Current Status of Sublingual Immunotherapy in the U.S.

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Conflicts of Interest

- Speaker's Bureau: AstraZeneca, Merck, GSK, Sunovion, Takeda, Allergan, Nestle's, Genentech, Meda, Bausch and Lomb
- Consultant: Sanofi, Merck, Sunovion, Allergan, Proctor & Gamble, Takeda, Allergan, JDP Therapeutics, Pfizer, Vectura

Learning Objectives

- Cite the reasons for the difficulty to get approval of SLIT in the US.
- Understand the US data on the different methods of SLIT in front of the FDA
- Be familiar with possible issues for SLIT use and be able to clearly recognize potential side effects

Introduction

- Though SLIT is commonly used in many parts of the world but presently are no approved FDA SLIT materials
- Numerous studies have been performed all over the world but only a small number were DBPC
- Remote practice of allergy commonly using SLIT
  - August 2011-BC Allergists doing SLIT-11.4%*
- This review will focus on US trials with SLIT

*Sikora JM, Tankersley MS. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. Ann Allergy. 2013.

The Allergies, Immunotherapy & RhinoconjunctivitiS (AIRS) Patient and Provider Surveys

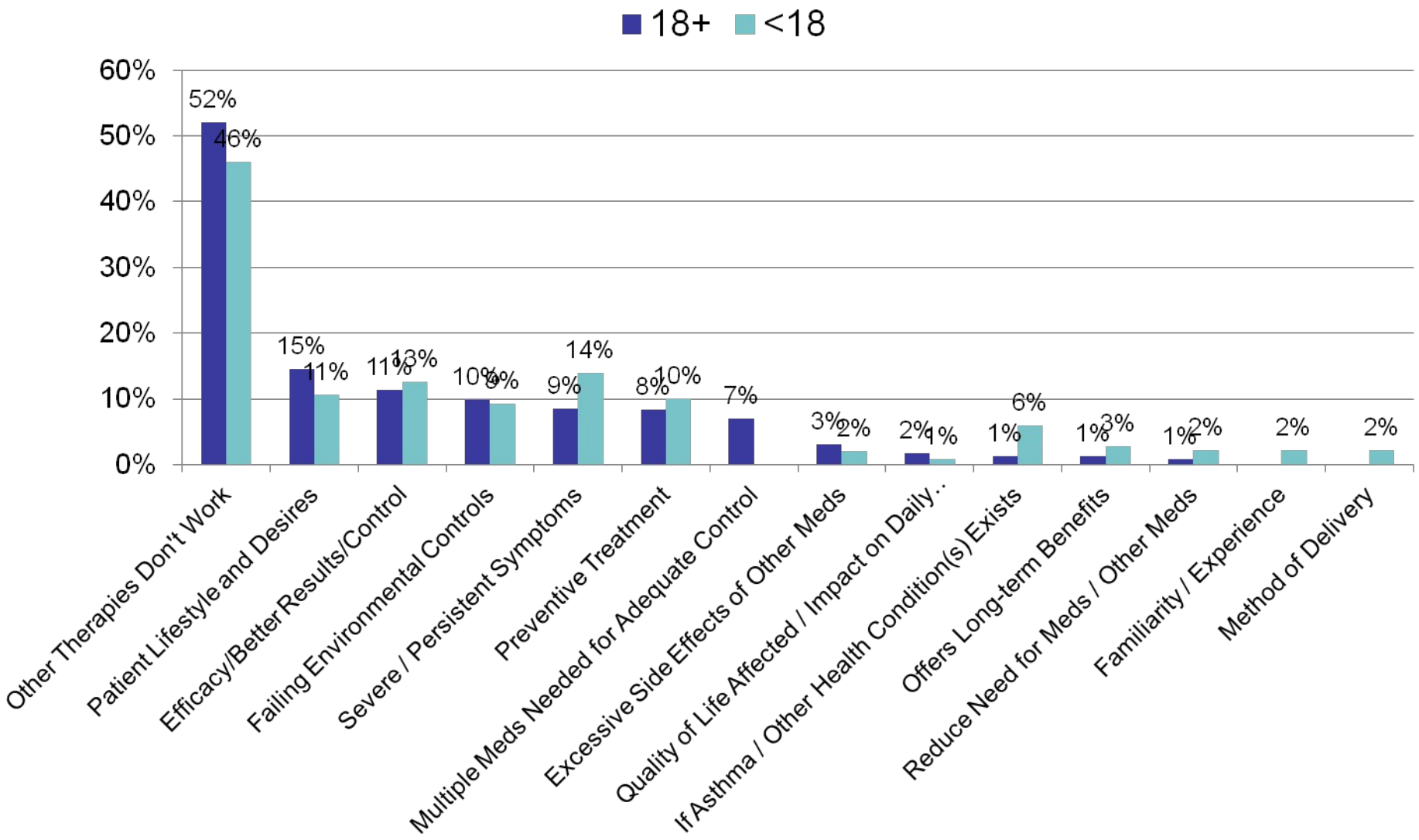
- Leonard Bielory, MD
- Michael Blaiss, MD
- Timothy Craig, MD
- Mark Dykewicz, MD
- James Hadley, MD
- Bryan Leatherman, MD
- Jodi Luchs, MD
- Gabriel Ortiz, PA-C
- David Skoner, MD
- Nicole Walstein, PA-C

- Underwritten by Merck

Overall Survey Design

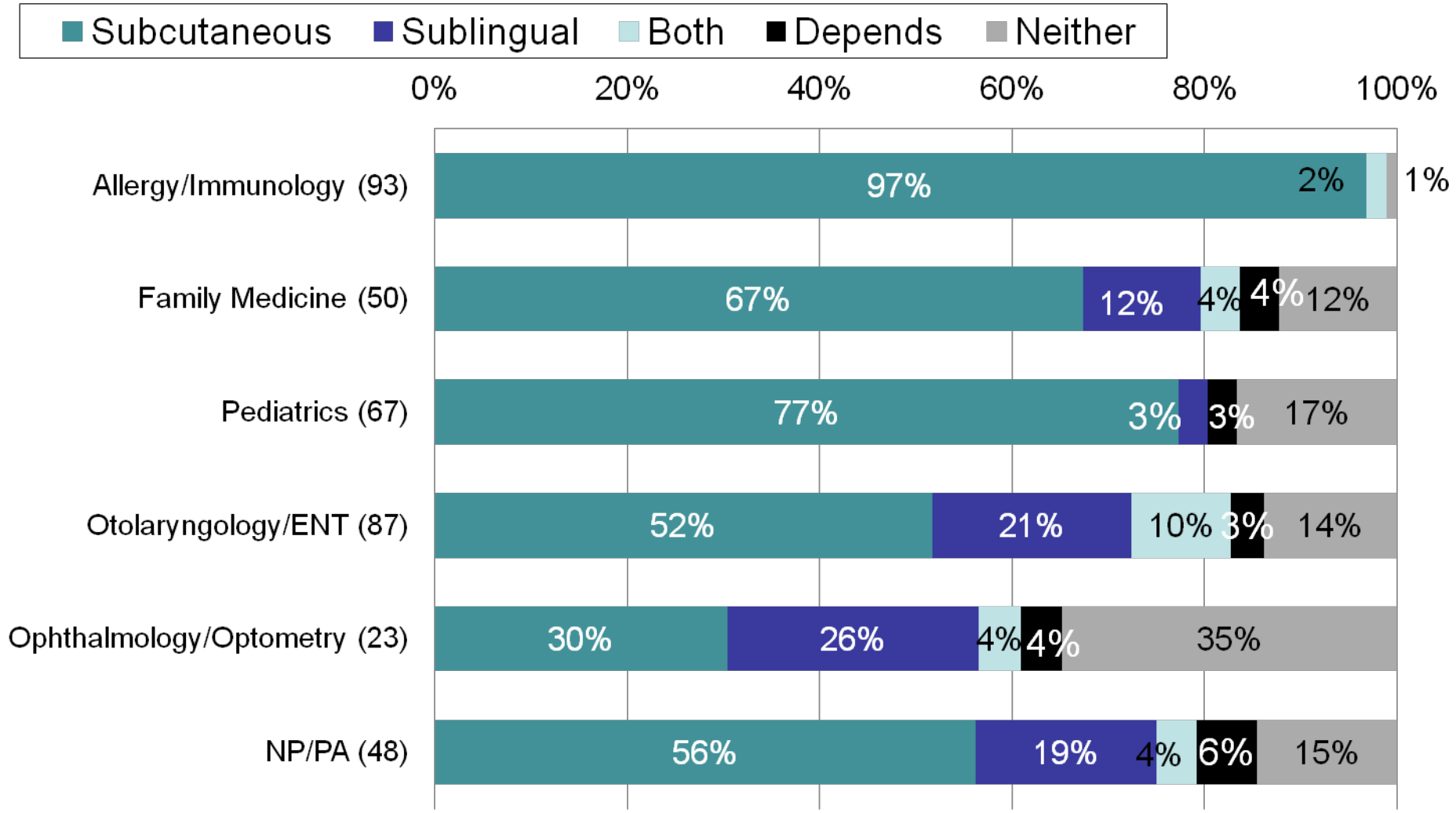
Population	Sampling Frame	Interview Length	Completed Sample
Patient Survey: 2/28/2012-5/2/2012 Diagnosed with hay fever, allergic rhinitis, rhino-conjunctivitis, nasal or eye allergies, and symptoms or medication for condition in past 12 months.			
Current Allergic Rhinoconjunctivitis: Aged 5+	National LL + Cell RDD 34,030 HH Screened	24.5 minutes	2,765
Health Care Provider Survey: 2/2/2012– 4/2/2012 Direct patient care in an outpatient setting and see patients with allergies at least weekly.			
Allergist	AMA/AOA Master List		100
Family Medicine	AMA/AOA Master List		75
Otolaryngology/ENT	AMA/AOA Master List		100
Ophthalmologist/Optometrist	Optometrist National List		50
Pediatrician	AMA/AOA Master List		75
Nurse Practitioners	NP National List		50
Physician Assistants	PA National List		50
TOTAL		17.9 minutes	500

Why Recommend IT?



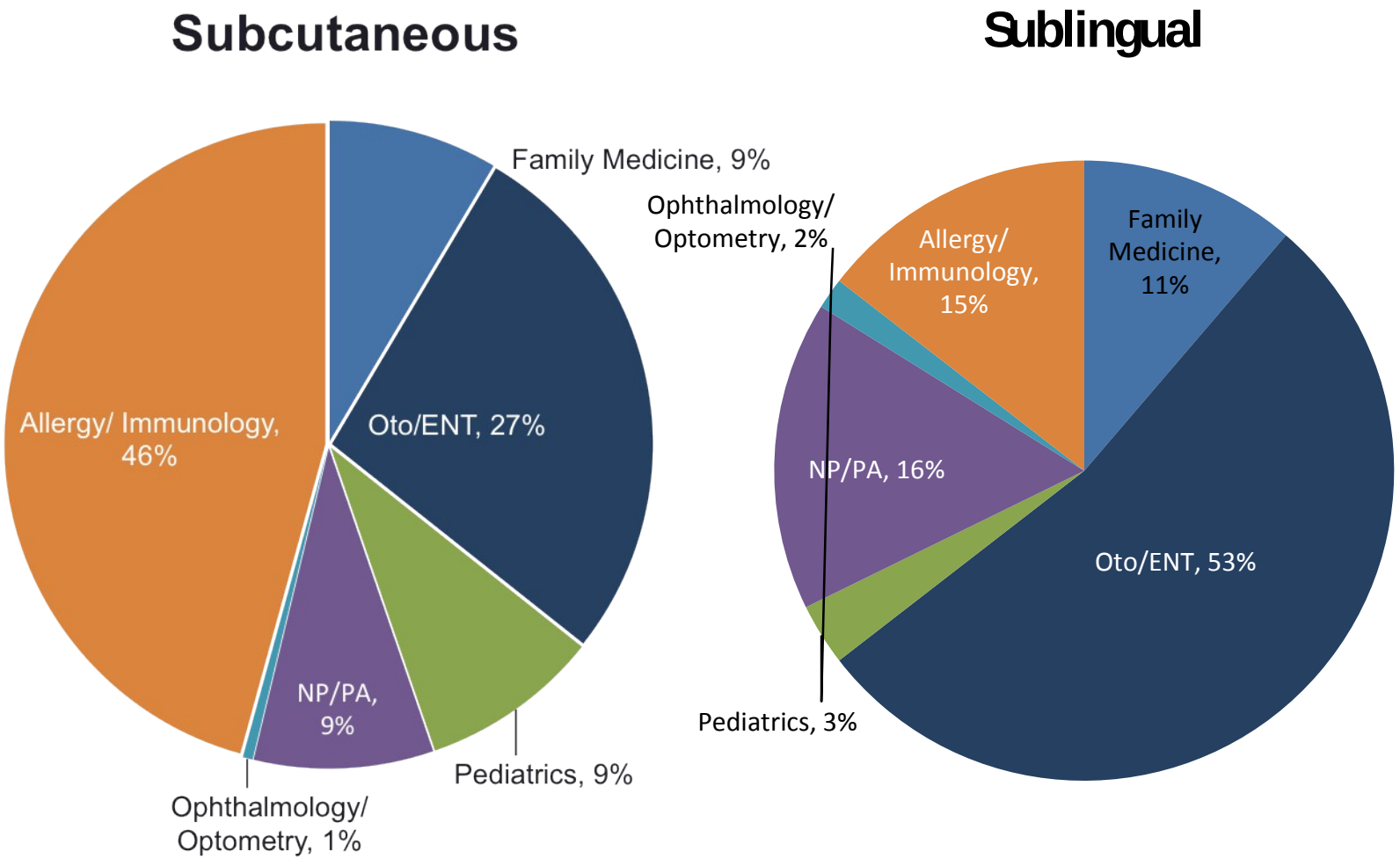
QIT4/11Why do you recommend immunotherapy for your patients? *Multiple response.* Base: providers who see 1+ patient with allergic rhinoconjunctivitis per week and recommend immunotherapy, 18+ N=398; <18 N=368. *Don't Know* and <2% responses not shown.

Recommend Subcutaneous or Sublingual Immunotherapy to Children



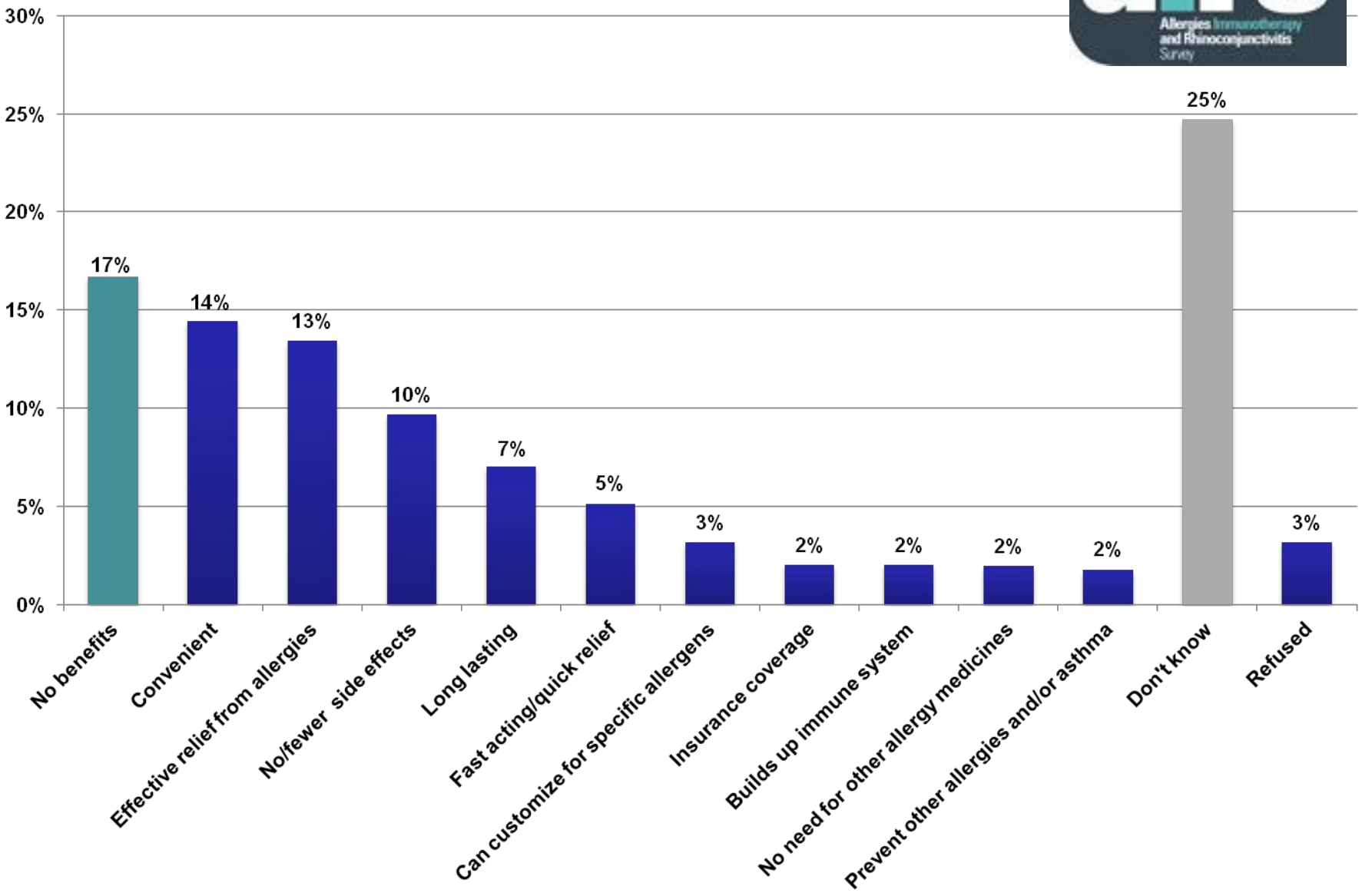
QIT10a: Do you usually recommend subcutaneous or sublingual immunotherapy? Base: providers who see at least one patient <18 with ARC per week and recommend immunotherapy, N=368. Ns by specialty are shown in parentheses. Two (2) *Don't Know* responses not shown.

Specialty Distribution by Type of Immunotherapy Provided



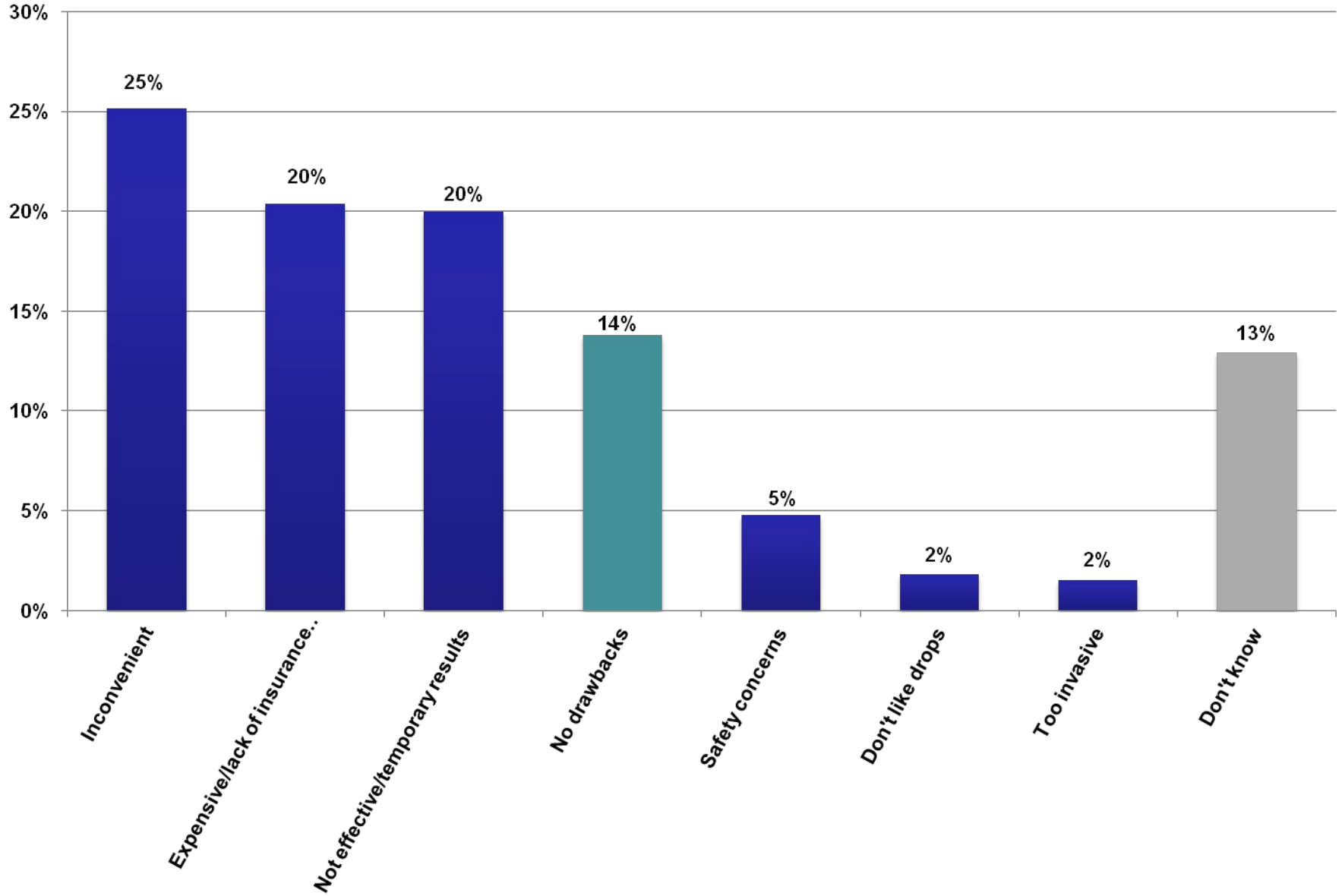
Subcutaneous N=199; Sublingual N=62. These Ns represent those providers who provide IT (IT17a) and who did not indicate that they had no patients on subcutaneous (IT18a) or sublingual (IT19a) IT. Ns by specialty are shown in parentheses with subcutaneous first.

Primary Benefits of Allergy Drops



I17. What do you believe are the primary benefits of allergy drops over other treatments for allergies? *Multiple Response.*
Base: Respondents who have received allergy drops, N=50

Primary Drawbacks of Allergy Drops



I18. What do you believe are the primary drawbacks of allergy drops over other treatments for allergies? *Multiple Response.*
Base: Respondents who have received allergy drops, N=50

What's the Bottom-line?

Why has it been so hard to get SLIT approved by the FDA in the USA?

How SLIT studies differ from allergy and asthma medication studies?

- Not dealing with just population variation but allergen exposure variation
  - Patients aren't symptomatic prior to treatment
  - Pollen levels vary and may not see as much variation in symptoms between groups
- Total composite scores-symptom improvement and medication decrease
  - Symptom scores-nose and eye
  - Medication scores-no standardized way to evaluate

FDA Requirements for SLIT are not clear

- FDA will probably require more efficacy than $p < 0.05$ vs placebo seen in medication studies
- 10% efficacy above the 95% CI (mean treatment difference vs placebo)
- May also require at least 20% improvement in composite score compared to placebo

Sublingual Immunotherapy Techniques

- Sublingual-swallow
- Allergen Immunotherapy Tablet
  - Orosoluble tablet
    - Northern grasses
    - Ragweed

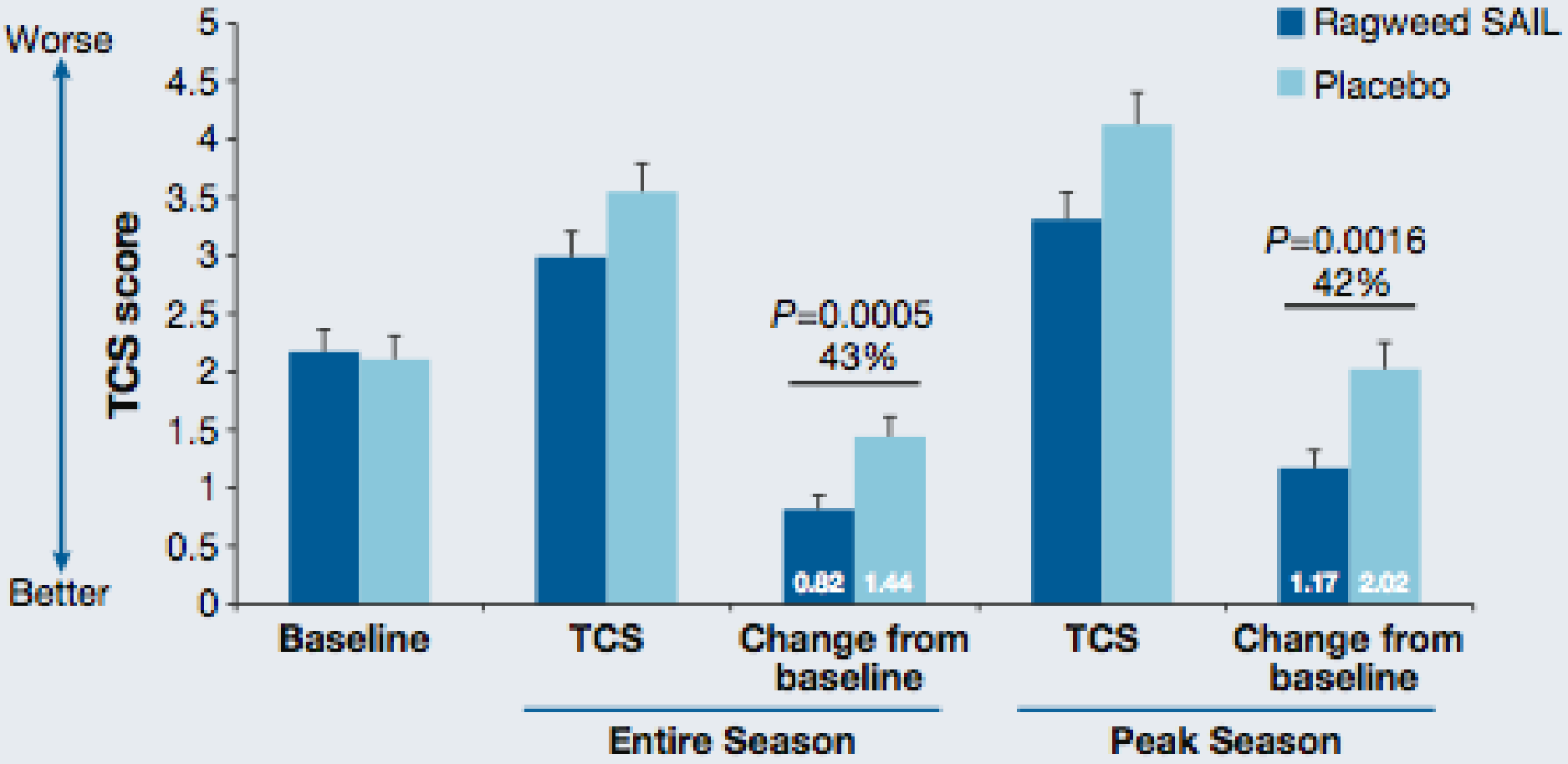
Sublingual-swallow

A Randomized, Double-Blind, Placebo-Controlled, Parallel Trial of Standardized Short Ragweed (RW) Sublingual Allergy Immunotherapy Liquid (SAIL) Extract in Adult Subjects with Ragweed-Induced Allergic Rhinoconjunctivitis

Peter S. Creticos, MD

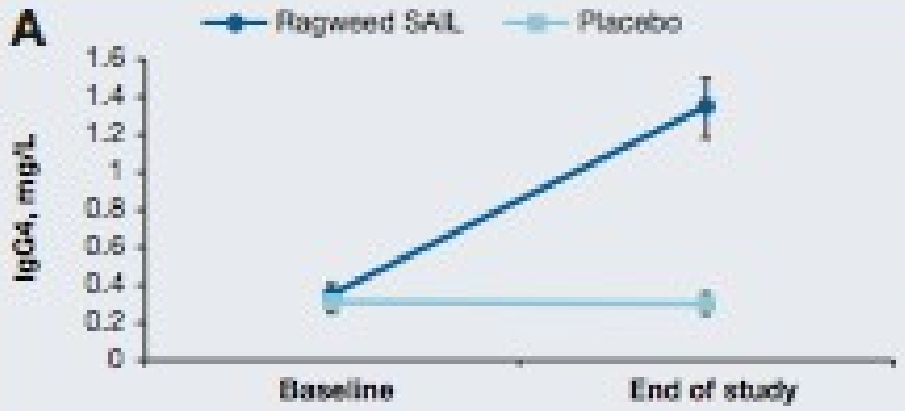
- Phase III—Ragweed extract in 429 patients ages 18-55 with 2 year history of moderate to severe rhinoconjunctivitis
- Self-administered RW-SAIL (target maintenance dose: 42 units Amb a 1 daily) or placebo (PL) [1:1 ratio] started 8–16 weeks prior and continued through the 2011 RW season. Three step process-placebo, 18 units Amb a 1, and 50 units Amb a1
- Pts maintained daily symptom and rescue medication e-diaries. Efficacy endpoints included total combined symptom + medication scores (TCS), daily symptom scores (DSS), IgG4 and IgE ragweed-specific antibody
- Safety was evaluated by AE diaries/lab tests/physical exams

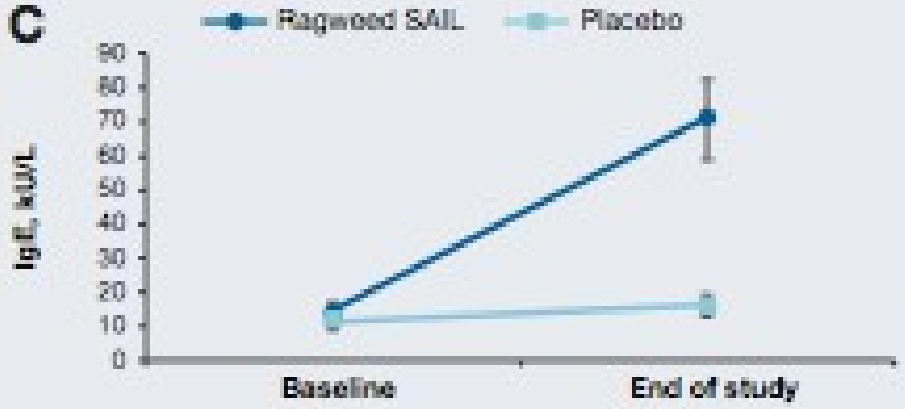
Figure 3. Mean TCS During the Entire and Peak Ragweed Season

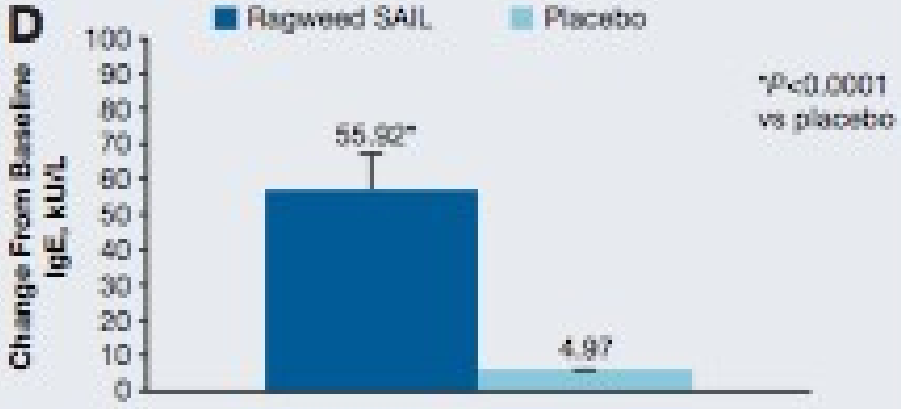


Error bars indicate SE. *P* values designate difference in LS means. Percentages indicate improvement from baseline relative to placebo.
SAIL=sublingual allergen immunotherapy liquid extract; TCS=total combined medication and symptom score.

Figure 5. A) IgG4 at Baseline and End of Study, B) IgG4 Change from Baseline, C) IgE at Baseline and End of Study, and D) IgE Change from Baseline







Error bars indicate SE. *P* values designate difference in LS means.
SAIL=sublingual allergen immunotherapy liquid extract.

Table 2. Most Commonly Reported Treatment-emergent Adverse Events in Study Subjects, Events Reported by ≥2% of Subjects in Either Group

AE, n (%)	Placebo (n=211)	Ragweed SAIL (n=218)
Headache	20 (9)	17 (8)
URI	22 (10)	11 (5)
GI Disorder	13 (6)	18 (8)
Abdominal discomfort/pain	4 (2)	3 (1)
Constipation	0	4 (2)
Diarrhea	7 (3)	5 (2)
Dyspepsia	2 (1)	4 (2)
Oromucosal	5 (2)	22 (10)
Edema/swelling	0	12 (6)
Pain	6 (3)	5 (2)
Pruritus	0	5 (2)
Nasopharyngitis	9 (14)	12 (6)
Skin	8 (4)	10 (5)
Sinus/nasal congestion	10 (5)	4 (2)
Muscle strain	7 (3)	6 (3)
Back pain	7 (3)	6 (3)
Ear disorder	1 (0.5)	4 (2)

SAIL=sublingual allergen immunotherapy liquid extract; URI=upper respiratory infection.

Allergen Immunotherapy Tablets

Timothy Grass AIT

- Nelson HS, Nolte H, Creticos P, Maloney J, Bernstein DI. Efficacy and Safety of Timothy Grass Allergy Immunotherapy Tablet Treatment in North American Adults. JACI Jan 2011; 127(1):72-80

- Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner DP. Efficacy and Safety of Timothy Grass Allergy Immunotherapy Tablet Treatment in North American Children and Adolescents. JACI Jan 2011; 127(1):64-71

Symptom and Medication Scoring

Daily Symptom Score (DSS; Maximum=18)

Individual Symptoms	Maximum Daily Score*
Runny nose	3
Blocked nose	3
Sneezing	3
Itchy nose	3
Red/itchy/gritty eyes	3
Watery eyes	3

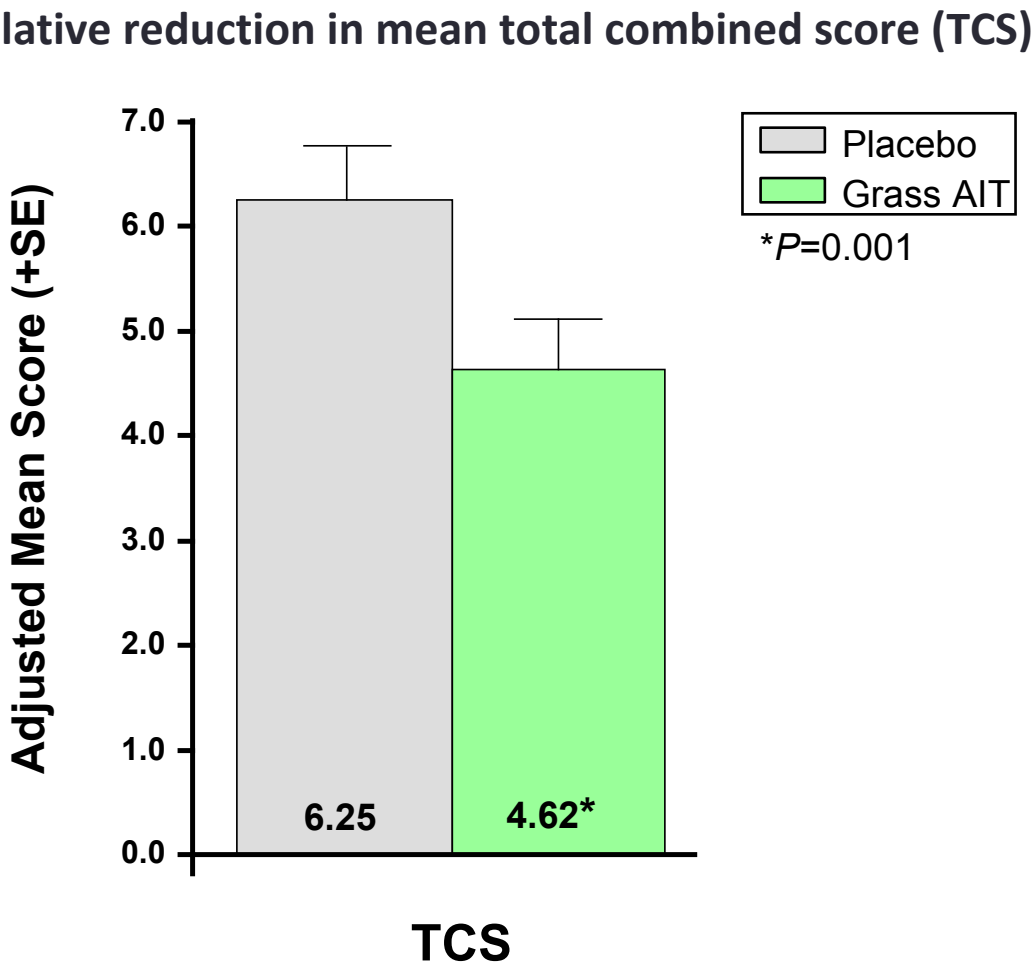
*Symptoms: 0=none; 1=mild; 2=moderate; 3=severe

Daily Medication Score (DMS; Maximum=36)

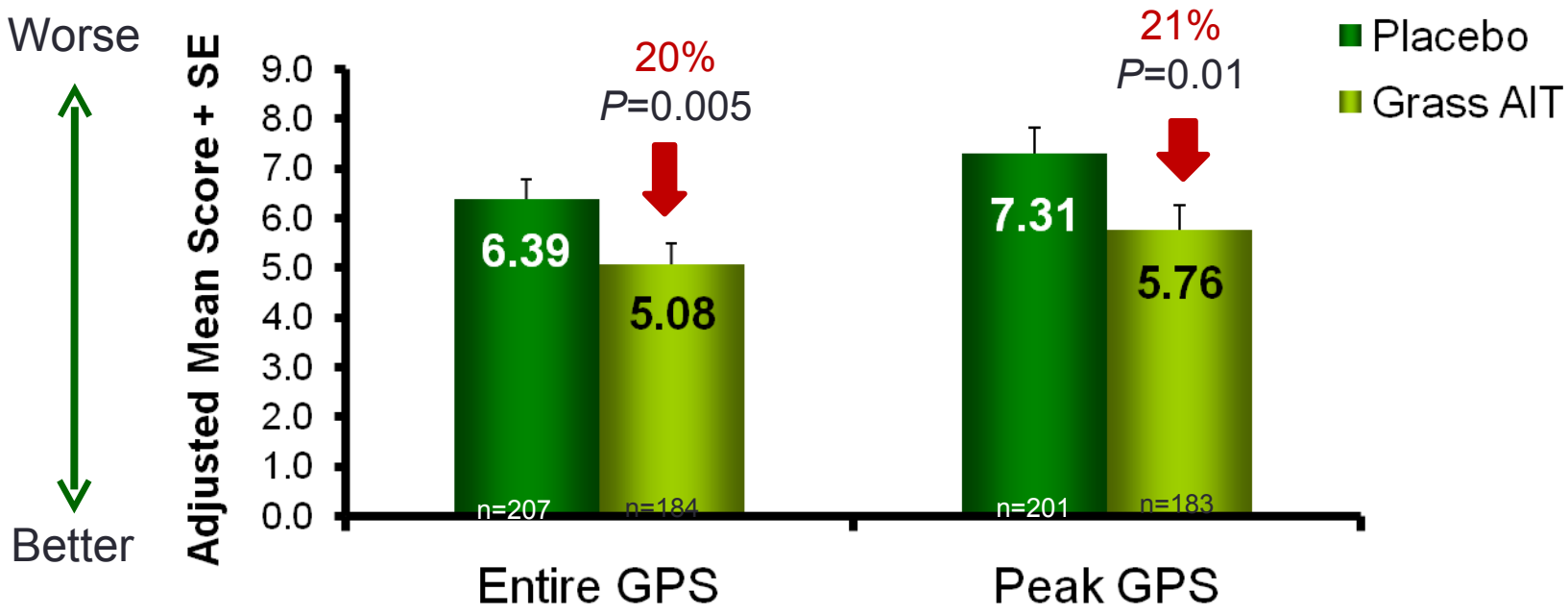
Rescue Medication	Score/Dose Unit	Maximum Daily Score
Loratadine 10-mg tablet*	6 points/tablet	6
Olopatadine HCl 0.1% ophthalmic solution†	1.5 points/drop	6
Mometasone furoate nasal spray 50 µg‡	2 points/spray	8
Prednisone 5-mg tablet§	1.6 points/tablet	16

*One tablet per day ; †1 drop per affected eye twice daily; ‡2 sprays in each nostril once daily; §up to 10 tablets per day.

Total Combined Symptom and Medication Scores: All Sensitization Types Grouped



Reduction in TCS Relative to Placebo



Nelson H, Nolte H, et al. Journal Allergy Clin Immuno 127:72-80, 2011.

Treatment-Related Adverse Events in ≥5% of Subjects

- Most treatment-related adverse events were transient oropharyngeal reactions
- Local oropharyngeal reactions rarely (<4%) led to discontinuation

	Adult Studies		Pediatric Studies	
Treatment-Related Adverse Event, n (%)	**Grass AIT (n=1060)**	**Placebo (n=1036)**	**Grass AIT (n=302)**	**Placebo (n=296)**
Oral pruritus	409 (39%)	47 (5%)	107 (35%)	9 (3%)
Throat irritation	227 (21%)	26 (3%)	75 (25%)	7 (2%)
Ear pruritus	145 (14%)	10 (1%)	25 (8%)	1 (<1%)
Mouth edema	121 (11%)	6 (<1%)	23 (8%)	1 (<1%)
Oral paresthesia	86 (8%)	13 (1%)	N/A	N/A
Stomatitis*	N/A	N/A	26 (9%)	2 (1%)
Lip swelling	N/A	N/A	21 (7%)	0

N/A=not applicable; AE was experienced by <5% of subjects.
*Indicates mild erythema, not lesions or infection.

Grass AIT Was Well Tolerated

- The vast majority (≥96%) of subjects with treatment-related adverse events reported them to be of mild or moderate severity
- Systemic allergic reactions and use of epinephrine were seldom observed

	Adult Studies		Pediatric Studies	
	Grass AIT (n=1060)	**Placebo (n=1036)**	**Grass AIT (n=302)**	**Placebo (n=296)**
Treatment-related adverse event, n (%)				
Any	742 (70%)	236 (23%)	188 (62%)	80 (27%)
Severe	31 (3%)	8 (1%)	3 (1%)	0 (0%)
Systemic allergic reaction, n (%)	5 (<1%)	0 (0%)	0 (0%)	0 (0%)
Epinephrine use, n (%)	5 (<1%)	1 (<1%)	2 (1%)	1 (<1%)

Rhinitis, sinusitis, and upper airway disease

Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: The importance of allergen-specific serum IgE

Linda S. Cox, MD,[a] Thomas B. Casale, MD,[b] Anjuli S. Nayak, MD,[c] David I. Bernstein, MD,[d] Peter S. Creticos, MD,[e] Laurence Ambroisine, MSc,[f] Michel Melac, MD,[f] and Robert K. Zeldin, MD[f] *Fort Lauderdale, Fla, Omaha, Neb, Normal, Ill, Cincinnati, Ohio, Baltimore, Md, and Antony, France*

J Allergy Clin Immunol 2012;130:1327-34

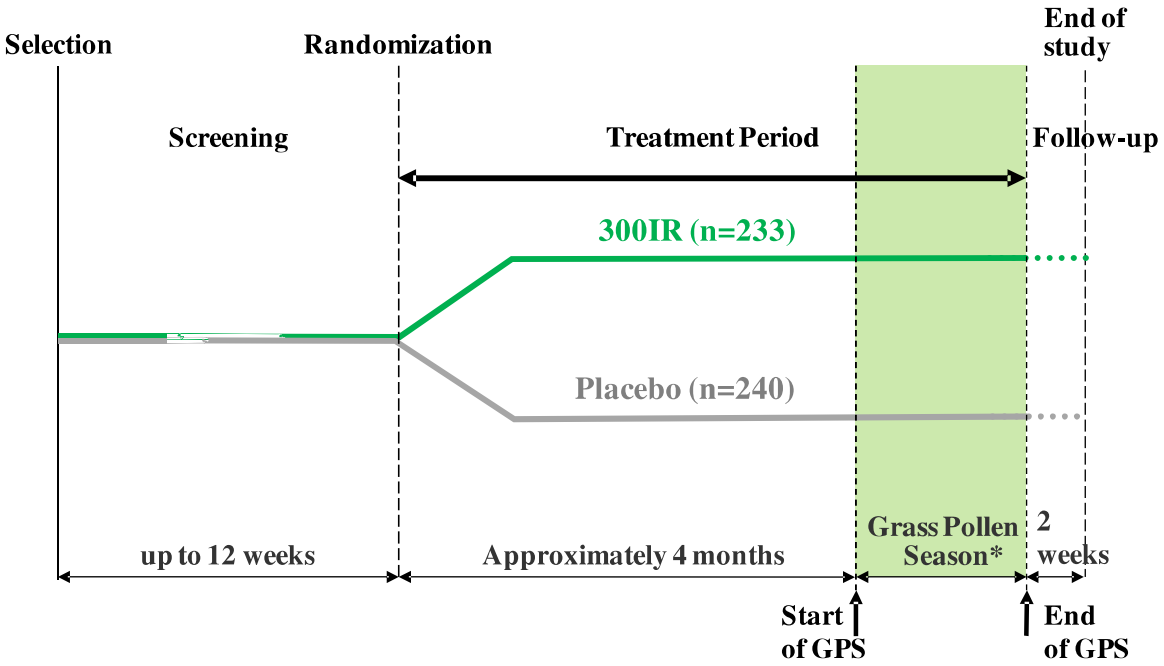
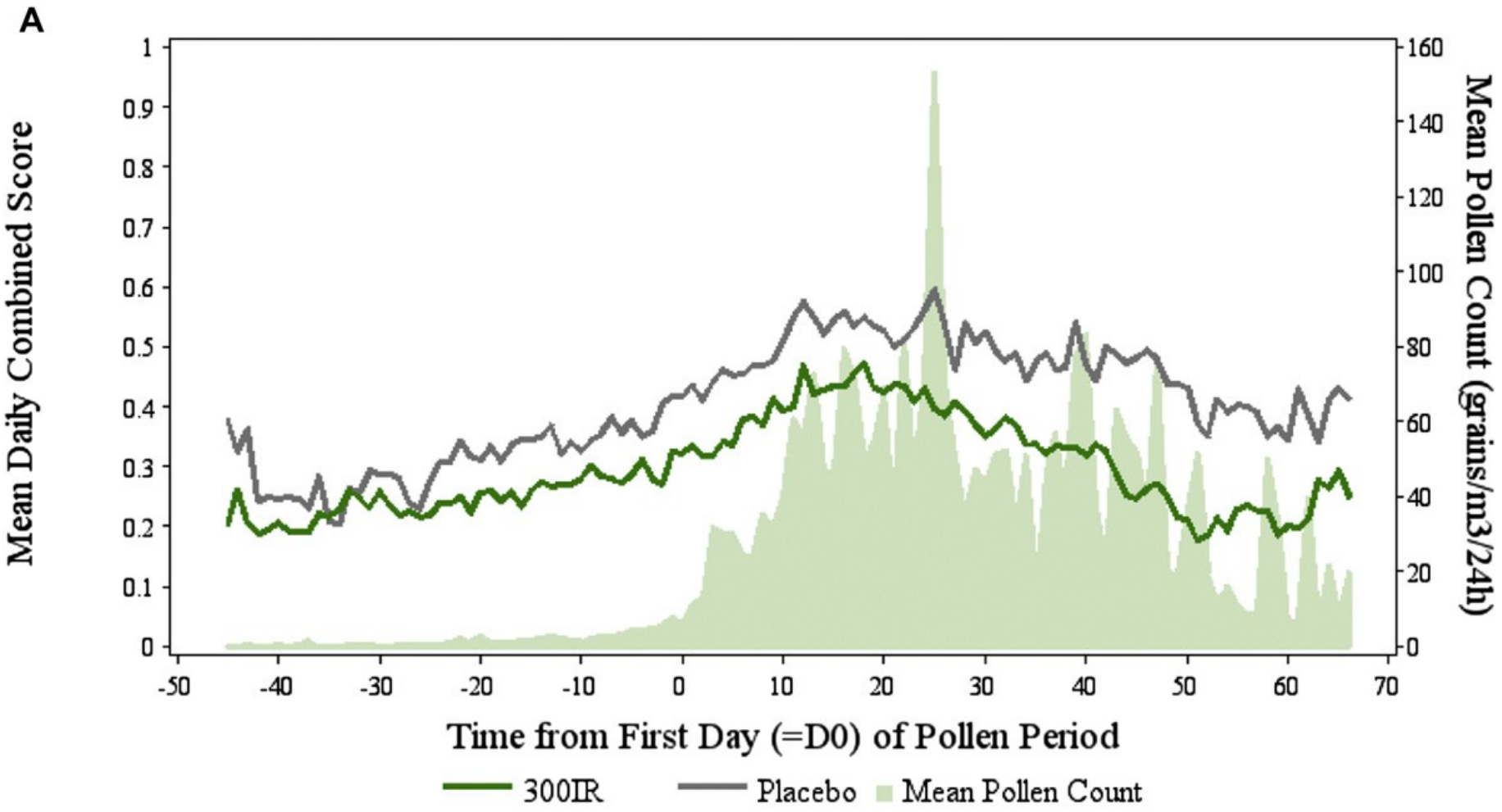


FIG 1. Study design. *Pollen season was defined as starting on the first of 3 consecutive days with a grass pollen count of at least 10 grains/m^3 of air and ending on the last of 3 consecutive days with a grass pollen count of at least 10 grains/m^3 of air. *GPS*, Grass pollen season.

A 5-grass pollen allergen extract (Cocksfoot , Sweet vernal grass , Rye grass , Meadow grass and Timothy)


A
Mean Daily Combined Score
Mean Pollen Count (grains/m3/24h)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160
140
120
100
80
60
40
20
0
-50
-40
-30
-20
-10
0
10
20
30
40
50
60
70
Time from First Day (=D0) of Pollen Period
300IR
Placebo
Mean Pollen Count

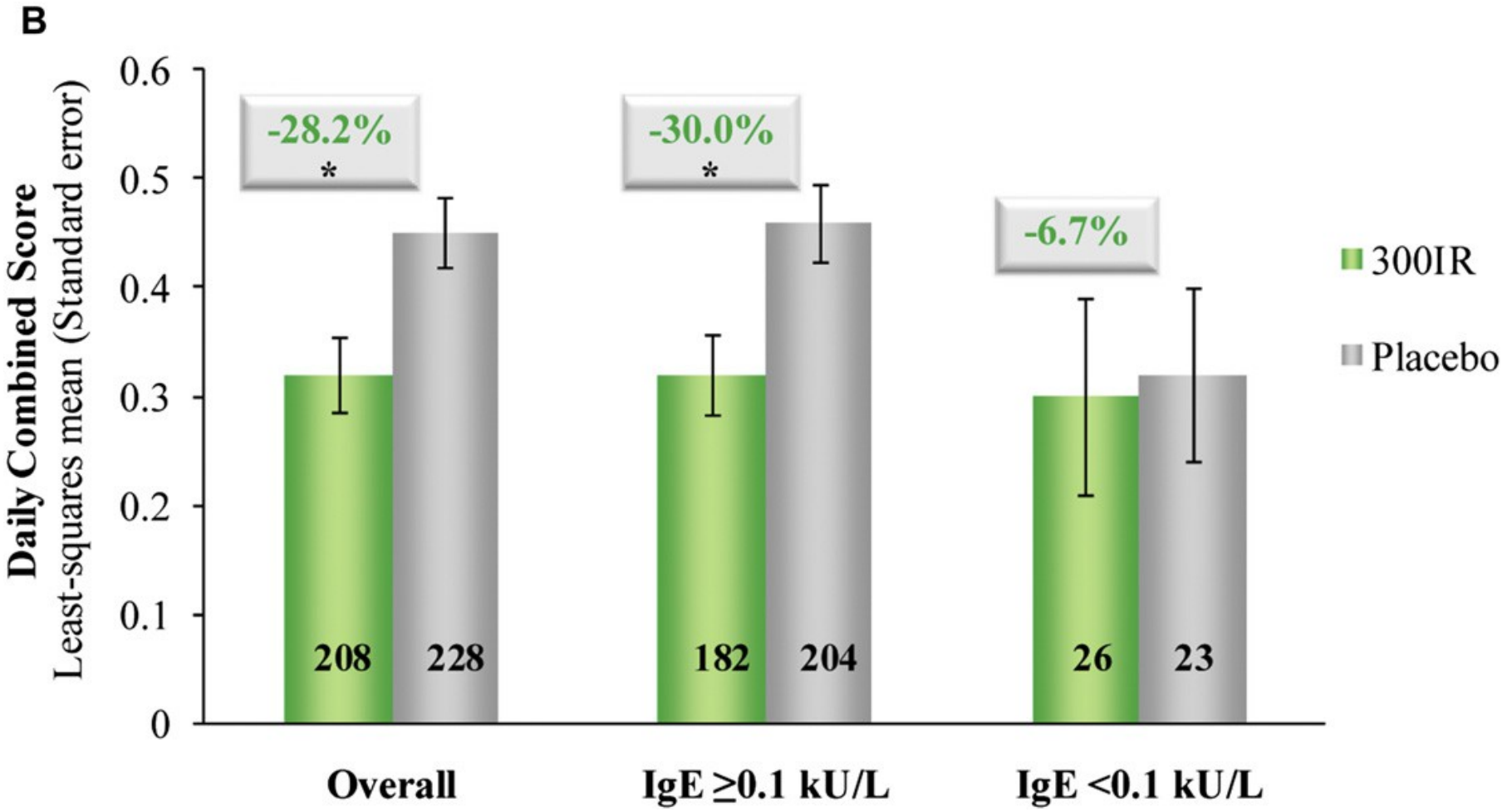


FIG 3. Daily CS (FAS). **A,** Mean daily CS and pollen count. **B,** Daily CS (LS mean ± SE) overall and in subgroups based on timothy grass–specific serum IgE at baseline. The number of participants per group is displayed in each bar. Note: IgE data were not obtained for 1 placebo-treated subject. *$P < .001$ versus placebo.

Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults

Hendrik Nolte, MD, PhD [*]; Jacques Hébert, MD [†]; Gary Berman, MD [‡]; Sandra Gawchik, DO [§]; Martha White, MD [||]; Amarjot Kaur, PhD [*]; Nancy Liu, PhD [*]; William Lumry, MD [¶]; and Jennifer Maloney, MD [*]

Ann Allergy Asthma Immunol 110 (2013) 450–456

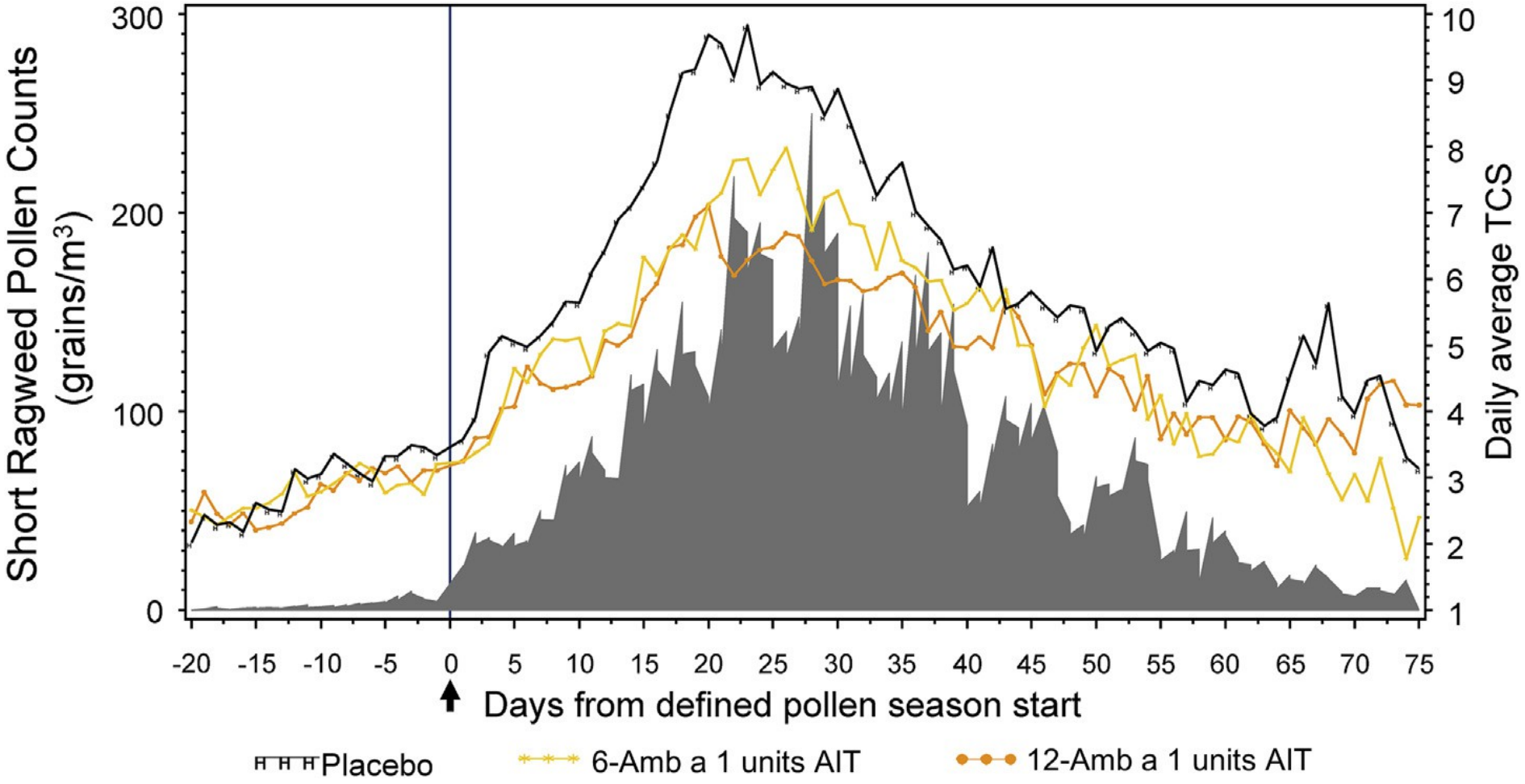


Figure 1. Total combined score (TCS) plotted against pollen count. AIT indicates allergy immunotherapy tablet.

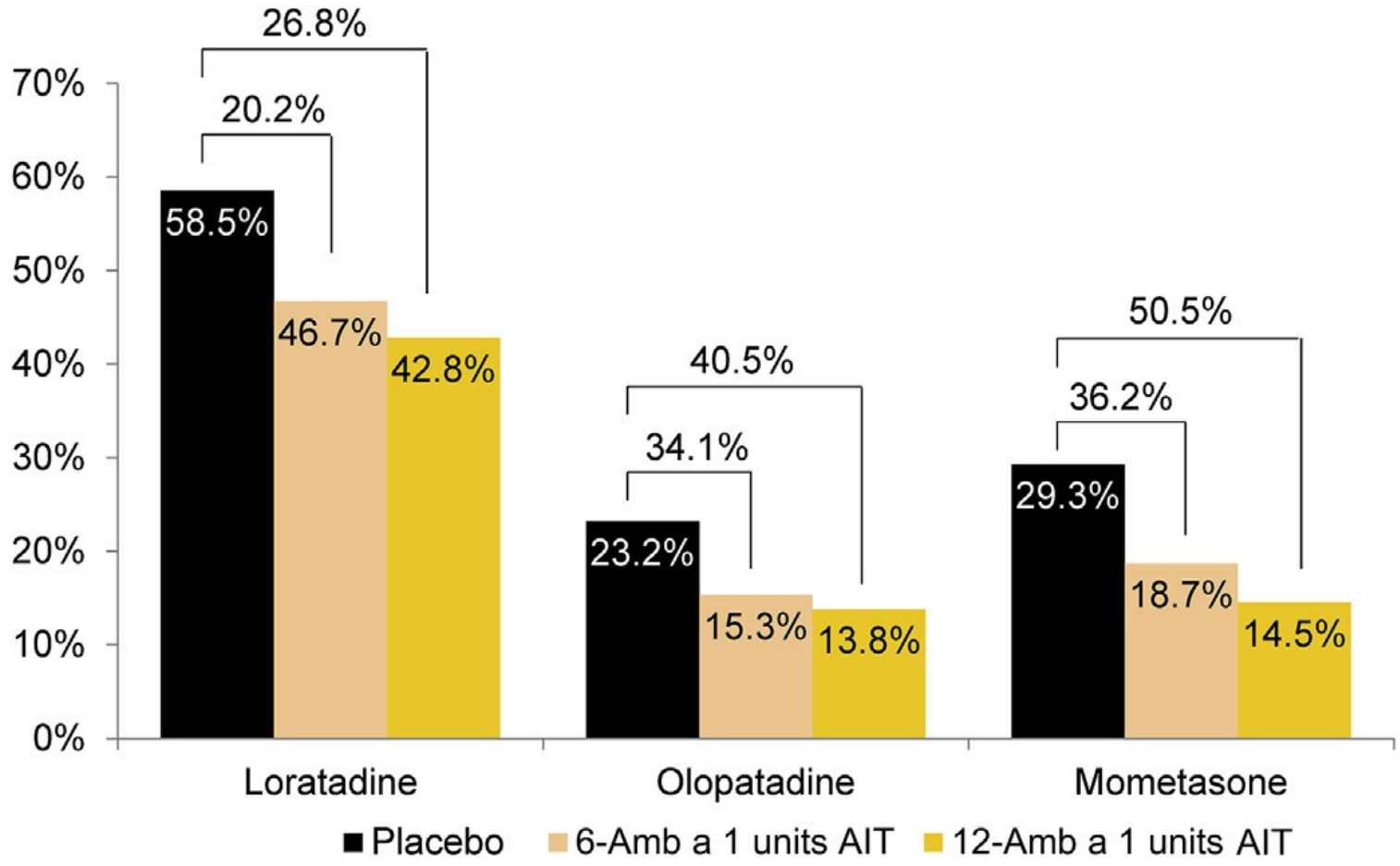


Figure 3. Percentages of patients reporting rescue medication use during peak ragweed season. Values above lines between columns indicate percentage difference vs placebo. AIT, allergy immunotherapy tablet; RS, ragweed pollen season. Difference in rates of rescue medication use between groups were summarized with descriptive statistics only and no assessment of statistical significance was made.

Table 2
Treatment-related treatment-emergent AEs occurring in 2% of patients or more[a]

AE	Patients, %		
	Placebo (n = 188)	Ragweed AIT, 6 Amb a 1 units (n = 190)	Ragweed AIT, 12 Amb a 1 units (n = 187)
Any AE	28.2	58.9	68.4
Ear pruritus	2.1	15.8	16.0
Eye pruritus	0.5	4.2	4.3
Lip swelling	1.6	3.2	7.5
Nausea	0.5	2.1	3.7
Oral pruritus	3.2	18.4	19.2
Oral paraesthesia	2.1	7.4	10.7
Swollen tongue	3.2	11.6	19.3
Tongue edema	0.5	2.1	4.3
Tongue pruritus	1.6	16.8	14.4
Cough	0.0	2.6	4.3
Dry throat	0.5	4.7	2.1
Pharyngeal edema	1.1	3.7	4.8
Throat irritation	5.3	25.3	28.9
Pruritus	0.0	6.3	4.8

Abbreviations: AE, adverse event; AIT, allergy immunotherapy tablet.
[a]Treatment-emergent AE was defined as a new or worsening AE reported on or after treatment start date through treatment stop date plus 30 days; relationship to treatment was assessed by the investigator.

Persistence with Specific Immunotherapy (SCIT & SLIT) Among AR Patients in A US Allergy Practice

- ***Anolik et al AAAAI San Antonio 2013***
- **Methods:** Data from a retrospective chart review study of allergic rhinitis patients managed at a group allergy practice in the US initiating subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) from 2005-2011 were analyzed.

Results

- A total of 3,182 patients were identified, 78% chose SCIT and 22% chose SLIT.
- Only 32.5% of patients completed treatment; 35% of SCIT and 23.7% of SLIT patients.
- Median time on therapy was longer for SCIT patients (3.6 years) versus SLIT patients (2.6 years).
- The full treatment course was completed by 30.2% of adult patients.
- The median time on treatment was substantially greater for adult patients on SCIT compared to SLIT (3 vs.1.6 years, respectively).
- Similar patterns were seen among children

Should all patients on SLIT have a auto-injector of epinephrine available for use? If so, why?

Yes

- Since treatment is done at home
- There is a risk potential risk of anaphylaxis
- Medical-legal concerns

No

- No deaths from AIT; mild systemic reactions only
- Improper use of epinephrine by the patient
- Not required in Europe and UK
- Most allergists in US do not require auto-injectors for patients on SCIT

What are the Cost issues with SLIT in the US?

- Since approved SLIT will be by prescription, coverage may be dramatically different than coverage for SCIT that is prepared and billed by the allergist
- Costs will effect adherence to SLIT
  - de-Olano et al. Annals Allergy 2013 looked at adherence pre and during the recent Spanish recession and showed a significant decrease in SCIT and SLIT adherence during the recession
- With the changes in healthcare, will IT be covered as well as the past?
- Will there be a difference in SCIT vs SLIT in coverage?

Conclusions

- With both grass tablets and ragweed in review by the FDA, we should know within the next 2 months if approved for the US
- Will allergists and others in the US use these new treatments, continue to mix their own SLIT (without clinical data), or only continue SCIT?
- Financial aspects are important
  - Allergists-income on SCIT
  - Changes in healthcare-coverage for SLIT and SCIT