Practical Approach to Food Immunotherapy in Childhood

Western Society of Allergy, Asthma & Immunology

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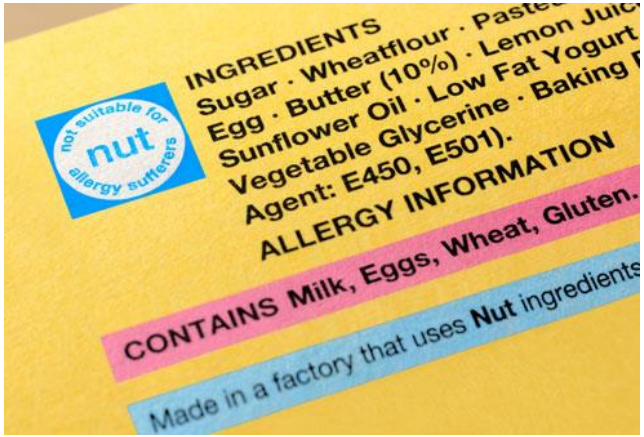
Avoidance can be really hard

- Voluntary precautionary allergen labels (PAL) complicate label reading
- Accidental ingestions still happen[1]
  - » 72% in prospective observational study

- Avoidance leads to isolation, fear, restricted daily activities, and poor quality of life[2-4]

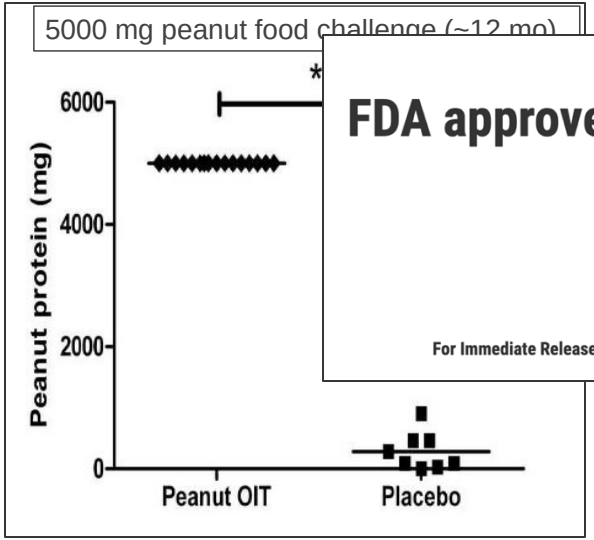


- Food allergies can last many years, and some are life-long
- Multiple food allergies amplifies these concerns

1. Fleischer. Pediatrics. 2012; 130:e25-32
2. Valentine. Appetite. 2011; 57-467-74
3. Cummings. Pediatr Allergy Immunol. 2010; 21:586-94
4. Peterson. Ann Allergy Asthma Immunol. 2018; 120:327-8

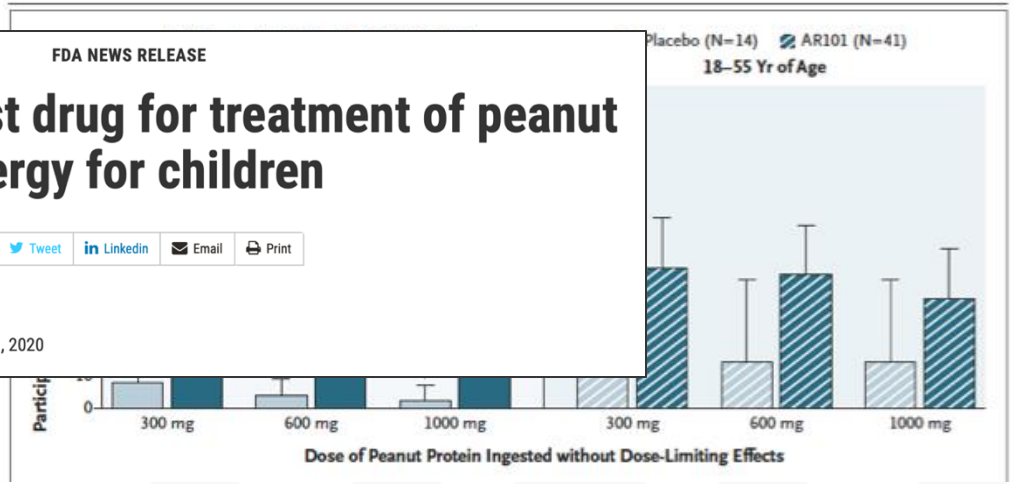
OIT has been shown in study after study to be effective at desensitizing peanut-allergic children

2011: First double-blind study of OIT



Varshney, JACI. 2011; doi: 10.1016/j.jaci.2010.12.1111

2018: Multinational phase 3 study of OIT



Vickery, NEJM. 2018; doi: 10.1056/NEJMoa1812856

FDA NEWS RELEASE

FDA approves first drug for treatment of peanut allergy for children

Share Tweet Linkedin Email Print

For Immediate Release: January 31, 2020

OIT is limited by its considerable risk

- "Peanut Allergen immunotherapy, Clarifying the Evidence" (PACE) systematic review
  - » Increased chance of anaphylaxis (RR 3.12)
  - » Increased anaphylaxis frequency (RR 2.72)
  - » Increased risk of needing epinephrine (RR 2.21)

OIT is limited by its difficult administration

- Practical issues with doing OIT for patients *and* provider offices
  - Requires daily dosing, possibly indefinitely
  - Dosing is restricted around exercise and while sick
  - Taste, smell and texture aversion for some
  - Frequent in-office visits (10+ over 6-mo buildup with FDA product)
  - Unscheduled visits for dosing reactions and missed doses
  - Product requires cold storage and prep space
  - On-call support
  - No dedicated OIT billing codes

Does the benefit of OIT outweigh the risk?

Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study

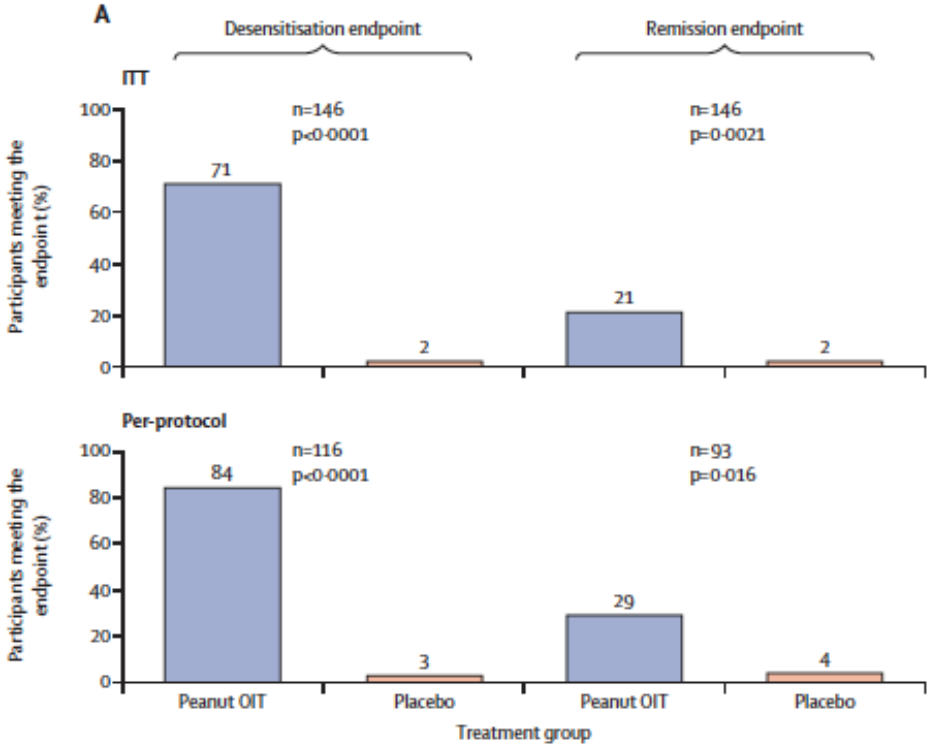
Stacie M Jones, Edwin H Kim, Kari C Nadeau, Anna Nowak-Wegrzyn, Robert A Wood, Hugh A Sampson, Amy M Scurlock, Sharon Chinthrajah, Julie Wang, Robert D Pesek, Sayantani B Sindher, Mike Kulis, Jacqueline Johnson, Katharine Spain, Denise C Babineau, Hyunsook Chin, Joy Laurienzo-Panza, Rachel Yan, David Larson, Tielin Qin, Don Whitehouse, Michelle L Sever, Srinath Sanda, Marshall Plaut, Lisa M Wheatley, A Wesley Burks, for the Immune Tolerance Network

impact PEANUT ALLERGY STUDY

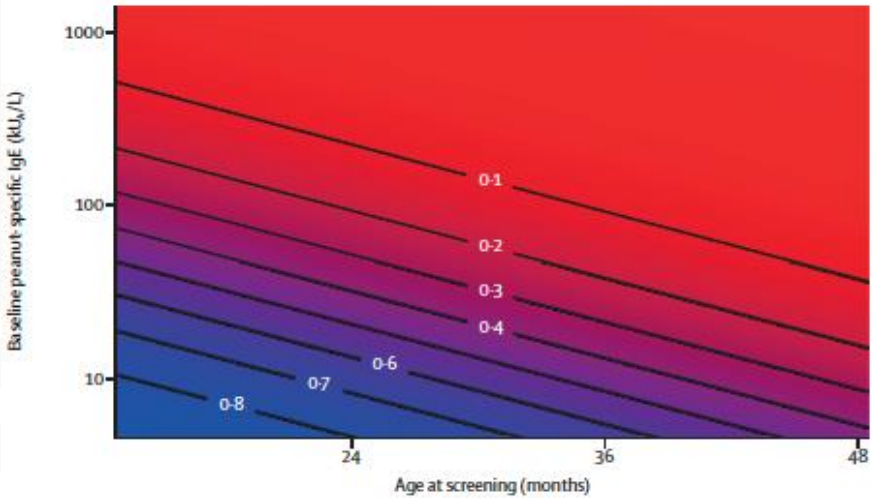
Immune Tolerance Network

Jones. Lancet. 2022; doi: 10.1016/S0140-6736(21)02390-4

6-month remission after 2.5 yr peanut OIT (2000 mg)



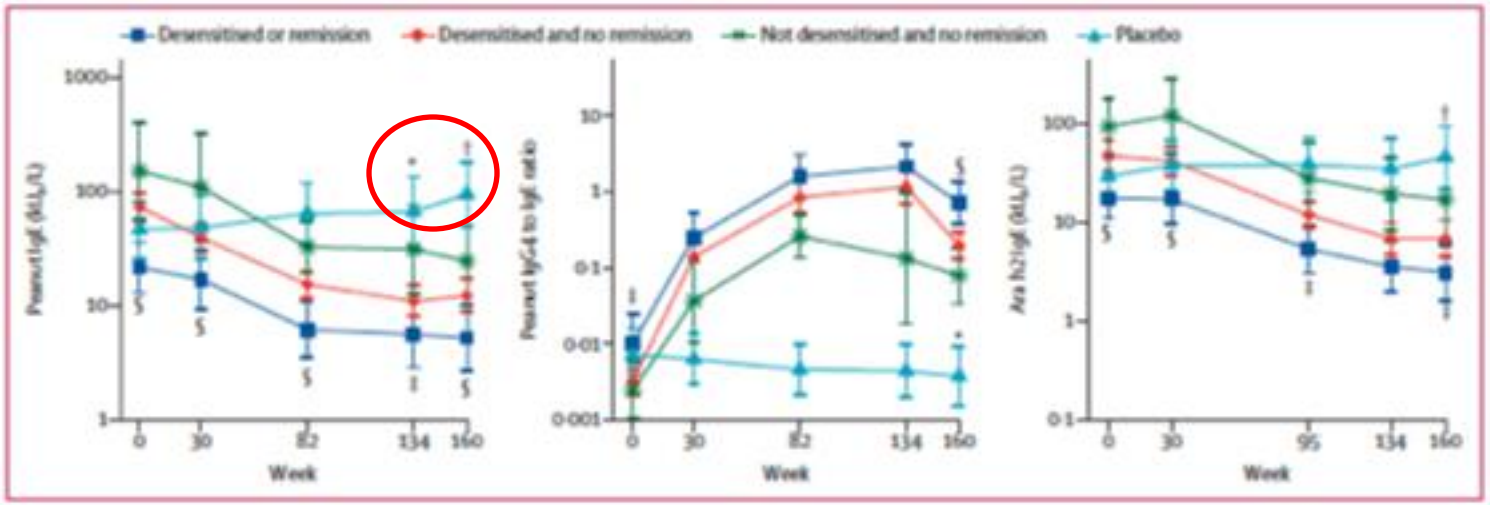
- Remission seems more likely if you start young
  - 1-2 y/o: 71% (5/7)
  - 2-3 y/o: 35% (7/20)
  - 3-4 y/o: 19% (8/43)



Jones. Lancet. 2022; doi: 10.1016/S0140-6736(21)02390-4

Biomarkers may play a role in the decision to start OIT

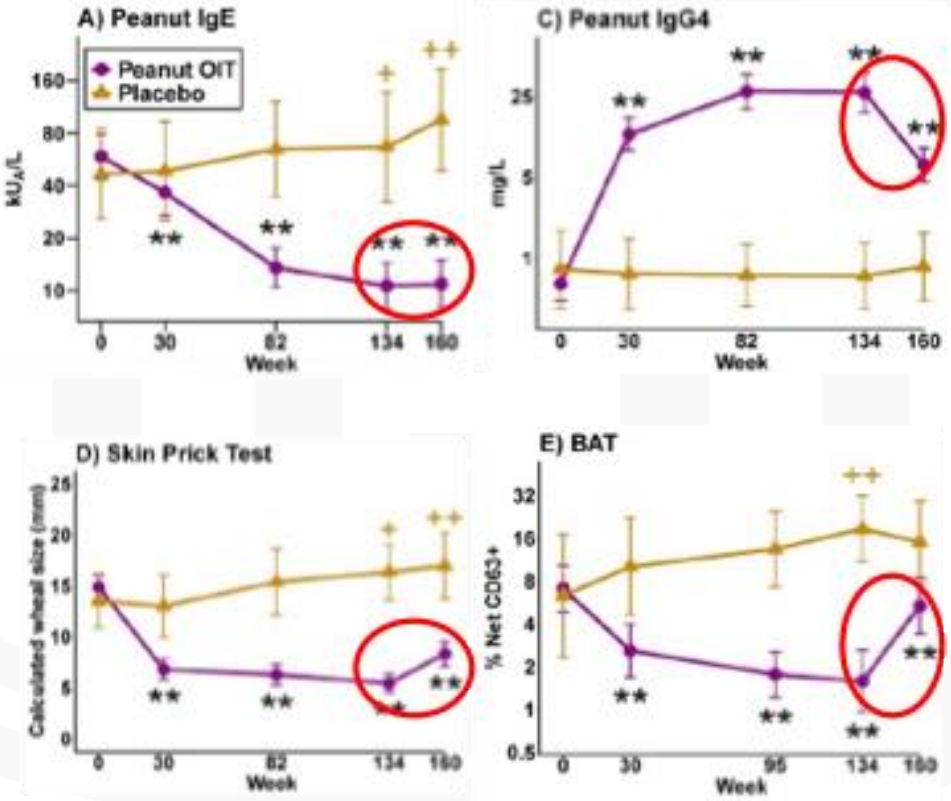
- Biomarkers separate by remission, no remission, no desensitization
  - » Pre- and post-OIT peanut IgE and Ara h2 IgE lowest in remission group
  - » Highest peanut IgG4/IgE ratio in remission group
- "Window of opportunity" – increasing IgE on placebo



Jones. Lancet. 2022; doi: 10.1016/S0140-6736(21)02390-4

Is remission the same as cure?

- Biomarkers revert after OIT is stopped (week 160)
  - » SPT and BAT increase off OIT, peanut IgE flat
  - » Peanut IgG4 decreases off OIT
- Continued exposure may be needed to maintain remission
- IMPACT PLuS study
  - » Follow-up of IMPACT participants after study completion



Jones. Lancet. 2022; doi: 10.1016/S0140-6736(21)02390-4

Is low and slow OIT safer? Does it still work?

Original Article

Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy

Katharina Blumchen, MD[a,b], Valerie Trendelenburg, MSc, PhD[b], Frank Ahrens, MD[c], Armin Gruebl, MD[d], Eckard Hamelmann, MD[e,f], Gesine Hansen, MD[g], Andrea Heinzmann, MD[h], Katja Nemat, MD[i], Thomas Holzhauser, PhD[j], Martin Roeder, PhD[j,k], Leonard Rosenfeld, MD[b], Oliver Hartmann, PhD[l], Bodo Niggemann, MD[b], and Kirsten Beyer, MD[b]

Frankfurt am Main, Berlin, Hamburg, Munich, Bochum, Bielefeld, Hannover, Freiburg, Dresden, Langen, and Hennigsdorf, Germany

- Escalation: up to 33-steps, every 2-weeks, maximum 14 months
- 8-week maintenance: 125 mg (baseline <143 mg) or 250 mg (baseline ≥143 mg)
- 74% vs 16% tolerated 300 mg (1 peanut)
- 42% vs 3% tolerated 4500 mg (15 peanut)

Blumchen. JACI 2019; doi: 10.1016/j.jaip.2018.10.048

Low and slow OIT may lead to better retention

TABLE III. Patients with AEs related to OIT in the placebo-OIT and peanut-OIT groups

Patients with adverse events and treatment	Placebo-OIT group (n = 31)	Peanut-OIT group (n = 30)	*P* value
Total no. of AEs, n (%*)	2866 (20.7)	2515 (20.3)	0.71
Total no. of SAEs, n (%*)	5 (0.04)	3 (0.02)	0.73
No. of SAEs related to OIT, n (%*)	1 (0.007)	1 (0.008)	1.0
No. of patients who discontinued the study because of AEs, n (%†)	2 (6.5)	2 (6.7)	1.0
No. of patients with …/receiving …			
AEs related to OIT, n (%†)	24 (77.4)	27 (90.0)	0.3
Subjective AEs related to OIT, n (%†)	14 (45.2)	25 (83.3)	**0.002**
OAS related to OIT, n (%†)	8 (25.8)	18 (60.0)	**0.007**
Abdominal pain related to OIT, n (%†)	6 (19.4)	20 (66.7)	**<0.001**
Nausea related to OIT, n (%†)	2 (6.5)	7 (23.3)	0.06
Lower respiratory tract symptoms related to OIT (coughing, wheezing, shortness of breath), n (%†)	9 (29.0)	13 (43.3)	0.25
Coughing related to OIT, n (%†)	6 (19.4)	11 (36.7)	0.13
Wheezing related to OIT, n (%†)	1 (3.2)	6 (20.0)	**0.04**
Shortness of breath related to OIT, n (%†)	4 (12.9)	3 (10.0)	0.72
Accidental reactions, total n (average per person)	24 (0.77)	8 (0.27)	**<0.001**
No. of patients with accidental reactions, n (%†)	14 (45.2)	5 (16.7)	**0.026**

Blumchen. JACI 2019; doi: 10.1016/j.jaip.2018.10.048

Very low dose OIT may be an option too

- Upton, et al. 2023 AAAAI abstract
  - » Very Low Dose OIT (VLOIT) in peanut-allergic children reactive to ≤ 443 mg
  - » 12 months of 30 mg VLOIT vs 300 mg standard OIT vs avoidance

	443 mg peanut	1043 mg peanut
VLOIT	10/12 (83%)	5/12 (42%)
Standard OIT	8/9 (89%)	6/9 (67%)
Avoidance	0	0

Upton. JACI. 2023; doi: 10.1016/j.jaci.2022.12.382

OIT in multi-food allergic patients

- FDA-approved OIT is only available for peanut
- OIT is provided in select allergy offices to a broader range of foods using store-bought foods

- Treatment for all foods can be administered simultaneously
  - » Mixed OIT dosing
  - » Consecutive dosing of individual food OIT
- Treatment can be administered one food at a time
  - » Buildup a single food to maintenance then initiate the next food

Simultaneous vs sequential approaches to multi-food OIT

Simultaneous

- Less overall office visits
- Protection to all foods at the same time
- May achieve goals of therapy sooner

- Larger food volumes
- Increased potential for reactions
- Harder to identify cause of reactions
- May require multiple protocol adjustments

Sequential

- Allows for food-specific protocols based on risk, threshold
- Allows prioritization of the most important food
- Buildup may have less reactions

- More overall office visits
- Longer time to achieving protection to all foods

Other considerations with multi-food OIT

- Optimal dose for less common foods is not well-defined
- Importance of lot-to-lot variability in protein content is unknown
- Standardized multi-OIT product paused in development

- How many foods is too many foods?
- Is protecting against some but not all foods an acceptable outcome?
- How do allergen-non-specific treatments compare?

- Multi-food OIT can involve significant treatment burden and risk. Potential benefit varies by the food, the number of foods, and age of the child.

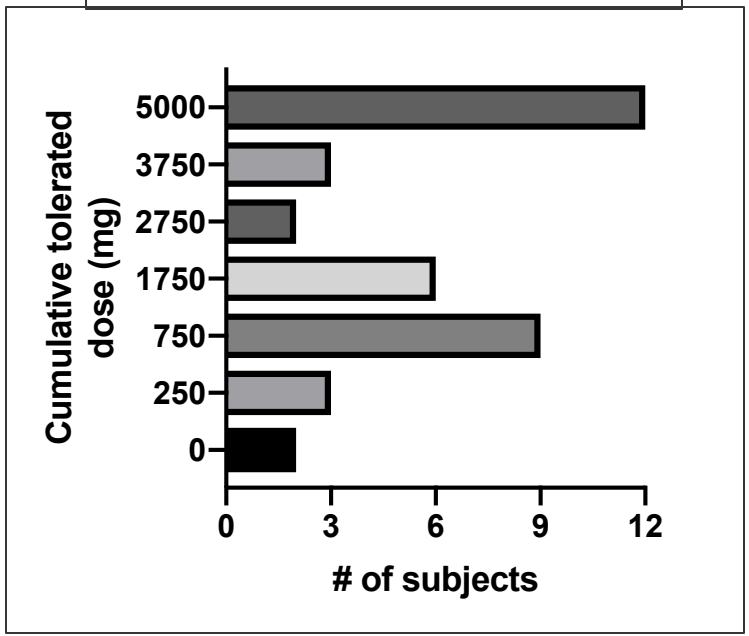
UNC peanut sublingual immunotherapy (SLIT)

- Peanut extract in glycerin
- 2-4 mg peanut maintenance dose
  - » 0.4-0.8 ml liquid volume
- No exercise or meal-time restrictions
- Recommend holding dose when febrile

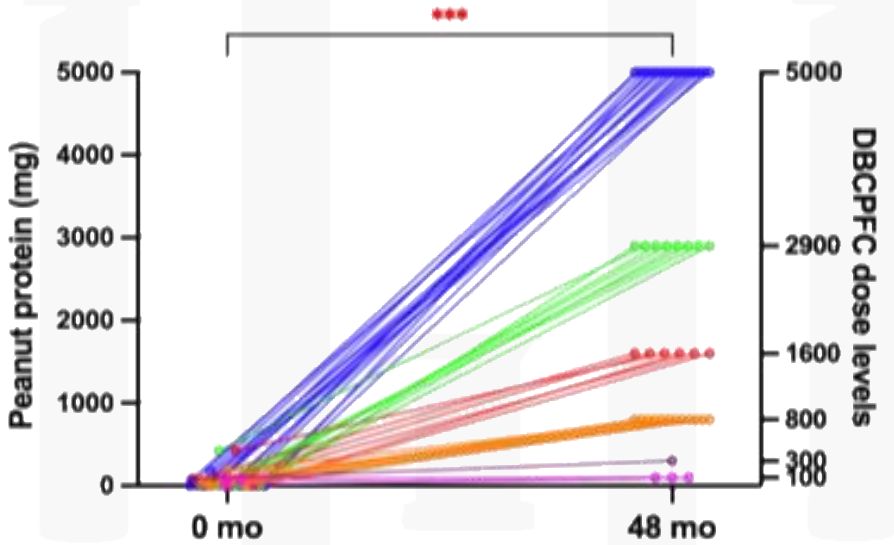
- Held under the tongue for 2 min, then swallowed
- 30 min observation

Majority improve with SLIT but with a range of results

3 to 5-year SLIT therapy (2 mg peanut)

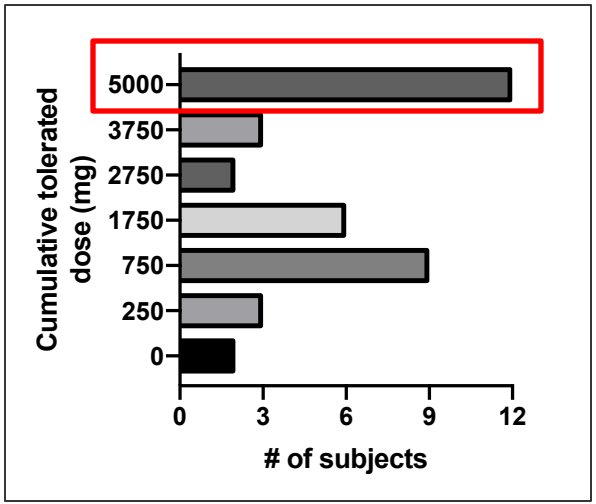


4-year SLIT therapy (4 mg peanut)

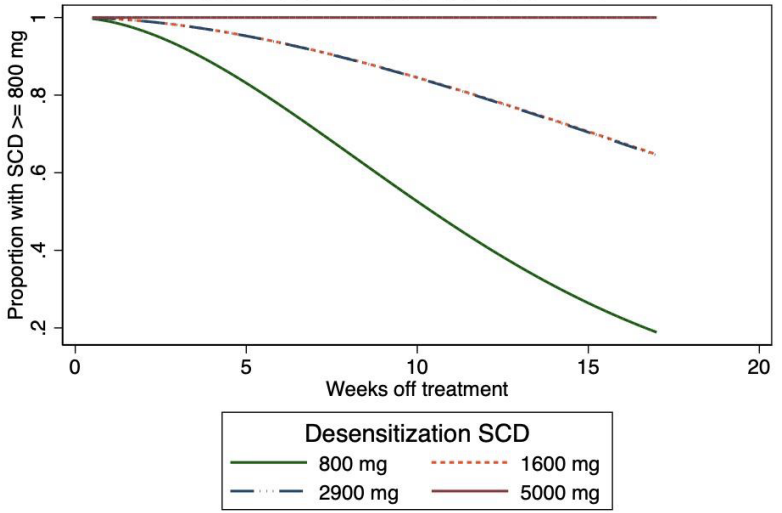


Kim. JACI. 2019; doi: 10.1016/j.jaci.2019.07.030
Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.01.036

Durable response possible with extended therapy but relapse appears likely with time



12/48 pass 5000 mg DBPCFC
10/12 pass DBPCFC after 1 month peanut avoidance



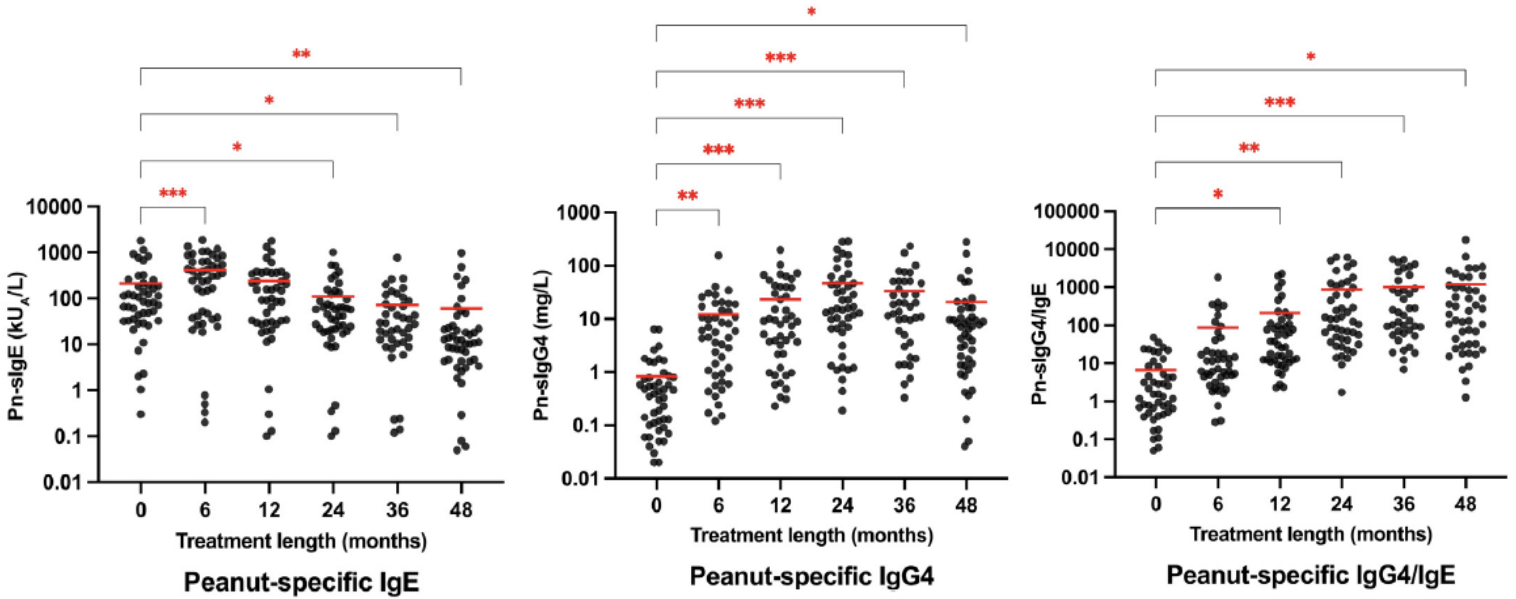
Statistical model: 22 weeks before clinical protection is lost (threshold < 800 mg)

No participants fell below 300 mg

Kim. JACI. 2019; doi: 10.1016/j.jaci.2019.07.030

Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.01.036

IgE and IgG4 may provide a general marker of response

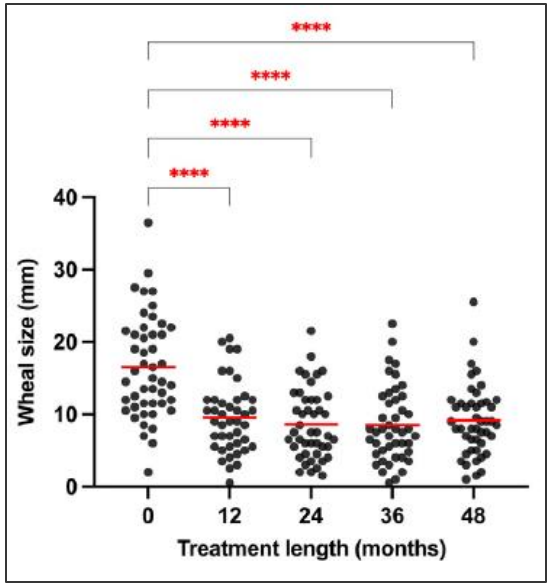


- Correlation of IgE and IgG4 to specific thresholds is still lacking
- IgE and IgG4 at 6 and 12 months could inform treatment decisions

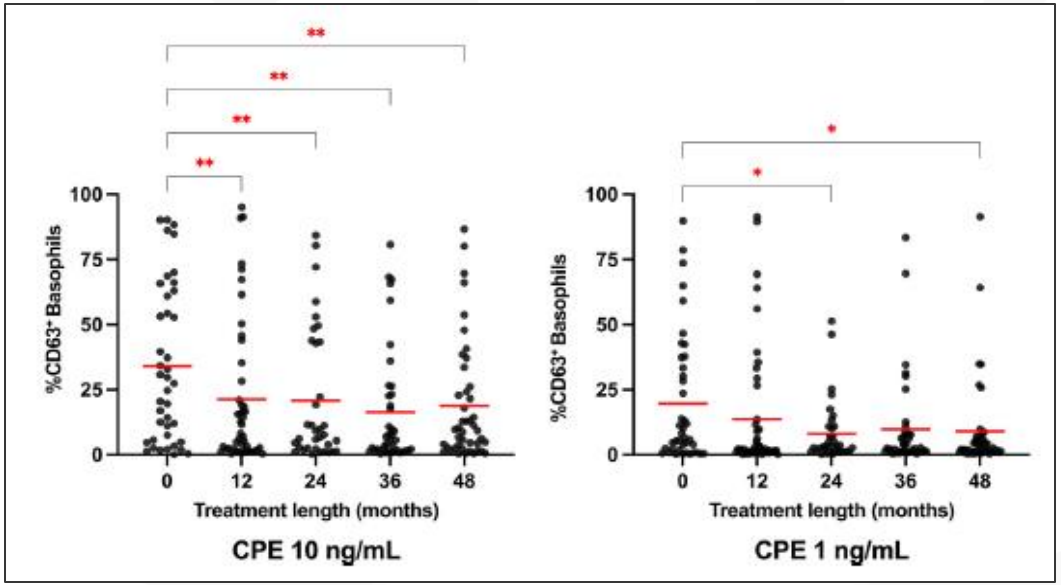
Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.01.036

SPT and BAT might also be clinic-based markers for SLIT

Skin prick testing



Basophil activation testing CD123+/CD203c+



Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.01.036

Even with extended multi-year SLIT therapy, severe and systemic reactions are likely to be rare

TABLE II. Peanut SLIT dosing safety and compliance

	Peanut SLIT (n = 48)
Total dosing days	78,915
Missed doses	3,549 (4.5%)
Total doses taken	75,366 (95.5%)
Dosing symptoms	3,599 (4.8%)
Local	
Oropharyngeal pruritus	2699 (3.6%)
Lip swelling	115 (0.2%)
Skin	387 (0.5%)
Upper respiratory tract	75 (0.1%)
Lower respiratory tract	69 (0.1%)
Gastrointestinal	
Belly pain	225 (0.3%)
Vomiting	20 (0.03%)
Diarrhea	5 (0.01%)
Treatment administered	
Antihistamine	158 (0.2%)
Epinephrine	0

Upper respiratory tract symptoms included runny nose, sneeze, and nasal congestion. Lower respiratory tract symptoms included cough and wheeze.

Dosing	Peanut SLIT (n = 54)
Total dosing days	81,031
Missed doses	2,019 (2.49)
Total doses taken	79,012 (97.51)
Dosing symptoms, n (% doses taken)	3,203 (4.05)
Local	
Oropharyngeal pruritus	2,841 (3.60)
Lip swelling	50 (0.06)
Skin	113 (0.14)
Upper respiratory tract	7 (0.01)
Lower respiratory tract	28 (0.03)
Abdominal	
Belly pain	89 (0.11)
Vomiting	18 (0.02)
Diarrhea	5 (0.01)
Treatment administered, n (% doses taken)	
Antihistamine	143 (0.18)
Epinephrine	0

Kim. JACI. 2019; doi: 10.1016/j.jaci.2019.07.030

Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.01.036

Can earlier treatment with peanut SLIT work better?

- Peanut Immunotherapy Sublingual (PITS) trial
  - » 50 peanut-allergic children ages 1-4 years
    - Positive SPT and peanut IgE
    - React <1000 mg on peanut food challenge
  - » 1:1 randomization (4 mg peanut SLIT vs placebo)
  - » 36 months blinded therapy (desensitization)
  - » 3 month peanut avoidance (remission)
    - PRACTALL 4443 mg peanut food challenge

NIH National Center for Complementary and Integrative Health

FARE Food Allergy Research & Education

Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.08.032

Strong desensitization and potential for 3-month remission

Desensitization = pass 4443 mg OFC

Remission = pass after 3 months

Kim. JACI. 2023; doi: 10.1016/j.jaci.2023.08.032

UNC peanut SLIT summary

- Using 2-4 mg peanut SLIT
  - Protective desensitization (>750 mg) seen in majority
  - Full 5000 mg pass in 36%
  - Gradual loss of desensitization after stopping SLIT
- Higher percentage pass in toddlers with the possibility of 3-month remission
- Transient mouth itch was common; severe and systemic reactions were not seen and likely to be rare
- Low burden for patients *and* providers due to its good safety, fewer clinic visits, and minimal dosing restrictions

Peanut SLIT unanswered questions

- How important is holding it for 2 minutes?
- How important is characterization and standardization of the extract?
- What's the right dose? Is more necessarily better?
- Does it work for older teens and adult patients?
- How do we know it is working? Labs? OFC?
- How long should someone stay on SLIT? Should patients transition to dietary ingestion or higher dose OIT?
- Are there any advantages to combining SLIT with other therapies?

Fast-dissolving tablet-based peanut SLIT

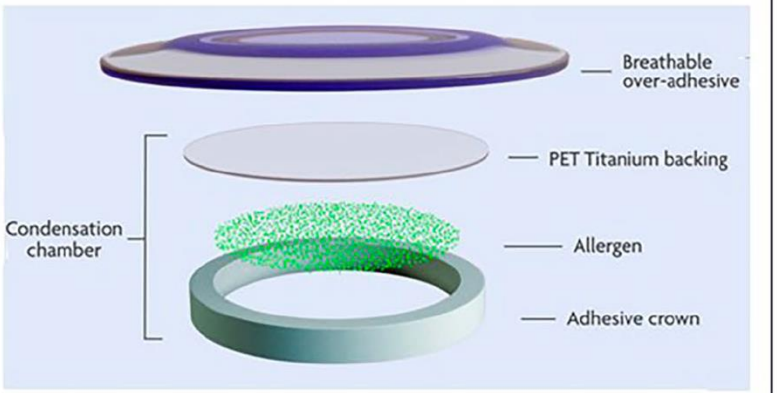
- ALLIANCE trial
  - Phase 1/2 study of PT-01 (NCT05440643)
  - Tablet composition similar to FDA-approved grass, ragweed, dust mite tablets
    - Standardized peanut protein per tablet
  - Part 1: 14-day dosing tolerability – completed
  - Part 2: Up-dosing to maintenance dose tolerability – completed
  - Part 3: Safety and efficacy after maintenance dosing – pending
- Large volume and early swallowing with extracts may be addressed by small size and instant dissolving and allow for more efficient sublingual absorption

Where does peanut SLIT fit in the peanut allergy treatment paradigm?

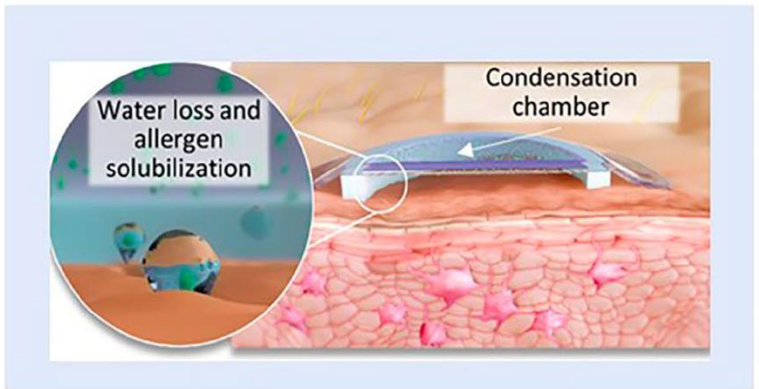
- Patients that might benefit from peanut SLIT
  - Ok with moderate desensitization
  - Concerns about GI/EoE side effects with OIT
  - Young children and toddlers not interested or able to do OIT
  - Needle/injection phobia

  - Prioritizing combination of safety and simple administration

Peanut epicutaneous immunotherapy (EPIT)



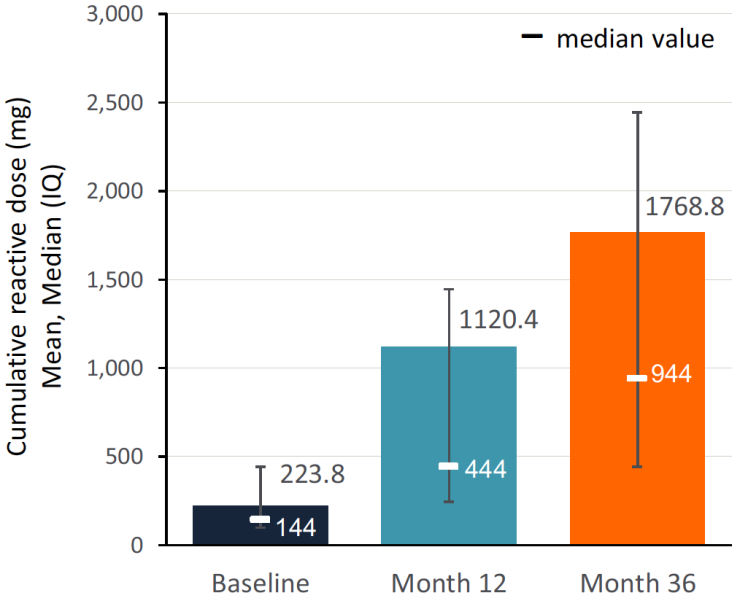
Condensation Chamber
Formed by adhesive crown, allergen and titanium backing, secured by adhesive overlay

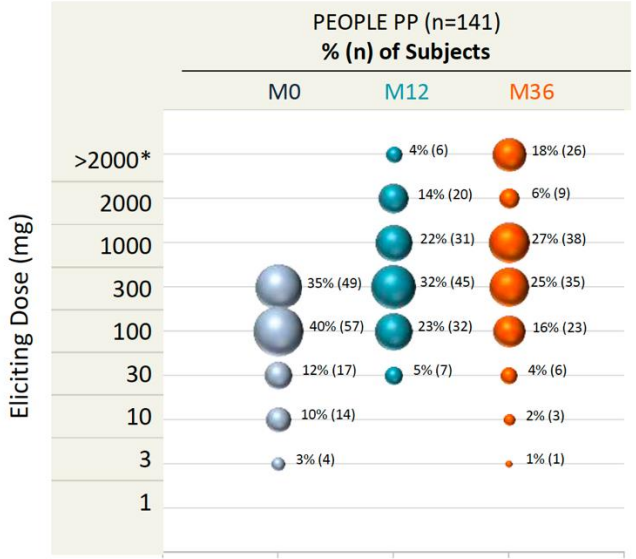


Allergen Solubilization
Occurs within condensation chamber when natural epidermal water loss solubilizes dry antigen on titanium backing

Ravindran. Allergy. 2024; doi: 10.1111/all.16324

Improved outcomes with longer duration peanut EPIT

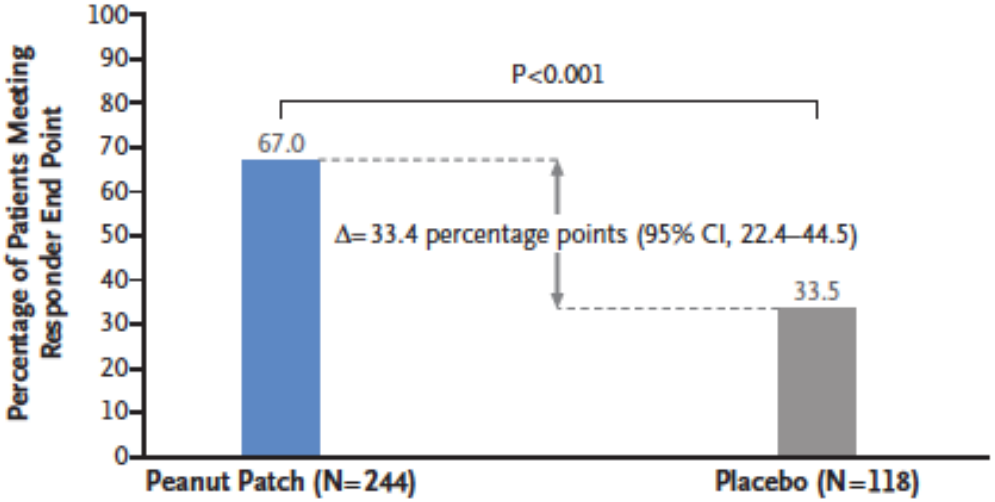




- Phase 3 PEPITES study did not meet primary endpoint at 12-months
- PEOPLE 3-year extension study demonstrated continued increasing thresholds

Fleischer. JACI 2020; doi: 10.1016/j.jaci.2020.06.028

Peanut EPIT in toddlers: EPITOPE study



- 1-4 year-old peanut-allergic kids
  - » Eliciting dose ≤ 443 mg peanut
- 12-month responder definition:
  - » ED ≤ 10mg → ≥ 300mg
  - » ED > 10mg → ≥ 1000mg
- 4 cases of anaphylaxis attributed to patch
- 10% used epi on patch vs 7% on placebo
- 8/244 patch vs 0/118 placebo withdrew from AEs

Greenhawt. NEJM 2023; doi: 10.1056/NEJMoa2212895

EPITOPE open-label extension: EPOPEX study

- Peanut EPIT in toddlers 3-year extension results
  - 68.2% pass OFC after 36 months, versus 30.7% after 12 months
  - No anaphylaxis and no serious TEAEs in the extension study

- Improved efficacy in the toddler age group, with further improvement after extended therapy

Where are we with EPIT?

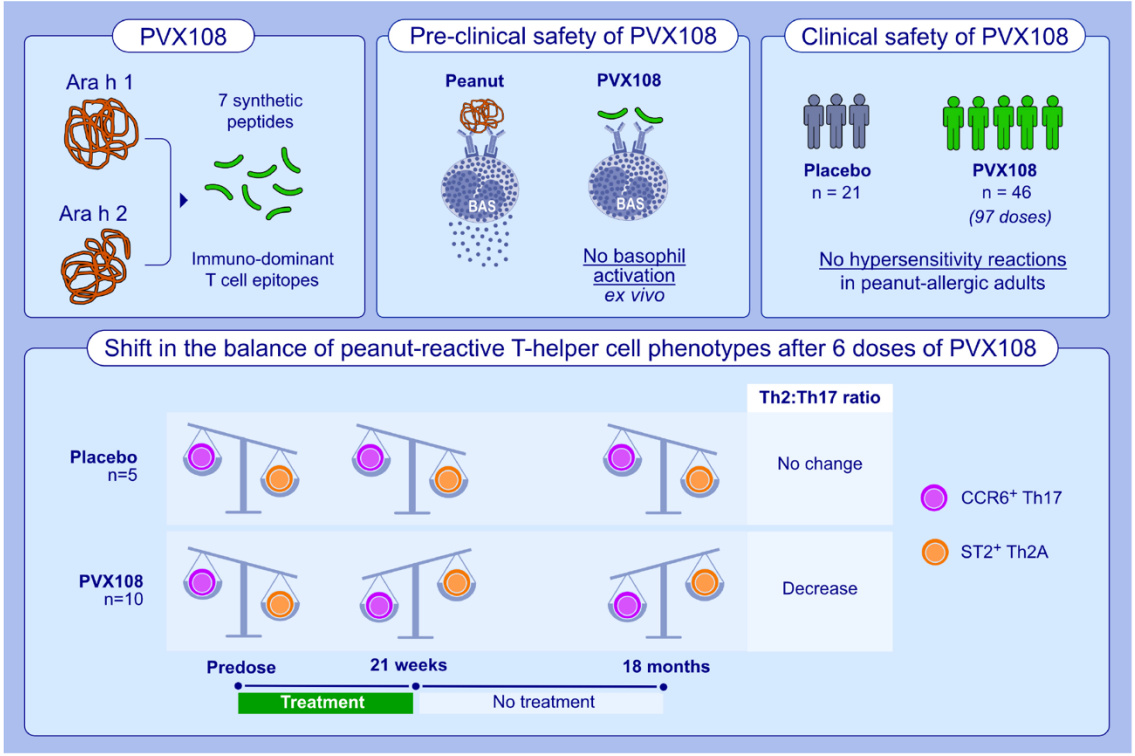
- EPIT remains promising due to its simple administration, good safety, and feasibility for long-term use

- Patch design revised to improve adhesion per FDA guidance
- VITESSE phase 3 study of revised patch has been fully enrolled
  - » Topline results expected late 2025

- Pathway for accelerated approval of peanut EPIT for 1-3 year olds discussed with FDA

Peanut peptide immunotherapy

- Peptides are too small to cross-link IgE on mast cells
- T-cell epitopes modulate T-helper cells in non-inflammatory state promoting tolerance
- Every 2-4 week intradermal dosing
- Phase 1 AVX-101 study in adults completed



Voskamp. Allergy. 2024; doi: 10.1111/all.15966

Phase 2 peanut peptide immunotherapy underway

- AVX-201 study (NCT05621317)
  - Phase 2 study ongoing at 14 sites across US and Australia
  - Peanut-allergic participants ages 4-17 years, reactive < 443mg
  - Twelve monthly intradermal injections
  - Primary endpoint: ratio of maximum tolerated dose at week 46 and baseline

Voskamp. Allergy. 2024; doi: 10.1111/all.15966

Its not immunotherapy but we have a second FDA approved option!

FDA NEWS RELEASE

FDA Approves First Medication to Help Reduce Allergic Reactions to Multiple Foods After Accidental Exposure

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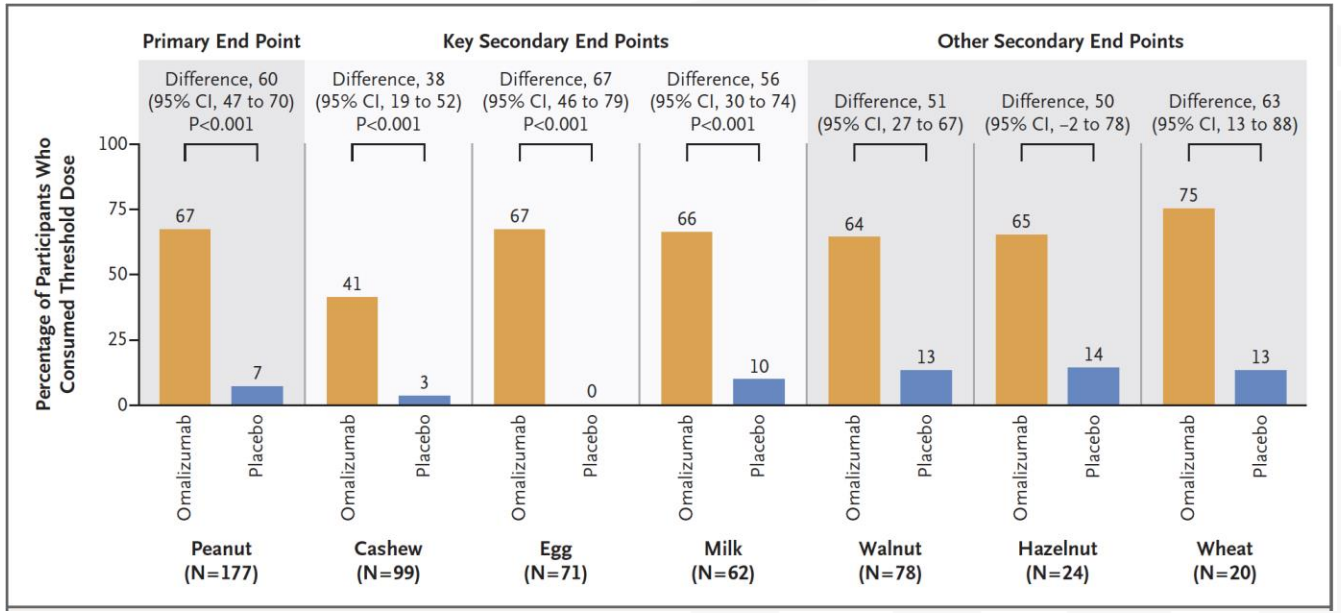
More Press Announcements

For Immediate Release: February 16, 2024

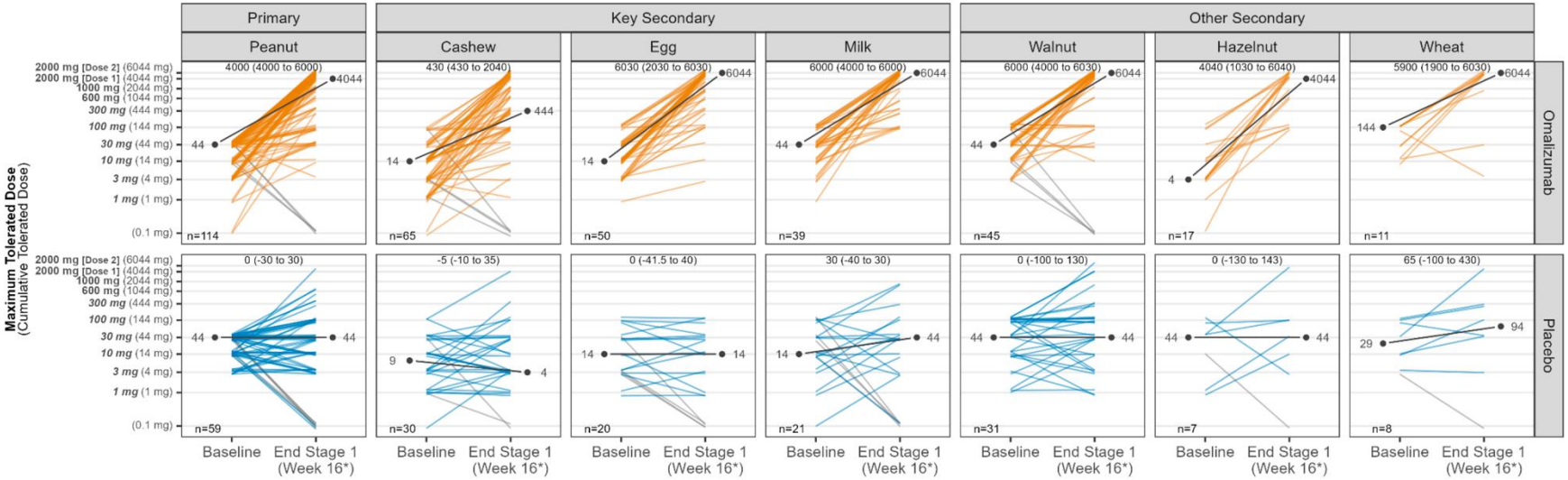
Content current as

OUtMATCH food challenge outcomes



- Responder criteria:
  - Peanut: ≥ 600 mg (1044 mg cumulative)
  - Other foods: ≥ 1000 mg (2044 mg cumulative)

Wood. NEJM. 2024; doi: 10.1056/NEJMoa2312382



- Almost all orange lines go up showing improvement from baseline on omalizumab
- Treatment failures: 14% did not reach 30 mg of peanut

Wood. NEJM. 2024; doi: 10.1056/NEJMoa2312382

Hooray its approved, now what?

- Lots of real-world questions
  - Who should we prescribe it for? Is there an ideal patient?
  - Do we need food challenges to prescribe it? To know its working?
  - How long should someone stay on it?
  - Should we combine it with OIT?

- It will be great for a lot of people, but it will not be for everyone
  - Injection route, out-of-pocket cost, general concerns about biologics may limit use
  - Lack of long-term efficacy may be reason for some to pursue food immunotherapy

- OUtMATCH stage 2 will compare omalizumab vs multi-food OIT
- OUtMATCH stage 3 will assess ability to transition to real food after omalizumab

Food immunotherapy take-home points

- OIT works, but risk and treatment burden make it difficult
  - » Potential for remission may make it worthwhile for some
  - » Slower protocols may improve safety
- SLIT is simple and safe with desensitization levels approaching OIT
  - » Range of responses is wide and extract can be unwieldy
- EPIT is simple and safe and desensitization continues to improve with longer therapy
  - » Like OIT and SLIT, toddlers may respond even better
- Peptide immunotherapy is in development and appears safe
  - » Requires injections, but monthly intradermal may be more acceptable
- Avoidance can be hard but is always an option. Much more is on the horizon…

- Finally there are options for food allergy, shared decision making will be essential.