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Sublingual Immunotherapy For Environmental and Food Allergies Is Safe in Real-World Telemedicine Care: Evidence from 23,118 Patient-Years

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Abstract

Background

Sublingual immunotherapy (SLIT) is an effective disease-modifying treatment for allergic respiratory disease and is generally considered safer than subcutaneous immunotherapy. However, large-scale safety data from fully remote telemedicine-based care models remain limited.

Methods

This retrospective longitudinal observational study included patients receiving personalized SLIT through a telemedicine platform between 2020 and 2025. Eligible participants received at least three months of SLIT treatment supply and completed at least one follow-up survey. Adverse events were captured using structured patient-reported surveys and classified according to the Common Terminology Criteria for Adverse Events (CTCAE). Safety outcomes were summarized as patient-level proportion and exposure-adjusted event rates per 100 patient-years. Kaplan–Meier methods were used to evaluate time to first adverse event.

Results

A total of 15,409 patients met inclusion criteria, contributing 23,118 patient-years of treatment exposure. Median treatment duration was 16.3 months (IQR 8.9–25.4), and patients received a median of 5 treatment shipments (equivalent to 15 months of treatment supply). Adverse events were infrequent and predominantly mild. At the patient level, 6.87% reported at least one Grade I adverse event, 1.72% reported Grade II events, 0.08% reported Grade III events, and one patient (0.01%) experienced a Grade IV event unrelated to SLIT. No Grade V events (death) were reported. The overall adverse event rate was 6.40 events per 100 patient-years (95% CI 6.08–6.74), driven primarily by Grade I events (5.10 per 100 patient-years). The most frequently reported adverse events involved the upper respiratory tract and were predominantly mild in severity. Eosinophilic esophagitis was rare, with five new diagnoses (0.03%) and three exacerbations of pre-existing disease (0.02%). Two cases of anaphylaxis (0.01%) were identified, only one of which was considered treatment-related. Kaplan–Meier analysis demonstrated gradual accumulation of adverse events over time without evidence of increasing risk in relationship with treatment duration. Sensitivity analyses found no evidence that adverse events were associated with premature treatment discontinuation.

Conclusion

In this large real-world telemedicine cohort, home-administered SLIT demonstrated a favorable safety profile characterized by predominantly mild adverse events and exceptionally low rates of severe

reactions. Serious systemic reactions, anaphylaxis, and eosinophilic esophagitis were rare despite more than 23,000 patient-years of exposure. These findings support the safety of SLIT in routine clinical practice and suggest that telemedicine-based delivery models can safely facilitate long-term allergen immunotherapy at scale.

Introduction

Allergic rhinitis and related environmental allergies are among the most prevalent chronic conditions worldwide and are associated with substantial symptom burden, impaired quality of life, and increased healthcare utilization [1, 2]. Allergen immunotherapy is distinct from symptomatic pharmacotherapy in that it targets the underlying allergic mechanism and is widely regarded as the only disease-modifying treatment for allergic respiratory disease [3, 4].

Sublingual immunotherapy (SLIT) offers an effective and non-invasive alternative to subcutaneous immunotherapy, with the practical advantage of daily at-home administration [5, 6]. Randomized controlled trials and meta-analyses have consistently demonstrated that SLIT is associated predominantly with mild, localized adverse events, while severe systemic reactions are rare [7, 8].

However, safety findings derived from randomized trials may not fully generalize to routine clinical practice, as study populations are often highly selected and managed under controlled conditions [9, 10]. This distinction is particularly relevant as allergy care increasingly incorporates telemedicine-based models, in which treatment is prescribed and monitored remotely and where patterns of adverse event reporting, adherence, and treatment persistence may differ from traditional settings [11, 12].

Although real-world evidence has become increasingly important in allergen immunotherapy research, large-scale safety data for SLIT in fully remote care environments remain limited. Existing real-world studies have largely been conducted within conventional clinical pathways rather than end-to-end telemedicine platforms [13, 14]. Longitudinal patient-reported data collected through digital platforms may therefore complement trial-based evidence by capturing safety signals across broader and more heterogeneous populations over extended treatment durations [2].

In this study, we evaluated the safety profile of home-administered SLIT using a large real-world registry derived from a telemedicine platform. Leveraging over 23,000 patient-years of exposure, we characterized the incidence, severity, and spectrum of adverse events, as well as their temporal distribution and relationship with treatment duration.

Method

Study Design and Data Source

This retrospective, longitudinal, observational study evaluated the safety profile of home-administered sublingual immunotherapy (SLIT) for environmental and food allergies delivered through a telemedicine

platform (Curex). Patients received personalized SLIT formulations based on allergen sensitivities and were monitored remotely through periodic structured online surveys. At the time of analysis, the platform included 15,409 registered users who had received at least one treatment cycle, defined as a prescription shipment providing a 3-month course of daily SLIT administration, and had submitted at least one follow-up survey. Treatment exposure was defined as the interval from the date of first shipment to the date of last shipment plus the duration of the final 3-month cycle. Total exposure time was aggregated across patients and expressed in patient-years.

Data Collection and Adverse Events

Patient-reported data were collected using the Allergy Response Tracker (ART) survey, a structured longitudinal instrument for repeated remote assessment in a telemedicine setting. In addition to treatment response metrics described elsewhere[15], the ART survey captured patient-reported adverse events, recorded through structured survey fields and classified according to the *Common Terminology Criteria for Adverse Events* (CTCAE). Events were categorized by system organ class and graded by severity (Grade I-V). Event severity was inferred from structured survey responses. For each patient, the highest severity grade experienced for a given event type was recorded; patients could contribute to multiple event categories and severity levels if distinct events occurred. Given the overlap between allergic disease manifestations and known local or systemic reactions to SLIT, certain reported events (e.g., ocular, oropharyngeal, or respiratory symptoms) may reflect underlying disease activity rather than treatment-attributable effects. Attribution of AE to treatment was based on clinical context and available longitudinal records.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics and the occurrence of adverse events. Safety outcomes were reported at patient-level as the proportion experiencing at least one adverse event of a given severity grade, and as exposure-adjusted event rates, calculated as the number of reported events of a given severity grade per 100 patient-years with corresponding 95% confidence intervals. Time-to-event analysis was performed using Kaplan–Meier methods to evaluate time to first adverse event (stratified by severity). Stratified analysis was performed to evaluate AE reporting across observed treatment duration strata and SLIT initiation calendar cohorts. A sensitivity analysis excluding the administratively censored 2025 calendar cohort was performed.

Ethics

All participants provided electronic informed consent at treatment initiation permitting the use of de-identified clinical and survey data for research and quality monitoring. The study was reviewed by an institutional review board (IRB #20254902) and determined not to constitute human subjects research under U.S. federal regulations, and was therefore exempt from approval.

Results

Study Cohort

A total of 15,409 patients met inclusion criteria for the safety study. The mean age was 36.1 years (SD 12.6), and 53.2% of participants were female. Most patients (95.9%) had confirmed IgE sensitization, identified either through prior clinical laboratory testing (n = 6,582, 42.7%) or referral for ImmunoCAP™ testing (n = 8,342, 54.1%); the remaining 485 patients (3.14%) elected to initiate treatment based on clinical history alone, postponing IgE sensitization testing during the study observation period. Patients received SLIT for environmental (n = 15,403, 100.0%) and food allergies (n = 93, 0.60%), of whom 6 patients (0.04%) received treatment exclusively for food allergies. Formulations encompassed a median of 10 antigens per treatment regimen (IQR 5–14, range 1–25). Over two-thirds of the cohort received treatment for allergies to house dust mites (72.7%), cat (72.6%) and dog (67.5%) dander (Table 1). Median treatment duration, based on shipment activity, was 16.3 months (IQR 8.88–25.4; range 2.95–61.3), corresponding to a median of 5 shipments (IQR 3–8, range 1–28) at 3-month dispensing intervals. Participants completed a median of 2 surveys from treatment initiation (IQR 1–4, range 1–18). Across the cohort, total treatment exposure amounted to 23,118 patient-years.

Table 1
Antigens used in SLIT formulations

Antigen	N Treated	%
House dust mite	11207	72.73%
Cat dander	11191	72.63%
Dog dander	10399	67.49%
Orchard grass (*Dactylis glomerata*)	10028	65.08%
Short ragweed (*Ambrosia artemisiifolia*)	9822	63.74%
Bermuda grass (*Cynodon dactylon*)	8780	56.98%
Oak (*Quercus* spp.)	8703	56.48%
Birch (*Betula* spp.)	8297	53.85%
Box elder maple (*Acer negundo*)	7806	50.66%
Cedar (*Juniperus* spp.)	7565	49.09%
Lamb's quarters (*Chenopodium album*)	7540	48.93%
Ash (*Fraxinus* spp.)	7298	47.36%
American elm (*Ulmus americana*)	6944	45.06%
Black walnut tree (*Juglans nigra*)	6830	44.32%
Cottonwood (*Populus* spp.)	6654	43.18%
Alternaria alternata	5485	35.60%
American sycamore (*Platanus occidentalis*)	5405	35.08%
Mold Mix I	246	1.60%
Mesquite (*Prosopis* spp.)	168	1.09%
Cocklebur (*Xanthium* spp.)	68	0.44%
Marsh elder (*Iva* spp.)	51	0.33%
Mold Mix II	44	0.29%
Peanut	30	0.19%
Tree Nut Mix II	29	0.19%
Olive (*Olea europaea*)	28	0.18%
Tree Nut Mix I	25	0.16%
Hen's egg	22	0.14%

Antigen	N Treated	%
English walnut	20	0.13%
Hazelnut	20	0.13%
Almond	16	0.10%
Shellfish Mix	19	0.12%
Cow’s milk	17	0.11%
Fish Mix	16	0.10%
Pecan	12	0.08%
Wheat	14	0.09%
Pistachio	12	0.08%
Soybean	12	0.08%
Cashew	10	0.06%
Shrimp	9	0.06%
Brazil nut	6	0.04%
Crab	6	0.04%
Scallop	6	0.04%
Lobster	4	0.03%
Clam	3	0.02%
Tuna	3	0.02%
Oyster	2	0.01%
Kentucky bluegrass (*Poa pratensis*)	2	0.01%
Lenscale (*Atriplex* spp.)	1	0.01%
Codfish	1	0.01%
Halibut	1	0.01%

Antigen	N Treated	%
*The percentage points add up to > 100% due to treatment with multiple antigens at a time.		
[1]Comprises *Alternaria, Aspergillus, Cladosporium, Helminthosporium*, and *Penicillium* species		
[2]Comprises *Aureobasidium pullulans, Curvularia, Fusarium, Mucor*, and *Rhizopus* species		
[3]Comprises Cashew, Pecan, Pistachio, Walnut		
[4]Comprises Almond, Brazil nut, Coconut, Hazelnut, Peanut		
[5]Comprises Clam, Crab, Maine lobster (*Homarus americanus*), Oyster, Shrimp, Scallops		
[6]Comprises Flounder, Halibut, Codfish, Tuna, Mackerel		

Adverse Events

Adverse events were infrequent and predominantly mild (Table 2). At the patient level, 6.87% of patients reported at least one Grade I AE, 1.72% reported at least one Grade II AE, 0.08% reported Grade III AE, and 0.01% (one patient) reported a grade IV event. No Grade V events (death) were reported. The overall AE rate was 6.40 events per 100 patient-years (95% CI [6.08–6.74]), driven primarily by Grade I events (5.10 per 100 patient-years [4.82–5.40]), with substantially lower rates for Grade II (1.24 [1.10–1.39]), Grade III events (0.05 [0.03–0.09]), and Grade IV events (0.00 [0.00–0.02]).

Table 2
Patent-level summary of reported adverse events

Adverse Event*	Grade I		Grade II		Grade III		Grade IV	
	n	%	n	%	n	%	n	%
Ocular								
Eye pruritus	63	0.41%	23	0.15%	–		–	
Lacrimation	44	0.29%	10	0.06%	–		–	
Eye edema	14	0.08%	3	0.02%	–		–	
Dry eyes	14	0.09%	2	0.01%	–		–	
Eye redness	6	0.04%	–		–		–	
Eye pain	4	0.03%	–		–		–	
ENT								
Nasal congestion	147	0.95%	39	0.25%	–		–	
Sneezing	98	0.64%	21	0.14%	–		–	
Rhinorrhea or post-nasal drip	73	0.47%	19	0.12%	–		–	
Sinusitis	41	0.27%	14	0.09%	–		–	
Throat irritation or pain	78	0.51%	12	0.08%	–		–	
Ear pruritus or congestion	34	0.22%	11	0.07%	–		–	
Nasal irritation or dryness	10	0.06%	4	0.03%	–		–	
Epistaxis	10	0.06%	2	0.01%	–		–	
Tinnitus	7	0.05%	2	0.01%	–		–	
Throat edema	8	0.05%	1	0.01%	–		–	
Gastrointestinal								
Eosinophilic Esophagitis (new onset)	1	0.01%	2	0.01%	2	0.01%	–	
Oral edema	60	0.39%	6	0.04%	1	0.01%	–	
Abdominal pain	11	0.06%	4	0.02%	1	0.01%	–	
Dysphagia	2	0.01%	2	0.01%	1	0.01%	–	
Reflux or dyspepsia	30	0.19%	11	0.07%	–		–	
Oral pruritus or tingling	47	0.31%	9	0.06%	–		–	

Adverse Event*	Grade I		Grade II		Grade III		Grade IV	
	n	%	n	%	n	%	n	%
Ocular								
Nausea	17	0.11%	5	0.03%	–		–	
Eosinophilic Esophagitis (Exacerbation)	–		3	0.02%	–		–	
Vomiting	6	0.04%	2	0.01%	–		–	
Oral pain	5	0.03%	2	0.01%	–		–	
Constipation	4	0.03%	1	0.01%	–		–	
Oral mucositis	4	0.03%	1	0.01%	–		–	
Dry mouth	3	0.02%	1	0.01%	–		–	
Diarrhea	4	0.03%	–		–		–	
Dysgeusia	1	0.01%	–		–		–	
Cardiovascular								
Palpitations and/or tachycardia	8	0.05%	3	0.02%	1	0.01%	1	0.01%
Ventricular tachycardia	–		–		–		1	0.01%
Cardiac arrest	–		–		–		1	0.01%
Respiratory								
Dyspnea	11	0.07%	9	0.06%	2	0.01%	–	
Chest pain	7	0.05%	2	0.01%	1	0.01%	–	
Asthma (new onset)	–		6	0.04%	1	0.01%	–	
Asthma (exacerbation)	38	0.25%	28	0.18%	–		–	
Cough	63	0.41%	24	0.16%	–		–	
Wheezing	21	0.14%	9	0.06%	–		–	
Cutaneous and Hypersensitivity								
Anaphylaxis	–		–		2	0.01%	–	
Urticaria	50	0.32%	18	0.12%	1	0.01%	–	
Generalized angioedema	1	0.01%	2	0.01%	1	0.01%	–	
Eczema	55	0.36%	17	0.11%	–		–	

Adverse Event*	Grade I		Grade II		Grade III		Grade IV	
	n	%	n	%	n	%	n	%
Ocular								
Generalized pruritus	74	0.48%	15	0.10%	–		–	
Non-urticarial rash	88	0.57%	13	0.08%	–		–	
Alopecia	7	0.05%	–		–		–	
Systemic and Constitutional								
Infections	164	1.06%	50	0.32%	1	0.01%	–	
Headache	83	0.54%	22	0.14%	1	0.01%	–	
Dizziness	18	0.12%	5	0.03%	1	0.01%	–	
Somnolence	62	0.40%	11	0.07%	–		–	
Fatigue	23	0.15%	6	0.04%	–		–	
Brain fog	4	0.03%	–		–		–	
Any adverse event	**1058**	**6.87%**	**265**	**1.72%**	**12**	**0.08%**	**1**	**0.01%**

*Severity classified per Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Percentages represent the proportion of patients experiencing at least one event of the specified grade (N = 15,409).

Patients may be counted in multiple severity categories if they experienced events of different grades

The only Grade IV cardiovascular adverse event was a patient-reported cardiac arrest occurring approximately 12 months after SLIT initiation, followed by a ventricular tachyarrhythmia three months later that triggered activation of an implanted cardioverter-defibrillator. The event occurred in the setting of an underlying cardiac arrhythmia disorder and was considered unrelated to SLIT. Treatment was continued thereafter without recurrence of any life-threatening cardiovascular events.

Median time to adverse event was not reached for any adverse event grade during follow-up (Fig. 1). Kaplan–Meier estimated event-free probabilities for severity grades I, II, and III were 91.4% (95% CI [90.8–92.0]), 97.7% (95% CI [97.3–98.0]), and 99.9% (95% CI [99.8–100.0]) at 12 months; 83.5% (95% CI [82.3–84.6]), 95.5% (95% CI [94.9–96.2]), and 99.7% (95% CI [99.5–99.9]) at 24 months; and 75.8% (95% CI [73.5–78.2]), 92.8% (95% CI [91.4–94.2]), and 99.7% (95% CI [99.5–99.9]) at 36 months of follow-up. The probabilities of not reporting adverse events of any severity at 12, 24, and 36 months were 89.8% (95% CI [89.2–90.5]), 81.1% (95% CI [79.9–82.3]) and 72.7% (95% CI [70.4–75.1]), respectively.

The most commonly reported adverse events involved the upper respiratory tract and were predominantly mild in severity. These included nasal congestion (0.95% Grade I; 0.25% Grade II),

sneezing (0.64% Grade I; 0.14% Grade II), rhinorrhea or post-nasal drip (0.47% Grade I; 0.12% Grade II), throat irritation or pain (0.51% Grade I; 0.08% Grade II), and sinusitis (0.27% Grade I; 0.09% Grade II). Lower respiratory symptoms were less frequent and generally mild to moderate, including asthma exacerbations (0.25% Grade I; 0.18% Grade II), cough (0.41% Grade I; 0.16% Grade II), wheezing (0.14% Grade I; 0.06% Grade II), and dyspnea (0.07% Grade I; 0.06% Grade II; 0.01% Grade III). Chest pain was uncommon (0.05% Grade I, 0.01% Grade II, 0.01% Grade III). New-onset asthma was reportedly rare, reported by 0.04% of patients at Grade II and 0.01% at Grade III severity.

Three cases of generalized angioedema (0.02%), including one Grade III event, and two cases of anaphylaxis (0.01% Grade III) were reported. The remainder of cutaneous and hypersensitivity-related events occurred at low frequencies and were predominantly mild. The most frequently reported events included non-urticarial rash (0.57% Grade I; 0.08% Grade II), generalized pruritus (0.48% Grade I; 0.10% Grade II), eczema (0.36% Grade I; 0.11% Grade II), and urticaria (0.32% Grade I; 0.12% Grade II; 0.01% Grade III).

Ocular symptoms included eye pruritus (0.41% Grade I; 0.15% Grade II), lacrimation (0.29% Grade I; 0.06% Grade II), and eye edema (0.08% Grade I; 0.02% Grade II). Gastrointestinal events included oral edema (0.39% Grade I; 0.04% Grade II; 0.01% Grade III), oral pruritus or tingling (0.31% Grade I; 0.06% Grade II), reflux or dyspepsia (0.19% Grade I; 0.07% Grade II), and nausea (0.11% Grade I; 0.03% Grade II). Eosinophilic esophagitis was rare, with five cases of new-onset disease (0.03%) and three exacerbations of pre-existing disease (0.02%).

Systemic and constitutional symptoms were generally mild and included respiratory infections (1.06% Grade I; 0.32% Grade II; 0.01% Grade III), headache (0.54% Grade I; 0.14% Grade II; 0.01% Grade III), somnolence (0.40% Grade I; 0.07% Grade II), fatigue (0.15% Grade I; 0.04% Grade II), dizziness (0.12% Grade I; 0.03% Grade II; 0.01% Grade III), and brain fog (0.03% Grade I) representing the most frequently reported events.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) was identified in n = 5 patients (CTCAE Grades I, II, II, III, III) without a documented diagnosis prior to SLIT initiation (0.02 events per 100 patient-years, 95% CI [0.007–0.050]). Two cases (n = 2) were suspected to be treatment-related (both Grade III). One of these cases developed sublingual swelling and EoE symptoms during treatment, was subsequently diagnosed with EoE, and discontinued SLIT. The other patient experienced esophageal swelling with food impaction while on therapy; EoE was suspected by the treating gastroenterologist, and symptoms reportedly resolved following treatment discontinuation without recurrence. The relationship to treatment was unclear among the remaining identified EoE cases (n = 3). One patient reported dysphagia symptoms predating therapy and subsequently received a formal EoE diagnosis while receiving SLIT, effectively discontinuing treatment (Grade II). A second patient was incidentally diagnosed with asymptomatic esophageal eosinophilia (AEE) while on therapy and discontinued treatment 1 year following diagnoses because of

lack of perceived benefit (Grade I). A third patient received an EoE diagnosis during SLIT and continued treatment while undergoing management with pantoprazole and budesonide (Grade II).

Notably, n = 6 patients with a documented diagnosis of eosinophilic esophagitis (EoE) prior to SLIT initiation were included in this safety evaluation. Five of these patients (n = 5) remained on treatment throughout follow-up despite the underlying EoE diagnosis and only one patient (n = 1) discontinued treatment due to an unrelated reason. Among the five cases continuing treatment, three participants reported flare-ups characterized by recurrence or exacerbation of dysphagia, heartburn, and nausea (n = 3, all Grade II). In two of these cases EoE management was escalated to include *dupilumab*, one of which was associated with a period of high environmental pollen exposure (n = 1).

Notably, none of the patients with newly identified eosinophilic esophagitis or exacerbations of pre-existing disease were receiving food-allergen SLIT formulations. All cases occurred in patients treated for environmental allergies alone.

Anaphylaxis

Two reports of anaphylaxis (both Grade 3) were identified (0.008 events per 100 patient-years, 95% CI [0.001–0.031]). One event was considered treatment-related based on the occurrence of severe anaphylaxis following administration of low-dose therapy, requiring treatment with prednisone and inhalers and resulting in provider-directed discontinuation of SLIT. The second event was classified as unlikely to be treatment-related based on the clinical timeline and subsequent course: the patient experienced a severe allergic reaction of uncertain etiology; no definitive trigger was identified, although chemical, latex, or food exposure was suspected; SLIT was successfully resumed without recurrence of symptoms.

Adverse Event Reporting Across Calendar Cohorts and Treatment Duration

The majority of patients (62.3%) remained on therapy beyond 12 months and a substantial proportion (26.7%) continued for longer than 24 months. Stratified by treatment duration, adverse events were reported by 1.6%, 5.2%, and 5.0% of patients treated for ≤ 3, 4–6, and 7–12 months vs. 9.4%, 13.3%, 16.2%, and 12.8% of patients treated for 13–24, 25–36, 37–48, and ≥ 49 months, respectively (Fig. 2). Across treatment duration strata, reported adverse events were predominantly of Grade I severity; Grade II events were uncommon and Grade III–IV events were rare.

In the overall study cohort, 4.4% initiated SLIT in 2020–2021, 13.5% in 2022, 30.9% in 2023, 34.6% in 2024, and 16.6% in 2025 calendar years (Fig. 3). In calendar cohorts starting treatment in 2020–2021, 2022, 2023, and 2024, treatment was administered for at least 12 months in 94.4%, 77.1%, 81.8% and 64.7%. The longer-term follow-up of the 2025 cohort (N = 2,554) was censored. In calendar cohorts of 2020–2021, 2022, 2023, and 2024, early treatment cessation occurred within 3 months in 0.0%, 4.0%, 1.9%, and 6.5%, between 3 to 6 months in 0.3%, 4.1%, 3.5%, 7.6%, and between 6 to 12 months in 5.3%, 14.8%, 12.8%, 21.2%, respectively.

Adverse event reporting was similar across cohorts with ≥ 2 years of available follow-up, despite the differences in treatment duration, and was observed at lower rates in calendar cohorts censored at the longest available follow-up (Fig. 3). The proportion of patients reporting AE of any severity was 11.9%, 11.6%, and 12.0% among patients initiating treatment during 2020–2021, 2022, and 2023, and was 7.0% and 2.7% in 2024 and 2025 cohorts, respectively. The occurrence of Grade II (range 0.7–3.4%) and Grade III events (range 0.0–0.2%) was uniformly low across calendar cohorts. A sensitivity analysis restricted to calendar cohorts with longer available follow-up (2020–2024) found no evidence of increased AE reporting among patients with early treatment discontinuation (**Supplemental Table 1**).

Discussion

In this large real-world evaluation of home-administered sublingual immunotherapy delivered through a telemedicine platform, adverse events were infrequent and predominantly mild in severity. Across 15,409 treated patients and 23,118 patient-years of exposure, most adverse events were Grade I reactions, while Grade III events were uncommon and only a single Grade IV event was identified. Importantly, the sole Grade IV event occurred in the setting of a pre-existing cardiac arrhythmia disorder and was not attributed to SLIT. No Grade V events were reported. Although local and upper respiratory symptoms represented the most commonly reported adverse events, serious systemic reactions, anaphylaxis, and eosinophilic esophagitis were rare.

Our findings are consistent with the broader SLIT literature demonstrating that adverse events are generally mild, self-limited, and predominantly localized to the oropharyngeal and upper respiratory tract [16–18]. Clinical trials and post-marketing evaluations have consistently reported low rates of severe systemic reactions and a predominance of local symptoms such as oral pruritus, throat irritation, rhinorrhea, and nasal congestion [16, 19]. Similarly, recent pharmacovigilance and real-world studies have concluded that SLIT maintains a favorable benefit-risk profile, with serious adverse events occurring infrequently [18, 20]. The adverse event spectrum observed in the present study closely mirrors these prior observations despite being derived from a large, heterogeneous telemedicine population treated outside of traditional supervised clinical environments.

When considered alongside the published safety literature for subcutaneous immunotherapy (SCIT), the safety profile of SLIT observed in the present study appears particularly favorable. Contemporary comparative analyses have demonstrated significantly lower adverse event rates among patients receiving SLIT relative to SCIT while maintaining comparable treatment effectiveness for allergic conditions [21]. Long-term SCIT cohorts have reported adverse events in approximately one-quarter of treated patients, including measurable rates of systemic reactions and anaphylaxis requiring medical intervention [22]. Similarly, pediatric SCIT studies and meta-analyses have documented systemic reaction rates ranging from approximately 8% to 10%, with occasional severe reactions requiring epinephrine administration [23, 24]. Recent reviews have likewise concluded that systemic reactions occur more frequently with SCIT, whereas SLIT is predominantly associated with mild local adverse effects [17]. Severe reactions in the present SLIT cohort were exceptionally uncommon despite

treatment being administered in an unsupervised home setting. No treatment-related Grade IV or Grade V events were identified, and only two reports of anaphylaxis were observed across more than 23,000 patient-years of exposure, only one of which was directly attributed to treatment. Although direct comparisons between studies should be interpreted cautiously because of differences in patient populations, reporting methodologies, and outcome definitions, the present findings are consistent with the growing body of evidence suggesting that SLIT offers a substantially more favorable safety profile than SCIT.

The occurrence of eosinophilic esophagitis (EoE) remains one of the most frequently cited safety concerns associated with allergen immunotherapy [20, 25, 26]. Previous reviews have identified multiple biopsy-confirmed cases of EoE developing during both oral and sublingual immunotherapy, leading some investigators to propose a causal relationship between repeated allergen exposure and esophageal eosinophilic inflammation [26]. At the same time, analyses of SLIT-tablet clinical trials have reported EoE incidences similar to those observed in the general population [25], while real-world studies have documented only isolated cases during long-term follow-up [20]. In the present study, five patients without a documented prior diagnosis of EoE were identified. Following detailed review, only two cases were considered plausibly treatment-related, while the remaining cases were characterized by pre-existing symptoms, asymptomatic esophageal eosinophilia, or continued treatment despite diagnosis. Notably, six patients with documented EoE prior to SLIT initiation were also identified. Most remained on therapy throughout follow-up and none experienced complications necessitating urgent intervention. Although current SLIT prescribing information generally lists active EoE as a contraindication, emerging evidence suggests that aeroallergen immunotherapy may not uniformly worsen disease activity and may even be associated with improvement in selected patients [27]. While EoE should remain a recognized potential adverse event during SLIT, its occurrence appears uncommon and causal attribution may be challenging in a population characterized by substantial baseline atopic disease.

Similarly, anaphylaxis was rare. Two Grade III anaphylaxis reports were identified, corresponding to 8 events per 100,000 patient-years of exposure. One event was considered likely treatment-related and resulted in discontinuation of therapy, whereas the second occurred in the context of multiple alternative potential triggers and did not recur following successful re-initiation of SLIT. These findings align with prior clinical trial and real-world data demonstrating that anaphylaxis during SLIT is uncommon [20]. Across SLIT-tablet clinical development programs, reported rates of anaphylaxis have been approximately 0.02% of the treated population, with no treatment-related fatalities reported [25]. No fatalities occurred in the present study and no signal suggesting increasing risk with prolonged treatment duration was observed.

We were unable to identify a relationship between adverse event occurrence and premature treatment discontinuation. In sensitivity analyses restricted to calendar cohorts with longer available follow-up, adverse event reporting was not elevated among patients discontinuing treatment within the first year of therapy. Instead, adverse event reporting increased modestly with longer attained treatment duration, likely reflecting greater cumulative opportunity for event reporting rather than treatment intolerance.

Similarly, previous analyses within this cohort demonstrated longer persistence among patients reporting adverse events compared with those who did not [15]. Although these findings should not be interpreted causally, they suggest that adverse events, the majority of which were mild, were not a major driver of treatment discontinuation in this setting. This is also consistent with comparative evidence suggesting that treatment persistence may not substantially differ between SLIT and SCIT despite their differing safety profiles [21].

The favorable safety profile observed in this study has important implications for telemedicine-based allergy care. Unlike SCIT, which generally requires administration in a medical setting because of its parenteral route and the concerns for severe systemic reactions [28, 29], SLIT can be administered at home following prescription and patient education [14, 16, 19, 30, 31]. The present study demonstrates that this approach can be implemented at scale while maintaining low rates of serious adverse events. Our findings support the continued expansion of telemedicine-enabled immunotherapy programs and suggest that remote treatment delivery can preserve safety outcomes comparable to those reported in traditional clinical practice.

Several limitations warrant consideration. First, adverse events were identified through patient-reported survey data and were not subject to direct clinical evaluation, creating the potential for both under-reporting and misclassification. Second, many reported symptoms, particularly those involving the respiratory tract, eyes, and oropharynx, overlap with manifestations of allergic disease itself, making attribution to treatment inherently challenging. Third, the observational design precludes causal inference, particularly regarding the relationship between adverse events and treatment discontinuation. Fourth, although comparisons with SCIT provide useful clinical context, the present study did not include a concurrent SCIT comparator group and therefore any comparison with SCIT remains indirect. Finally, the study reflects the experience of a single telemedicine platform and may not be fully generalizable to other care settings or immunotherapy protocols.

Despite these limitations, this study represents one of the largest real-world evaluations of SLIT safety reported to date and, to our knowledge, the largest conducted within a fully remote care model. Across more than 23,000 patient-years of exposure, home-administered SLIT demonstrated a favorable safety profile characterized by predominantly mild adverse events and exceptionally low rates of severe reactions. Contrasted with the published SCIT safety literature, these findings support the view that SLIT provides a safe immunotherapy modality and enables effective treatment administration through a telemedicine-based care model.

Declarations

Conflicts of Interest:

Several authors were affiliated with Curex Inc., the telemedicine organization operating the personalized SLIT program evaluated in this study. Curex-affiliated authors participated in study design, clinical

operations, data collection, interpretation of findings, and manuscript preparation. Statistical analysis was independently performed by Arx Sciartis LLC, which provided biostatistical support for the study.

Competing Interests

Several authors were affiliated with Curex Inc., the organization operating the personalized SLIT program evaluated in this study. Curex-affiliated authors participated in study design, clinical operations, data collection, interpretation of findings, and manuscript preparation. Statistical analysis was independently performed by Arx Sciartis LLC, which provided biostatistical support for the study.

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Author Contribution

Author contributions: CT, CS, and GK conceived and supervised the study. BH performed the formal analysis, developed the methodology, and prepared the visualizations. CT, JD, KM, CS, GK, TK, JH, and MS contributed to data curation and investigation, with CS and GK also overseeing project administration, funding acquisition, and resources. All authors contributed to validation, manuscript preparation, and critical revision, and approved the final manuscript.

Data Availability

The data analyzed in this study were collected through the Curex telemedicine platform as part of routine clinical care and longitudinal patient-reported follow-up. De-identified data may be made available by the corresponding author upon reasonable request, subject to applicable ethical, legal, and data use requirements.

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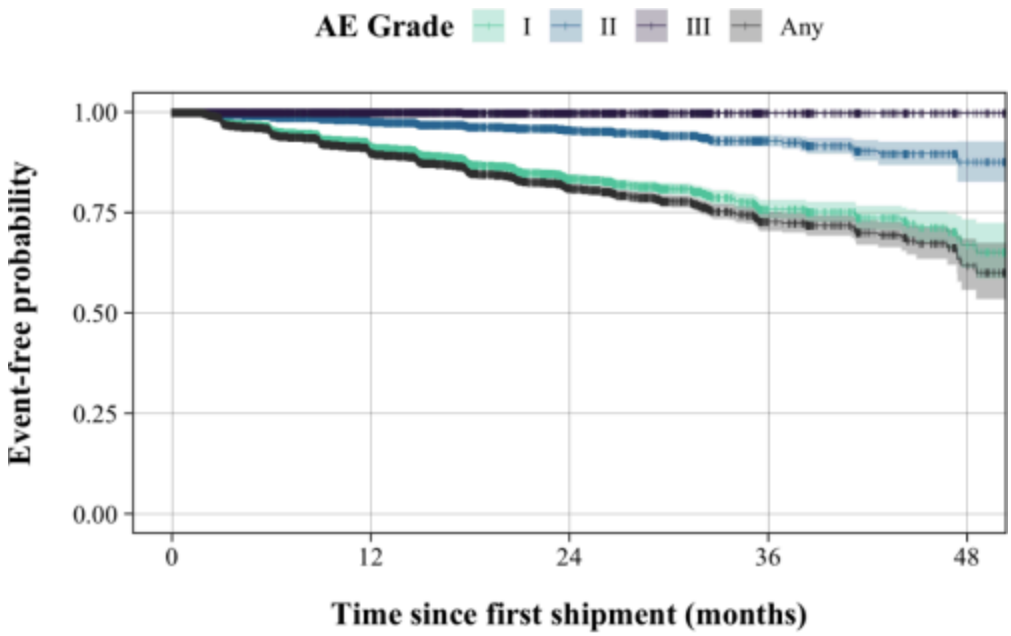
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Figures



Number at risk

I	15200	4542	1295	252	40
II	14407	4312	1253	247	39
III	14154	4228	1226	240	39
Any	15409	4596	1311	256	40

Cumulative number of events

I	0	740	989	1046	1057
II	0	177	238	258	265
III	0	8	12	12	12
Any	0	895	1182	1251	1266

Cumulative number of censoring

I	0	9918	12916	13902	14103
II	0	9918	12916	13902	14103
III	0	9918	12916	13902	14103
Any	0	9918	12916	13902	14103

Figure 1

Time to reported adverse event, stratified by CTCAE severity grade. Adverse event severity grades are non-exclusive; each patient may report events of different severity at a time.

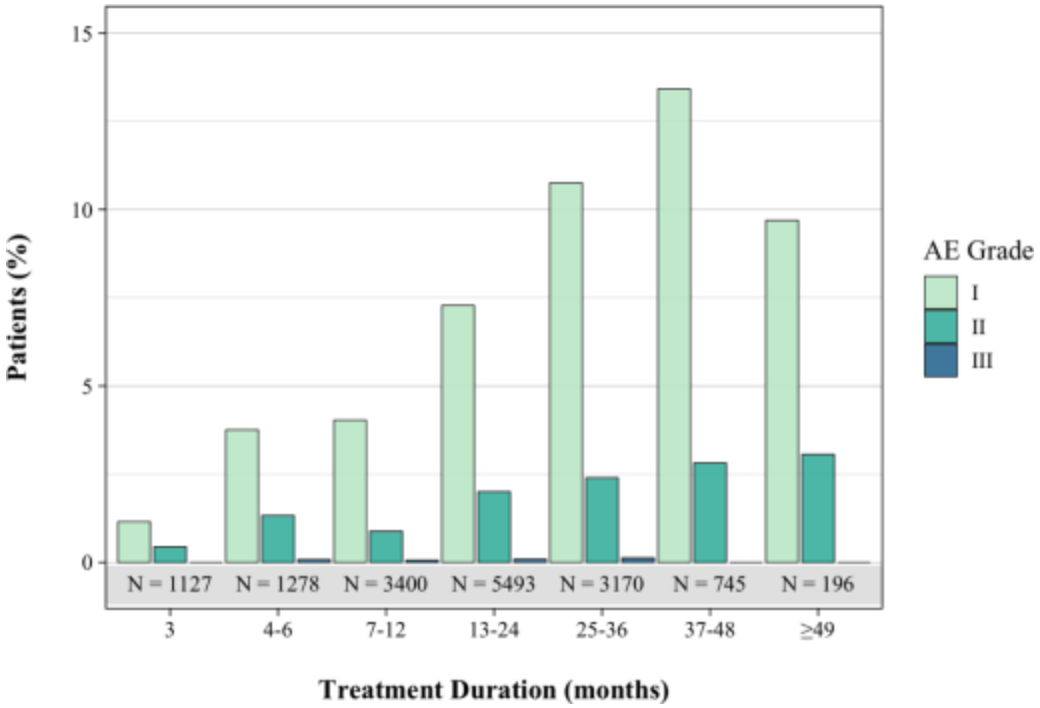
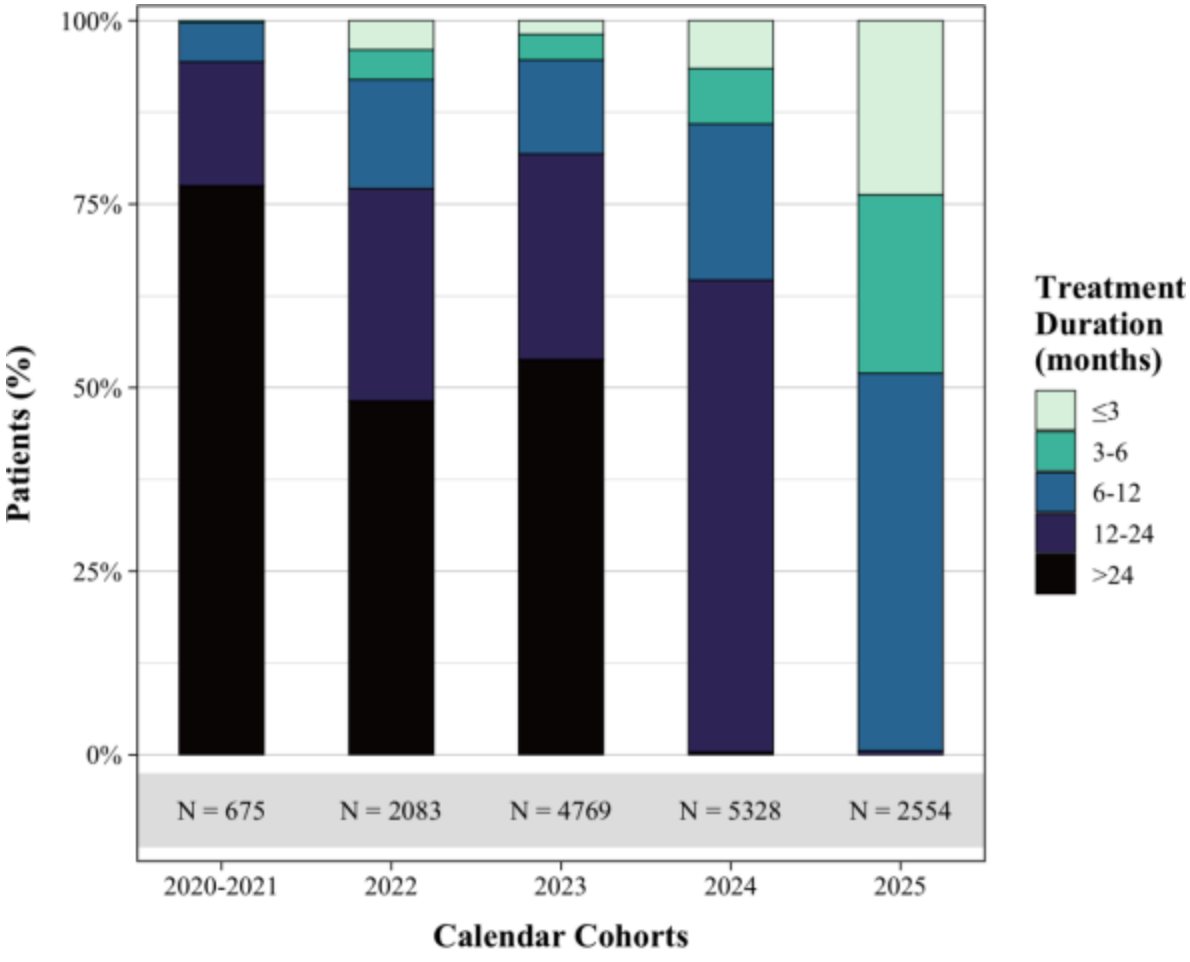


Figure 2

Proportion of patients reporting at least one adverse event of given CTCAE severity grade across treatment duration strata. Treatment duration bins are mutually exclusive; e.g., patients treated for 4-6 months are not included in the 3-months bin. Group sizes are displayed on the gray strip below each bar.



AE Grade	2020-2021	2022	2023	2024	2025
I	62 (9.2%)	202 (9.7%)	464 (9.7%)	278 (5.2%)	52 (2.0%)
II	18 (2.7%)	36 (1.7%)	102 (2.1%)	92 (1.7%)	17 (0.7%)
III	0 (0.0%)	4 (0.2%)	4 (0.1%)	4 (0.1%)	0 (0.0%)
IV	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)
Any	**80 (11.9%)**	**242 (11.6%)**	**571 (12.0%)**	**374 (7.0%)**	**69 (2.7%)**

Figure 3

Treatment duration and adverse event reporting across cohorts starting treatment 2020 through 2025. Stacked bars show the distribution of observed treatment durations. Cohort sizes are displayed beneath each bar. The table presents adverse events by CTCAE grade, reported as patient n (%); grade categories are not mutually exclusive.

Supplementary Files

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- SupplementAACI2026.07.01.docx