The Evolution of Food Allergy Therapy: Past, Present, and Future

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Disclosures

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- Member, Joint Task Force on Allergy Practice Parameters
- Member of Nutricia, DBV, Aimmune, Kaleo and Monsanto specialty advisory boards and has received honorarium
- Co-chair, Nestle international consensus panel on the use of hydrolyzed formula and received honorarium
- Member, CSACI Food Allergy in Schools Guideline Panel
- Member of the Medical Advisory team for the Allergy and Asthma Foundation of America and the International Association for Food Protein Enterocolitis (nonfinancial)
- Has received honorarium from Thermo Fisher, Symbiotix, Hybrid Health, ClinicalMind, Vindico, Before Brands, multiple state allergy societies for CME/non-CME presentations
- Consultant to Aimmune, Intrommune, Thermo Fisher
- Receiving support from K08-HS024599 (Agency for Healthcare Quality and Research)
- Member of AAAAI EGID, Anaphylaxis, Adverse Reaction to Food committees
- Co-chair, AAAAI Primary Prevention of Food Allergy Working Group; Co-chair, AAAAI Oral Immunotherapy Office-based Practice Working Group
- Member ACAAI Annual Meeting Planning Committee, Chair, GI/Food Allergy Track chair; Chair, Food Allergy Committee
- ACAAI representative to consensus statement on interim consensus on early peanut introduction guidelines
- Member, NIAID Expert Panel on early introduction of peanut to prevent peanut allergy
- Associate Editor, *Annals of Allergy, Asthma, and Immunology*
- Editorial board: *Allergy and Rhinology*; *Medscape Pediatrics*; *Infectious Diseases in Children*
- Member, Scientific Advisory Council, National Peanut Board
- Member, EAACI Task Force on Nutrition and Immunomodulation

Goals

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- Recognize OIT, EPIT and their present potential risks and benefits
- Identify potential alternative approaches to treating food allergy
- Consider how to define and track safety as an outcome in therapy

OIT, oral immunotherapy.

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Fast-tracked Approaches to Treatment

Oral and Epicutaneous Immunotherapy

OIT: What Do We Know?

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- OIT involves slow medically supervised re-feeding of increasing doses of one's allergen
- Many achieve some degree of desensitization
  - Threshold increased for most, but not all, but few develop sustained unresponsiveness
  - No indication of the duration of therapy, or how long the effects last
- Fairly equal effects were seen with milk, egg, peanut in ability to achieve desensitization
- Markers of allergen sensitivity diminish significantly
  - See shift in allergen-specific IgE >IgG_4 and part of allergen recognized
- See variable effect of immune cell shut down
  - No consistent biomarker pattern shown, but are many targets of interest

Buchanan et al *J Allergy Clin Immunol* 2007; 119: 199-205; Blumchen et al *J Allergy Clin Immunol* 2010: 126: 83-91. Hofman et al. *J Allergy Clin Immunol* 2009: 124: 1154-60. Jones SM et al *J Allergy Clin Immunol* 2009: 124: 292-300. Skripak et al *J Allergy Clin Immunol* 2008; 122: 1154-60; Narisety et al *J Allergy Clin Immunol* 2009; 124: 610-12. Varshney et al *J Allergy Clin Immunol* 2011: 127: 654-60. Kim et al *J Allergy Clin Immunol* 2011; 127 640-6. Burks et al. *N Engl J Med* 2012; 367:233-243. Fleischer et al *J Allergy Clin Immunol* 2013: 131: 119-27

“Typical” OIT Protocol

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Buchanan et al *J Allergy Clin Immunol* 2007; 119: 199-205; Blumchen et al *J Allergy Clin Immunol* 2010: 126: 83-91. Hofman et al. *J Allergy Clin Immunol* 2009: 124: 1154-60. Jones SM et al *J Allergy Clin Immunol* 2009: 124: 292-300. Skripak et al *J Allergy Clin Immunol* 2008; 122: 1154-60; Narisety et al *J Allergy Clin Immunol* 2009; 124: 610-12. Varshney et al *J Allergy Clin Immunol* 2011: 127: 654-60. Kim et al *J Allergy Clin Immunol* 2011; 127 640-6. Burks et al. *N Engl J Med* 2012; 367:233-243. Fleischer et al *J Allergy Clin Immunol* 2013: 131: 119-27

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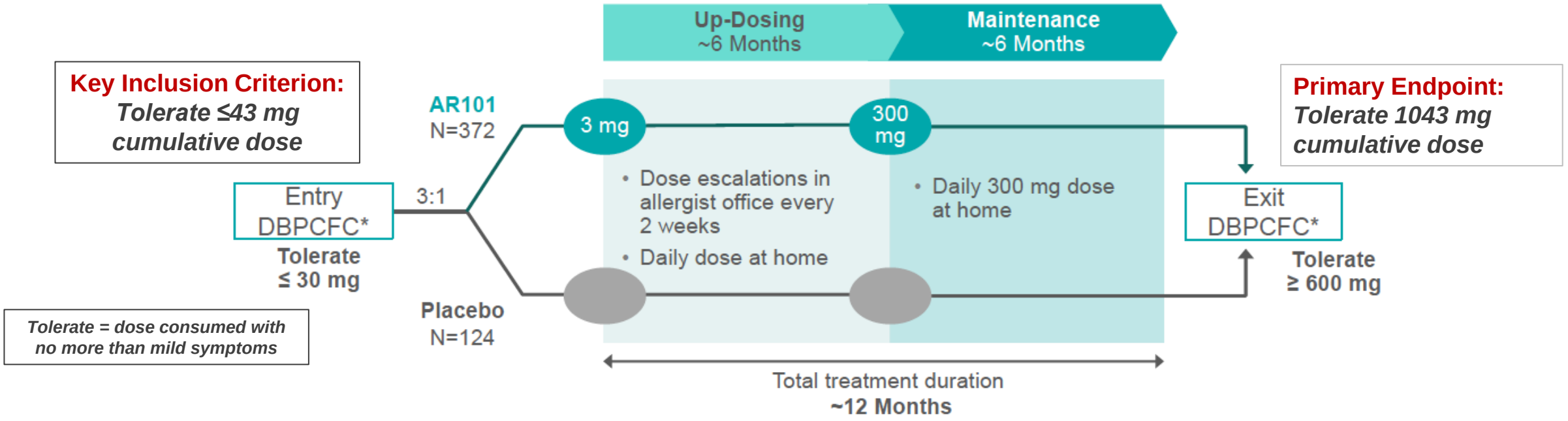
PALISADES Entry Characteristics



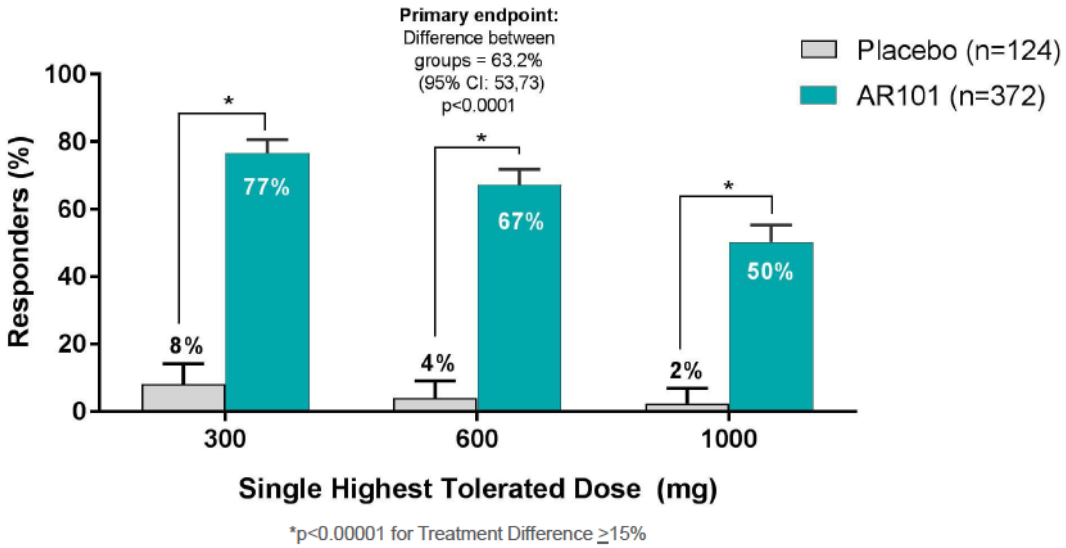
- 90% were ages 4-17 years
- 72% had history of anaphylaxis, 53% had asthma, 66% with multiple food allergies
- 43% had peanut sIgE > 100 KU/L
- Median entry OFC challenge tolerance was 10mg (1/30th peanut)
- Entry/exit criteria different—very strict no tolerance on the entry challenge, but at the exit challenge were allowed to have “mild” symptoms per investigator discretion

Jones et al. PALISADES Phase III data presentation, 2018 AAAAI. Obtained from www.aimmune.com publically available slide deck

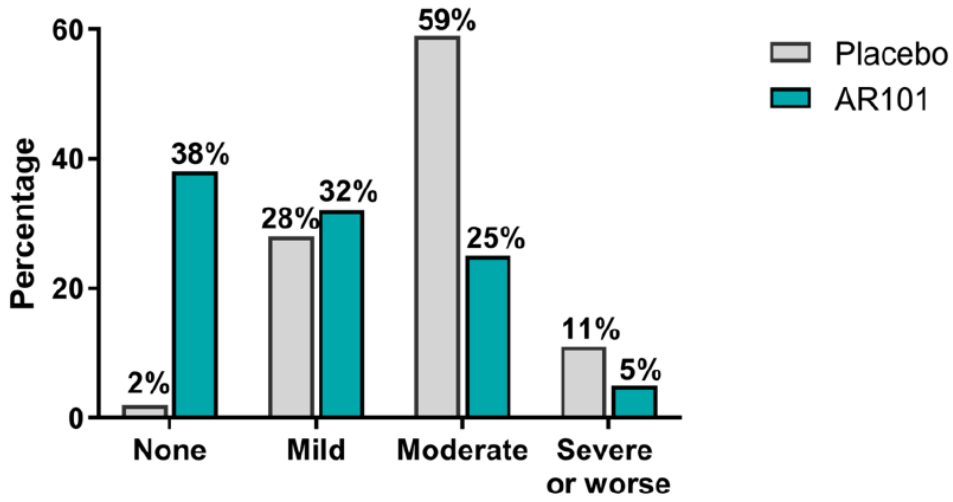
PALISADES Main Results

Intention to treat population

Patients Ages 4-17 Who Tolerated Each Dose Level at Exit DBPCFC



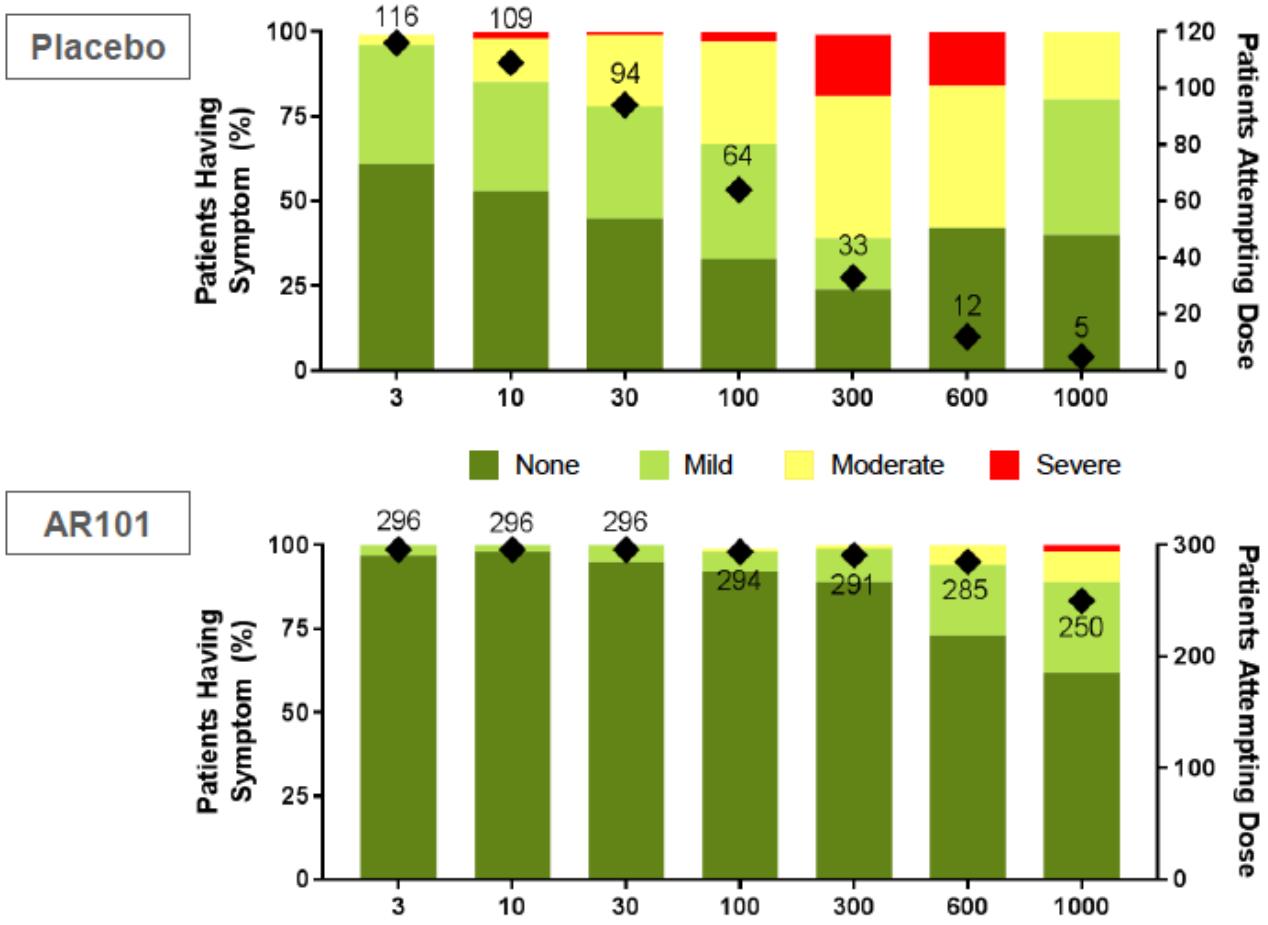
Exit DBPCFC Severity



- NNT of 1.58 (ARR 63.2%) for primary endpoint
- NNT of 2.08 (ARR 48%) for secondary endpoint
- 44% with sIgE >100 kU/L tolerated 1000mg

Vickery et al NEJM 2018; 379:1991-2001

PALISADES End OFC Characteristics



Epinephrine Use†	AR101	Placebo
None	268 (91%)	54 (47%)
1	25 (8%)	43 (37%)
2	3 (1%)*	17 (15%)
≥ 3	0	2 (2%)

†p<0.0001 for overall between-group difference
* One patient at 600 mg and two patients at 1000 mg

Key Findings

Compared to placebo, the AR101 group:

1. Developed fewer moderate and severe symptoms;
2. Required more peanut exposure for the onset of symptoms;
3. Was more likely to complete the challenge;
4. Needed less epinephrine

Vickery et al NEJM 2018; 379:1991-2001 and a table obtained from www.aimmune.com

PALISADES Safety

	AR101 (N=372)	
	%	N
Total discontinuations regardless of causality	20.4%	76
Discontinuations not related to adverse events	8.0%	30
Discontinuations related to adverse events	12.4%	46
• Gastrointestinal	6.7%	25
• Systemic hypersensitivity reactions	2.7%	10
• Respiratory system	1.1%	4
• Cutaneous	0.8%	3
• Other (e.g., eye pruritus)	1.1%	4

62 of the 76 dropouts (~82%) occurred during up-dosing

7 were anaphylaxis (6 mild or moderate, 1 severe)

	AR101 (n=372) n (%)	Placebo (n=124) n (%)
Withdrawals not due to AEs	37 (9.9)	7 (5.6)
Withdrawals due to AEs, total and by category*	43 (11.6)	3 (2.4)
• Acute / chronic / recurrent GI†	24 (6.5)	2 (1.6)
• Systemic allergic reactions‡	7 (1.9)	0
• Respiratory system	11 (3.0)	3 (2.4)
• Skin and subcutaneous	5 (1.3)	2 (1.6)
• Other*	14 (3.8)	0

- 9 SAE in 8 participants (2.2%), 1 placebo SAE, 4 “related” events, 5 prompted discontinuation
- 1 case of anaphylaxis in early maintenance (high baseline sIgE)
- 1 case of EoE developed, patient withdrew (2 others underwent endoscopy)
- 14.5% experienced investigator reported systemic hypersensitivity reactions, 98% of which were considered mild or moderate (using WAO SCIT criteria)

Vickery et al NEJM 2018; 379:1991-2001 and a table obtained from www.aimmune.com publically available slide deck

Overall PALISADE Events

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Table 2. Adverse Events Affecting More Than 5% of the Participants 4 to 17 Years of Age in Either Group, According to Trial Phase.*

Event	Initial Dose-Escalation Phase		Increasing-Dose Phase		Maintenance Phase		Overall	
	AR101 (N=372)	Placebo (N=124)	AR101 (N=366)	Placebo (N=123)	AR101 (N=310)	Placebo (N=118)	AR101 (N=372)	Placebo (N=124)
	number of participants with event (percent)							
≥1 Adverse event	189 (50.8)	36 (29.0)	353 (96.4)	108 (87.8)	270 (87.1)	94 (79.7)	367 (98.7)	118 (95.2)
Abdominal pain	83 (22.3)	8 (6.5)	156 (42.6)	25 (20.3)	46 (14.8)	7 (5.9)	194 (52.2)	30 (24.2)
Vomiting	15 (4.0)	0	127 (34.7)	22 (17.9)	50 (16.1)	14 (11.9)	154 (41.4)	30 (24.2)
Upper abdominal pain	9 (2.4)	3 (2.4)	136 (37.2)	17 (13.8)	41 (13.2)	9 (7.6)	152 (40.9)	26 (21.0)
Oral pruritus	36 (9.7)	8 (6.5)	131 (35.8)	15 (12.2)	39 (12.6)	5 (4.2)	151 (40.6)	20 (16.1)
Nausea	31 (8.3)	1 (0.8)	128 (35.0)	22 (17.9)	45 (14.5)	8 (6.8)	146 (39.2)	29 (23.4)
Oral paresthesia	4 (1.1)	2 (1.6)	57 (15.6)	5 (4.1)	23 (7.4)	2 (1.7)	65 (17.5)	8 (6.5)
Lip swelling	2 (0.5)	0	25 (6.8)	3 (2.4)	13 (4.2)	2 (1.7)	38 (10.2)	5 (4.0)
Cough	10 (2.7)	0	117 (32.0)	30 (24.4)	61 (19.7)	22 (18.6)	152 (40.9)	42 (33.9)
Throat irritation	28 (7.5)	5 (4.0)	131 (35.8)	26 (21.1)	43 (13.9)	11 (9.3)	152 (40.9)	34 (27.4)
Rhinorrhea	6 (1.6)	1 (0.8)	82 (22.4)	25 (20.3)	46 (14.8)	9 (7.6)	113 (30.4)	28 (22.6)
Sneezing	16 (4.3)	3 (2.4)	76 (20.8)	15 (12.2)	33 (10.6)	5 (4.2)	98 (26.3)	18 (14.5)
Throat tightness	14 (3.8)	3 (2.4)	70 (19.1)	6 (4.9)	20 (6.5)	0	86 (23.1)	8 (6.5)
Dyspnea	2 (0.5)	1 (0.8)	32 (8.7)	3 (2.4)	17 (5.5)	1 (0.8)	44 (11.8)	5 (4.0)
Dysphonia	1 (0.3)	0	19 (5.2)	2 (1.6)	8 (2.6)	1 (0.8)	25 (6.7)	2 (1.6)
Pruritus	25 (6.7)	8 (6.5)	117 (32.0)	25 (20.3)	45 (14.5)	14 (11.9)	153 (41.1)	34 (27.4)
Urticaria	16 (4.3)	3 (2.4)	115 (31.4)	23 (18.7)	63 (20.3)	17 (14.4)	143 (38.4)	30 (24.2)
Rash	12 (3.2)	1 (0.8)	61 (16.7)	15 (12.2)	24 (7.7)	7 (5.9)	81 (21.8)	18 (14.5)
Chest discomfort	2 (0.5)	0	19 (5.2)	1 (0.8)	8 (2.6)	0	24 (6.5)	1 (0.8)
Systemic allergic reaction†	1 (0.3)	0	31 (8.5)	2 (1.6)	27 (8.7)	2 (1.7)	53 (14.2)	4 (3.2)
Ear pruritus	3 (0.8)	0	23 (6.3)	0	7 (2.3)	0	25 (6.7)	0

* The data in the maintenance-phase and overall columns exclude symptoms that were recorded during the exit double-blind, placebo-controlled food challenge.
† Events of systemic allergic reaction included one case of severe anaphylaxis in the active-drug group during the maintenance phase.

- 98% had 1 event
- 96% had 1 event in build up
- 87.8% had one event in maintenance
- Fairly equal numbers of systemic allergic reactions occurred in build up and maintenance phase
- GI issues in build up were the predominant issue reported

Vickery et al NEJM 2018; 379:1991-2001

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Other OIT with Published Outcomes

PPOIT and 4-Year Outcomes

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- Teng et al. demonstrated efficacy of 18 months of a novel peanut OIT + Lactobacillus Rhamnossus CGMCC combination in a 2015 double blind, randomized controlled study
- Initial effect demonstrated successful desensitization in 26/29 PPOIT patients and 2 week sustained unresponsiveness in 23/28 of these patients
- Probiotic dose the equivalent of "20 tubs" of yogurt/day!
- Now, following 48 of the original 56 participants for 4 years after discontinuation of OIT
- N=24 PPOIT and n=24 placebo patients followed after exit food challenge
- No set protocol for peanut ingestion in the PPOIT group
- At 4 years, both groups asked to discontinue peanut ingestion for 8 weeks and repeat challenge

Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105.

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PPOIT and 4-Year Outcomes

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- Noted 16/24 PPOIT vs. 1/24 subjects were regularly ingesting peanut ad libitum (NNT 1.6)
- Half of the PPOIT subjects were eating >2g/week(46% 1x/wk, 29% 1-2x/wk, 17% 3x or more/wk, with 16/20 PPOIT subjects consuming peanut "regularly", and 20/24 reporting no reactions since stopping PPOIT therapy
- N=27 agreed to the 8 week additional discontinuation. Of these 7/12 PPOIT vs. 1/15 placebo tolerated the challenge and resumed eating peanut (NNT=1.9)
- 7/12 who underwent PPOIT ate peanut ad lib for 4 years, then agreed to stop eating peanut for another 8 weeks demonstrated sustained unresponsiveness. ***This pattern mimics a non-allergic individual's consumption!***
- Study issues: no initial challenge for the 2015 study, some degree of drop out, small #'s
- ***The implications of this effect, if replicated, may completely change the game***

Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105..

“Non-proprietary” Peanut OIT Outcomes

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- Retrospective review of n=270 patients treated at a large Texas practice since 2009
- Inclusive of clinical observations of patients ages 4-18 in an office setting
- 214/270 reached 3g maintenance (3 w/reduced 2g target), 50% by 6 mo, 93% by 12 mo
  - All but 1 reaching 3g tolerated a 6g challenge
  - All offered ad libitum ingestion, but most stayed at 2g maintenance, 13 reduced dose for aversion
  - 63/270 (23%) required epi in escalation, predicted by asthma and starting sIgE; n=28 got epi in maintenance, linked to lack of adjusting dose for illness/exercise
  - ELORS experienced by 37 (13%), with 21 continuing therapy and 13 reaching maintenance
  - Of the 48 who dropped out in escalation, 65% either had ELORS or received epi
  - N=14/19 who volunteered for a 30d SU trial passed a 6g challenge

Wasserman et al J Allergy Clin Immunol Pract 2019; 7: 418-26

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“Non-proprietary” Peanut OIT Outcomes

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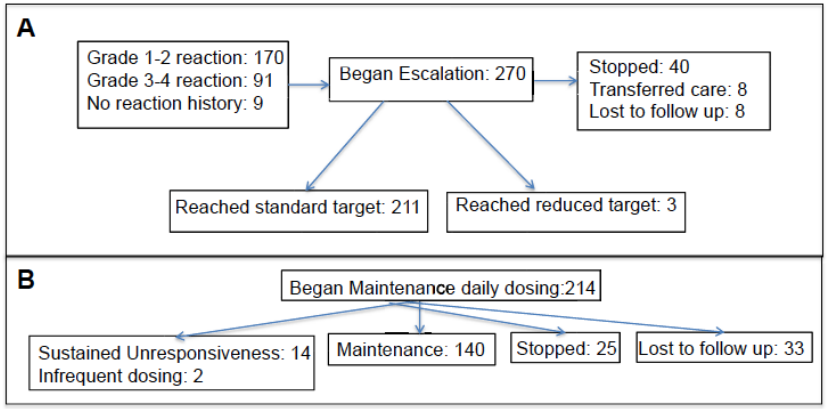

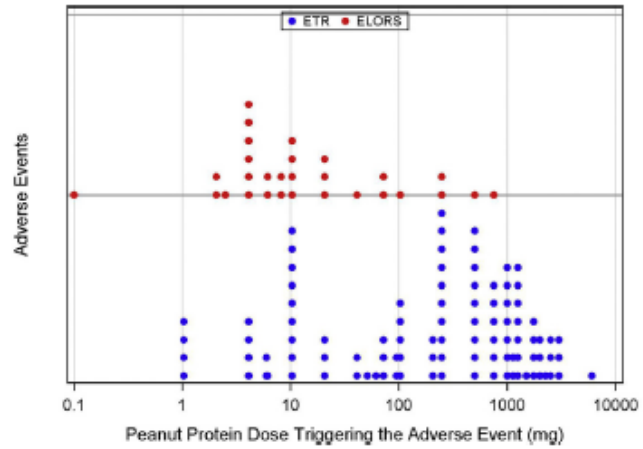

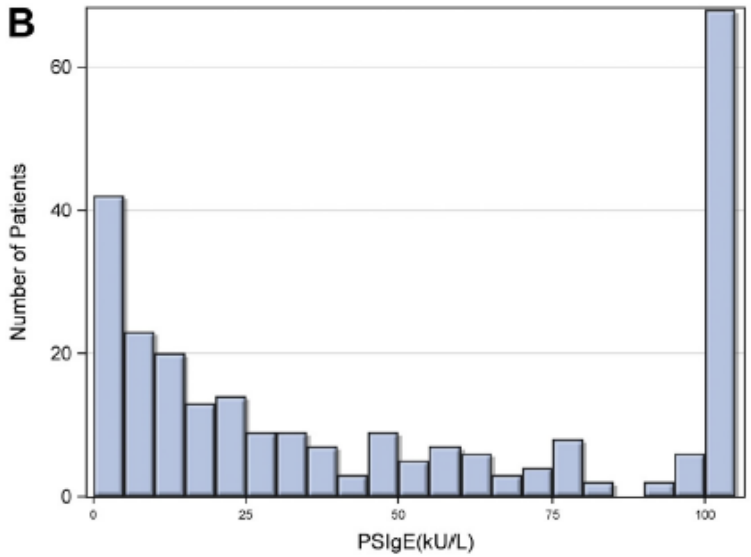

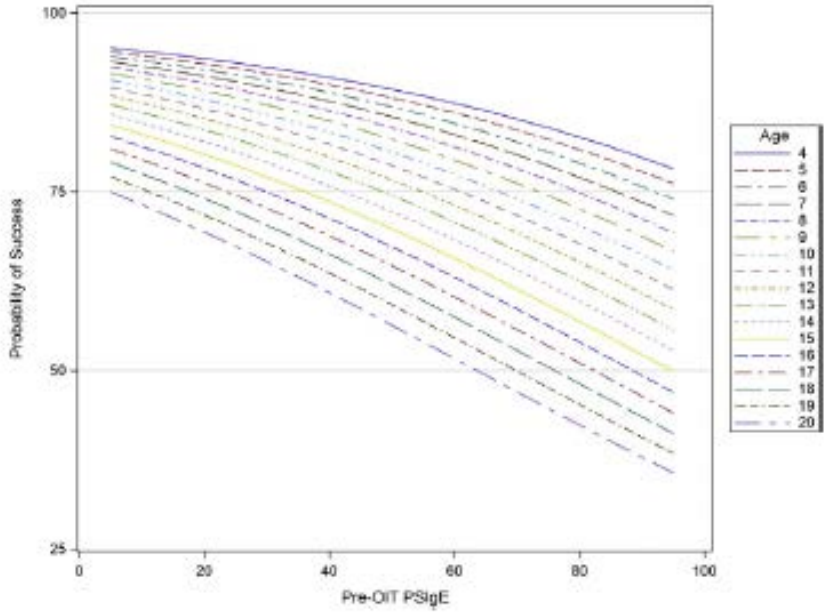

Wasserman et al J Allergy Clin Immunol Pract 2019; 7: 418-26

DEVIL Study: OIT in the Very Young

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- Safety and efficacy study of peanut OIT in 9-36mo olds—is this age more amenable to tx?
- 37 children randomized to 36 mo of 300mg or 3g peanut OIT, with 4 week 5g SU trial
- No entry challenge done, compared to a historical control group
  - 30/37 (81%) reached desensitization maintenance per goal of arm (78% 300mg, 71% 3g)
  - 17/20 (85%) in the 300mg vs 12/17 (71%) in the 3g achieved 4-week SU
  - 6/19 (32%) of a selected sample from the control group passed OFC
  - Immunomodulation in terms of lowered IgE and increased IgG4 seen in both treatment groups

Vickery et al J Allergy Clin Immunol 2017;139:173-81

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Other Published Peanut OIT Trials

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Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Jones et al	2009	Open label	29	1-16	1800	36 mo	93% passed 3.9-g peanut OFC
Blumchen et al	2010	Randomized open label	23	3-14	500	7-d Rush escalation, 8-wk maintenance period	64% reached maintenance of 500 mg of peanut
Varshney et al	2011	Randomized, placebo controlled	19	3-11	2000	48 wk	84% passed 5000-mg peanut OFC
Anagnostou et al	2011	Open label	22	4-18	800	32 wk	64% tolerated 6.6-g OFC
Anagnostou et al	2014	Randomized, controlled	39	7-16	800	26 wk	62% tolerated 1400-mg challenge
Vickery et al	2014	Open label	24	1-16	Up to 4000	Up to 5 y	50% SU to 5000-mg OFC after 4-wk avoidance
Narisety et al	2014	Randomized, placebo controlled	16	7-13	2000	12 mo	OIT > SLIT in OFC threshold, low rate of SU
Factor et al	2012	Open, uncontrolled	93	5-18	450 (3 M&M)	24 wk	90/100 pts able to tolerate 450 mg, showed improvement in pt FAQLQ score. Clinic-based study
Wasserman et al	2014	Open label	352	Median 5-9 y	415-8000	Variable, Weeks-yrs	Real-life experience of 5 practices. 281/352 (80%) reached maintenance. 10% of pts required epi (36/352)
Tang et al	2015	Randomized, placebo controlled	62	1-10	2 g with $2x10^2$ CFU *L. rhamnosu*	18 mo	23/28 (82.1%) vs 1/28 (3.6%) achieved SU at 2-5 wk post-discontinuation. 26/29 achieved desensitization.
Vickery et al	2016	Randomized, placebo controlled	40	9-36 mo	300 vs 3000	Up to 3 y	17/20 in 300-mg and 12/17 in 3000-mg arm achieved SU at 4 weeks (29/37 total)

Wood R. *J Allergy Clin Immunology* 2016: 137: 973-82. Tang et al *J Allergy Clin Immuno* 2015; 135: 737-44. Factor J et al. *Ann Allergy Asthma Immunol* 2012; 109: 348-52. Wasserman et al *J Allergy Clin Immunol Pract* 2014; 2; 91-6. Vickery et al *J Allergy Clin Immunol* 2017; 139: 173-181. Hsiao K-C et al *Lancet Child Adolesc Health* 2017; 1: 97-105.

Published Egg and Milk OIT Studies

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TABLE II. Egg OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (g)	Duration (mo)	Primary outcome
Buchanan et al[34]	2007	Open label	7	1-16	0.3	24	57% Passed 8-g OFC
Vickery et al[35]	2010	Open label	8	3-13	0.3-3.6	18-50	75% Passed OFC 1 mo after stopping OIT
Burks et al[26]	2012	Randomized, placebo controlled	40	5-11	1.6	22	75% Passed 10-g OFC but SU in only 28% at 6-8 wk later

TABLE III. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al[36]	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al[37]	2008	Randomized, open label	30	5-17	150 mL	10-d Rush escalation, 1 y of maintenance	36% Tolerant (≥150 mL) and 54% partially tolerant (5-150 mL)
Skripak et al[38]	2008	Randomized, placebo controlled	13	6-17	500 mg	23 wk	Median OFC threshold increased from 40 to 5,140 mg after OIT
Narisety et al[31]	2009	Open label (follow-up)	13	6-16	500-4,000 mg	3-17 mo	Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)
Pajno et al[40]	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al[39]	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al[25]	2012	Randomized, placebo controlled	20 for OIT	6-17	1,000-2,000 mg	60 wk	70% Desensitized to 8-g OFC, SU in 40% after 6 wk
Wood et al[41]	2015	Omalizumab DBPC, open-label OIT	57	7-32	3,300 mg	24 mo	80% Desensitized to 10-g OFC, SU in 42% after 8 wk

Wood R. J Allergy Clin Immunology 2016: 137: 973-82

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Defining Safety in Food OIT Trials

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- The condition of being protected from or unlikely to cause danger, risk, or injury: "they should leave for their own safety"; *synonyms:* welfare, well-being, protection, security
- Aim to do no harm, but is this relative standard considering we are re-feeding an allergen?
  - Does safety mean "mutually acceptable/acknowledged risks an investigator promises to minimize"?
  - Can OIT be done with a total absence of symptoms (and is this realistic)?
  - Should AE's be defined at the dose level or patient level?
  - Is there minimum burden that needs to be demonstrated before this is "community" ready vs trial safe?
- Multiple papers have stated that OIT is "safe" but do the data match the perception?
- Should safety statements by necessity include long term outcomes vs. just trial data?
- Are we biased towards only "counting" specific data vs. all available data?

Predicting Symptoms from OIT

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Incidence rate ratios of the influence of baseline characteristics on the prevalence of AEs, overall and during the buildup and maintenance phases of OIT

Variable	Overall AEs		Buildup AEs		Maintenance AEs	
	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Sex (female compared with male)	0.7 (0.4-1.2)	.24	0.6 (0.3-1.0)	.06	1.2 (0.6-2.4)	.54
Age (per 1-y increase)	1.0 (0.9-1.1)	.89	1.1 (0.9-1.2)	.40	1.1 (1.0-1.2)	.20*
Asthma	0.9 (0.5-1.4)	.55	0.6 (0.4-1.1)	.11	2.3 (1.1-4.9)	.03*
Atopic dermatitis	1.2 (0.6-2.2)	.59	1.2 (0.6-2.3)	.63	1.1 (0.5-2.4)	.89
AR	2.9 (1.6-5.0)	<.001*	2.1 (1.2-3.8)	.01*	6.9 (2.5-18.7)	<.001*
Peanut SPT wheal size (per 5-mm increase)	1.4 (1.1-1.7)	.005*	1.4 (1.1-1.8)	.01*	1.3 (1.0-1.8)	.07*
Log peanut IgE (per log increase)	0.9 (0.7-1.0)	.14	0.9 (0.7-1.0)	.10	0.9 (0.7-1.2)	.44

Virkund et al *J Allergy Clin Immunol* 2017; 139: 882-888.e5.

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Predicting Symptoms from OIT

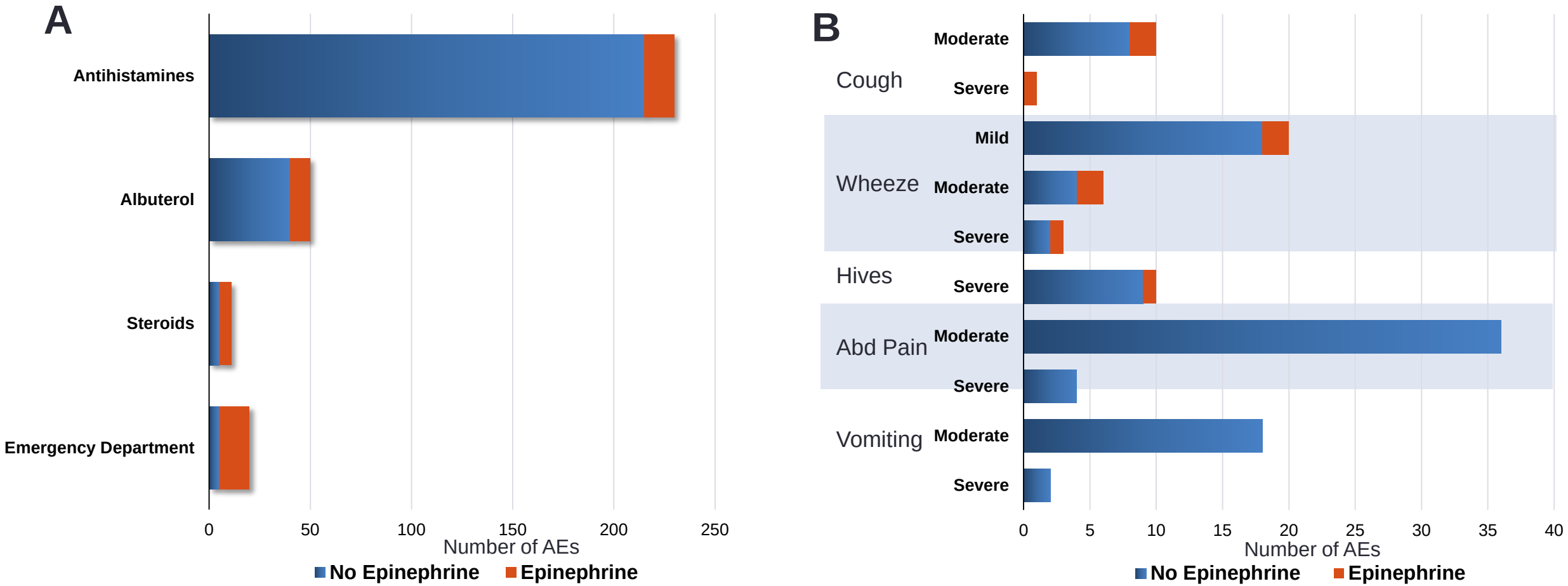

FIG 4. Frequencies of AEs resulting in epinephrine use. Patterns of use of epinephrine concurrently with administration of antihistamines, albuterol, oral corticosteroids, or an ED visit (A), and in response to specific symptoms (cough, wheeze, hives, abdominal [Abd] pain, or vomiting) (B). Overlap of AEs with 2 or more given symptoms (ex: cough and wheeze) may be present.

Virkund et al *J Allergy Clin Immunol* 2017; 139: 882-888.e5

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Is Peanut OIT Safer Than Avoidance

Children's Hospital Colorado

- PACE study meta-analysis of 12 randomized trials (n=1041) of peanut OIT vs. no OIT
- Mean follow up of patients in these studies 5.8 years
- Outcomes of interest included safety (rates of anaphylaxis, rates of severe reactions and reactions by organ system) and efficacy (passed OFC, QoL)
- Goal was to define health benefits of therapy using meta-analysis given concern if it is truly "ready" for routine clinical use
- Formal GRADE systematic review with meta-analysis performed by the McMasters group
- Anaphylaxis rating using NIAID criteria

Chu et al Lancet 2019; DOI 10.1016/S0140-6736(19)30420-9

PACE Study: Key Findings

Children's Hospital Colorado

	Sample size	Risk ratio* (95% CI)	Anticipated absolute effects (95% CI) per 1000 individuals			Grades of evidence	Main findings†‡§
			No OIT	OIT	Risk difference		
Anaphylaxis	9 RCTs; 891 participants	3·12 (1·76–5·55)	71¶	222 (125–394)	151 (54–323)	High	Peanut OIT results in large increase in anaphylaxis; NNT_H 7 (3–19); IRR 2·72 (1·57–4·72)
Epinephrine use‡	9 RCTs; 984 participants	2·21 (1·27–3·83)	37	82 (47 to 142)	45 (10–105)	High	Peanut OIT results in large increase in epinephrine use; NNT_H 22 (10–100); IRR 2·87 (1·70–4·85)
Serious adverse events	12 RCTs; 1041 participants	1·92 (1·00–3·66)	62‖	119 (62–227)	57 (0–165)	Moderate**	Peanut OIT probably increases serious adverse events (death, life threatening, disability, or requiring urgent medical intervention or hospitalisation to prevent these events); NNT_H 18 (6–5376)
Vomiting, representative of gastrointestinal reactions††	6 RCTs; 755 participants	1·79 (1·35–2·38)	186	334 (252–444)	147 (65 to 257 more)	High	Peanut OIT results in large increase in vomiting frequency; NNT_H 6 (4–14); IRR 2·11 (1·54–2·89)
Angioedema, representative of mucocutaneous reactions‡‡	5 RCTs; 694 participants	2·25 (1·13–4·47)	39	88 (44–174)	49 (5 to 135 more)	High§§	Peanut OIT increases angioedema; NNT_H 20 (7–200); IRR 2·51 (1·79–3·51)
Nasal congestion or blockage, representative of respiratory reactions§§	6 RCTs; 724 participants	1·36 (1·02–1·81)	178	241 (181–321)	64 (4 to 144 more)	Moderate¶¶	Peanut OIT probably increases nasal congestion or blockage (rhinitis); NNT_H 16 (7–250); IRR 1·48 (1·04–2·10)
Surrogate for exposure to peanut outside of clinic without a reaction: passing a supervised food challenge in-clinic	9 RCTs; 917 participants	12·42 (6·82–22·61)	32	397 (218–723)	365 (186 to 691 more)	High‖‖	Peanut OIT results in large increase in completing a supervised oral food challenge without an allergic reaction, but this does not translate into less reactions outside of clinic; for every gram increase in total cumulative challenge dose, the chance of passing decreases by 26%; NNT 3 (1–5)

Chu et al Lancet 2019; DOI 10.1016/S0140-6736(19)30420-9

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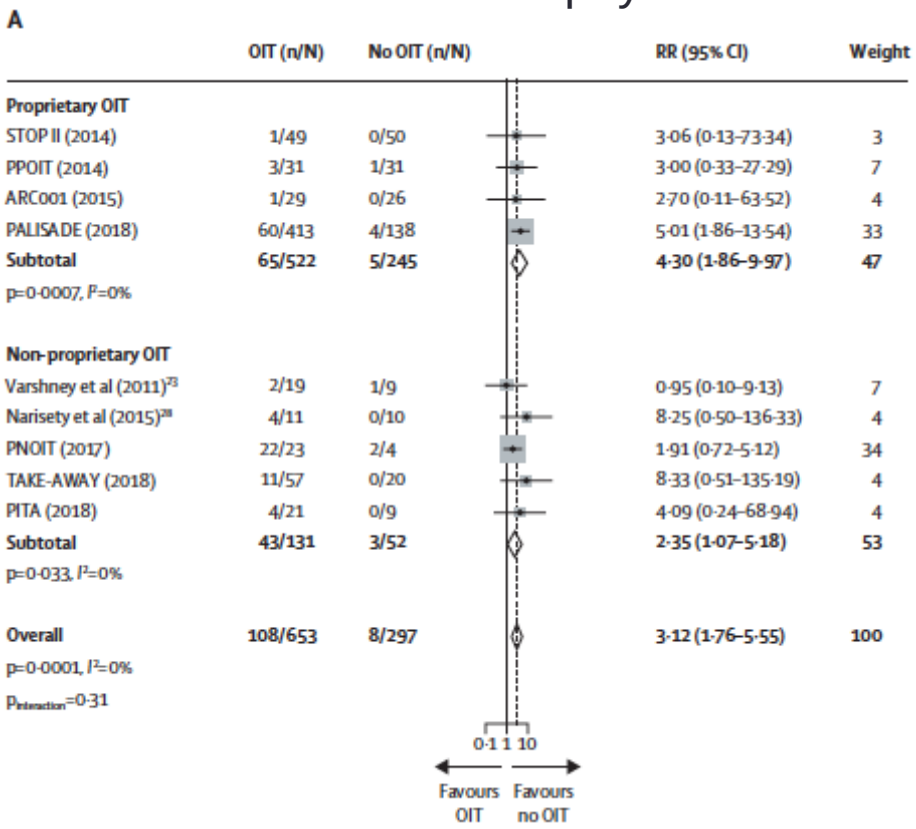
Risk of Anaphylaxis in OIT

Children's Hospital Colorado

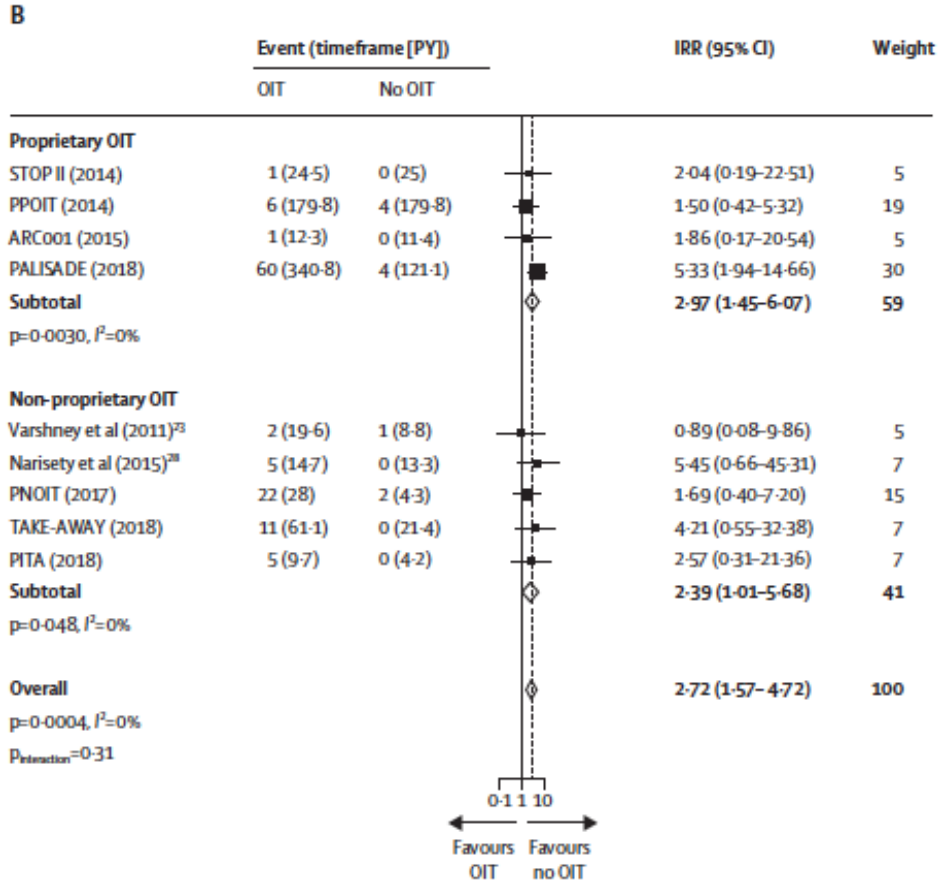
Risk of Anaphylaxis



A

	OIT (n/N)	No OIT (n/N)	RR (95% CI)	Weight
Proprietary OIT				
STOP II (2014)	1/49	0/50	3·06 (0·13–73·34)	3
PPOIT (2014)	3/31	1/31	3·00 (0·33–27·29)	7
ARC001 (2015)	1/29	0/26	2·70 (0·11–63·52)	4
PALISADE (2018)	60/413	4/138	5·01 (1·86–13·54)	33
Subtotal	**65/522**	**5/245**	**4·30 (1·86–9·97)**	**47**
p=0·0007, I^2=0%				
Non-proprietary OIT				
Varshney et al (2011)[23]	2/19	1/9	0·95 (0·10–9·13)	7
Narisety et al (2015)[28]	4/11	0/10	8·25 (0·50–136·33)	4
PNOIT (2017)	22/23	2/4	1·91 (0·72–5·12)	34
TAKE-AWAY (2018)	11/57	0/20	8·33 (0·51–135·19)	4
PITA (2018)	4/21	0/9	4·09 (0·24–68·94)	4
Subtotal	**43/131**	**3/52**	**2·35 (1·07–5·18)**	**53**
p=0·033, I^2=0%				
Overall	**108/653**	**8/297**	**3·12 (1·76–5·55)**	**100**
p=0·0001, I^2=0%				
$p_{interaction}$=0·31				

Frequency of Anaphylaxis



B

	Event (timeframe [PY])		IRR (95% CI)	Weight
	OIT	No OIT		
Proprietary OIT				
STOP II (2014)	1 (24·5)	0 (25)	2·04 (0·19–22·51)	5
PPOIT (2014)	6 (179·8)	4 (179·8)	1·50 (0·42–5·32)	19
ARC001 (2015)	1 (12·3)	0 (11·4)	1·86 (0·17–20·54)	5
PALISADE (2018)	60 (340·8)	4 (121·1)	5·33 (1·94–14·66)	30
Subtotal			**2·97 (1·45–6·07)**	**59**
p=0·0030, I^2=0%				
Non-proprietary OIT				
Varshney et al (2011)[23]	2 (19·6)	1 (8·8)	0·89 (0·08–9·86)	5
Narisety et al (2015)[28]	5 (14·7)	0 (13·3)	5·45 (0·66–45·31)	7
PNOIT (2017)	22 (28)	2 (4·3)	1·69 (0·40–7·20)	15
TAKE-AWAY (2018)	11 (61·1)	0 (21·4)	4·21 (0·55–32·38)	7
PITA (2018)	5 (9·7)	0 (4·2)	2·57 (0·31–21·36)	7
Subtotal			**2·39 (1·01–5·68)**	**41**
p=0·048, I^2=0%				
Overall			**2·72 (1·57–4·72)**	**100**
p=0·0004, I^2=0%				
$p_{interaction}$=0·31				

Finding: In OIT is elevated risk (3.12) and frequency of anaphylaxis vs. no OIT (placebo/avoidance)

Chu et al Lancet 2019; DOI 10.1016/S0140-6736(19)30420-9

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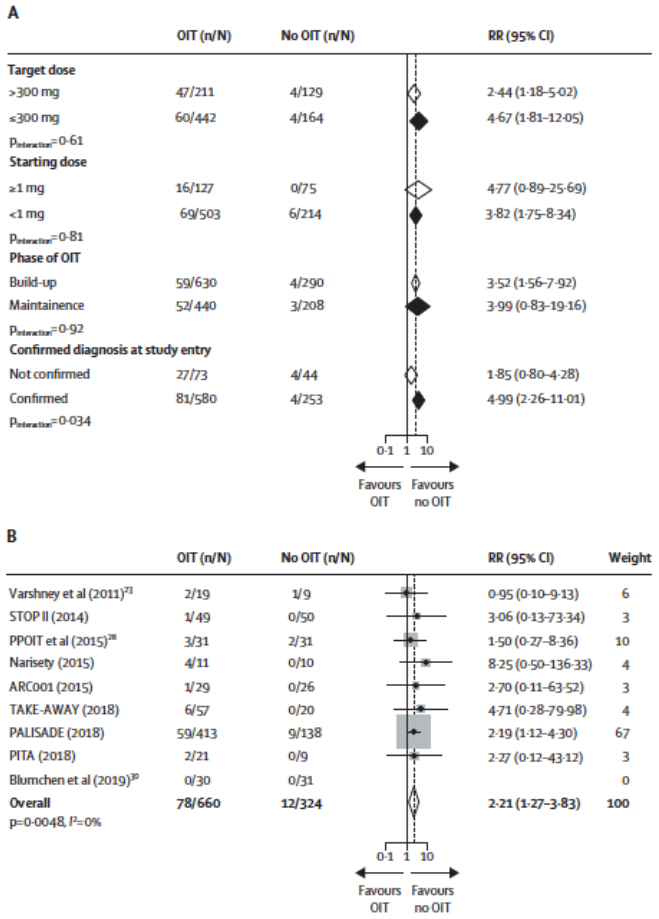
SAE's and Treatment of SAE

Children's Hospital Colorado

Risk of Anaphylaxis and Risk of Epinephrine Use



A

	OIT (n/N)	No OIT (n/N)	RR (95% CI)
Target dose			
>300 mg	47/211	4/129	2·44 (1·18–5·02)
≤300 mg	60/442	4/164	4·67 (1·81–12·05)
$p_{interaction}$=0·61			
Starting dose			
≥1 mg	16/127	0/75	4·77 (0·89–25·69)
<1 mg	69/503	6/214	3·82 (1·75–8·34)
$p_{interaction}$=0·81			
Phase of OIT			
Build-up	59/630	4/290	3·52 (1·56–7·92)
Maintainence	52/440	3/208	3·99 (0·83–19·16)
$p_{interaction}$=0·92			
Confirmed diagnosis at study entry			
Not confirmed	27/73	4/44	1·85 (0·80–4·28)
Confirmed	81/580	4/253	4·99 (2·26–11·01)
$p_{interaction}$=0·034			

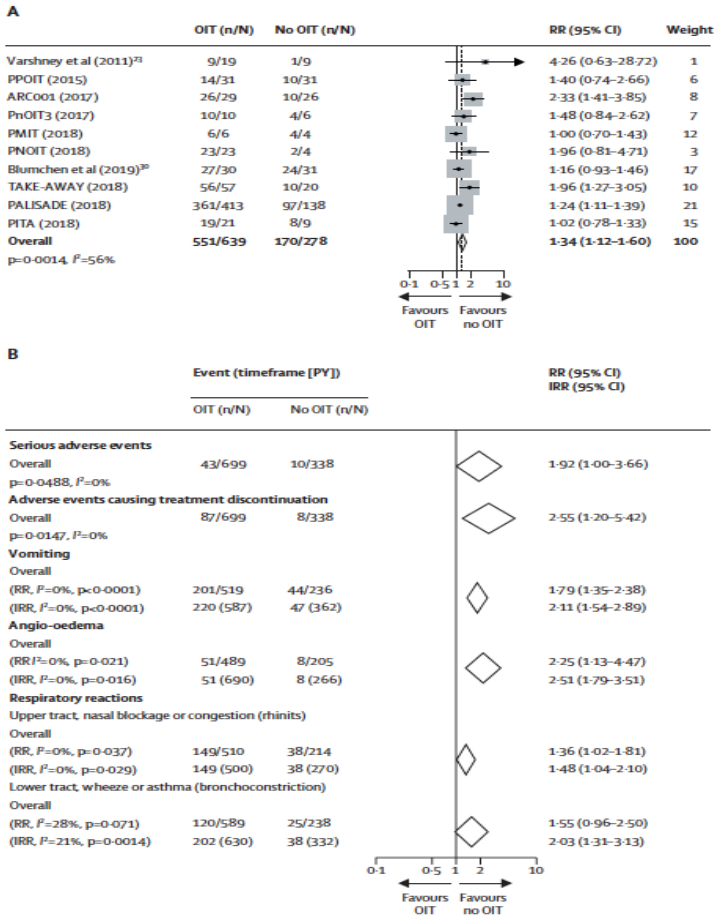
0·1 1 10
Favours OIT | Favours no OIT

B

	OIT (n/N)	No OIT (n/N)	RR (95% CI)	Weight
Varshney et al (2011)[73]	2/19	1/9	0·95 (0·10–9·13)	6
STOP II (2014)	1/49	0/50	3·06 (0·13–73·34)	3
PPOIT et al (2015)[28]	3/31	2/31	1·50 (0·27–8·36)	10
Narisety (2015)	4/11	0/10	8·25 (0·50–136·33)	4
ARC001 (2015)	1/29	0/26	2·70 (0·11–63·52)	3
TAKE-AWAY (2018)	6/57	0/20	4·71 (0·28–79·98)	4
PALISADE (2018)	59/413	9/138	2·19 (1·12–4·30)	67
PITA (2018)	2/21	0/9	2·27 (0·12–43·12)	3
Blumchen et al (2019)[39]	0/30	0/31		0
Overall	**78/660**	**12/324**	**2·21 (1·27–3·83)**	**100**
p=0·0048, I^2=0%				

0·1 1 10
Favours OIT | Favours no OIT

Risk of SAE, Discontinuation and Risk of Event by Organ System



A

	OIT (n/N)	No OIT (n/N)	RR (95% CI)	Weight
Varshney et al (2011)[73]	9/19	1/9	4·26 (0·63–28·72)	1
PPOIT (2015)	14/31	10/31	1·40 (0·74–2·66)	6
ARC001 (2017)	26/29	10/26	2·33 (1·41–3·85)	8
PnOIT3 (2017)	10/10	4/6	1·48 (0·84–2·62)	7
PMIT (2018)	6/6	4/4	1·00 (0·70–1·43)	12
PNOIT (2018)	23/23	2/4	1·96 (0·81–4·71)	3
Blumchen et al (2019)[39]	27/30	24/31	1·16 (0·93–1·46)	17
TAKE-AWAY (2018)	56/57	10/20	1·96 (1·27–3·05)	10
PALISADE (2018)	361/413	97/138	1·24 (1·11–1·39)	21
PITA (2018)	19/21	8/9	1·02 (0·78–1·33)	15
Overall	**551/639**	**170/278**	**1·34 (1·12–1·60)**	**100**
p=0·0014, I^2=56%				

0·1 0·5 1 2 10
Favours OIT | Favours no OIT

B

	Event (timeframe [PY]) OIT (n/N)	Event (timeframe [PY]) No OIT (n/N)	RR (95% CI) IRR (95% CI)
Serious adverse events			
Overall	43/699	10/338	1·92 (1·00–3·66)
p=0·0488, I^2=0%			
Adverse events causing treatment discontinuation			
Overall	87/699	8/338	2·55 (1·20–5·42)
p=0·0147, I^2=0%			
Vomiting			
Overall			
(RR, I^2=0%, p<0·0001)	201/519	44/236	1·79 (1·35–2·38)
(IRR, I^2=0%, p<0·0001)	220 (587)	47 (362)	2·11 (1·54–2·89)
Angio-oedema			
Overall			
(RR I^2=0%, p=0·021)	51/489	8/205	2·25 (1·13–4·47)
(IRR, I^2=0%, p=0·016)	51 (690)	8 (266)	2·51 (1·79–3·51)
Respiratory reactions			
Upper tract, nasal blockage or congestion (rhinits)			
Overall			
(RR, I^2=0%, p=0·037)	149/510	38/214	1·36 (1·02–1·81)
(IRR, I^2=0%, p=0·029)	149 (500)	38 (270)	1·48 (1·04–2·10)
Lower tract, wheeze or asthma (bronchoconstriction)			
Overall			
(RR, I^2=28%, p=0·071)	120/589	25/238	1·55 (0·96–2·50)
(IRR, I^2=21%, p=0·0014)	202 (630)	38 (332)	2·03 (1·31–3·13)

0·1 0·5 1 2 10
Favours OIT | Favours no OIT

Findings: OIT increases the risk of use and frequency of use of epinephrine, and risk for serious adverse events

Chu et al Lancet 2019; DOI 10.1016/S0140-6736(19)30420-9

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PACE Study: Take Home Message

- OIT significantly increases risks for adverse events, anaphylaxis, epi use and frequency of these events vs. no therapy/placebo (moderate to high confidence)
- All risks were lower in trials without entry OFC, interestingly
- No difference in findings if stratified by proprietary or non-proprietary product
- No QoL benefit noted (low certainty)
- Still only 12 trials and 1000 patients (most from the PALISADE trial)
- Overall take—no one debates the potential that OIT has to desensitize, however, there is significant concern that therapy promotes more adverse events than it may prevent
- Is there a role for shared decision making here?

Chu et al Lancet 2019; DOI 10.1016/S0140-6736(19)30420-9

OIT Safety Pooled Data (EAACI)

Children's Hospital Colorado

Study name	Statistics for each study			Events / Total		Risk ratio and 95% CI	Relative weight
	Risk ratio	Lower limit	Upper limit	Control	Experimental		
Caminiti 2015	1.200	0.939	1.534	14 / 14	14 / 17		13.24
Enrigue 2005	0.992	0.770	1.277	10 / 11	11 / 12		12.48
Fernandez-Rivas 2009	0.974	0.812	1.167	17 / 19	34 / 37		24.24
Lee 2013	1.127	0.900	1.412	12 / 12	14 / 16		15.73
Mansouri 2007	1.227	0.961	1.568	13 / 13	16 / 20		13.30
Pajno 2010	1.240	0.943	1.631	15 / 15	12 / 15		10.65
Varshney 2011	0.993	0.753	1.312	8 / 9	17 / 19		10.36
	1.089	0.996	1.190	89 / 93	118 / 136		

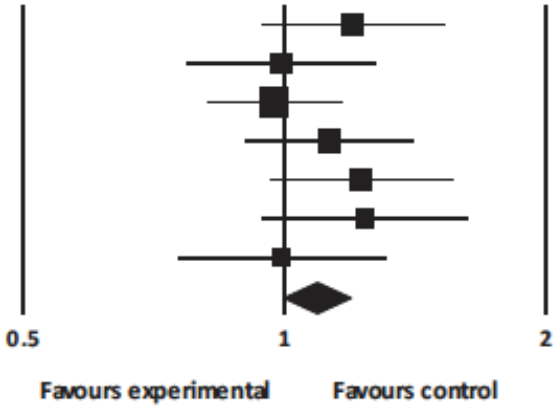

Figure 8 Safety data – absence of systemic reactions during OIT or SLIT for food allergy. RR, risk ratio (random-effects model). Heterogeneity: $\tau^2 = 0.0001$; $\chi^2 = 4.87$, df = 6 ($P < 0.56$); $I^2 = 0\%$; Test for overall effect: $Z = 1.86$ ($P < 0.06$).

- PACE findings are just more peanut specific but risk of AE's with OIT ***IS NOT A NEW FINDING***
- Significant risk (OIT vs Control) for systemic and local reactions (25 studies noted, 7 pooled)
- RR = 1.09, (95% CI 1.00, 1.19) for not experiencing a systemic rxn higher in control group

Nurmatoff et al Allergy 2017; 72: 1133-47

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DEVIL Study: Infant OIT Safety

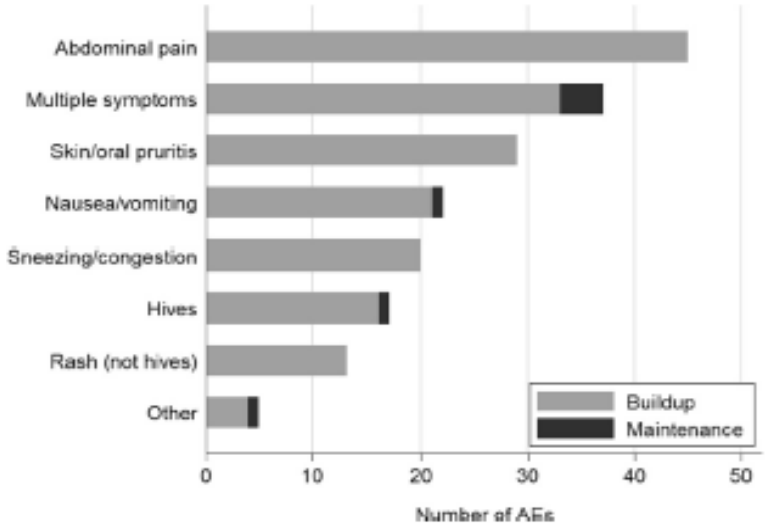


FIG E2. Distribution of all allergic AEs during buildup and maintenance phases. Multiple symptoms included any single reaction that involved multiple systems (skin/gastrointestinal/upper respiratory/lower respiratory). This group does not overlap with the other groups that involved isolated symptoms in each specified category. The "Other" category included isolated symptoms that occurred with less than 5% frequency (isolated cough at 2%, isolated angioedema at 1%, and isolated eye-tearing at 0.5%).

TABLE E3. Safety data by treatment arm

Population	Overall	Buildup	Maintenance
Subjects affected by AEs			
All subjects	95% (35 of 37)	92% (34 of 37)	27% (9 of 33)
High dose	100% (17 of 17)	100% (17 of 17)	43% (6 of 14)
Low dose	90% (18 of 20)	85% (17 of 20)	16% (3 of 19)
Average rate of AEs per person per dose (95% CI)			
All subjects*	0.8% (0.3%-1.4%)	1.5% (0.9%-2.2%)	0.06% (0%-0.1%)
High dose*	1.1% (0%-2.3%)	1.9% (0.6%-3.2%)	0.06% (0.01%-0.1%)
Low dose	0.6% (0.3%-0.9%)	1.2% (0.5%-2.0%)	0.05% (0%-0.2%)
Total number of AEs			
All subjects	211	195	16
High dose	133	126	7
Low dose	78	69	9
Proportion of moderate-severity AEs†			
All subjects	17% (36 of 211)	17% (33 of 195)	19% (3 of 16)
High dose	13% (17 of 133)	12% (15 of 126)	29% (2 of 7)
Low dose	24% (19 of 78)‡	26% (18 of 69)§	11% (1 of 9)
Study withdrawals			
All subjects	14% (5 of 37)	11% (4 of 37)	3% (1 of 33)
High dose	24% (4 of 17)	18% (3 of 17)	7% (1 of 14)
Low dose	5% (1 of 20)	5% (1 of 20)	0% (0 of 19)

*Rate of AE = number of AEs/d on therapy. Because subject 36 was never able to start therapy because of inability to complete the modified rush, this subject was excluded from these calculations.
†All AEs were either mild or moderate (no severe AEs reported).
‡P = .04, compared with high-dose group.
§P = .02, compared with high-dose group.

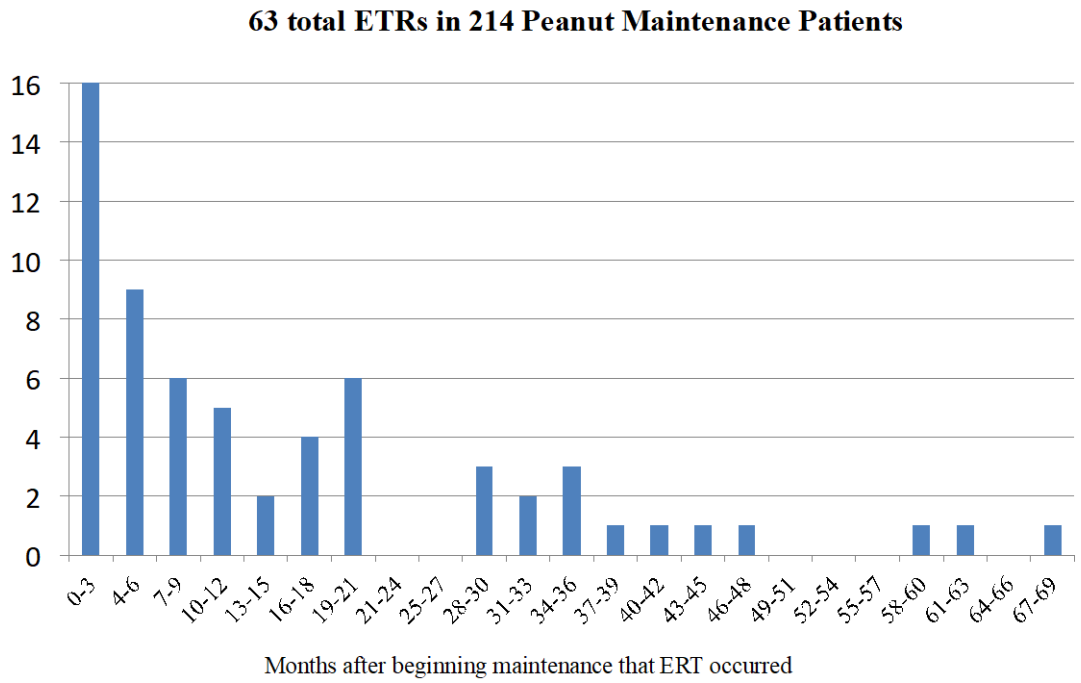
- "At both doses tested, E-OIT had an *acceptable* safety profile and was highly successful in rapidly suppressing allergic immune responses and achieving safe dietary reintroduction."
- 29 of 37 (78%) in the ITT analysis achieved 4-SU (300-mg arm, 17/20 [85%]; 3000 mg, 12/17 [71%])

Vickery et al J Allergy Clin Immunol 2017;139:173-81

Non-proprietary OIT Adverse Events

Children's Hospital Colorado

Peanut OIT Maintenance Events Requiring Treatment



Events Requiring Epinephrine Per 1,000 Doses

	Egg	MIlk	Peanut	Total
Escalation	0.95	0.76	1.3	1.0
Maintenance	0.02	0.17	0.26	0.19

Wasserman et al J Allergy Clin Immunol Pract 2019; 7: 418-26
Slide courtesy Richard Wasserman, MD, PhD Allergy Partners of North Texas

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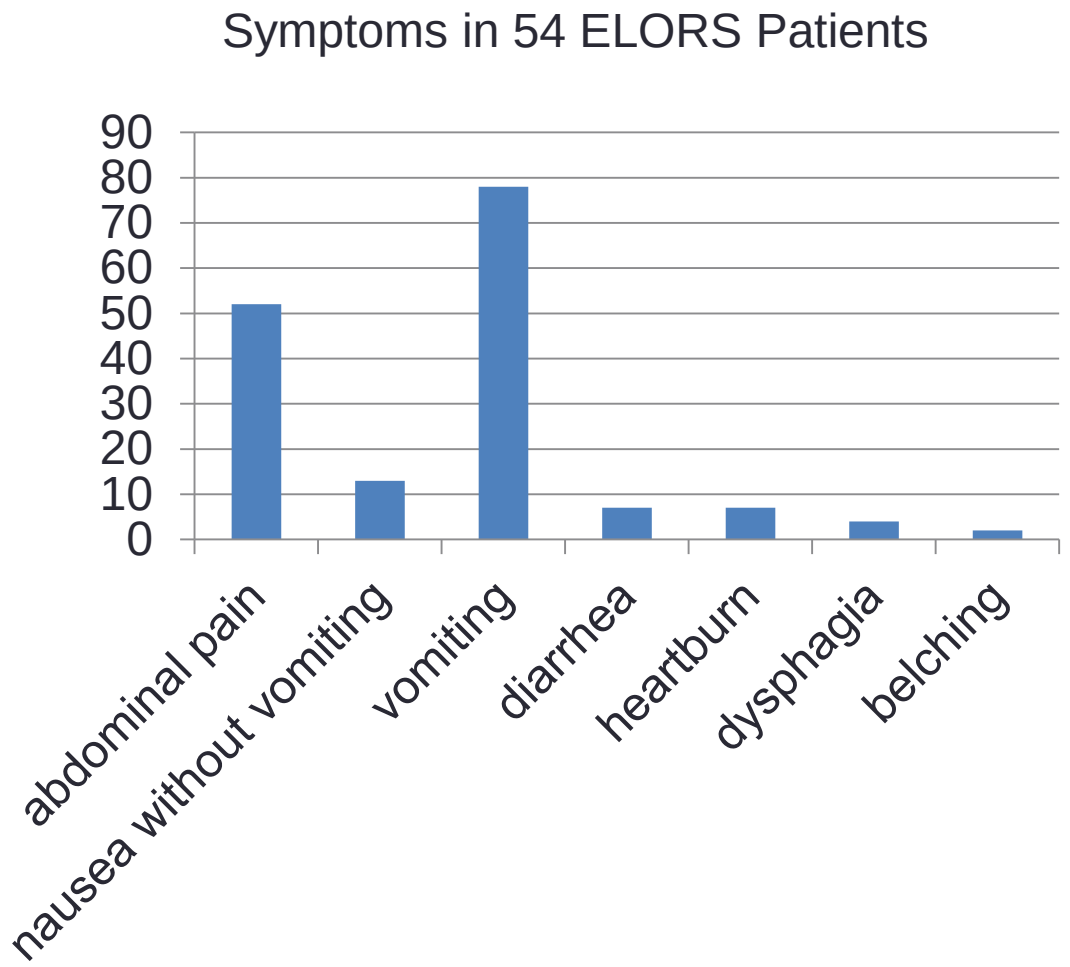
Eosinophilic Esophagitis Like, OIT-Related Syndrome (ELORS)

- Vomiting more than four hours after dosing is the predominant symptom
- 10.8% of treated patients
  - Peanut 13.7%
  - Milk 12.7%
  - Egg 0%
  - Cashew 6.3%
  - Multi-food 8.1%
- 32/54 patients treated
  - Dose reduction alone
  - Some treated with a PPI
  - 53% reached maintenance
- High pre-treatment IgE is the major risk factor



Wasserman et al J Allergy Clin Immunol Pract 2019; 7: 418-26
Slide courtesy Richard Wasserman, MD, PhD Allergy Partners of North Texas

Milk OIT: Different Experience

- Associated with much higher rate of reactions
  - Skripak et al 35% of doses provoked symptoms (4 requiring epi, all 20 pts experienced symptoms)
- In the Skripak et al trial, in the follow up they had first confirmed case of EoE
- Keet et al long term f/u for milk OIT—is this worth it?
  - 22% percent reported limiting their consumption because of symptoms
  - Notably, some subjects who initially did well and passed interim OFCs subsequently had increased symptoms and began to restrict CM.
  - Some had significant symptoms after study completion including 1 subject using epinephrine at least twice per month for reactions to CM.

Skirpak et al J Allergy Clin Immunol 2008; 122: 1154-60
Keet CA et al J Allergy Clin Immunol 2013;132:737-739.e6.

Long-Term Issues with Milk OIT

Children's Hospital Colorado

TABLE II. Milk consumption status and symptoms during follow-up

Symptoms with milk consumption	Total	Milk consumption status: Unlimited	≥1 Serving per day	<1 Serving but some uncooked	Trace or baked only	None
Totals	32	6 (19%)	10 (31%)	9 (28%)	2 (6%)	5 (16%)
No symptoms	8 (25%)	3 (50%)	4 (40%)	1 (11%)	0 (0%)	NA
Frequent/predictable symptoms	12 (38%)	2 (33%)	2 (20%)	6 (67%)	2 (100%)	
Frequent/predictable, more than oral/pharyngeal	9 (28%)	2 (33%)	1 (10%)	4 (44%)	2 (100%)	
Sporadic symptoms	7 (22%)	1 (17%)	4 (40%)	2 (22%)	0 (0%)	
Sporadic, more than oral/pharyngeal	5 (16%)	0 (0%)	3 (30%)	2 (22%)	0 (0%)	
Not consuming milk	5 (16%)			NA		
Anaphylaxis at least once	6 (19%)	0 (0%)	4 (40%)	1 (11%)	1 (50%)	
Used epinephrine at least once	3 (9%)	0 (0%)	0 (0%)	1 (11%)	2 (100%)	

NA, Not applicable.

TABLE E1. Types of ongoing and sporadic symptoms

Milk consumption category	Total	Frequent/predictable: Subtotal	Oral	GI	UR	Skin	LR	Sporadic: Subtotal	Oral	GI	UR	Skin	LR
Totals	32	12	6	8	2	2	1	7	4	0	2	2	2
Unlimited	6	2	0	1	1	0	0	1	1	0	0	0	0
≥1 Serving per day	10	2	1	1	0	1	0	4	2	0	1	1	2
<1 Serving but some uncooked	9	6	3	4	0	1	0	2	1	0	1	1	0
Trace or baked only	2	2	2	2	1	0	1	0	0	0	0	0	0
None	5						Not applicable						

GI, Gastrointestinal; *LR*, lower respiratory tract; *UR*, upper respiratory tract.

Keet et al J Allergy Clin Immunol 2013; 132:737-9.e6

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Japan/Spain: Reasons to Worry?

Children's Hospital Colorado

- In the 2015 Japanese survey, 11 patients developed EG (5 egg, 6 milk), 2 developed EoE
  - Additional news reported in November 2017 at JSPACI Meeting of updated survey
  - 9 children with very severe reactions: 5 reactions related to OFC, 3 had anaphylaxis requiring ICU
  - One child in month 3 of milk OIT maintenance (135ml) who suffered cardiac arrest. This child had mild asthma symptoms for 2d prior to the event and continued his home dose. He developed acute respiratory symptoms while in the car with his mom who then rushed him home and he was given IM epi but he required cardiopulmonary resuscitation and ICU care, followed by prolonged intubation. Suffered severe anoxic brain damage but is alive.
  - Details of this are mostly anecdotal and from media reports
- Spain: new reports of an 11 year old undergoing entry OFC prior to starting peanut OIT who developed acute bronchospasm and cardiac failure at 16mg CRD, requiring ICU prior to death

www.asahi.com. November 20, 2017 and personal communication M Ebisawa
Pouessel G et al. Allergy 2019; In press. doi: 10.1111/all.13791

Final Thoughts on OIT Safety

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- OIT safety is relative, but is milk OIT more risky than peanut?
- No study has been conducted without large percentage of patients having AE's
- While most AE's are reportedly "minor", nearly all patients experience them
- Events are poorly predictable
- Should there be a bigger focus on reporting standardization?
- There is a distinct risk of anaphylaxis and some risk of developing EoE
- Home reactions do occur
- Have to decide limits of tolerable/acceptable events, patients should have input

EPIT—Where Do We Stand?

- DBV Viaskin MILES and PEPITES in Phase 2/3
- Far fewer published data vs OIT
  - Early data note that 70% had a 10-fold dose increase, no serious AEs
  - MILES data noted all AEs associated with site urticaria/redness
  - Milk EPIT induced T_{regs} protect from anaphylaxis in adoptive transfer
  - Higher numbers of T_{regs} were produced in EPIT vs OIT, persisted after EPIT stopped
  - EPIT was not associated with EoE in murine models vs OIT
- Phase III peanut trial showed significant effect for 250mcg patch with good safety
- Phase II milk trial showed significant effect for 250mcg patch also with good safety

Sampson et al 2016 AAAAI oral abstract; Rutalt et al 2016 AAAAI oral abstract; Mondoulet et al 2016 AAAAI oral abstract; Dioszeghy et al 2016 AAAAI oral abstract; Mondoulet et al 2016 EAACI oral abstract

PEPITES Design

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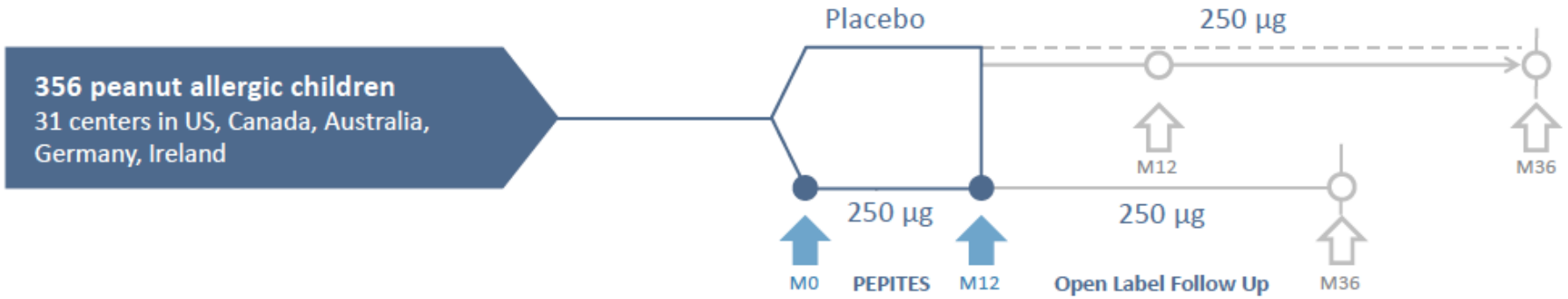
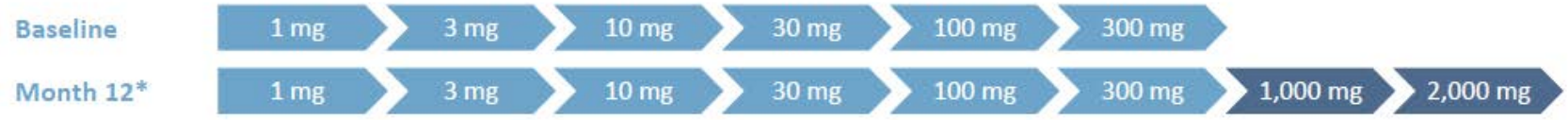


Study Population	Efficacy Endpoints
Highly allergic patients ages 4-11 ▪ > 0.7 kU/ L peanut-specific IgE and ≥ 6mm or 8 mm SPT* wheal ▪ Reactive dose at M0 ≤ 300 mg peanut protein (i.e. approx 1 peanut)	**Treatment responder definition:** ▪ Assessed using DBPCFC** ▪ For subjects with a M0 ED*** ≤ 10mg: responder if ED ≥ 300 mg at M12 ▪ For subjects with a M0 ED > 10mg: responder if ED ≥ 1,000 mg at M12 **Key secondary endpoints:** ▪ CRD****, changes in peanut sIgE and sIgG4

OFC protocol



Fleischer et al JAMA 2019;321(10):946-955. doi:10.1001/jama.2019.1113
https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

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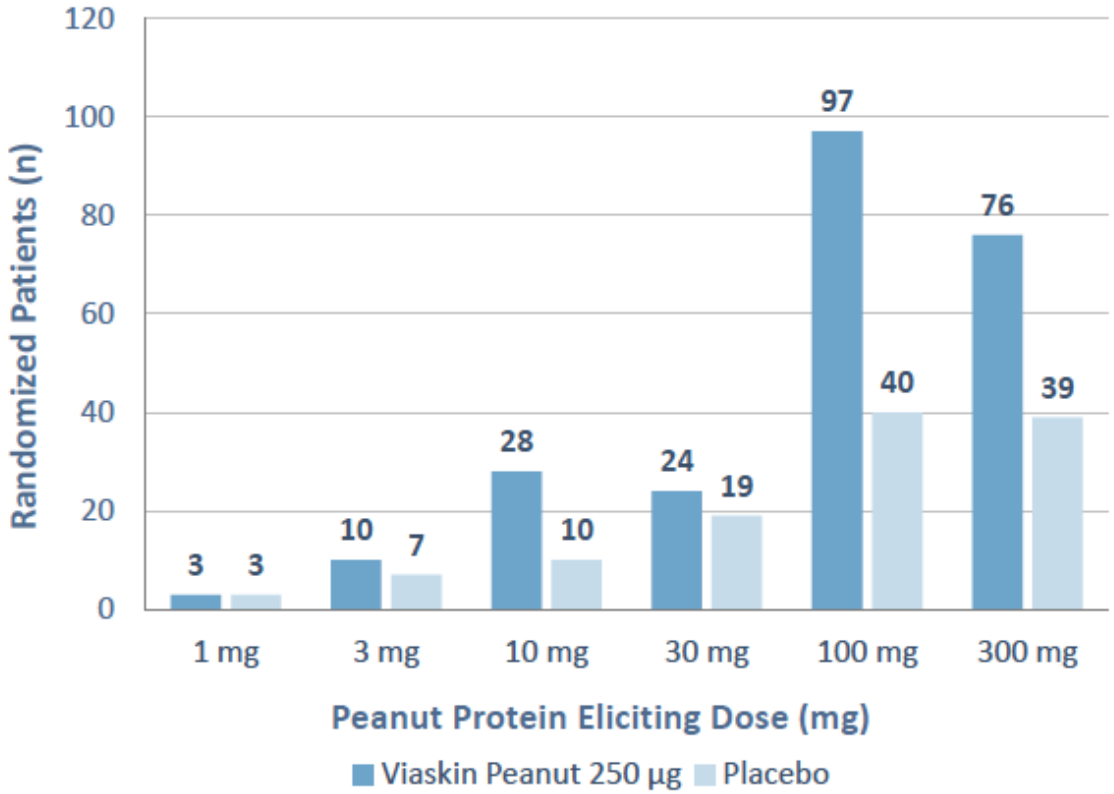
PEPITES Entry Characteristics



356 Patients Randomized

- Active: 238
- Placebo: 118

Peanut Eliciting Dose (mg)

- Median: 100
- Mean: ~140

Medical History of Patients

	n	%
Asthma	169	47.5
Eczema/Atopic Dermatitis	218	61.2
Allergic Rhinitis	199	55.9
Polyallergic	305	85.7

Fleischer et al JAMA 2019;321(10):946-955. doi:10.1001/jama.2019.1113
https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

PEPITES Main Results

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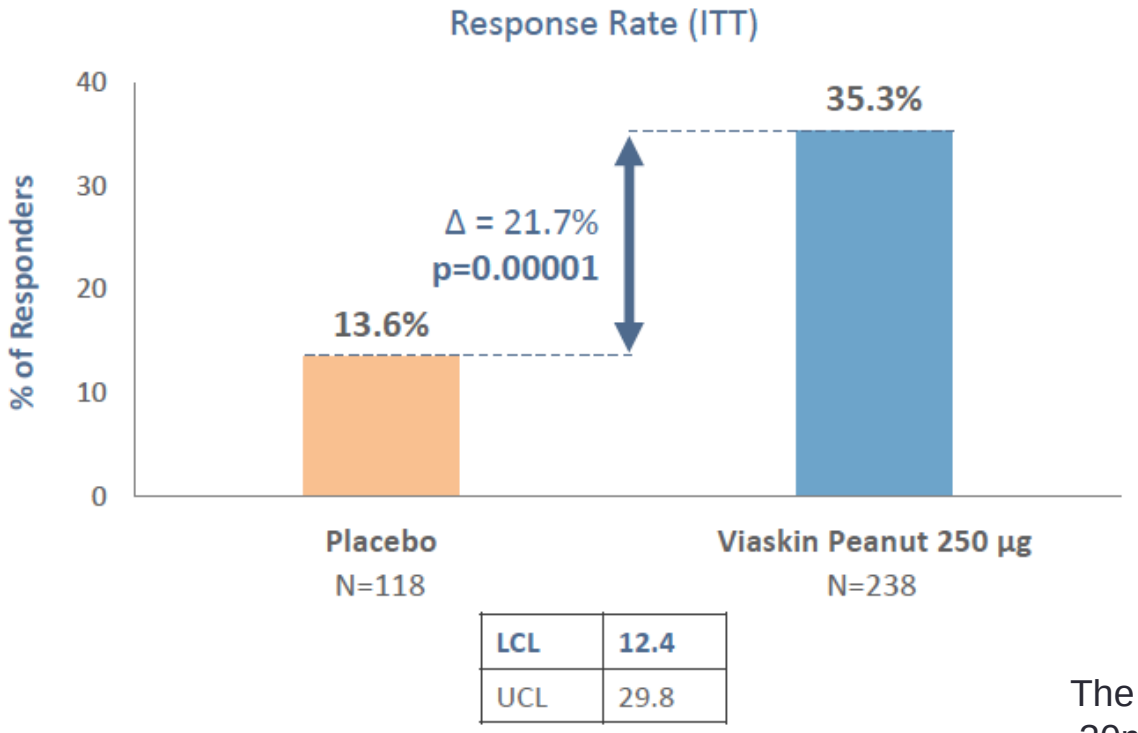
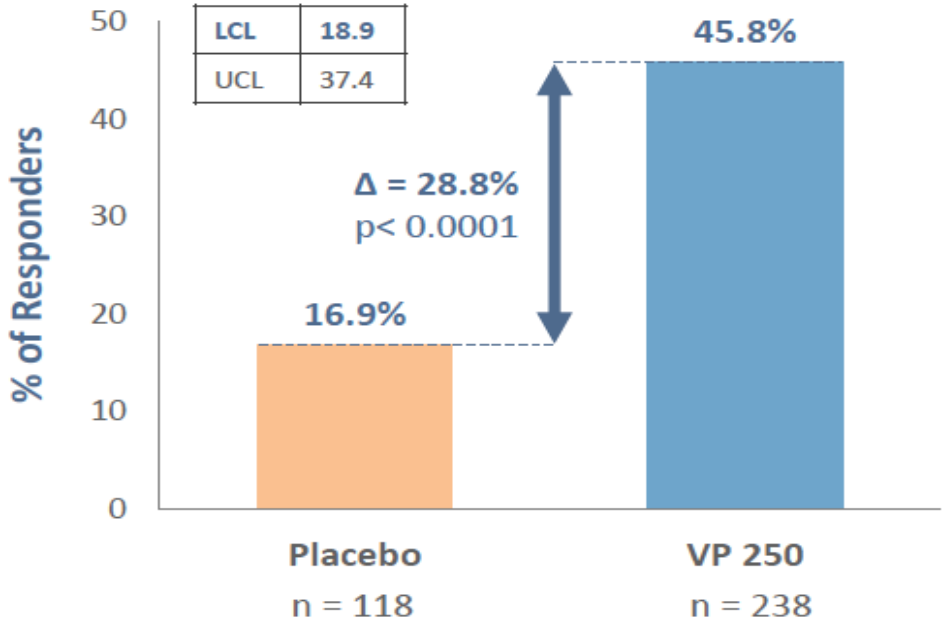
Response rate was statistically significant, but 15% lower bound of the 95% CI proposed in the SAP submitted to FDA was not reached



LCL	12.4
UCL	29.8

NNT 4.6 (ARR 21.7%)

PEPITES Response Rate Using the VIPES Response Criteria

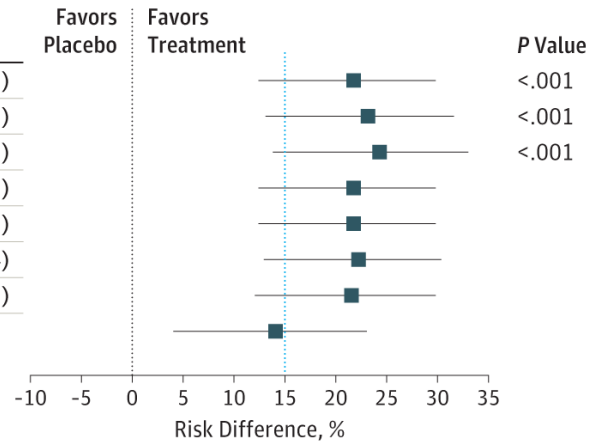


The difference is VIPES allowed either 10x or ED1000. Someone with an ED of 30mg would be a responder if reached ED300 in VIPES, whereas in PEPITES they needed to have an ED1000 to be considered a responder

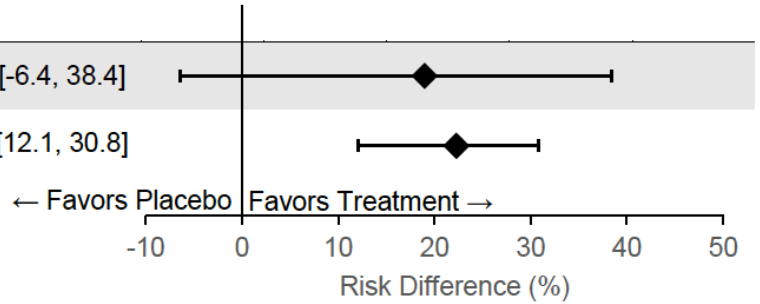
Fleischer et al JAMA 2019;321(10):946-955. doi:10.1001/jama.2019.1113
https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

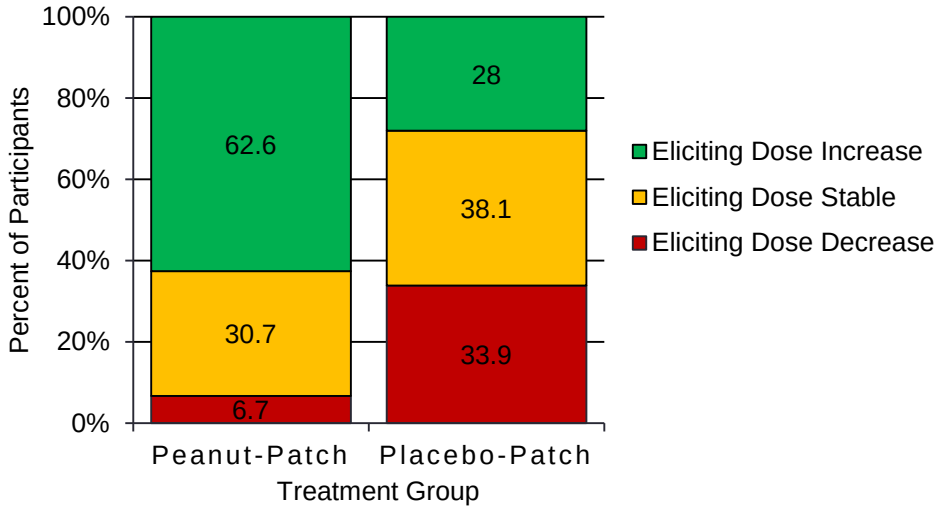
PEPITES: Response Patterns

Analysis	No./Total No. (%) Peanut Patch	Placebo Patch	Risk Difference, % (95% CI)	*P* Value
Intention to treat	84/238 (35.3)	16/118 (13.6)	21.7 (12.4-29.8)	<.001
Full analysis set	84/222 (37.8)	16/109 (14.7)	23.2 (13.2-31.7)	<.001
Per protocol	77/201 (38.3)	14/100 (14.0)	24.3 (13.9-33.1)	<.001
Eliciting dose strata adjusted[a]			21.7 (12.4-29.8)	
Region adjusted[a]			21.7 (12.4-29.8)	
Age adjusted[a]			22.3 (12.9-30.4)	
Multiple imputation[b]	36.4	14.8	21.6 (12.1-29.8)	
Worst case[c]	84/238 (35.3)	25/118 (21.2)	14.1 (4.1-23.1)	



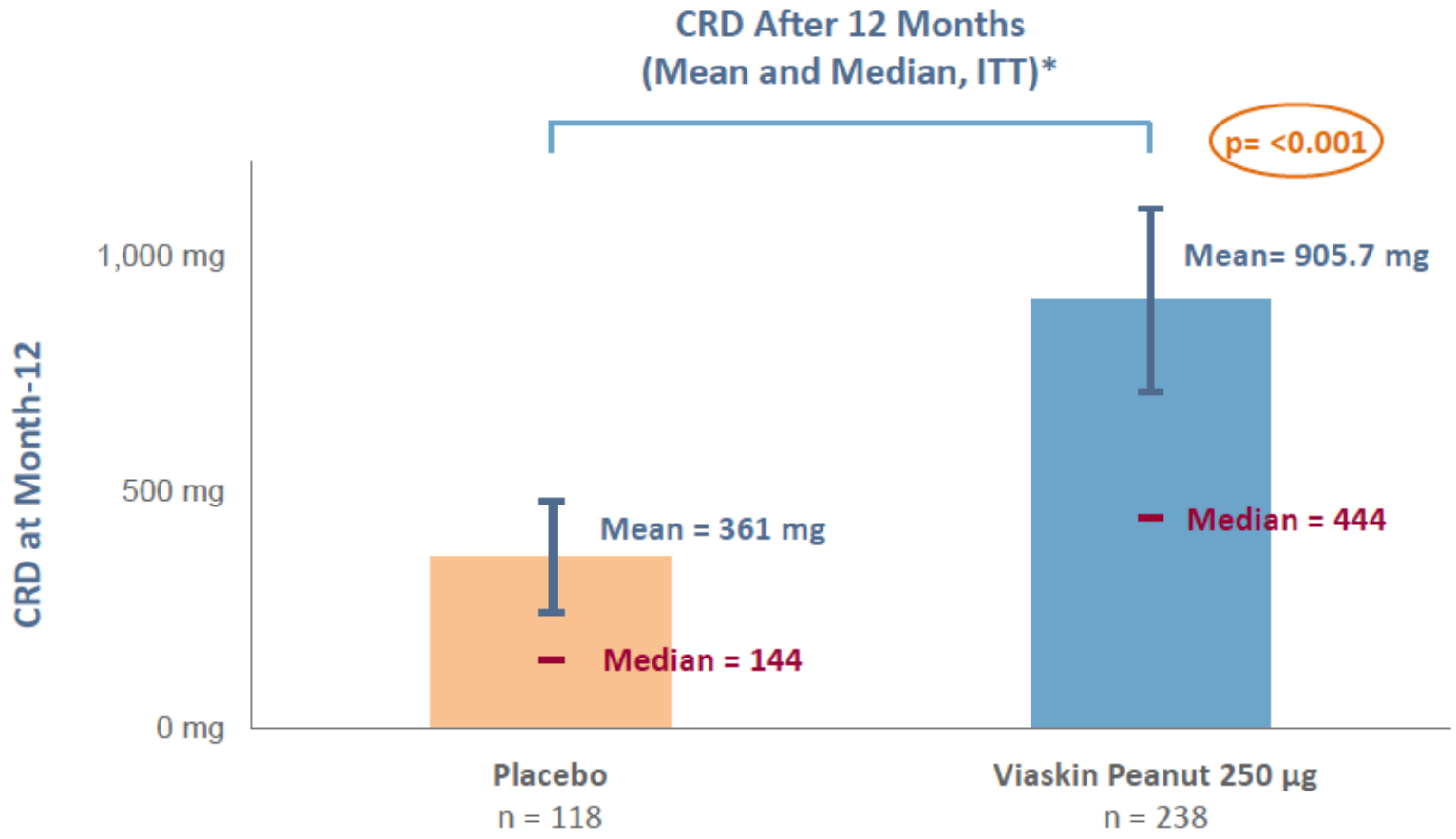
Analysis	Peanut-Patch % (n/N)	Placebo-Patch % (n/N)	Risk Difference (%)	CI
Low–eliciting dose subgroup	39.0 (16/41)	20.0 (4/20)	19.0	[-6.4, 38.4]
High–eliciting dose subgroup	34.5 (68/197)	12.2 (12/98)	22.3	[12.1, 30.8]





Fleischer et al JAMA 2019;321(10):946-955. doi:10.1001/jama.2019.1113

PEPITES Change in Reactive Dose



Fleischer et al JAMA 2019;321(10):946-955. doi:10.1001/jama.2019.1113
https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

Longer Term Outcomes: VIPES Study

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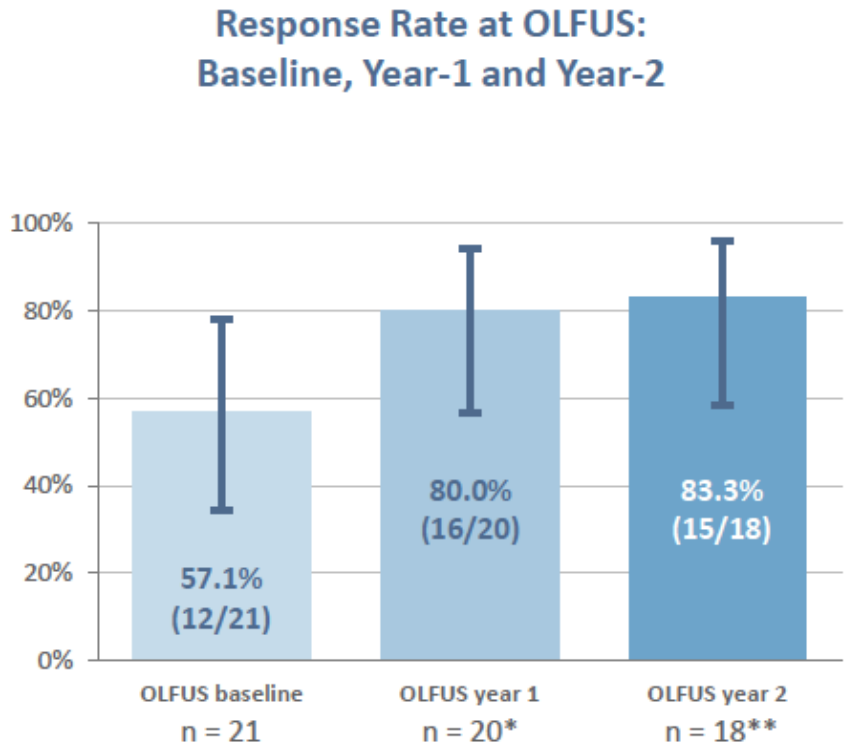
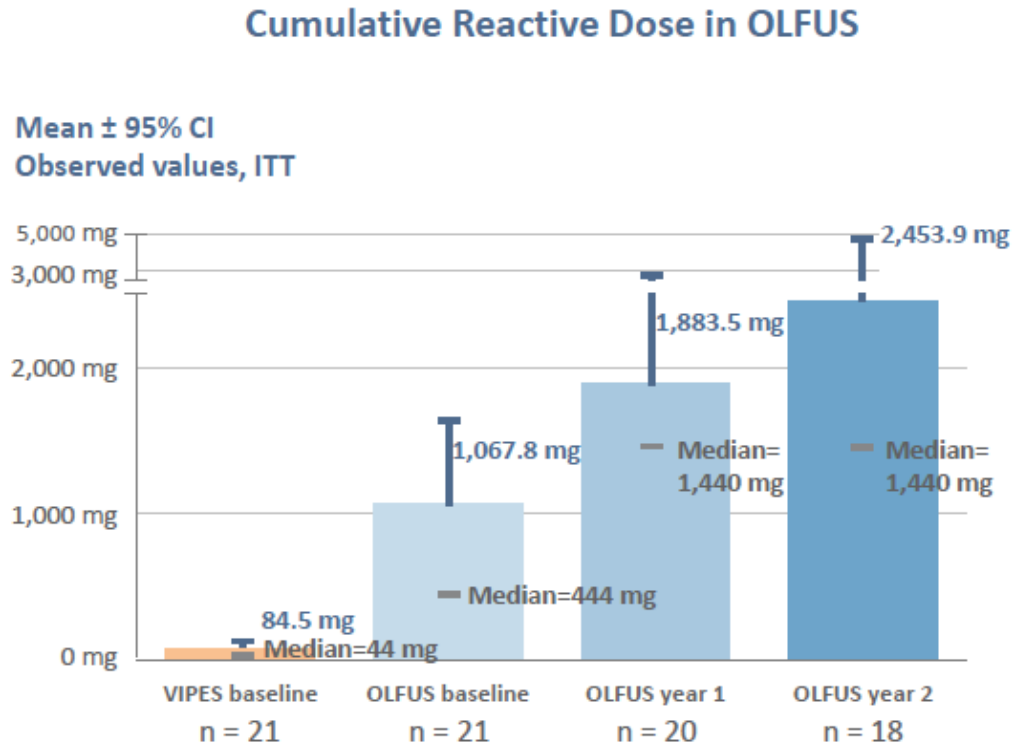


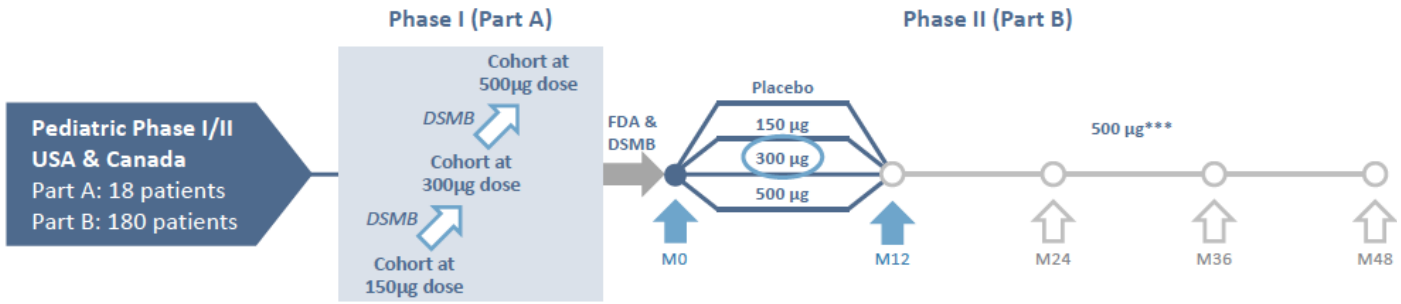


- Unlike in OIT, changes in EPIT may occur over a longer horizon
- Data on mean CRD and response improved through year 2 and 3 of study

Sampson et al JAMA. 2017;318(18):1798–1809
https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

MILES Entry Criteria and Design

Children's Hospital Colorado



Study Population

- Children (2-11) and adolescents (12-17)
- Highly sensitive to milk (≥ 10 kU/L milk-specific IgE and ≥ 6 mm SPT* wheal)
- Reactive dose at baseline (M0) ≤300 mg cow's milk protein (CMP) (~≤9.4 mL of cow's milk)

Efficacy Endpoints

Treatment responder definition at M12:

- ≥ 10-fold increase in CRD** and at least 144 mg of CMP
- OR CRD ≥ 1,444 mg

Key secondary endpoints:

- Change from baseline in IgE, IgG4

198 patients randomized

- 152 Children (2-11)
- 46 Adolescents (12-17)

CRD of Cow's Milk

Mean

- Children: 216.3 mg
- Adolescents: 222.0 mg

Median

- Children: 144 mg
- Adolescents: 144 mg

Medical history of patients

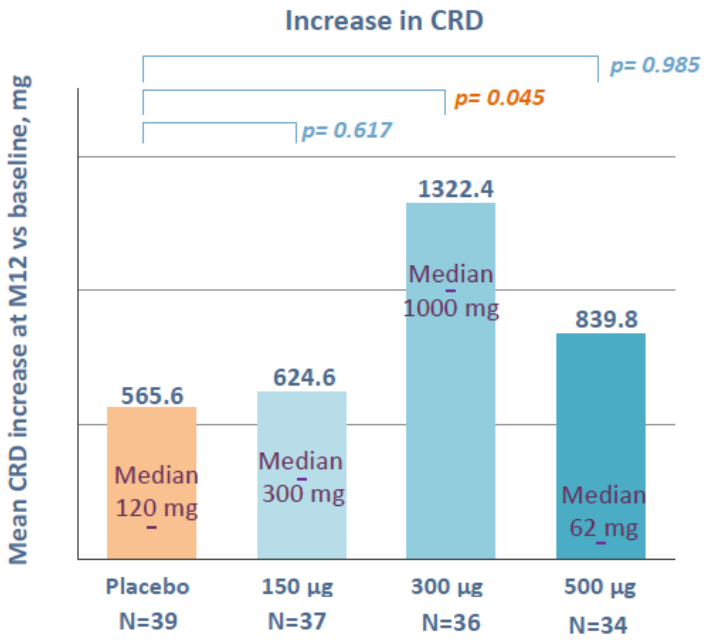
	n	%
Asthma	139	70.2
Atopic Dermatitis	139	70.2
Allergic Rhinitis	144	72.7
Polyallergic	178	89.9

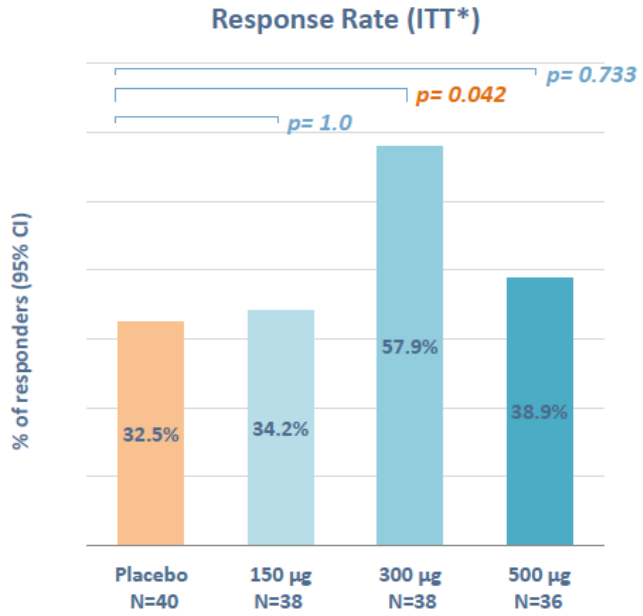
Mean Cow's Milk sIgE

- Children: 135.2 kU/L
- Adolescents: 127.9 kU/L

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

MILES Phase II Results





Favorable safety, tolerability and compliance

- Overall discontinuation rate of 4.5%
  - 1.5% dropout due to adverse events
- Most adverse events were related to application site, and were mild to moderate
- No SAEs or epinephrine use related to treatment
- Treatment adherence was high, with a mean patient compliance > 95%

- For the 300ug dose, NNT was 3.93 (ARR 25.4%)
- Unclear why response at 300ug was optimal but similar dose effect seen with peanut
- High placebo rate likely reflects difficulty of treating an allergen that has a favorable natural history

https://www.dbv-technologies.com/wp-content/uploads/2018/04/dbv-technologies-investor-presentation_april-2018.pdf

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Other Approaches to Treatment

Past, Present, and Future Attempts

Anti-IgE Therapy for Food Allergy

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- EPIT and OIT are limited by lack of uniform vehicle (OIT), indeterminate success rates (both), unclear long-term outcomes (both), and high rate of treatment-related SAE (OIT)
- Anti-IgE therapy has shown limited success in previous trial as a stand-alone therapy.
- TNX-901 associated with 9-fold increase in peanut threshold but not further developed.
- A 2004 phase II Omalizumab trial (Q2788g) was initiated and showed interim success through 15 enrolled patients, but DSMB discontinued the study due to significant anaphylaxis related to irregular capsule absorption in the oral food challenges
- Since 2004, this approach has not been further developed to date
- Omalizumab has been used with success in small studies to decrease AE's in buildup with milk and peanut OIT

Proof of Concept

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- TNX-901 trial compared 150mg, 300mg, 450mg dose vs. placebo.
  - Noted dose response was not related to the entry challenge threshold.
  - Primary endpoint of a 0.9 log dose met by 22% of placebo and 53%/47%/76% of those randomized to the three doses
  - In optimal case, saw a moderate effect size (0.55) between 450mg and placebo, translating to NNT=1.8
  - Only 21% (300mg) and 24% (450mg) tolerated the full dose of the end OFC
- Q2788g trial tested wt/IgE based standard Omalizumab dosing, comparing low vs. moderate vs. high responders
  - 7/9 active vs. 0/5 placebo subjects met new FDA dosing criteria (mean dose 240mg vs. 1447mg)
  - Mean dose response from baseline was 1,437mg (1,600mg among responders), though 4/8 were low dose responders that did not eclipse 500mg
  - Trial halted due to 2 adverse reactions in OFC phase, but not due to study drug itself

Leung DY et al N Eng J Med 2003; 348: 986-93.
Sampson

OutMATCH Trial (CoFAR)

Children's Hospital Colorado

- Subjects ages 2-55yr must have peanut allergy plus two other food allergies
- Testing Omalizumab monotherapy and Omalizumab/multi-OIT efficacy in same trial
- Stage 1:RCT of Omalizumab q2-4 weeks for 16 to 20 weeks, followed by DBPCFC to a cumulative dose of 6044 mg protein of primary and 2 secondary foods. Initial 60 completers move to OLE x 24 weeks with re-challenge, everyone else to stage 2
- Stage 2: 8 weeks omalizumab at same dosing, then 1:1 randomization to omalizumab + Multi-allergen OIT for eight weeks, followed by placebo + Multi-allergen OIT for 44 weeks OR omalizumab + placebo OIT for eight weeks, followed by omalizumab + placebo for Multi-allergen OIT for 44 weeks.
- Outcome: # successfully consume ≥600 mg of peanut protein without dose-limiting symptoms (investigator dependent, like AR101) wk 16 DBPCFC

https://www.clinicaltrials.gov/ct2/show/NCT03881696

Why Revive Anti-IgE Therapy?

- The anti-IgE therapy approach offers a number of advantages over the daily rigors of OIT and EPIT
- Omalizumab is a monthly or bi-monthly injection, sparing families the daily inconvenience of having to adhere to a medication regimen
- With Omalizumab stand-alone therapy, patients would not experience daily symptoms related to build-up/maintenance allergen ingestion or patch application.
- Omalizumab likely protects against multiple allergens simultaneously
- This potential to address multiple food allergy simultaneously represents a distinct strategic advantage of using anti-IgE therapy for food allergy treatment.
- Omalizumab in combination with OIT has been shown to decrease the occurrence and severity of OIT related AE's, but it is unclear if adding OIT is necessary to provide protection

Novel Early Attempts: SCIT

- SCIT was tried in early 1990s with limited early success
  - The study was abandoned after a dosing error leading to death (not the therapy), showing promise with similar ADR to OIT
  - 11 adult patients randomized in a RCT to placebo vs. aqueous 1:20 peanut extract, all challenged confirmed cases
  - 5 day rush protocol based on end-point titration of PST at entry, then weekly maintenance dose
  - Trial halted when maintenance dose accidentally given to placebo subject, who had fatal anaphylaxis. 8 had started therapy, 6 had finished
  - Silver linings were abundant however….
  - All 3 active subjects had reduction in PST vs no change in placebo and all 3 had significantly reduced symptoms on exit FC
  - 13% rate of adverse events in the rush buildup phase and no anaphylaxis occurred due to therapy (active subjects)

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Oppenheimer JJ et al. J Allergy Clin Immunol 1992;90:256-62.

Conclusions

- Multiple options to desensitize against peanut and other allergens are being developed
- The pipeline is bright, and the strategies are evolving
- No long-term safety and efficacy data exist and no “curative” option exists
- Safety has often been subjectively and not objectively defined--this is a big issue to fix
- All therapies have distinct limitations and adverse events—no perfect solution exists
- What is an appropriate trial endpoint: tolerated with mild symptoms vs. a dose where symptoms objectively occur? Should this be based on a cross-sectional event?
- Everything we do has consequences—the issue is what patients may want, and what risks they choose to leverage. This isn’t our choice necessarily.
- Not every patient will want or benefit from treatment—keep that in mind