New Evidence in AIT

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Conflict of Interest Statement
Piotr Kuna MD, PhD

Listed are all my relationship that may be related to this presentation that have existed during the past 3 years

Industry Sponsored Clinical Trials: Allergopharma, ALK, Almiral, Amgen, AstraZeneca, Boehringer-Ingelheim, Chiesi, FAES, Genetech, GSK, Hal, MSD, Novartis, Roche, Sanofi-Aventis, Teva,

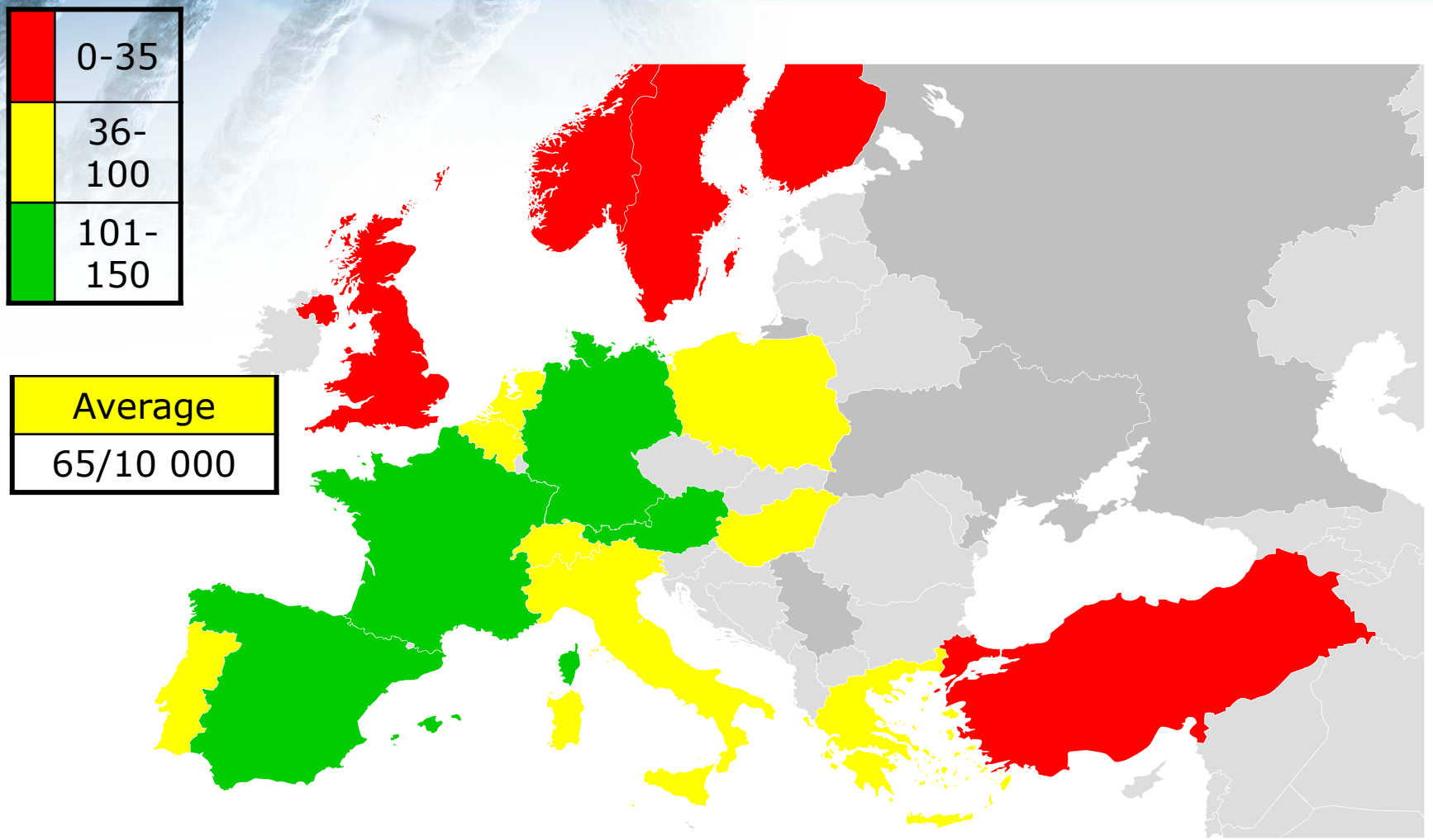
Consultancies and Advisory Boards: Allergopharma, ALK, Almiral, AstraZeneca, Boehringer-Ingelheim, Chiesi, MSD, Novartis,

Lectures: Allergopharma, ALK, Almiral, Amgen, AstraZeneca, Boehringer-Ingelheim, Chiesi, FAES, Genetech, GSK, Hal, MSD, Novartis, Roche, Sanofi-Aventis, Sandoz, Teva,

No personal relationship with tobacco industry entities

No Off Label Disclosure

Number of prescribed Immunotherapy Vaccines per 10 000 Inhabitants (Initial and Maintenance Therapy)



Contents

- Regulatory background allergen IT
- The TAV (Therapie-allergene Verordnung)
- Effects of the TAV
- The most recent achievements in the field published in 2016

The Therapieallergene-Verordnung (TAV)
What is it and what does it mean for allergen IT

Regulatory Background Allergens

- Allergens subjected to European pharmaceutical legislation in 1989 (Directive 89/342/EEC)

- Definition of directive 2001/83/EC:“medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent”

Directive 2001/83/EC

Marketing authorization (Article 6)

1. No medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued by the competent authorities of that Member State in accordance with this Directive or an authorization has been granted in accordance with Regulation (EEC) No 2309/93.

Increasing regulatory demand for allergen products in Europe

Outline German regulation “Therapieallergene-Verordnung” (14-11-2008)

TAV - Allergens		other Allergens
grasses, spring trees, house dust mites, bee/wasp		epithelia, moulds etc
batch release by Paul-Ehrlich-Institute (PEI)		In-House quality control
Indication to register	Sell-out	
MA application before 01-12-2010 Transition period to solve 1. Technical deficiencies 2. Clinical deficiencies* * Up to 7y upon receipt deficiency letter	Until 14-11-2011	Available without limitations

Increasing regulatory demand for allergen products: steps required for evidence-based medicine

Objective		Study type	Population	Product claim
1	Establish optimal dosage	**Dose Tolerability Study (DTS)** to define highest tolerated dose (safety)	Adults	N/A
		Dose Range Finding (DRF) optimal efficacy & safety	Adults	N/A
2	Confirm efficacy and safety in a larger population	**Short-term Pivotal** to show that the product is safe and that it's efficacy is clinically relevant	Adults	Treatment of allergic symptoms
		Long-term Pivotal to show that the product is still effective 2 years after a treatment of 3 years	Adults	Long-term efficacy and disease modifying effect
3	Show efficacy and safety of the product in children	**Long-term Pivotal** with one product per company	Children	
		Short-term Pivotal	Children	Treatment of allergic symptoms

This program is an enormous investment on existing products and new products required by national (e.g. PEI) and European authorities (EMA)

- **Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases** (CHMP/EWP/18504/2006

Clinical trials for the TAV products

Current status

Genehmigte/evtl. abgeschlossene Studien für TAV-Präparate
(„Nachzulassung"), nach www.clinicaltrialsregister.eu

Stand: 15.01.2017

Subkutane Präparate		Bäume	Gräser	Milben
ALK-Abelló	Avanz	---	Ph II (2013-005130-38) Ph II (2011-000057-23) Ph II/III (2011-000120-15)	Ph II (2011-002017-11)
Allergopharma	Acaroid	n/a	n/a	Ph II (2011-002248-29) Ph III (2015-000188-15)
Bencard Allergie	Pollinex Quattro	Ph II (2012-004336-28) Ph II (2015-000984-15) PH III (2016-002781-31)	---	n/a
Bencard Allergie	Tyro Milbe	n/a	n/a	---
HAL Allergie	Purethal	zugelassen	zugelassen	Ph II (2008-006261-81) Ph II (2011-000393-61) Ph III (2016-000051-27)
LETI-Pharma	Depigoid	Ph II (2008-008448-26) Ph III (2012-000414-11)	Ph II (2012-000416-28) Ph II (2014-004732-19)	zugelassen
Lofarma	ModAll	n/a	n/a	---
Roxall	Clustoid	---	Ph II (2010-022083-12) Ph III (2008-000513-29)	---
Roxall	Roxoid	---	---	---

Sublinguale Präparate		Bäume	Gräser	Milben
ALK-Abelló	SLIT One plus	---	---	---
ALK-Abelló	SLIT One ultra	---	---	---
Bencard Allergie	Oralvac Compact	---	---	---
HAL Allergie	Sublivac fix	Ph II (2011-004550-25) Ph III (2013-005550-30)	Ph II (2010-021235-13)	Ph II (2014-002047-18)
Lofarma	LAIS Tabletten	Ph II (2012-001822-89) Ph III (2013-002129-43)	Ph II (2011-002174-23) Ph III (2012-004916-79)	Ph II (2013-000617-20)
Lofarma	LAIS Tropfen	---	---	---
Roxall	Sulgen Spray	---	---	---

What is the effect of the TAV for physicians?

- Possible decrease of allergen portfolio
- Less companies on the market
- Less flexibility in treatment options

BUT

- Higher quality of products, due to state of the art CMC
- Products are clinically substantiated via a complete phase I, II, III program

The most recent achievements in the field published in 2016:

- **Updating clinical and CMC dossiers of marketed products to obtain registration/market authorization**
  - SCIT HDM allergoïd HAL Allergy
  - SLIT birch pollen HAL Allergy

- **Clinical evaluation of novel products to obtain registration**
  - SLIT HDM tablet Stallergènes
  - SLIT HDM tablet ALK

- **Innovation for treatment of food allergy**
  - SCIT peanut allergoïd HAL Allergy

Allergy
EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY
EAACI

Allergy
2016; 71: 967-976

ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

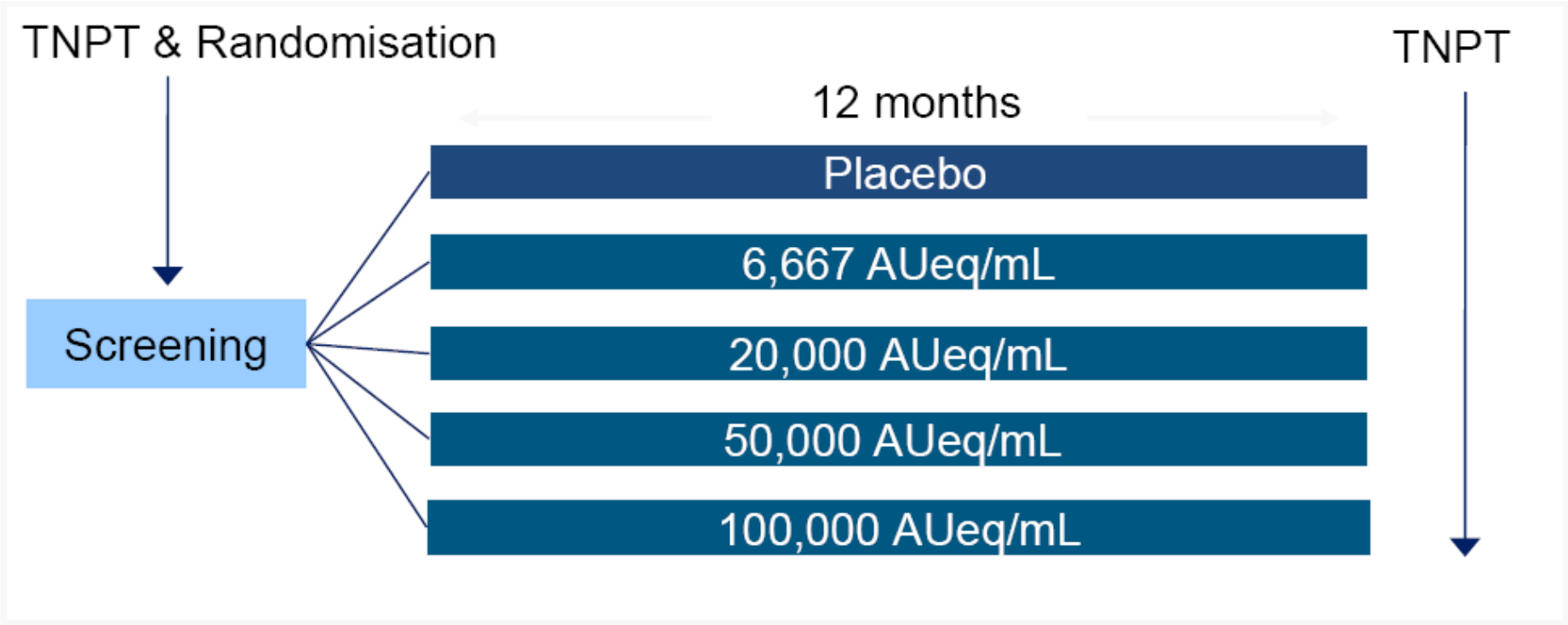
A randomized, 5-arm dose finding study with a mite allergoid SCIT in allergic rhinoconjunctivitis patients

O. Pfaar[1,2], M. J. Nell[3], J. D. Boot[3], S. A. Versteeg[4], R. van Ree[4,5], A. Roger[6], H. Riechelmann[7], A. Sperl[1], J. N. G. Oude Elberink[8], Z. Diamant[9,10] & C. Bachert[11]

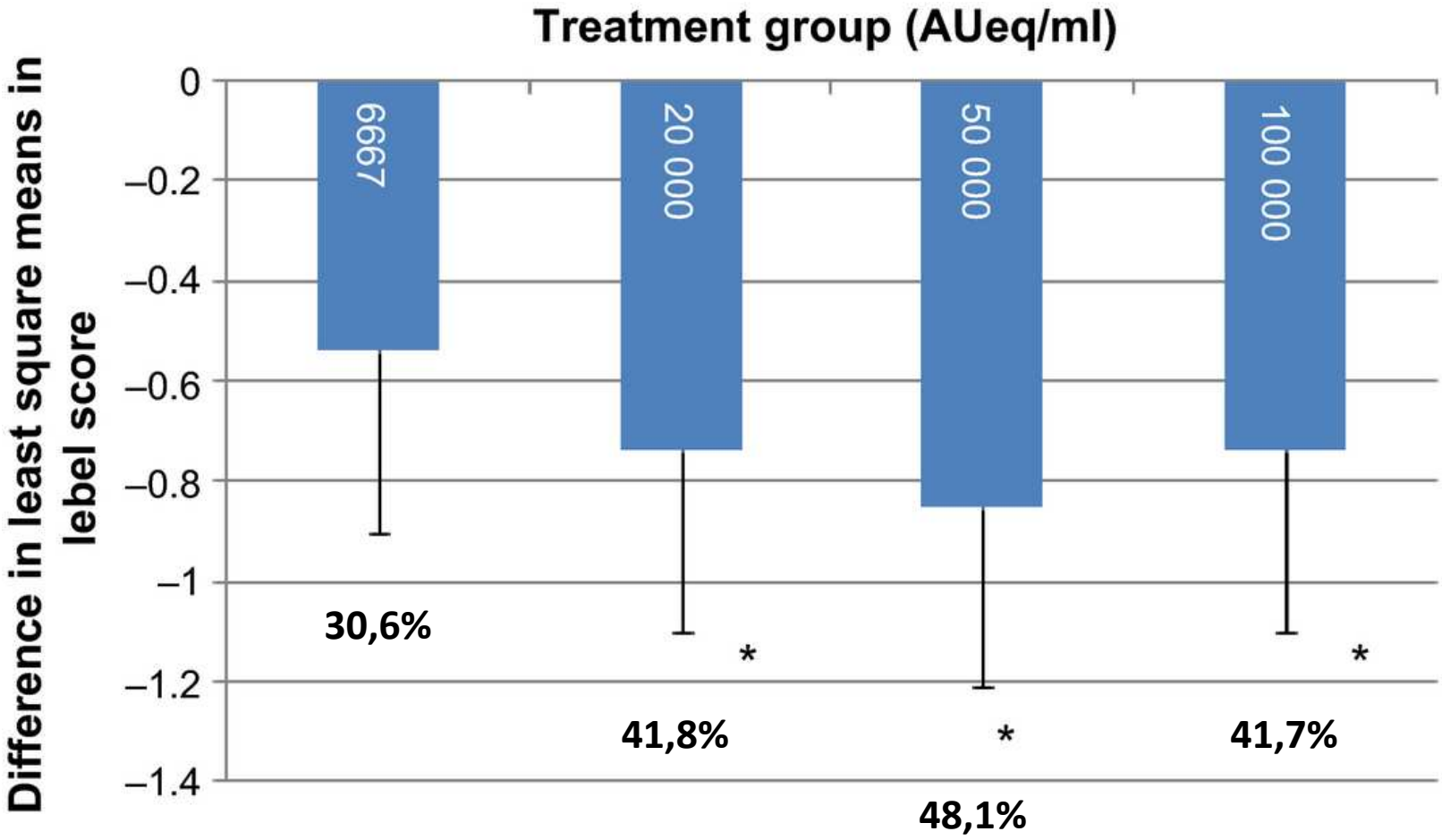
[1]Center for Rhinology and Allergology, Wiesbaden; [2]Department of Otorhinolaryngology, Head and Neck Surgery, Universitätsmedizin Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [3]HAL Allergy BV, Leiden, The Netherlands; [4]Experimental Immunology, Academic Medical Center; [5]Department of Otorhino-laryngology, Academic Medical Center, Amsterdam, The Netherlands; [6]Unitat d'Allèrgia, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [7]Department of Otorhinolaryngology - Head & Neck Surgery, Medical University of Innsbruck, Innsbruck, Austria; [8]Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [9]Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund, Sweden; [10]Department of Clinical Pharmacy & Pharmacology and Department of Gen Practice, University Medical Center Groningen, University Groningen, Groningen, The Netherlands; [11]Upper Airways Research Laboratory, Ghent University, Ghent, Belgium

Scientific Question: What is the optimally safe and effective dose of Mite Allergoid

Study Design

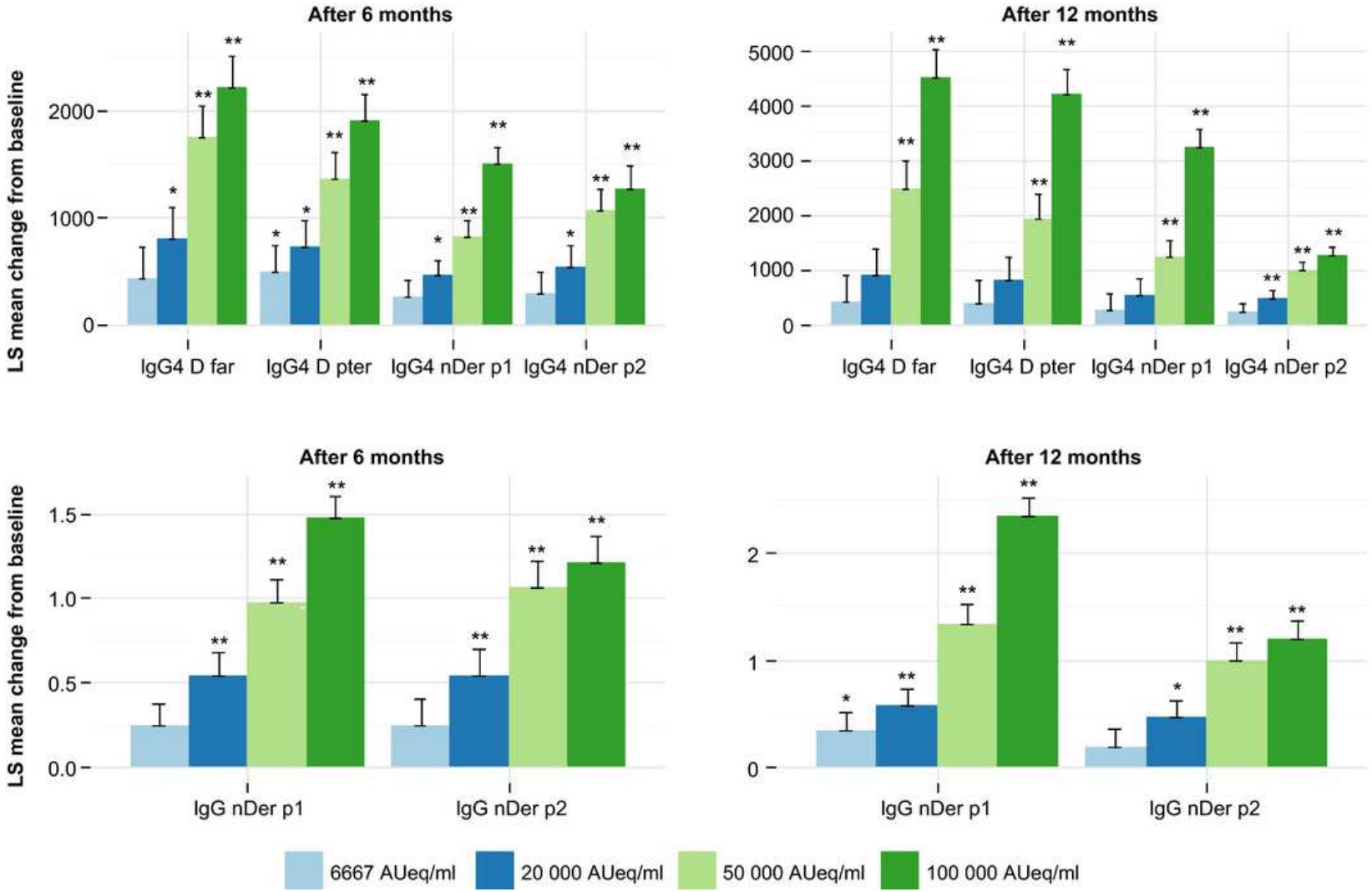


Significant dose- dependent reduction in titrated nasal provocation (Lebel score)



Current dose is effective (20.000) – difference between current and higher dosages is not significant.

Clear dose-response in antibody response



Trend towards more severe side-effects in 5x current dose but still safe

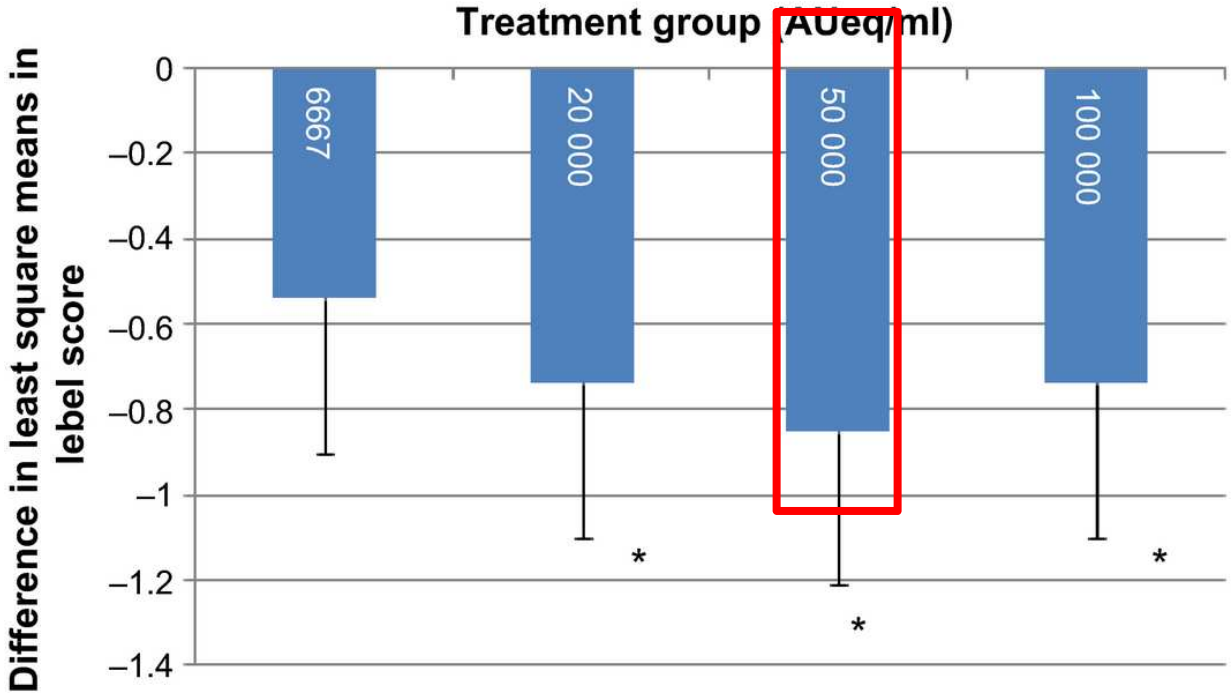
Table 2: Safety overview

	Placebo (n=56)	**6,667 AUeq/mL (n=57)**	**20,000 AUeq/mL (n=59)**	**50,000 AUeq/mL (n=59)**	**100,000 AUeq/mL (n=57)**
Injections given	844	824	933	870	842
Total early local reactions Reaction I/II/III*	10 10/0/0	54 54/0/0	70 69/1/0	56 56/0/0	55 54/0/1
Total late local reactions Reaction I/II/III*	9 9/0/0	178 129/48/1	156 95/59/2	235 127/103/5	250 116/117/17
Early systemic reactions n (pts) Grade I/II/III	1 (1) 1/0/0	1 (1) 1/0/0	0 (0) 0/0/0	2 (2) 1/0/1	2 (2) 2/0/0
Late systemic reactions n (pts) Grade I/II/III Other ** n (pts)	13 (9) 10/0/0 3 (3)	20 (11) 12/1/0 7 (4)	15 (12) 12/0/0 3 (3)	17 (14) 8/0/0 9 (8)	43 (16) 23/3/0 17 (4)

* Local reaction I = redness, II = swelling 5-12 cm, III = swelling > 12 cm

* *Reactions not identified as Grade I or higher

Next Step



Next step in progress: Phase III /50.000 Aueq/ml – 1 year pivotal

Highest efficacy with strong IgG4 and less severe/systemic side-effects.

Study News

PM/0041 Recruitment Newsflash

03-Apr-2017

Congratulations:

5 patients randomised:

Prof. Zielen and his team at site 41122 in Germany
Dr. Leitz and his team at site 41124 in Germany
Dr. Pauer and his team at site 41208 in Hungary
Dr. Roger and his team at site 41608 in Spain

10 patients randomised:

Dr. Morete and her team at site 41404 in Portugal

Study overview (continued)

i am INC Research

	PM/0041
Rationale	Product is marketed already but needs a full development program now per EMA Guideline. A higher dose (50.000 AUeq/ml) than the currently marketed one is tested.
Subjects randomized	730
Sites	80
Regions	Europe
Enrollment / Recruitment period	26Sep2016 – 31Mar2017
Last Patient Last Visit	01Apr2018
Database Lock	01Jun2018

Efficacy and safety of sublingual tablets of house dust mite allergen extracts: Results of a dose-ranging study in an environmental exposure chamber

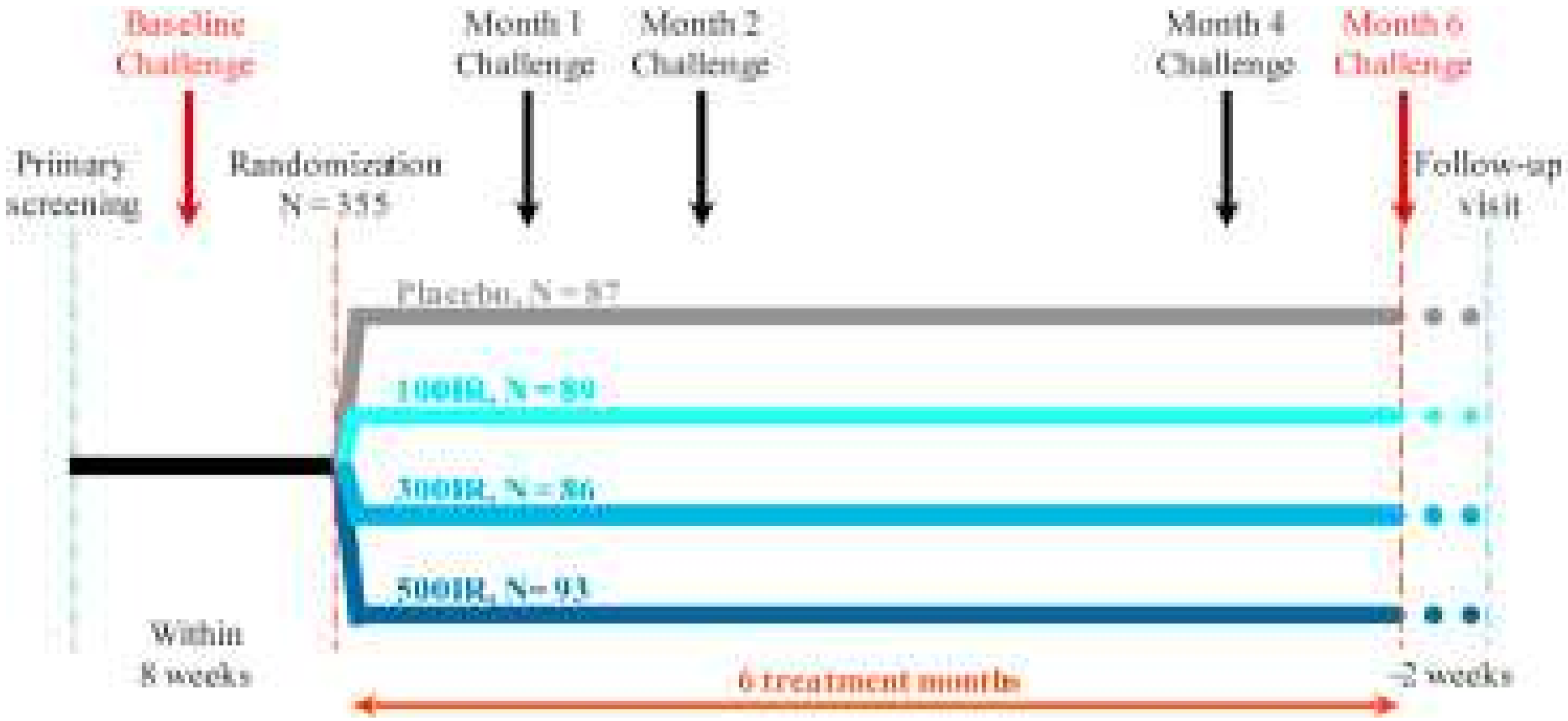
Michel Roux, MD,[a] Philippe Devillier, MD, PhD,[b] William H. Yang, MD,[c] Armelle Montagut, MSc,[a] Kathy Abiteboul, PharmD,[a] Agnès Viatte, MSc,[a] and Robert K. Zeldin, MD[a] *Antony and Suresnes, France, and Ottawa, Ontario, Canada*

Background: In a natural field study, sublingual tablets of house dust mite (HDM) allergen extracts (STG320) were efficacious in treating HDM-associated allergic rhinitis.
Objectives: We sought to assess the efficacy and safety of 3 doses

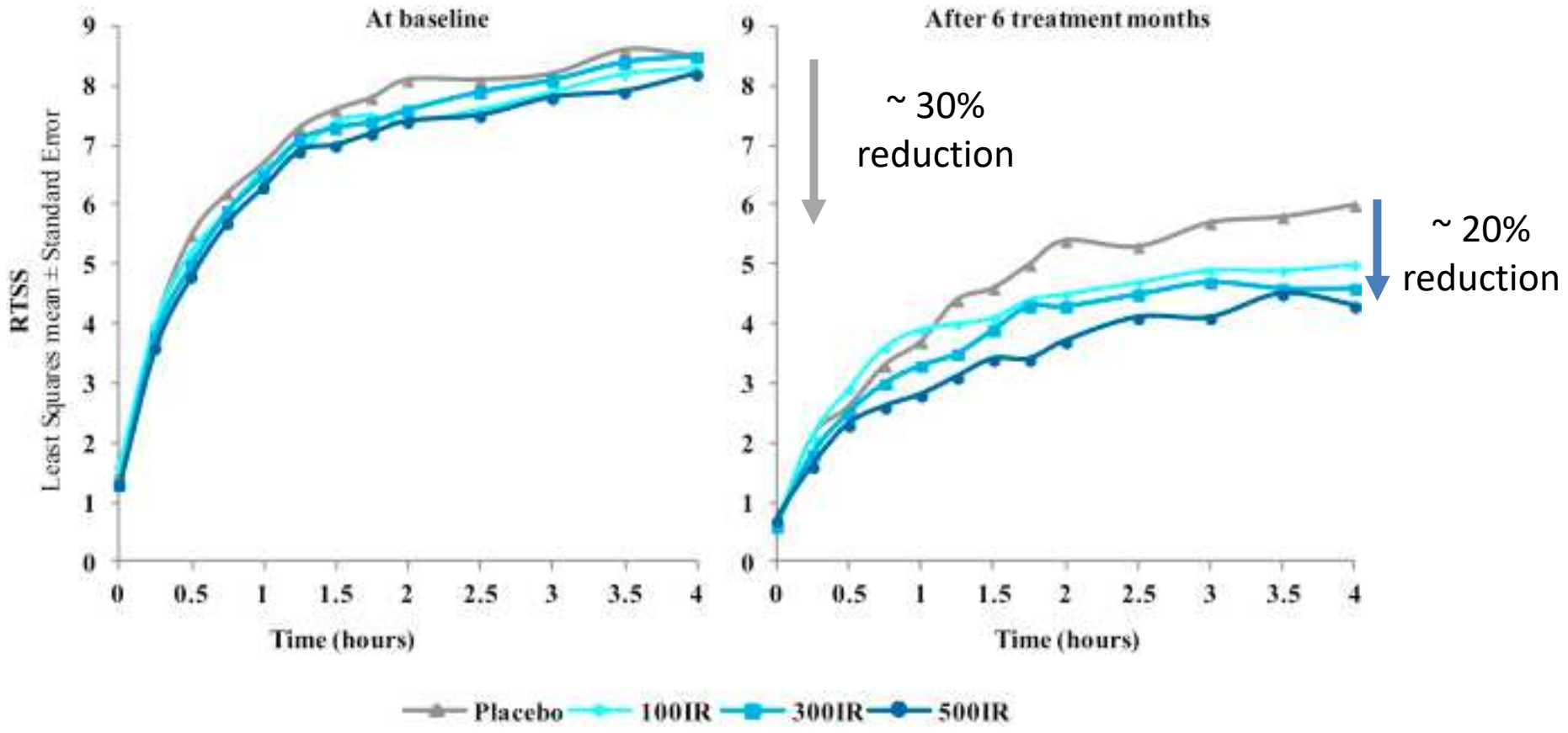
Conclusions: A dose-dependent effect of sublingual HDM immunotherapy was demonstrated in this environmental exposure chamber study, supporting further development of this treatment. (J Allergy Clin Immunol 2016;138:451-8.)

Sc. Question: Assess the efficacy and safety of 3 doses of STG320 (HDM) in an environmental exposure chamber.

Three dosages – primary outcome challenge chamber



Symptoms in challenge chamber: significant reduction



Problem in many clinical trials for HDM: strong placebo effect

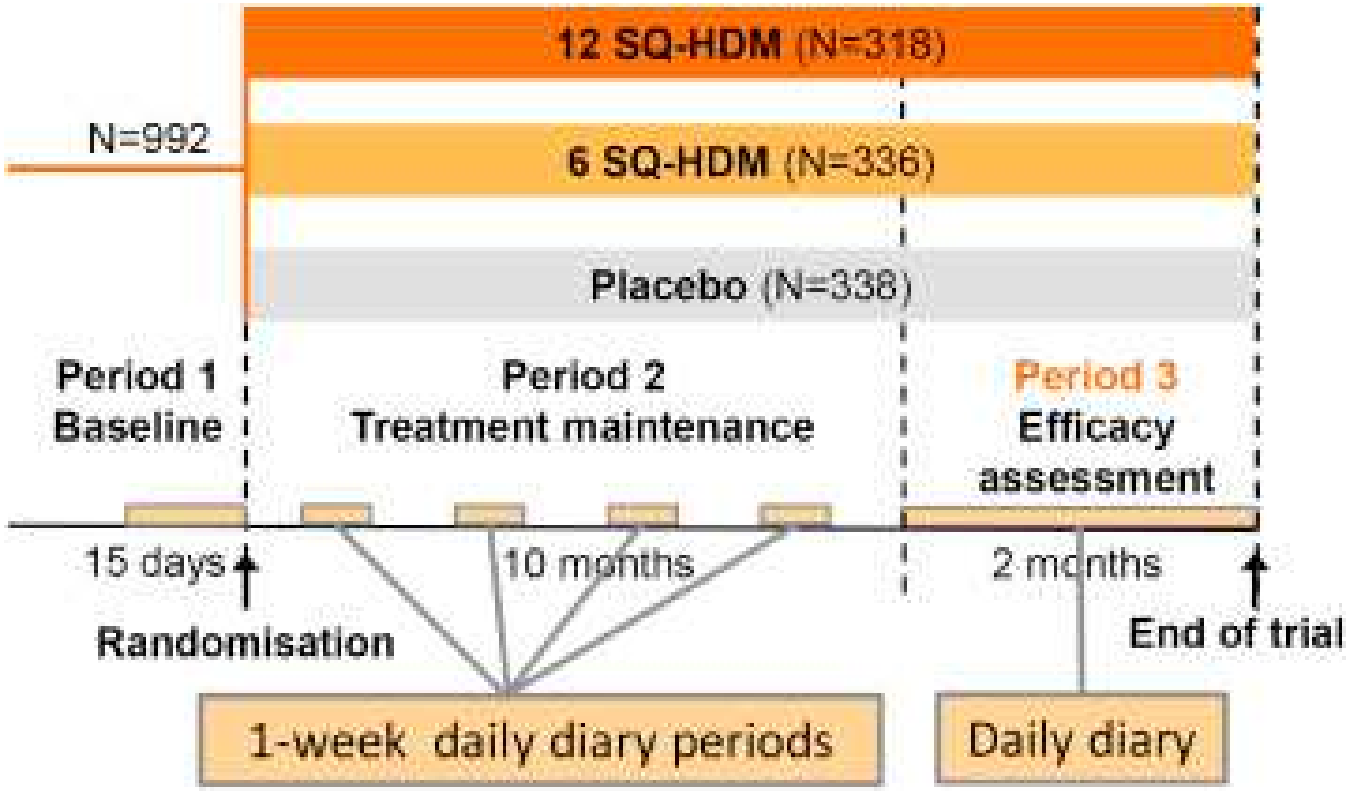
Effective treatment of house dust mite–induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial

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*

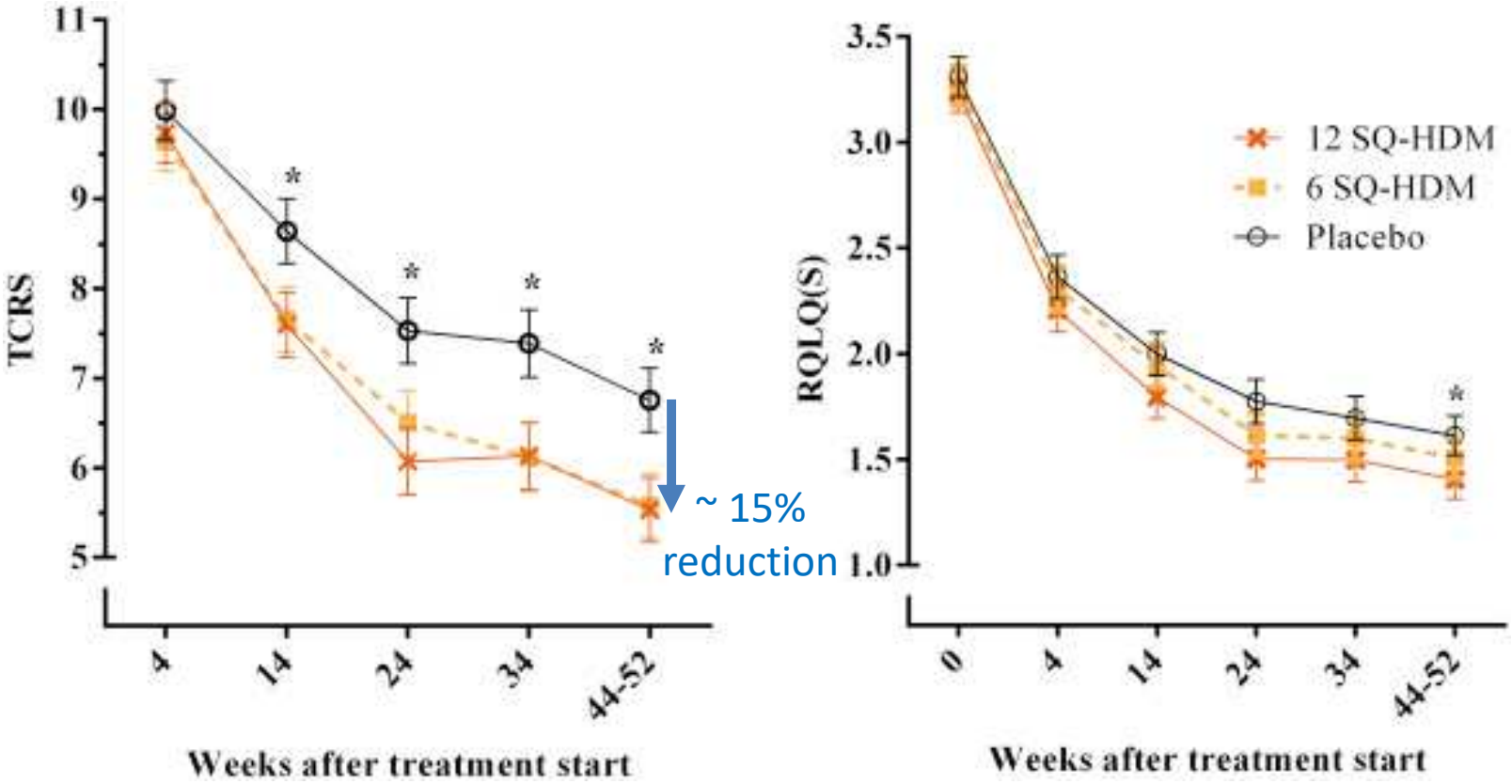
Background: The SQ HDM SLIT-tablet (ALK) has been developed for treatment of house dust mite (HDM)–induced respiratory allergic disease.
Objective: This trial investigated the efficacy and safety of the SQ HDM SLIT-tablet in adults with moderate-to-severe HDM-induced allergic rhinitis (AR).
Methods: The trial was a randomized, double-blind, placebo-controlled phase III trial conducted in 12 European countries including 992 adults with moderate-to-severe HDM-induced AR despite treatment with pharmacotherapy. Subjects were randomized 1:1:1 to 1 year of daily treatment with placebo, 6 SQ-HDM, or 12 SQ-HDM. The primary end point was the total combined rhinitis score (ie, the sum of rhinitis symptom and 1.18 ($P = .002$) and 1.22 ($P = .001$) compared with placebo for 6 SQ-HDM and 12 SQ-HDM, respectively. The statistically significant treatment effect was evident from 14 weeks of treatment onward. For all key secondary end points, efficacy was confirmed for 12 SQ-HDM, with statistically significant reductions of rhinitis symptoms and medication scores, improved quality of life, and a reduced combined rhinoconjunctivitis score in the efficacy assessment period compared with placebo. The treatment was well tolerated.
Conclusion: The trial confirmed the efficacy and favorable safety profile of both 6 SQ-HDM and 12 SQ-HDM in adults with HDM-induced AR. The treatment effect was present from 14 weeks of treatment onward. (J Allergy Clin Immunol 2016;137:444-51.)

Sc. Question: Assess efficacy and safety of the SQ HDM SLIT-tablet in adults with HDM-induced allergic rhinitis.

Pivotal with 2 dosage schemes

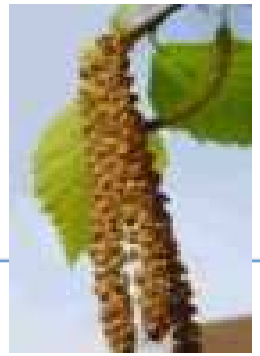


Overall ~15% reduction over placebo



Again: quite impressive placebo effect (~30%)

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY



EAACI

2016; 71: 99-107

Allergy

ORIGINAL ARTICLE AIRWAY DISEASES

A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study

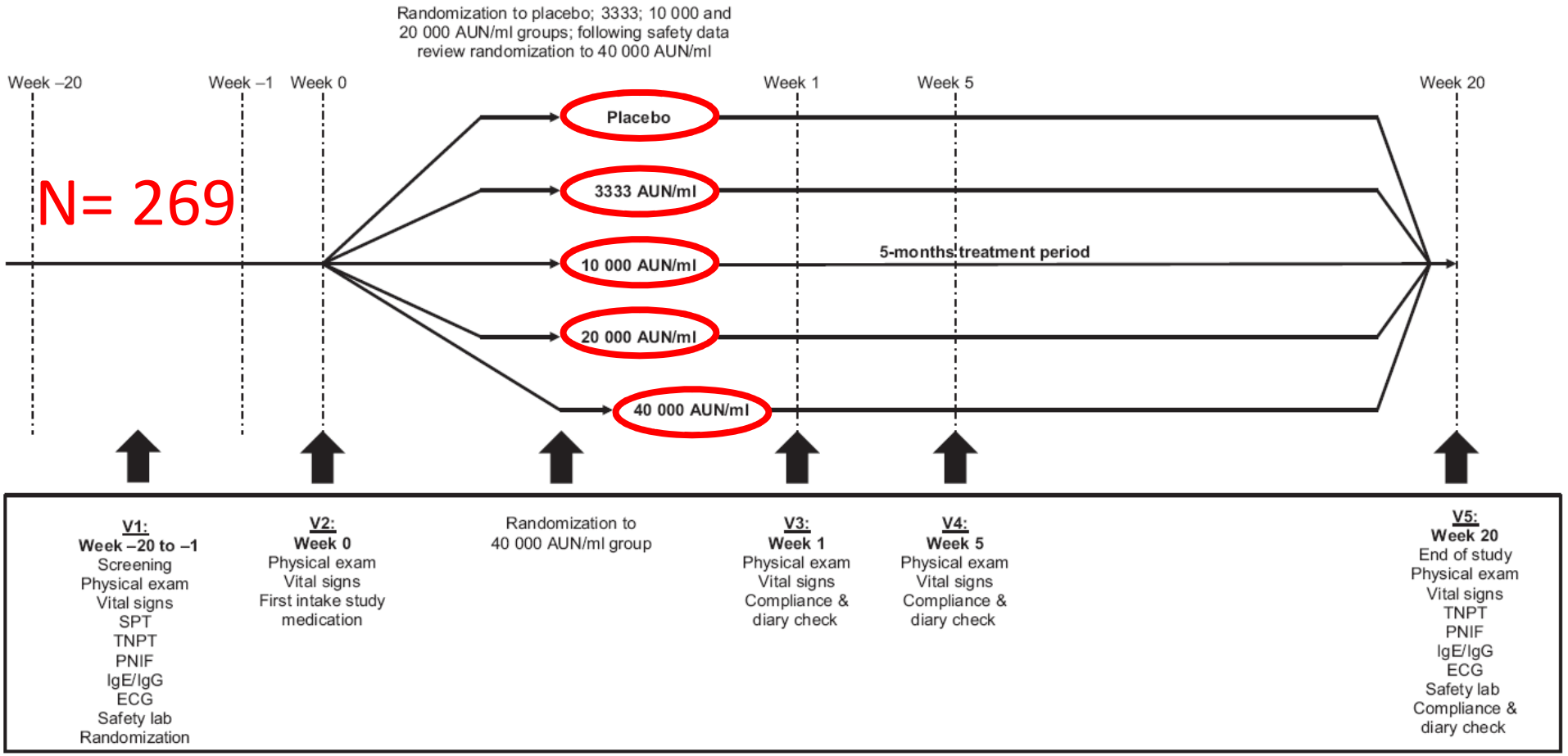
O. Pfaar[1,2], E. van Twuijver[3], J. D. Boot[3], D. J. E. Opstelten[3], L. Klimek[1], R. van Ree[4], Z. Diamant[5,6], P. Kuna[7] & P. Panzner[8]

[1]Center for Rhinology and Allergology, Wiesbaden; [2]Department of Otorhinolaryngology, Head and Neck Surgery, Medical Faculty Mannheim, Universitätsmedizin Mannheim, Heidelberg University, Mannheim, Germany; [3]HAL Allergy BV, Leiden; [4]Departments of Experimental Immunology and of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; [5]Department of Respiratory Medicine & Allergology, Institute for Clinical Science, Skane University Hospital, Lund, Sweden; [6]Departments of Clinical Pharmacy & Pharmacology and General Practice, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [7]Dept. of Internal Medicine, Asthma and Allergy Medical University of Lodz, Lodz, Poland; [8]Department of Allergology and Immunology, Medical Faculty in Plzen, Charles University Prague, Prague, Czech Republic

This is Dose Finding Study for SLIT Birch Pollen

Birch pollen SLIT: dose-range finding

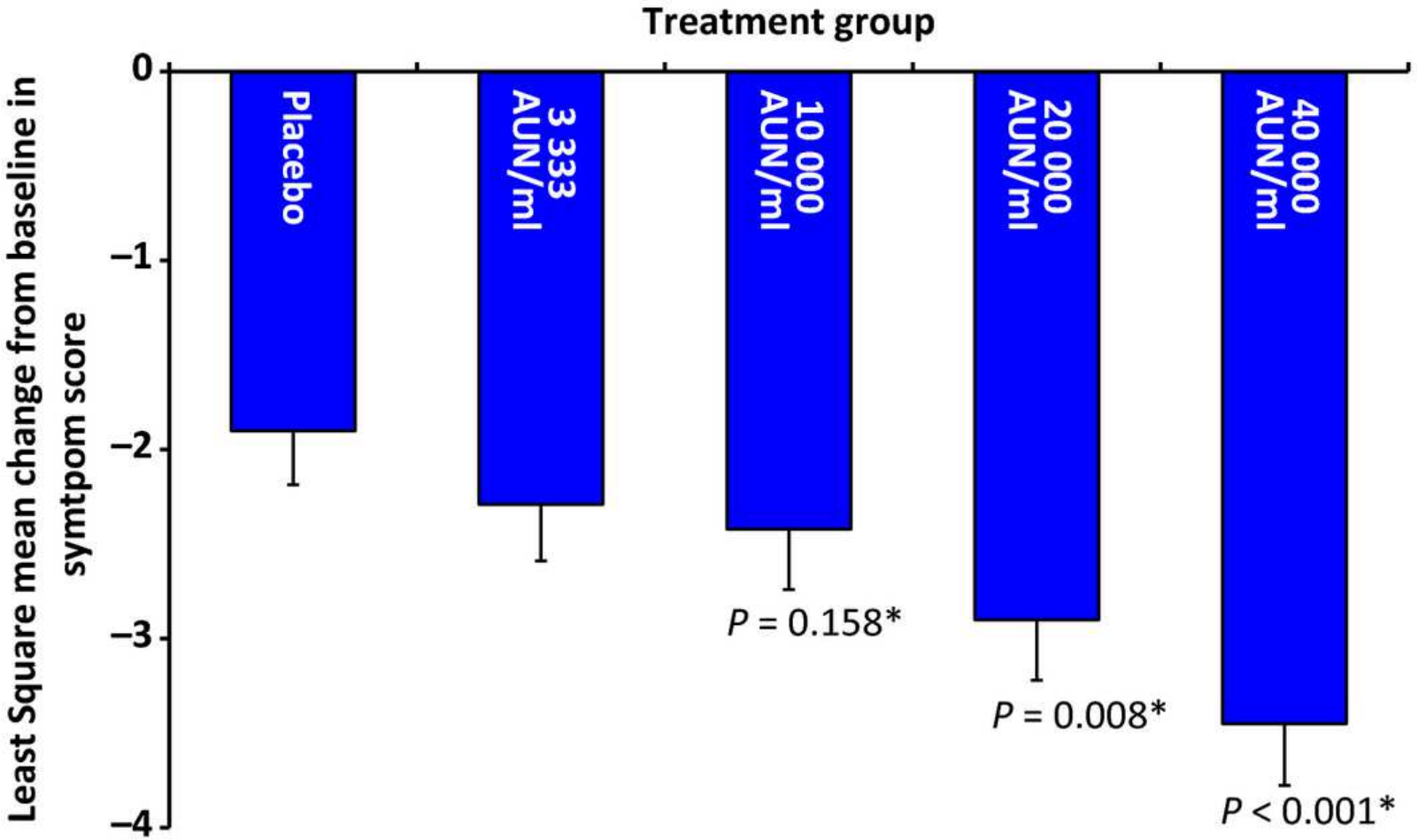
primary outcome: Titrated Nasal Provocation Test



Study Design

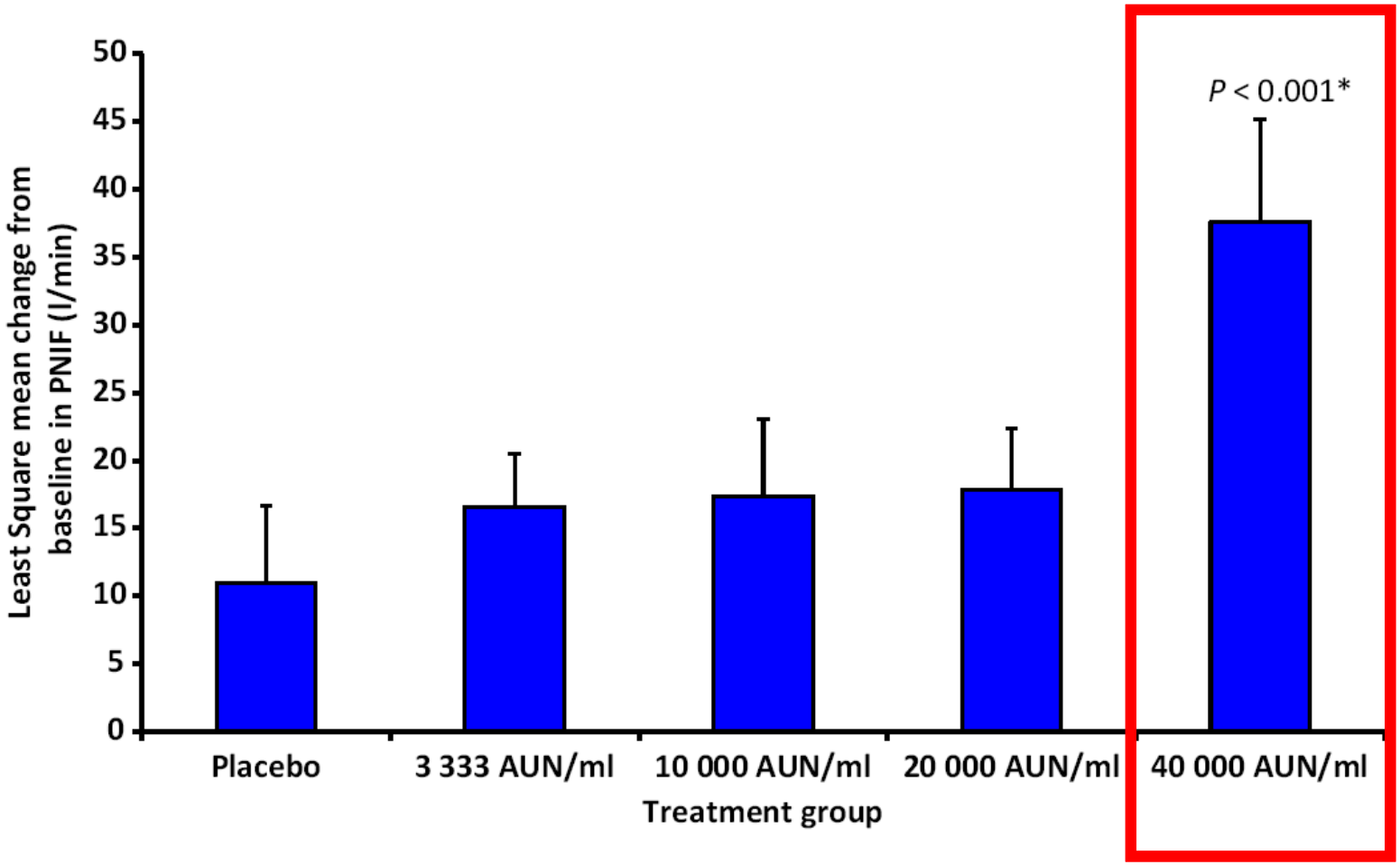
Pfaar O et al. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. Allergy 2016; 71: 99–107

Significant dose-dependent reduction of symptom score in TNPT



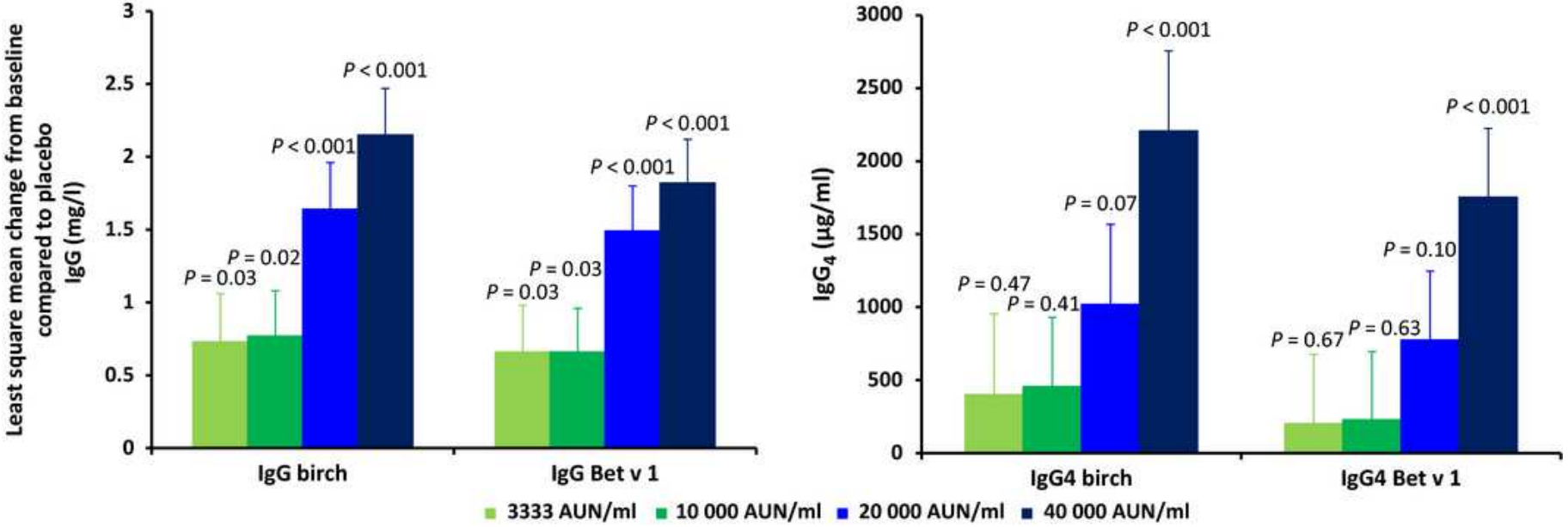
Current dose is effective (20.000) – difference with higher dose is not significant .

Secondary endpoint: nasal flow



Pfaar O et al. A randomized DBPC trial to determine the optimal effective and safe dose of a SLIT-birch pollen extract for the treatment of allergic rhinitis: results of a phase II study. Allergy 2016; 71: 99–107

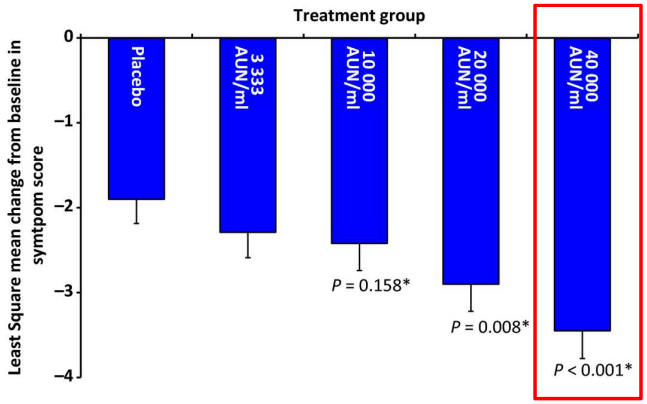
Antibody responses

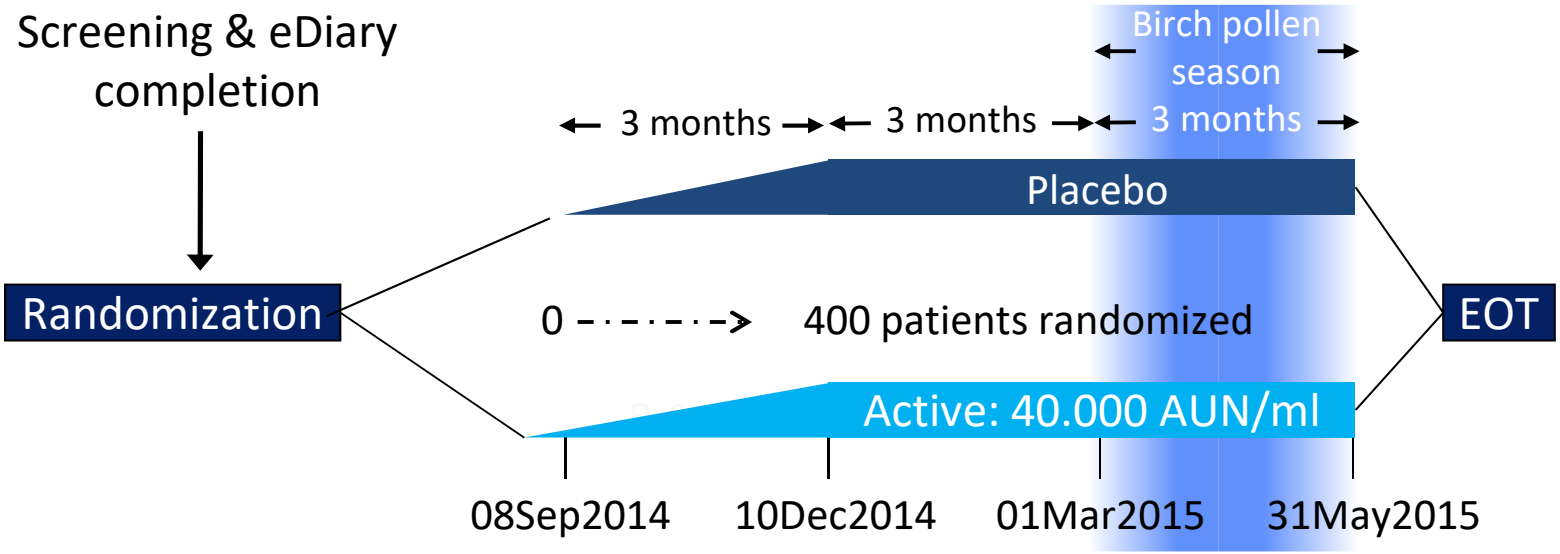


Safety

Adverse reactions were generally mild and well-controlled

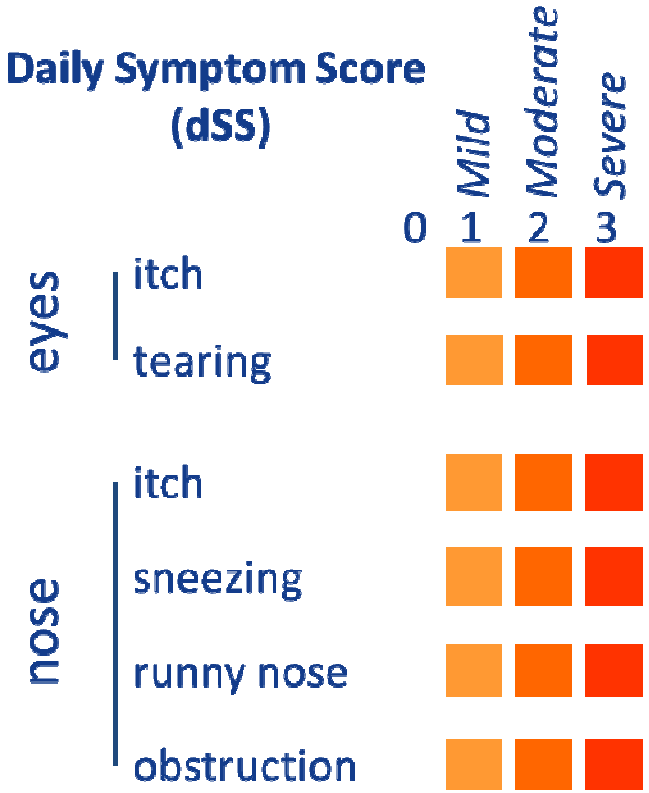
Phase III short-term trial with highest dose from DRF



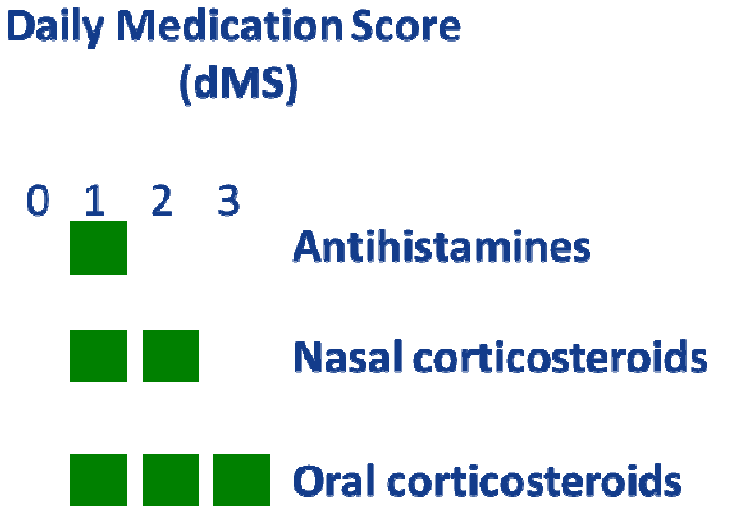


Pfaar O et al. Phase III trial with allergen specific sublingual immunotherapy in birch allergic patients: Significant and clinical relevant reduction of the Combined Symptom and Medication Score

Primary endpoint: CSMS



(maximum dSS: 6 x 3 = 18/6 = 3)

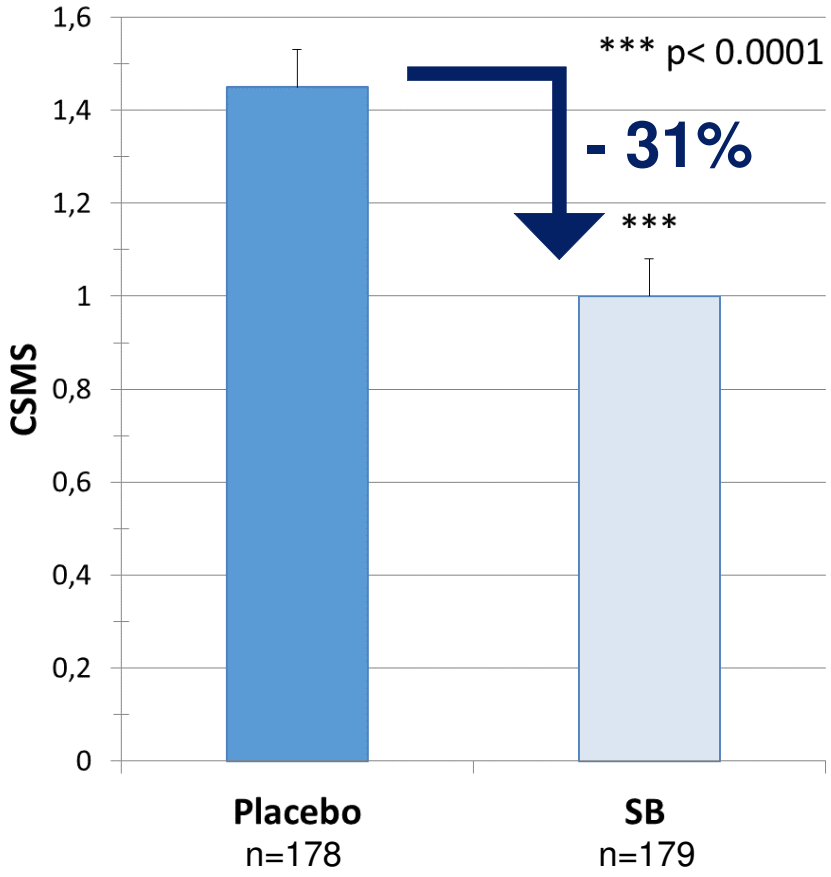


(maximum dMS = 3)

Primary endpoint: CSMS = dSS + dMS (range 0-6)

Pfaar O et al. Phase III trial with allergen specific sublingual immunotherapy in birch allergic patients: Significant and clinical relevant reduction of the Combined Symptom and Medication Score

Significant improvement in primary endpoint CSMS during pollen season (ITT)

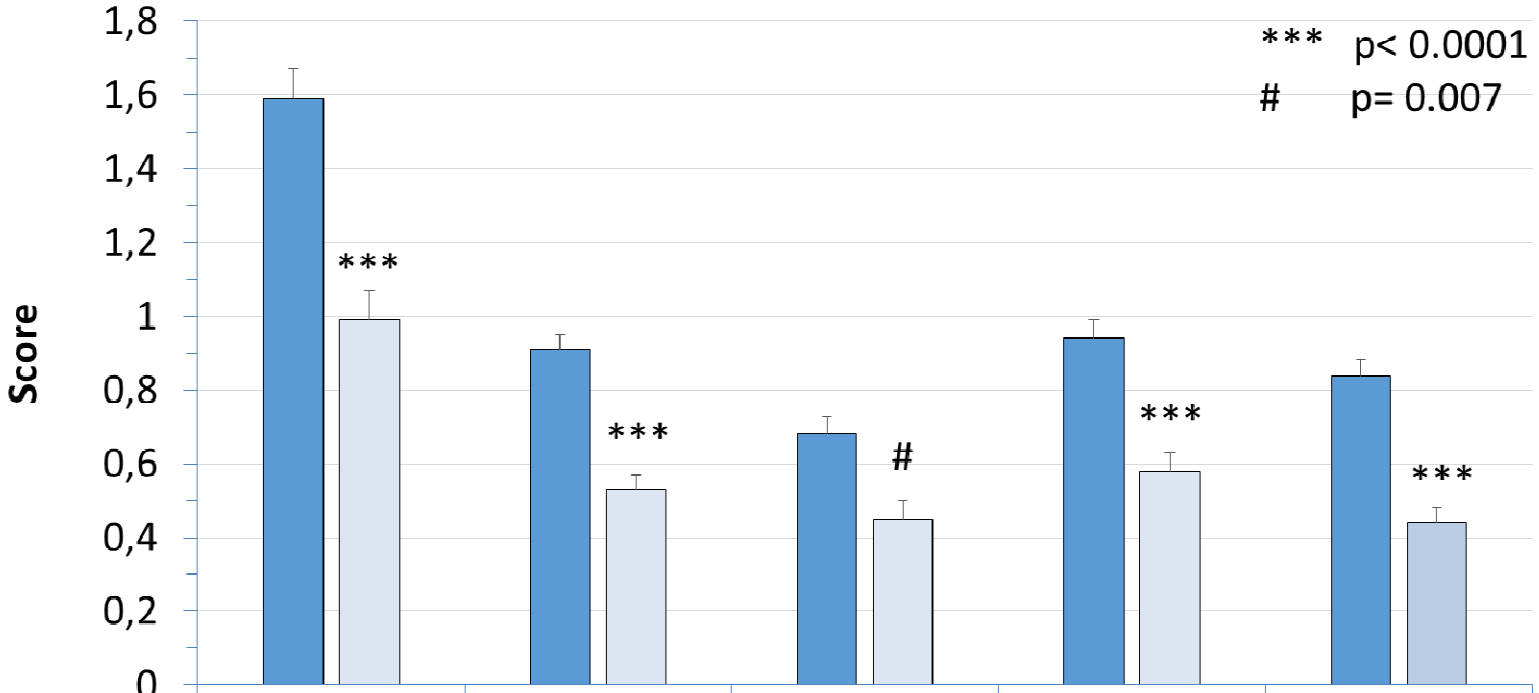


Results

- Statistically significant (p<0,0001)
- Effect size: 31%
- Effect size is greater than the minimal clinical important difference (MCID was predefined as 23%)

31% Decrease in CSMS during pollen season

Even more pronounced effects during peak pollen season



	CSMS	Symptom Score	Medication Score	Nasal SS	Ocular SS
Placebo	1,59	0,91	0,68	0,94	0,84
SB	0,99	0,53	0,45	0,58	0,44

Significant 34-48% decrease in individual symptom and medication scores during peak pollen season

Next steps in building a strong evidence base for AIT

- **Long term studies / 5 years (3+2) to establish persistence of treatment effect (disease modifying).**

- **Studies in children (PIP) – discussions with EMA**

A new approach for AIT in food allergy: SCIT with modified extract

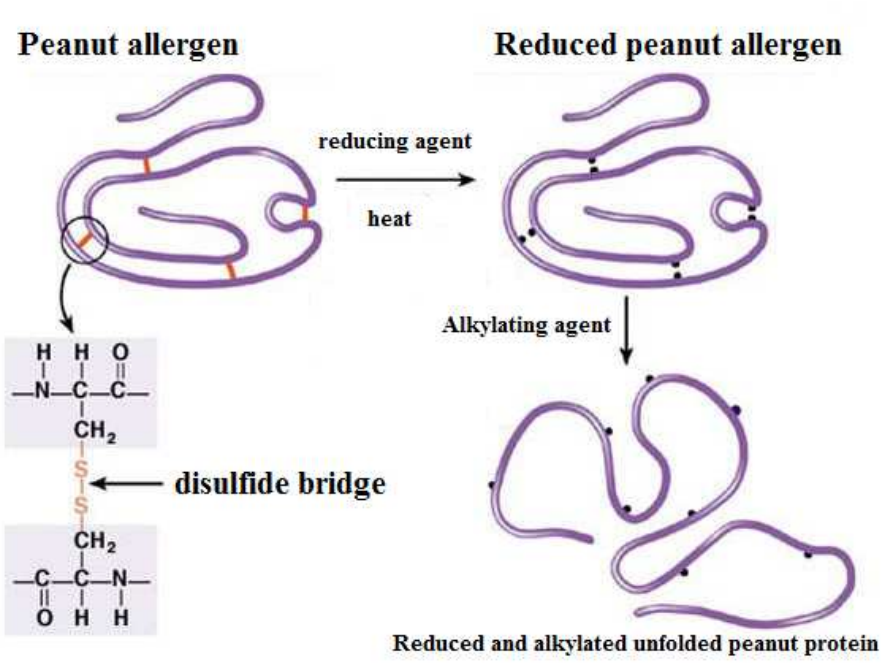
Subcutaneous AIT for peanut allergy with modified extract: Why this choice ?

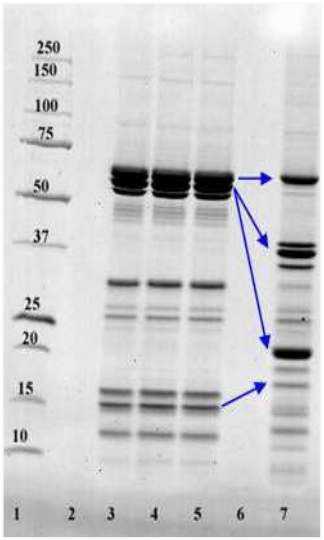
- **Subcutaneous administration → preferred administration route**
  - proven efficacy track record in treatment of allergic rhinitis and venom allergies
  - well-controlled product delivery to the patient by healthcare specialist
  - patient's safety ensured by in-clinic observation period after injection
  - superior treatment compliance compared to other administration modalities (e.g., sublingual)
- **Standardized, hypo-allergenic peanut extract used as drug product**
  - standardization (e.g., major allergen content, potency, and total protein content) ensures a consistent pharmaceutical-grade product
  - hypoallergenic preparations elicit fewer and less severe unwanted side-effects while maintaining their immunogenicity

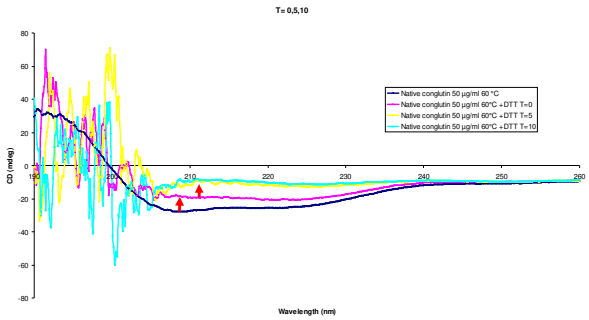
A novel modification method for peanut extract

Chemistry

- Reduction and alkylation of peanut extract
- Unfolding and loss of IgE-binding epitopes







Modification and unfolding of peanut allergens investigated by SDS-PAGE (left panel) and Circular Dichroism (right panel) analyses

Mainly Ara h 2 and 6 are sensitive to this modification

Modification reduces the anaphylactic potency peanut extract

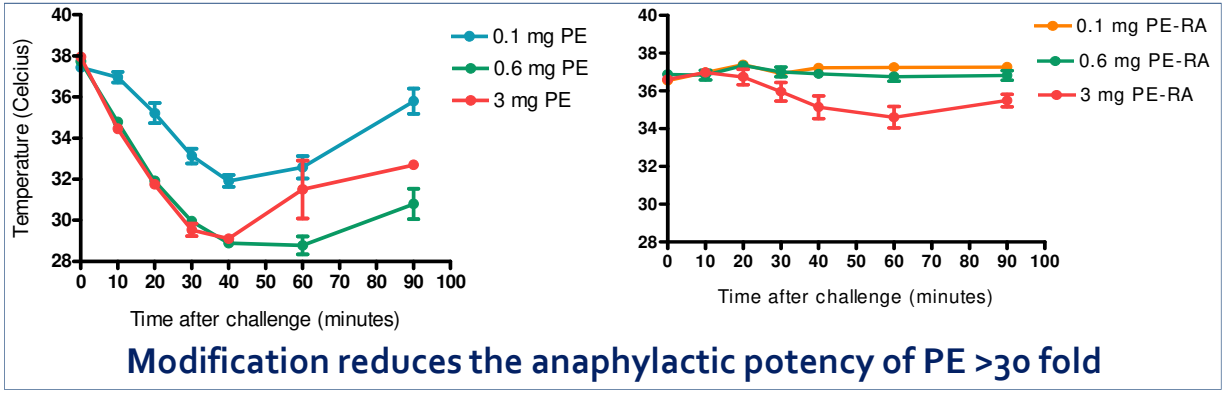
Impact of modification assessed in mouse model for anaphylaxis

Universiteit Utrecht
Institute for Risk Assessment Sciences

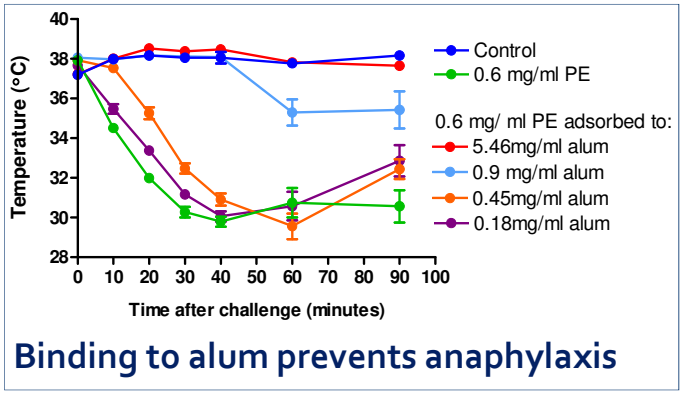
peanut allergic mice

s.c. challenge with peanut extract

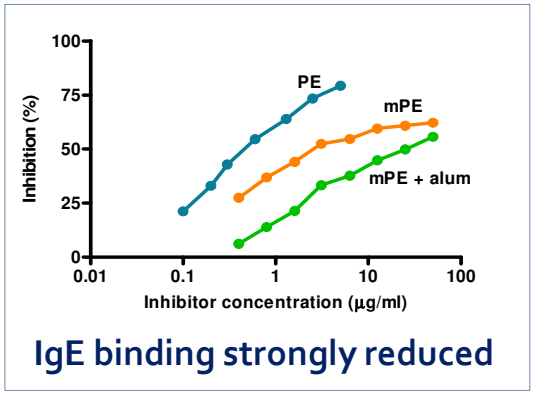
anaphylaxis (body temperature ↓)



Modification reduces the anaphylactic potency of PE >30 fold



Binding to alum prevents anaphylaxis



IgE binding strongly reduced

Combination of modified peanut extract and binding to aluminum hydroxide offers double safety warranty

Safety and tolerability of SCIT treatment with modified peanut extract in peanut allergic patients

First-in-human study design in Odense (DK) – Carsten Bindslev Jensen

- Randomized (2 active:1 placebo), double-blind, placebo controlled, single-centre, Phase I study
- Subjects 18-65 years of age with peanut allergy as assessed by
  - Well-documented medical history of systemic reactions after ingestion of peanut
  - Positive food challenge at ≤1.5 gram peanut protein ingestion within the last 2 years
  - Positive serum specific anti-peanut and Ara h 2 IgE-test (>0.7 kU/L) within the last 2 years
  - Primary objective: evaluation of the safety and tolerability of a SCIT-treatment with modified peanut extract in patients with peanut allergy
  - Secondary objective: short-term immunologic effect of modified peanut extract compared to placebo

Acceptable local reaction profile

Late local reaction	Placebo		HAL-MPE1		
	No. of subjects	No. of events / intensity	No. of subjects	No. of events / intensity	Dose amount (µg)
Injection site pain	0	0	1	1 / mild	10.0
			1	1 / mild	37.5
			2	2 / mild	93.75
			2	2 / mild	187.5
Injection site pruritus	1	1 / mild	1	1 / mild	0.5
			1	1 / mild	10.0
			2	2 / mild	93.75
			1	1 / mild	187.5
			3	4 / mild	375 (M1)
Injection site swelling	0	0	1	1 / mild	37.5
			1	1 / moderate	93.75
Injection site urticaria	0	0	1	1 / mild	20.0

Local reactions more frequently observed in the active treatment group compared to the placebo group, mainly consisting of redness
no wheal sizes exceeding 5 cm were recorded

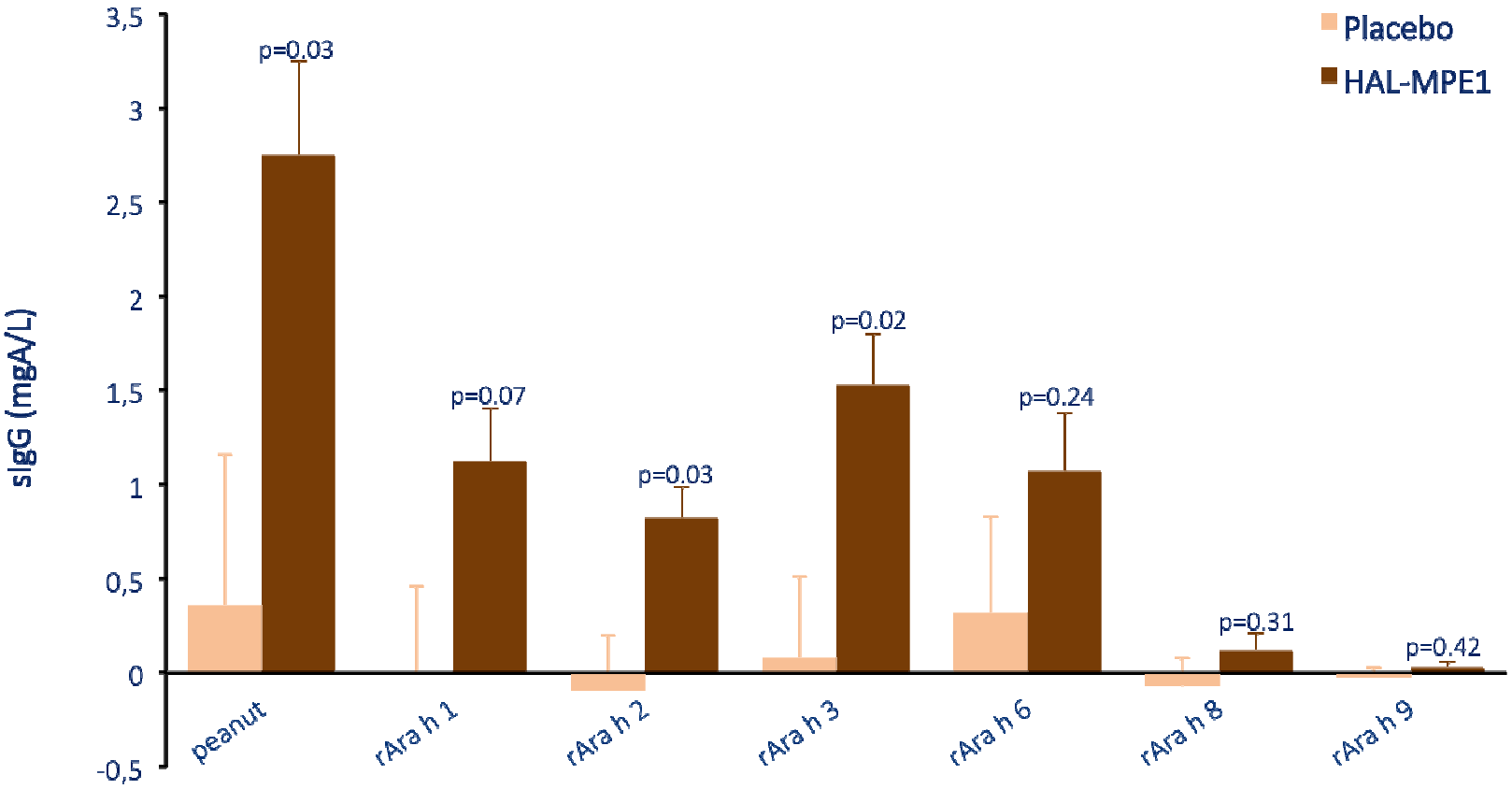
Acceptable systemic reaction profile

No Grade IV (anaphylaxis), asthma control is important

Subject no.	Dose amount (µg)	Post-Dose Assessment	Description Early Systemic AE	Severity (Grade)	Remedial therapy	Outcome
1-03	93.75	3-4 hours	Drop in peak flow	I	Yes	Recovered/resolved with sequelae
1-05	93.75	3-4 hours	Urticaria*	II	Yes	Recovered/resolved
			Asthma*	I	Yes	Recovered/resolved
			Rhinitis*	I	Yes	Recovered/resolved
	375	1-2 hours	Asthma	II	Yes	Recovered/resolved
	187.5	0-30 min	Asthma	II	Yes	Recovered/resolved
1-11	375	0-30 min	Urticaria*	II	Yes	Recovered/resolved
		30-60 min	Asthma*	II	Yes	Recovered/resolved
	375	0-30 min	Asthma	I	Yes	Recovered/resolved
1-13	0.25	2-3 hours	Eczema on face*	I	Yes	Recovered/resolved
		3-4 hours	Rhinoconjunctivitis*	I	Yes	Recovered/resolved
	10.0	1-2 hours	Abdominal pain	I	No	Recovered/resolved
	20.0	3-4 hours	Red eye (left)	I	No	Recovered/resolved
1-16	20.0	0-30 min	Itching on body	I	No	Recovered/resolved
	93.75	0-30 min	Asthma*	II	Yes	Recovered/resolved
		30-60 min	Urticaria*	II	Yes	Recovered/resolved
		1-2 hours	Rhinitis*	II	Yes	Recovered/resolved
1-17	187.5	2-3 hours	Throat irritation	II	No	Recovered/resolved
		3-4 hours	Flushing*	II	Yes	Recovered/resolved
			Stridor*	III	Yes	Recovered/resolved
			Hypersensitivity**	II	Yes	Recovered/resolved

Patients 1-11, 1-16, and 1-17 known to have stable asthma turned out not to adhere to their asthma medication

Increase in serum specific IgG already after short treatment



Important: also IgG against Ara h 2/6

Conclusions first-in-human peanut SCIT study with modified peanut extract

- The incidence, time course and intensity of the early and late local and systemic reactions following HAL-MPE1 treatment did not raise major safety concerns
- The main drug-related TEAEs commonly occur with SCIT
- Treatment was generally safe and well tolerated
- An increase in peanut specific IgG and IgG_4 levels, a decreased peanut specific basophil histamine release and a reduction peanut specific SPT sensitivity was observed following treatment compared to placebo
- The combined results of the secondary parameters indicate that subcutaneous administration is capable of inducing desensitization to peanut allergens following 3-4 months of weekly dose escalation

Modification of peanut extract is a promising candidate for SCIT in peanut allergic patients

The field of AIT is rapidly building its clinical evidence base, a process from which the patient will benefit and the market will be cleaned up

THANK YOU