Oral Immunotherapy in Infants and Toddlers

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Traditional Understanding of Peanut Allergy

- Peanut allergy 2-5% of U.S. School-aged children & vast majority remain allergic throughout their lifetime.
- Most common cause of fatal food reactions; common anaphylaxis to be treated in ED
- 20% of peanut-allergic children achieve tolerance by age 4.
- SPT > 8mm & sIgE>2.1 kU/L = 95% PPV for persistent peanut allergy
- OIT believed to work better in younger children, age most study are children starting between ages 4 and 7.
- Sustained Unresponsiveness (SU) more likely with earlier starts.

Early Studies in Children < 6 years

- **81 to 90%** of children were **desensitized to peanuts** (1.2-20 kernels) (2 single-arm studies N=37[1], N=270[2]); **90% desensitized to 200 mL milk** versus **23%** control (RCT[3], N=30 OIT, 30 controls)
- **78%** of children who had had a baseline reaction to peanut **tolerated 16 peanuts** after 1 year of consuming 1.2 peanuts per day (N=87)
- **78%** reached **sustained unresponsiveness to peanuts** versus **4%** control (retrospectively controlled trial[1]: N=37 OIT, 154 control)
- **90%** continued to consume **200 mL milk** per day (RCT:[3] N=30)

- 1. Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. JAllergy Clin Immunol. 2017;139(1):173–81.e8. https ://doi.org/10.1016/jaci.2016.05.027..
- 2. Soller L, Abrams EM, Carr S, et al. First real-world safety analysis of preschool peanut oral immunotherapy. J Allergy Clin Immunol Pract. 2019. https ://doi.org/10.1016/j.jaip.2019.04.010.
- 3. Martorell A, De la Hoz B, Ibanez MD, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011;41(9):1297–304. https ://doi.org/10.1111/j.1365-2222.2011.03749 .x.

According to Canadian Guidelines (2020)

- Across four reports of OIT clinical practice with children and adolescents (age 4 years), **two** found **no association between age and reaching the target dose.**[1,2]
- One found that **older children were less likely to reach the target dose** (17% reduction each year after age 5, P<.001)[3]
- One found that children who failed desensitization were younger than those desensitized (median 4.2 vs 6 yrs).54 (case series, N= 145 to 295)[4]

- 1. Levy MB, Elizur A, Goldberg MR, et al. Clinical predictors for favorable outcomes in an oral immunotherapy program for IgE-mediated cow's milk allergy. Ann Allergy Asthma Immunol. 2014;112(1):58–63.e1. https://doi.org/10.1016/j.anai.2013.10.001.
- 2. Kauppila TK, Paassilta M, Kukkonen AK, et al. Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland. Pediatr Allergy Immunol. 2019. https ://doi. org/10.1111/pai.13025
- 3. Wasserman RL, Hague AR, Pence DM, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. J Allergy Clin Immunol Pract. 2019;7(2):418–426.e4. https ://doi.
- org/10.1016/j.jaip.2018.05.023.
- 4. Nachshon L, Goldberg MR, Katz Y, et al. Long-term outcome of peanut oral immunotherapy-real-life experience. Pediatr Allergy Immunol. 2018;29(5):519–26. https ://doi.org/10.1111/pai.12914 .

Determining the Efficacy & Value of Immunotherapy on the Likelihood of Peanut Tolerance (DEVIL; 2017) – Introduction

- In a multicenter DBPCRCT of 37 peanut allergic children aged 9-36 months (determined by OFCs)
- No threshold ingestion amount specified
- 1:1 allocation ratio to PnOIT 300 mg daily vs. 3000 mg daily for at **maintenance of least 12 months followed by 4 weeks of avoidance**
- Median age: 28.5 months
- Used a control population consisting of patients demographics-matched patients and meeting I/Es in allergy clinical database
- **14% drop-out rate (n=5, 3 for TRAEs, 2 for non-adherence)**

Determining the Efficacy & Value of Immunotherapy on the Likelihood of Peanut Tolerance (DEVIL; 2017) – Results

1/37 (3%) desensitization failure / 97% desensitized to 3000 mg

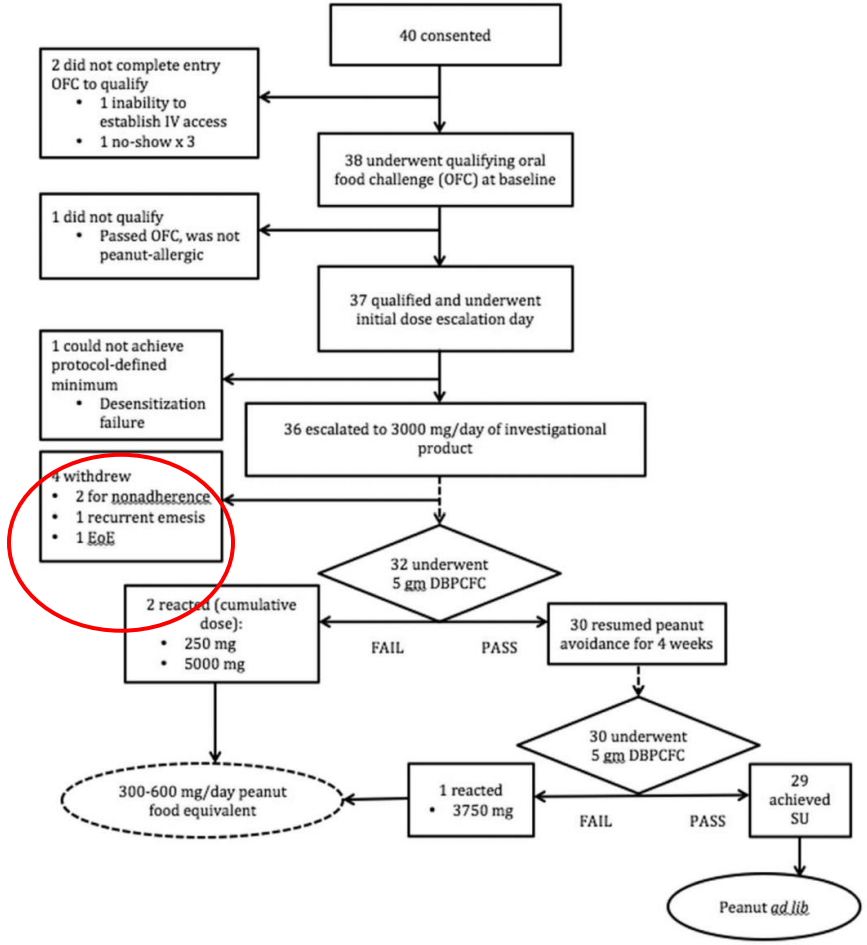
4 more withdrew during maintenance (86% reached DBPCFC)

95% had reactions: 85% mild, 15% mod., 1 epi

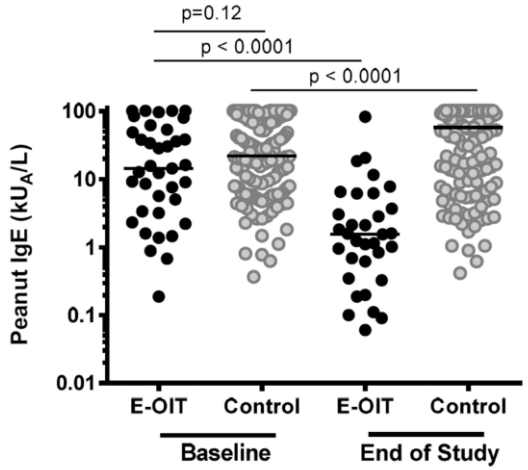
Maintenance ~1.5 yr, 16 peanut challenge: 81% passed

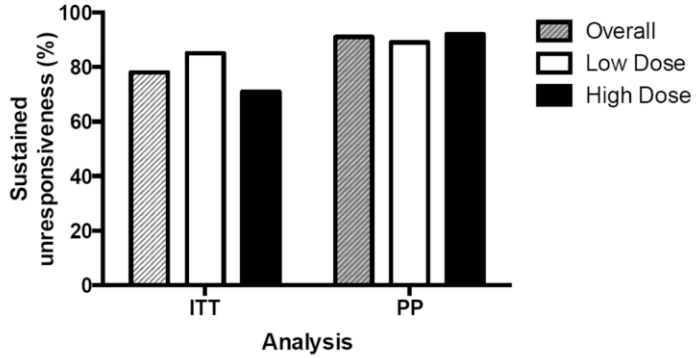
1 month no peanut, re-challenge: 78% sustained unresponsiveness

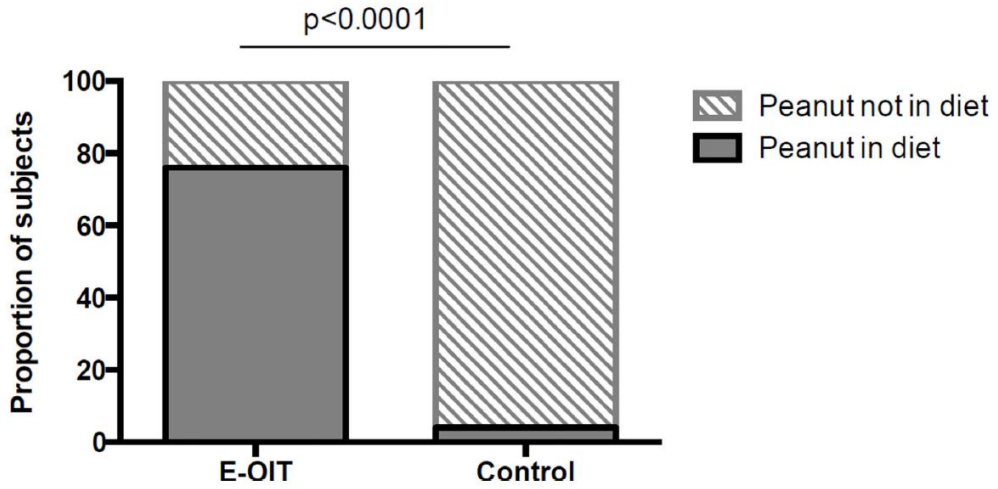
No difference in clinical or immunologic responses between 1 or 10 peanut per day cohorts



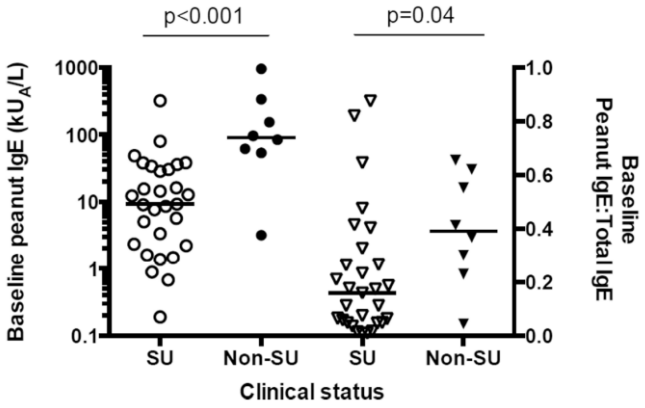
Determining the Efficacy & Value of Immunotherapy on the Likelihood of Peanut Tolerance (DEVIL; 2017) – Results Illustrated







Determining the Efficacy & Value of Immunotherapy on the Likelihood of Peanut Tolerance (DEVIL; 2017) – Results Illustrated



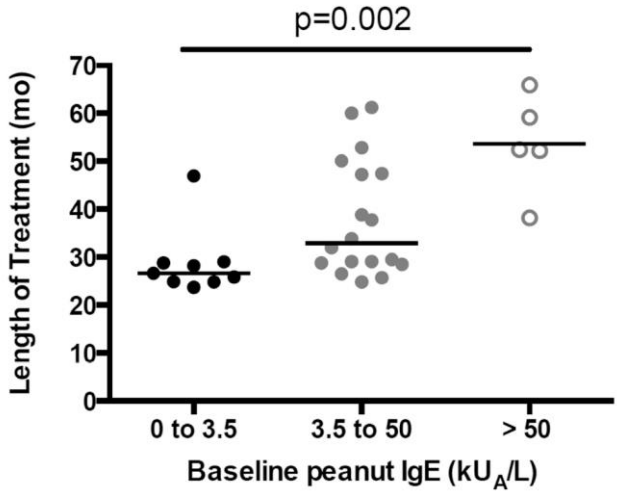


Figure 3.
Association of baseline peanut-specific IgE characteristics and outcomes. (A) Both the baseline peanut-specific IgE, and the ratio of peanut-specific to total IgE, are significantly lower among successes than failures in the ITT population. (B) Length of treatment broken down by tertiles of baseline peanut-specific IgE. Significance testing by one-way ANOVA.

Early Peanut OIT - 5 Year Follow Up- Vickery

- 29/37 (78%) responders to phone survey

- 93% continued to eat peanut
- 62% regularly carried epinephrine devices
- 59% no longer saw an allergist
- 31% chronic GI complaints (2 EoE: 1 egg, 1 peanut: 3%)

Peanut Desensitization Rate – IMPACT Trial (2020)

- In a multicenter DBPCRCT of 146 peanut allergic children aged 1-4 years old
- Reactive to ≤ 500 mg of peanut protein (~2 peanuts)
- 2:1 allocation ratio to PnOIT vs. placebo for **134 weeks (2.5 yrs)**
- 2000 mg/day followed by **26 weeks of avoidance (6 months)**
- Median age: 39.3 months (IQR: 30.8, 44.7)
- **36% drop-out rate** (long duration, higher in placebo)

Results – IMPACT Trial

At week 134:

- 71% (**68/96**) treatment arm desensitized vs. 2% (**1/50**) placebo

- Cumulative Tolerated Doses (CTD): 5005 mg vs. 5 mg

After 26 weeks of avoidance:

- 21% (20/96) vs. 2% (1/50) remained desensitized

- CTD: 755 mg vs. 0 mg

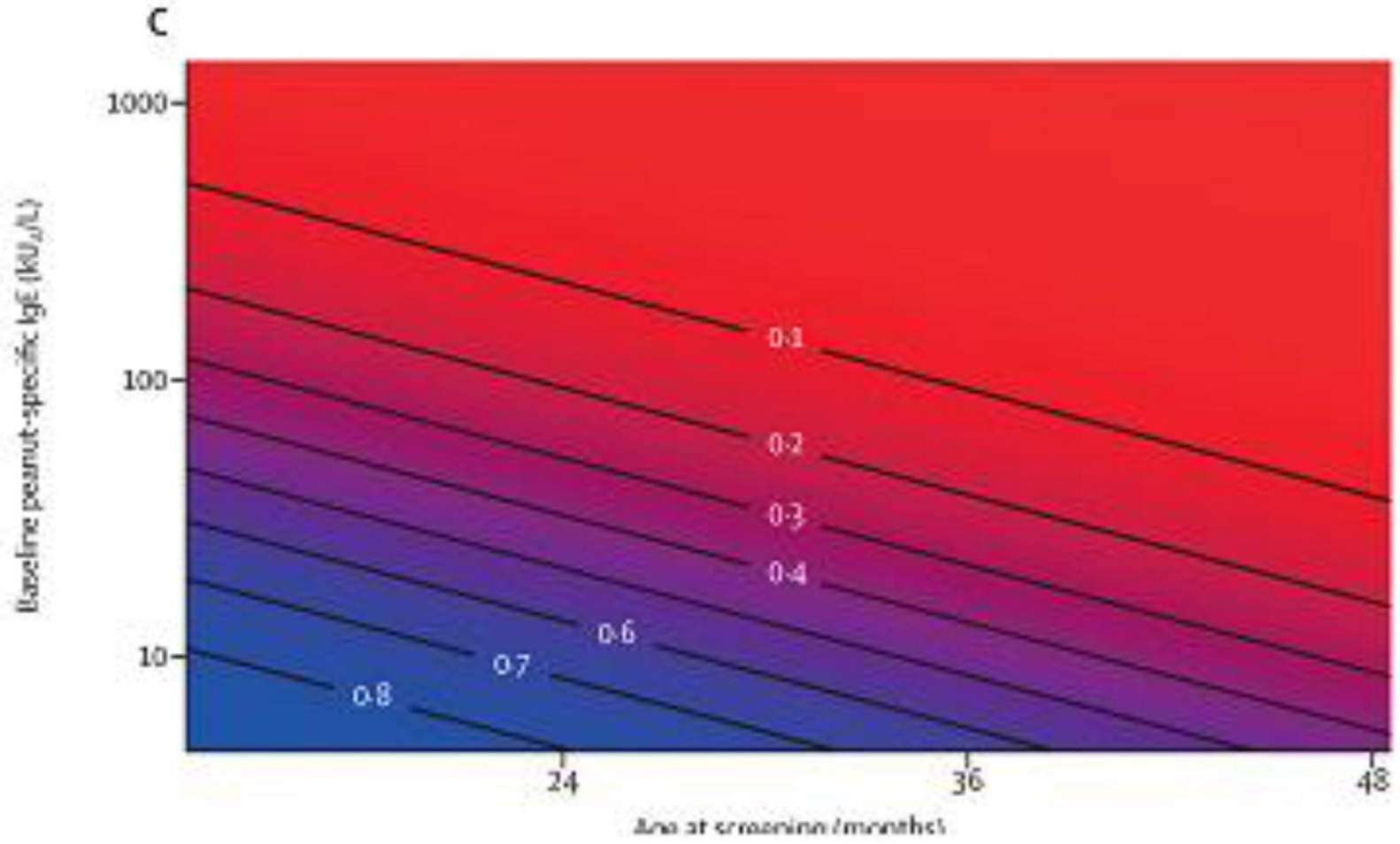
Results – IMPACT Trial

Authors' major conclusions:

1. Biomarkers improved with desensitization (IgE, component IgE, IgG4)
2. 98% PnOIT vs. 80% experienced a dosing reaction. 35 epinephrine injections (21 to PnOIT patients)
3. Younger age and lower baseline peanut sIgE predictive of remission

"Initiation of PnOIT before 4 years is associated w/ increases in both desensitization and remission."

Probability of Remission – IMPACT Trial



A contour plot of predicted probability of remission from the logistic regression model plotted against baseline peanut-specific IgE (kUA/L) on the y axis and age at screening (months) on the x axis. Values in blue show >50% probability of remission, while values in red show <50% probability of remission.

et al. Page 19 Lancet.

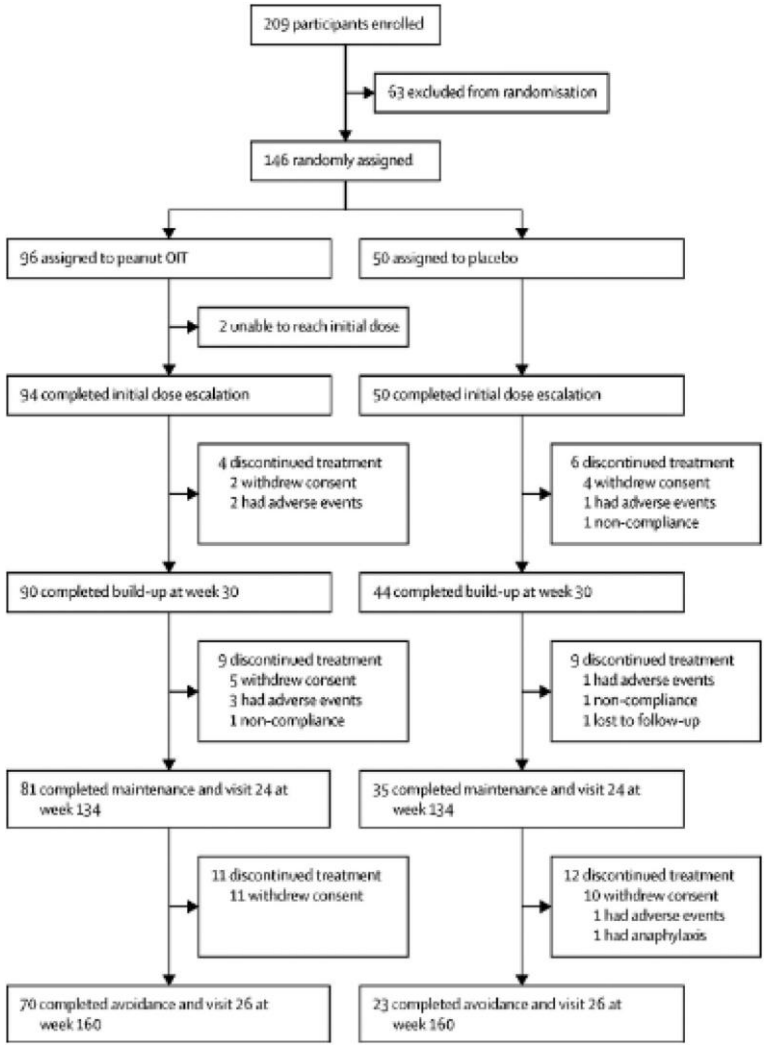
Notes

- Predominantly male (68%) and white (65%)
- Only 12% aged 1 to 2 years
- Only 2/146 (1%) reported a history of anaphylaxis
- Median peanut sIgE: 53.1 kU/L
- Median SPT result: 15 mm wheal
- 70/96 (73%) and 23/50 (56%) completed the study to 160 weeks
- Enrolled patients with low peanut reaction threshold (25 mg)

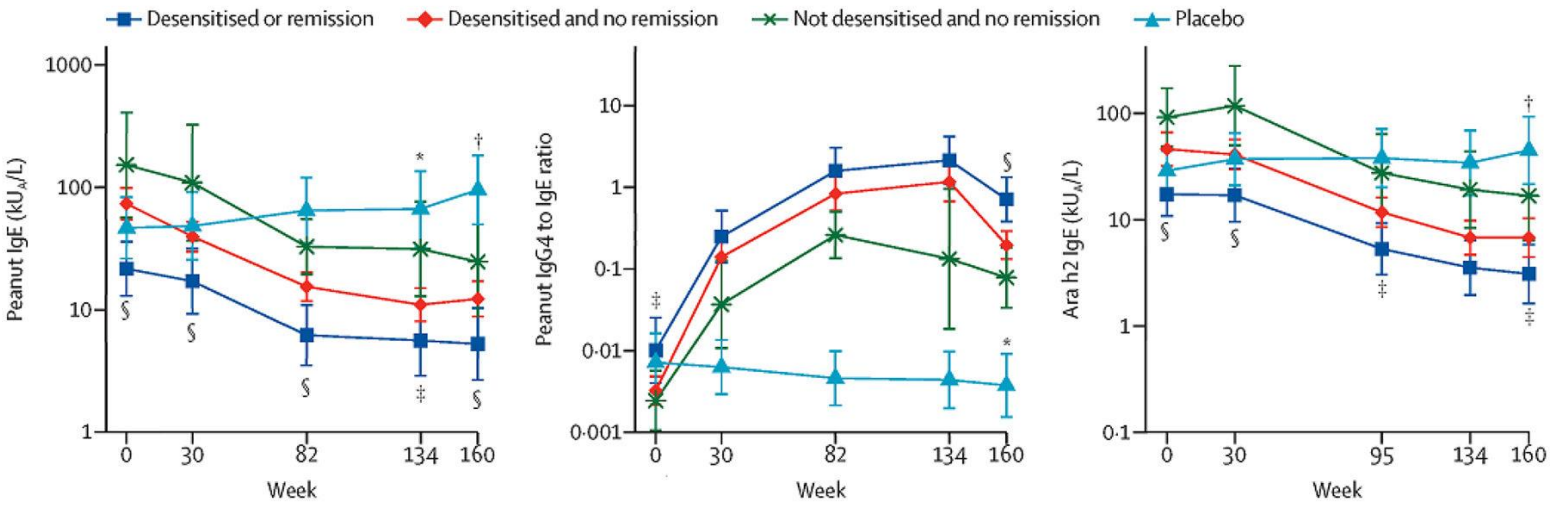
ITT Protocol

- 2/96 subjects unable to reach initial dose escalation in PnOIT.
- 2/94 vs. 1/50 stopped during build-up due to adverse events (AEs).
- 3/90 vs. 1/44 had AEs during maintenance in PnOIT

Conclusion: high number of drop-outs in the placebo which increased over time, and drop-outs not related to AE's



Change in biomarkers



Conclusion

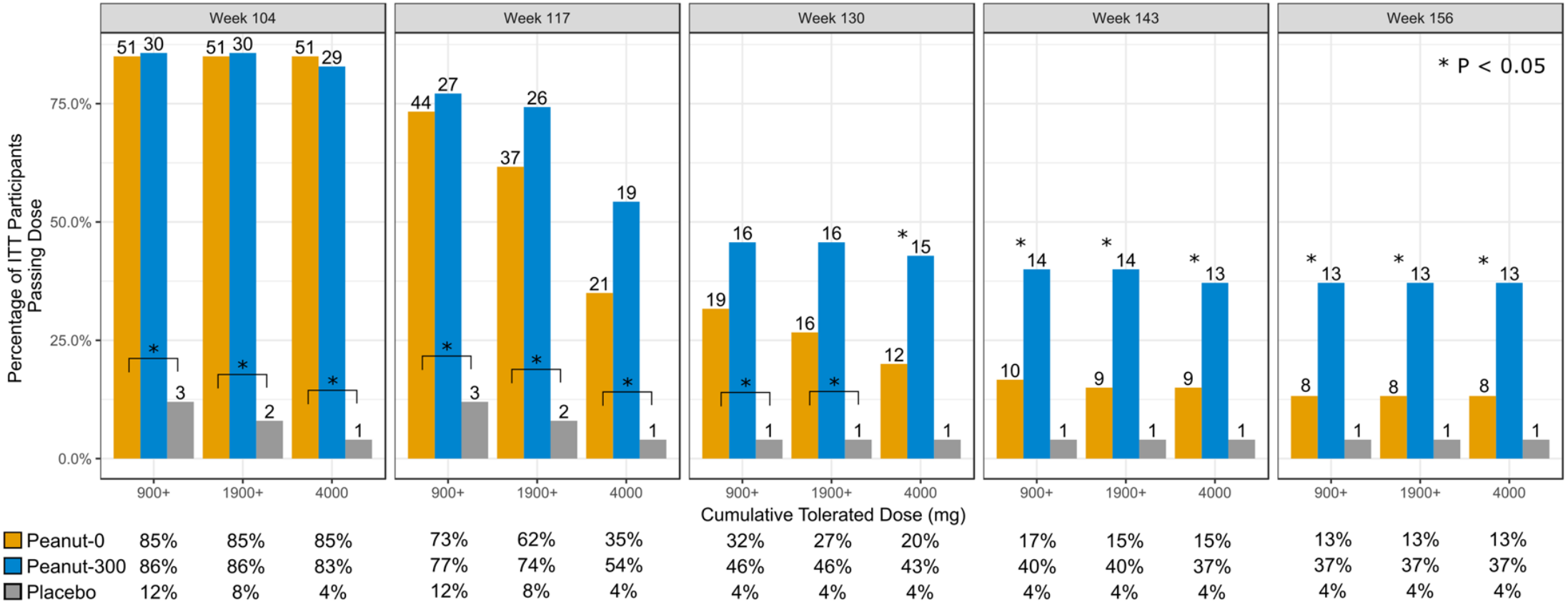
At a relatively high daily dose (2000mg), for those that did not drop out, typically for 'other' reasons, the majority (68/81; 84%) were able to be desensitized and (20/70; 29%) maintained desensitization after 6 months. Trends showed that those who were younger did better and only 12% were ages 1 to 2 years of age.

Peanut Desensitization – POISED Study

- 120 peanut allergic participants, aged 7 to 55 years of age in a DBPCT enrolled in 1 of 3 arms (peanut-0, peanut-300, placebo)
- Reactive to ≤ 500mg of peanut protein
- Built up and maintained on 4g of peanut protein / day OIT by week 104 followed by avoidance in 3 arms
- DBPCFCs to 4 g peanut protein were conducted at baseline, weeks 104, 117, 130, 143 and 156
- Overall drop-out rate: 13%, and not significantly different across groups
- Peanut and placebo food challenges at screening were dosed in the following increments of peanut protein (mg): 5, 20, 50, 100, 100, 100 and 125; or placebo (oat): 5, 20, 50, 100, 100, 100 and 125.

Notes (POISED Study)

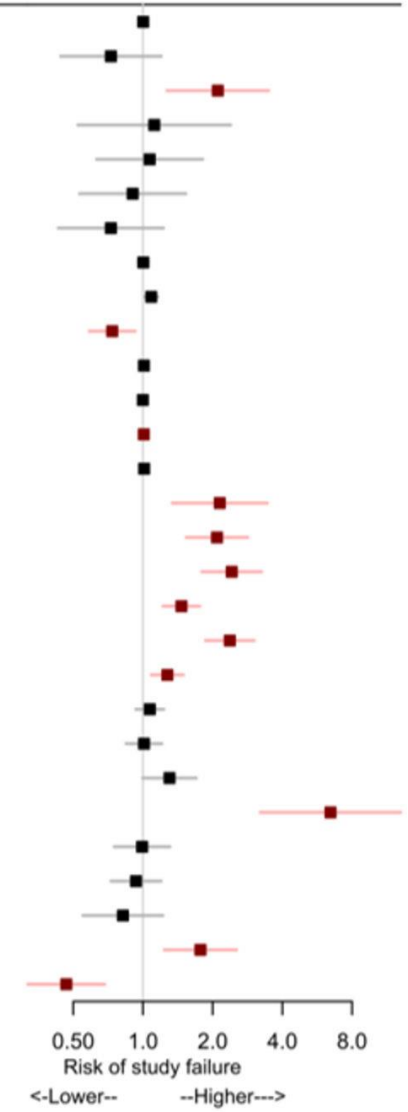
- 120 participants
- Median age: 11 years;
- 22 participants were > 22 years of age (18%)
- 62% Caucasian, 27% Asian, 68% male
- Median peanut sIgE: **79.1**
- Median SPT result: 12 mm
- Median CTD on screening: 25 mg
- Most reached maintenance between **42-60 weeks**
- AE's due to accidental ingestions decreased significantly between treatment and placebo (1 % vs. 16% in year 2)
- No history of severe anaphylaxis or severe asthma



Percentage of participants who tolerated cumulative peanut challenge dose of 900 mg, 1900 mg and 4 g by DBPCFC week and treatment arm for the ITT population. Number on the top of each bar is the number of participants. P-values based on Fisher's exact test between peanut-0 (orange bar) and peanut-300 (blue bar), or, highlighted by brackets, comparisons between placebo and peanut-0. Although not noted in the figure, all comparisons between placebo and peanut-300 had $P < 0.05$. Further detailed percentages are provided below each panel. Peanut-0 = oral immunotherapy with peanut discontinuation arm; Peanut-300 = oral immunotherapy with peanut continuation arm (300 mg).

Predictors of success (POISED Study)

Baseline Characteristic	Hazard Ratio	P-value	Q-value
Age	1	0.87	0.97
Male	0.73	0.21	0.43
Asian	2.11	0.004	0.01
Multi-racial	1.12	0.77	0.97
History of Asthma	1.07	0.81	0.97
History of atopic dermatitis	0.9	0.71	0.92
History of allergic rhinitis	0.73	0.23	0.44
BMI	1	0.9	0.97
Number of doctor diagnosed food allergies	1.09	0.02	0.04
Age at diagnosis of peanut allergy	0.74	0.009	0.02
Time since diagnosis of peanut allergy	1.01	0.46	0.69
Cumulative tolerated dose	1	0.42	0.66
%CD63high area under peanut dose curve	1.01	0.001	0.005
Peanut skin prick test	1.01	0.57	0.8
Total serum IgE (log10)	2.15	0.002	0.006
Peanut sIgE/Total IgE (log10)	2.09	< 0.001	< 0.001
Peanut sIgE (log10)	2.42	< 0.001	< 0.001
Ara h 1 IgE (log10)	1.47	< 0.001	< 0.001
Ara h 2 IgE (log10)	2.37	< 0.001	< 0.001
Ara h 3 IgE (log10)	1.28	0.003	0.009
Ara h 8 IgE (log10)	1.07	0.34	0.57
Ara h 9 IgE (log10)	1.01	0.91	0.97
Ara h 1 IgE/Peanut sIgE (log10)	1.3	0.05	0.11
Ara h 2 IgE/Peanut sIgE (log10)	6.46	< 0.001	< 0.001
Ara h 3 IgE/Peanut sIgE (log10)	0.99	0.95	0.99
Ara h 8 IgE/Peanut sIgE (log10)	0.93	0.59	0.8
Ara h 9 IgE/Peanut sIgE (log10)	0.82	0.33	0.57
Peanut sIgG4 (log10)	1.77	0.002	0.006
Peanut sIgG4/Peanut sIgE (log10)	0.47	< 0.001	0.001



Conclusions of the POISED Study

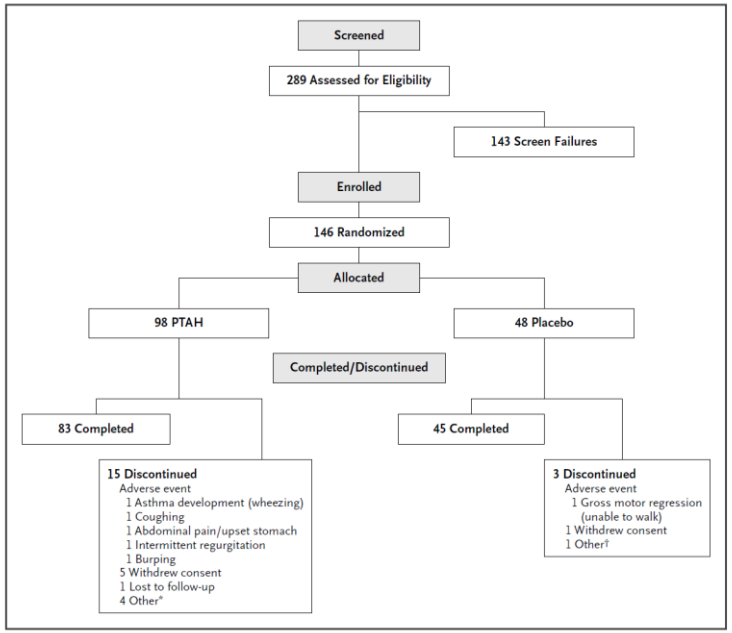
Desensitization was successful in those that remain enrolled in the clinical trial to 13-16 peanuts even among older cohort. The optimal dose for maintaining desensitization to 13–16 peanuts requires further testing but is likely to be greater than 300 mg per day in this mostly adolescent population.

There were 22 participants over 18 years old in the study; we found no differences compared to younger participants at week 117 in AE rates, DBPCFC outcomes,29,30 or peanut-0 or peanut-300 success. The dropout rate was increased in adults vs. children (32% vs. 9%)

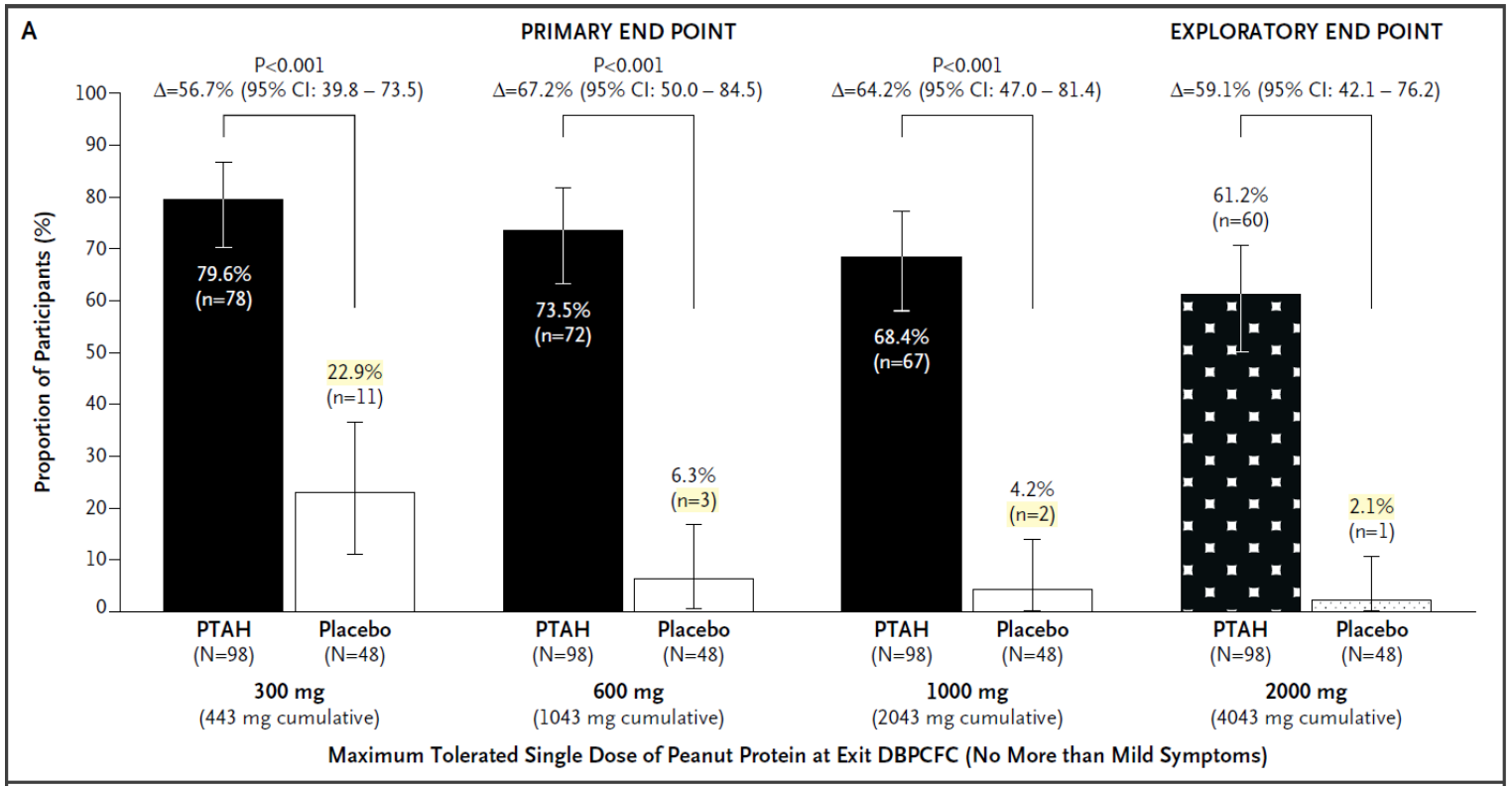
- *Predictors of success:* Lower peanut sIgE, Ara h 1 and Ara h 2, trajectories of peanut sIgE after de-escalation phase, but not age.

Peanut Oral Immunotherapy Study of Early Intervention for Desensitization [POSEIDON]) - Introduction

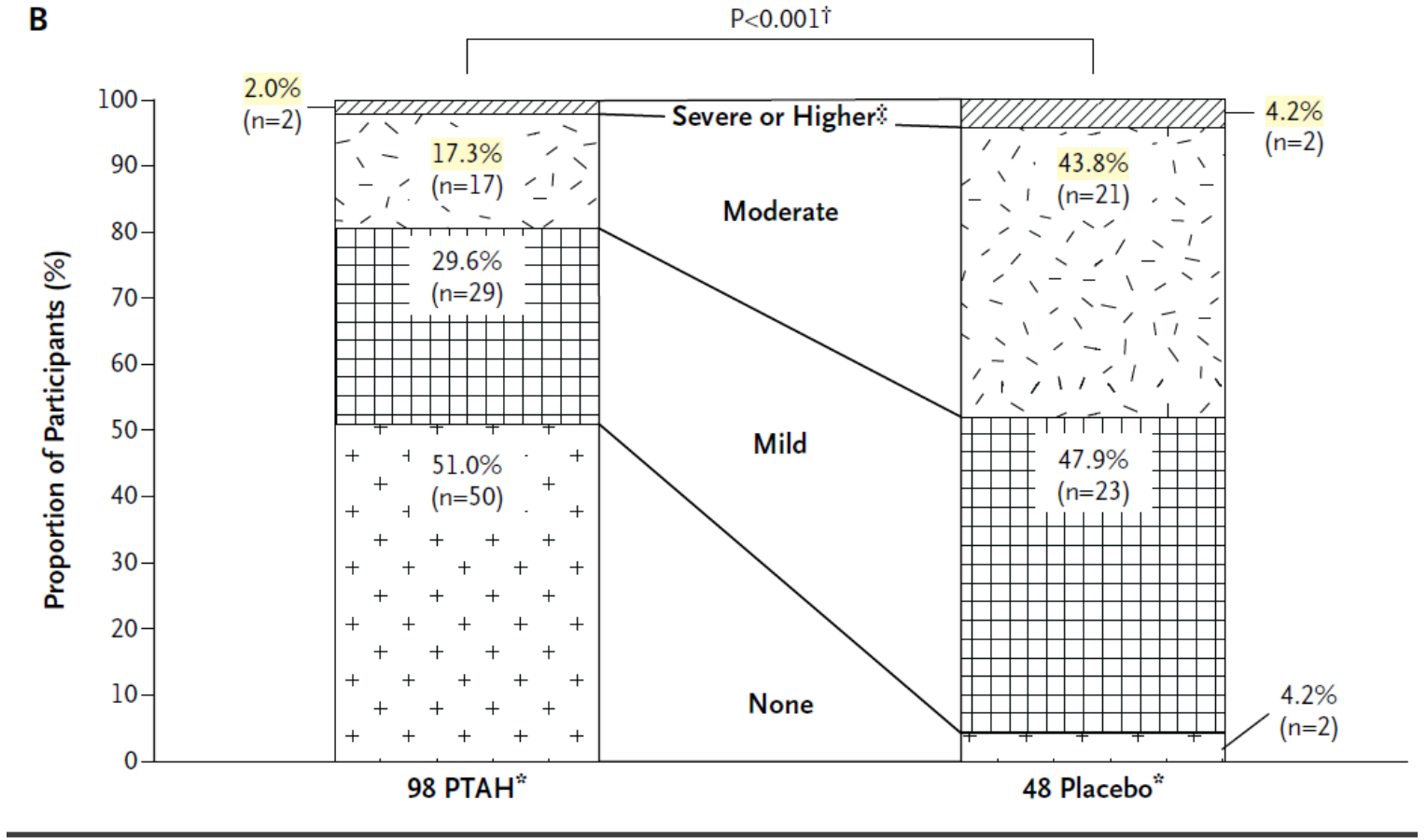
- POSEIDON (2023) built of the DEVIL (2017; 1:1 trial with LDPnOIT vs. HDPnOIT in 37 toddlers) and IMPACT (2022, DBPCRCT of 146 peanut allergic children)
- Phase 3, DBPCRCT in 146 children ages 1 to <4 years with 2:1 randomization
- Experienced symptoms < 300 mg at baseline
- Up-dosed every weeks to 300mg daily for approximately 6 months, then treated x12 months
- Drop-outs: 15% treatment vs. 94% placebo



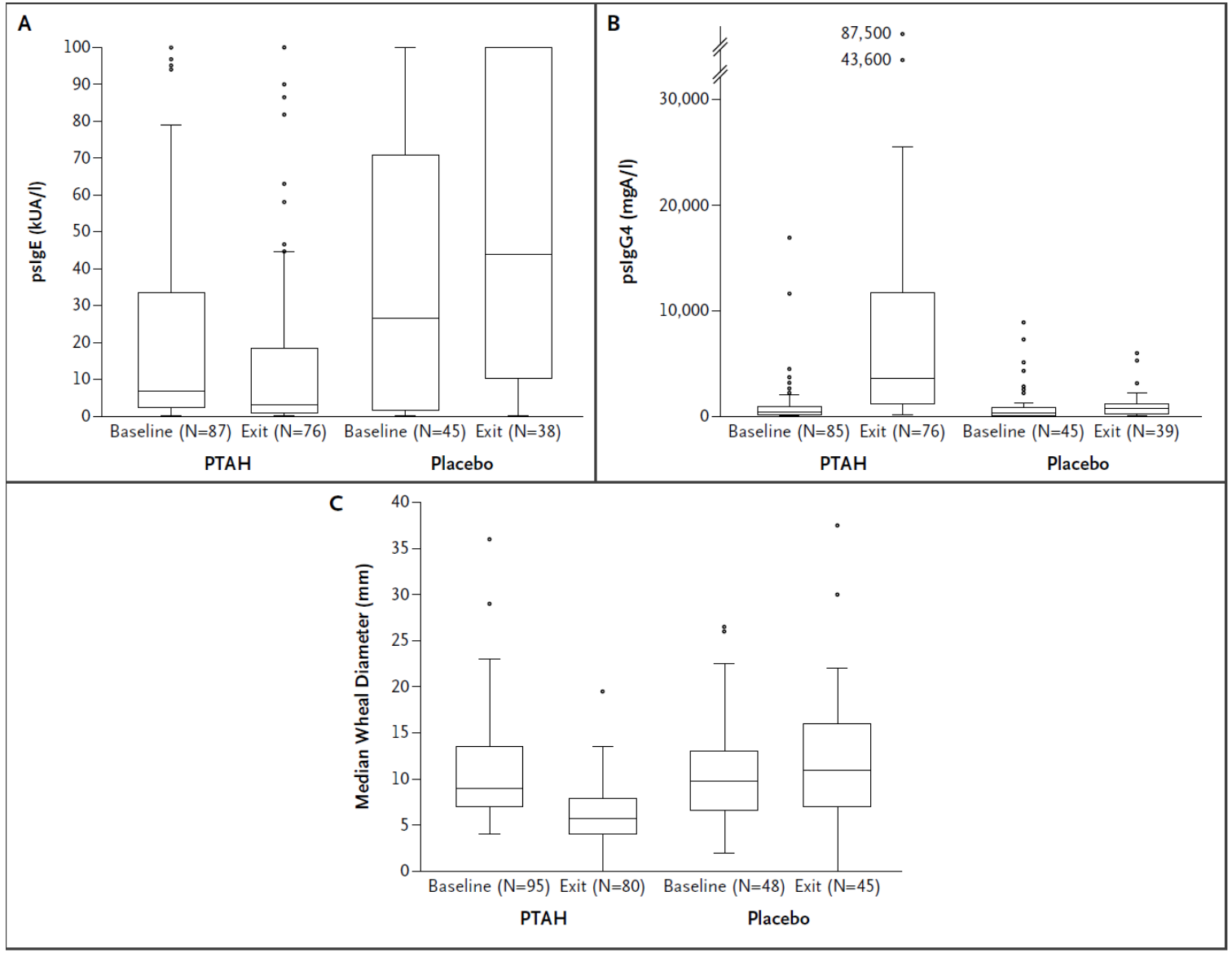
POSEIDON: Differences in Primary Endpoint Strongly Apparent



POSEIDON: Strongest Difference is in Moderate % of Reactions

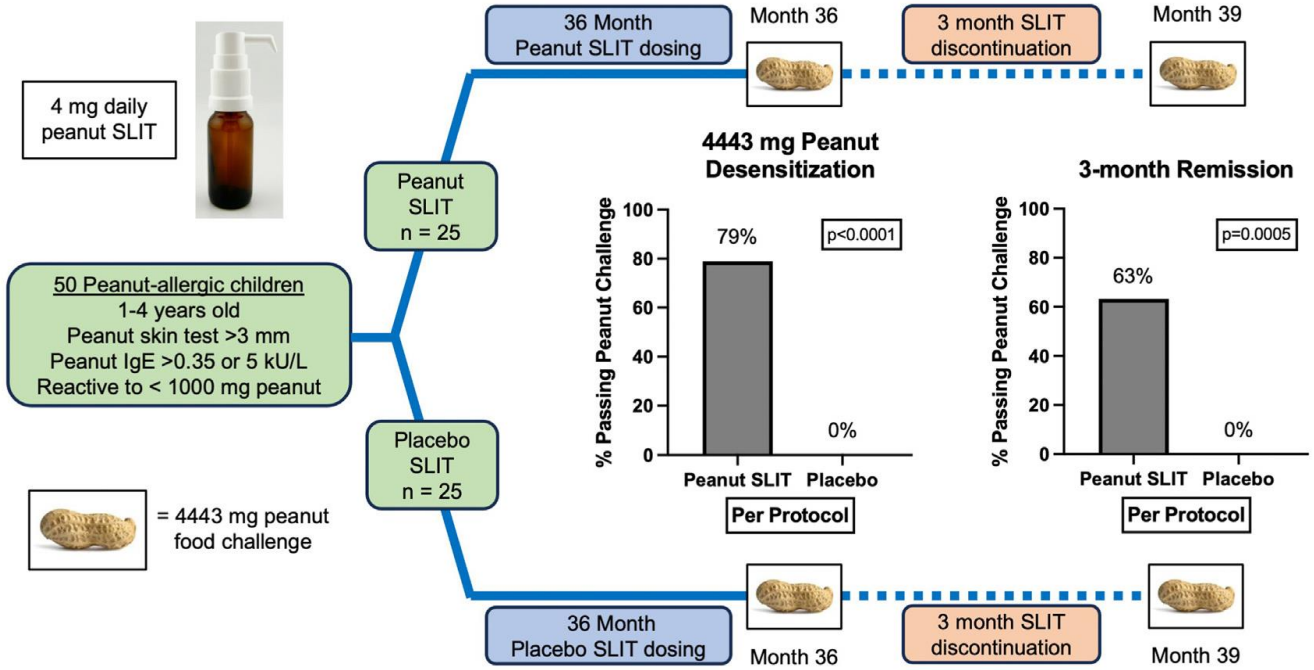


POSEIDON: Strong Changes Demonstrated in Biomarkers (psIgE, psIgG4, wheal diameter)



SLIT Therapy:
Desensitization and remission after peanut sublingual immunotherapy in 1- to 4-year-old peanut-allergic children: A randomized, placebocontrolled trial – Introduction to Study Design

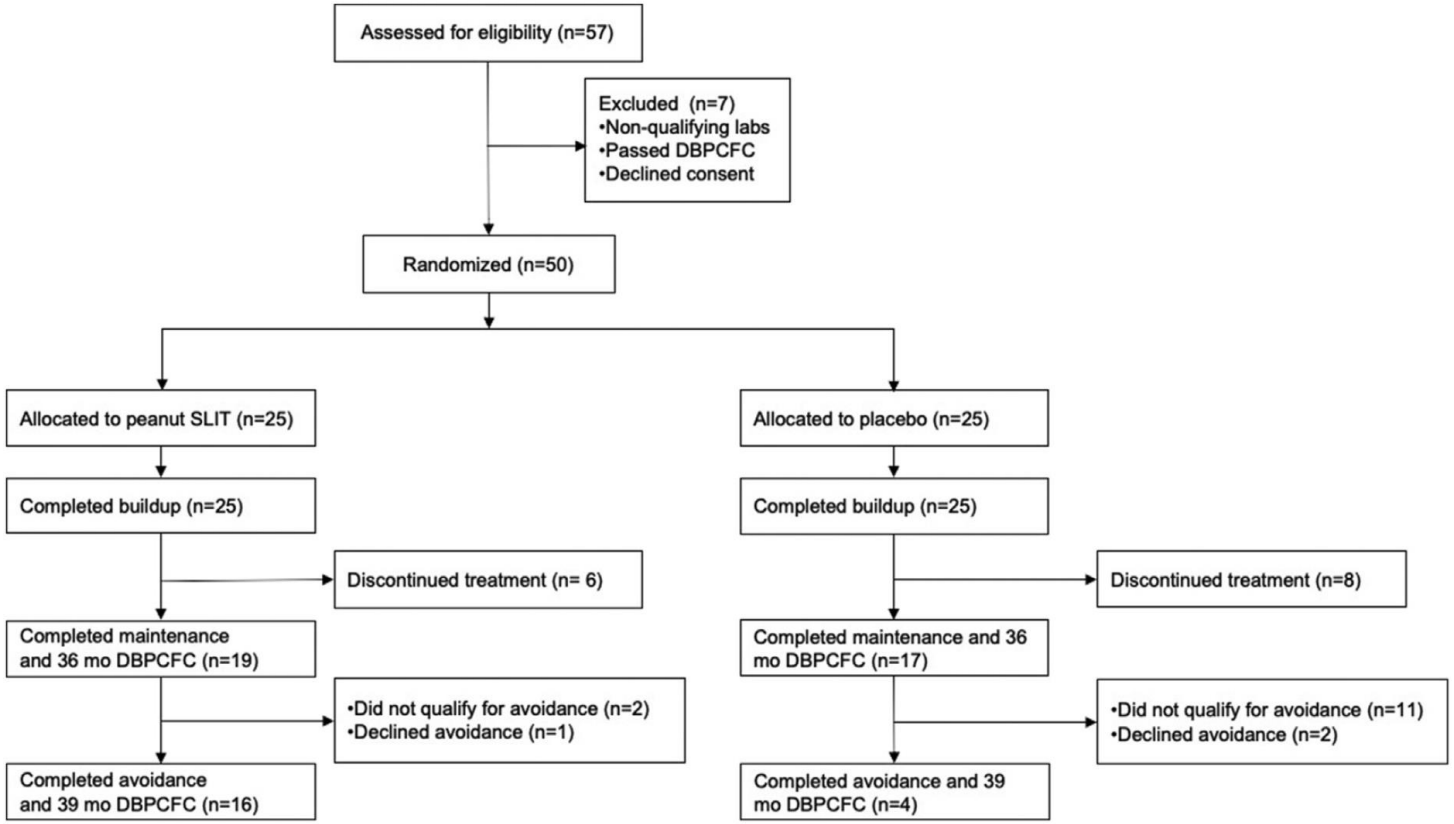
Desensitization and Remission after Peanut Sublingual Immunotherapy in 1-4 year-old Peanut Allergic Children: a Randomized, Placebo-Controlled Trial



SLIT: Desensitization and remission after peanut sublingual immunotherapy in 1- to 4-year-old peanut-allergic children – Introduction to Study Design

- Multicenter DBPCRCT of **50** peanut allergic children **aged 1-4** years old
- Reactive to ≤ 1000 mg of peanut protein
- 1:1 allocation ratio to Pn SLIT vs. placebo
- 4 mg/day for 36 months followed by **3 months of avoidance**
- Median age: 2.2 years (IQR: 1.5-3.5)
- **% drop-out rate** (long duration, higher in placebo)

SLIT Peanut Study – How the Study Performed



SLIT Peanut Study – Desensitization Outcome

15 peanut
SLIT participants (ITT 60%, PP 78.9%) versus 0 placebo participants passed the month 36 DBPCFC by ingesting the full 4443
mg of peanut protein without dose-limiting symptoms (P < .0001) (Fig 2, A).

12 peanut SLIT participants (ITT 48%, PP 63%) versus 0 placebo participants went on to pass the month 39 DBPCFC, demonstrating remission (P 5.0005) (Fig 2, B).

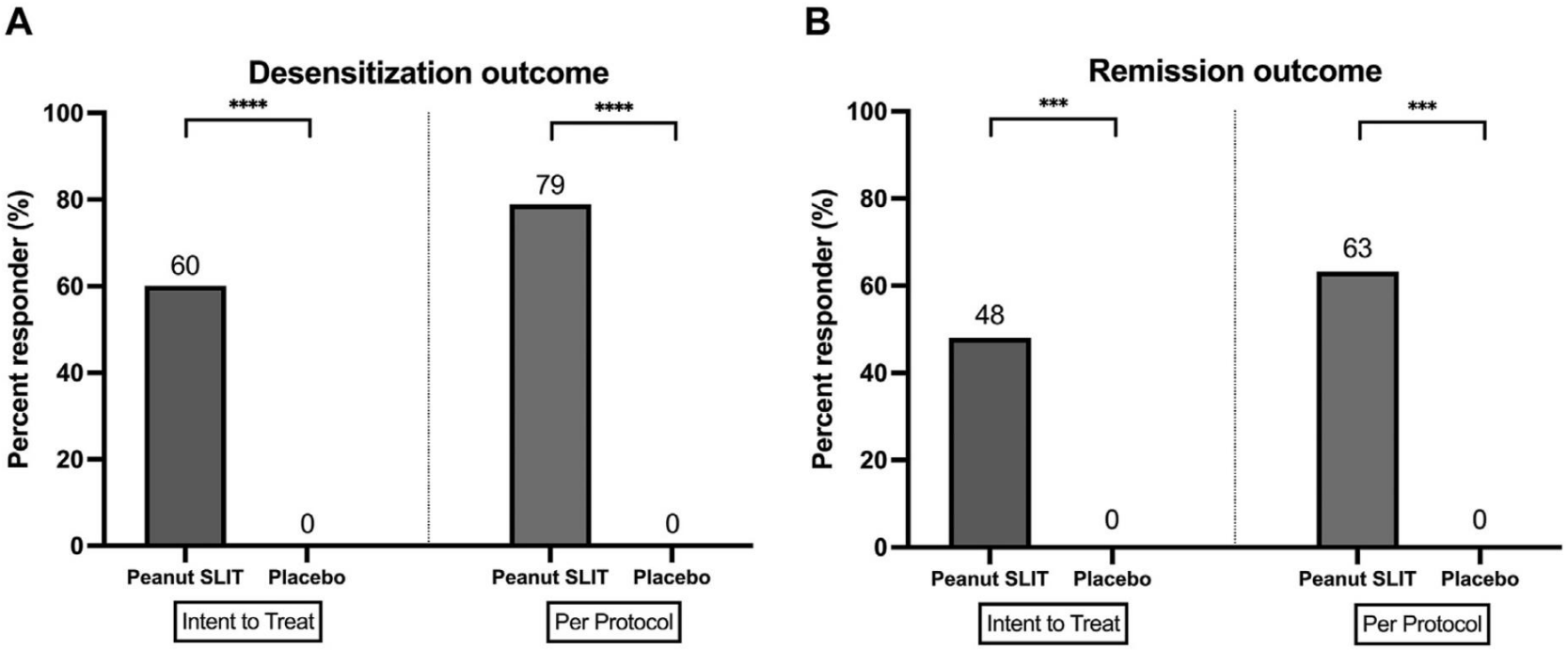


FIG 2. Percentage of participants passing peanut oral food challenge during **(A)** month 36 desensitization DBPCFC and **(B)** month 39 remission DBPCFC. ITT group includes 25 participants per arm. PP group includes 19 peanut SLIT and 17 placebo participants. ***$P = .005$, ****$P < .0001$.

Peanut SLIT Study Results

- In 18 children, aged 1 to 11 years old, 2 mg of peanut SLIT for 12 months increased the reaction threshold to 1,710 mg of peanut protein in the peanut treatment arm compared to 85 mg of those on placebo, which was maintained over an extended 3-5 years (*12*).

- In comparison, peanut reactions are often caused by the ingestion of less than 100 mg of peanut (*13*). There were no dropouts and most adverse reactions were oropharyngeal that uncommonly required treatment. SLIT therapy significantly reduced wheal size to peanut skin prick tests (SPTs) from 11.8 to 7.8 mm (medians), and after 5 years of therapy, peanut specific IgE levels decreased from a median of 83.9 to 20 kU/L. Basophil activation decreased across all 4 concentrations of crude peanut extract tested.

Comparison to Peanut OIT Study Results –PALISADE Trial

- In a follow-up, open-label trial of these participants, it was demonstrated that longer daily dosing for up to 2 years resulted in improved safety and efficacy, and that daily dosing regimens for longer durations were superior to non-daily regimens (i.e., every other day, twice weekly).

- 81% of children receiving 300 mg daily dosing regimen for 2 years tolerated a 2,000 mg challenge during an exit DBPCFC.

Observational Trials Support Safety and Efficacy in OIT

- Soller, JACI Pract 2019, First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy
- Soller, JACI Pract 2020, First Real-World Effectiveness Analysis of Preschool Peanut Oral Immunotherapy
- Soller JACI Pract 2022 Real-world peanut OIT in infants may be safer than non-infant preschool OIT and equally effective
- Soller JACI Pract 2023 Real-World Safety Analysis of Preschool Tree Nut Oral Immunotherapy
- Shaker, JACI Pract 2021, The Cost-Effectiveness of Preschool Peanut Oral Immunotherapy in the Real-World Setting
- Wasserman, JACI Pract 2019 Real-World Experience with Peanut Oral Immunotherapy: Lessons Learned From 270 Patients

First Real-World Safety Analysis/Effectiveness of Preschool Peanut OIT – Soller et al.

270 Canadian preschoolers

- 90% Reached targeted maintenance of 1 peanut daily
- 68% Had OIT reactions - most mild/moderate, 1 severe
- 11 Received epi (4%)

Follow up: 1 year on 1 peanut daily

- 79% Passed 13 peanuts
- 98% Passed > 3 peanuts

First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy
Lianne Soller, PhDa,b lsoller@bcchr.ca · Elissa M. Abrams, MDb,c,d · Stuart Carr, MDe · … · Nicole J. Lee, MSca,b · Scott B. Cameron, MD, PhDb,j,* · Edmond S. Chan, MDa,b,*

Sub-Analysis of the Soller et al. cohort in 2022

- 62/69 (90%) infants reached maintenance
- Infants who completed Build-up had fewer grade 2+ reactions during baseiine OFC or build-up
- Infants had no grade 2+ reactions during follow-up 13 peanut challenges
- In terms of safety, infants who completed P-OIT buildup had fewer grade 2+ reactions during baseline OFC or P-OIT buildup than did NI-preschoolers (33.9% vs 53.7%; *P* = .002) (Table I).
- One infant (1.60%) received epinephrine (during build-up), compared with NI-preschoolers (5.90%), although this difference was not statistically significant

Soller JACI Pract 2022 Real-world peanut OIT in infants may be safer than non-infant preschool OIT and equally effective.

Preschool Tree Nut OIT

- 92 patients started Tree Nut-OIT
  - 79 (85.9%) underwent single-food TN-OIT
  - 13 (14.1%) underwent multi-food TN-OIT to 2 (10.8%) or 3 (3.3%) Tree Nuts
- Eighty-nine (96.7%) patients reached maintenance
- Sixty-five (70.7%) patients experienced reactions during buildup:
  - 35 (38.0%) grade 1 reactions
  - 30 (32.6%) grade 2 reactions
  - no grade 3 or 4 reactions
  - 2 (2.17%) received epinephrine

Each year of delay after age 5 decreases the likelihood of success by 17%.

Wasserman JACI Pract 2019

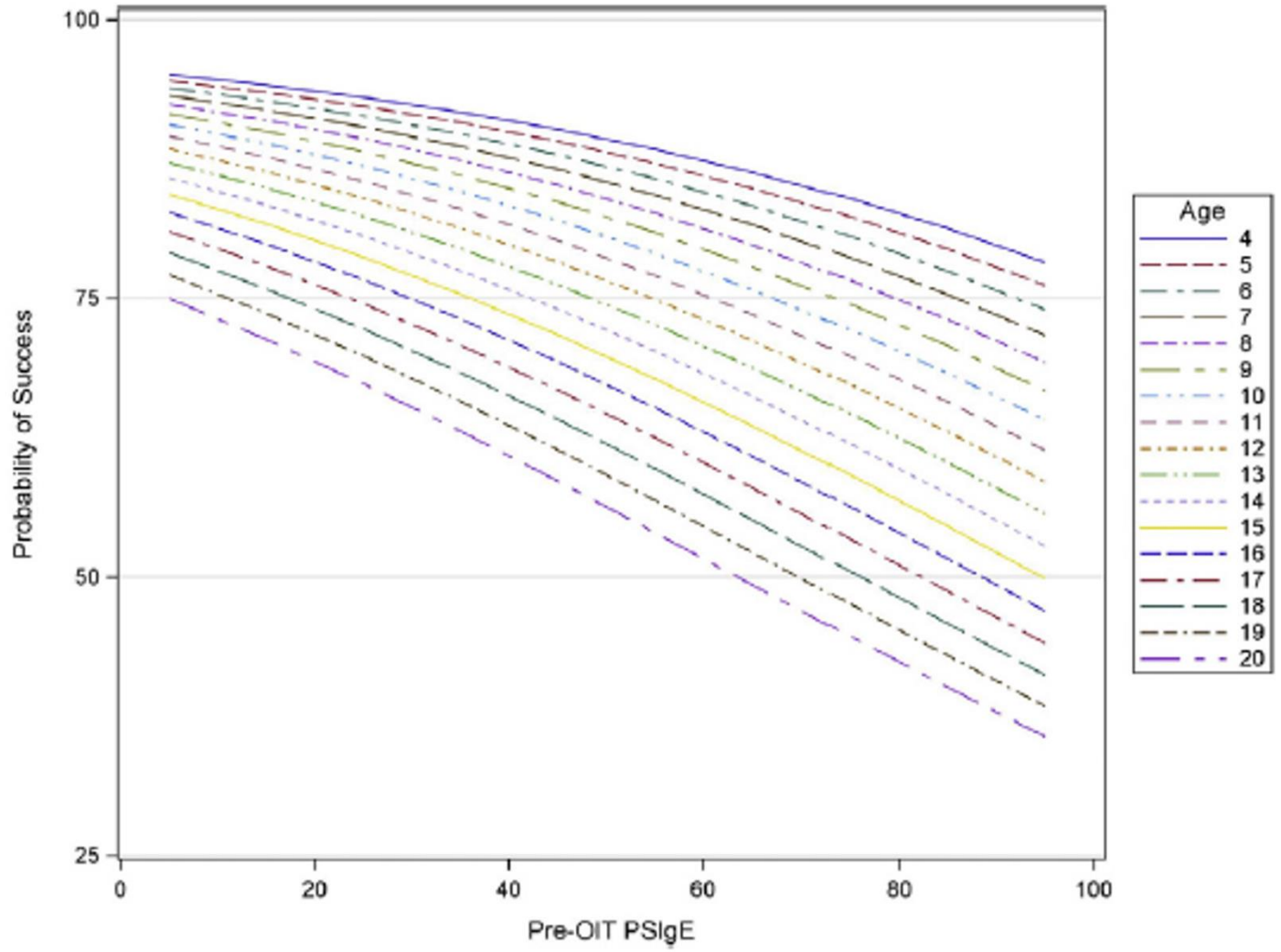


FIGURE 4. The probability of reaching the escalation target based on pretreatment PSIgE level and age at the start of therapy.

Infant OIT is safe and manageable: real world data

- **Huang et al. (2025)** reported on the safety and feasibility of peanut, tree nut, and sesame OIT in infants and toddlers (≤24 months) in a real-world setting.
  - This retrospective study found that OIT was generally safe, with most adverse reactions being mild and no cases requiring epinephrine or emergency care.
  - No increased adverse outcomes were observed on multifood OIT.
  - The majority of infants tolerated at-home updosing (73%), supporting the feasibility of OIT in this age group
  - 51.9% had no reactions while updosing. Some had low-grade cutaneous reactions, none requiring epinephrine or emergency evaluation.

- Link: https://pubmed.ncbi.nlm.nih.gov/39357559/

- **Barten et al. (2023)** reviewed current evidence and mechanisms for OIT in preschool children, highlighting that early OIT (e-OIT) in children under 4 years shows higher rates of desensitization, sustained unresponsiveness, and reduced AEs.

    - **Desensitization rates: 70–90% and sustained unresponsiveness (SU) rates: 20–70%**
    - Most adverse events are mild to moderate, with systemic reactions requiring epinephrine occurring in a minority (approximately 20% of participants in the IMPACT trial required epinephrine at least once during OIT).
    - No deaths or life-threatening events were reported, and the majority of reactions were managed with antihistamines or observation

- Link: https://pubmed.ncbi.nlm.nih.gov/38010006/

OUtMATCH Study (Omalizumab for the Treatment of Multiple Food Allergies)

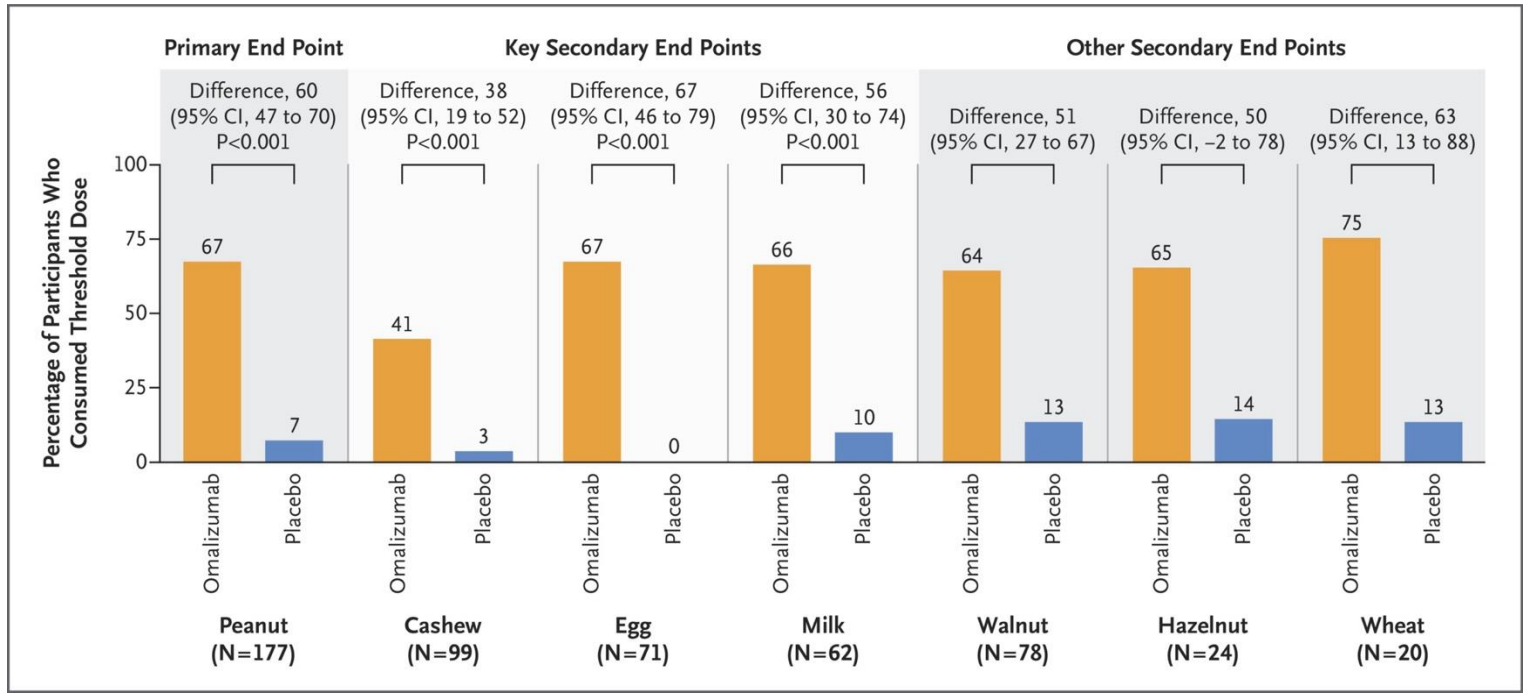
1 to 55 years of age; allergic to peanuts and at least two other trial-specified foods (cashew, milk, egg, walnut, wheat, and hazelnut) were screened.

Reacted to 100 mg or less of peanut protein and 300 mg or less of the two other foods.

Randomized 2:1 (omalizumab vs placebo every 2 to 4 weeks for 16 to 20 weeks, after which the challenges were repeated.

Primary end point = ingestion of peanut protein in a single dose of 600 mg or more without dose-limiting symptoms

OUtMATCH – Illustration of Phase 1 Read Out



Treatment of Multi-Food Allergy with Omalizumab Compared to Omalizumab-Facilitated Multi-Allergen OIT – Phase 2 Read-out

- Double-blind multi-allergen OIT and placebo omalizumab vs omalizumab/placebo OIT.
- Initially, all participants received 16 weeks of open-label omalizumab; at Week 9 OIT/placebo-OIT was initiated and was escalated to a maintenance goal of 1000mg for each participant's study-specific foods.
- At week 16 participants transitioned to blinded injection therapy (omalizumab or placebo) for **44 weeks** before being re-challenged (**cumulative 8044mg protein/food**). T
- 117 participants were included (55% male, median age 7 years). **51/58 (88%)** in the omalizumab group and **30/59 (51%)** in the OIT group completed Stage 2. In the intent-to-treat analysis of the primary endpoint, omalizumab was superior to OIT (success 36% versus 19%, OR 2.6, P=0.031).
- ***Conclusion****: Omalizumab was superior to multi-allergen OIT in the treatment of multi-food allergy. These differences were largely driven by the high rate of AEs*

My conclusion: For the Xolair vs. OIT, superiority was based drop-outs w/ the OIT group (considerably higher than other OIT studies)

- What were the reactions?
- What was the escalation protocol?
- What would have happened w/ a lower maintenance dose, longer time to maintenance, SLIT.
- High variation in drop-out rates between studies

How I Select Preschool OIT Candidates

Are they likely to outgrow peanut allergy?

- **Is resolution likely or in-process?**
- **Severity of reaction**
- **Severity of eczema**
- **Testing 95% PPV persistent allergy:**

1 yo 13 mm wheal, sIgE 5 **Peters, JACI 2015**

2 yo 6 mm wheal, sIgE 3 **HO, JACI 2008**

- **Uncontrolled or severe asthma?**
- **Windom Allergy: sIgE/total IgE, repeat testing in 6 mon**
- **Proactive Parents/Anxiety/Shared Decision**

Take home points

OIT in infants and preschool children under 4 years old is associated with:

- high rates of desensitization
- moderate rates of sustained unresponsiveness
- an acceptable safety profile