



Safety of semi-depot house dust mite allergen extract in children and adolescents with allergic rhinitis and asthma

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Aim: Multicenter study to investigate the safety of mite extract product Novo-Helisen Depot, Strengths 1 to 3 (NHD3), as subcutaneous immunotherapy (SCIT), in Chinese children and adolescents with allergic rhinitis (AR) and allergic asthma (AA). **Patients & methods:** We evaluated SCIT-related adverse events (AEs) during NHD3 14-week initial therapy in children (5–11 years) and adolescents (12–17 years) with perennial symptomatic AR and AA. **Results:** Among 3600 injections in 250 patients, 361/3600 (10.0%) injections caused SCIT-related AEs in 96/250 (38.4%) patients, 321/3600 injections (8.9%) caused local reactions in 89/250 (35.6%) and 40/3600 injections (1.1%) caused systemic reactions in 23/250 (9.2%). **Conclusion:** Initial SCIT treatment using NHD3 was safe and well tolerated in Chinese children and adolescents with AR and AA.

Tweetable abstract: Semi-depot house dust mite allergen extract is safe and well tolerated in children and adolescents with allergic rhinitis and asthma.

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Allergic rhinitis (AR) and asthma are the most common airway allergic diseases, characterized by an inflammatory response mediated by immunoglobulin E (IgE) in allergen-sensitized individuals [1]. The prevalence of AR ranges from 10 to 30% among adults, and up to 40% among children worldwide [2]. In China, the self-reported AR prevalence was 34.3% [3], and in children, the prevalence of AR was found to vary widely (9.8–22.4%) [4]. Asthma is a chronic and heterogeneous respiratory disease; its estimated prevalence is 4.3% worldwide [5]. The latest surveys have indicated that the prevalence of asthma in China is 4.2% in adults and 3.02% in children [6,7]. Co-morbidities of allergic asthma (AA) and AR, which are present in more than 50% of asthmatic children [7], result in a considerable psychological and economic burden for patients, the effects of which extend not only to the families of these patients but also the wider community and entire healthcare systems [8–10].

Dermatophagoides farinae (*Der. f*) and *Dermatophagoides pteronyssinus* (*Der. p*) are the most common aeroallergen triggers associated with persistent perennial symptoms of patients with AR and AA in China [4]. A cross-sectional survey of Chinese patients with asthma and rhinitis showed that patients were highly sensitized to *Der. f* (59.0%) and *Der. p* (57.6%) [11], while another study indicated 83.7% of patients were concomitantly sensitized to *Der. f* and *Der. p* [12].

Allergen avoidance, pharmacotherapy, allergen immunotherapy (AIT) and patient education comprise the main approaches to allergic disease management. Although controller and reliever medications might provide relief of symptoms of AA and AR specifically, they fail to prevent the ‘allergic march’ (i.e., the typical progression of atopic conditions resulting from IgE responses generally beginning in childhood and persisting over the years) [13]. However, the side effects of long-term treatment with such medications are a clear factor resulting in poor adherence [1].

AIT, which entails the gradual administration of increasing doses of allergen extracts, is the only available etiological treatment that can potentially modify the immune system allergic reaction status [14–16]. The history of AIT development spans more than a century [17–19], and through its widespread use in clinical practice, AIT has been confirmed to be effective and safe [20,21]. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) administration routes are available for the treatment of Chinese patients with dust mite allergy [22,23].

Novo-Helisen Depot (NHD), a semi-depot allergen extract containing *Der. f* (50%) and *Der. p* (50%), was initially available in four strengths (NHD4; Strength 0 [5 TU/ml], Strength 1 [50 TU/ml], Strength 2 [500 TU/ml] and Strength 3 [5000 TU/ml]). In a multicenter study, 272 Chinese patients with AR and AA received AIT with NHD4 for 1 year. Significant symptom improvements were seen after 6 and 12 months of treatment. In addition, treatment adherence was high, and no serious drug-related adverse events (AEs) were reported [24].

In China, AIT has been in use for only 20 years, and so far, there are only natural mite extracts available in clinical practice. Exploring an optimal way to shorten the duration and procedure of dose escalation among limited products is of particular importance in China. NHD4 (including Strengths 0, 1, 2 and 3) has been used in China for nearly two decades with good tolerance. Per previous recommendations stated in the Summary of Product Characteristics, children and hypersensitive patients were recommended to undergo treatment with Strength 0. Since the end of 2015, Strength 0 was unavailable worldwide, and NHD3 (including Strengths 1, 2 and 3) was used for children as an alternative to NHD4. This usage was approved by the China FDA since September 2016. At present, the Summary of Product Characteristics in Germany does not contain a specific dosing scheme for children and adolescents aged 5 years and older. Based on clinical experience, it is well known that NHD3 use can shorten the dose-escalation phase and result in a considerable benefit to patients. In Europe, AIT tends to consist of shorter treatment durations and dose-escalation procedures [25]. However, as there have been no safety data on NHD3 in the Chinese population thus far, the application of NHD3 in China has been limited, especially for children and adolescent patients. Thus, such data are needed to promote standardized dose-escalation procedures for optimized AIT. Therefore, the objective of this study was to investigate the safety of NHD Strengths 1–3 as initial treatment in Chinese children and adolescents with AR and AA.

Methods

Study design

This was a prospective, multicenter, single-arm, open-label, observational, Phase IV study conducted between December 2016 and March 2019 at 17 hospitals in China. Chinese children (aged 5–11 years) and adolescents

(aged 12–17 years) with AR and AA were enrolled and were planned to receive treatment for 14 weeks. The overall safety follow-up period was 30 days post-treatment.

The ethical review board at each participating site approved the study protocol and related documents. The study was in compliance with the principles of the 1964 Declaration of Helsinki and its later amendments and local regulations. Written informed consent/assent to participate in the study was obtained from each patient's parent or guardian before any study-related activities were performed. This study was registered at www.chictr.org under the identifier ChiCTR-OIH-17012492.

Patients

Inclusion criteria were as follows: children (aged 5–11 years) and adolescents (aged 12–17 years) of both sexes; a definite diagnosis of AR (according to the Chinese Guidelines for Diagnosis and Treatment of Allergic Rhinitis and Pediatric Rhinitis; Position Paper of the European Academy of Allergy and Clinical Immunology 2013) [13,26] or AA (according to the Guideline on Pediatric Bronchial Asthma Diagnosis, Prevention and Treatment, and Global Initiative for Asthma [GINA 2015]) [27,28]; sensitization to *Der. p* and/or *Der. f* determined within 6 months before the screening visit by a skin prick test (wheal diameter ≥ 3 mm for *Der. p* and/or *Der. f* and greater than or equal to the diameter of the positive control [histamine]) or IgE serum test measured by enzyme-linked fluorescent immunoassay method (≥ 0.7 kU/l for *Der. p* and/or *Der. f*); and perennial symptoms of AR or AA.

The exclusion criteria were as follows: participation in another clinical study simultaneously or within the 30 days before the start of the present study; history of drug abuse; forced expiratory volume in 1 s (FEV₁) for AA <80% of the predicted value; contraindications to specific AIT; previous specific immunotherapy with house dust mite allergen standardized extracts; pregnancy or lactation; and allergies to excipients contained in NHD.

Treatment

Patients were recommended to receive initial treatment with NHD3 according to the Summary of Product Characteristics and the dosage was titrated according to tolerability. Treatment was initiated with the minimum dose and concentration (Strength 1) and was escalated to the maximum dose of Strength 3. The injection interval during the escalation phase was between 7 and 14 days. If the patient tolerated the previous injection well, the dosage was then increased, step by step, to 1.0 ml of Strength 3 or the individual maximum dose. For Strength 1 and Strength 2, the dose was increased to 0.1, 0.2, 0.4 and then 0.8 ml. For Strength 3, the dose was increased to 0.1, 0.2, 0.4, 0.6, 0.8 and, finally, 1.0 ml. If the last injection was not well tolerated, the dose was maintained or reduced. The dose was then increased according to the patient's reaction to the injection. The decision to continue treatment was based on the course and severity of the allergic reactions to treatment. In addition to AIT, treating physicians evaluated all the patients based on AR symptom severity and AA control level and prescribed appropriate medication for airway symptoms. Dose escalation with NHD3 generally lasted for 14 weeks or more.

Visit schedule

This study comprised six visits. The investigators recorded AE information after every injection. For Visits 1–4, the investigators collected safety data on site; for Visit 5, the investigators collected safety information through a telephone call 1 week after the last injection. Safety assessments and recording of AEs began when the patient was initially included in the study (i.e., on the date of informed consent provision) and continued to the end of the safety follow-up period. Visit 0 was the Screening Visit. In Visit 1, Visit 2 and Visit 3, respectively, patients were administered 0.1 ml of Strength 1, Strength 2, and Strength 3 of NHD via subcutaneous injection. In Visit 4, patients were administered 1.0 ml of Strength 3 via subcutaneous injection. The patient's local physician administered the remaining doses of each strength according to the instructions provided previously. Visit 5 comprised only safety information collection after the last injection (Supplementary Figure 1).

Outcomes

The primary end point was the incidence of SCIT-related AEs, coded by data management professionals according to the Medical Dictionary for Regulatory Activities (MedDRA, version 22.1) System Organ Class and Preferred Term classifications. Secondary end points were the incidence of all AEs and serious AEs (SAEs), the clinical outcome of AEs and SAEs, the severity of local and systemic AEs, the adherence rate and tolerability.

An AE was defined as any unexpected medical event that occurred in a patient after administering a pharmaceutical product and that was not necessarily found to have a causal relationship with the study treatment. A SCIT-related AE

was defined as a harmful and unintended adverse drug reaction that occurred as a response to a medicinal product. According to International Council for Harmonization E6 guidelines, an SAE was defined as any unexpected medical event or effect resulting in death or persistent or significant disability or incapacity, or that was possibly fatal, required hospitalization or prolonged hospitalization, was a congenital abnormality or disorder, or another medically relevant condition.

The severity of AEs was classified as: mild (the patient was aware of the event or system, but the event or system was easily tolerated); moderate (the patient experienced sufficient discomfort to interfere with or reduce his/her usual level of activity); or severe (the patient experienced significant impairment of functioning and was not able to carry out usual activities). Local reaction was defined as either an intense local reaction (wheal diameter >8 cm, with flush, pruritus or pseudopodia) or a nonintense local reaction (wheal diameter ≤8 cm).

The adherence rate was calculated using the following formula: $(1 - [\text{total delayed injections}/\text{total injections}]) \times 100\%$. A dose delayed more than 14 days was considered as a delayed injection. The adherence rate for each patient was classified into three levels: poor adherence (adherence rate <50%), average adherence (adherence rate ≥50% but <75%) and good adherence (adherence rate ≥75%) [24]. Tolerability assessments were used to calculate the number of patients who reached the maximum dose of NHD Strength 3 during initial treatment.

All end points were further analyzed by age group (5–11 vs 12–17 years of age) and by indication (AR vs AA vs both AR and AA).

Statistical methods

The sample size of 250 patients was calculated based on the normal approximations method with 95% CI, an allowed precision of 4% and a reference dropout rate of 10.6% [24].

Descriptive statistics (n, mean, standard deviation [SD] and median) were used for continuous variables and frequencies and percentages for categorical and ordinal variables; where appropriate, 95% CIs were calculated. Additionally, categorical (qualitative) variables were displayed using numbers and percentages.

The analyses reported in this paper were based on the safety set (SAF), which comprised the group of patients who received at least one dose of the study medication. The software used for statistical analyses was SAS version 9.4 (SAS Institute, NC, USA).

Results

Patients

Of the 290 patients who were screened in this study, 250 (86.2%) were enrolled (200 children and 50 adolescents) from 17 institutions, and all 250 patients, who comprise the safety analysis set by definition, received at least one dose of the study treatment. The distribution of patients across the 17 sites is shown in Supplementary Table 1. Of the enrolled patients, 38.8% (97/250), 11.2% (28/250) and 50.0% (125/250) suffered from AR, AA or both, respectively. 15 patients (5.2%), including 14 children (6.1%) and one adolescent (1.9%), discontinued the study (Figure 1).

Overall, 68.8% (172/250) of patients were male. The median (range) age of patients was 9.15 (5.0–17.9) years, and 54.8% (137/250) of patients had a family history of allergic disease (Table 1). Of the 233 patients who underwent a skin prick test, 87.1% (203/233) were positive for *Der. p* and 99.6% (232/233) were positive for *Der. f*.

Primary end point

SCIT-related AEs during initial treatment

A total of 250 patients received 3600 injections. In total, 361 (10.0%, 361/3600) SCIT-related AEs occurred in 96 (38.4%, 96/250; 95% CI: 32.3–44.7%) patients; 321 (8.9%, 321/3600) injections caused local reactions in 89 (35.6%, 89/250) patients and 40 (1.1%, 40/3600) injections led to systemic reactions in 23 (9.2%, 23/250) patients. The percentages of injections that caused nonintense local reactions and intense local reactions were 8.7% (313/3600) and 0.2% (8/3600), respectively.

By age, 278 SCIT-related AEs occurred in 79 children, and 83 SCIT-related AEs occurred in 17 adolescents (Table 2). The SCIT-related AEs were numerically higher among children (39.5%) than adolescents (34.0%). By age group (children and adolescents, respectively), the most frequent SCIT-related AEs were injection site urticaria (14.5, 20.0%), injection site pruritus (8.0, 4.0%), injection site erythema (7.0, 2.0%) and injection site rash (5.0, 12.0%).

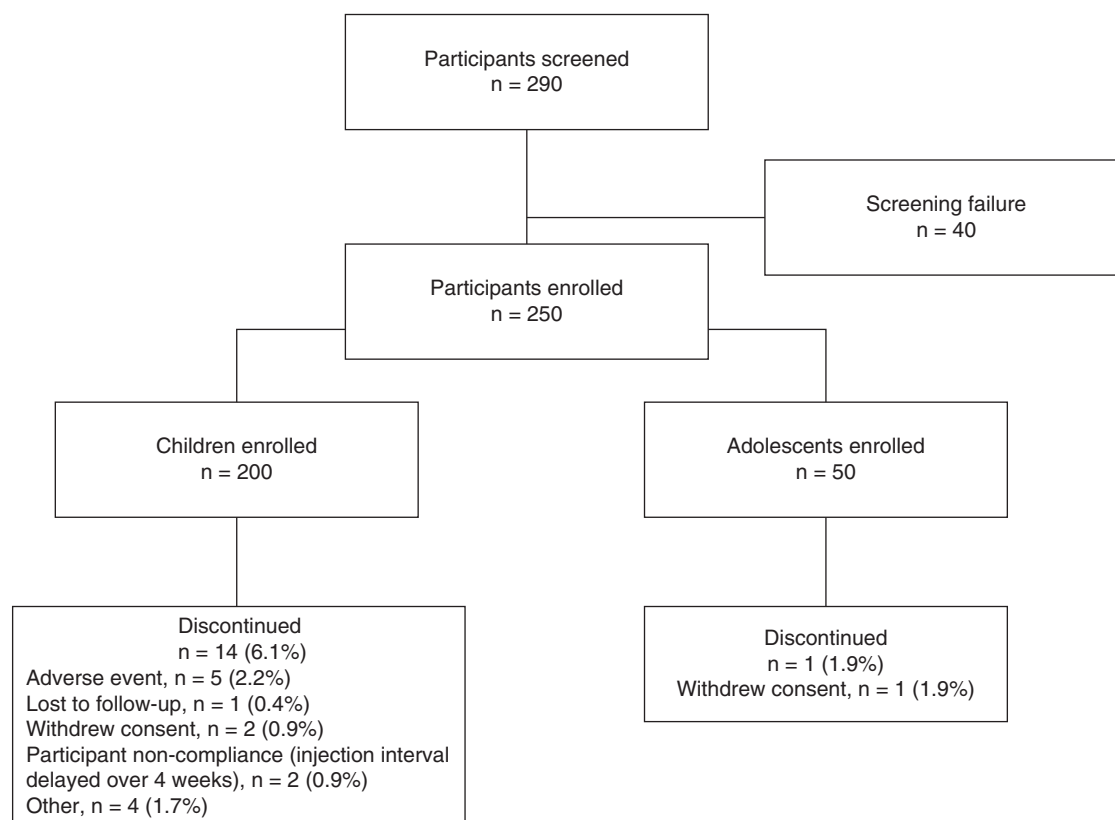


Figure 1. Patients' disposition. The disposition of patients included in the safety set, defined as all enrolled patients who received at least one dose of the study medication, is shown. The discontinuations detailed in the figure reflect those that occurred after patients had received at least one dose of the study medication. Thus, although 14 children and one adolescent patient did not complete the study, 250 patients had initially been enrolled in the study.

By type of allergy (AR, asthma and both, respectively), the most frequent SCIT-related AEs were injection site urticaria (26.8, 10.7, 8.0%), injection site pruritus (11.3, 7.1, 4.0%), injection site rash (6.2, 0, 8.0%), injection site induration (2.1, 7.1, 4.8%), injection site erythema (1.0, 28.6, 4.8%) and urticaria (1.0, 7.1, 3.2%) (Table 3).

One 11-year-old patient diagnosed with AR and AA experienced an SAE 1 h after the injection with a dose of 0.4 ml of Strength 3, manifested as rash in the face, neck, chest and back. Oral antihistamine drug administration did not relieve the symptom after 2 h. Subsequently, the patient was prescribed prophylactically with epinephrine; no other life-threatening reactions occurred and peak expiratory flow was maintained within the normal range. 30 min later, the anaphylactic rash resolved. Because epinephrine was used, this SCIT-related AE was considered an SAE and led to dose reduction.

Secondary end points

AEs & SAEs

The incidence of AEs is shown by age group in Supplementary Table 2 and by type of allergy in Supplementary Table 3. Overall, 136 patients (54.4%) had 545 AEs. In children, the most frequently reported AEs were injection site urticaria, injection site pruritus, upper respiratory tract infection, cough, rash and urticaria. In adolescents, the most frequently reported AE was injection site urticaria. The most frequent AEs were injection site urticaria, injection site pruritus and upper respiratory tract infection in patients with AR; injection site erythema and upper respiratory tract infection in patients with AA; and injection site rash, injection site swelling, upper respiratory tract infection and cough in patients with both AR and asthma.

The incidence of SAEs was 2.0% ($n = 5$; i.e., hand, foot and mouth disease, pneumonia, pneumonia mycoplasma, tonsillitis, urinary tract infection and rash). Rash was the only SCIT-related SAE. No deaths were reported in this study.

Table 1. Baseline demographic and clinical characteristics of patients by age group (safety set).

Variable	Children (5–11 years) (n = 200)	Adolescents (12–17 years) (n = 50)	Overall (n = 250)
Sex, n (%)			
Male	132 (66.0%)	40 (80.0%)	172 (68.8%)
Female	68 (34.0%)	10 (20.0%)	78 (31.2%)
Age, years			
Mean (SD)	8.16 (2.13)	14.51 (1.86)	9.43 (3.28)
Median (range)	8.05 (5.0–11.9)	14.20 (12.0–17.9)	9.15 (5.0–17.9)
BMI (kg/m ²), mean (SD)	16.95 (3.63)	20.59 (3.85)	17.68 (3.94)
Diagnosis, n (%)			
AR	73 (36.5%)	24 (48.0%)	97 (38.8%)
Allergic asthma	26 (13.0%)	2 (4.0%)	28 (11.2%)
AR + allergic asthma	101 (50.5%)	24 (48.0%)	125 (50.0%)
Family history of allergy, yes, n (%)	109 (54.5%)	28 (56.0%)	137 (54.8%)
Skin prick test, yes, n (%)	186 (93.0%)	47 (94.0%)	233 (93.2%)
Positive skin prick test, n (%)			
Der. p	160 (86.0%)	43 (91.5%)	203 (87.1%)
Der. f	185 (99.5%)	47 (100.0%)	232 (99.6%)
IgE serum (kU/l), median (range)			
Der. p	38.5 (0.61–100.0)	29.2 (1.31–100.0)	36.8 (0.61–100.0)
Der. f	59.2 (0.07–100.0)	37.7 (1.18–100.0)	56.2 (0.07–100.0)
Percentage of tested FEV1 of predicted value (%), mean (SD)	99.3 (20.2)	95.9 (14.4)	98.6 (19.2)

Age = (date of Informed consent – date of Birth + 1)/365.25.
Denominator for % calculation was the total number of patients in each respective group from SAF.
The value of sIgE is calculated as 100 kU/l, if test result is above 100 kU/l.
AR: Allergic rhinitis; FEV1: Forced expiratory volume in 1 s; IgE: Immunoglobulin E; SAF: Safety set; SD: Standard deviation.

Outcomes

AEs led to dose reduction in 19 children and four adolescents (Supplementary Table 4); suspension of treatment was observed in 12 children and one adolescent; and treatment discontinuation was observed in six children but among none of the adolescents. Nine patients with AR, three patients with AA and 11 patients with both AR and AA had AEs leading to dose reduction (Supplementary Table 5). Three patients with AR, one patient with AA and two patients with both AR and AA had AEs leading to treatment discontinuation.

Severity of SCIT-related AEs

Of the 82 patients (32.8%) with nonintense local reactions, 78 (31.2%) were mild and four (1.6%) were moderate reactions. Intense local reactions in seven patients (2.8%) were all mild. Of the 23 patients (9.2%) with systemic reactions, 14 (5.6%), seven (2.8%) and two (0.8%) patients had mild, moderate and severe reactions, respectively.

Adherence rate

The mean duration of treatment was 111.7 days overall, 110.8 and 115.1 days in children and adolescents, respectively, and 113.8, 108.2 and 110.8 days in patients with AR, AA and both, respectively. Overall, 30 patients (12.0%) had at least one delayed injection. 27 (13.5%) children and three (6.0%) adolescents had at least one delayed injection. Additionally, 14 (14.4%), two (7.1%) and 14 (11.2%) patients with AR, AA and both AR and AA had at least one delayed reaction, respectively. By age and allergy subgroups, all patients had good adherence ($\geq 75\%$).

Tolerability

Of the 250 patients, 217 (86.8%) reached the maximum dose of 1.0 ml of Strength 3. The omission of Strength 0 and the start of dose escalation with Strength 1 was generally well tolerated by all subjects. By age, 85.5% (171/200) of children and 92.0% (46/50) of adolescents reached the maximum dose of 1.0 ml of Strength 3. By allergy type,

Table 2. Subcutaneous immunotherapy-related adverse events by age group (safety set).

System organ class preferred term	Children (5–11 years) (n = 200)			Adolescents (12–17 years) (n = 50)			Overall (n = 250)		
	n (%)	n of events	95% CI	n (%)	n of events	95% CI	n (%)	n of events	95% CI
Overall	79 (39.5)	278	32.7, 46.6	17 (34.0)	83	21.2, 48.8	96 (38.4%)	361	32.3, 44.7
General disorders and administration site conditions	72 (36.0)	248	29.4, 43.1	17 (34.0)	74	21.2, 48.8	89 (35.6%)	322	29.7, 41.9
Injection site urticaria	29 (14.5)	69	9.9, 20.2	10 (20.0)	48	10.0, 33.7	39 (15.6)	117	11.3, 20.7
Injection site pruritus	16 (8.0)	36	4.6, 12.7	2 (4.0)	6		18 (7.2)	42	4.3, 11.
Injection site erythema	14 (7.0)	76	3.9, 11.5	1 (2.0)	2		15 (6.0)	78	3.4, 9.7
Injection site rash	10 (5.0)	22	2.4, 9.0	6 (12.0)	12	4.5, 24.3	16 (6.4)	34	3.7, 10.2
Injection site induration	8 (4.0)	15	1.7, 7.7	2 (4.0)	2		10 (4.0)	17	1.9, 7.2
Injection site papule	6 (3.0)	14	1.1, 6.4	0	0		6 (2.4)	14	0.9, 5.2
Injection site nodule	3 (1.5)	3	0.3, 4.3	1 (2.0)	2		4 (1.6)	5	0.4, 4.0
Injection site macule	2 (1.0)	3		1 (2.0)	2		3 (1.2)	5	0.2, 3.5
Injection site reaction	2 (1.0)	3		0	0		2 (0.8)	3	
Injection site swelling	2 (1.0)	3		0	0		2 (0.8)	3	
Pyrexia	1 (0.5)	1		0	0		1 (0.4)	1	
Chest discomfort	1 (0.5)	1		0	0		1 (0.4)	1	
Immune system disorders	1 (0.5)	1		0	0		1 (0.4)	1	
Hypersensitivity	1 (0.5)	1		0	0		1 (0.4)	1	
Respiratory, thoracic and mediastinal disorders	7 (3.5)	9	1.4, 7.1	4 (8.0)	5	2.2, 19.2	11 (4.4)	14	2.2, 7.7
Asthma	3 (1.5)	3	0.3, 4.3	0	0		3 (1.2)	3	0.2, 3.5
Cough	3 (1.5)	3	0.3, 4.3	0	0		3 (1.2)	3	0.2, 3.5
Dyspnea	2 (1.0)	2		2 (1.0)	2		3 (1.2)	4	0.2, 3.5
Laryngeal edema	0	0		1 (2.0)	1		1 (0.4)	1	
Nasal obstruction	1 (0.5)	1		0	0		1 (0.4)	1	
Suffocating feeling	0	0		1 (2.0)	1		1 (0.4)	1	
Throat irritation	0	0		1 (2.0)	1		1 (0.4)	1	
Skin and subcutaneous tissue disorders	14 (7.0)	19	3.9, 11.5	2 (4.0)	4		16 (6.4)	23	3.7, 10.2
Urticaria	5 (2.5)	6	0.8, 5.7	2 (4.0)	3		7 (2.8)	9	1.1, 5.7
Rash	4 (2.0)	7	0.5, 5.0	0	0		4 (1.6)	7	0.4, 4.0
Erythema	2 (1.0)	2		0	0		2 (0.8)	2	
Cold sweat	1 (0.5)	1		0	0		1 (0.4)	1	
Drug eruption	1 (0.5)	1		0	0		1 (0.4)	1	
Pruritus generalized	1 (0.5)	1		0	0		1 (0.4)	1	
Rash maculopapular	1 (0.5)	1		0	0		1 (0.4)	1	
Dermatitis atopic	0	0		1 (2.0)	1		1 (0.4)	1	
Vascular disorders	1 (0.5)	1		0	0		1 (0.4)	1	
Pallor	1 (0.5)	1		0	0		1 (0.4)	1	

Denominator for % calculation was the total number of patients in each respective group from SAF.

If $n \leq 2$, then the 95% CI was not provided in the above table.

SAF: Safety set.

77.3% (75/97) of patients with AR, 89.3% (25/28) of patients with AA, and 93.6% (117/125) of patients with both AR and AA reached the maximum 1.0 ml dose of Strength 3.

Discussion

Der. p and *Der. f* are the predominant allergens in AR and AA throughout China [4]. A multicenter study from China found that positive skin prick responses to *Der. p* and *Der. f* were identified in nearly 60% of tested individuals with asthma or AR [11,29]. Furthermore, the prevalence rates of allergy to house dust mites in children were significantly

Table 3. Subcutaneous immunotherapy-related adverse events by type of allergy (safety set).

System organ class preferred term	AR (n = 97)			Allergic asthma (n = 28)			AR & allergic asthma (n = 125)			Overall (n = 250)		
	n (%)	n of events	95% CI	n (%)	n of events	95% CI	n (%)	n of events	95% CI	n (%)	n of events	95% CI
Overall	44 (45.4)	145	35.2, 55.8	14 (50.0)	86	30.6, 69.4	38 (30.4)	130	22.5, 39.3	96 (38.4)	361	32.3, 44.7
General disorders and administration site conditions	40 (41.2)	131	31.3, 51.7	14 (50.0)	80	30.6, 69.4	35 (28.0)	111	20.3, 36.7	89 (35.6)	322	29.7, 41.9
Injection site urticaria	26 (26.8)	68	18.3, 36.8	3 (10.7)	24	2.3, 28.2	10 (8.0)	25	3.9, 14.2	39 (15.6)	117	11.3, 20.7
Injection site pruritus	11 (11.3)	31	5.8, 19.4	2 (7.1)	2		5 (4.0)	9	1.3, 9.1	18 (7.2)	42	4.3, 11.1
Injection site rash	6 (6.2)	11	2.3, 13.0	0	0		10 (8.0)	23	3.9, 14.2	16 (6.4)	34	3.7, 10.2
Injection site macule	3 (3.1)	5	0.6, 8.8	0	0		0	0		3 (1.2)	5	0.2, 3.5
Injection site induration	2 (2.1)	6		2 (7.1)	3		6 (4.8)	8	1.8, 10.2	10 (4.0)	17	1.9, 7.2
Injection site reaction	2 (2.1)	3		0	0		0	0		2 (0.8)	3	
Injection site swelling	2 (2.1)	3		0	0		0	0		2 (0.8)	3	
Injection site erythema	1 (1.0)	1		8 (28.6)	48	13.2, 48.7	6 (4.8)	29	1.8, 10.2	15 (6.0)	78	3.4, 9.7
Injection site pain	1 (1.0)	1		1 (3.6)	1		0	0		2 (0.8)	2	
Injection site nodule	0	0		0	0		4 (3.2)	5	0.9, 8.0	4 (1.6)	5	0.4, 4.0
Injection site papule	0	0		0	0		4 (3.2)	5	0.9, 8.0	4 (1.6)	5	0.4, 4.0
Pyrexia	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Chest discomfort	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Immune system disorders	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Hypersensitivity	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Respiratory, thoracic and mediastinal disorders	5 (5.2)	7	1.7, 11.6	2 (7.1)	2		4 (3.2)	5	0.9, 8.0	11 (4.4)	14	2.2, 7.7
Cough	2 (2.1)	2		0	0		1 (0.8)	1		3 (1.2)	3	0.2, 3.5
Asthma	1 (1.0)	1		0	0		2 (1.6)	2		3 (1.2)	3	0.2, 3.5
Dyspnea	1 (1.0)	1		1 (3.6)	1		1 (0.8)	2		3 (1.2)	4	0.2, 3.5
Laryngeal edema	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Nasal obstruction	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Suffocating feeling	0	0		1 (3.6)	1		0	0		1 (0.4)	1	
Throat irritation	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Skin and subcutaneous tissue disorders	5 (5.2)	5	1.7, 11.6	3 (10.7)	4	2.3, 28.2	8 (6.4)	14	2.8, 12.2	16 (6.4)	23	3.7, 10.2
Cold sweat	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Drug eruption	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Erythema	1 (1.0)	1		1 (3.6)	1		0	0		2 (0.8)	2	
Pruritus generalized	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Urticaria	1 (1.0)	1		2 (7.1)	2		4 (3.2)	6	0.9, 8.0	7 (2.8)	9	1.1, 5.7
Rash	0	0		1 (3.6)	1		3 (2.4)	6	0.5, 6.9	4 (1.6)	7	0.4, 4.0
Rash maculopapular	0	0		0	0		1 (0.8)	1		1 (0.4)	1	
Dermatitis atopic	0	0		0	0		1 (0.8)	1		1 (0.4)	1	
Vascular disorders	1 (1.0)	1		0	0		0	0		1 (0.4)	1	
Pallor	1 (1.0)	1		0	0		0	0		1 (0.4)	1	

Denominator for % calculation was the total number of patients in each respective group from SAF.
 If $n \leq 2$, then the 95% CI was not provided in the above table.
 AR: Allergic rhinitis; SAF: Safety set.

higher than those in adults [11]. Allergic diseases can have detrimental effects on patients' education, quality of life and psychological health, especially for children and adolescents [30,31]. It is crucial to consider AIT as an etiological treatment that could potentially modify the immune system and stabilize the allergic response [14–16]. Not only can AIT improve temporary allergic symptoms but it can also provide long-term relief, prevent new sensitizations and impede the progression of AR to asthma [14–16].

The safety profile is an important consideration when initiating SCIT, and multiple clinical trials have evaluated the safety of SCIT. A recent review of SCIT found that local reactions are common, occurring in 26–86% of patients, while the rate of SCIT-associated systemic reactions was only 0.1–0.2% [32]. Furthermore, the majority of SCIT-related AEs occur during the build-up phase [33].

As there are limited real-world data from China on NHD3 with house dust mite allergen extract for AR and AA, this Phase IV clinical study evaluated the safety of NHD3 in 250 Chinese children and adolescents. The incidence of SCIT-related AEs was 38.4% overall and was similar between age (children and adolescents; 34.0–39.5%) and disease subgroups (i.e., patients with AR, AA or both; 30.4–50.0%). The majority of SCIT-related AEs were injection site reactions, and few systemic SCIT-related AEs were reported. All SCIT-related AEs were expected and previously reported [34]. The most common AEs were injection site urticaria, injection site pruritus and injection site erythema. Intense local reactions and systemic reactions occurred at a low percentage. By age subgroup, the incidence of AEs in children and adolescents was similar. Additionally, when assessed by type of allergy, patients with both AR and AA had fewer AEs than patients with only AR or AA. This may suggest that the patients with co-morbidities of upper and lower airway allergic inflammation would have better adherence to the controller medication and better control, which may lead to fewer AEs. As for tolerability to treatment, most patients reached the maximum dose of NHD3, regardless of age and type of allergy.

A previous study by Li and colleagues evaluated the effectiveness and safety of NHD4 in Chinese patients with AR and asthma for 1 year [24]. That study was conducted between 2011 and 2013 and included 272 Chinese patients aged 4–55 years. The results showed that the rate of intense local reactions and systemic reactions with NHD4 was 16.9%, which is comparable to the rate of occurrence observed in this study (12%). However, it is important to note that the NHD3 safety data reported here were obtained over a period of 14 weeks, whereas the NHD4 data from the previous study were collected over 12 months. Notably, prolonged treatment with the SCIT allergen extract tends to decrease the occurrence rate of local reactions, which might be attributable to individual tolerance to allergens. Another study reported the rate of systemic reactions for SCIT in all age groups was approximately 0.9%, which is also similar to the rate of systemic reactions with NHD3 (1.1%) in children and adolescents [35].

In the present study, a patient presented with a rash beyond the injection site range that was considered a severe systemic reaction. The condition was resolved after prophylactic treatment with epinephrine. The delayed administration of epinephrine is one of the risk factors associated with a systemic reaction during AIT and may lead to the onset of life-threatening allergic reactions and anaphylaxis [25]. Thus, the administration of epinephrine is key in the management of such reactions to ensure the safety of the patient, as recommended in the current guidelines for the management of anaphylaxis [36].

Patient adherence is not only key to the success of AIT but it is also an important factor to avoid AEs [23]. In this study, the number of patients with at least one delayed injection was low, indicating that all patients, regardless of age and type of allergy, had good adherence to the treatment. Good treatment adherence is vital in achieving positive clinical outcomes, particularly among patients with chronic conditions such as AR and asthma [29]. Furthermore, sustained treatment for at least 3 years is needed to achieve the long-term benefits of AIT. However, it is reported that most patients stop treatment with SCIT or SLIT during the first year of treatment [37], albeit patient adherence with SCIT has been found to be higher than that with SLIT [38]. Among patients with asthma, low adherence rates have been associated with higher hospitalization rates and death [39]. Although many factors affect adherence to treatment [40], short-term use of NHD3 could reduce the number of subcutaneous injections, accelerate dose escalation, help reach the maintenance dose faster and improve symptoms in the shorter term for allergic patients, which in turn could contribute to improved long-term treatment adherence.

This study has some strengths. Patients were enrolled from 17 different sites in China; therefore, the study comprised a diverse Chinese population, increasing the generalizability of the results. Another strength is that this is the first study to evaluate and provide safety data on a shortened initial regimen of NHD3 in children and adolescents in China.

The main limitation of this study was the small sample size for the adolescent group, which limits generalizability between age subgroups. We speculate that the small number of patients in the adolescent group enrolled in the

study is partly attributable to the time consuming process of SCIT injection and investigation after each allergy injection, which may be considered inconvenient for adolescents in middle school or high school compared with children in primary school. Additionally, increasing polysensitization to many aeroallergens with age may preclude some adolescents from meeting the inclusion criteria compared with patients monosensitized to house mites. In our sample of children and adolescents, male patients outnumbered female patients, and this may be viewed as a limitation. As mentioned above, the small sample size of the adolescent group may have been a contributing factor. Several studies on house dust mite immunotherapy in AR patients in China have reported a similar proportion of male and female patients, both in children and adolescents [41–43]. This is an interesting phenomenon when compared with other immunotherapy studies outside China, the reasons for which warrant further investigation in future studies. Regarding the proportion of male and female patients, we consider our sample to be representative of children and adolescents with AR and AA due to dust mites in China.

Conclusion

The safety profile of NHD3 in Chinese children and adolescents with AR and AA is favorable, with most AEs being mild-to-moderate local site reactions. Thus, the treatment of AR and AA with NHD3 is considered safe and well tolerated, with good adherence observed in Chinese children and adolescents.

Future perspective

House dust mites are the most common aeroallergens to trigger AR or asthmatic symptoms in sensitized children and adolescents in China. As real-world safety data are limited on mite extract product NHD, Strengths 1 to 3 (NHD3), as an altered and shorter initial treatment for SCIT, we investigated the safety of NHD3 during initial treatment in Chinese children and adolescents with AR and AA. We found that SCIT in Chinese children and adolescents with AR and AA using NHD3 as the initial treatment regimen was safe and well tolerated, with good treatment adherence. Further studies on the short-term use of NHD3 are warranted to confirm if this approach could reduce the number of subcutaneous injections, accelerate dose escalation, achieve the maintenance dose faster, improve symptoms in the shorter term for allergic patients and contribute to improved long-term treatment adherence in children and adolescents with AR and AA.

Summary points

- Mite extract product Novo-Helisen Depot is available in China in Strengths 1 to 3 (NHD3) as allergen immunotherapy (AIT) for allergic rhinitis (AR) and allergic asthma (AA).
- Safety data are needed to promote standardized dose-escalation procedures for optimized AIT with NHD3 in Chinese children and adolescents with AR or AA.
- This study evaluated the safety and tolerability of NHD3 during 14-week initial therapy in Chinese children (5–11 years) and adolescents (12–17 years) with perennial symptomatic AR and AA, focusing on subcutaneous immunotherapy (SCIT)-related events.
- There was a total of 3600 subcutaneous injections in 250 patients.
- Of these, there were 361/3600 (10.0%) SCIT-related adverse events (AEs) in 96/250 (38.4%) patients.
- Of the 3600 injections, 321 (8.9%) caused local reactions in 89/250 (35.6%) patients, the most frequent being injection site urticaria (15.6%), injection site pruritus (7.2%), injection site rash (6.4%) and injection site erythema (6.0%).
- 40 injections (1.1%) caused systemic reactions in 23/250 (9.2%) patients, most commonly urticaria (2.8%), rash (1.6%), dyspnea (1.2%) and asthma (1.2%).
- Initial treatment for 14 weeks with SCIT using NHD3 was safe and well tolerated in Chinese children and adolescents with AR and AA.
- Short-term use of NHD3 could reduce the number of subcutaneous injections, accelerate dose escalation and improve symptoms more quickly, in turn improving long-term treatment adherence.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2020-0232

Author contributions

L Xiang was the principal investigator and contributed to all aspects of this study. All the remaining authors contributed to study design and participated in conducting the study as investigators. Q Zhou participated as a study assistant and contributed to manuscript writing. P Chang was responsible for statistical analysis. All the authors have reviewed the final version of the text.

Financial & competing interests disclosure

This study was funded by Merck Serono China Co. Ltd, an affiliate of Merck KGaA, Darmstadt, Germany. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

The study protocol and associated documents were approved by the participating sites' ethical review boards, and the study was conducted in compliance with the principles of the 1964 Declaration of Helsinki and its later amendments as well as local regulations. Written informed consent/assent to participate in the study was obtained from each patient's parent or guardian.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data (ChiCTR-OIH-17012492). No individual participant data that underlies the results reported in the article will be available, and nor will information regarding the study protocol or statistical analysis, beyond what is reported in the text.

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Supplementary material

Table S1. Distribution of enrolled patients by participating institution

Institution name	Number of patients enrolled (N=250)
Beijing Children's Hospital	4
First Affiliated Hospital of Sun Yat-sen University	1
Weifang People's Hospital	43
Hospital 202 of Chinese People's Liberation Army*	8
Chengdu Women and Children's Central Hospital	11
Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology	13
The Second Hospital of Tianjin Medical University	21
The Second Affiliated Hospital of Guangzhou Medical University	9
Shenzhen Children's Hospital	14
Hubei Provincial Maternal and Child Health Hospital	16
Renmin Hospital of Wuhan University	13
Yantai Yuhuangding Hospital	15
The First Affiliated Hospital, Nanjing Medical University	5
Children's Hospital Affiliated to Zhengzhou University	5
Central Hospital of Zibo	31
Shenyang Command General Hospital*	20
Xiangya Hospital of Central South University	21

*Hospital 202 of Chinese People's Liberation Army and Shenyang Command General Hospital have since been merged into one hospital, General Hospital of Northern Theater Command.

Table S2. Adverse events by age group (SAF).

System Organ Class Preferred Term	Children (5–11 years) (N=200)		Adolescents (12–17 years) (N=50)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Overall	111 (55.5)	436	25 (50.0)	109	136 (54.4)	545
Blood and lymphatic system disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Lymphadenopathy	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Eye disorders	9 (4.5)	12	3 (6.0)	3	12 (4.8)	15
Conjunctivitis allergic	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Eye pruritus	7 (3.5)	10	3 (6.0)	3	10 (4.0)	13
Ocular hyperemia	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Gastrointestinal disorders	4 (2.0)	4	0 (0.0)	0	4 (1.6)	4
Abdominal pain	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Diarrhea	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Mouth ulceration	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Vomiting	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
General disorders and administration site conditions	81 (40.5)	262	20 (40.0)	84	101 (40.4)	346
Injection site erythema	14 (7.0)	76	1 (2.0)	2	15 (6.0)	78
Injection site induration	8 (4.0)	15	2 (4.0)	2	10 (4.0)	17
Injection site macule	2 (1.0)	3	1 (2.0)	2	3 (1.2)	5
Injection site nodule	3 (1.5)	3	1 (2.0)	2	4 (1.6)	5
Injection site pain	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Injection site papule	6 (3.0)	14	0 (0.0)	0	6 (2.4)	14
Injection site pruritus	17 (8.5)	38	3 (6.0)	7	20 (8.0)	45
Injection site rash	10 (5.0)	22	6 (12.0)	12	16 (6.4)	34
Injection site reaction	2 (1.0)	3	0 (0.0)	0	2 (0.8)	3
Injection site swelling	2 (1.0)	3	0 (0.0)	0	2 (0.8)	3
Injection site urticaria	29 (14.5)	69	11 (22.0)	55	40 (16.0)	124
Pyrexia	11 (5.5)	13	1 (2.0)	1	12 (4.8)	14
Chest discomfort	1 (0.5)	1	1 (2.0)	1	2 (0.8)	2
Immune system disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Hypersensitivity	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Infections and infestations	40 (20.0)	61	8 (16.0)	9	48 (19.2)	70
Bronchitis	3 (1.5)	3	0 (0.0)	0	3 (1.2)	3
Gastroenteritis	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Hand-foot-and-mouth disease	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Hordeolum	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Influenza	2 (1.0)	2	1 (2.0)	1	3 (1.2)	3
Laryngitis	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1

System Organ Class Preferred Term	Children (5–11 years) (N=200)		Adolescents (12–17 years) (N=50)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Myringitis	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Nasopharyngitis	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Otitis media	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Pharyngitis	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Pneumonia	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Pneumonia mycoplasmal	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Rhinitis	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Tonsillitis	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Upper respiratory tract infection	26 (13.0)	41	5 (10.0)	6	31 (12.4)	47
Urinary tract infection	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Varicella	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Injury, poisoning and procedural complications	2 (1.0)	2	1 (2.0)	1	3 (1.2)	3
Bite	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Limb injury	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Radius fracture	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Nervous system disorders	2 (1.0)	2	2 (4.0)	2	4 (1.6)	4
Dizziness	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Facial paralysis	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Headache	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Somnolence	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Renal and urinary disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Hematuria	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Respiratory, thoracic and mediastinal disorders	28 (14.0)	60	5 (10.0)	6	33 (13.2)	66
Asthma	4 (2.0)	5	0 (0.0)	0	4 (1.6)	5
Bronchitis chronic	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Cough	14 (7.0)	28	0 (0.0)	0	14 (5.6)	28
Dyspnea	2 (1.0)	2	1 (2.0)	2	3 (1.2)	4
Laryngeal edema	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Laryngeal pain	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Nasal obstruction	2 (1.0)	3	0 (0.0)	0	2 (0.8)	3
Nasal pruritus	2 (1.0)	3	1 (2.0)	1	3 (1.2)	4
Oropharyngeal pain	5 (2.5)	8	0 (0.0)	0	5 (2.0)	8
Productive cough	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Rhinitis allergic	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Rhinorrhea	1 (0.5)	2	0 (0.0)	0	1 (0.4)	2
Sneezing	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Suffocation feeling	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Throat irritation	1 (0.5)	1	1 (2.0)	1	2 (0.8)	2

System Organ Class Preferred Term	Children (5–11 years) (N=200)		Adolescents (12–17 years) (N=50)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Skin and subcutaneous tissue disorders	20 (10.0)	29	2 (4.0)	4	22 (8.8)	33
Cold sweat	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Dermatitis atopic	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Drug eruption	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Eczema	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Erythema	3 (1.5)	3	0 (0.0)	0	3 (1.2)	3
Pruritus	1 (0.5)	2	0 (0.0)	0	1 (0.4)	2
Pruritus generalized	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Rash	7 (3.5)	10	0 (0.0)	0	7 (2.8)	10
Rash erythematous	1 (0.5)	2	0 (0.0)	0	1 (0.4)	2
Rash maculo-papular	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Urticaria	6 (3.0)	7	2 (4.0)	3	8 (3.2)	10
Vascular disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Pallor	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1

Denominator for % calculation is the total number of patients in each respective group from SAF.
SAF, safety set.

Table S3. Adverse events by type of allergy (SAF).

System Organ Class Preferred Term	Allergic rhinitis (N=97)		Allergic asthma (N=28)		Both allergic rhinitis and allergic asthma (N=125)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Overall	55 (56.7)	226	20 (71.4)	114	61 (48.8)	205	136 (54.4)	545
Blood and lymphatic system disorders	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Lymphadenopathy	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Eye disorders	7 (7.2)	10	2 (7.1)	2	3 (2.4)	3	12 (4.8)	15
Conjunctivitis	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
allergic								
Eye pruritus	6 (6.2)	9	2 (7.1)	2	2 (1.6)	2	10 (4.0)	13
Ocular hyperemia	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Gastrointestinal disorders	2 (2.1)	2	1 (3.6)	1	1 (0.8)	1	4 (1.6)	4
Abdominal pain	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Diarrhea	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
Mouth ulceration	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Vomiting	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
General disorders and administration site conditions	44 (45.4)	138	16 (57.1)	90	41 (32.8)	118	101 (40.4)	346
Injection site erythema	1 (1.0)	1	8 (28.6)	48	6 (4.8)	29	15 (6.0)	78
Injection site induration	2 (2.1)	6	2 (7.1)	3	6 (4.8)	8	10 (4.0)	17
Injection site macule	3 (3.1)	5	0 (0.0)	0	0 (0.0)	0	3 (1.2)	5
Injection site nodule	0 (0.0)	0	0 (0.0)	0	4 (3.2)	5	4 (1.6)	5
Injection site pain	1 (1.0)	1	1 (3.6)	1	0 (0.0)	0	2 (0.8)	2
Injection site papule	0 (0.0)	0	1 (3.6)	2	5 (4.0)	12	6 (2.4)	14
Injection site pruritus	11 (11.3)	31	4 (14.3)	5	5 (4.0)	9	20 (8.0)	45
Injection site rash	6 (6.2)	11	0 (0.0)	0	10 (8.0)	23	16 (6.4)	34
Injection site reaction	2 (2.1)	3	0 (0.0)	0	0 (0.0)	0	2 (0.8)	3
Injection site swelling	2 (2.1)	3	0 (0.0)	0	0 (0.0)	0	2 (0.8)	3
Injection site urticaria	26 (26.8)	68	4 (14.3)	31	10 (8.0)	25	40 (16.0)	124
Pyrexia	6 (6.2)	8	0 (0.0)	0	6 (4.8)	6	12 (4.8)	14
Chest discomfort	1 (1.0)	1	0 (0.0)	0	1 (0.8)	1	2 (0.8)	2
Immune system disorders	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1

System Organ Class Preferred Term	Allergic rhinitis (N=97)		Allergic asthma (N=28)		Both allergic rhinitis and allergic asthma (N=125)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Hypersensitivity	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Infections and infestations	17 (17.5)	28	10 (35.7)	14	21 (16.8)	28	48 (19.2)	70
Bronchitis	1 (1.0)	1	2 (7.1)	2	0 (0.0)	0	3 (1.2)	3
Gastroenteritis	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Hand-foot-and- mouth disease	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Hordeolum	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Influenza	1 (1.0)	1	1 (3.6)	1	1 (0.8)	1	3 (1.2)	3
Laryngitis	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Myringitis	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Nasopharyngitis	0 (0.0)	0	1 (3.6)	1	1 (0.8)	1	2 (0.8)	2
Otitis media	0 (0.0)	0	0 (0.0)	0	2 (1.6)	2	2 (0.8)	2
Pharyngitis	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Pneumonia	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Pneumonia mycoplasmal	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Rhinitis	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
Tonsillitis	1 (1.0)	1	0 (0.0)	0	1 (0.8)	1	2 (0.8)	2
Upper respiratory tract infection	13 (13.4)	21	6 (21.4)	9	12 (9.6)	17	31 (12.4)	47
Urinary tract infection	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Varicella	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Injury, poisoning and procedural complications	0 (0.0)	0	1 (3.6)	1	2 (1.6)	2	3 (1.2)	3
Bite	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
Limb injury	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Radius fracture	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Nervous system disorders	3 (3.1)	3	0 (0.0)	0	1 (0.8)	1	4 (1.6)	4
Dizziness	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Facial paralysis	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Headache	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Somnolence	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Renal and urinary disorders	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Hematuria	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Respiratory, thoracic and mediastinal disorders	12 (12.4)	32	2 (7.1)	2	19 (15.2)	32	33 (13.2)	66
Asthma	2 (2.1)	3	0 (0.0)	0	2 (1.6)	2	4 (1.6)	5
Bronchitis chronic	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Cough	4 (4.1)	11	0 (0.0)	0	10 (8.0)	17	14 (5.6)	28

System Organ Class Preferred Term	Allergic rhinitis (N=97)		Allergic asthma (N=28)		Both allergic rhinitis and allergic asthma (N=125)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Dyspnea	1 (1.0)	1	1 (3.6)	1	1 (0.8)	2	3 (1.2)	4
Laryngeal edema	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Laryngeal pain	0 (0.0)	0	0 (0.0)	0	2 (1.6)	2	2 (0.8)	2
Nasal obstruction	2 (2.1)	3	0 (0.0)	0	0 (0.0)	0	2 (0.8)	3
Nasal pruritus	3 (3.1)	4	0 (0.0)	0	0 (0.0)	0	3 (1.2)	4
Oropharyngeal pain	0 (0.0)	0	0 (0.0)	0	5 (4.0)	8	5 (2.0)	8
Productive cough	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Rhinitis allergic	2 (2.1)	2	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Rhinorrhea	1 (1.0)	2	0 (0.0)	0	0 (0.0)	0	1 (0.4)	2
Sneezing	1 (1.0)	1	0 (0.0)	0	1 (0.8)	1	2 (0.8)	2
Suffocation feeling	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
Throat irritation	2 (2.1)	2	0 (0.0)	0	0 (0.0)	0	2 (0.8)	2
Skin and subcutaneous tissue disorders	9 (9.3)	11	3 (10.7)	4	10 (8.0)	18	22 (8.8)	33
Cold sweat	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Dermatitis atopic	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Drug eruption	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Eczema	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Erythema	1 (1.0)	1	1 (3.6)	1	1 (0.8)	1	3 (1.2)	3
Pruritus	1 (1.0)	2	0 (0.0)	0	0 (0.0)	0	1 (0.4)	2
Pruritus generalized	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Rash	1 (1.0)	1	1 (3.6)	1	5 (4.0)	8	7 (2.8)	10
Rash erythematous	1 (1.0)	2	0 (0.0)	0	0 (0.0)	0	1 (0.4)	2
Rash maculo- papular	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Urticaria	1 (1.0)	1	2 (7.1)	2	5 (4.0)	7	8 (3.2)	10
Vascular disorders	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Pallor	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1

SAF, safety set.

Table S4. Adverse events leading to dose reduction, treatment suspension, and study withdrawal by age group (SAF).

System Organ Class Preferred Term	Children (5–11 years) (N=200)		Adolescents (12–17 years) (N=50)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Overall	19 (9.5)	33	4 (8.0)	13	23 (9.2)	46
General disorders and administration site conditions	5 (2.5)	6	3 (6.0)	5	8 (3.2)	11
Injection site induration	1 (0.5)	2	0 (0.0)	0	1 (0.4)	2
Injection site nodule	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Injection site pruritus	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Injection site urticaria	1 (0.5)	1	2 (4.0)	4	3 (1.2)	5
Chest discomfort	1 (0.5)	1	1 (2.0)	1	2 (0.8)	2
Immune system disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Hypersensitivity	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Infections and infestations	3 (1.5)	4	1 (2.0)	1	4 (1.6)	5
Influenza	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Pneumonia	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
mycoplasmal						
Upper respiratory tract infection	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Varicella	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Respiratory, thoracic and mediastinal disorders	6 (3.0)	10	3 (6.0)	4	9 (3.6)	14
Asthma	3 (1.5)	4	0 (0.0)	0	3 (1.2)	4
Cough	3 (1.5)	4	0 (0.0)	0	3 (1.2)	4
Dyspnea	2 (1.0)	2	1 (2.0)	2	3 (1.2)	4
Laryngeal edema	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Suffocation feeling	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Skin and subcutaneous tissue disorders	10 (5.0)	11	2 (4.0)	3	12 (4.8)	14
Cold sweat	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Dermatitis atopic	0 (0.0)	0	1 (2.0)	1	1 (0.4)	1
Erythema	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2
Pruritus generalized	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Rash	2 (1.0)	2	0 (0.0)	0	2 (0.8)	2

System Organ Class Preferred Term	Children (5–11 years) (N=200)		Adolescents (12–17 years) (N=50)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Rash erythematous	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Urticaria	4 (2.0)	4	2 (4.0)	2	6 (2.4)	6
Vascular disorders	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1
Pallor	1 (0.5)	1	0 (0.0)	0	1 (0.4)	1

Denominator for % calculation is the total number of patients in each respective group from SAF.
SAF, safety set.

Table S5. Adverse events leading to dose reduction, treatment suspension, and study withdrawal by type of allergy (SAF).

System Organ Class Preferred Term	Allergic rhinitis (N=97)		Allergic asthma (N=28)		Both allergic rhinitis and allergic asthma (N=125)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Overall	9 (9.3)	19	3 (10.7)	9	11 (8.8)	18	23 (9.2)	46
General disorders and administration site conditions	3 (3.1)	4	3 (10.7)	5	2 (1.6)	2	8 (3.2)	11
Injection site induration	1 (1.0)	2	0 (0.0)	0	0 (0.0)	0	1 (0.4)	2
Injection site nodule	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Injection site pruritus	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
Injection site urticaria	1 (1.0)	1	2 (7.1)	4	0 (0.0)	0	3 (1.2)	5
Chest discomfort	1 (1.0)	1	0 (0.0)	0	1 (0.8)	1	2 (0.8)	2
Immune system disorders	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Hypersensitivity	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Infections and infestations	1 (1.0)	1	0 (0.0)	0	3 (2.4)	4	4 (1.6)	5
Influenza	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Pneumonia	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
mycoplasmal								
Upper respiratory tract infection	1 (1.0)	1	0 (0.0)	0	1 (0.8)	1	2 (0.8)	2
Varicella	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Respiratory, thoracic and mediastinal disorders	3 (3.1)	7	2 (7.1)	2	4 (3.2)	5	9 (3.6)	14
Asthma	1 (1.0)	2	0 (0.0)	0	2 (1.6)	2	3 (1.2)	4
Cough	2 (2.1)	3	0 (0.0)	0	1 (0.8)	1	3 (1.2)	4
Dyspnea	1 (1.0)	1	1 (3.6)	1	1 (0.8)	2	3 (1.2)	4
Laryngeal edema	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Suffocation	0 (0.0)	0	1 (3.6)	1	0 (0.0)	0	1 (0.4)	1
feeling								
Skin and subcutaneous tissue disorders	5 (5.2)	5	1 (3.6)	2	6 (4.8)	7	12 (4.8)	14
Cold sweat	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Dermatitis atopic	0 (0.0)	0	0 (0.0)	0	1 (0.8)	1	1 (0.4)	1
Erythema	1 (1.0)	1	1 (3.6)	1	0 (0.0)	0	2 (0.8)	2

System Organ Class Preferred Term	Allergic rhinitis (N=97)		Allergic asthma (N=28)		Both allergic rhinitis and allergic asthma (N=125)		Overall (N=250)	
	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events	n (%)	No. of events
Pruritus generalized	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Rash	0 (0.0)	0	1 (3.6)	1	1 (0.8)	1	2 (0.8)	2
Rash erythematous	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Urticaria	1 (1.0)	1	0 (0.0)	0	5 (4.0)	5	6 (2.4)	6
Vascular disorders	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Pallor	1 (1.0)	1	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1

Denominator for% calculation is the total number of patients in each respective group from SAF.

SAF, safety set.