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Non-interventional observational study, following the first year of SLIT-Tablet treatment with GRAZAX® or ITULAZAX® to assess persistence and adherence among patients in Norwegian primary care

Anders Østrem

anders.ostrem@outlook.com

Gransdalen Legesenter

Peter Arvidsson

ALK-Abelló (Denmark)

Roger Indbryn

ALK-Abelló (Denmark)

Sverre Steinsvåg

University of Bergen

Article

Keywords:

Posted Date: September 14th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10656823/v1

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Additional Declarations: No competing interests reported.

Title of study

Non-interventional observational study, following the first year of SLIT-Tablet treatment with GRAZAX® or ITULAZAX® to assess persistence and adherence among patients in Norwegian primary care.

A. Østrem[1]; P. Arvidsson[2]; R. Indbryn[2]; S. Steinsvåg[3]
1Gransdalen medical center, Oslo, Norway; 2ALK Nordic A/S Danmark Filial, Gothenburg, Sweden; 3 Depts of ORL, Sørlandet Hospital/ Haukeland University Hospital, University of Bergen, Norway

Corresponding author: Anders Østrem, anders.ostrem@outlook.com

Summary

Sublingual allergen immunotherapy (SLIT) is an effective disease-modifying treatment for moderate to severe allergic rhinitis, but long-term benefit depends on patients completing the recommended three-year treatment course. Real-world evidence on treatment persistence in primary care remains limited. In this prospective, non-interventional, observational study conducted in 17 Norwegian general practices included 204 patients between 6 to 65 years of age. We evaluated one-year persistence, adherence, symptom control, medication use, patient satisfaction and safety among patients treated with the grass and birch pollen SLIT-tablets Grazax and Itulazax. Overall, 78% of patients remained on treatment after one year, exceeding the predefined persistence target of 70%, while self-reported daily adherence remained above 90% throughout the follow-up. Patients reported clinically meaningful improvements in nasal, ocular, bronchial and general allergy symptoms, accompanied by reduced use of symptomatic medication and high treatment satisfaction. Adverse events were common but were predominantly mild or moderate, with no serious treatment-related safety concerns. These findings indicate that SLIT-tablet treatment can be effectively initiated and monitored in routine general practice. Persistence was comparable to that reported from specialist settings, supporting an expanding role for primary care in delivering disease-modifying treatment for allergic rhinitis. Structured follow-up within general practice may contribute to sustained treatment persistence and improve the real-world effectiveness of allergen immunotherapy.

Introduction

Allergic respiratory disease is one of the most prevalent chronic conditions managed in primary care, with allergic rhinoconjunctivitis affecting a substantial proportion of the European population and frequently coexisting with asthma.[1,2,3] In Nordic countries, seasonal pollen allergy represents a major cause of impaired quality of life, reduced work productivity and increased healthcare utilisation. Although often perceived as a trivial disease, allergic rhinitis is associated with significant physical, psychological and socioeconomic burden across age groups.[4,5, 6,7]

Conventional pharmacotherapy, including intranasal corticosteroids and oral antihistamines, provides effective symptomatic relief. However, these treatments do neither modify the underlying immunopathology nor prevent progression of allergic disease. Allergen immunotherapy (AIT) remains the only intervention with disease-modifying potential in IgE-mediated respiratory allergy, capable of inducing long-term immunological tolerance when administered according to guideline-recommended duration.[Error! Bookmark not defined.,Error! Bookmark not defined.,8]

The introduction of sublingual immunotherapy (SLIT) tablets has facilitated the delivery of allergen immunotherapy by enabling home administration after treatment initiation under medical supervision. Compared with subcutaneous immunotherapy (SCIT), this approach reduces the need for repeated clinic visits and may facilitate provision of AIT in appropriately trained primary care settings.[9] In Norway, sublingual allergen immunotherapy (SLIT) is commonly initiated and followed in primary care, with treatment administered at home after the first supervised dose. This model enables general practitioners to play an important role in the delivery and follow-up of disease-modifying treatment for allergic respiratory disease.[10]

However, the clinical effectiveness of AIT in real-world practice is critically dependent on long-term persistence and adherence. Treatment is recommended for a minimum of three consecutive years with daily dosage to achieve sustained benefit. As with other long-term therapies, adherence in routine care is frequently suboptimal, and early discontinuation may substantially attenuate long-term outcomes.[11,12] While prescription database studies and retrospective analyses have reported variable long-term completion rates for SLIT[13,14], prospective real-world data from primary care settings remain scarce. This represents a key evidence gap, particularly in healthcare systems were GPs act as primary prescribers.

Understanding early treatment persistence is especially important, as the first year of therapy may determine the likelihood of completing the recommended treatment course. Evaluating SLIT performance in routine primary care - outside specialist allergy clinics - is therefore essential to improve implementation strategies and optimise population-level impact.

The present prospective non-interventional observational multicentre study aimed to assess persistence and adherence among patients initiating SLIT tablets during the first year of treatment in Norwegian primary care. Secondary objectives included evaluation of safety, symptom evaluation and use of concomitant medication during routine clinical practice. By focusing on real-world delivery within general practice, this study seeks to contribute implementation-relevant evidence to the evolving role of primary care in disease-modifying respiratory allergy management.

Method

Overall study design

This study was a non-interventional, observational, multi-centre, open-label study to investigate persistence, adherence, reasons for early termination, safety, allergy symptoms and symptomatic medication(s) during the pollen season, and to assess patient satisfaction from the first year of treatment with Grazax and Itulazax in adults and paediatric patients in primary care in Norway.
The patients were prescribed Grazax or Itulazax in accordance with the current national approved SmPC and normal clinical practice. The physician's decision to prescribe Grazax or Itulazax was taken independently from the inclusion of the patient in the study. A decision for SLIT treatment on clinical indication was a prerequisite for the inclusion. Patients selected for Grazax treatment were between 5-65 years and Itulazax between the age of 18-65 years, in accordance with the indication at study initiation.
The study was initiated in 2023, and patients were followed for 12 months after first dosing. In total 204 patients were included in the study, and 17 investigators participated in enrolling patients.
When starting a subject on Grazax or Itulazax, the investigator planned 4 patient visits for the study period. Visit 1 was for initiating treatment where the first tablet was taken at the GP's office. Approximately 4 weeks was scheduled between visit 1 and visit 2. Visit 3 was performed after the pollen season 2024, and the final visit one year after initiation (visit 1), see figure 1.

Figure 1. Study design.



Since the study was non-interventional based on the investigator's prescription of Grazax or Itulazax, the number of visits and the duration between the visits were only intended as a guide. However, the Norwegian guidelines also suggest this treatment schedule for initiation and follow up of SLIT.[Error! Bookmark not defined.]
No blood samples were taken, and no renumeration was given to the patients.

Persistence/adherence estimates

At each study visit, patients were asked to report the average number of SLIT-tablets they had taken since the previous visit. For those who had missed doses, the primary reason for non-adherence was recorded. This approach allowed assessment not only of overall adherence levels, but also of factors contributing to missed dosing.
No objective measures of adherence (e.g., electronic monitoring or prescription refill data) were employed in this study.

Patient-reported treatment satisfaction and global assessment

At Visit 3, patients evaluated their rhinoconjunctivitis symptoms during the current pollen season compared with the previous season using a global rating scale (much better, better, same, worse, or much worse). Worsening of symptoms was recorded and assessed as a potential adverse event where applicable.
At the final visit, both patients and investigators independently rated the overall treatment satisfaction (global evaluation) with the SLIT treatment as very satisfied, satisfied, unsatisfied, or very unsatisfied.

Allergy symptoms and medications

Allergy symptoms and use of symptomatic medication were recorded at Visit 1 and Visit 3. Patients reported the presence and severity of nasal, ocular, asthma-related, cutaneous and general symptoms (e.g. fatigue, impaired concentration, reduced physical activity), as well as any other allergy-related complaints.
Symptom severity was graded as mild (transient symptoms without interference with daily activities), moderate (marked symptoms with moderate interference), or severe (considerable interference with daily activities).
Use of symptomatic medication was documented and categorised by route of administration: oral (antihistamines, corticosteroids, leukotriene receptor antagonists), intranasal (antihistamines, corticosteroids, chromones), conjunctival (antihistamines, corticosteroids, chromones), inhaled (corticosteroids, short-acting β_2-agonists, long-acting β_2-agonists), and injectable corticosteroids. Absence of symptomatic medication use was also recorded.

Side effects and safety.

Adverse events (AEs) were defined as any untoward medical occurrence/incident associated with study treatment, regardless of causal relationship. Pre-planned procedures documented at screening and pre-existing conditions identified during screening were not considered AEs unless worsening occurred after informed consent. Serious adverse events (SAEs) were defined as events resulting in death, life-threatening condition, inpatient hospitalisation or prolonged hospital stay, persistent or significant disability/incapacity, congenital anomaly, or other medically important events requiring intervention to prevent such outcomes. Non-serious AEs were those not fulfilling SAE criteria.
Investigators assessed AE severity as mild (transient symptoms, no interference with daily activities), moderate (marked symptoms with moderate interference), or severe (considerable interference with daily activities). Causality was categorised as possible or unlikely in relation to study treatment. Outcomes were recorded as recovered, recovered with sequelae, not recovered, fatal, or unknown.
All AEs occurring from the time of informed consent until the final study visit were systematically recorded in the electronic case report form. Whenever possible, a clinical diagnosis was documented; otherwise, individual symptoms were recorded.
As Grazax has been on the market since 2007, substantial information was available from both clinical trials and post-marketing use, and the product was evaluated to have a well-established safety profile. Thus, it was considered that systematic collection of

non-serious AEs with Grazax would not provide significant new information, and thus not included in this non-interventional study.

Statistical methods.

All data were summarised by descriptive statistics. No formal statistical tests were performed except for the primary objective.

The primary objective was to investigate the proportion of patients that were still in the study at visit 4 (i.e. one year after start of treatment) and still undergoing treatment of Grazax or Itulazax. These patients are defined as “responders”.

The null-hypothesis that the proportion of responders was above 70% was tested using the Exact Binomial test. Assuming the proportion of responders in an infinitively large group is 80%, it was necessary to include 200 patients in order to reach 90% statistical power.

To obtain a ‘real life’ picture, it was important to have a large group of investigators, with a geographical spread and each with a sample of patients, eligible for treatment with Grazax or Itulazax.

Data availability

Data generated by the study site and relevant for the study were recorded in an electronic CRF (eCRF). The sponsor supplied sites with access to eCRF and trained the site staff in the use of the eCRF. There was no access to the eCRF without documented training in the system. All eCRF data were verified and approved by an investigator at the site.

Ethics and data protection

The study was approved by the Norwegian regional ethical committee (REK sør-øst) October 2023. Ref.: 656601.
The patients' written informed consent for collection, processing and use of their data was obtained. The physician's decision to prescribe Grazax or Itulazax was taken independently from the inclusion of the patient in the study. Direct identification of the patients was restricted to the sites that participated in the study.

Results:

A total of 204 patients (123 male and 81 female) were included in the study. Seventeen participating centres, spread across Norway enrolled between one and twenty patients each. The patients’ ages ranged from 6 to 65 years. Nine patients were under 18 years of age, with an age range of 6 to 17 years within this subgroup. Baseline demographic characteristics of the patients are presented in Table 1.

Table 1

Patents characteristics

N=204	Min.	Median	Max	Mean	Std.
Age (years)	6	35.0	65	36.2	11.8
Gender	**Males**	**Females**			
N (%)	123 (60%)	81 (40%)			
Treatment	**GRAZAX®**	**ITULAZAX®**	**Total**		
N (%)	96 (47.1%)	108 (52.9%)	204 (100%)		

N=204	Min.	Median	Max	Mean	Std.
Height (cm)	128.0	175.0	195.0	174.4	11.10
Weight (kg)	26	76.5	150.0	77.8	17.17
BMI	13.5	24.9	46.5	25.4	4.57

N, number of patients; Min., minimum; Max., maximum, Std, standard deviation; BMI, body mass index

Allergy history:

Among the 204 patients, 131 (64%) and 135 (66%) reported having grass and tree pollen allergies, respectively. The primary symptom was rhinoconjunctivitis. As shown in Table 2, a variety of other allergies were also present within the group. The most reported concomitant allergies were animal hair/dander (30%) followed by food (18%), grass (15%) and house dust mite (15%) as shown in table 3.

Table 2:

Primary allergy with rhinoconjunctivitis

Category	Grass	Trees (birch, hazel, alder)	House dust mite	Weed	Animal hair/dander	Mould	Other
Yes	131 (64%)	135 (66%)	8 (4%)	1 (0,5%)	16 (8%)	0 (0%)	1 (0,5%)
No	73 (36%)	69 (34%)	196 (96%)	203 (100%)	188 (92%)	204 (100%)	203 (100%)
Total	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)

Table 3:

Other concomitant allergies

	Grass	Trees (birch, hazel, alder)	House dust mite	Weed	Animal hair/dander	Mould	Food	Other
Yes	31 (15%)	29 (14%)	30 (15%)	4 (2%)	62 (30%)	6 (3%)	37 (18%)	4 (2%)
No	173 (85%)	175 (86%)	174 (85%)	200 (98%)	142 (70%)	198 (97%)	167 (82%)	200 (98%)
Total	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)	204 (100%)

Primary outcome: persistence

The proportion of patients remaining on treatment according to the study protocol decreased over time but remained high throughout the study. At Visit 2, 93% of patients were persistent with treatment, decreasing to 81% at Visit 3 and 78% at the final visit.

The proportion of patients who discontinued treatment was low, at 4% at Visit 2, 8% at Visit 3, and 1% at the final visit. Missing data increased over time, from 3% at Visit 2 to 20% at the final visit.

The proportion of patients who were still following the study protocol and continued treatment is displayed in Error! Reference source not found. 4.

Table 4.

Persistence during the study period.

	Visit 2	Visit 3	Visit 4/Last visit
Missing	6 (2,9%)	22 (10,8%)	41 (20,1%)
Yes	190 (93,1%)	165 (80,9%)	160 (78,4%)
No	8 (3,9%)	17 (8,3%)	3 (1,5%)
Total	204 (100%)	204 (100%)	204 (100%)
One-sided P-value[1] H_0 proportion "Yes"<70%	0.0000	0.0003	0.0088
95% CI "Yes"	89% , 96%	75% , 86%	72% , 84%

[1] Exact Binomial Test. One-sided.

Persistence rates were consistently above the predefined threshold of 70% at all time points. The lower bounds of the 95% confidence intervals were 89% at Visit 2, 75% at Visit 3, and 72% at the final visit, with statistically significant one-sided p-values at all visits ($p \leq 0.0088$).

Secondary outcomes

Patient adherence

Adherence to treatment was high across all visits. At Visit 2, 90% of patients reported taking the treatment daily, with similar proportions observed at Visit 3 (90%) and the final visit (92%). A small proportion of patients reported taking treatment six times per week (5%, 7%, and 8% at Visits 2, 3, and final visit, respectively), while very few patients reported lower adherence levels, as shown in table 5.

Table 5.

Adherence during the study period.

Category	Visit 2	Visit 3	Visit 4/Last visit
Missing	6 (NA)	25 (NA)	42 (NA)
Every day	179 (90%)	151 (90%)	140 (92%)
6 times/week	10 (5%)	12 (7%)	13 (8%)
5 times/week	0 (0%)	0 (0%)	0 (0%)
4 times/week	0 (0%)	5 (3%)	0 (0%)
3 times/week	9 (5%)	0 (0%)	0 (0%)
Total	204 (NA)	193 (NA)	195 (NA)

** NA: Not applicable*

Among patients who did not take treatment every day, the most reported reason was forgetfulness, accounting for 53% (10 patients) at Visit 2, 71% (20 patients) at Visit 3, and 95% (21 patients) at the final visit. Adverse events were a less frequent reason (11% at Visit 2 and 7% at Visit 3) and were not reported at the final visit. Other reasons were infrequently reported.

Early discontinuations

Overall, 160 patients (78%) completed the study, while 44 patients (22%) discontinued treatment and/or withdrew from the study. Adverse events were the primary reason for discontinuation in 24 patients (12% of the total study population), corresponding to 54.5% of those who discontinued. The primary reasons for discontinuation are displayed in table 6.

Table 6.

Discontinuation from the study.

Primary reason for discontinuation from the study	N=44 (%)
Adverse event	24 (54.5%)
Lost to follow-up	10 (22.7%)
Non-compliance with protocol	6 (13.6%)
Never bought the study medicine	1 (2.3%)
Did not want to continue, no other reason	1 (2.3%)
Mental health issues	1 (2.3%)
Other health issues hindered adherence to study medication	1 (2.3%)

Allergy symptoms and symptomatic medications during the pollen season

Allergy symptoms showed a general improvement from Visit 1 to Visit 3 across all symptom domains.

At Visit 1, nasal symptoms were moderate (65%) or severe (30%), improving at Visit 3 to 34% and 5% respectively, while patients reporting no symptoms increased from 1% to 15%. Similarly, eye symptoms improved over time: moderate and severe symptoms

decreased from 59% and 26% at Visit 1 to 27% and 6% at Visit 3, respectively, while the proportion of patients without symptoms increased from 1% to 22%. (See figure 2 and table 7)

Figure 2.

Change in allergy symptoms.

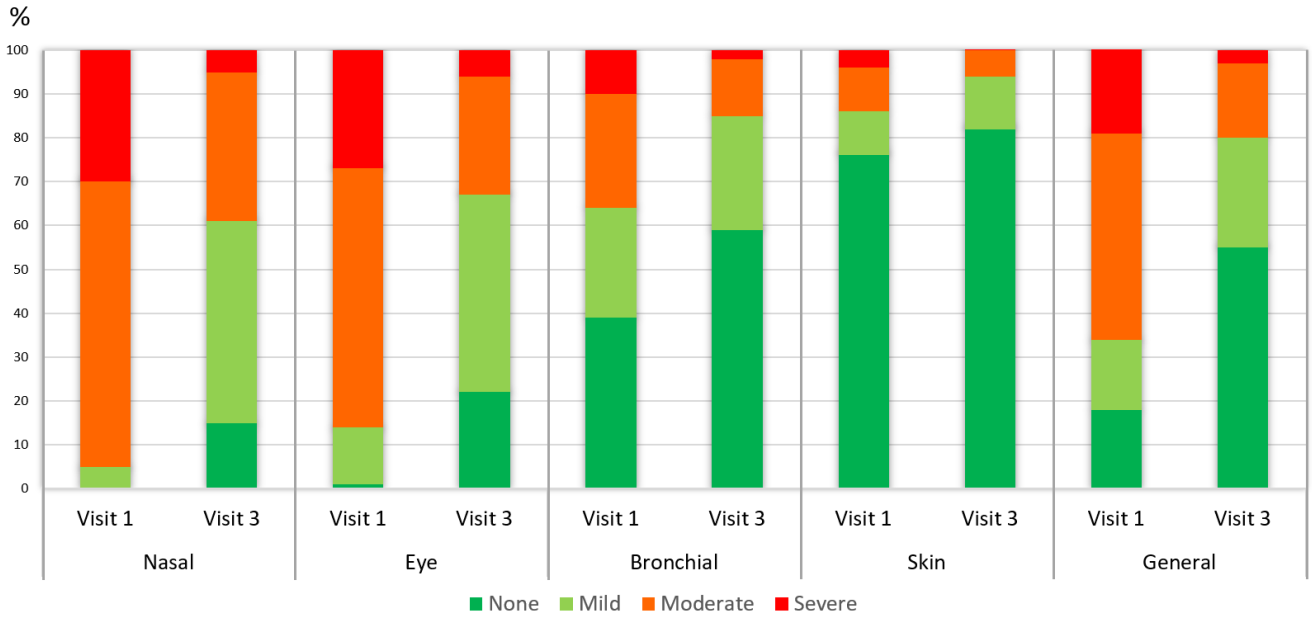


Table 7.

Allergy symptoms during the pollen season

Category	Nasal symptoms		Eye symptoms		Bronchial symptoms	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
None	1 (0%)	27 (15%)	3 (1%)	40 (22%)	80 (39%)	105 (59%)
Mild	10 (5%)	83 (46%)	27 (13%)	80 (45%)	50 (25%)	47 (26%)
Moderate	132 (65%)	60 (34%)	120 (59%)	48 (27%)	54 (26%)	23 (13%)
Severe	61 (30%)	9 (5%)	54 (26%)	11 (6%)	20 (10%)	4 (2%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)

Category	Skin symptoms		General symptoms	
	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)
None	156 (76%)	146 (82%)	36 (18%)	99 (55%)
Mild	20 (10%)	21 (12%)	33 (16%)	45 (25%)
Moderate	20 (10%)	10 (6%)	95 (47%)	30 (17%)
Severe	8 (4%)	2 (1%)	40 (20%)	5 (3%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)

Bronchial symptoms were less common, but also improved, with the proportion of patients reporting no symptoms increasing from 39% at Visit 1 to 59% at Visit 3, and severe symptoms decreasing from 10% to 2%. Skin symptoms were infrequent, with most patients reporting no symptoms at both visits (76% and 82%, respectively), and only small proportions reporting moderate or severe symptoms.

General symptoms were more pronounced at baseline, with 47% and 20% of patients reporting moderate and severe symptoms, respectively. By Visit 3, this had improved substantially, with 17% and 3% reporting moderate and severe symptoms respectively. Patients reporting no symptoms increased from 18% to 55% at Visit 3.

Use of symptomatic allergy medications was common, particularly oral antihistamines, which were reported by 99% of patients at Visit 1 and 84% at Visit 3. Oral corticosteroids were used by a minority of patients (8% at Visit 1 and 2% at Visit 3), while leukotriene antagonists were rarely used (1% and 0%, respectively). No use of other oral medications was reported.

Intranasal treatments were also frequently used. Nasal antihistamines were reported by 42% of patients at Visit 1 and 34% at Visit 3, while nasal corticosteroids were used by 50% and 27%, respectively. Other nasal treatments, including chromones, were rarely used (≤2%).

Conjunctival antihistamines were used by 54% of patients at Visit 1 and 37% at Visit 3. Conjunctival corticosteroids, chromones, and other treatments were infrequently reported (≤5% at both visits). See table 8 and figure 3

Table 8.

Symptomatic allergy medications during the last pollen season

Category	Oral		Oral		Oral	
	Antihistamines		**Corticosteroids**		**Leukotriene antagonists**	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	202 (99%)	151 (84%)	17 (8%)	3 (2%)	2 (1%)	0 (0%)
No	2 (1%)	28 (16%)	187 (92%)	176 (98%)	202 (99%)	179 (100%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)
Category	**Oral**		**Nasal**		**Nasal**	
	Other		**Antihistamines**		**Corticosteroids**	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	0 (0%)	0 (0%)	85 (42%)	61 (34%)	103 (50%)	48 (27%)
No	204 (100%)	179 (100%)	119 (58%)	118 (66%)	101 (50%)	131 (73%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)
Category	**Nasal**		**Nasal**		**Conjunctival**	

Category	Oral		Oral		Oral	
	Antihistamines		Corticosteroids		Leukotriene antagonists	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
	Chromones		Other		Antihistamines	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	1 (0%)	0 (0%)	3 (1%)	3 (2%)	110 (54%)	66 (37%)
No	203 (100%)	179 (100%)	201 (99%)	176 (98%)	94 (46%)	113 (63%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)
Category	Conjunctival		Conjunctival		Conjunctival	
	Corticosteroids		Chromones		Other	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	4 (2%)	1 (1%)	4 (2%)	3 (2%)	10 (5%)	3 (2%)
No	200 (98%)	178 (99%)	200 (98%)	176 (98%)	194 (95%)	176 (98%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)

Symptomatic asthma treatment was reported less frequently. Inhaled corticosteroids were used by 12% of patients at both visits. Use of short-acting β2-agonists decreased from 12% at Visit 1 to 8% at Visit 3, while long-acting β2-agonists decreased from 6% to 4%. Injectable corticosteroids were reported by 19% of patients at Visit 1, declining to 4% at Visit 3. Other inhaled or injectable treatments were rarely used (≤1%). (See table 9 and figure 3)

Table 9.

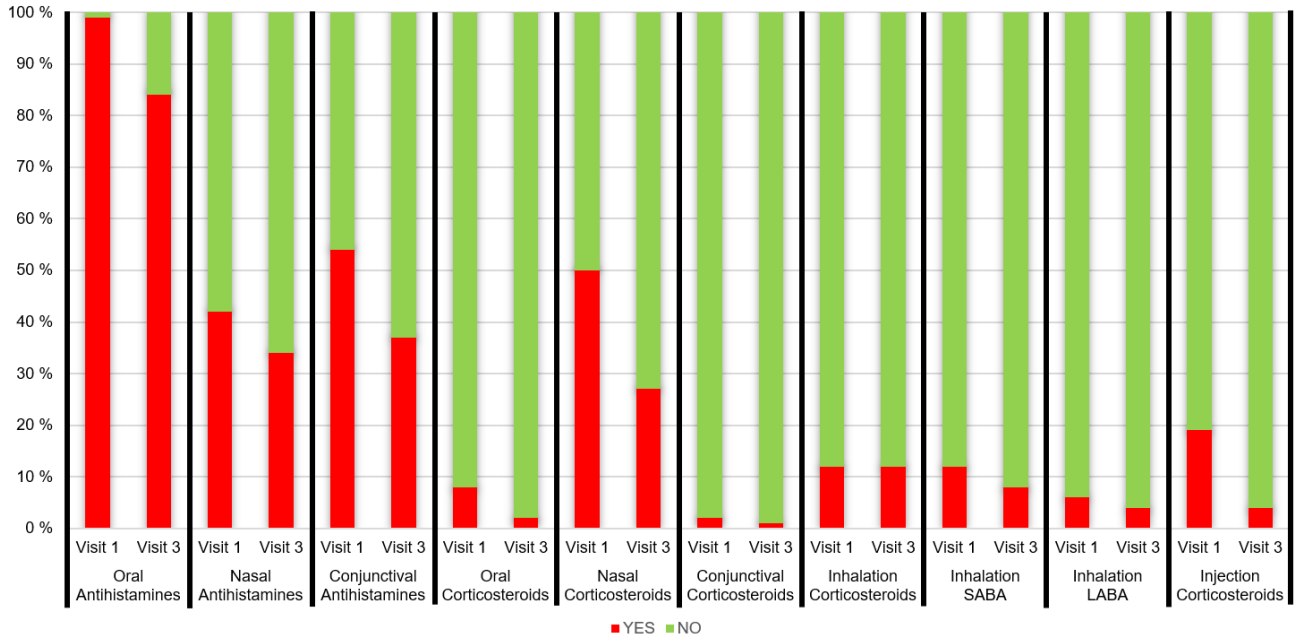
Symptomatic asthma treatment during the last pollen season

Category	Inhalation		Inhalation		Inhalation	
	Corticosteroids		Short acting β2-agonists (SABA)		Long acting β2-agonists (LABA)	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	24 (12%)	22 (12%)	24 (12%)	14 (8%)	12 (6%)	8 (4%)
No	180 (88%)	157 (88%)	180 (88%)	165 (92%)	192 (94%)	171 (96%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)
Category	Inhalation		Injection		Injection	
	Other		Corticosteroids		Other	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3

Category	Inhalation Corticosteroids		Inhalation Short acting β2-agonists (SABA)		Inhalation Long acting β2-agonists (LABA)	
	Visit 1	Visit 3	Visit 1	Visit 3	Visit 1	Visit 3
Missing	0 (NA)	25 (NA)	0 (NA)	25 (NA)	0 (NA)	25 (NA)
Yes	1 (0%)	2 (1%)	39 (19%)	8 (4%)	0 (0%)	0 (0%)
No	203 (100%)	177 (99%)	165 (81%)	171 (96%)	204 (100%)	179 (100%)
Total	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)	204 (NA)

Figure 3.

Change in symptomatic medication



Patient satisfaction during the first year of treatment

Patient-reported satisfaction after the first year of treatment indicated generally positive outcomes. Overall, 27% of patients reported feeling much better and 41% reported feeling better, while 31% experienced no change. Only 1% reported feeling much worse, and no patients reported feeling worse. Data were missing for 25 patients.

At Visit 4, overall experience with treatment was assessed both by patients and investigators. Among patients, 38% reported being very satisfied and 54% satisfied, while 7% reported being unsatisfied and none reported being very unsatisfied. Investigators reported similar findings, with 43% rating patients as very satisfied and 51% as satisfied, while 6% were considered unsatisfied and none very unsatisfied. Data were missing for 42 patients in both assessments.

Overall, both patient- and investigator-reported outcomes indicate a high level of satisfaction with treatment using Grazax or Itulazax. At the final visit (after one year of treatment), both patients and investigators expressed high satisfaction, with 94% and 95% respectively reporting Satisfied or Very satisfied experience of treatment. (Table 10)

Table 10.

Overall experience by taking Grazax or Itulazax (Visit 4)

Category	What is the subject's overall experience of the Grazax or Itulazax treatment?	What is the investigator's overall experience of the Grazax or Itulazax treatment?
Missing	44 (NA)	44 (NA)
Very satisfied	62 (39%)	70 (44%)
Satisfied	88 (55%)	82 (51%)
Unsatisfied	10 (6%)	8 (5%)
Very unsatisfied	0 (0%)	0 (0%)
Totalt	204 (NA)	204 (NA)

Safety results

Adverse events

All patients received the first dose under medical supervision. During the first administration, adverse events were reported in 46 patients (23%) treated with Itulazax, corresponding to 43% of patients in that group. As collection of adverse events for Grazax were not a requirement for this study, no events were recorded. Overall, 77% of patients experienced no adverse events at first dosing, and data were missing for one patient.

Across the full study period, 96 patients (47%) experienced a total of 195 adverse events. Most events were assessed as possibly related to treatment (98%), while 2% were considered unlikely to be related.

Most adverse events were mild (57%) or moderate (36%) in severity, with a smaller proportion classified as severe (7%). No serious adverse events were reported. Consequently, all recorded events were considered non-serious.

Severe and serious adverse events

Eight patients (4%) experienced a total of 13 severe adverse events (7% of all events). Treatment was permanently discontinued in five patients and temporarily interrupted in one patient. Of the severe events, 11 resolved, one reporting urticaria leading to discontinuation of the treatment, and one reporting tingling in the mouth, continued the treatment without any action or additional treatment given. A total of 24 patients (12%)

discontinued treatment due to adverse events. No serious adverse events were reported during the study.

Discussion

This non-interventional study provides a real-world evaluation of persistence, adherence, symptom development, patient-reported outcomes, and safety during the first year of sublingual immunotherapy (SLIT) with Grazax or Itulazax in Norwegian primary care. Overall, the findings suggest that SLIT-tablet treatment can be effectively implemented in a general practice setting, with outcomes comparable to those reported in specialist care.[Error! Bookmark not defined.,15,16]

The primary objective, i.e. patients remaining on treatment after one year, was achieved in 78% of the participants, exceeding the predefined threshold of 70%. This level of persistence is clinically relevant, as allergen immunotherapy requires long-term adherence to achieve sustained benefit. The observed persistence indicates that general practitioners are able to support continued treatment over time. Factors such as structured follow-up, patient education, and expectation management are likely to have contributed to this outcome. Most doctors have since the launch of the first SLIT tablet (Grazax 2007) recommended patient contact after one month of treatment, to check on adherence and, not least, check that patients have not had any unwanted side effects. After that, yearly controls after grass pollen season are common procedures for most doctors, for renewals of prescriptions and to support continuous treatment. This is supported in the national guidelines for following up patients on SLIT treatment.[Error! Bookmark not defined.]

Adherence to treatment was consistently high. At Visit 2, 90% of patients reported taking the treatment daily, with similar proportions observed at Visit 3 (90%) and the final visit (92%). A small proportion of patients reported taking treatment six times weekly (5%, 7%, and 8% at Visits 2, 3, and the final visit, respectively), while very few patients reported lower adherence levels. Non-adherence was primarily attributed to forgetfulness rather than tolerability or access-related issues. Only a small proportion of patients reported adverse events as a reason for missed doses.

Although self-reported adherence may overestimate actual medication use, this method has the advantage of being simple to implement and minimally intrusive, thereby reflecting routine clinical practice without influencing patient behavior. These findings suggest that adherence in primary care is not inferior to that reported in specialist settings, and that behavioral factors may play a greater role than treatment-related barriers once therapy is initiated.

Clinical outcomes improved over the first pollen season, with reductions in symptom severity observed across nasal, ocular, bronchial, skin, and general symptom domains. These improvements were accompanied by a decrease in the use of symptomatic

medications, indicating reduced reliance on rescue therapies. Together, these findings support the effectiveness of SLIT-tablet treatment in routine clinical practice.

Looking at the individual groups of medication one could argue there was an overuse of oral antihistamines, (99% at visit 1) while only 50% used the preferred first line treatment with nasal steroids. Oral corticosteroids were used by a minority of patients (8% at Visit 1 and 2% at Visit 3), however 19% still received injectable corticosteroids at visit 1. Reduction in both oral and injectable corticosteroids were marked between visit 1 and 3. With the option of SLIT treatment for moderate and severe patients, it is hoped that a further reduction in systemic corticosteroid treatment is implemented over time, which is in line with both international and national guidelines.[Error! Bookmark not defined.,Error! Bookmark not defined.]

Patient-reported outcomes were consistent with the observed clinical improvements. A majority of patients reported an overall improvement in their condition after one year of treatment, and both patients and investigators reported high levels of satisfaction at the final visit. Notably, patients who completed the study tended to report more favourable outcomes than those who discontinued early, suggesting that early perceived benefit may be an important factor in maintaining long-term persistence.

The safety profile observed in this study was consistent with the established tolerability of SLIT-tablet treatments. Nearly half of the patients experienced at least one adverse event; however, the majority were mild or moderate, and no serious adverse events were reported. The observed adverse events were predominantly local reactions, which are well recognized for this treatment modality. Although adverse events contributed to some treatment discontinuations, most events resolved without sequelae, and overall treatment satisfaction remained high. These findings indicate that SLIT can be safely managed in a primary care setting.

The high treatment persistence observed in this study may partly reflect the strengths of longitudinal primary care. Continuity of care allows general practitioners to reinforce treatment expectations, address adverse effects and encourage sustained adherence over time. Continuity has consistently been associated with improved patient outcomes and greater adherence to long-term treatment across a range of chronic conditions, suggesting that it may also facilitate successful delivery of allergen immunotherapy in routine practice.[17]

Strengths and weaknesses with the study.

To obtain a lasting effect with tolerance 3 years continuous treatment is recommended. One could argue that it is a weakness of the study that we only followed the patients for one year. However, previous real-world studies suggest that most discontinuations of allergen immunotherapy occur during the first year of treatment. The patients who remain adherent during the first year appear most likely to complete the recommended 3-year treatment course[Error! Bookmark not defined.,18] This highlights the importance of structured follow-up and adherence support early in treatment. Also, adherence was

based on self-report and may therefore overestimate true treatment adherence. However, objective monitoring of daily SLIT administration is rarely feasible in routine clinical practice, making self-report a pragmatic approach that reflects real-world care.

Important strengths of the study were the geographical spread, the number of participating centers and that the design is “real-life”. Also, no additional reminders or financial incentives were used, making it as close as possible to primary care practice in Norway of today.

Conclusion

This prospective real-world study demonstrates that grass and birch pollen SLIT-tablets can be successfully administered within routine primary care, with high one-year persistence, good adherence, favourable safety and clinically meaningful improvements in symptoms. These findings support an expanding role for general practice in administering disease-modifying treatment for allergic rhinitis and suggest that structured primary care follow-up may improve the long-term effectiveness of allergen immunotherapy.

Acknowledgments;

Statistical analyses were carried out by Mikael Åström, Msc, Ph.L., Stat Cons, Lund, Sweden.

Funding declaration;
The study was funded by ALK-Abelló (Denmark), Hørsholm, Denmark

Study sites

Site	Senter	Investigator
01	Gransdalen legesenter	Anders Østrem
02	Bentsebro legesenter	Arrjun Ragavan
03	CC Vest legesenter	Christian F. Johnsen
04	St.Olav Medisinske	Hans Arnkværn
05	Ullevål Stadion legesenter	Andre Storm Larsen
06	Torshovdalen legesenter	Anette Østrem
07	Lille Grensen legesenter	Trond Daae-Johansen
08	Borg legekontor	Anette Elvestad
09	Bryn legesenter	Trine Lise S. Strand
10	Sentrum legesenter	Eirik Knapskog
11	Søsterhjemmet legesenter	Esben Storvand
12	Legene sentrum vest	Ragnar Sundby
13	Tananger legesenter	Kristian J. Høines
14	Granåsen legesenter	Arne Winsnes
15	Mathesongården Legesenter	Tine Molden
16	Bentsebro Legesenter	Henrik Siverts
17	SYMRA Legesenter	Andrea Ulsund

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