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ORIGINAL RESEARCH ARTICLE

A Retrospective Nationwide Non-Interventional Study of an Aqueous Sublingual Immunotherapy Formulation Administered with a 200-µL Dosing Pump

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Abstract

Background Convenient dosing is a key component of treatment adherence and thus efficacy and safety. Aqueous sublingual immunotherapy (SLIT) formulations can be administered with a dosing pump that delivers 200 µL of volume per actuation.

Objective The objective of this study was to describe the use of Staloral® 300 Rapid in its new dosing pump presentation and to evaluate the safety and satisfaction from both the patient and doctor.

Patients and Methods We performed a retrospective non-interventional study in a population (aged 5 years or over) of individuals with allergic rhinitis or allergic asthma who were being treated with aqueous 300 index of reactivity SLIT formulations of various allergens (grass pollen, tree pollen, house dust mites). Based on a detailed, SLIT-specific, patient self-questionnaire (Quartis®) and the inspection of medical records, we assessed the characteristics of the SLIT, safety, patient satisfaction and willingness to continue SLIT. The physician's satisfaction with the treatment was measured on a 0–100 visual analogue scale. Adverse events were coded with the Medical Dictionary for Regulatory Activities.

Results A total of 801 valid patients were included (52.4% male; mean ± standard deviation age: 25.9 ± 17.2 years; mean time since diagnosis: 4.56 ± 4.68 years; mean time using the previous dosing pump: 19.2 ± 13.0 months; time using the 200-µL dosing pump: 14.95 ± 3.80 months). Among the study population, 317 subjects comprised the paediatric subgroup (57%: male; mean age: 9.8 ± 2.5 years). Overall, 54 patients (6.7%) reported a total of 68 adverse events (including 51 gastrointestinal adverse events). The large majority of adverse events were mild, local and transient and did not require treatment. There were no severe adverse events. The level of patient satisfaction with the ease of SLIT administration was high (84.3% overall, and 82.6% in the paediatric subgroup). The mean ± standard deviation visual analogue scale score for physician satisfaction with the treatment was 70.6 ± 25.1 out of 100.

Conclusions Administration of 300 index of reactivity SLIT with a 200-µL dosing pump is safe, well tolerated and associated with good levels of patient satisfaction.

Key Points

The safety profile of a new dosing pump of 200 µL for sublingual immunotherapy is high.

The incidence of adverse events is lower in the adolescent population.

Satisfaction of 300 index of reactivity sublingual immunotherapy with a new dosing pump of 200 µL is high.

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1 Background

The incidence of respiratory allergic disease (allergic rhinitis [AR] and allergic asthma [AA]) is increasing worldwide, especially in developing countries [1–3]. In addition to the significant healthcare burden, these conditions have a negative impact on work and academic performance [4, 5]. Allergen immunotherapy (AIT) is currently the only disease-modifying treatment for respiratory allergic disease [6–10]. It consists of the periodic administration of an allergen extract preparation, based on the allergenic cause of the disease, either by a subcutaneous or sublingual route. Modern, clinically validated pharmaceutical preparations are now available for the treatment of respiratory allergies induced by aeroallergens such as grass, tree and weed pollens, house-dust-mite components and moulds [11, 12]. The efficacy and safety of AIT (whether sublingual immunotherapy [SLIT] or subcutaneous immunotherapy) in patients experiencing moderate-to-severe AR or mild-to-moderate AA is acknowledged by the latest international guidelines [6, 7, 13].

A large body of evidence shows that by virtue of its mucosal administration route, SLIT is particularly safe and well tolerated by patients with respiratory allergies [11–16]. Most countries have authorised the home administration of maintenance SLIT by the patient, after the initiation of treatment under medical supervision. Although SLIT-associated adverse events (AEs) do occur, they tend to be rare, mild, local and transient (lasting for 5–10 min after administration) and decrease in the frequency of occurrence as the treatment proceeds [11, 17]. Systemic AEs (e.g. urticaria, hypotension, oedema, and exacerbations of rhinitis or asthma) are infrequent and generally appear in the first few days after starting treatment [11].

For all medications, easy accurate dosing is an important determinant of compliance, safety and efficacy; this is just as true for SLIT [18–21]. The present study investigated the use of a 200-µL dosing pump to dispense standardised aqueous extracts of frequently encountered allergens, such as house dust mites (HDMs), pollens, moulds and animal dander (Staloral®; Stallergenes Greer, Antony, France) [11]. A maintenance dose of 300 index of reactivity (IR) SLIT consistently provides optimal safety and efficacy in patients with AR induced by grass pollen, birch pollen, or HDMs or in patients with moderate persistent AA induced by HDMs [21]. The SLIT solution is administered under the tongue (via a pre-dosed actuator often referred to as a pump), held there for 2 min and then swallowed.

To facilitate the sublingual application of the SLIT solutions, the manufacturer launched a dosing pump that doubles the volume (and thus the dose) delivered per actuation (i.e. from 100 µL and ~ 30 IR with the previous pump to 200 µL and ~ 60 IR with this pump). It was hypothesised that halving the number of actuations per administration would improve the pump's ease of use, accuracy of administration and, potentially, the associated treatment compliance. Hence, we performed a retrospective, nationwide, multicentre, non-interventional study in Spain of patients consulting a specialist physician for AA or AR and having already been treated with SLIT (Staloral® 300 Rapid; Stallergenes Greer, Antony, France, administered using the 200-µL dosing pump; from now on, SLIT 200 µL). For each patient, data on AEs, ease of use and satisfaction were self-reported during a scheduled consultation. Additional data on AEs were extracted from the patients' medical records by the investigating allergist. The goal of the present study was to describe the use of SLIT 200 µL and to evaluate the safety and satisfaction from both the patient and doctor.

2 Methods

2.1 Study Design

We performed a retrospective, nationwide, multicentre, non-interventional study in Spain. The study population comprised adult and paediatric patients (over the age of 5 years) with seasonal or perennial AR (including allergic conjunctivitis or rhinoconjunctivitis) and/or intermittent or persistent mild-to-moderate AA. During a consultation with an allergist (scheduled as part of normal care), patients who had already initiated treatment with SLIT 200 µL were asked if they would like to participate in the study. Patients who agreed were given information about the study's objectives and procedures, and were then invited to give their written informed consent to participate. All patient-reported information was collected retrospectively during this same consultation and was subsequently completed (if required) by the allergist after an analysis of the patient's medical records. Participation in this non-interventional study did not influence the patients' care. The study was sponsored by Stallergenes Greer Ibérica SA (Barcelona, Spain). Logistic aspects were managed by a contracted research organisation (BioClever, Barcelona, Spain).

2.2 Ethical Aspects

The study's objectives and procedures were approved by an independent ethics committee (Clinical Research Ethics Committee, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain; approval reference number: EPA-14-050; approval date; 9 December, 2014) and registered with the Spanish regulatory authority (Agencia Española

de Medicamentos y Productos Sanitarios). Furthermore, the study was carried out in accordance with the precepts of the Declaration of Helsinki and in compliance with good clinical practice and applicable Spanish regulations. Before participation in the study, written informed consent was provided by each patient or (for under-age patients) by the patient's parents or legal guardian.

2.3 Study Objectives

The present study's primary objective was to describe the characteristics of SLIT 200 µL in a population of children, adolescents and adults with AR or AA. The study's secondary objectives (based on patient self-reports and the inspection of medical records) were as follows:

- To describe the patients' demographic and clinical profiles (including the sensitisation profile and the allergens administered).
- To describe the safety and tolerability of initial and maintenance treatment with SLIT 200 µL.
- To evaluate the patient's self-reported opinion of SLIT with the nine scales of the Quartis® questionnaire.
- To describe the physician's satisfaction with the treatment (scored for each patient).

2.4 Study Population

A total of 60 recruiting centres (allergy clinics throughout Spain) participated in the study. Each centre was asked to include 10–15 patients. Study participants were recruited consecutively, i.e. each centre included the first 15 (at most) patients meeting the inclusion criteria in the order of presentation. The study was designed to assess children (aged 5–11 years, inclusive), adolescents (aged 12–17 years, inclusive) and adults (aged 18 years and over) with ongoing or previous treatment of AR or AA with SLIT 200 µL. The main inclusion criteria were therefore (i) treatment with SLIT 200 µL at any point during the study period (September 2013 to November 2014), (ii) physician-diagnosed respiratory allergic disease [seasonal or perennial AR (including allergic conjunctivitis or rhinoconjunctivitis) and/or intermittent or persistent mild-to-moderate AA], (iii) age 5 years or over and (iv) provision of written informed consent. The main exclusion criterion was simultaneous participation in another clinical trial. We also assessed a paediatric subgroup (all the children, plus adolescents aged 12, 13 or 14 years), as well as children, adolescents and adults separately. A comparison group was not considered because the old pump was not available at the time the study was established.

2.5 Study Treatment

The 300 IR/mL aqueous formulation studied (Staloral® 300 Rapid) is supplied as a 10-mL vial fitted with the 200-µL dosing pump. This SLIT 200-µL formulation can be used for SLIT initiation (i.e. daily up-dosing, with the dose adjusted by varying the number of actuations) and maintenance. The study participants had variously been treated with SLIT 200-µL formulations of different allergens (grass pollen, tree pollen, HDMs). These treatments were not paid for by the study sponsor.

2.6 Study Assessments

2.6.1 Demographic and Clinical Characteristics

The following characteristics were recorded: the patients' age, the disease-inducing allergens identified by the physicians, seasonal vs perennial allergy disease, the presence or absence of AA, the symptoms experienced during the study period, and the dosing used during SLIT initiation and/or maintenance.

2.6.2 Safety and Tolerability

Estimation of the prevalence of local and systemic AEs during treatment with SLIT 200 µL was based on the patient interview and the investigating physician's review of the patient's medical records. The AEs were coded by the contracted research organisation in accordance with the *Medical Dictionary for Regulatory Activities* (version 14.1) preferred terms and system organ classes. Each event's severity (mild, moderate or severe), phase of occurrence (SLIT initiation or maintenance), onset (during or after SLIT administration) and action taken (treatment with medication, withdrawal of immunotherapy, dose reduction) were noted. Last, the investigating physician evaluated whether the AE was causally related to the administration of SLIT.

2.6.3 Patient's Self-Reported Opinion of SLIT

The proprietary Quartis® questionnaire (Stallergenes Greer) was used to assess the patients' expectations of SLIT, level of satisfaction, adherence and attitudes concerning SLIT [22, 23]. The questionnaire comprises questions on nasal, respiratory and ocular symptoms, the impact of the allergy on daily and professional activities, ease of administration, disadvantages and the cost of SLIT, satisfaction with SLIT and side effects. Quartis® also contains three questions on whether the patient is willing to continue SLIT, and reasons for this choice. Each section contains one to four questions with 4- or 5-item Likert scales with answers from "strongly agree" to "strongly disagree" or from "not at all" to "extremely".

The total score for each section (maximum possible = 5, 10, 15 or 20, depending on the section) is calculated by adding together and then averaging the individual question scores; the lower the overall score or subscale score, the greater the level of satisfaction. Conversely, a high score indicates that SLIT constitutes a problem for a particular aspect of treatment.

2.6.4 Allergist's Satisfaction with SLIT

The investigating physician recorded his/her own satisfaction with each patient's SLIT on a visual analogue scale (VAS) from 0 mm (worst) to 100 mm (best).

2.7 Sample Size Calculation

In the absence of predetermined hypotheses concerning the study variables, the sample size was calculated considering the maximum value of indetermination ($p = 0.5$). With an alpha risk of 5% in a two-tailed test, the required sample size for obtaining an estimation with a 3.5% accuracy was 753. Assuming a missing data rate of 5%, the target sample size was set to 800 patients.

2.8 Data Management and Statistical Analysis

All study data were entered by the investigator into a specifically designed online database. Datasets were then loaded into SAS® software (version 9.3; SAS Institute Inc., Cary, NC, USA) for statistical analysis. Continuous variables are quoted as the mean ± standard deviation, the median (interquartile range) and range. Correlations between two continuous variables were assessed by calculating Pearson's or Spearman's coefficient. Categorical variables are quoted as the number (percentage). Intergroup comparisons of categorical variables were performed with a chi-squared test or Fisher's exact test. Unless otherwise stated, the threshold for statistical significance was set to $p < 0.05$.

3 Results

A total of 826 patients were selected, corresponding to an average of 13 patients per investigating centre. After verification of the inclusion criteria, 25 patients were excluded for various reasons (mainly the absence of treatment with SLIT 200 µL, or the absence of confirmed AR and/or AA). Hence, the final dataset for the analysis comprised 801 valid patients (230 children, 138 adolescents and 433 adults [male: 52.4%; mean ± standard deviation [SD] age: 25.9 ± 17.2 years; mean time since diagnosis: 4.56 ± 4.68 years]) (Table 1). The paediatric subgroup (i.e. children plus adolescents aged 12, 13 or 14 years) comprised 317 patients (57%: male; mean age: 9.8 ± 2.5 years).

3.1 Treatments

The mean time since the initiation of SLIT solutions was 13.35 ± 4.94 months. Treatment with a mixture of extracts had been given to 50.8% of patients. Among the 783 patients for whom data on AIT preparations were available, 247 (31.5%) had been treated with an HDM extract (*Dermatophagoides pteronyssinus* plus *Dermatophagoides farinae*), 148 (18.9%) had received a grass- and olive-pollen mixture, 133 (17.0%) had received a grass-pollen extract and 63 (8.3%) had received an olive-pollen extract.

A 3-day initiation phase was applied by 96.6% of the participants. In the maintenance phase, the median dose was 4.0 actuations applied 3 days per week. Three-hundred-and-eighteen participants (39.7%) had received SLIT solutions treatment with the previous dosing pump (SLIT 100 µL) [for a mean period of 19.2 ± 13.0 months] and with the SLIT 200 µL (for 14.95 ± 3.80 months).

In the paediatric subgroup, the mean time from the start of treatment was 13.69 ± 4.7 months. Of the paediatric participants, 161 (50.8%) had been treated with mixed extracts. The most frequently administered treatments (> 5% of participants) were HDM mixtures (*D. pteronyssinus* plus *D. farinae*, $n = 139$, 44.3%), grass pollen ($n = 57$, 18.2%), grass plus olive pollen mixtures ($n = 48$, 15.3%), *D. pteronyssinus* alone ($n = 19$, 6.1%) and olive pollen ($n = 17$, 5.4%). The initiation phase lasted for 3 days in 95.9% of the paediatric participants. As with the adults, the median maintenance dose was four actuations, administered 3 days a week. Of the paediatric participants, 33.8% had received treatment for a mean period of 18.8 ± 12.71 months with the previous dosing pump and for 14.61 ± 3.31 months with the 200-µL dosing pump.

3.2 Demographic and Disease-Related Characteristics of the Study Population

Overall, 95.3% of the study participants had either AR or allergic rhinoconjunctivitis, which was of moderate-to-severe intensity in 91.4% of the participants. The AR was persistent in 63% of the participants. A diagnosis of asthma had been made in 38% of the study participants.

When considering the 801 participants, 69.2% had a positive skin-prick test for pollen (grasses: 54.7%; olive: 47.8%), 52.4% were sensitised to HDMs and 30.3% were sensitised to moulds or animal dander (Fig. 1).

In the paediatric subgroup, 89.6% of the patients had rhinitis or rhinoconjunctivitis, which was moderate or severe in 82.6% of cases and persistent in 56% of cases. A diagnosis of asthma had been made in 48.3% of the

Table 1 Demographic, clinical and treatment-related characteristics of the study population

Demographic characteristics	
Age, years, mean ± SD (range)	25.9 ± 17.2 (5−77)
Sex, male, %	52.4
Children (5−11 years of age), *n* (%)	230 (28.7)
Adolescents (12−17 years of age), *n* (%)	138 (17.2)
Adults (18 years of age and over), *n* (%)	433 (54.1)
Clinical characteristics	
Diagnosis of allergic rhinitis or rhinoconjunctivitis, *n* (%)	763 (95.3)
Diagnosis of allergic asthma, *n* (%)	304 (38.0)
Time since diagnosis, years, mean ± SD (range)	4.56 ± 4.68 (0−34.2)
Patients with sneezing at diagnosis (*n* = 664), *n* (%)	568 (85.5)
Patients with rhinorrhoea at diagnosis (*n* = 664), *n* (%)	532 (80.1)
Patients with nasal congestion at diagnosis (*n* = 664), *n* (%)	543 (81.8)
Patients with cough at diagnosis (*n* = 664), *n* (%)	205 (30.9)
Classification of AR at diagnosis (ARIA)	
No rhinitis, *n* (%)	15 (2.1)
Mild intermittent, *n* (%)	34 (4.8)
Mild persistent, *n* (%)	12 (1.7)
Moderate intermittent, *n* (%)	184 (25.9)
Moderate persistent, *n* (%)	271 (38.1)
Severe intermittent, *n* (%)	30 (4.2)
Severe persistent, *n* (%)	165 (23.2)
Missing data, *n*	90
Classification of AR at study visit (ARIA)	75 (10.6)
No rhinitis, *n* (%)	304 (42.9)
Mild intermittent, *n* (%)	21 (3.0)
Mild persistent, *n* (%)	223 (31.5)
Moderate intermittent, *n* (%)	70 (9.9)
Moderate persistent, *n* (%)	2 (0.3)
Severe intermittent, *n* (%)	13 (1.8)
Severe persistent, *n*	93
Missing data, *n*	0
Treatment characteristics	
Time since initiation of SLIT, months, mean ± SD (range)	13.35 ± 4.94 (0.3−21.7)
Treated with the previous dosing pump, %	318 (39.7)
Time using Staloral® 300 IR with the 200-µL dosing pump, months, mean ± SD (range)	14.95 ± 3.80 (2.9−21.7)
Prescribed SLIT extract(s)	
Dermatophagoides + *Dermatophagoides farina*, *n* (%)	247 (31.5)
Dermatophagoides pteronyssinus only, *n* (%)	55 (7.0)
Grass pollen mix, *n* (%)	148 (18.9)
Olive pollen, *n* (%)	65 (8.3)
Grass pollen mix + olive pollen, *n* (%)	133 (17.0)
Others, *n* (%)	135 (17.2)
Missing data, *n*	18

AR allergic rhinitis, *ARIA* Allergic Rhinitis and its Impact on Asthma, *IR* index of reactivity, *SD* standard deviation, *SLIT* sublingual immunotherapy

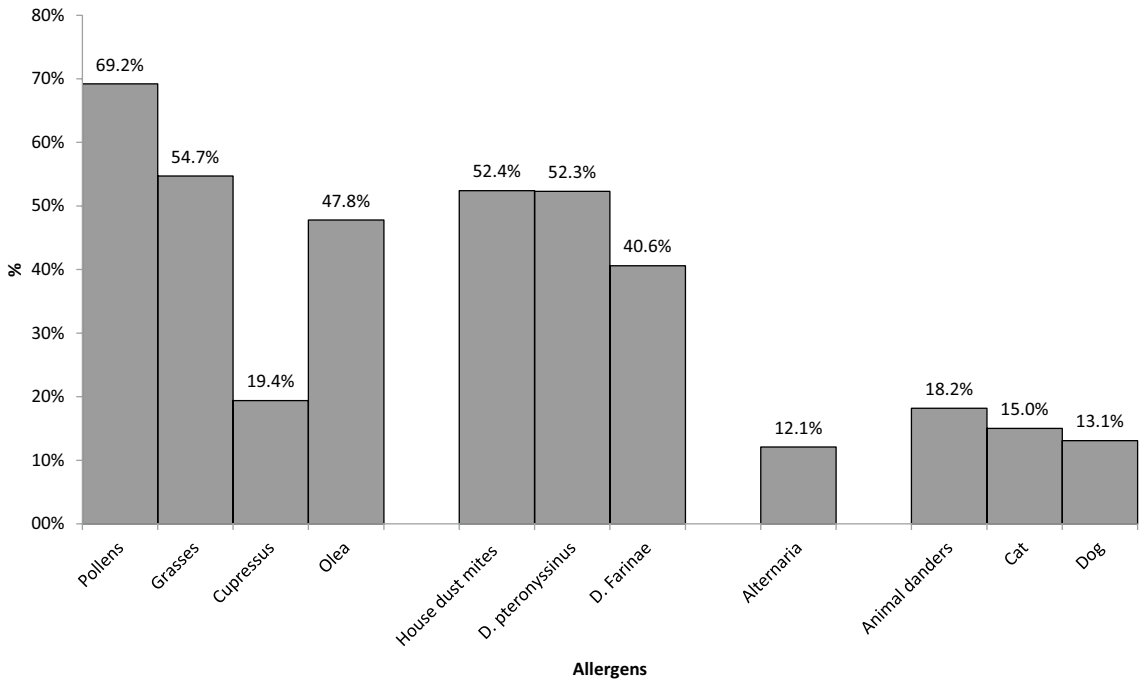

Fig. 1 Sensitization to allergens (proportion of the study participants affected), as reported by the physician

Table 2 Characteristics and distribution of adverse events (AEs)

	Certain	Probable	Possible	Unlikely	
Causality, *n*	24	31	10	2	
	Local	Systemic			
Type of AE, *n*	57	24			
	Immediate	Delayed			
Time of onset, *n*	56	12			
	Mild	Moderate	Severe		
Severity, *n*	58	10	0		
	Initiation	Maintenance			
Treatment phase, *n*	29	39			
	None	Dose reduction	Temporary suspension	Added premedication	Restart with premedication
Action taken, *n*	48	6	4	5	5

patients in the paediatric subgroup. With regard to the skin-prick test results, 57.7% of the paediatric patients were sensitised to pollens (grasses: 44.8%; olive: 37.2%), 56.2% were sensitised to HDMs and 25.8% were sensitised to moulds or animal dander.

3.3 Safety

Overall, 54 patients (6.7% of the total population) reported a total of 68 AEs (Table 2): 40 patients (5%) experienced one AE each and 14 (1.7%) experienced two AEs each. None of the patients experienced three or more AEs. Overall, 747 (93.3%) of the study participants did not experience any AEs.

A detailed description of AE characteristics is shown in Tables 2 and 3. As expected with SLIT, the most frequent AEs were classified as local gastrointestinal disorders (51 events in 44 patients); 30 of these were due to oral pruritus or pruritus of the tongue. Other system organ classes were rarely affected. Importantly (in a population in which

Table 3 Adverse events by age group

	Children ($n = 230$)		Adolescents ($n = 138$)		Adults ($n = 433$)	
	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*	Patients, *n* (%)	Events, *n*
Total	13 (5.7)	15	5 (3.6)[a]	6	36 (8.3)	47
Gastrointestinal disorders	10 (4.3)	10	4 (2.9)	5	30 (6.9)	36
Oral pruritus	4 (1.7)	4	3 (2.2)	3	15 (3.5)	15
Pruritus of tongue	0	0	1 (0.7)	1	7 (1.6)	7
Abdominal pain	4 (1.7)	4	0	0	1 (0.2)	1
Glossodynia	2 (0.9)	2	1 (0.7)	1	1 (0.2)	1
Upper abdominal pain	0	0	0	0	3 (0.7)	3
Swollen tongue	0	0	0	0	2 (0.5)	2
Pruritus of the lips	0	0	0	0	2 (0.5)	2
Gastrointestinal disorder	0	0	0	0	2 (0.5)	2
Diarrhoea	0	0	0	0	1 (0.2)	1
Gastroesophageal reflux disease	0	0	0	0	1 (0.2)	1
Gastric reflux	0	0	0	0	1 (0.2)	1
Skin and skin structure disorders	2 (0.9)	2	1 (0.7)	1	5 (1.2)	5
Angioedema	0	0	0	0	3 (0.7)	3
Pruritus	1 (0.4)	1	1 (0.7)	1	1 (0.2)	1
Urticaria	1 (0.4)	1	0	0	1 (0.2)	1
Nervous system disorders	1 (0.4)	1	0	0	1 (0.2)	1
Headache	1 (0.4)	1	0	0	1 (0.2)	1
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1	0	0	1 (0.2)	1
Dyspnoea	0	0	0	0	1 (0.2)	1
Irritated throat	1 (0.4)	1	0	0	0	0
Infections and infestations	1 (0.4)	1	0	0	0	0
Rhinitis	1 (0.4)	1	0	0	0	0
Ear and labyrinth disorders	0	0	0	0	1 (0.2)	1
Pruritus in the ear	0	0	0	0	1 (0.2)	1
General disorders and changes in administration site	0	0	0	0	1 (0.2)	1
Poorly defined disorder	0	0	0	0	1 (0.2)	1
Ocular disorders	0	0	0	0	1 (0.2)	1
Pruritus in the eye	0	0	0	0	1 (0.2)	1
Psychiatric disorders	0	0	0	0	1 (0.2)	1
Anxiety	0	0	0	0	1 (0.2)	1

The list of adverse events is presented using the system organ class and preferred terms of the *Medical Dictionary for Regulatory Activities*

[a]No differences were identified between age groups ($p > 0.05$), except for the total number of cases in adolescents, significantly lower than in the adult group ($p = 0.0012$)

38% of the participants had been diagnosed with asthma), there were only two AEs classified as respiratory, thoracic and mediastinal disorders (one case of dyspnoea and one case of irritated throat). Abdominal pain, diarrhoea and gastric reflux were also very rare. The AE rate was significantly lower in adolescents (3.6%) than in adults (8.3%; $p = 0.0012$) (Table 3), confirming a previous report of good safety in children using the 200-µL dosing pump [24].

In the analysis of AE occurrence in different subpopulations, there were no differences between those having used the previous pump or not; the percentage of AEs was not different between patients receiving SLIT in a single allergen vs a mixture (6.9% vs 6.6%, $p > 0.05$); interestingly, the AE rate was significantly lower in asthmatic patients compared with non-asthmatic patients (4.8% vs 9.9%, $p = 0.0447$).

3.4 Satisfaction with Treatment

Based on the results of the Quartis® questionnaire, participants were reasonably satisfied with SLIT (Table 4); the mean scores for each domain were in the middle of the defined range and were only above the mid-range score for the AE and cost subscores. The level of satisfaction with

Table 4 Results for the Quartis questionnaire in the overall study population

	n	Mean ± SD	Median (IQR)	Range (best, worst)	Missing data
Nasal symptoms	801	4.0 (1.8) out of 10	4.0 (3.0–5.0)	2–10	0
Respiratory symptoms	801	2.3 (1.1) out of 10	2.0 (1.0–3.0)	1–5	0
Ocular symptoms	801	3.8 (2.1) out of 10	3.0 (2.0–4.0)	2–10	0
Daily allergy	801	5.7 (2.5) out of 15	5.0 (4.0–7.0)	3–15	0
Ease of administration	801	9.1 (2.2) out of 20	9.0 (7.0–11.0)	5–19	0
Inconveniences	801	7.6 (2.4) out of 20	7.0 (6.0–9.0)	5–18	0
Cost of treatment	801	3.1 (1.2) out of 5	3.0 (2.0–4.0)	1–5	0
Satisfaction	801	8.7 (2.7) out of 20	8.0 (7.0–10.0)	4–18	0
Adverse events	801	3.8 (1.0) out of 5	4.0 (3.0–5.0)	1–5	0

Note that the lower the score, the greater the level of patient satisfaction with SLIT for a given aspect of treatment

IQR interquartile range, *SD* standard deviation, *SLIT* sublingual immunotherapy

Table 5 Wish to complete the course of sublingual immunotherapy in the overall study population

	Total ($n = 801$)
"I want to complete my course of sublingual allergen immunotherapy"	
Total non-missing, *n*	801
Totally agree, *n* (%)	603 (75.3)
Somewhat agree, *n* (%)	120 (15.0)
Somewhat disagree, *n* (%)	36 (4.5)
Totally disagree, *n* (%)	42 (5.2)
Missing, *n*	0

the treatment administration was high: 609 (76.0%) of the participants fully agreed that the treatment was easy to take at home, 661 (82.5%) fully agreed that administration was rapid and 675 (84.3%) considered that SLIT was easy to use.

Of the participants, 90.3% somewhat agreed or totally agreed with the statement "I want to complete my course of SLIT" (Table 5). The mean level of motivation for continuing treatment (on a 1–10 scale) was 7.6 ± 2.1. The main reasons for not wishing to continue were poor symptom reduction (49.3% of the participants) and the cost of treatment (58.7%). When assessed by the physician, the level of patient satisfaction on a 0–100 VAS was high (mean ± SD score: 70.6 ± 25.1; median [interquartile range score]: 80.0 [61.0−90.0]).

As with the overall study population, the results of the Quartis® questionnaire showed that paediatric participants (or their parents) were moderately satisfied with SLIT (Table 6). The level of satisfaction with the treatment administration was high; 219 (69.1%) of the participants fully agreed that the treatment was easy to take at home, 251 (79.2%) fully agreed that administration was rapid and 262 (82.6%) considered that SLIT was easy to use.

Of the participants, 92.1% somewhat agreed or totally agreed with the statement "I want to complete my course of SLIT", and the mean ± SD score for the wish to continue treatment was 7.7 ± 1.8 out of 10. The mean level of patient

Table 6 Results for the Quartis questionnaire in the paediatric subgroup

	n	Mean (± SD)	Median (IQR)	Range	Missing data
Nasal symptoms	317	3.8 (1.7) out of 10	3.0 (3.0–4.0)	2–10	0
Respiratory symptoms	317	2.3 (1.1) out of 5	2.0 (2.0–3.0)	1–5	0
Ocular symptoms	317	3.7 (2.0) out of 10	3.0 (2.0–4.0)	2–10	0
Daily allergy	317	5.2 (2.1) out of 15	5.0 (3.0–6.0)	3–13	0
Ease of administration	317	9.2 (2.3) out of 20	9.0 (8.0–11.0)	5–19	0
Inconvenience	317	7.4 (2.2) out of 20	7.0 (6.0–9.0)	5–18	0
Cost of treatment	317	3.0 (1.2) out of 5	3.0 (2.0–4.0)	1–5	0
Satisfaction	317	8.8 (2.7) out of 20	9.0 (7.0–10.0)	4–18	0
Adverse events	317	3.8 (1.0) out of 5	4.0 (3.0–5.0)	1–5	0

Note that the lower the score, the greater the level of patient satisfaction with SLIT for a given aspect of treatment

IQR interquartile range, *SD* standard deviation, *SLIT* sublingual immunotherapy

satisfaction (as assessed by the investigating physician on a 0–100 VAS) was 69.2 ± 25.6.

4 Discussion

In the present, retrospective, nationwide, non-interventional study of an aqueous SLIT formulation administered with a 200-µL dosing pump, we found that patients reported high levels of safety. In the overall population, only 6.7% of the patients reported an AE. This proportion is far below the prevalence reported in the highly controlled and scrutinised environment of clinical trials. For example, 76.9% of the 1514 patients having received a five-grass pollen SLIT tablet in a series of clinical trials reported a treatment-emergent AE [12]. However, the corresponding proportion in the placebo group was also relatively high (69.8%). Similar results were reported for a Europe-wide trial of pre- and co-seasonal 300 IR birch pollen SLIT in 574 adult immunotherapy-naïve patients, where the frequency of treatment-emergent AEs was 70.7% in the SLIT group and 64.0% in the placebo group [25]. However, birch pollen SLIT was not extensively used in the present study; 247 (31.5%) of the 783 patients for whom data on AIT preparations were available had been treated with an HDM extract (*D. pteronyssinus* plus *D. farinae*). In a study of 218 patients aged from 4 to 64 years at five Spanish centres, it was found that an ultra-rush regime (incremental doses of a 50:50 *D. pteronyssinus*:*D. farinae* mixture, with 30, 60, 120 and then 240 IR in 30-min intervals) could be safely administered [25].

In the present study, 94% of the AEs resolved rapidly without treatment, and there were very few severe or delayed-onset events, further supporting the option of prescribing SLIT for home administration after the initial dosing is performed in a medical environment. Most of the AEs were application-site reactions (such as oral pruritus, throat irritation and mouth oedema) that were coded as affecting the gastrointestinal organ class. These findings agree with the abundant literature data showing that SLIT is predominantly associated with mild local AEs that resolve without treatment [26]. However, we were surprised to observe more AEs during the maintenance phase (39 out of 68 events) than during the initiation phase (29 events); in most studies of AIT, the opposite is true and the frequency of AEs decreases as treatment progresses time [11, 17, 26]. In the above-mentioned multicentre study of 300 IR HDM SLIT with an ultra-rush initiation regime in a Spanish population [21], 12.4% of the patients experienced an AE in the ultra-rush phase and 12% experienced an AE in the maintenance phase. One can speculate that poorly controlled asthma was one factor associated with the occurrence of AEs during the maintenance phase in the present study.

The choice of an AIT prescription in children is increasingly based on practical and personal considerations (convenience, satisfaction, compliance) [21, 25, 26]. In the present study, the levels of patient satisfaction with SLIT were moderate to good. There are few directly comparative, detailed data in this field, although a few SLIT- or AIT-specific questionnaires have recently been developed and validated [20, 21, 27–30]. However, many studies have sought to determine levels of patient satisfaction, and these are generally correlated with the degree of symptom relief. For example, Chang et al. evaluated patient satisfaction with HDM SLIT with regard to three possible responses: "satisfied" (45.7%), "fairly satisfied" (42.4%) and "unsatisfied" (12%) [31]. Hence, 88% of the patients in Chang et al.'s study were satisfied or fairly satisfied. The ESPIA (Satisfaction Scale for Patients Receiving Allergen Immunotherapy) questionnaire was used to assess satisfaction in patients having undergone either 4–6 months or 9–12 months of HDM SLIT [29]. The median total satisfaction rate was 60% and 73%, respectively. Biardiani et al. administered a 28-question survey to assess knowledge, perceptions, expectations and satisfaction with regard to SLIT in 434 patients (74% of whom were receiving SLIT with various allergen formulations) [32]. Most of the patients perceived AIT to be safe and easy to integrate into their daily routine. In Baiardini et al.'s study, the mean level of patient satisfaction was high (74 out of 100 on a VAS), as was physician satisfaction (78 out of 100) [32]. Overall, these data suggest that 70–90% of SLIT users are satisfied with their treatment; this was true for the patients using the 200-µL dosing pump in the present study.

The study had several limitations. First, it was a retrospective study, with all the associated drawbacks; all patient-reported data were gathered retrospectively during a single study visit (at the same time as inclusion) and thus may have been affected by recall bias. Indeed, patients were asked to assess events that (in some cases) had occurred months previously (e.g. forgetting mild and old events but remembering moderate-to-severe or recent events). However, no severe events were recorded. Second, the study did not feature a separate control or reference group (such as a group of patients using the old pump alone) for comparing levels of safety and satisfaction; however, the previous pump was not available at the time of the study for comparison. Third, we did not measure compliance and cannot prove the hypothesis whereby fewer actuations lead to better compliance. Compliance is a key component of treatment efficacy, and thus further research on this topic is warranted. Fourth, the study participants variously used SLIT 200-µL formulations of different allergens (grass pollen, tree pollen, HDMs). However, the goal of the present study was to assess safety, tolerance

and patient satisfaction with a 200-µL dosing pump, rather than to measure the efficacy of a particular allergen SLIT formulation. Fifth, the questionnaire supplied by the study sponsor (Quartis®) is a proprietary tool, and only summary details of its validation have been published [22, 23]. The first validation of a treatment-specific questionnaire for the assessment of patient satisfaction with allergen immunotherapy (the ESPIA questionnaire) took place after the present study had been planned [29].

5 Conclusions

Administration of SLIT 200 µL was safe and well tolerated. The large majority of AEs were mild, local, and transient and did not require treatment. No severe AEs occurred. Adverse events were more frequent in adults than in paediatric patients and were more frequent in patients without asthma than in patients with asthma. The patients and physicians were satisfied with the SLIT administered with the 200-µL dosing pump, although expectations of symptom relief appear to be high and thus are not easy to meet. The patients were keen to continue SLIT.

Declarations

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Conflict of interest Albert Roger Reig has received a grant for his participation as coordinator of the study, support for travel to meetings for the study and manuscript preparation and honorarium for writing and reviewing the manuscript from Stallergenes Greer; Clara Padró Casas has received support for travel to meetings for the study and consulting fees from Stallergenes Greer; Diego Gutiérrez Fernández has received honorarium for his participation in the study; José Carlos Orta Cuevas has received honorarium for his participation in the study; Germán Sánchez López has received honorarium for his participation in the study; José Luis Corzo Higueras has no conflicts of interest that are directly relevant to the content of this article.

Ethics approval The study's objectives and procedures were approved by an independent ethics committee (Clinical Research Ethics Committee, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain; approval reference number: EPA-14-050; approval date; 9 December, 2014) and registered with the Spanish regulatory authority (Agencia Española de Medicamentos y Productos Sanitarios).

Consent to participate Before participation in the study, written informed consent was provided by each patient or (for under-age patients) by the patient's parents or legal guardian.

Consent for publication Not applicable.

Availability of data and material The authors declare that the data supporting the findings of this study are available within the article.

Code Availability Not applicable.

Author contributions All authors contributed to the study conception and design, material preparation, data collection and analysis. All authors read and approved the final manuscript.

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