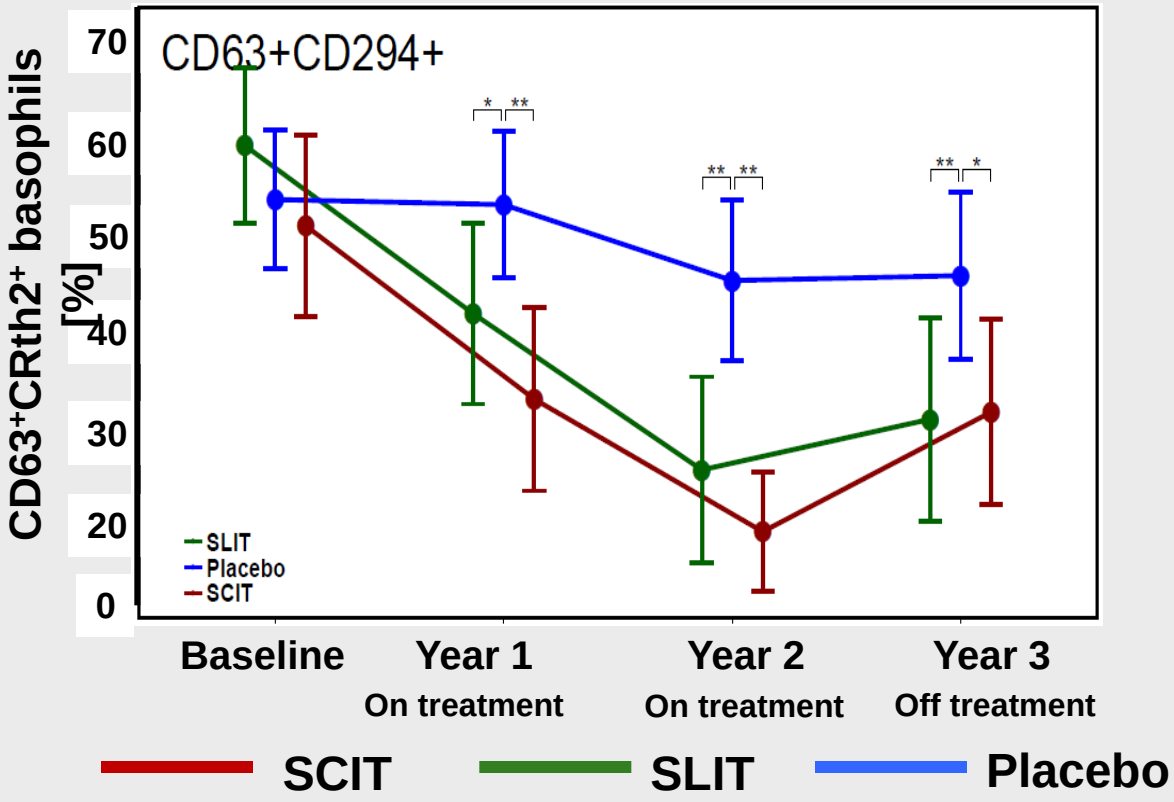
IgE/IgG4 ratio and IgE-Blocking activity





Renand A, Shamji M et al J Allergy Clin Immunol 2018;141:1750-60

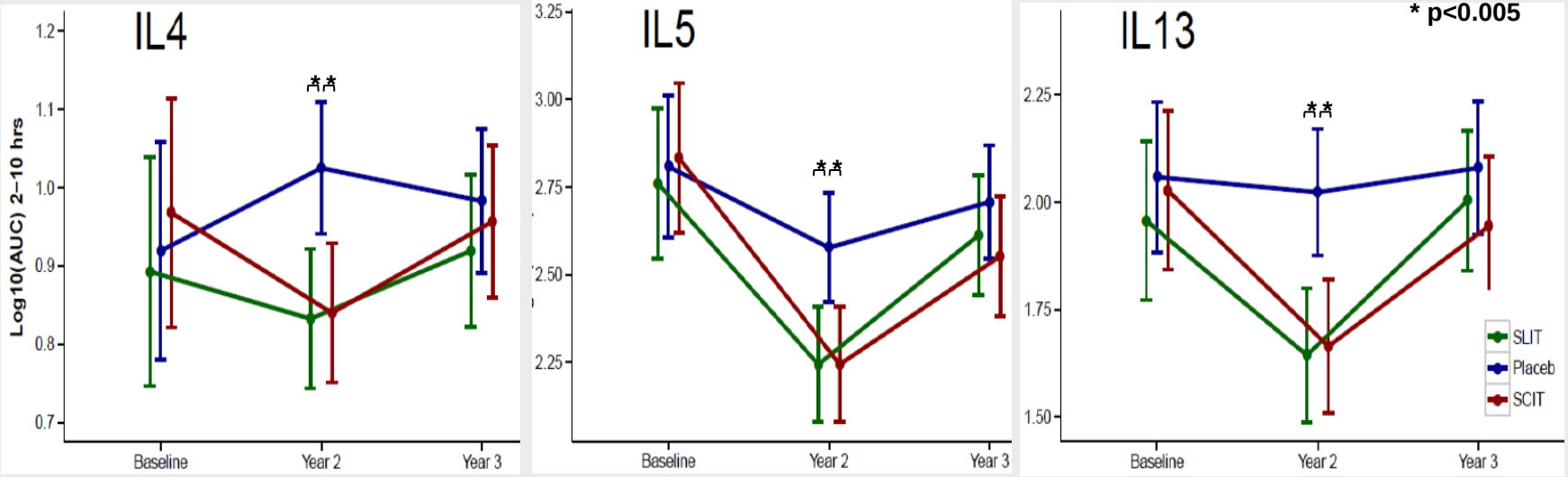
Basophil activation (surface CD63)



Renand A, Shamji M et al J Allergy Clin Immunol 2018;141:1750-60

Nasal fluid collection

Th2 cytokines in nasal fluid



Renand A, Shamji M et al J Allergy Clin Immunol 2018;141:1750-60

GRASS: mechanistic conclusions

- SLIT and SCIT were similar in suppressing Th2 immunity and inducing local and systemic blocking antibodies
- Suppression of Th2 T cell immunity is essential for *induction of tolerance* and closely paralleled clinical response
- Modified B cell responses (IgG4/IgE-FAB inhibition) may be necessary for *persistence of long-term tolerance*

Renand A, Shamji M et al J Allergy Clin Immunol 2018;141:1750-60

TAKE HOME MESSAGE

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

Allergy: Outline

1. Allergen immunotherapy – what's new?

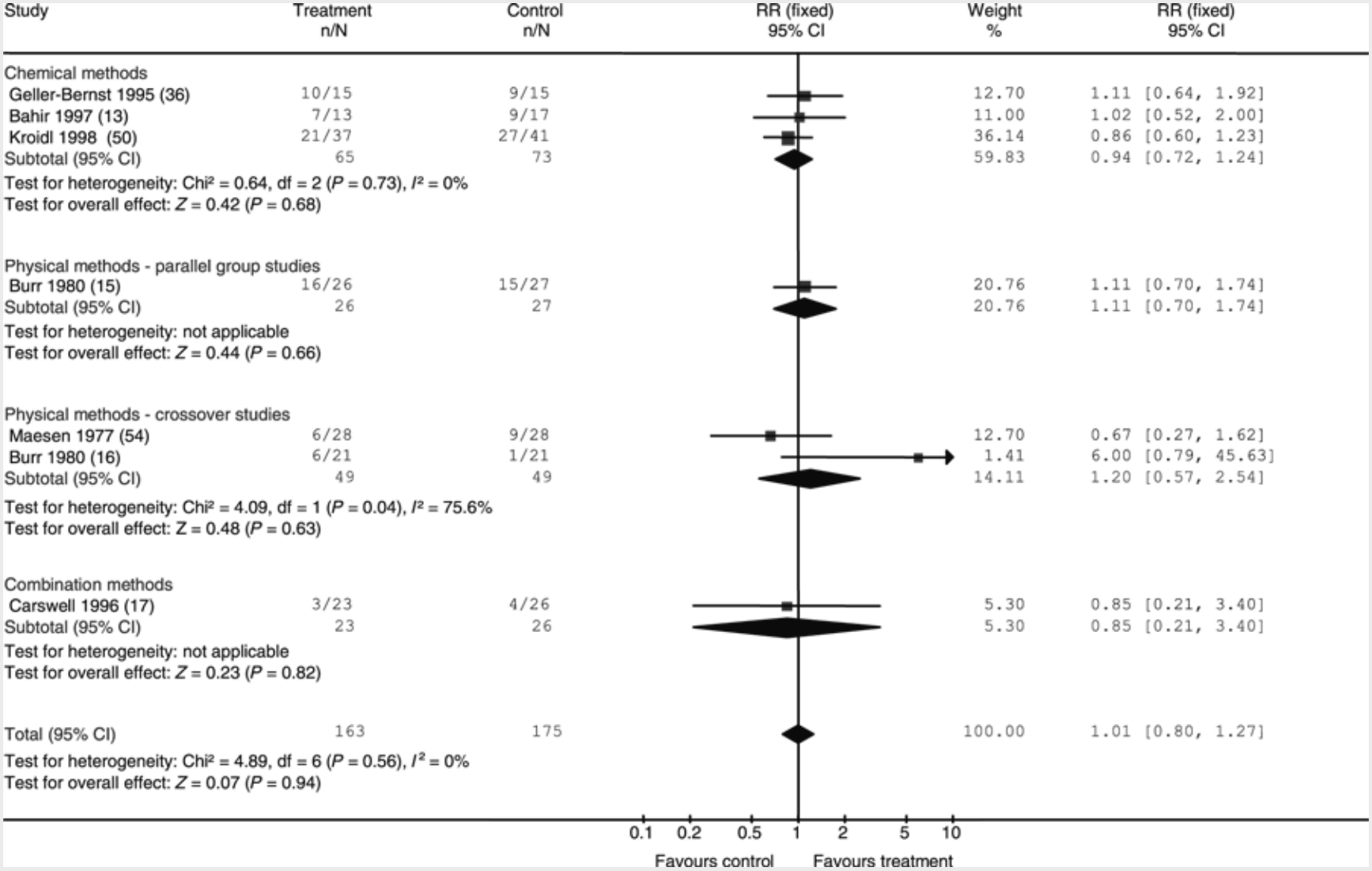
2. **Allergen avoidance – new evidence in children**

3. Allergy prevention - update on the LEAP and GAP trials

4. Upper airway disease – nasal polyps

5. Monoclonal Abs directed against *Fel d 1* for cat allergy

House dust mite control measures for asthma: systematic review



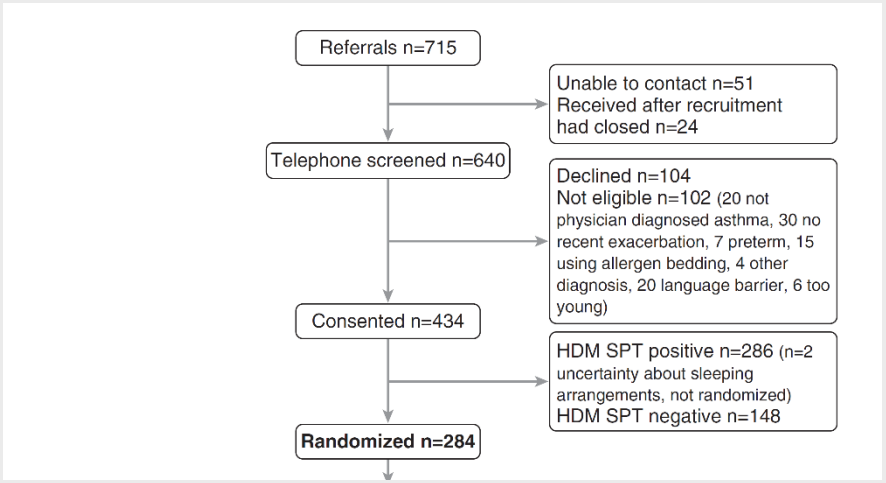
Gotzsche P, Johansen P, et al. Allergy 2008; 63: 646 – 659

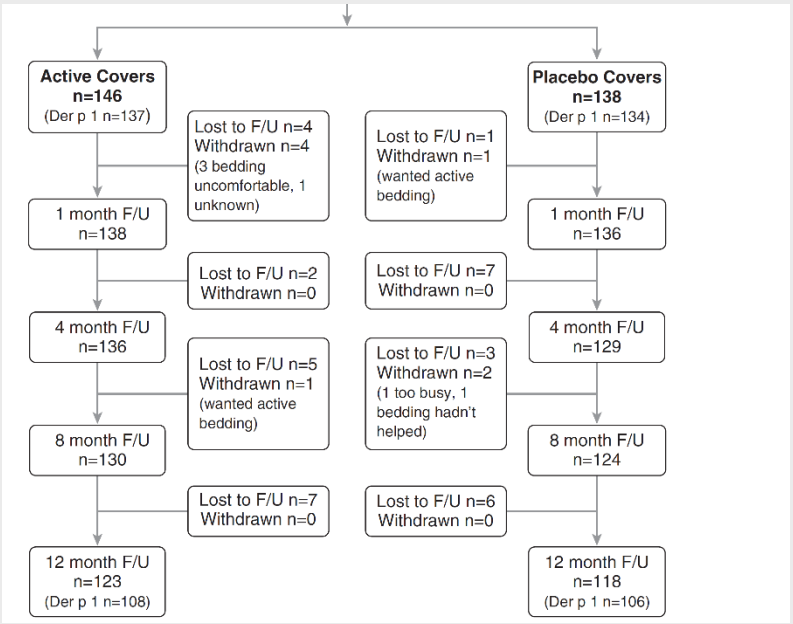
Preventing Severe Asthma Exacerbations in Children

A Randomized Trial of Mite-Impermeable Bedcovers

Clare S. Murray[1,2,3], Philip Foden[1,2], Helen Sumner[1], Elizabeth Shepley[1,2,4], Adnan Custovic[5], and Angela Simpson[1,2]

[1]Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom; [2]University Hospital of South Manchester, Manchester, United Kingdom; [3]Royal Manchester Children's Hospital, Central Manchester University Hospitals National Health Service Foundation Trust, Manchester, United Kingdom; [4]National Institute for Health Research South Manchester Respiratory and Allergy Clinical Research Facility, University Hospital of South Manchester, United Kingdom; and [5]Department of Paediatrics, Imperial College London, London, United Kingdom





Murray CS et al. Am J Respir Crit Care Med 2017; 196: 150-8.

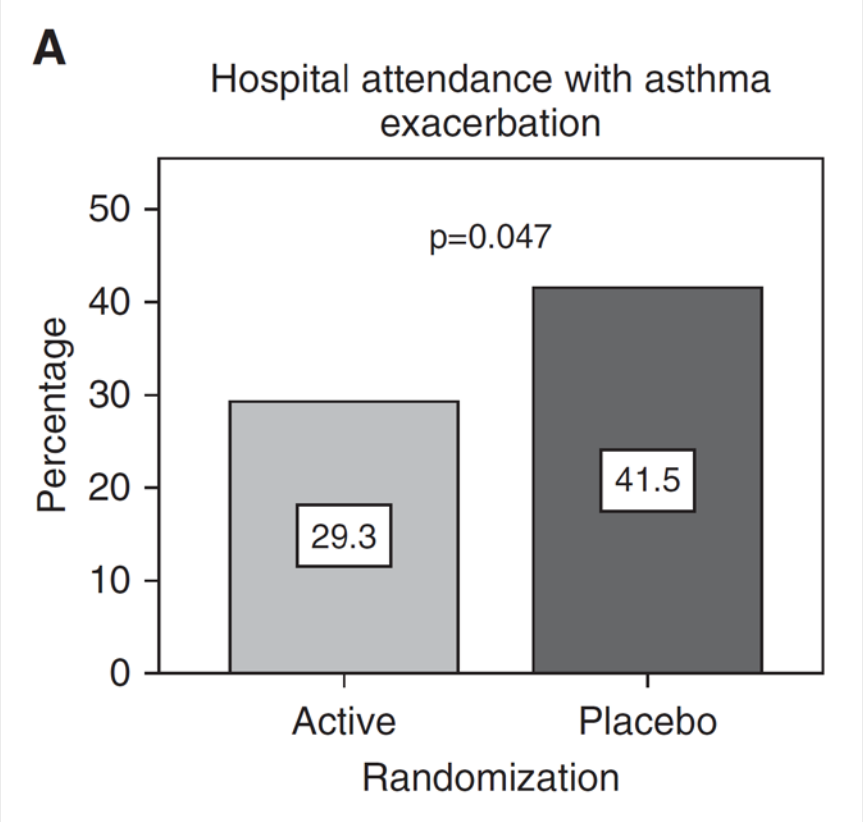
Participant demographics

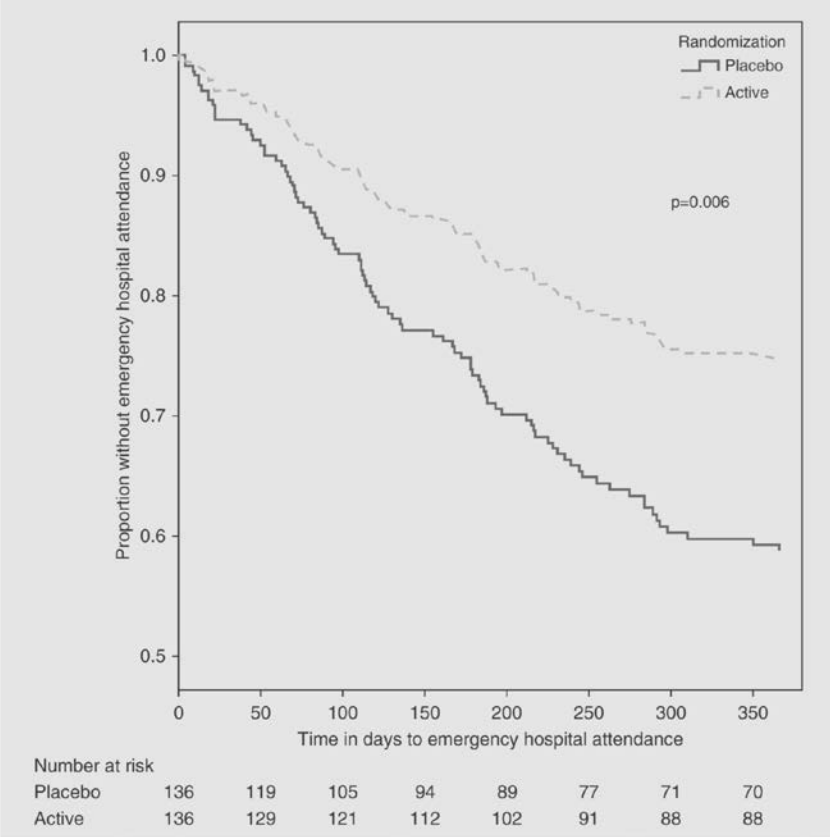
	Placebo Bedcovers (*n* = 138)	Mite-Impermeable Bedcovers (Active) (*n* = 146)	*P* Value
Age, yr, mean (SD)	7.45 (3.55)	7.11 (3.49)	0.42
Ages 3–10 yr	106 (76.8%)	117 (80.1%)	0.50
Ages 11–17 yr	32 (23.2%)	29 (19.9%)	
Male sex	94 (68.1%)	93 (63.7%)	0.43
Race/ethnicity		(n = 143)	0.96
White	89 (64.5%)	91 (63.6%)	
Asian	35 (25.4%)	36 (25.2%)	
Other	14 (10.1%)	16 (11.2%)	
Current hay fever	41 of 134 (30.6%)	46 of 129 (35.7%)	0.38
Current eczema	71 (51.8%)	57 of 140 (40.7%)	0.07
Food allergy	26 of 130 (20.0%)	40 of 138 (29.0%)	0.09
Maternal asthma	43 (31.2%)	39 of 142 (27.5%)	0.50
Paternal asthma	30 of 134 (22.4%)	40 of 142 (28.2%)	0.27
Maternal smoking	35 (25.4%)	34 of 145 (23.4%)	0.71
Paternal smoking	31 of 133 (23.3%)	43 of 141 (30.5%)	0.18
Smoking by a household member	57 (41.3%)	67 (45.9%)	0.44
Deprivation index, mean (SD)	34.16 (19.34)	34.74 (17.32)	0.79
Sensitized to*			
Mite	138 of 138 (100%)	146 of 146 (100%)	
Mite only	50 of 125 (40%)	60 of 130 (46.1%)	0.28
Cat	46 of 125 (36.8%)	46 of 130 (35.4%)	0.81
Dog	45 of 125 (36.0%)	44 of 130 (33.8%)	0.72
Grass	49 of 129 (38.0%)	46 of 136 (33.8%)	0.48
Aspergillus	8 of 126 (6.3%)	3 of 136 (2.2%)	0.09
Tree pollen	7 of 125 (5.6%)	4 of 135 (3.0%)	0.29
Number of allergens sensitized to, excluding HDM, median (IQR)	1 (0–2) (n = 131)	1 (0–2) (n = 135)	0.55
Pet contact	58 of 137 (42.3%)	64 of 145 (44.1%)	0.76
Cat owner	22 of 137 (16.1%)	21 of 145 (14.5%)	0.71
Dog owner	31 of 137 (22.6%)	36 of 145 (24.8%)	0.66
Sensitized and exposed to pet†	29 (21.0%)	31 (21.2%)	0.96
GINA step			0.98
GINA steps 1–2	72 (52.2%)	76 (52.1%)	
GINA step ⩾3	66 (47.8%)	70 (47.9%)	

Definition of abbreviations: GINA = Global Initiative for Asthma; HDM = house dust mite; IQR = interquartile range.
*All children had positive skin test results to house dust mite, but not all children completed the skin test for other allergens.
†Ascertained on the basis of skin prick testing or symptom reports from parents and pet ownership/exposure.

Murray CS et al. Am J Respir Crit Care Med 2017; 196: 150-8.

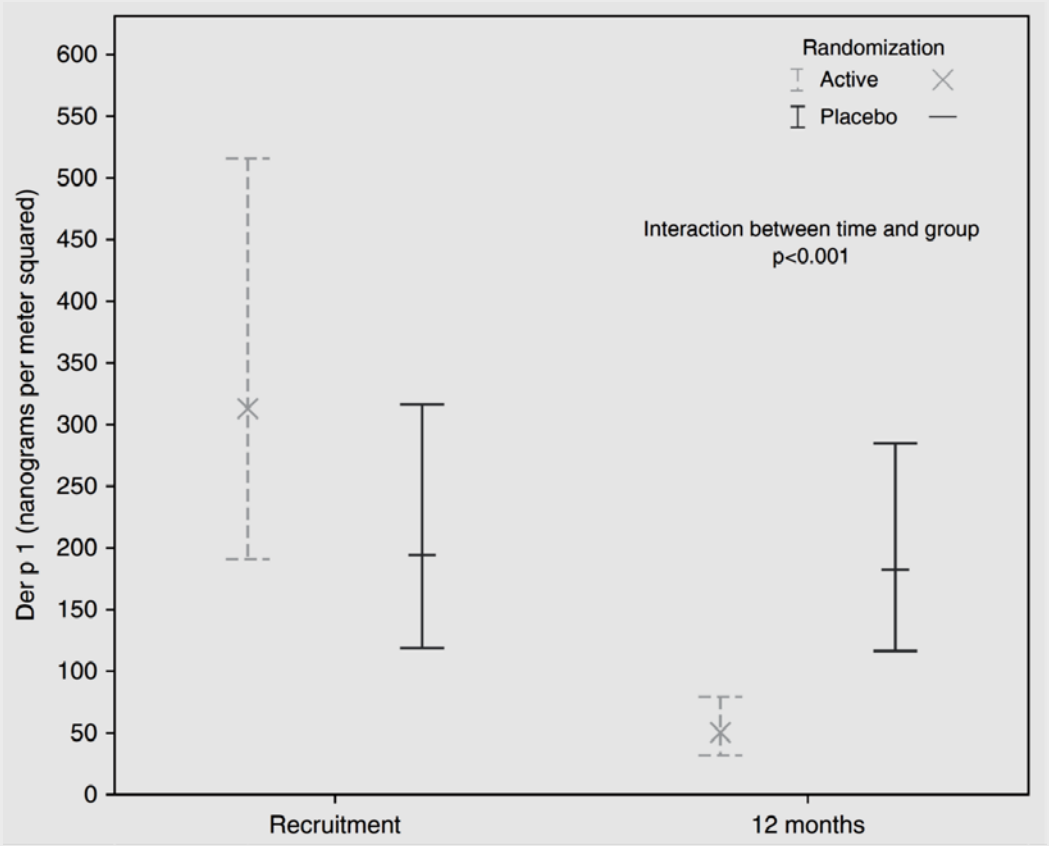
Asthma exacerbations and time to first exacerbation





Murray CS et al. Am J Respir Crit Care Med 2017; 196: 150-8.

HDM Der p 1 levels in mattress



Mite allergen (Der p 1) levels in child's mattress (ng/m2) at recruitment and 12 months after intervention. Results are shown as geometric mean and 95% confidence intervals for active (mite- impermeable) bedcovers (dashed line) and placebo bedcovers (solid line).

At a Glance Commentary

Scientific Knowledge on the Subject: Asthma exacerbations in children are a leading cause of hospitalization. Exposure in sensitized individuals, in synergy with viral infections, greatly increases hospital admission risk. In the developed world, the house dust mite is the commonest sensitizing allergen. In no studies done to date have researchers investigated the effect of allergen avoidance on asthma exacerbations and hospital admissions in children.

What This Study Adds to the Field: The use of mite-impermeable bedding for mite-sensitized children with asthma can significantly reduce the risk of severe exacerbations that would result in emergency hospital attendance.

Murray CS et al. Am J Respir Crit Care Med 2017; 196: 150-8.

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3. **Allergy prevention - update on the LEAP and GAP trials**

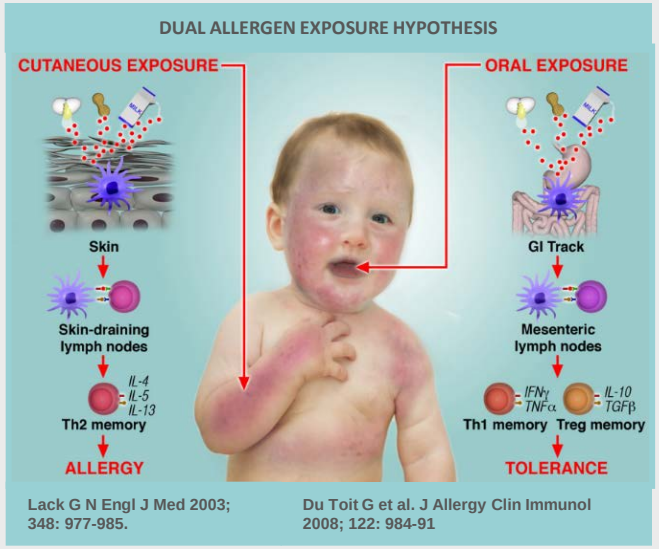
4. Upper airway disease – nasal polyps

5. Monoclonal Abs directed against *Fel d 1* for cat allergy

ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

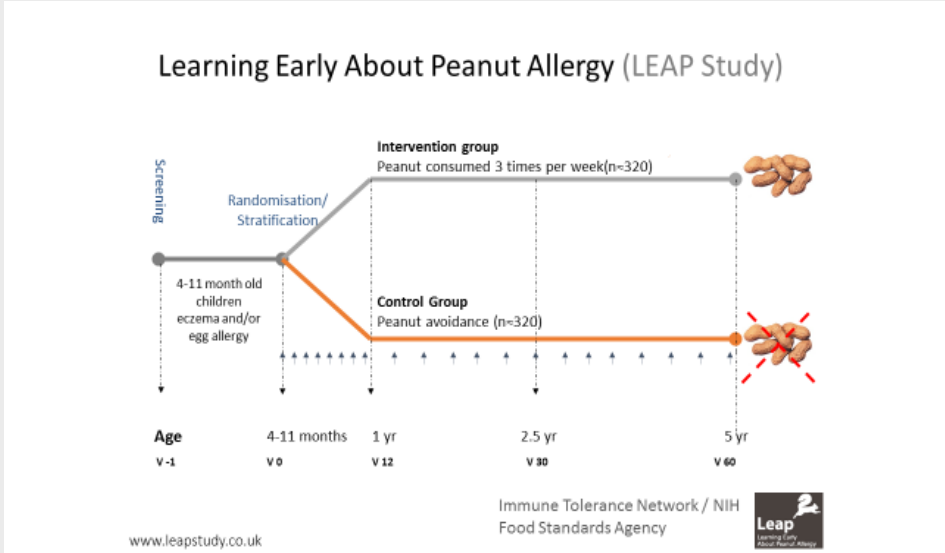
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*



Lack G N Engl J Med 2003; 348: 977-985.

Du Toit G et al. J Allergy Clin Immunol 2008; 122: 984-91

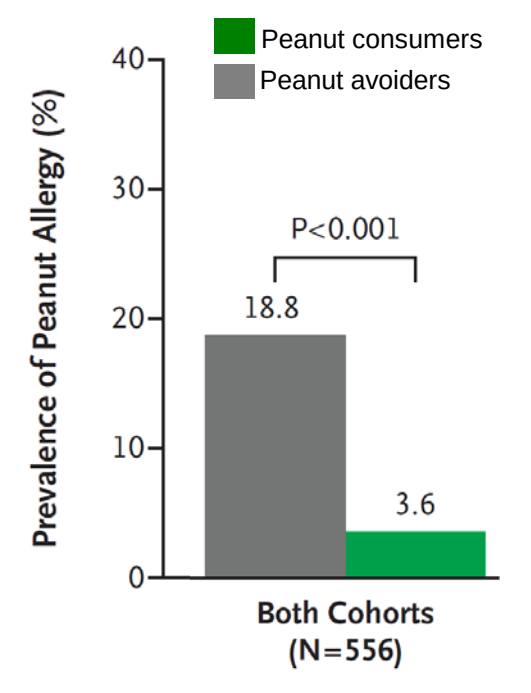


N Engl J Med. 2015;372:803-13.
N Engl J Med. 2016 ;374:1435-43.

Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

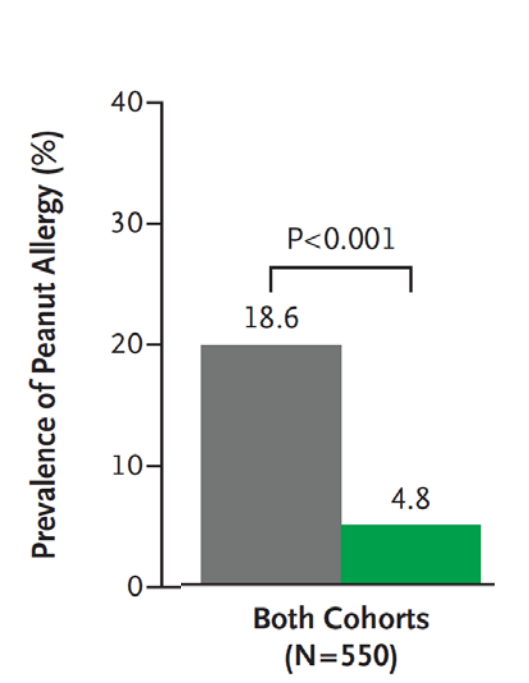
George Du Toit, M.B., B.Ch., Peter H. Sayre, M.D., Ph.D., Graham Roberts, D.M.,

60 months after Randomisation to eat or not eat peanut



N Engl J Med. 2015;372:803-13.

At 72 months (12 months avoidance both groups)



N Engl J Med. 2016 ;374:1435-43.

LEAP cohort (0-72 months):allergen specificity

(no difference in IgE to common aeroallergens in consumers v avoiders)

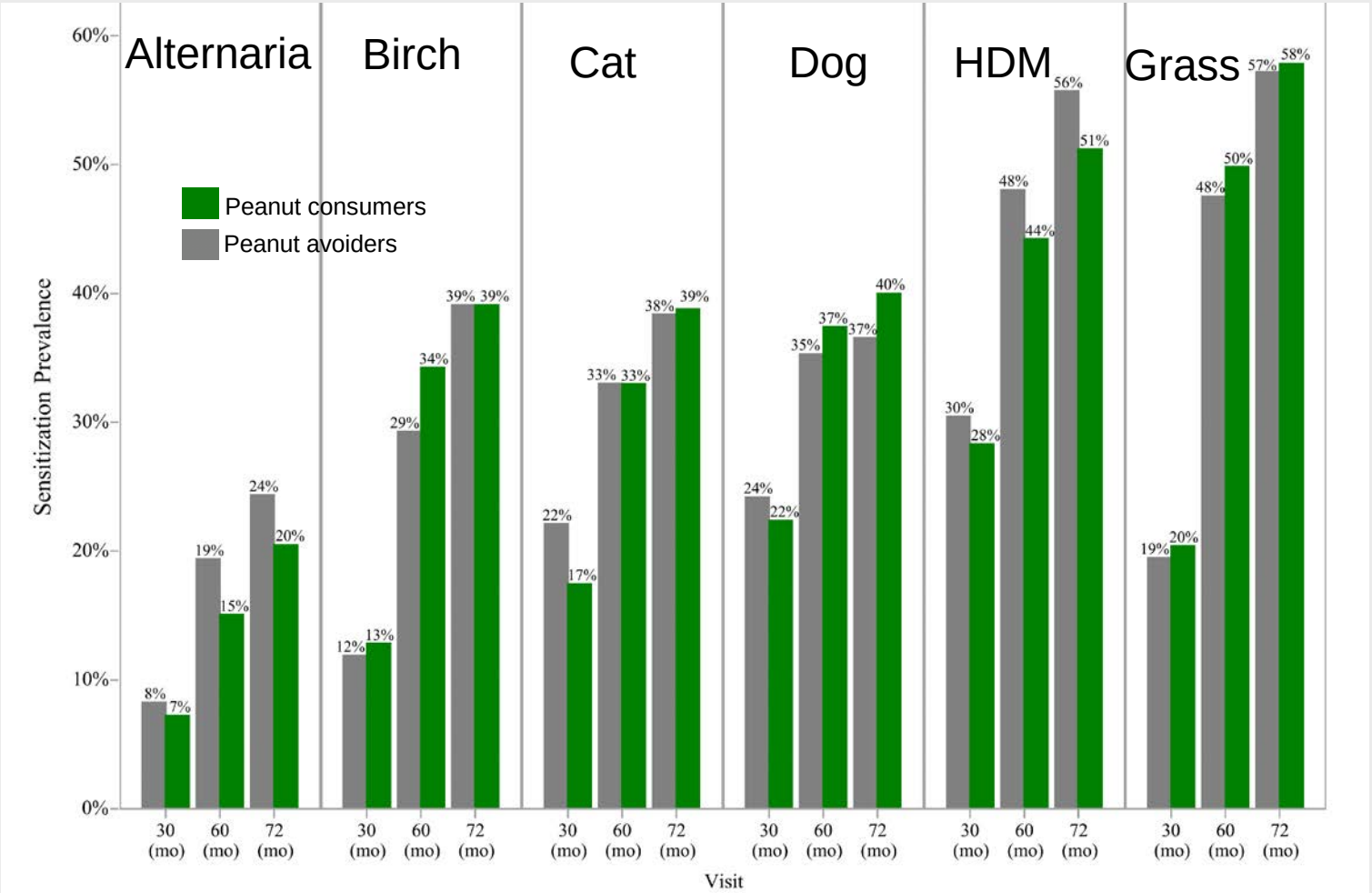


FIG 6. Aeroallergen sensitization. Prevalence of an IgE level of 0.35 kU/L or greater for several aeroallergens in the consumption *(green bars)* and avoidance *(gray bars)* groups at 30, 60, and 72 months of age are shown.

LEAP cohort (0-72 months): asthma and rhinitis prevalence

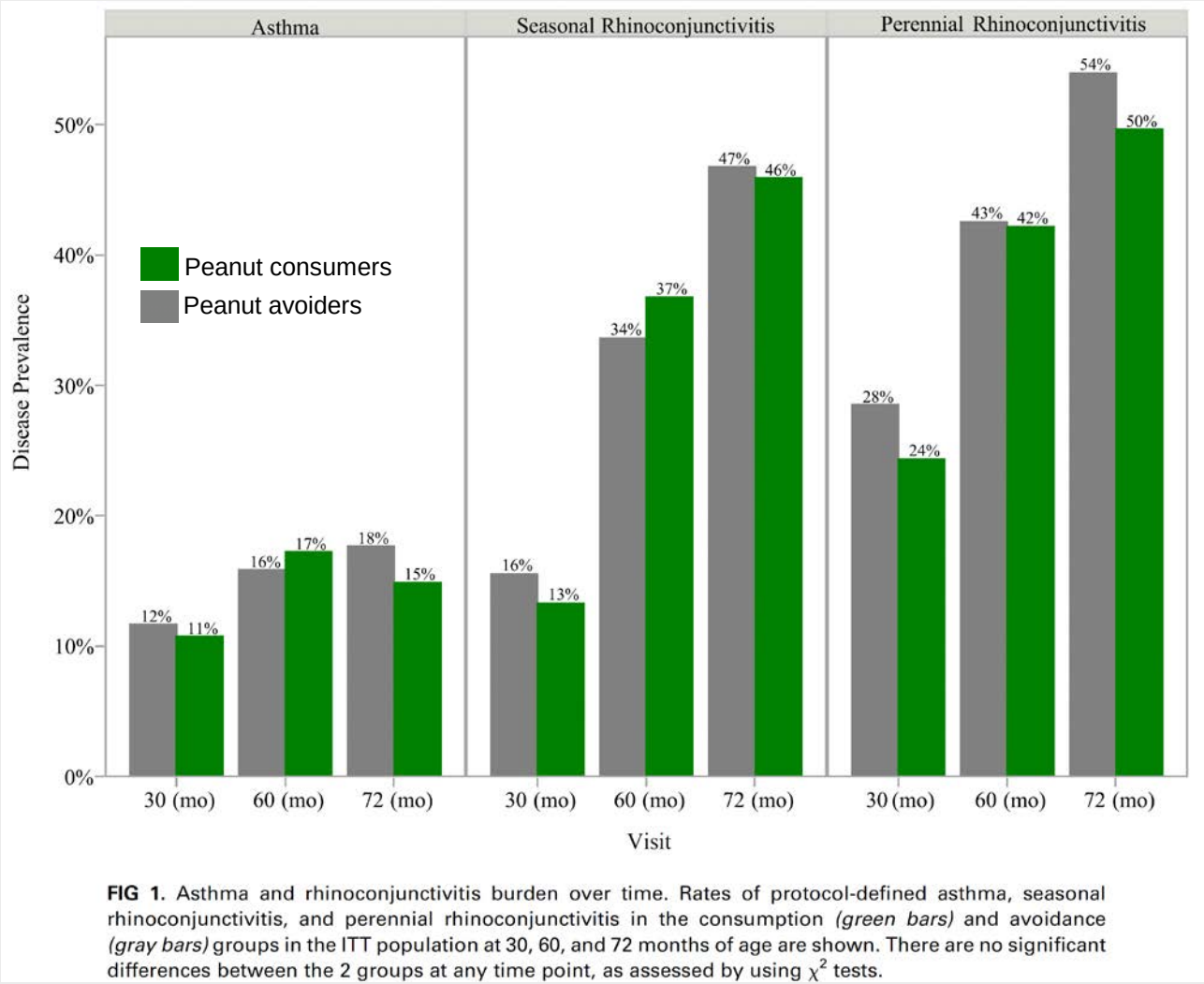


FIG 1. Asthma and rhinoconjunctivitis burden over time. Rates of protocol-defined asthma, seasonal rhinoconjunctivitis, and perennial rhinoconjunctivitis in the consumption *(green bars)* and avoidance *(gray bars)* groups in the ITT population at 30, 60, and 72 months of age are shown. There are no significant differences between the 2 groups at any time point, as assessed by using χ^2 tests.

LEAP cohort (0-72 months):
Atopic eczema (SCORAD) severity bands

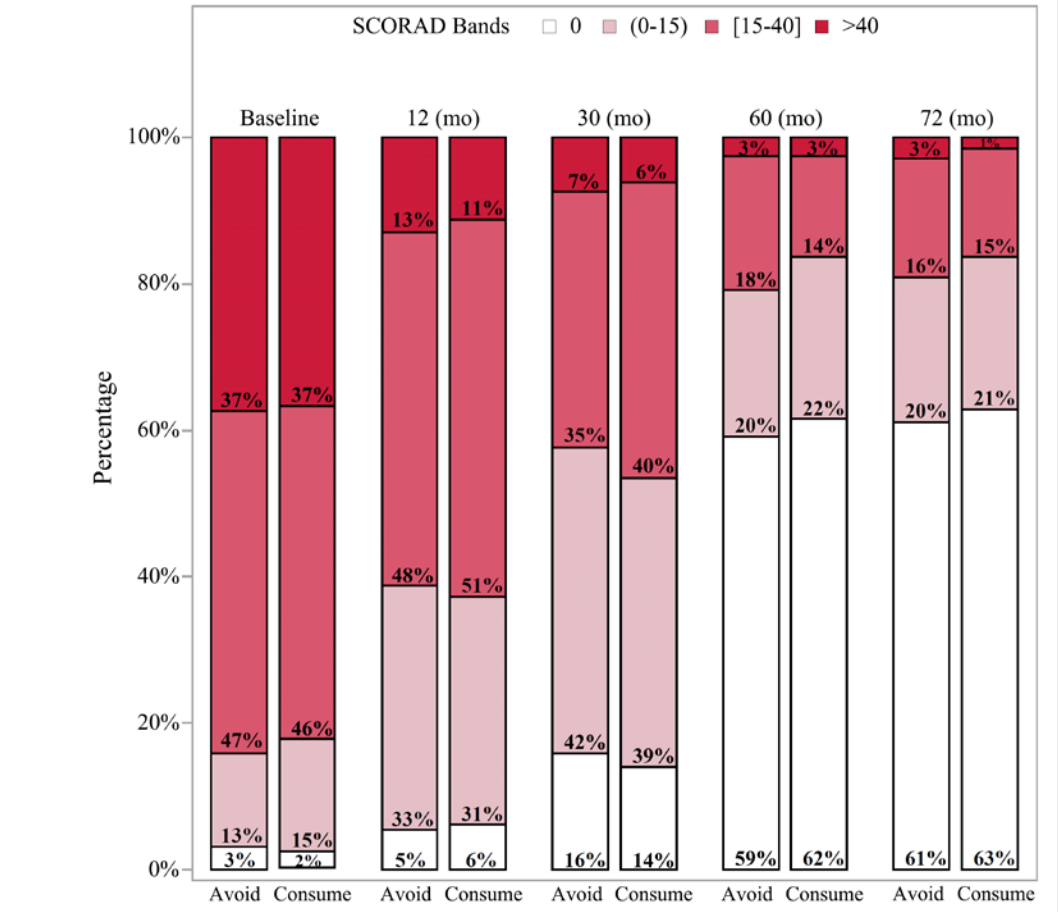


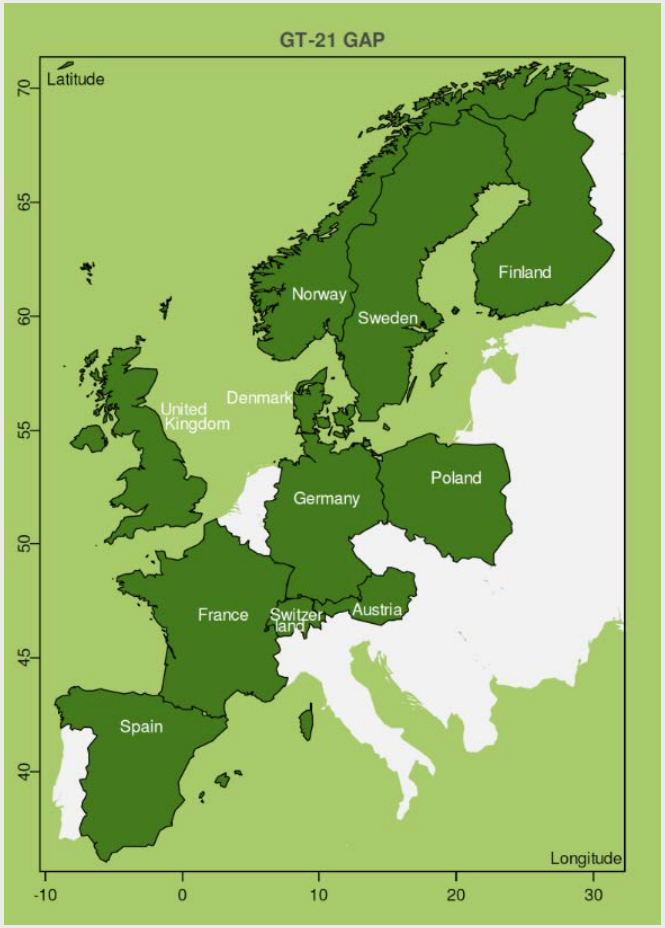
FIG 2. Eczema severity bands over time (SCORAD). Percentage of subjects with SCORAD assessments for eczema of 0, greater than 0 to 15, 15 or greater to 40, and greater than 40 are shown at baseline and at 12, 30, 60, and 72 months in the avoidance (*left bar* of each pair) and consumption (*right bar* of each pair) groups in the ITT population. There are no significant differences between the 2 groups at any time point, as assessed by using χ^2 tests.

Take-Home Message

- Protection afforded by early peanut introduction is allergen and allergic disease-specific

 duToit G, Sayre PH, Roberts G J Allergy Clin Immunol 2018; 141: 1343-53

Grass Asthma Prevention Trial -preventive effect on asthma development of an grass allergy immunotherapy tablet in children



- **101 trial centers distributed over 11 countries: Austria, Denmark, Finland, France, Germany, Norway, Poland, Spain, Sweden, Switzerland, and the United Kingdom.**
- **First child screened on Nov 24, 2009, and the screening target was met on June 21, 2010.**
- **Screening resulted in 812 randomized children.**

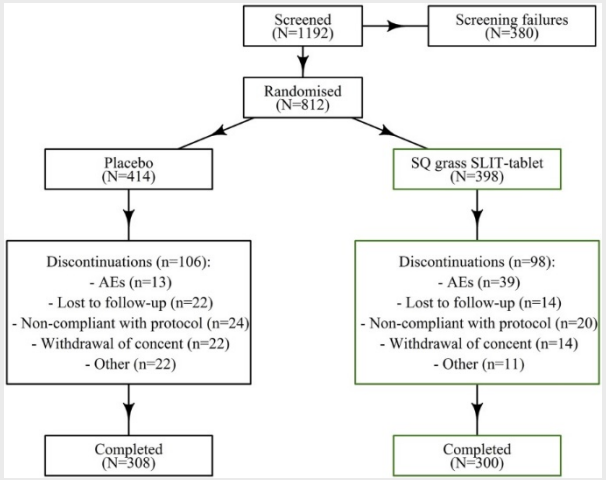
Valovirta E et al., J Allergy Clin Immunol.2018;141:529-538.

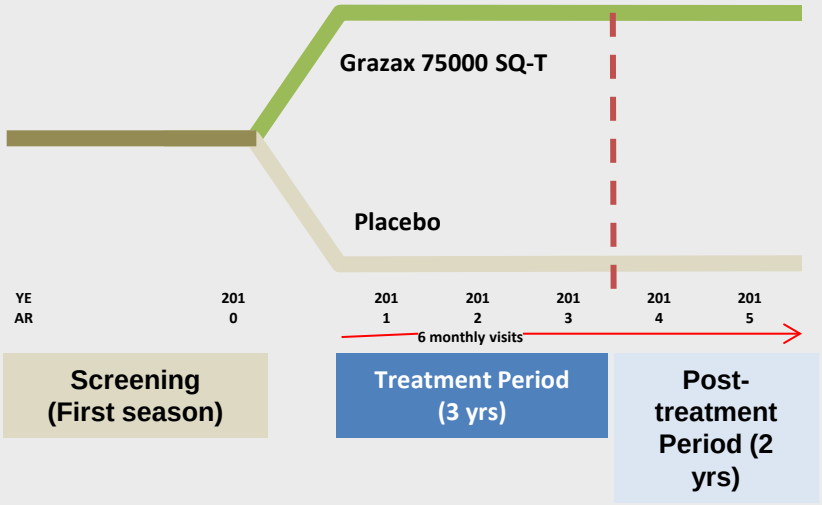
Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy

Erkka Valovirta, MD,[a,b] Thomas H. Petersen, MD,[c] Teresa Piotrowska, MD,[d] Mette K. Laursen, MSc,[e] Jens S. Andersen, MSc, PhD,[e] Helle F. Sørensen, MSc, PhD,[e] and Rabih Klink, MD,[f] on behalf of the GAP investigators*

Turku, Finland, Kolding and Hørsholm, Denmark, Białystok, Poland, and Laon, France

J Allergy Clin Immunol. 2018;141:529-538.





GAP trial: results

TABLE I. Asthma endpoints

Primary endpoint: time to onset of asthma by protocol definition (FAS)

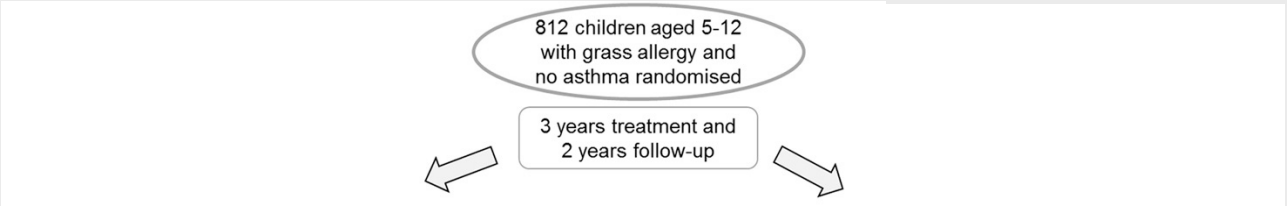
Group	n	Diagnosed with asthma: n	Proportion	HR*	95% CI	*P* value
Placebo	414	39	9.42	0.9	0.57-1.43	.667
SQ grass SLIT tablet	398	34	8.54			

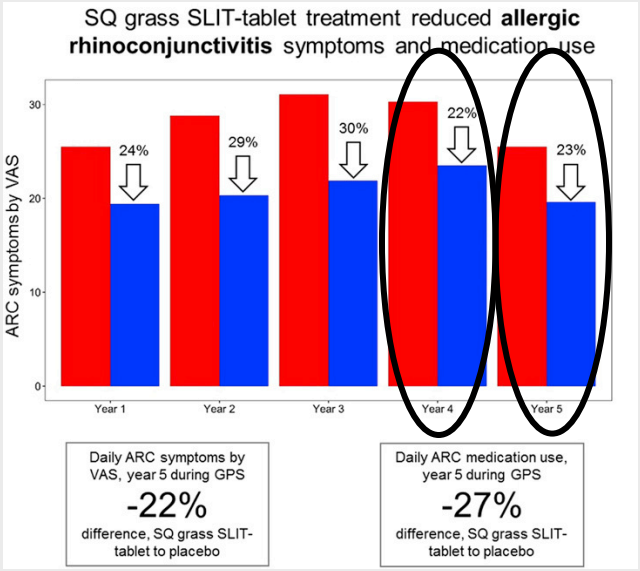
Group	n	symptoms or asthma medication use: n	Proportion	OR‡	95% CI	*P* value
Placebo	398	81	20.35	0.66	0.45-0.97	.036
SQ grass SLIT tablet	377	59	15.65			

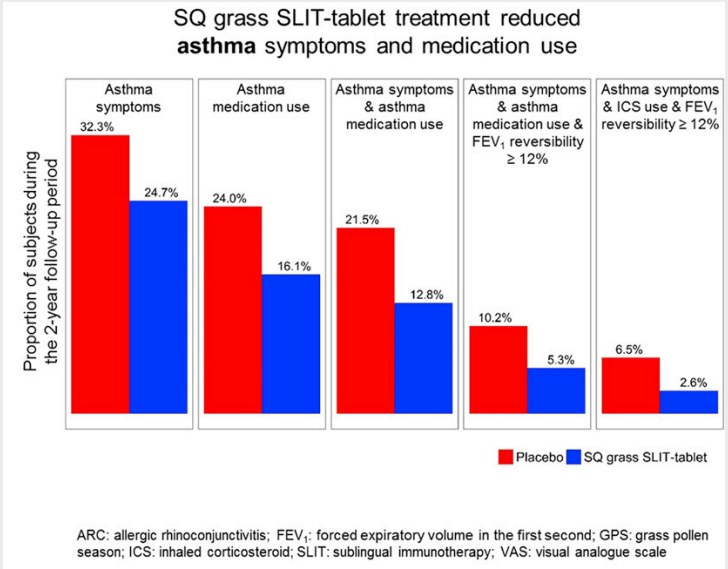
*Hazard ratio SQ grass SLIT tablet versus placebo.

Valovirta E et al., J Allergy Clin Immunol.2018;141:529-538.

Five-year GAP (Grass Asthma Prevention) Trial







Valovirta E et al., J Allergy Clin Immunol.2018;141:529-538.

Overview of adverse events

Treatment group	Placebo group n = 414		SQ grass SLIT tablet group n = 398	
	n (%)	e (%)	n (%)	e (%)
All AEs	385 (93)	3772 (100)	380 (95)	4025 (100)
Causality				
Unlikely	378 (91)	3612 (96)	354 (89)	4313 (85)
Possible	95 (23)	160 (4)	244 (61)	612 (15)
Severity of all AEs				
Mild	369 (89)	2834 (75)	367 (92)	3090 (77)
Moderate	262 (63)	837 (22)	248 (62)	834 (21)
Severe	50 (12)	101 (3)	59 (15)	101 (3)
By worst case*				
Mild	114 (28)		122 (31)	
Moderate	221 (53)		199 (50)	
Severe	50 (12)		59 (15)	
Seriousness				
Serious	30 (7)	36 (<1)	43 (11)	62 (2)
Nonserious	385 (93)	3736 (>99)	380 (95)	3963 (98)
Action taken				
NA†	24 (6)	68 (2)	27 (7)	62 (2)
None	376 (91)	3354 (89)	362 (91)	3470 (86)
Temporarily interrupted	148 (36)	333 (9)	155 (39)	423 (11)
IMP discontinued	12 (3)	17 (<1)	38 (10)	70 (2)
Outcome				
Recovering	12 (3)	19 (<1)	16 (4)	18 (<1)
Recovered	385 (93)	3657 (97)	379 (95)	3916 (97)
Not recovered	73 (18)	88 (2)	68 (17)	86 (2)
Unknown	6 (1)	8 (<1)	4 (1)	5 (1)
Leading to trial discontinuation				
Yes	13 (3)	18 (<1)	39 (10)	71 (2)
No	383 (93)	3754 (>99)	369 (93)	3954 (98)

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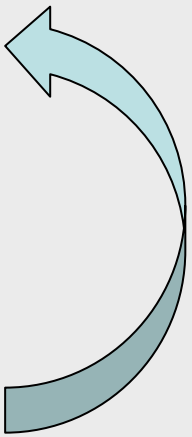


Summary

- In children aged 5-12 y with grass pollen induced seasonal allergic rhinoconjunctivitis, 3 years treatment with SQ grass pollen tablets:
  - prevented progression from allergic rhinoconjunctivitis symptoms to asthma symptoms.
  - did not show an effect on time to onset of asthma
  - reduced rhinoconjunctivitis symptoms and medication use during treatment and for two years after treatment discontinuation
  - reduced Serum IgE and skin test to grass pollen at 3-5 years
  - was well-tolerated with no serious systemic allergic reactions
  - Local side effects (mouth itch, lip swelling) were common, generally mild and resolved in median of 14.5 days

Allergy: Outline

1. Allergen immunotherapy – what's new?

2. Allergen avoidance strategies – new evidence in children

3. Allergy prevention - update on the LEAP and GAP trials

4. **Upper airway disease – nasal polyps**

5. Monoclonal Abs directed against *Fel d 1* for cat allergy

4. Nasal polyps : 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

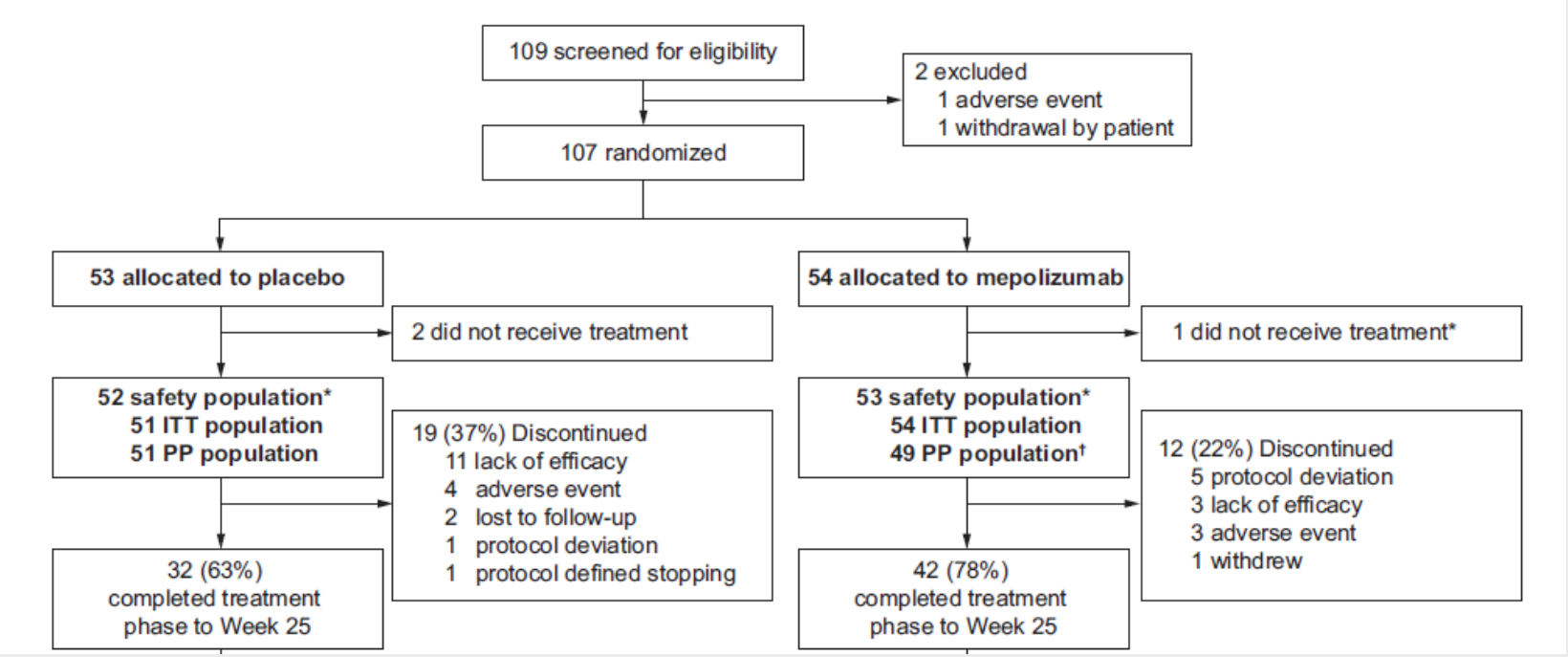
- Eosinophils are the most common infiltrating inflammatory cells and Th2 cytokines are predominant in eosinophilic polyps

Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial

Claus Bachert, PhD,[a,b] Ana R. Sousa, PhD,[c] Valerie J. Lund, MD,[d] Glenis K. Scadding, MD,[d] Philippe Gevaert, MD,[a] Shuaib Nasser, MD,[e] Stephen R. Durham, MD,[f] Marjolein E. Cornet, MD,[g] Harsha H. Kariyawasam, PhD,[d] Jane Gilbert, MSc,[h] Daren Austin, PhD,[c] Aoife C. Maxwell, PhD,[i] Richard P. Marshall, PhD,[c] and Wytske J. Fokkens, PhD[g]

Ghent, Belgium; Stockholm, Sweden; Uxbridge, London, and Cambridge, United Kingdom; and Amsterdam, The Netherlands

J Allergy Clin Immunol 2017;140:1024-31



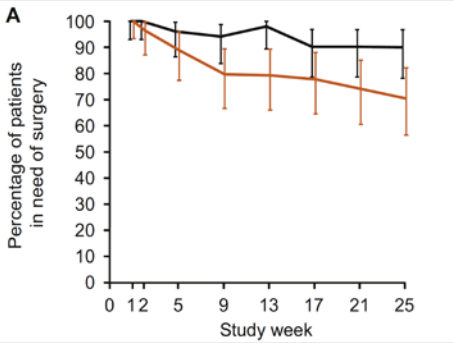
Participant Demographics

Demographics	Placebo (n = 51)	Mepolizumab, 750 mg IV (n = 54)
Age (y), mean (SD)	50 (10)	51 (11)
Sex, no. (%)		
Female	17 (33)	13 (24)
Male	34 (67)	41 (76)
BMI (kg/m^2), mean (SD)	25.1 (3.0)	26.1 (2.7)
Height (cm), mean (SD)	175 (9)	176 (9)
Weight (kg), mean (SD)	77.2 (13.1)	81.1 (10.7)
Baseline symptom severity VAS symptom score*		
Nasal polyposis, LS mean (95% CI)	8.55 (7.88-9.23)	8.50 (7.84-9.16)
Loss of smell, LS mean (95% CI)	9.10 (8.45-9.75)	9.06 (8.43-9.69)
Baseline total endoscopic nasal	6.31 (0.88)	6.28 (0.88)
Baseline SNOT-22 score, mean (SD)‡	49.5 (19.0)	51.5 (17.0)

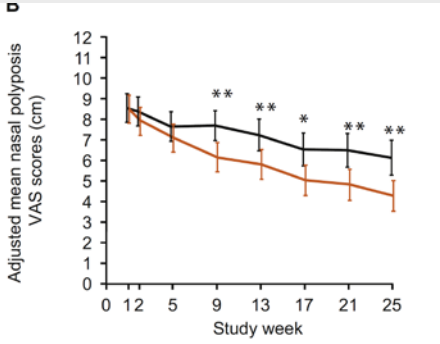
Bachert C, et al. J Allergy Clin Immunol 2017;140:1024-31.

Mepolizumab for nasal polyposis

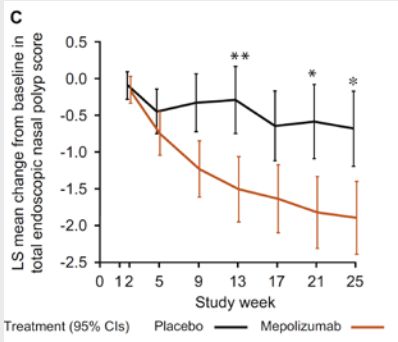
Percentage of patients in need of surgery



Mean overall symptom severity VAS scores



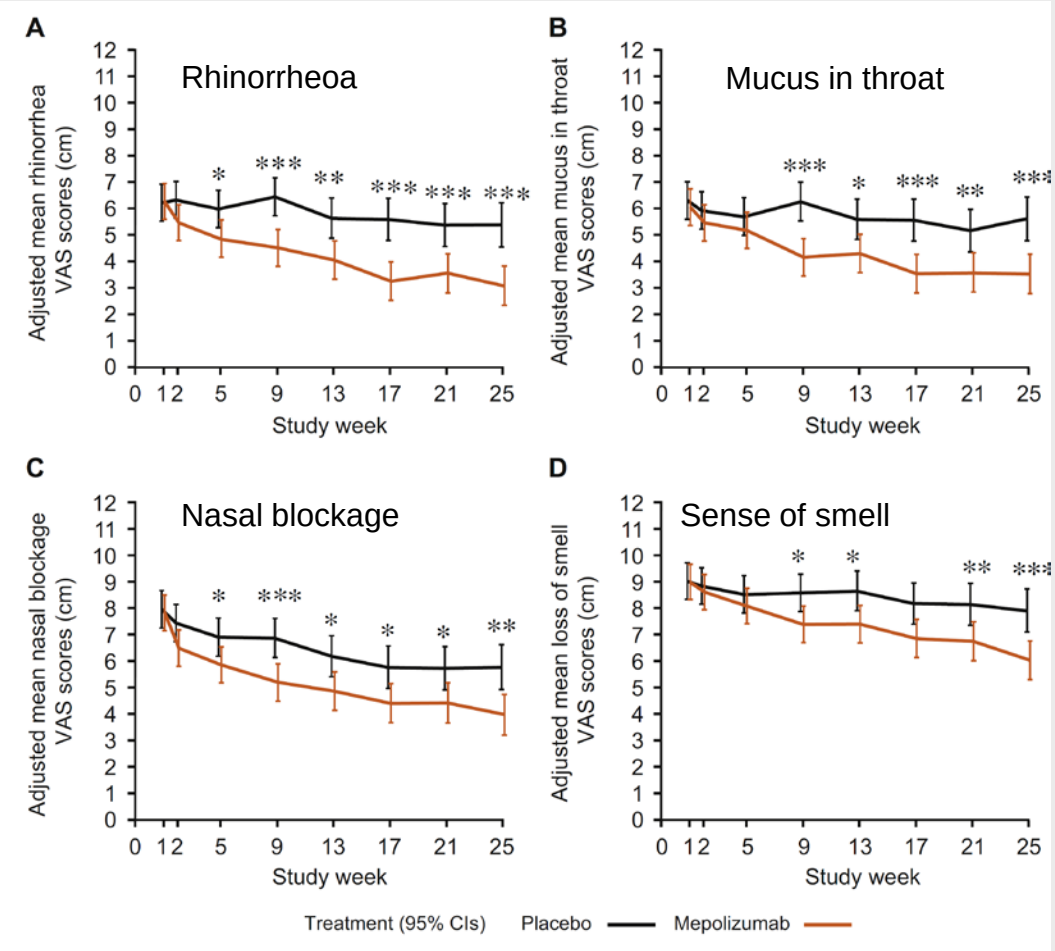
Change in endoscopic pollen score



Treatment (95% CIs) Placebo Mepolizumab

Bachert C, et al. J Allergy Clin Immunol 2017;140:1024-31.

Mepolizumab for nasal polyposis



Bachert C, et al. J Allergy Clin Immunol 2017;140:1024-31.

TAKE HOME MESSAGE

- In nasal polyposis refractory to intranasal corticosteroids, the addition of mepolizumab to INCS compared with INCS alone:

1. reduced endoscopic nasal polyp burden
2. improved sense of smell
3. reduced need for hospitalisation for surgery

Allergy: Outline

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5. **Monoclonal Abs directed against *Fel d 1* for cat allergy**

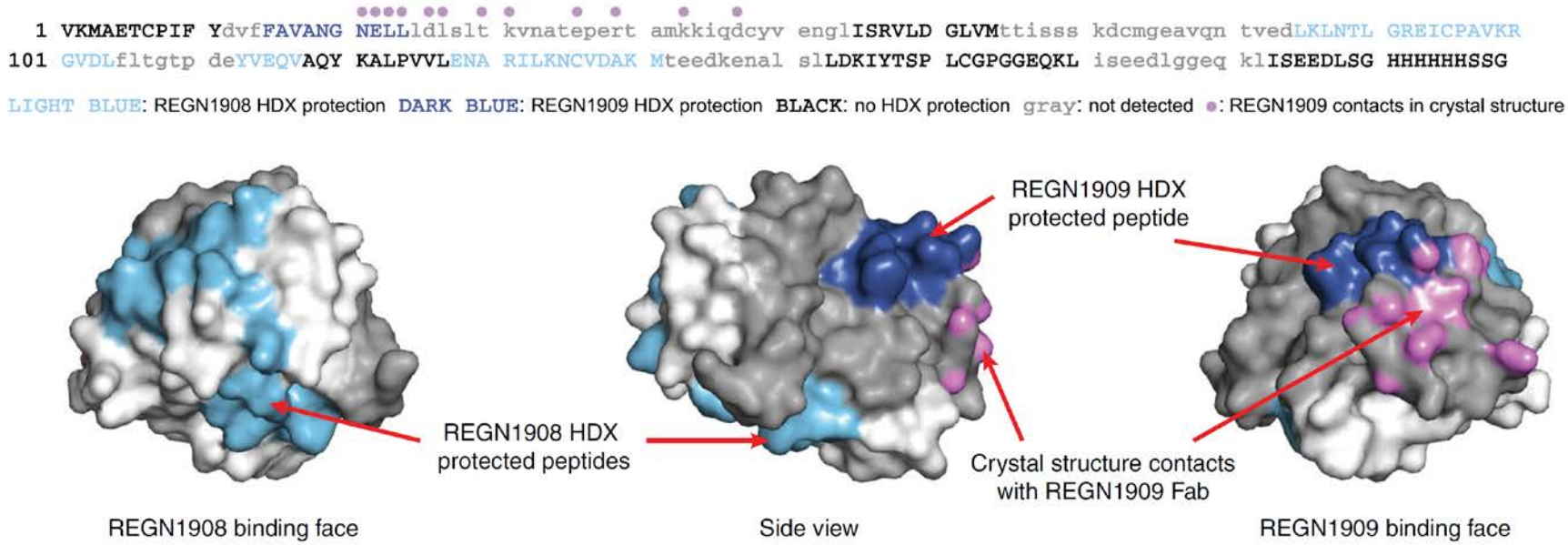
Cat Allergy – state of the art

- Cat allergy is common (affects 10%-15% of adults)
- Fel d 1 is the major allergen provoking IgE responses
- Current management of cat allergy is less than optimal
  - Avoidance of allergen is often impractical
  - Anti-allergic medication is symptomatic-only,no long-term effects
  - Allergen immunotherapy (AIT) is effective, but requires 3 years for long-term tolerance and carries risk of anaphylactic side-effects
  - Recent failure of cat peptide immunotherapy highlights ongoing unmet need
- Passive immunotherapy using monoclonal antibodies?

Gronlund H et al. *Int Arch Allergy Immunol* 2010;151:265-274.
Durham SR, Penagos M. 2016. J Allergy Clin Immunol 2016;137:339-349.

Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement

J.M. Orengo[1], A.R. Radin[1], V. Kamat[1], A. Badithe[1], L.H. Ben[1], B.L. Bennett[1], S. Zhong[1], D. Birchard[1], A. Limnander[1], A. Rafique[1], J. Bautista[1], A. Kostic[1], D. Newell[1], X. Duan[1], M.C. Franklin[1], W. Olson[1], T. Huang[1], N.A. Gandhi[1], L. Lipsich[1], N. Stahl[1], N.J. Papadopoulos[1], A.J. Murphy[1] & G.D. Yancopoulos[1]



Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

REG1908 and REGN1909:

Fully Human IgG4P Antibodies Specific for Fel d 1

- Allergen-specific polyclonal IgG increase during immunotherapy
- Inhibit FcεRI and FcεRII mediated allergic inflammation
- Passive immunotherapy with high-affinity monoclonal antibodies: a novel approach based on observations from AIT
- REGN1908 and REGN1909:fully human IgG4P antibodies specific for Fel d 1were generated using VelocImmune® mice
- IgG4P is a hinge-stabilized human mAb based on an IgG4 isotype

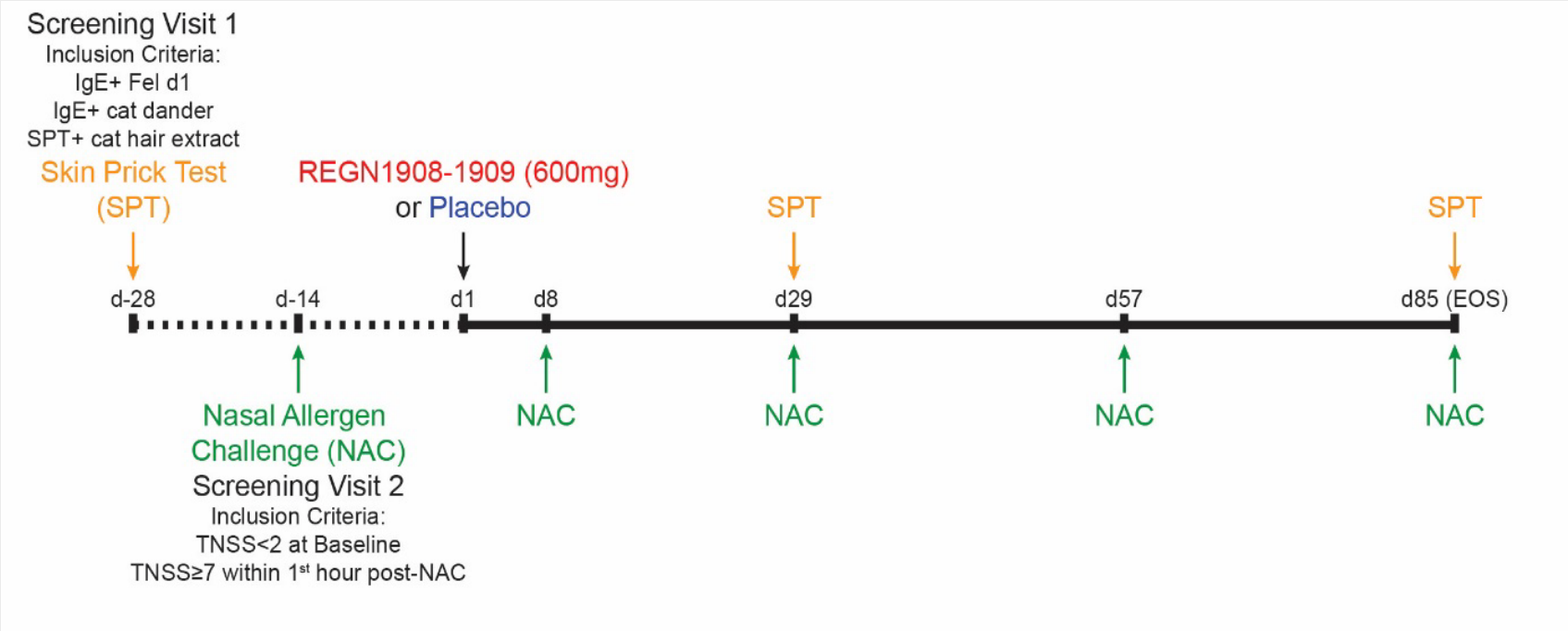
Shamji MH et al. J Immunol Methods 2006;317:71-79.
Murphy AJ et al. Proc Natl Acad Sci U S A. 2014;111:5153-5158.

Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Inclusion and Exclusion Criteria

Inclusion Criteria	Key Exclusion Criteria
• Adults 18 to 55 years • BMI 18.0 kg/m^2 to 32.0 kg/m^2 • Allergic rhinitis, symptoms on cat exposure • Cat IgE-sensitization confirmed by both: – Positive SPT (≥3 mm cf negative control) – Positive sIgE to Cat and Fel d 1 (≥0.35 kAU/l) • Positive NAC with cat hair extract (TNSS ≥7) • Normal lung function	• Significant mechanical nasal obstruction, or nasal or sinus surgery to interfere with NAC • AIT with cat allergen • AIT with any allergen in previous 3 months • Cat in the home (or similar chronic exposure) • Severe asthmatic reaction or anaphylaxis after exposure to cats • Pregnant or breastfeeding women

Study Procedures

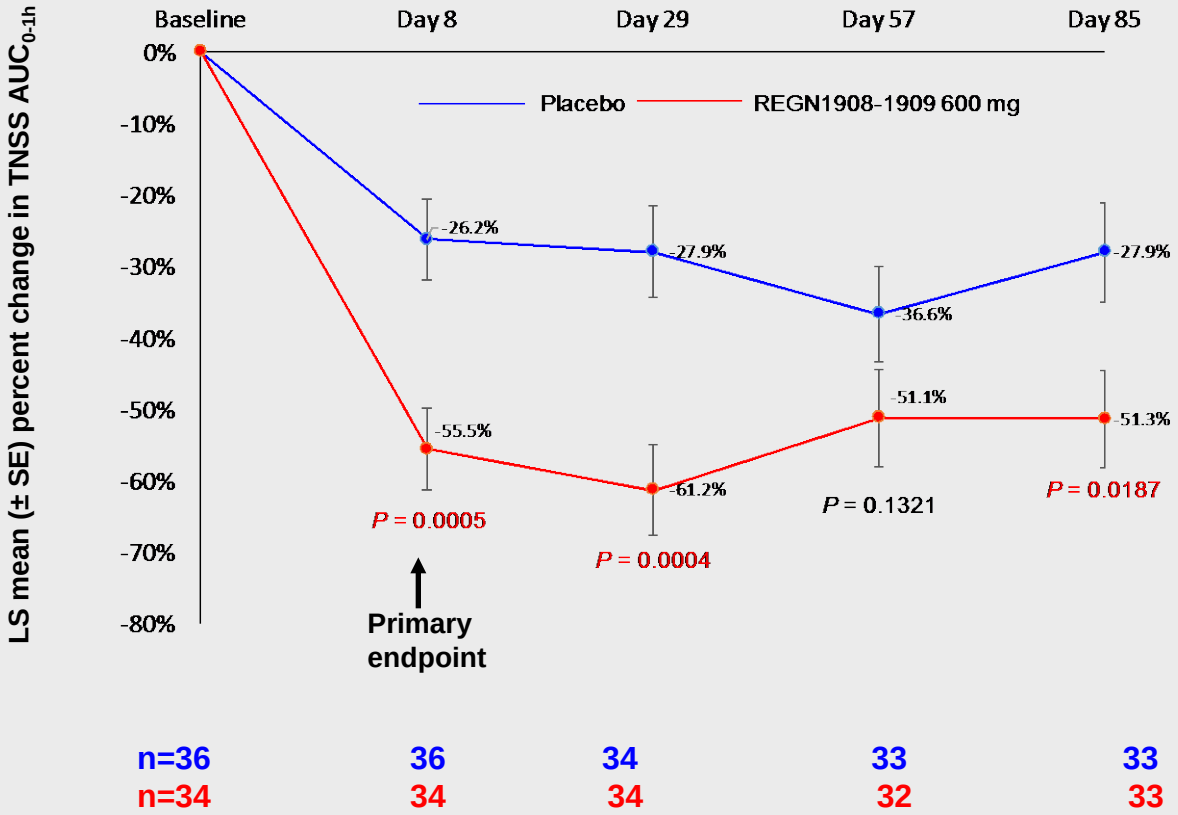


- NAC: Increasing cat allergen concentrations (100-33,000 SQ-U/ml) until TNSS > 7
- Same doses on days 8, 29, 57 and 85 following REGN1908-1909 or placebo
- TNSS, VAS and PNIF were determined pre-NAC and at 10, 30, and 60 minutes

Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Nasal challenge with cat allergen extract:

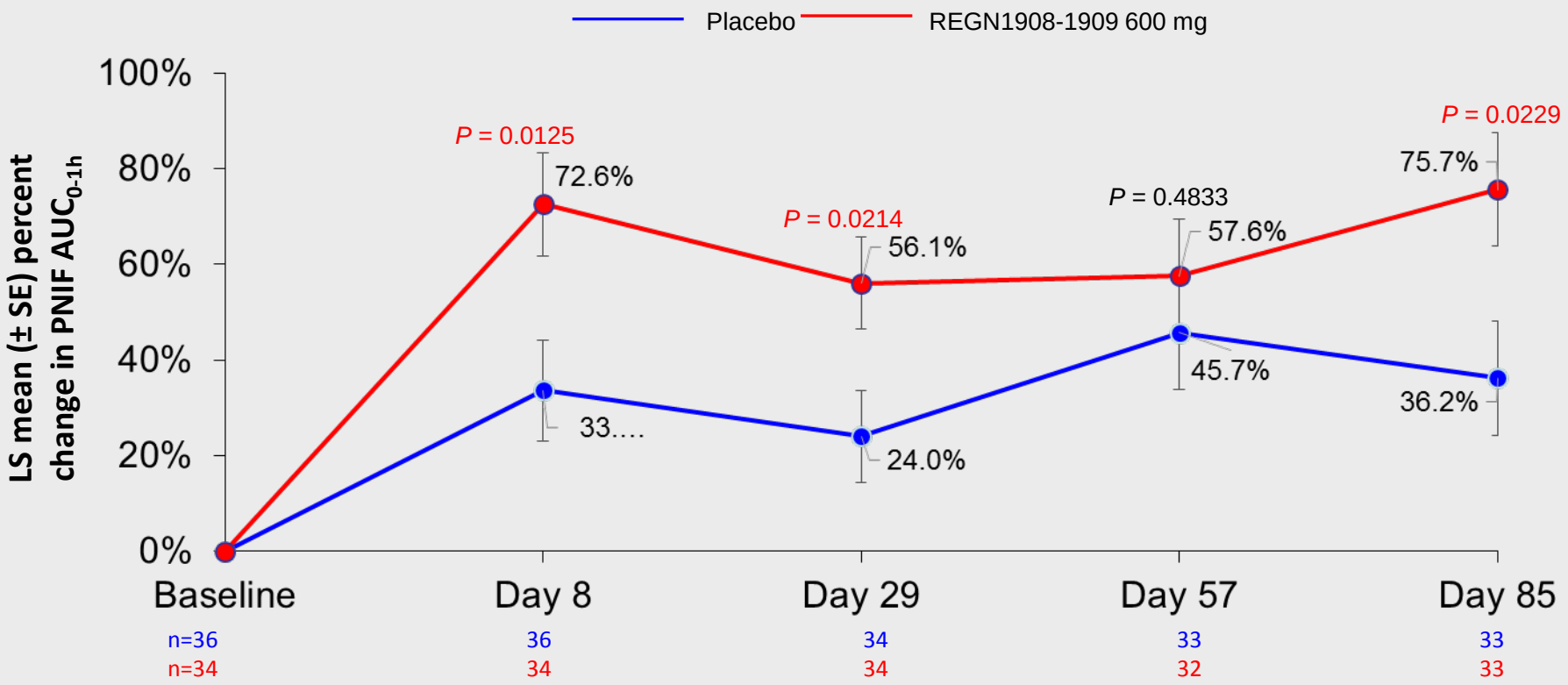
Nasal symptom scores (% change in TNSS $AUC_{0\text{-}1h}$)



Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Nasal challenge with cat allergen extract:

Peak Nasal inspiratory flow (% change)

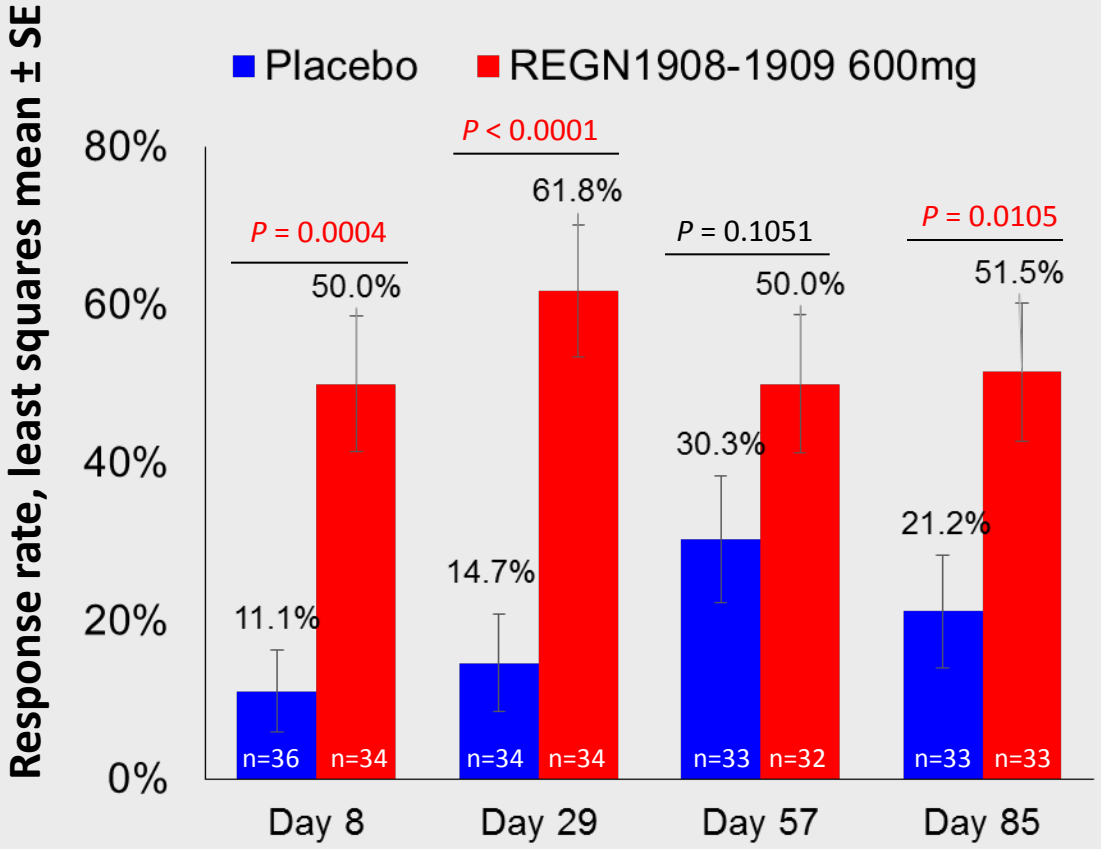


Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

TNSS Responder Analysis

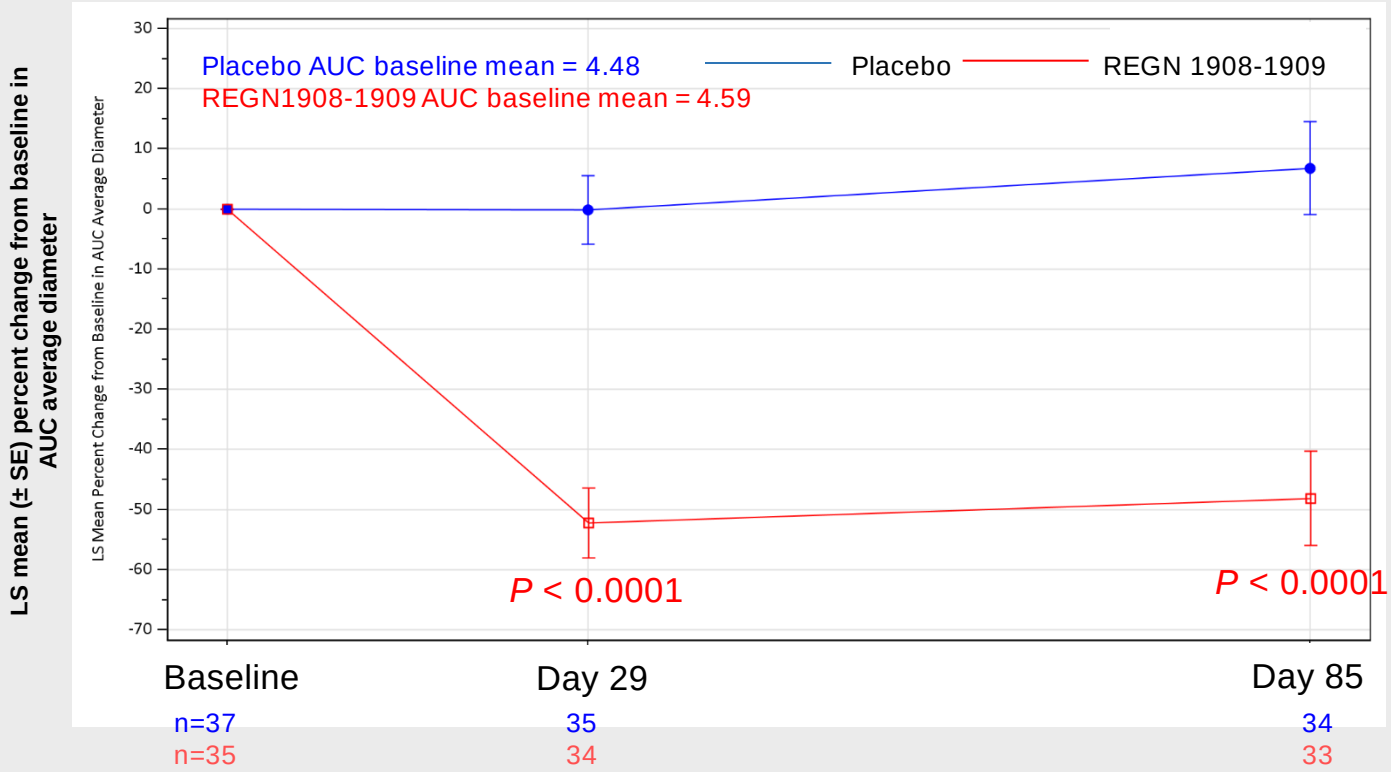
Percentage of patients with ≥ 60% Reduction in TNSS $AUC_{0\text{-}1h}$

- Half the patients treated with REGN1908-1909 had a ≥ 60% reduction in TNSS $AUC_{0\text{-}1h}$
  - Maintained over the study duration and significantly greater than placebo except at Day 57



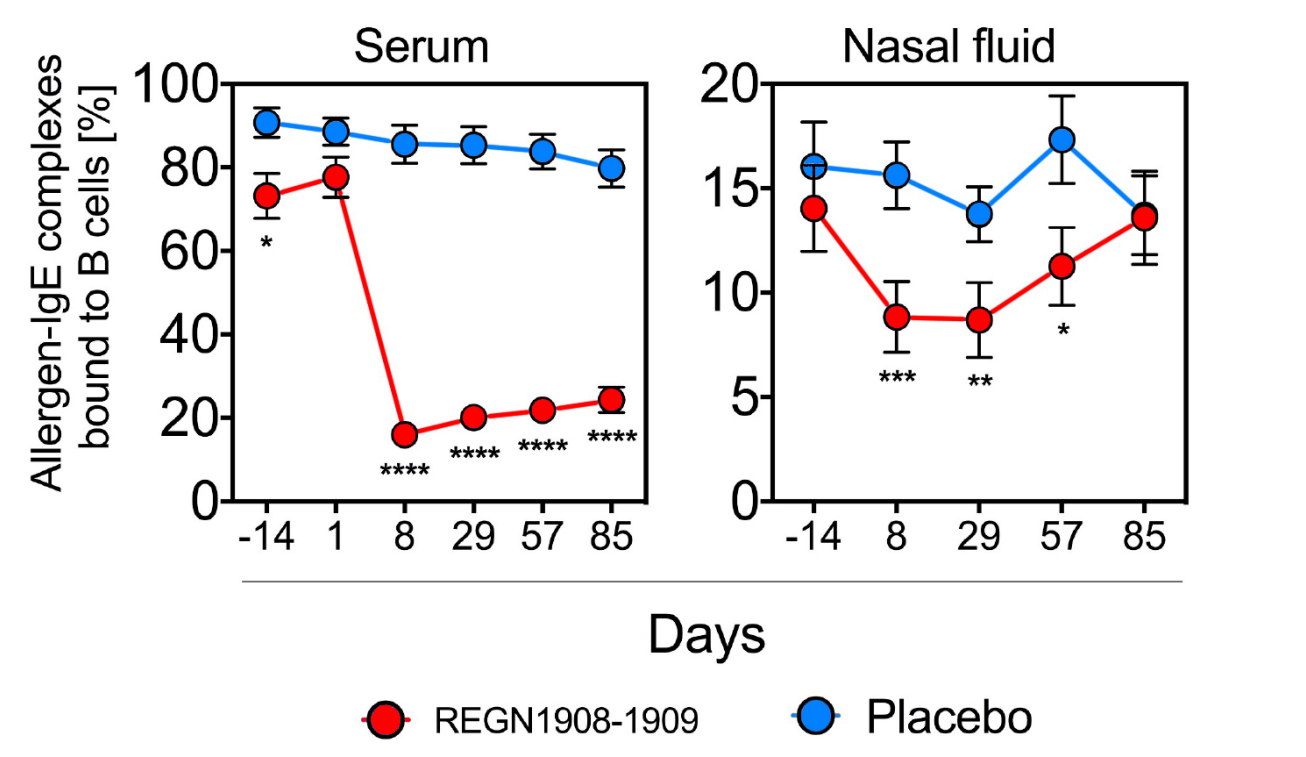
Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Single dose SC REGN1908-1909 resulted in a 50% inhibition of Cat Extract Skin Prick Test (day 29 and 85)



Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Effects of REGN1908-1909 on CD23-mediated IgE-facilitated Allergen Binding to B Cells



* *P*<0.05. ***P*<0.01, ****P*<0.001
Mann-Whitney U test

Orengo JM, et al. Nat Commun. 2018 Apr 12; 9: 1421.

Summary

- Proof-of-concept for passive immunization with REGN1908-1909
- Single 600 mg prophylactic dose Scut improved symptoms and PNIF in subjects with cat allergy
- Responses were maintained for 12 weeks
- REGN1908-1909 was well-tolerated, minor injection site reactions and no systemic allergic events
- REGN1908-1909 inhibited Ag-stimulated basophil responsiveness and systemic and local IgE-FAB thatpersisted up to 85 days

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