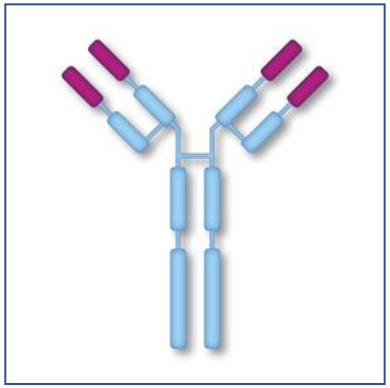
Pneumo Update Europe 2016

24-25 June, Prague

Allergy



Stephen R Durham, UK

Topics covered

- Food Allergy – early introduction during infancy induces long-term tolerance?
  - peanut (LEAP and LEAP ON)
  - six foods (EAT study)

- Allergen immunotherapy for seasonal rhinitis - sublingual or subcutaneous?

- Sublingual tablet immunotherapy for perennial house dust mite allergic rhinitis and asthma
  - efficacy in perennial rhinitis
  - corticosteroid sparing?
  - prevention of exacerbations?

Does early introduction of allergenic foods in infancy result in long-term tolerance?

Peanut allergy – State of the Art

- Peanut allergy prevalence is 1.4-3% in western countries
- Major cause of anaphylaxis and death due to food allergy
- Major risk factor for death in asthmatics
- Substantial psychosocial and economic burden

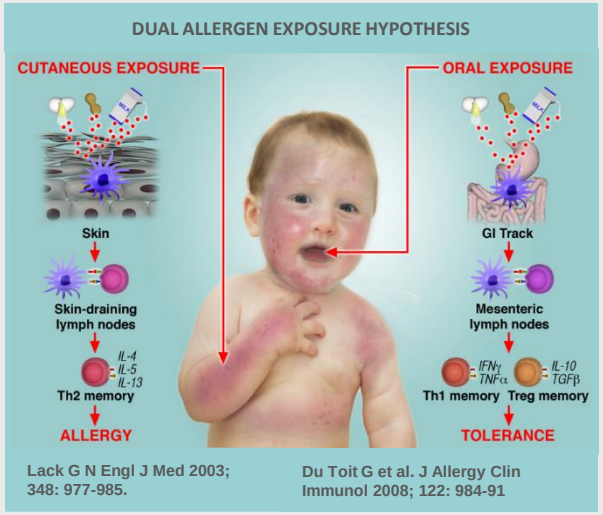
- Treatment
  - strict avoidance of peanut, dietary advice
  - auto-injectable adrenaline, training in use of devices

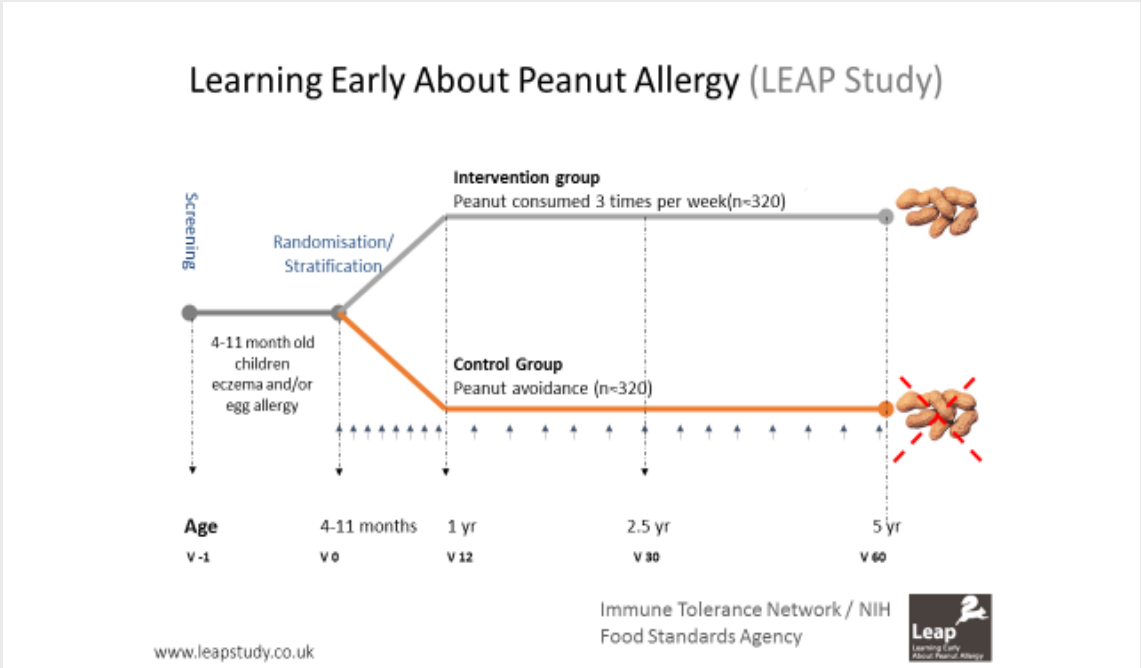
- Prevention
  - early avoidance in pregnancy and infants?
  - or early introduction?

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

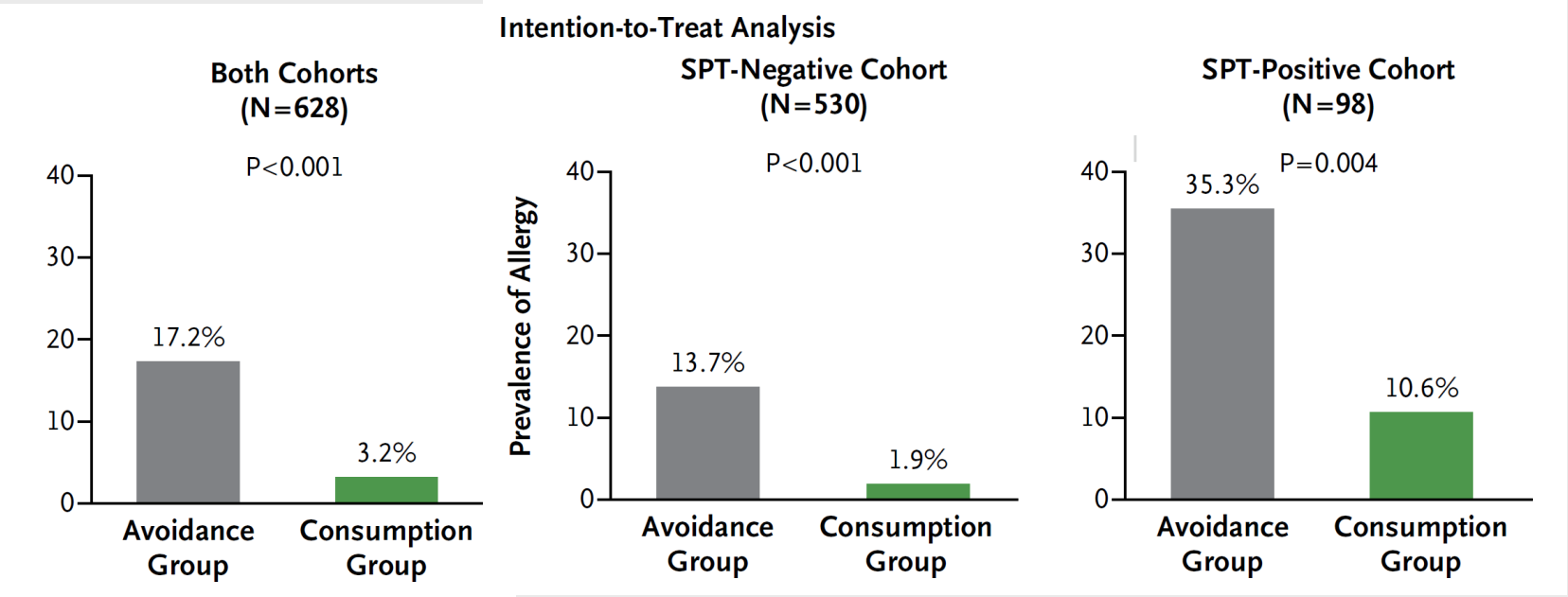
George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, 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*

N Engl J Med. 2015 Feb 26;372(9):803-13.





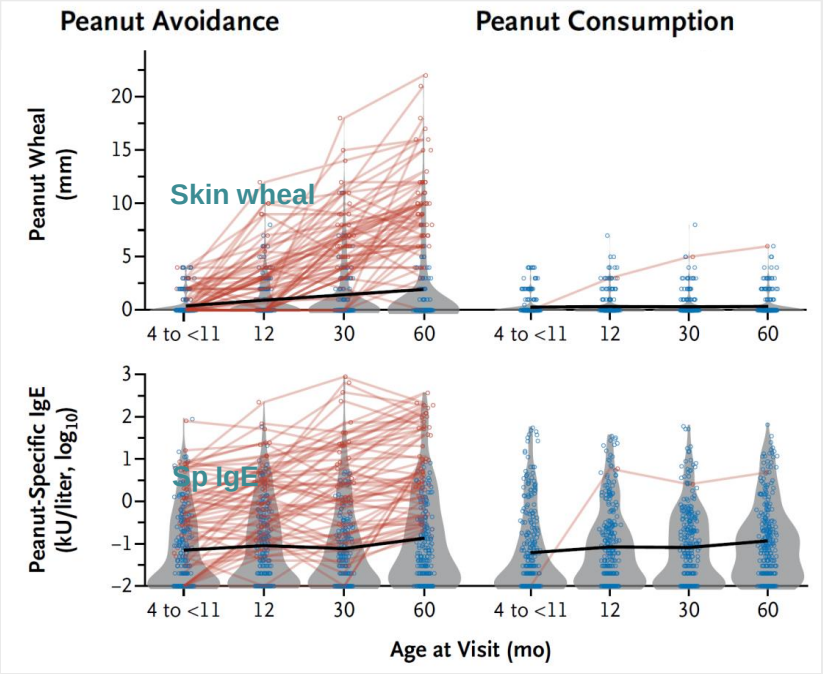
Results (primary outcome): prevalence of peanut allergy at 5 years of age

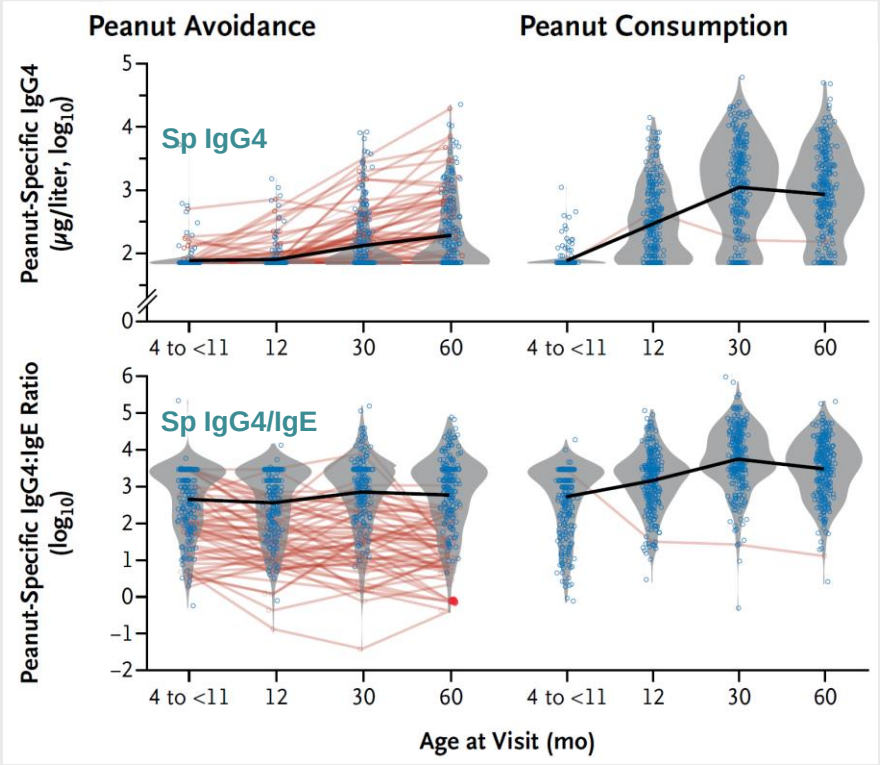


Toit et al., N Engl J Med. 2015 Feb 26;372(9):803-13.

Results – Specific IgE and Specific IgG4 levels

Toit et al., N Engl J Med. 2015 Feb 26;372(9):803-13





***Red lines show the trajectory of Ig responses in those participants who were allergic at 60 months**

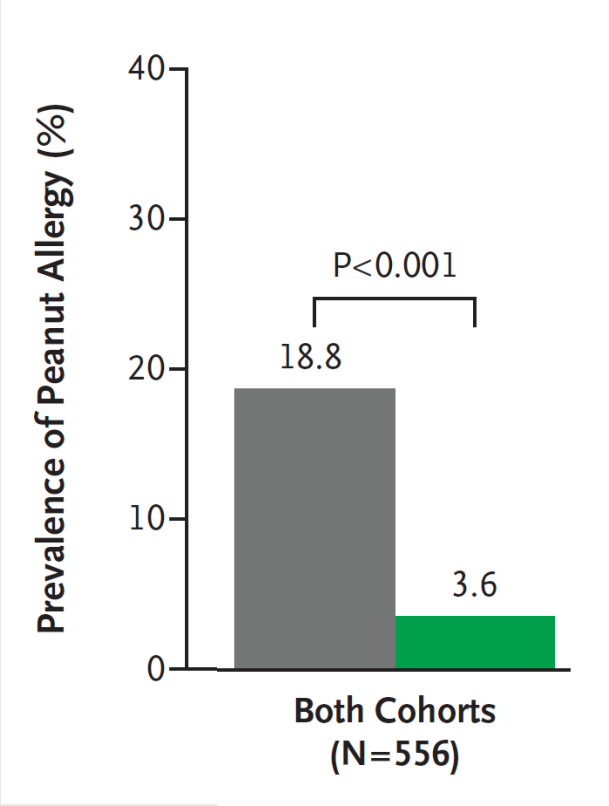
Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

George Du Toit, M.B., B.Ch., Peter H. Sayre, M.D., Ph.D., Graham Roberts, D.M., Michelle L. Sever, M.S.P.H., Ph.D., Kaitie Lawson, M.S., Henry T. Bahnson, M.P.H., Helen A. Brough, M.B., B.S., Ph.D., Alexandra F. Santos, M.D., Ph.D., Kristina M. Harris, Ph.D., Suzana Radulovic, M.D., Monica Basting, M.A., Victor Turcanu, M.D., Ph.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the Immune Tolerance Network LEAP-On Study Team*

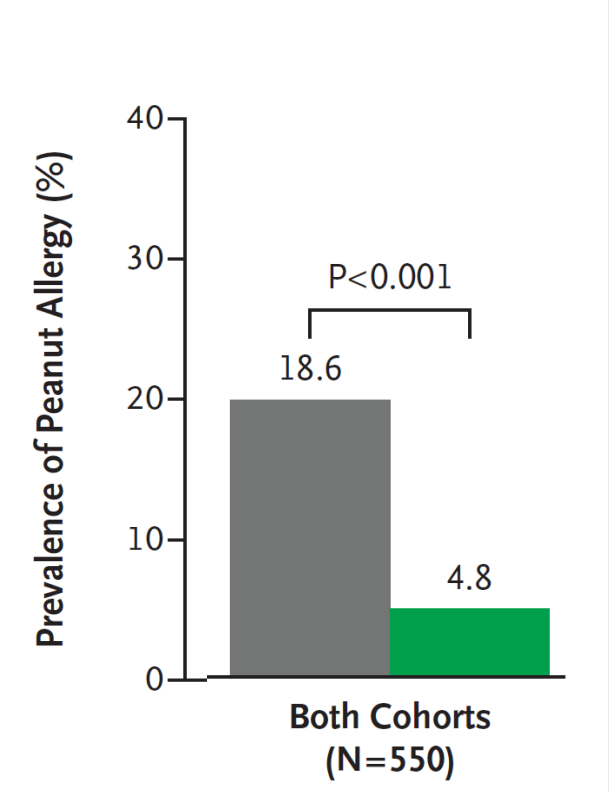
N Engl J Med. 2016 Apr 14;374(15):1435-43.

Toit et al., N Engl J Med. 2016 Apr 14;374(15):1435-43.

Intention-to-Treat Population in Primary Trial

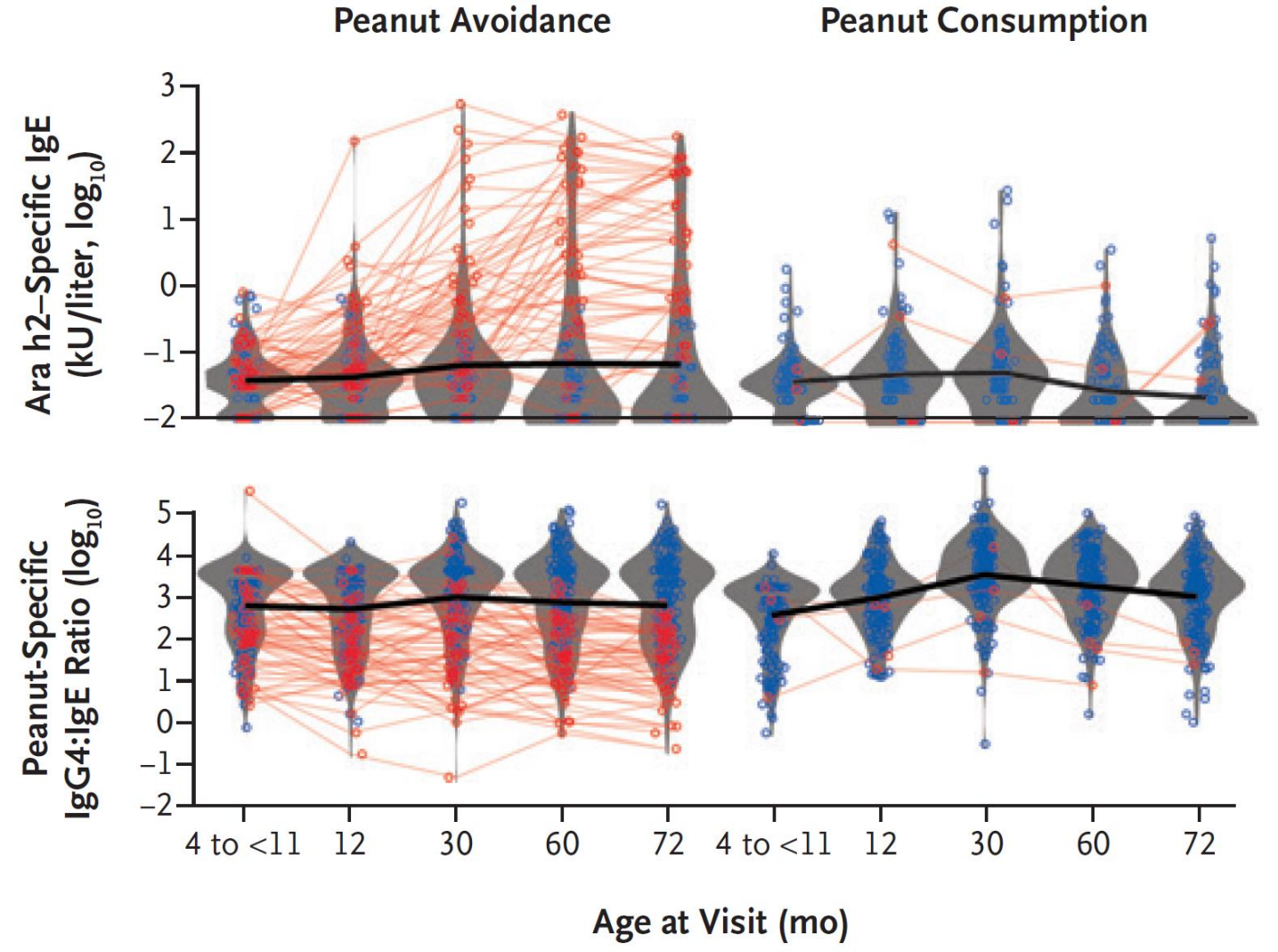


Intention-to-Treat Population in Follow-up Study



Results – Specific IgE and Specific IgG4 levels

Toit et al., N Engl J Med. 2016 Apr 14;374(15):1435-43



Conclusions of the LEAP trial and LEAP-On study

- Early introduction of peanut and continuation for 5 years induced unresponsiveness to peanut that persisted after 12 months of peanut avoidance

- It remains to be seen whether protection is maintained if peanuts are consumed *ad libertum* over the course of many years.

- The mechanism is likely to involve both induction of IgG blocking antibodies and suppression of Specific IgE , although the underlying immunological changes responsible are unknown

Take-Home Message

Gruchalla RS and Sampson H. Editorial, N Engl J Med 2015; 372:875-877

- Children aged 4-8/12 at risk of peanut allergy should undergo skin prick test with peanut:

  - if negative, start peanut consumption 2g 3 times per week for at least 3 years

  - if weak positive (</= 4mm), perform OFC with peanut to confirm negative result before commencing the diet

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D., Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D., Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H., Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*

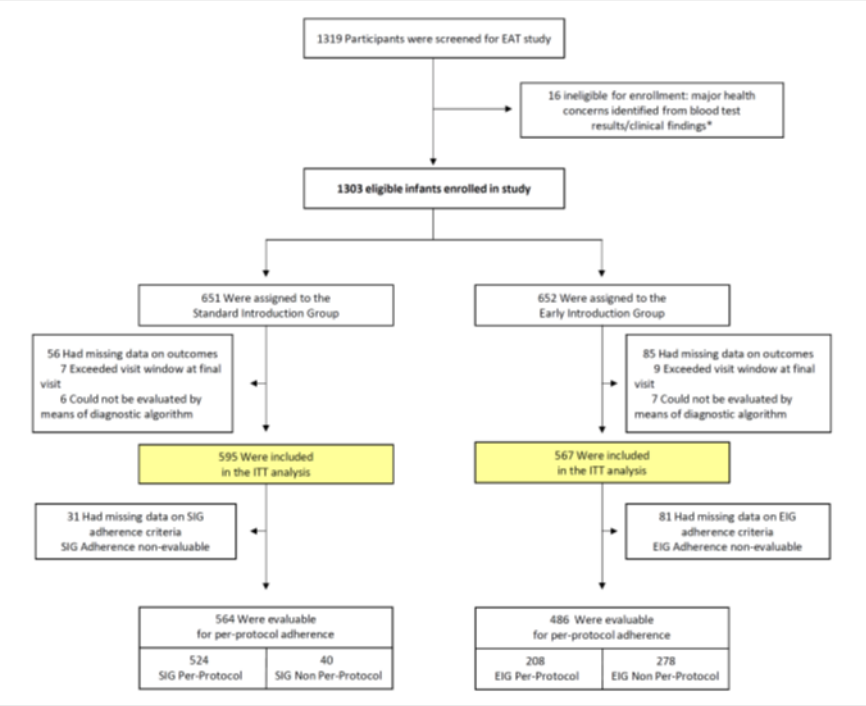
General population (not high risk of food allergy)

1303 exclusively breast-fed infants at 3 months of age
Randomised to:

Standard introduction of 6 foods (at 6 months)
Early introduction of 6 foods (at 3 months)

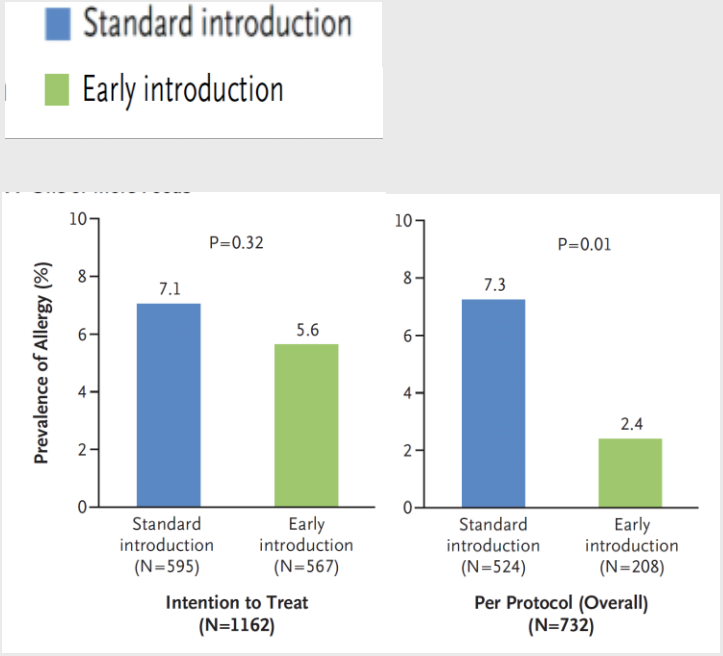
(peanut, cooked egg, cow's milk, sesame, whitefish, wheat)

Enrollment and Randomization

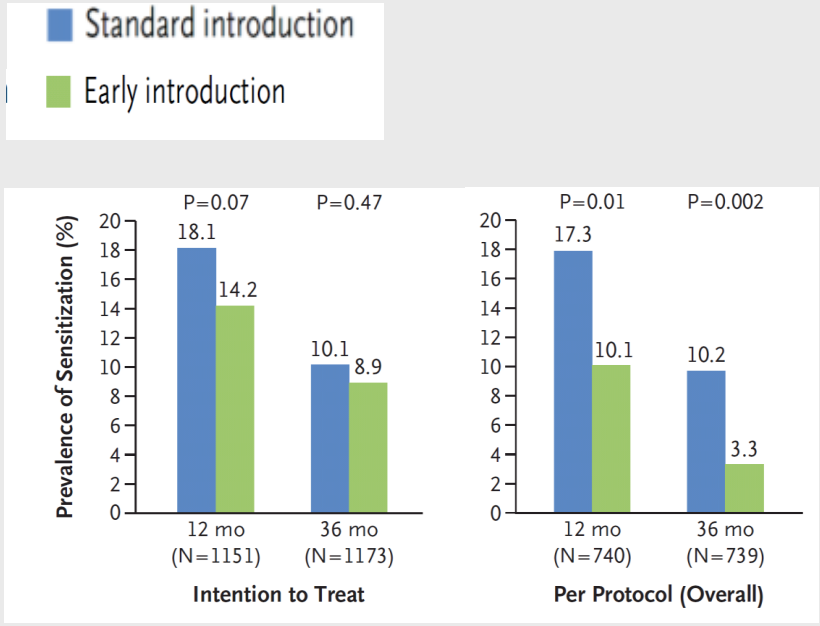


Perkin M et al., N Engl J Med. 2016 May 5;374(18):1733-43

Prevalence of IgE-mediated food allergy to one or more of 6 early intervention foods

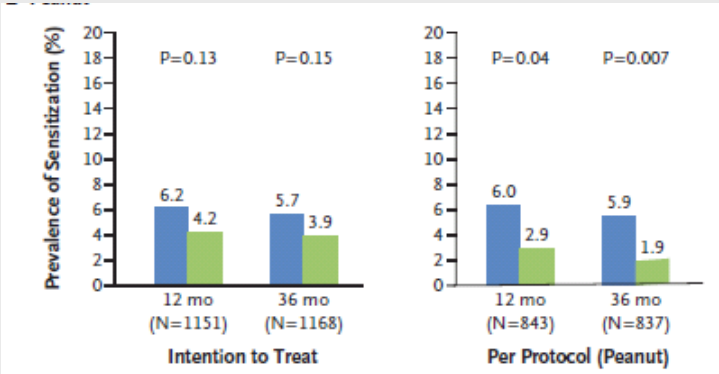


Prevalence of positive skin test prick test to one or more of the 6 early intervention foods at 12 and 36 months

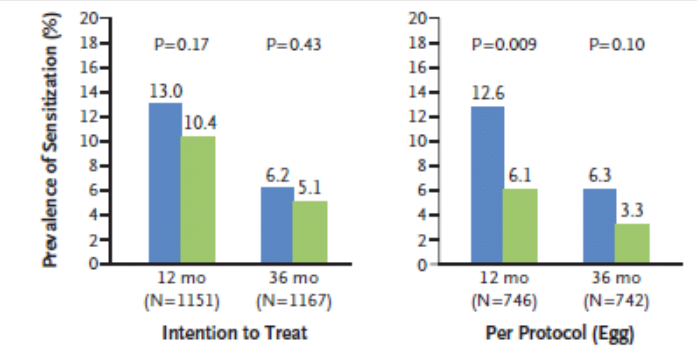


Perkin M et al., N Engl J Med. 2016 May 5;374(18):1733-43

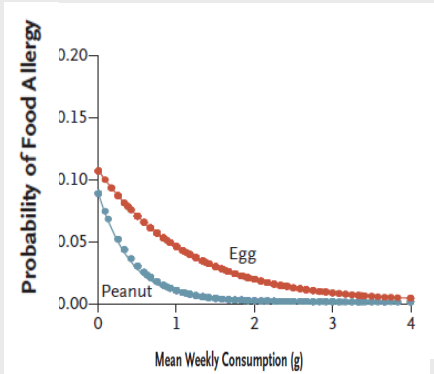
Prevalence of IgE-sensitisation to peanut at 12 and 36 months

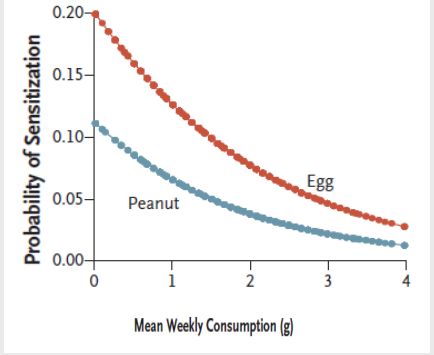


Prevalence of IgE-sensitisation to egg at 12 and 36 months



Dose-response analysis between mean weekly dose of food consumed and probability of food allergy and positive SPT





Perkin M et al., N Engl J Med. 2016 May 5;374(18):1733-43

TAKE-HOME MESSAGE
EAT Study - Enquiring about tolerance

- This trial failed to show the efficacy of early introduction of allergenic foods compared with standard introduction of those foods in an intention to treat analysis

- Further analysis suggests that the possibility of preventing food allergy by means of the early introduction of multiple allergenic foods in normal breast-fed infants may depend on adherence and dose

Perkin M et al., N Engl J Med. 2016 May 5;374(18):1733-43

Sublingual or subcutaneous immunotherapy for allergic rhinitis?

Stephen R. Durham, MD, FRCP, and Martin Penagos, MD, MSc *London, United Kingdom*

J Allergy Clin Immunol 2016;137:339-349

Daily sublingual tablets

Weekly updosing /monthly maintenance injectons

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

Slovick A, Durham SR, Till SJ. BMJ. 2014 Nov 17;349:g6586

Immunotherapy for Allergic Rhinitis

Cochrane Meta-analysis

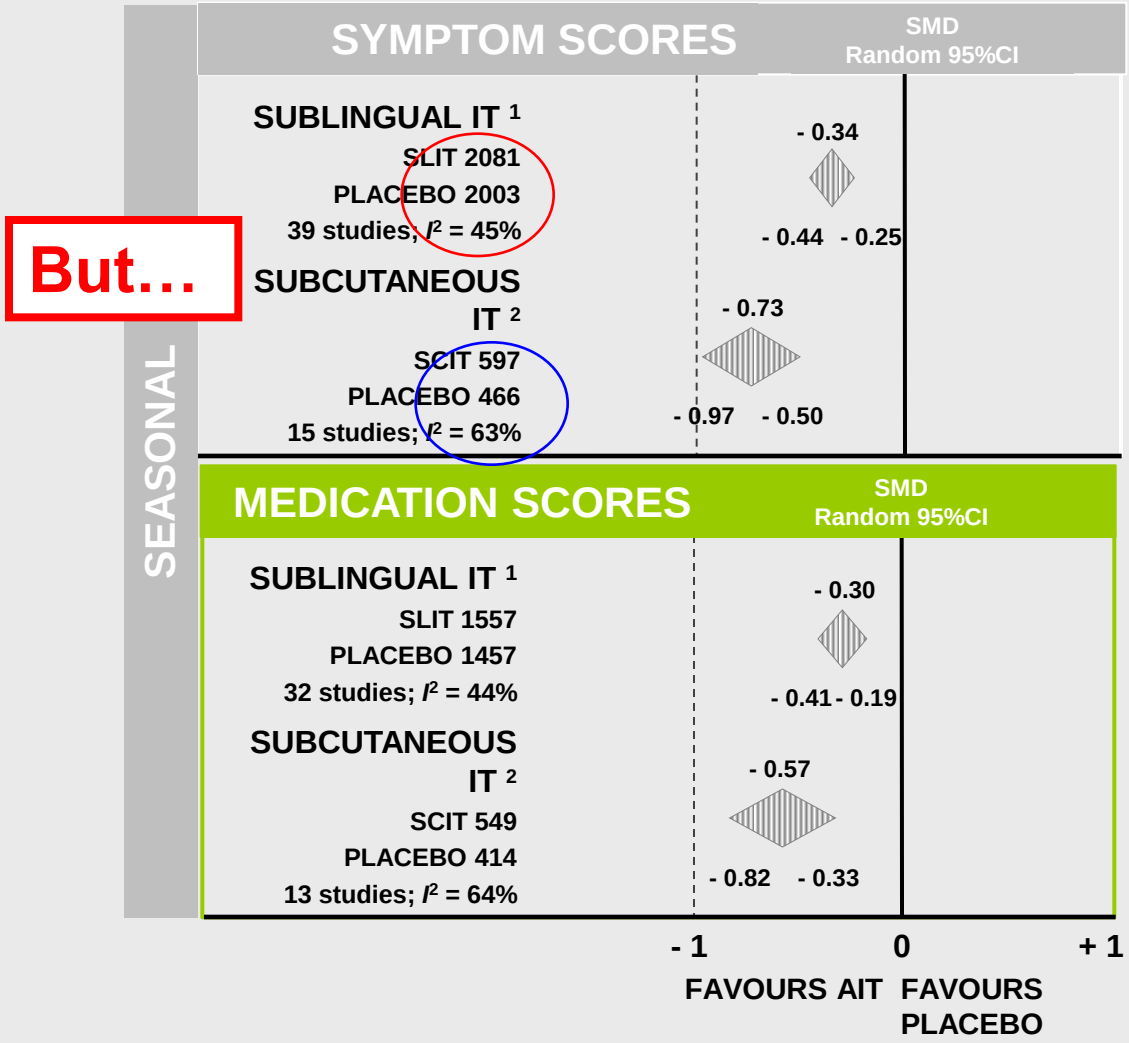
	SCIT SMD (95%CI)	SLIT SMD (95%CI)
	51*, n = 2,871	39*, n = 2,746
Symptoms	-0.73 (-0.97, -0.50)	-0.49 (-0.64, -0.34)
Medication	-0.57 (-0.82, -0.33)	-0.41 (-0.55, -0.28)
	Calderon M 2007	Radulovic S 2011

SMD = Standardised Mean Difference
*Total numbers of studies analyzed

Calderon M et al. Cochrane Database Syst Rev 2007 Jan 24;(1): CD001936.

Radulovic S et al, CochraneDatabase Syst Rev. 2011 June 66; (6): 740-752

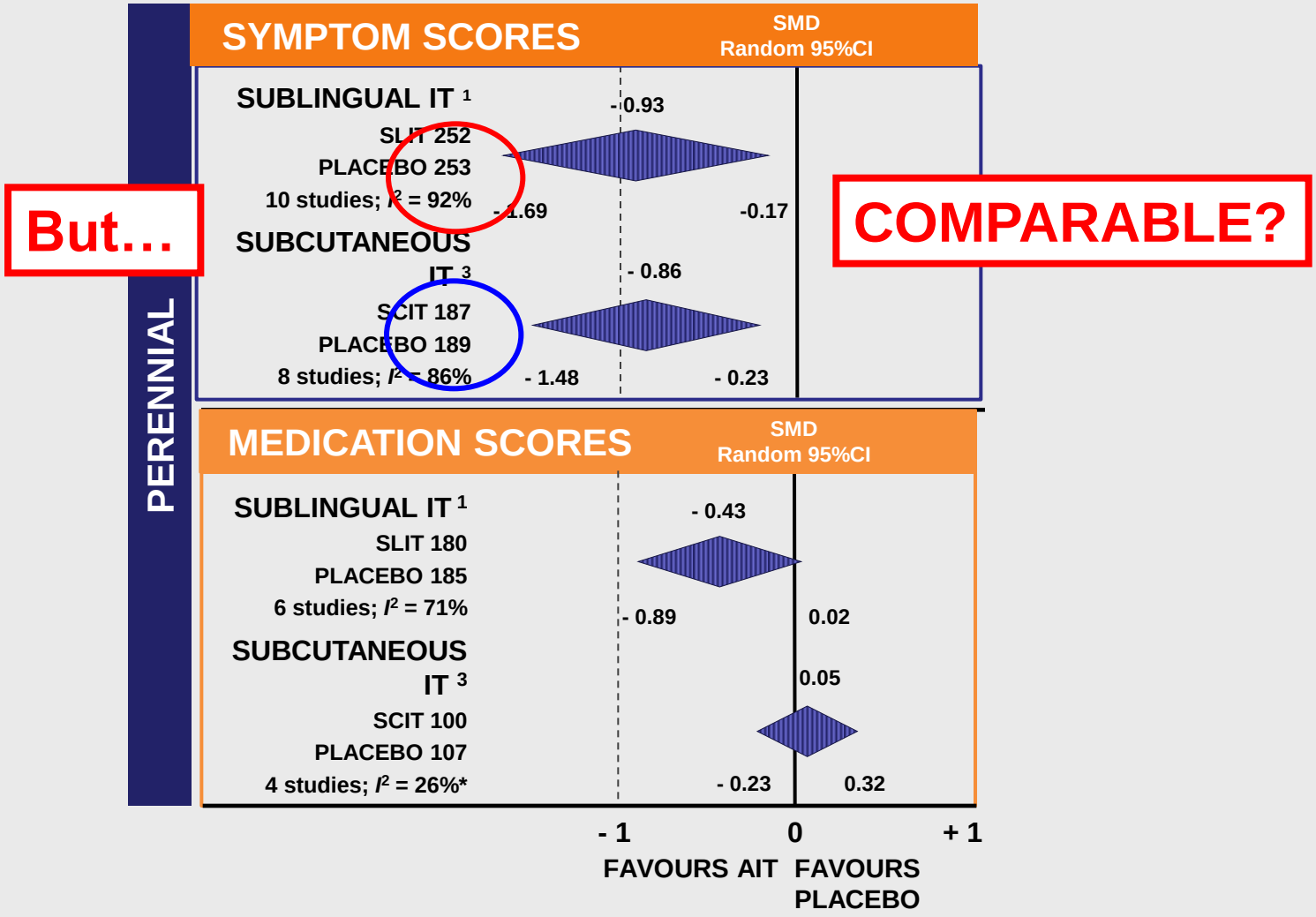
Cochrane meta-analyses: seasonal allergens



But…

[1] Radulovic S, et al. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD002893.
[2] Calderon MA, et al. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001936.

Cochrane meta-analyses: perennial allergens



[1] Radulovic S, et al. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD002893.
[3] Calderon MA, et al. Cochrane Database Syst Rev. 2016 [Ongoing].

Recent systematic reviews and meta-analyses of SLIT and SCIT (indirect comparisons)

AUTHOR, YEAR, COUNTRY	RCTs SCIT (n)	RCTs SLIT (n)	AIT (n)	PLAC (n)	AGE	ALLERGEN	SYMPTOM SCORES [COMPARISON AGAINST PLACEBO]	MEDICATION SCORES [COMPARISON AGAINST PLACEBO]
NELSON 2015 USA	9	14 D 14 T	4016	3743	Adults and children	Grass pollen	**SLIT D**: SMD: -0.17; (95% CI, -0.37 to 0.04); I^2: 65% **SLIT T**: SMD: -0.32; (95%CI, -0.41 to -0.23); I^2: 52% **SCIT**: SMD: -0.32; (95%CI, -0.45 to -0.18); I^2: 27%	**SLIT D**: SMD: -0.44; (95% CI, -0.83 to -0.06); I^2: 88% **SLIT T**: SMD: -0.23; (95%CI, -0.29 to -0.17); I^2: 0% **SCIT**: SMD: -0.33; (95%CI, -0.52 to -0.13); I^2: 61%
DI BONA 2015 Italy	0	13	2281	2378	Adults and children	Grass pollen	**SLIT T**: SMD: -0.28; (95%CI, -0.37 to -0.19); I^2: 54%	**SLIT T**: SMD: -0.24; (95%CI, -0.31 to -0.17); I^2: 22%
DI BONA 2012 Italy	14	10 D 12 T	3014	2768	Adults and children	Grass pollen	**SLIT D**: SMD: -0.25; (95% CI, -0.45 to -0.05); I^2: 48% **SLIT T**: SMD: -0.40; (95%CI, -0.54 to -0.27); I^2: 66% **SCIT**: SMD: -0.92; (95%CI, -1.26 to -0.58); I^2: 88%	**SLIT D**: SMD: -0.37; (95% CI, -0.74 to -0.00); I^2: 86.9% **SLIT T**: SMD: -0.30; (95% CI, -0.44 to -0.16); I^2: 64.3% **SCIT**: SMD: -0.58; (95% CI, -0.86 to -0.30); I^2: 81.1%
DRETZKE 2013 UK	17	42	2899	2904	Adults and children	Seasonal allergens	**SLIT**: SMD −0.33; (95% CI, −0.42 to −0.25); I^2: 42% **SCIT**: SMD: −0.65; (95% CI, −0.85 to −0.45); I^2: 57%	**SLIT**: SMD −0.27; (95% CI, −0.37 to −0.17); I^2: 49% **SCIT**: SMD: −0.55; (95% CI, −0.75 to −0.34); I^2: 57%
LIN 2013 USA	55+	52+	SCIT: 3487* SLIT:4384* SCIT vs SLIT: 412*		Adults and children	Any allergen	No pooled analysis was performed	No pooled analysis was performed

AIT: Allergen specific immunotherapy (SLIT or SCIT); D: Drops; T: Tablets; PLAC: Placebo

*Diverse comparators apart of placebo were included; +Studies including participants with AR or ARC with or without asthma.

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

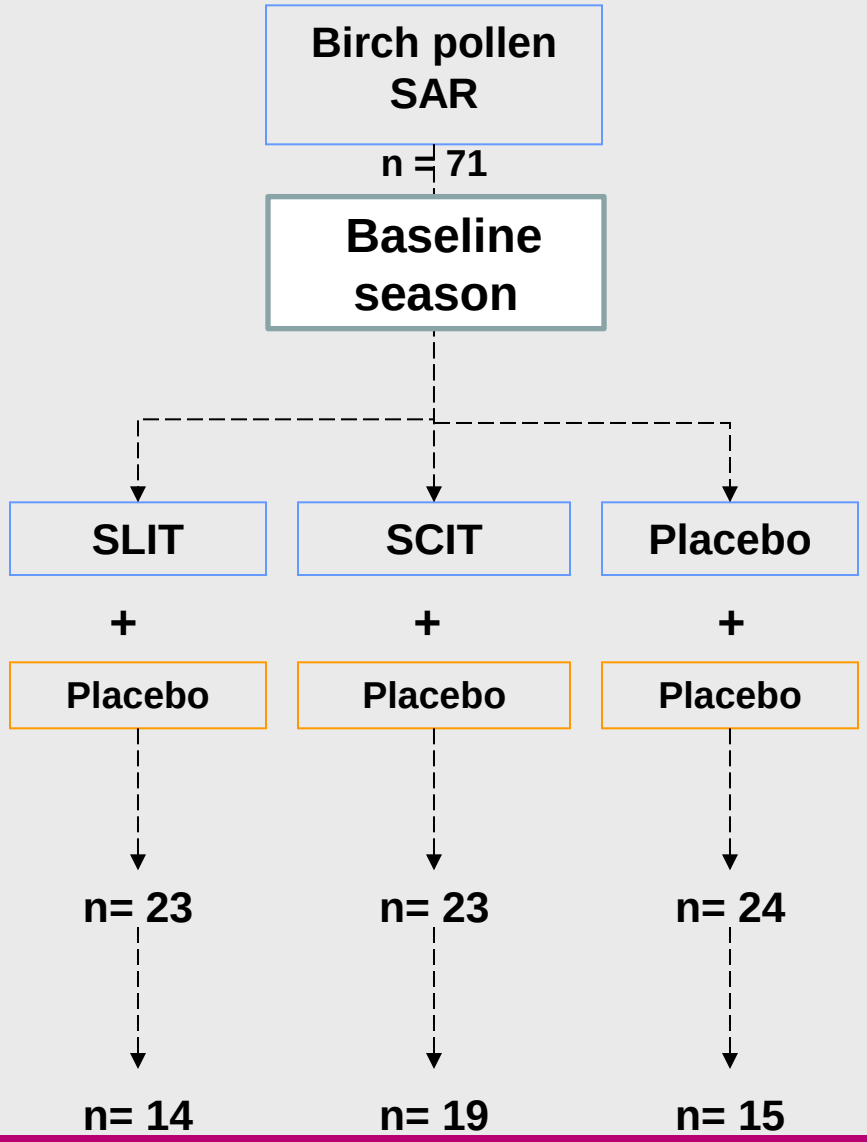
HEAD-TO-HEAD DOUBLE-BLIND TRIALS OF SLIT VERSUS SCIT FOR ALLERGIC RHINITIS

Author, Year, Country	Study design	Allergen	Groups (n)	SLIT group (n)	SCIT group (n)	PLAC group (n)	Age (Years)	Asthma (%)	Sensitization status
KHINCHI 2004 Denmark	Randomized, double-blind, double-dummy, placebo controlled study	Birch	**3**	23	24	24	30 (20-58)	SLIT: 39% SCIT: 29% Placebo: 37%	HDM sensitization: 11-14% Grass pollen symptoms Jun-Jul: 38-56%
QUIRINO 1996 Italy	Double-blind, double-dummy controlled study	Grass-mix	**2**	10	10	-	27 (13-39)	SLIT: 80% SCIT: 80%	Patients sensitized to other inhalant allergens were excluded.
VENTURA 2009 Italy	Randomized, double-blind, placebo-controlled study	*Juniperus ashei*	**4**	10	10	SL: 10 SC: 10	39 ± 2.4 (18-55)	SLIT: NA SCIT: NA	Participants in this study were monosensitized to cypress.
YUKSELEN 2012 Turkey	Randomized, double-blind, double-dummy, placebo controlled study	*D. pteronyssinus* and *D. farinae*	**3**	11	10	10	SLIT: 9.2±3.4 SCIT: 10.9±3.2 Plac: 10.1±2.7	SLIT: 100% SCIT: 100%	Participants included in this trial were monosensitized to HDM.

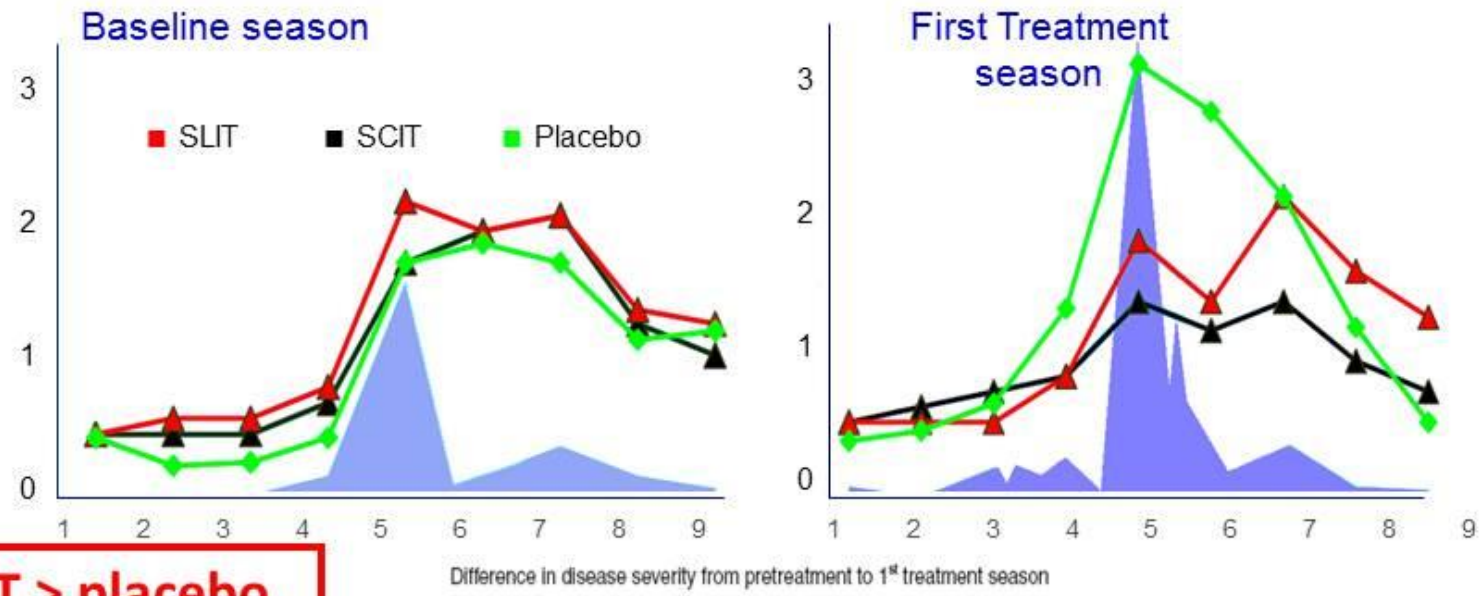
Durham SR, Penagos M. J Allergy Clin Immunol 2016; 137: 339-349.

Randomized, placebo-controlled, double-blind, double-dummy study of birch pollen SLIT and SCIT

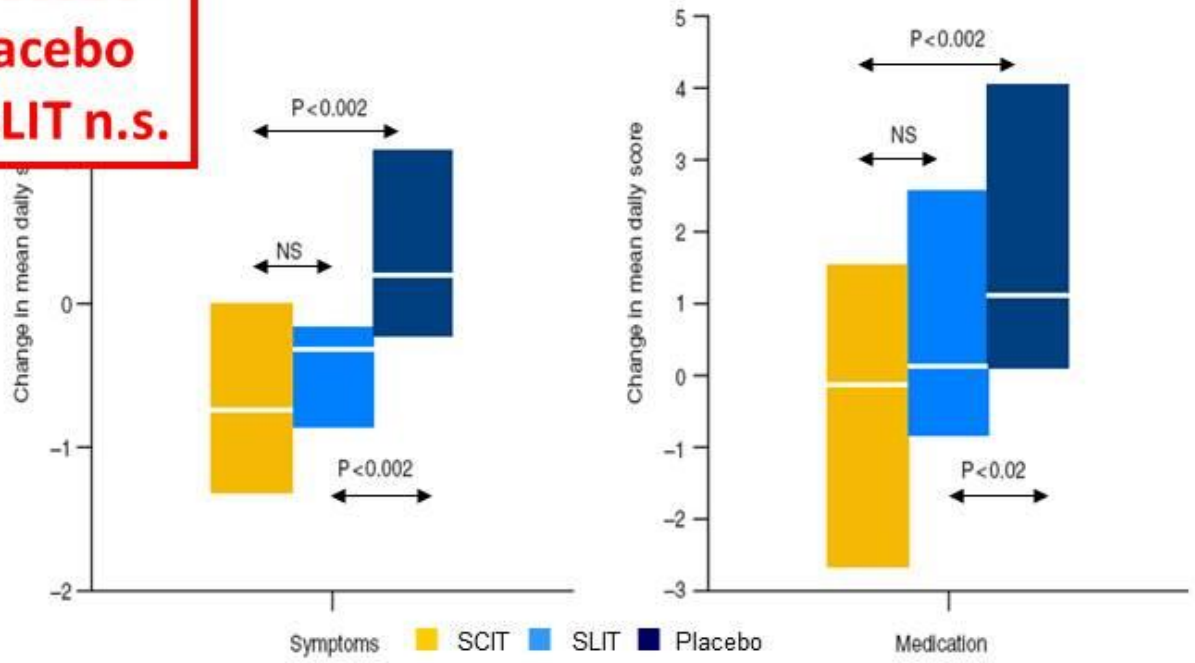
Study design	Randomized controlled double dummy
Control	Sublingual immunotherapy Placebo
Follow-up	24 months
Subjects	Adults
Interventions	Birch pollen IT (cumulative doses: SLIT: 11,182 mcg - SCIT: 51 mcg)
Outcomes	Symptom and medication scores QoL



Khinchi MS et al. Allergy 2004;59: 45-53



SCIT > placebo
SLIT > placebo
SCIT vs SLIT n.s.



Khinchi MS et al. Allergy 2004;59: 45-53

LOCAL AND SYSTEMIC REACTIONS AND ADRENALINE USE
COCHRANE SYSTEMATIC REVIEW OF RCT ON SCIT FOR AR

TYPE OF REACTION	RCTs	SCIT		PLACEBO	
		n	Total events (per participant)	n	Total events (per participant)
LOCAL					
NOT REQUIRING TREATMENT	24	907	834 (0.92)	697	227 (0.33)
REQUIRING TREATMENT	7	208	21 (0.10)	186	8 (0.04)
SYSTEMIC					
EARLY SR GRADE 2 (<30MIN)	17	706	154 (0.22)	566	44 (0.08)
EARLY SR GRADE 3 (< 30 MIN)	13	615	43 (0.07) Up to 7%	463	3 (0.006)
EARLY SR GRADE 4 (<30 MIN)	9	417	3 (0.007) Up to 0.7%	303	1 (0.003)
LATE SR (>30 MIN)	11	514	458 (0.89)	412	148 (0.36)
ADRENALINE USE	13	557	19 (0.037) [Injections 14,085 (0.13%)]	404	1 (0.002) [Injections 8,278 (0.01%)]

Calderon MA, et al. Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001936

Durham and Penagos. JACI 2016;137(2):339–349

LOCAL AND SYSTEMIC REACTIONS AND ADRENALINE USE
COCHRANE SYSTEMATIC REVIEW OF RCT ON SLIT FOR AR

TYPE OF REACTION	RCTs	SLIT		PLACEBO	
		n	Total events (per participant)	n	Total events (per participant)
LOCAL					
LABIAL OEDEMA	11	604	55 (0.09)	536	7 (0.01)
BUCCAL PRURITUS	21	1126	1798 (1.6)	1075	492 (0.46)
BUCCOLINGUAL OEDEMA	8	648	143 (0.22)	606	2 (0.003)
THROAT IRRITATION	10	770	243 (0.3)	747	29 (0.04)
ORAL (NONSPECIFIED)	3	68	143 (2.1)	71	24 (0.34)
LOCAL NONSPECIFIED	3	119	7 (0.06)	116	3 (0.03)
SYSTEMIC					
URTICARIA	8	204	7 (0.03)	199	9 (0.04)
PRURITIS/RASH	10	363	13 (0.04)	222	9 (0.04)
CONJUNCTIVITIS	8	262	774 (2.95)	238	786 (3.3)
RHINITIS	16	965	1403 (1.45)	912	1034 (1.13)
RHINOCONJUNCTIVITIS	6	184	60 (0.33)	176	58 (0.33)
ASTHMA/WHEEZE	15	488	51 (0.1)	450	42 (0.09)
COUGH	8	337	313 (0.93)	304	211 (0.69)
GASTROINTESTINAL	20	630	88 (0.14)	561	10 (0.02)
HEADACHE	6	535	70 (0.2)	548	68 (0.12)
ANAPHYLAXIS	6	291	0	288	0
SYSTEMIC NONSPECIFIED	5	330	4 (0.01)	36	0
ADRENALINE USE	0	0	0	0	0

Radulovic S, et al. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD002893.

Sublingual or subcutaneous immunotherapy :Summary

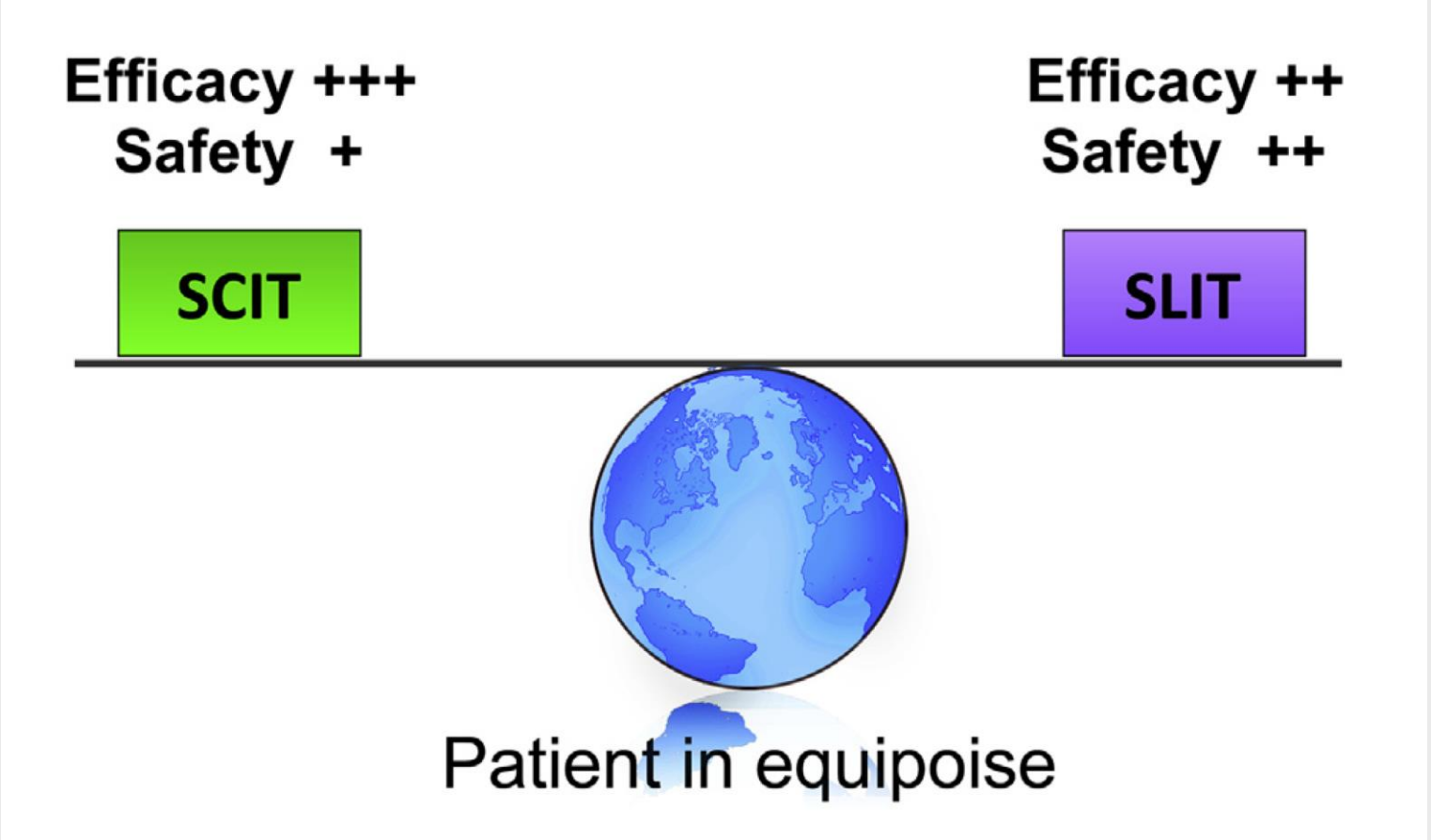
SUBCUTANEOUS IMMUNOTHERAPY

- Indirect evidence suggests SCIT more effective than SLIT in SAR (inconclusive)
- Direct comparative evidence v SLIT weak and definitive trials needed
- Local side effects common, but not usually bothersome

SUBLINGUAL IMMUNOTHERAPY

- Indirect evidence strongly suggests SLIT safer than SCIT in SAR
- Direct comparative evidence v SCIT weak and definitive trials needed
- Local side effects common and occasionally bothersome

TAKE-HOME MESSAGE



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

Sublingual immunotherapy for perennial rhinitis and asthma

State of the Art

- Sublingual immunotherapy is effective for seasonal rhinitis, suitable for self administration and induces long-term clinical benefits for years after discontinuation

- Until recently, evidence in favour of sublingual immunotherapy for perennial rhinitis and asthma was weak and inconsistent

- Recently sublingual tablet immunotherapy has been shown to be effective for perennial HDM allergic rhinitis and to reduce corticosteroid requirements and exacerbations in HDM asthma

Recent well-powered RCTs of HDM SLIT for perennial allergic rhinitis

First author, Year, Country	Allergen	Route	n (R)	Groups (n, R)	Age (Years)	Asthma (%)	Poly-sensitization (%)	Up-dosing	Frequency maintenance	SLIT duration	Treatment free observation
BERGMANN 2014 Germany	*D. pteronyssinus* and *D. farinae*	SLIT-T	**509**	500 IR = 169 300 IR = 170 Placebo = 170	18-50	29-32%	48-55%	Yes	Daily	12 months	12 months
MOSBECH 2015 Denmark	*D. pteronyssinus* and *D. farinae*	SLIT-T	**489**	6 SQ = 134 3 SQ = 131 1 SQ = 117 Placebo = 107	≥14	100%	83%	No	Daily	~12 months	0
DEMOLY 2015 France	*D. pteronyssinus* and *D. farinae*	SLIT-T	**992**	12 SQ = 318 6 SQ = 336 Placebo = 338	18-65	45-48%	66-71%	No	Daily	~12 months	0

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

Recent well-powered RCTs of HDM SLIT for perennial allergic rhinitis

First author, Year, Country	Allergen contents per dose (µg)	Cumulative dose	Units	Main outcome (means difference; $_{95\%}$CI; p value)	% Reduction vs. placebo	Dropout rate
BERGMANN 2014 Germany	**500 IR:** 28/120 µg Der p1/ Der f1 **300 IR:** 16/68 µg Der p1/ Der f1	500 IR: ~10.2/43.8 mg Der p1/Der f1 a year 300 IR: ~5.8/24.8 mg Der p1/Der f1 a year	IR	500 IR vs PLB: -0.78 (-1.34 to -0.22); p= 0.0066 300 IR vs PLB: -0.69 (-1.25 to -0.14); p= 0.0150 500 IR vs 300 IR: -0.09 (-0.66 to 0.49); p= 0.7638	**500 IR**: -20.2% **300 IR**: -17.9%	Y1 16% Y2 22%
MOSBECH 2015 Denmark	**6 SQ-HDM:** 7.5 µg Der 1 (Der p 1 and Der f 1) and 7.5 µg Der 2 (Der p 2 and Der f 2)	6 SQ = ~2190 SQ-HDM 3 SQ = ~1095 SQ-HDM 1 SQ = ~365 SQ-HDM	SQ-HDM	6 SQ-HDM: −0.78 (−1.52 to −0.04); p= 0.036 3 SQ-HDM: −0.70 (−1.45 to 0.04); p= 0.063 1 SQ-HDM: −0.47 (−1.24 to 0.30)p= 0.23	**6 SQ**: -28.8% **3 SQ**: - 26% **1 SQ**: -17.4	17%
DEMOLY 2015 France	**12 SQ-HDM:** 15 µg Der 1 (Der p 1 and Der f 1) and 15 µg Der 2 (Der p 2 and Der f 2)	12 SQ = ~4380 SQ-HDM 6 SQ = ~2190 SQ-HDM	SQ-HDM	TCRS: Difference from placebo ($_{95\%}$CI) 12 SQ-HDM: 1.22 (0.49-1.96); p=0.001 6 SQ-HDM: 1.18 (0.45-1.91); p=0.002	**12 SQ**: -18.2% **6 SQ**: -17.5%	12%

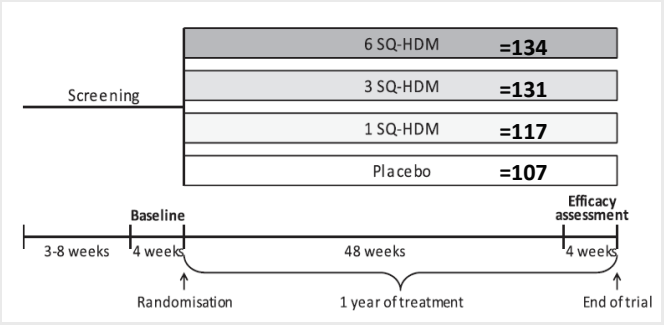
Durham SR, Penagos M. J Allergy Clin Immunol 2016; 137: 339-349.

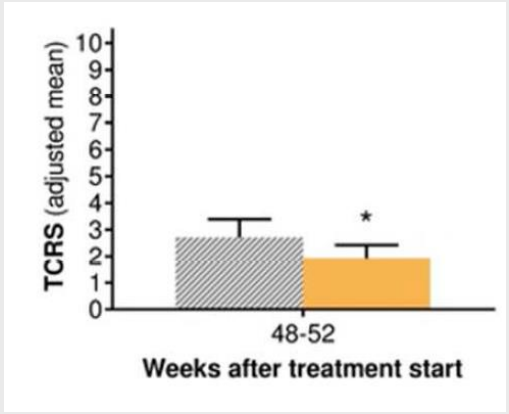
SQ house dust mite sublingually administered immunotherapy tablet (ALK) improves allergic rhinitis in patients with house dust mite allergic asthma and rhinitis symptoms

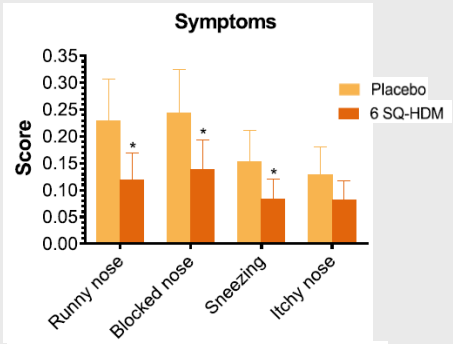
Holger Mosbech, MD [*]; G. Walter Canonica, MD [†]; Vibeke Backer, MD [‡]; Frederic de Blay, MD [§];

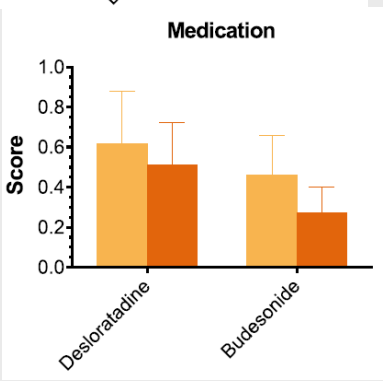
Ann Allergy Asthma Immunol 114 (2015) 134–140

- n= 489 Adolescent & Adults
- Moderate-severe AR
- DBPCT-Multi centre
- Dose ranging: 1, 3 & 6 SQ
- Duration12 months









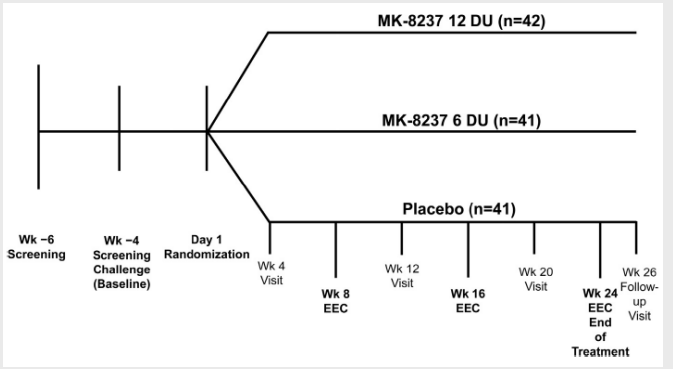
- No anaphylactic reactions, systemic allergic reactions or AEs requiring epinephrine.
- Treatment emergent AEs: 54%: 6 SQ-HDM, 57%:12 SQ-HDM, 43%: placebo
- Local AEs were the most commonly reported treatment-emergent AEs.
- Median duration of individual local AEs on 1st day ranged from 1 to 43 minutes

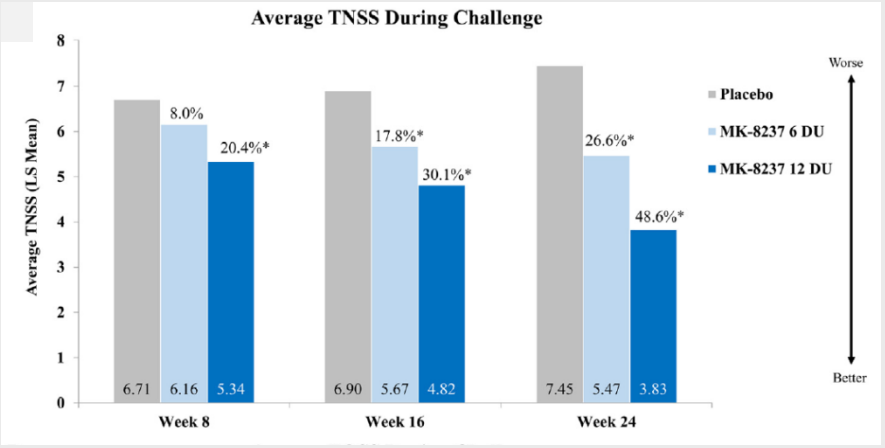
Mosbech et al., Ann Allergy Asthma Immunol 114 (2015) 134-140

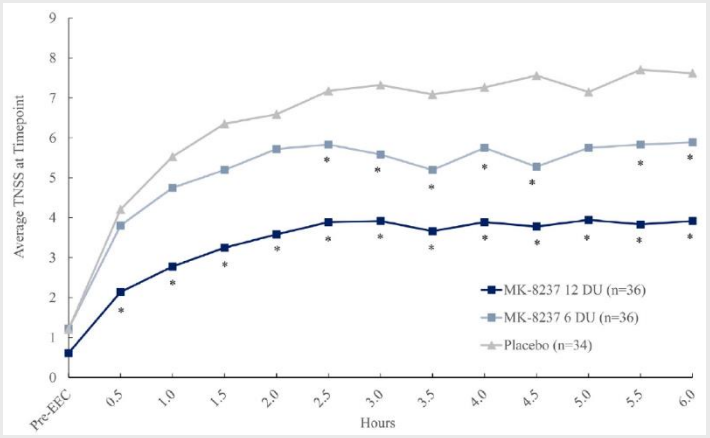
Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber

Hendrik Nolte, MD, PhD,[a] Jennifer Maloney, MD,[a] Harold S. Nelson, MD,[b] David I. Bernstein, MD,[c] Susan Lu, PharmD,[a] Ziliang Li, PhD,[a] Amarjot Kaur, PhD,[a] Petra Zieglmayer, MD,[d] René Zieglmayer, Dipl Ing,[d] Patrick Lemell, PhD,[d] and Friedrich Horak, MD[d]
Kenilworth, NJ, Denver, Colo, Cincinnati, Ohio, and Vienna, Austria

- n= 124 Adults
- Moderate-severe AR
- DBPCT-single centre Vienna Challenge chamber
- Dose ranging: 6 DU & 12 DU
- Onset-of action
- Duration 6 months





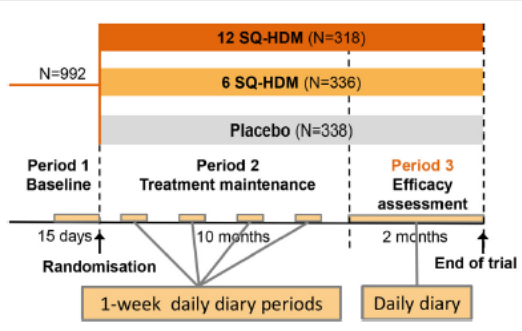


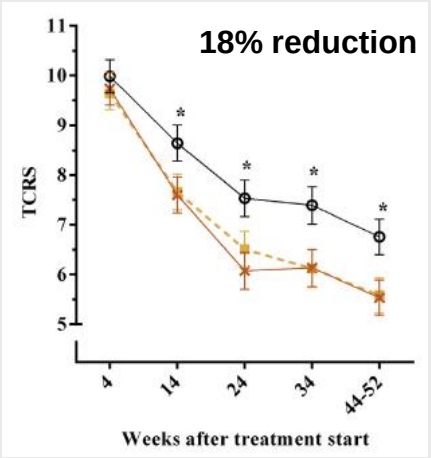
Nolte et al., J Allergy Clin Immunol 2015; 135, 1494

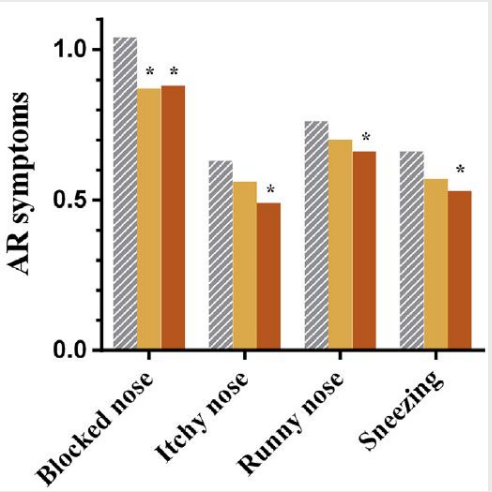
Effective treatment of house dust mite–induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial

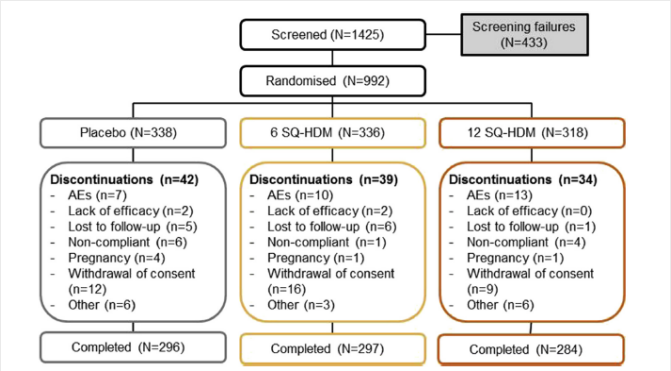
Pascal Demoly, MD, PhD,[a] Waltraud Emminger, MD,[b] Dorte Rehm, PhD,[c] Vibeke Backer, MD,[d] Lene Tommerup, MSc,[c] and Jörg Kleine-Tebbe, MD[e] *Paris, France, Vienna, Austria, Hørsholm and Copenhagen, Denmark, and Berlin, Germany*

- Phase 3 trial
- *n*: 992 adults multicntr
- Moderate-severe AR
- Duration 12 months
- 12 SQ: 15ug Der 1and Der 2
  6 SQ: 7.5ug Der1 &Der2
  Der1 (DP1+DF1), Der2 (DP2+DF2)









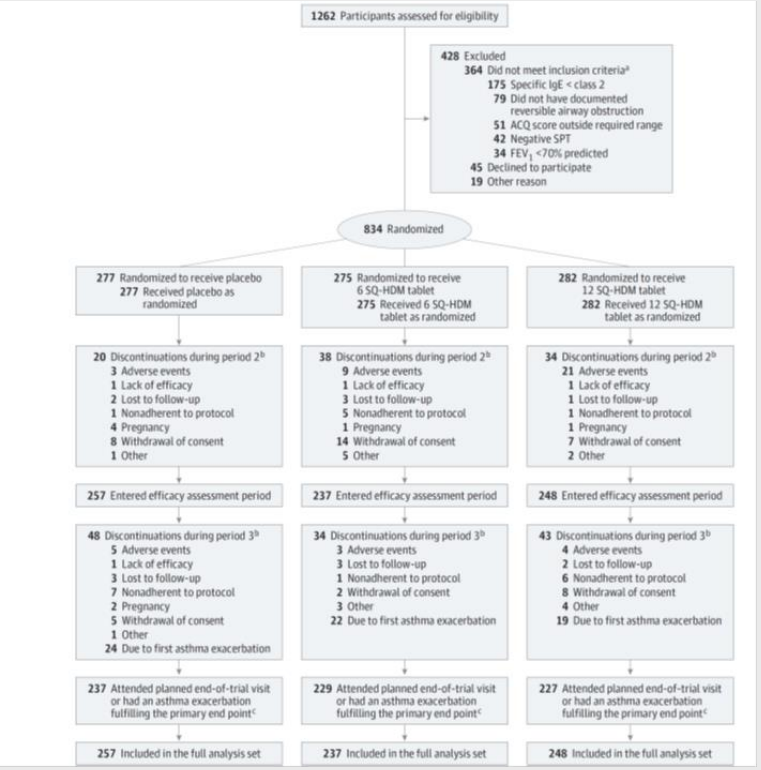
Demoly et al., J Allergy Clin Immunol 2016;137:444-451

Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma
A Randomized Clinical Trial

J. Christian Virchow, MD; Vibeke Backer, MD, DMSci; Piotr Kuna, MD; Luis Prieto, MD; Hendrik Nolte, MD, PhD; Hanne Hedegaard Villesen, MSc, PhD; Christian Ljørring, MSc; Bente Riis, MSc, PhD; Frederic de Blay, MD

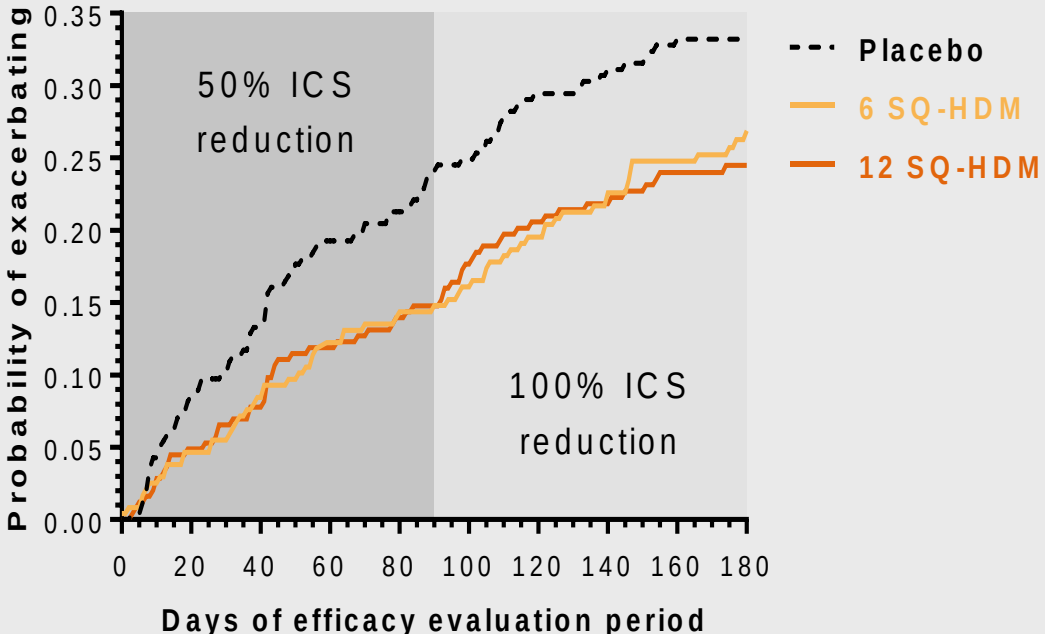
JAMA. 2016;315(16):1715-1725.

- **834 adults with HDM allergy–related asthma not well controlled by ICS or combination products, and with HDM allergy–related rhinitis**



SLIT in HDM allergic asthmatics

- Two doses and placebo, 1:1:1 randomisation
- Exclusions: FEV1 less than 70%; hospitalization due to asthma within last 3 months
- Reduction in risk of moderate or severe asthma exacerbation, HR 0.69 (0.50-0.96)
- Absolute risk difference 0.10 (0.02-0.16)



	6 SQ-HDM	12 SQ-HDM
Hazard ratio [95% CI]	**0.69** [0.49;0.96]	**0.66** [0.47;0.93]
Risk reduction	31%	34%
p-value	0.028	0.017

Virchow JC *JAMA* 2016;315(16):1715-1725

Take-Home Message

- Immunotherapy with House Dust Mite tablets is effective in perennial house dust mite-associated rhinitis.
- Among adults with HDM allergy-related asthma not well-controlled by ICS, HDM SLIT improved time to first moderate or severe asthma exacerbation.
- Estimated absolute reduction of 9 to 10 percentage points (31% – 34% reduction relative to placebo).
- Treatment-related adverse events were common. Further studies needed to assess long-term effcicacy and safety.

Table 2. Overview of Primary, Key Secondary, and Exploratory End Point Efficacy Results for Each Treatment Group

End Point	Total Participants	No. of Participants With Event	Treatment Effect	
			HR (95% CI)	*P* Value
Primary End Point				
Time to first asthma exacerbation from the start of period 3[a]				
FAS-MI[b]				
Placebo group	277	NA[c]	Reference	
6 SQ-HDM group	275	NA[c]	0.72 (0.52 to 0.99)	.045
12 SQ-HDM group	282	NA[c]	0.69 (0.50 to 0.96)	.03
FAS				
Placebo group	257	83 (32)	Reference	
6 SQ-HDM group	237	62 (26)	0.69 (0.49 to 0.96)[d]	.03
12 SQ-HDM group	248	59 (24)	0.66 (0.47 to 0.93)[d]	.02
Key Secondary End Points				
Time to first asthma exacerbation with deterioration in asthma symptoms or nocturnal awakenings				
Placebo group	257	57 (22)	Reference	
6 SQ-HDM group	237	45 (19)	0.72 (0.49 to 1.07)	.17
12 SQ-HDM group	248	39 (16)	0.64 (0.42 to 0.96)	.03

Virchow JC *JAMA* 2016;315(16):1715-1725

Definition of asthma exacerbation

An asthma exacerbation was defined according to the American Thoracic Society and European Respiratory Society (ATS/ERS) recommendation[19,20]; and in practice described by 1 or more of the following criteria for moderate or severe asthma exacerbation leading to a change in treatment.

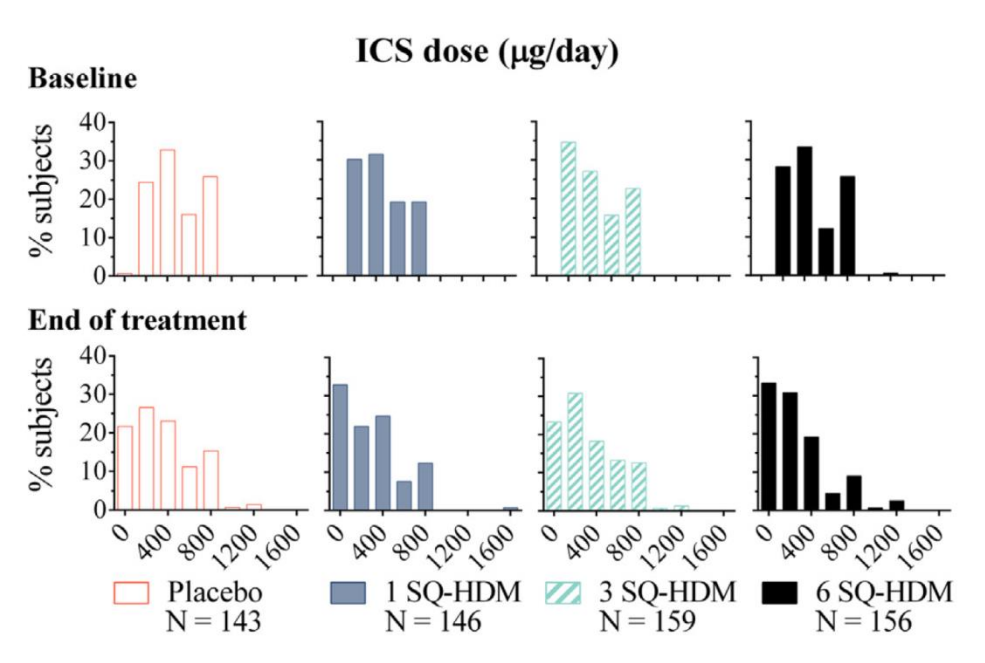
Criteria for a moderate asthma exacerbation included (1) nocturnal awakening(s) due to asthma requiring SABA use for at least 2 consecutive nights or an increase of at least 0.75 points in daily symptom score from baseline value on at least 2 consecutive days; (2) an increase from baseline in SABA use on at least 2 consecutive days (a minimum increase of 4 puffs per day); (3) a 20% or more decrease in peak expiratory flow from baseline on at least 2 consecutive mornings or evenings or a 20% or more decrease in FEV_1 from baseline; and (4) a visit to the emergency department or an unscheduled visit to the trial site for asthma treatment not requiring systemic corticosteroids.

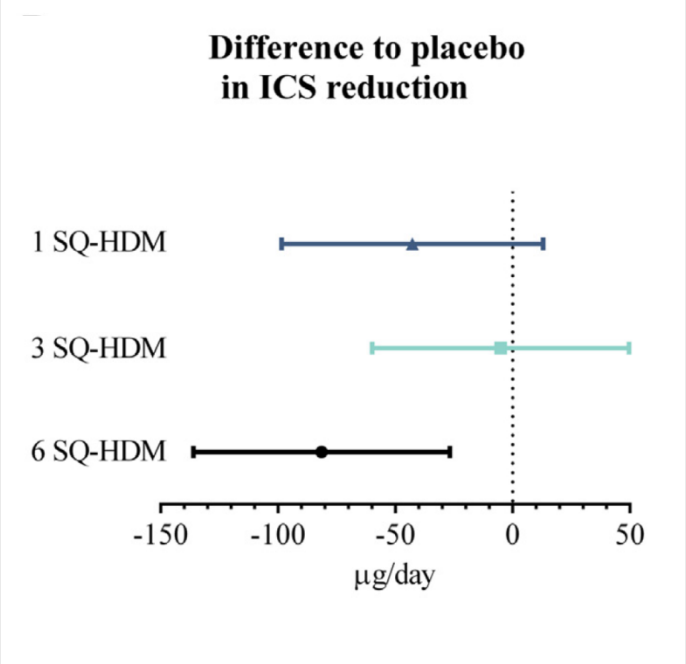
Criteria for a severe asthma exacerbation included (1) a requirement for systemic corticosteroids for the treatment of asthma symptoms for at least 3 days; and (2) an emergency department visit due to asthma requiring systemic corticosteroids, or a hospitalization for more than 12 hours due to asthma.

Virchow JC *JAMA* 2016;315(16):1715-1725

Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Holger Mosbech, MD,[a] Regina Deckelmann, MD,[b] Fréderic de Blay, MD,[c] Elide Anna Pastorello, MD,[d] Ewa Trebas-Pietras, MD,[e] Luis Prieto Andres, MD,[f] Inga Malcus, MD,[g] Christian Ljørring, MSc,[h] and Giorgio Walter Canonica, MD[i] *Gentofte, Denmark, Leipzig, Germany, Strasbourg, France, Milan and Genoa, Italy, Lublin, Poland, Valencia, Spain, Malmö, Sweden, and Hørsholm, Denmark*





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