

Journal Pre-proof

A 300°IR sublingual tablet is an effective, safe treatment for house-dust-mite-induced allergic rhinitis: an international, double-blind, placebo-controlled, randomized Phase III clinical trial

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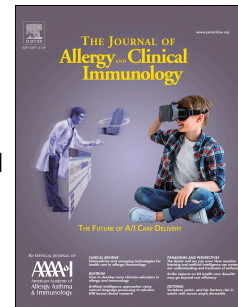
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A LARGE INTERNATIONAL PHASE III STUDY : THE 300 IR HDM SLIT TABLET HAS A CLINICALLY MEANINGFUL EFFECT ON KEY PATIENT DRIVERS

Phase III DBPC randomized trial 12 months of treatment



Efficacy and safety of a 300 IR HDM SLIT tablet



1,607 adolescents (aged ≥12) and adults with moderate-to-severe HDM-induced allergic rhinitis



300 IR HDM SLIT tablet (n=802) ; Placebo (n=805)

Clinical endpoints focused on key patient drivers

Primary endpoint

- aTCS over 4 weeks at the end of the treatment period

6 Key secondary Endpoints

- Average nasal congestion symptom score
- Overall RQLQ12+ score
- Average RMS
- Average CSMS
- Average RCTSS
- PSCD₂₋₀

Patient benefits

- aTCS: relative LS mean difference ([95% CI]) vs placebo: -16.9% [-24.0%; -9.2%]
- The analysis of six key secondary endpoints reached statistical significance for each of them (p-values ≤0.0082), demonstrating consistency and robustness of the results.
- 12 months of treatment with a 300IR HDM SLIT tablet (vs. placebo) is associated with reductions in AR symptoms, symptomatic medication use and a better quality of life.

A 300°IR sublingual tablet is an effective, safe treatment for house-dust-mite-induced allergic rhinitis: an international, double-blind, placebo-controlled, randomized Phase III clinical trial

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ABSTRACT

Background: Allergic rhinitis (AR) induced by house dust mites (HDMs) is a highly prevalent but often underdiagnosed and undertreated/untreated chronic disease. It often has a negative impact on sleep, work, leisure activities, and health-related quality of life. Allergen immunotherapy is a proven, safe treatment for respiratory allergies.

Objective: To assess the efficacy and safety of a 300 index of reactivity (IR) sublingual tablet formulation of *Dermatophagoides pteronyssinus*:*Dermatophagoides farinae* 1:1 extract in adolescents (aged ≥ 12) and adults with moderate-to-severe HDM-induced AR.

Methods: In a Phase III, international, double-blind, placebo-controlled, randomized clinical trial, participants received approximately 12 months of treatment with placebo or the 300°IR tablet. The primary endpoint was the average total combined score (aTCS) during 4 weeks at the end of the treatment period.

Results: 1,607 participants were randomized, and 1,476 (including 555 (37.6%) with concomitant mild controlled asthma at inclusion) comprised the full analysis set. Over the primary evaluation period, the least squares mean aTCS in the 300°IR group (3.62) was significantly lower ($p < 0.0001$) than in the placebo group (4.35), with a relative least squares mean difference of -16.9% [95% confidence interval: -24.0%; -9.2%]. All pre-specified secondary endpoints were consistently improved in the 300°IR group, relative to placebo. The 300°IR tablet was generally well tolerated. Treatment-related adverse events

(mainly mild or moderate local reactions) were reported for 51.0% of the patients in the 300°IR group and 14.9% in the placebo group.

Conclusions: The 300°IR sublingual HDM tablet is an effective, safe treatment for HDM-induced AR. (NCT02443805, EudraCT 2014-004223-46)

Clinical Implications: A 300 index of reactivity sublingual tablet formulation of *Dermatophagoides pteronyssinus*:*Dermatophagoides farinae* extract is a safe, effective treatment for moderate-to-severe house-dust-mite-induced allergic rhinitis.

Capsule summary

- In house dust mite allergy, 12 months of treatment with a sublingual immunotherapy tablet (vs. placebo) is associated with reductions in allergic rhinitis symptoms, symptomatic medication use and a better quality of life.

Key words: allergen immunotherapy, allergic rhinitis, allergy, house dust mite, sublingual immunotherapy, tablet, total combined score, symptom score, medication score

Abbreviations:

AE: Adverse event

AIT: Allergen immunotherapy

AR: Allergic rhinitis

CI: Confidence interval

CSMS: Combined symptom and medication score

aCSMS: Average combined symptom and medication score

CV: Coefficient of variation

Dfar: *Dermatophagoides farinae*

Dpte: *Dermatophagoides pteronyssinus*

FAS: Full analysis set

138	GINA: Global Initiative for Asthma
139	HDM: House dust mite
140	IP: Investigational product
141	IR: Index of reactivity
142	ISS: Individual rhinoconjunctivitis symptom score
143	LS: Least squares
144	PSCD: Proportion of symptom-controlled days
145	QoL: Quality of life
146	RCTSS: Rhinoconjunctivitis total symptom score
147	RMS: Rescue medication score
148	aRMS: Average rescue medication score
149	RQLQ12+: Standardized Rhinoconjunctivitis Quality of Life Questionnaire for 12 years and older
150	RTSS: Rhinitis total symptom score
151	aRTSS: Average rhinitis total symptom score
152	SPT: Skin prick test
153	SS: Safety set
154	TCS: Total combined score
155	aTCS: Average total combined score
156	TEAE: Treatment-emergent adverse event
157	V: Visit

158

159 INTRODUCTION

160 Allergic rhinitis (AR) is a highly prevalent but often underdiagnosed and undertreated/untreated chronic
 161 disease.(1-7) The symptoms - mainly nasal congestion, nasal pruritus, clear rhinorrhoea, and sneezing -
 162 are triggered by exposure to aeroallergens found outdoors and/or indoors (e.g. pollen, house dust mite
 163 (HDM) allergens, animal dander, and mould allergens). House dust mite allergy is particularly
 164 troublesome, given (i) the almost ubiquitous and often perennial presence of HDMs in indoor
 165 environments worldwide (and thus the limited efficacy of allergen eviction and avoidance measures), and

(ii) the wide range of allergenic components produced by HDMs (i.e. cuticle and faeces components, digestive tract enzymes, etc.).(1-3)

If not treated or only ineffectively treated, the symptoms of moderate-to-severe AR can have a negative impact on sleep and thus induce daytime drowsiness; in turn, this can impair work productivity, academic, sporting and leisure activities, and health-related quality of life (QoL), increase the risk of road accidents, and hasten the onset of other diseases (such as allergic asthma) as part of the “allergic march”.(4-11)

The symptoms of AR can be treated with symptomatic medications, such as H1 antihistamines, corticosteroids, chromones, and leukotriene receptor antagonists.(12-14) However, symptomatic medications may be unwanted, poorly tolerated or ineffective, and do not act on the underlying atopic disease mechanism.(15-18)

Allergen immunotherapy (AIT) is a proven, safe treatment for respiratory allergies; it exerts a systemic action, and can thus potentially affect both the upper and lower airways.(19-23) Various allergen formulations and administration routes have been tested and approved for the treatment of moderate-to-severe AR with or without mild-to-moderate allergic asthma induced by HDMs.(16, 24-30) In clinical trials conducted in Europe, Canada and Japan, a 300 index of reactivity (IR) sublingual tablet of *Dermatophagoides pteronyssinus* (Dpte) and *Dermatophagoides farinae* (Dfar) extract (total allergenic activity ratio: 1:1) has shown efficacy and safety in adults and adolescents with HDM-induced AR (irrespective of mono- or polysensitization status or the concomitant presence of mild asthma), and has been approved for commercialization in the Asia-Pacific region.(25, 26, 29-31) Even though 300 IR and 500 IR doses of the tablet had demonstrated efficacy in Phase II/III studies of adults and adolescents, the 500 IR dose did not show incremental benefit vs. the 300 IR dose; the latter was therefore chosen for further evaluation.

The overall goal of the present clinical trial was to confirm the efficacy and safety of a 12-month course of treatment with 300°IR sublingual tablets vs. placebo in adults and adolescents with HDM-induced AR in a broad set of patient populations (in Europe, the USA, Canada, Israel, and Russia). The primary clinical objective was to determine the tablet's efficacy over four weeks at the end of the treatment period (referred to henceforth as the primary evaluation period), as quantified by the average total combined

score (aTCS, where the TCS was defined as the sum of the patient's daily rhinitis total symptom score (RTSS) and a daily rescue/relief medication score (RMS); see the Endpoints and assessments section for full details). The secondary objectives were to confirm the 300°IR tablet's efficacy according to a range of endpoints (symptom scores, medication scores, symptom control, QoL, etc.) during the primary evaluation period and during interim evaluation periods (months 3, 6 and 9), and to describe the tablet's safety throughout the treatment and follow-up periods.

METHODS

Trial design

This international, double-blind, placebo-controlled, Phase III randomized clinical trial comprised a screening phase lasting 6 weeks to 6 months (including a 5-week, single-blind, placebo run-in period), a double-blind treatment phase lasting approximately 12 months, and a 2-week post-treatment follow-up phase (Fig 1).

All participants meeting the selection criteria entered the 5-week, placebo run-in period, and were provided with rescue medications. Rhinoconjunctivitis symptoms and rescue/relief medication use were noted in an electronic patient diary. Patients with an aTCS of ≥ 5 out of 15 (see the Endpoints and assessments subsection for full details) over the last 4 weeks of the 5-week run-in period were randomized 1:1 to receive HDM AIT or placebo for approximately 12 months. The total planned duration of the study for an individual patient was between 14 and 20 months, with a total of 10 study visits: a screening visit (V1), a run-in visit (V2), a randomization visit (V3), six regular visits (at months 1, 3, 6, 9, 11, and 12; V4 to V9, respectively) and a post-treatment visit (month 12.5; V10). The study was performed at 231 centres in 13 countries: Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Israel, Italy, Poland, Russian Federation, Slovakia, Spain, and the USA.

Trial population

The study's main inclusion criteria were as follows: (i) males or females aged between 12 and 65, (ii) physician-diagnosed, HDM-induced AR (with or without concomitant asthma, as recorded in a clinical assessment by the investigating physician) for at least the 12 months prior to inclusion in the study, with

self-reported troublesome symptoms with regard to leisure, sports, academic or work activities and/or sleep disturbance requiring regular symptomatic treatment; and (iii) sensitization to Dpte and/or Dfar, as confirmed by a skin prick test (SPT) wheal diameter at least 5 mm greater than the negative control, and an HDM-specific serum IgE level ≥ 3.5 kU/L. Serum-specific immunoglobulin assays were performed centrally.

The main exclusion criteria were (i) a potentially confounding allergic disease (rhinitis, rhinoconjunctivitis or asthma) likely to result in AR symptoms during the primary evaluation period (see below), (ii) recent nasal surgery or nasal or oral disease, (iii) partly controlled or uncontrolled asthma (as defined in the 2014 revision of the Global Initiative for Asthma (GINA) guidelines) (32), (iv) regular use of asthma medication consistent with GINA treatment steps 3, 4 or 5, (v) a previous life-threatening asthma attack or exacerbation that resulted in admission to an intensive care unit, (vi) HDM AIT within the previous 5 years or other AIT within the previous 6 months, and (vii) the standard contraindications to AIT.(13, 14, 33).

With regard to potentially confounding allergies, we excluded patients with a documented positive skin prick test or allergen specific serum IgE > 3.5 kU/L and a history of clinically relevant symptoms to allergens other than HDM and who were likely to be exposed to such allergens during the baseline and primary evaluation periods. For example, this corresponded to patients sensitized to cat or dog allergens and who were regularly exposed to these animals; patients sensitized to perennial allergens; and patients sensitized to seasonal allergens such as *Parietaria*, ragweed and mugwort pollen if these were endemic in the region during the baseline and primary evaluation periods.

Randomization

Only eligible patients with an aTCS ≥ 5 during the last 4 weeks of the run-in period were to be randomized. Patients were allotted a screening number via an interactive web/voice response system. A computer-generated randomization list (stratified by study site) was prepared by a statistician not involved in study data analyses. The randomization list was supplied to a contract manufacturing organization, which packaged the investigational product (IP). All randomized participants received an epinephrine auto-injector for use in the event of a severe allergic reaction.

Study treatments

Participants took placebo tablets during the single-blind run-in phase. After randomization, patients received either HDM AIT (a sublingual tablet formulation of standardized, purified, freeze-dried, sieved Dpte and Dfar extracts for daily administration) or placebo. As measured with commercial ELISA kits, the per-tablet allergen content of the 300 IR formulation varies from 14 to 17 µg Der p 1 and from 53 to 68 µg Der f 1, as reported previously.(25, 26) The allergen contents for the major allergens (i.e. groups 1 and 2) and most of the minor allergens (i.e. Der p 3-11, 14, 15, 18, 20, 21, 23, 36 and Der f 3, 6-8, 11, 13-16, 18, 20-22, 25-33, 36) in whole extracts of both *D. pteronyssinus* and *D. farinae* have also been reported previously.(34) The regimen during the dose escalation phase consisted of one 100°IR tablet on day 1, two 100°IR tablets on day 2, and one 300°IR tablet on day 3, or matching placebo tablets. The first dose of the study medication was taken under medical supervision for 30 minutes. Maintenance treatment consisted of a 300°IR tablet (or placebo) once daily.

Endpoints and assessments

The primary efficacy variable was the average of the non-missing daily TCSs during the 4-week primary evaluation period. The daily TCS (ranging from 0 (best possible score) to 15 (worst possible score)) was the sum of the patient's daily RTSS over the previous 24 hours (scale: 0-12; 0 = no symptoms in any category, 12 = severe symptoms in all categories) and daily RMS score in which only the "strongest" type of medication used on a given day was taken into account (scale: 0-3; 0 = no treatment, 1 = an oral H1 antihistamine, 2 = an intranasal corticosteroid, 3 = an oral corticosteroid). The RTSS was the sum of four rhinitis symptom scores (nasal pruritus, sneezing, rhinorrhoea, and nasal congestion), evaluated on a 4-point scale (0 = no symptoms; 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms).

The secondary endpoints included the RTSS, the RMS, the rhinoconjunctivitis total symptom score (RCTSS), the combined symptom and medication score (CSMS), six individual rhinoconjunctivitis symptom scores (ISSs), the proportion of symptom-controlled days (PSCD, days with RTSS ≤2 and RMS=0), and disease-specific QoL (the Standardized Rhinoconjunctivitis Quality of Life Questionnaire, RQLQ12+) (35) (Table E1). The proportion of patients with a rhinitis exacerbation (a daily TCS ≥5, with at least one of the four rhinitis symptoms rated as severe) over the primary period was summarized descriptively and compared in the two treatment groups using a chi-squared test.

The safety variables were adverse events, routine laboratory tests, data from physical examinations, and vital signs.

Sample size calculation and statistical analysis

A sample size of 739 patients per treatment group was determined to provide a power greater than 99% for detecting a relative difference of -20% in the active group (relative to placebo) at a level of significance of 0.05 (two-sided), assuming a mean aTCS in the placebo group of 3.65 and a CV of 75%. Moreover, this sample size was sufficient to achieve a power of around 80% for fulfilling the requirements of the US Food and Drug Administration (FDA) (relative difference versus placebo less than or equal to -15% and upper limit of the 95%CI less than or equal to -10%). (36). Based on a drop-out rate of 15%, a total study population of 1740 randomized patients (870 in each treatment group) was planned. (39, 40)

By definition, the full analysis set (FAS) comprised all participants who received at least one dose of the IP and had at least one evaluation of the aTCS at any timepoint during the overall treatment period. For the primary endpoint, patients in the FAS with no efficacy evaluation during the primary evaluation period were not included in the analysis. An analysis of covariance was performed on the square root of the aTCS with the following prespecified factors: treatment group as the main effect, and the pooled centre, square root of the baseline aTCS, age, gender, asthma status and sensitization status as covariates. The absolute and relative differences were calculated from the back-transformed least squares (LS) means (i.e. the adjusted means from the analysis of covariance, which took account of the potential effect of the covariate(s) on the aTCS). All 95%CIs were calculated using the bootstrap method with 10,000 replications. The per-protocol set was defined as all participants in the FAS with a valid TCS for at least 14 days during the primary evaluation period and no major deviations.

The multiplicity issue resulting from the analysis of one primary endpoint and six key secondary endpoints was addressed by employing a fixed-sequence procedure at a significance level of 0.05 with the following hierarchical order after the primary endpoint: average RTSS (aRTSS), overall RQLQ12+ score, average RCTSS, average nasal congestion score, PSCD, and average RMS (aRMS). The secondary endpoints were analysed similarly to the primary endpoint, except for the RQLQ12+ score (analysed using the same model but without square root transformation) and PSCD (analysed using a Wilcoxon rank-sum test).

The safety analysis was conducted on the safety set (SS) comprising all randomized patients having received at least one dose of the IP.

Statistical analyses were performed with SAS® software (version 9.4, SAS Institute Inc., Cary, NC).

Ethics

All participants aged 18 or over gave their written consent to participation, after having been informed of the study's objectives and procedures. Participants aged 17 or under gave their assent to participation, and the participants' parents or legal representatives gave their written consent. In some cases (depending on local regulations), patients aged 16 or 17 could also sign a consent form, rather than an assent form.

The study was approved by the appropriate independent ethics committees or institutional review boards, and complied with local regulatory and legislative requirements and the Declaration of Helsinki. The study was registered in the European Clinical Trials Database (EudraCT 2014-004223-46) and at ClinicalTrials.gov (NCT 02443805).

Results

Study patients

Patient enrolment started in September 2015. A total of 4,267 participants were screened, 1,607 were randomized and 1,601 were treated (Fig 2). There were 1,476 patients in the FAS (312 adolescents and 1,164 adults). The last patient completed the trial in June, 2018.

In the FAS, the mean age was 29.6 overall, 14.2 for adolescents, and 33.7 for adults (Table I, Table E2). There was male predominance in the adolescent population, and slight female predominance in the adult population. Overall, just over a third of the participants (37.6%) had concomitant asthma (50.0% of the adolescents, and 34.3% of the adults). After HDM allergens, the next most frequently observed sensitizing allergens (according to an SPT) were cat dander (in 23.1% of the participants) and grass pollen (in 18.7%) (Table E3). In line with the study's inclusion criteria, the mean (SD) aRTSS at baseline

was 7.01 (1.936) in the 300°IR group and 6.92 (1.880) in the placebo group (Table E4). The mean (SD) baseline aTCS was 7.84 (2.067) in the 300°IR group and 7.71 (1.961) in the placebo group. The mean (SD) overall RQLQ12+ score was 2.64 (1.106) in the 300°IR group and 2.64 (1.065) in the placebo group - testifying to moderate QoL (7).

There were no significant differences between the 300°IR and placebo groups with regard to baseline sociodemographic variables, allergen sensitization, clinical characteristics, and serum Dpte- or Dfar-specific IgG4 and IgE levels (Tables 1, E2, E3, E4, E6, E7 and E8).

In the SS, the median overall exposure to the study treatment was 362 days in the 300°IR group and 363 days in the placebo group. Compliance was good throughout the treatment period; 90.2% of the patients in the 300°IR group and 92.3% of those in the placebo group were compliant (i.e. with $\geq 80\%$ of the planned medication intake).

Primary endpoint

The FAS comprised 711 participants from the 300°IR group and 765 from the placebo group. As mentioned above, patients in the FAS with no efficacy evaluation during the primary evaluation period were not taken into account in the primary analysis. Hence, the analysis of the primary endpoint covered 586 participants in the 300°IR group and 676 in the placebo group (Table II).

During the primary evaluation period, the LS mean aTCS was significantly lower in the 300°IR group than in the placebo group (Table II). The relative LS mean difference between the two groups (-16.9% vs. placebo) was greater than the pre-specified threshold of -15%, and the 95%CI was [-24.0%; -9.2%]. This significant difference was confirmed in the per-protocol set (point estimate = -0.72, relative LS mean difference = -16.8%; $p=0.0003$). Sensitivity analyses on randomized patients accounting for missing data confirmed the significant difference in LS means in favour of the 300 IR group. The point estimate in the adolescents was -0.71 (relative LS mean difference = -15.5%).

With regard to the treatment period as a whole, the aTCS fell over time in both groups but fell more in the 300°IR group. A significant 300°IR vs. placebo difference was observed from the third month of treatment onwards (Fig. 3). Lastly, we performed a post hoc analysis of the 300°IR vs. placebo difference in the aTCS at Month 3, Month 6, Month 9 and Month 12, as a function of the aTCS at baseline. A higher baseline aTCS was associated with a greater 300°IR vs. placebo difference.

Secondary endpoints

During the primary evaluation period, all the 300°IR vs. placebo differences in the secondary endpoints (notably the aRTSS and the aRMS - the two components of the primary efficacy endpoint) were consistent with the results for the primary endpoint, i.e. significantly better in the 300°IR group (Table III and Fig 4). Hence, the difference in LS means of the average CSMS (aCSMS) during the primary period between the 300 IR group and the placebo group was statistically significant (point estimate= -0.26, relative LS mean difference -18.0%; $p<0.0001$). Furthermore, the mean PSCD was 31.82% in the 300°IR group and 25.44% in the placebo group ($p=0.0082$). The LS mean overall RQLQ12+ score at the end of the treatment period was 1.42 in the 300°IR group and 1.62 in the placebo group (with a mean of 2.64 at baseline in both groups) ($p=0.0004$). In both the 300°IR and placebo groups, the change from baseline (assessed in a post-hoc analysis) in the overall RQLQ12+ score (-1.20 and -1.00 points, respectively) exceeded the value of -0.5 points determined to be the minimal clinically important difference.(35)). The 300°IR group and placebo groups differed significantly with regard to the overall RQLQ12+ score and all the individual RQLQ12+ domain scores at the end of the treatment period (FIG 4). During the primary evaluation period, statistically significant differences between the 300°IR group and the placebo group were observed for each of the six ISSs: nasal pruritus, sneezing, rhinorrhoea, nasal congestion, ocular pruritus and tearing (Table E5). Lastly, the proportion of patients who did not experience any rhinitis exacerbations over the primary period was significantly greater in the 300 IR group (72.2%) than in the placebo group (61.4%) (Table E6).

At the end of the treatment period, the IgE and IgG4 levels had increased significantly in the 300°IR group but not in the placebo group (Tables E7 and E8).

Safety

During the 12-month treatment period, 561 (70.1%) of the patients in the 300°IR group and 440 (54.9%) of the patients in the placebo group reported at least one treatment-emergent adverse event (TEAE)

(Table E9). As expected, the most common drug-related TEAEs associated with the 300°IR tablet were mild or moderate application-site reactions typically associated with AIT (oral pruritus, throat irritation, ear pruritus, and mouth oedema) (Fig 5). The incidence and distribution of TEAEs were similar among the adolescents and the adults (Table E9). The presence of concomitant asthma did not appear to influence the safety profile in either study group, and the 300 IR HDM tablet was not associated with the appearance of asthma-related AEs.

No deaths occurred during the study. With regard to serious TEAEs, 24 were reported by 21 patients in the 300°IR group and 11 were reported by 9 patients in the placebo group. As mentioned above, all randomized participants had received an epinephrine auto-injector for use in the event of a severe allergic reaction. There were 5 epinephrine injections (concerning 4 participants) in the 300°IR group and 2 injections (concerning 2 participants) in the placebo group. Of the 5 injections in the 300°IR group, 2 were administered for an event that was suspected to be related to the IP; both events occurred upon treatment initiation (on treatment day 1 or 2). Details of serious TEAEs and epinephrine administrations are provided as Supplemental Material.

Overall, TEAEs led to premature study withdrawal by 99 (12.4%) patients in the 300 IR group (75 adults and 24 adolescents) and 17 (2.1%) in the placebo group (15 adults and 2 adolescents). Most of these premature study withdrawals in the 300°IR group were due to administration site reactions (e.g. mainly oral pruritus, tongue oedema, mouth oedema, and throat irritation) that occurred early in the study: 68 of the 99 (68.7%) withdrawals occurred during the first month after randomization. In the placebo group, this was the case for 6 of the 17 (35.3%) patients.

DISCUSSION

In this international Phase III clinical trial, the efficacy and safety of ~12 months of treatment with a 300°IR sublingual tablet (vs. placebo) were assessed in a large population of adults and adolescents with HDM-induced AR. The study's design enabled the accurate identification of HDM-allergic patients with moderate-to-severe perennial symptoms requiring medication, thanks to a relatively long placebo run-in period.

Treatment with the 300°IR tablet was associated with a significantly lower aTCS during the primary evaluation period (absolute LS mean difference: -0.74; relative LS mean difference: -16.9%), versus placebo. This difference is consistent with the previously published data on the 300°IR tablet's efficacy (25, 26, 29-31) and those reported in the literature for a different sublingual tablet formulation of an HDM extract.(16, 28). With regard to clinical efficacy and relevance, the relative LS mean difference of -16.9% for the primary evaluation period exceeded the value of -15% defined in the study protocol and recommended by the FDA(36). This relative difference of -16.9% is greater than that associated with some types of symptomatic medication (such as leukotriene receptor antagonists and oral antihistamines) used to treat perennial AR.(37, 38).

Further insight into the 300°IR tablet's likely clinical relevance can be gained by considering the nature of the TCS. As specified in the Methods section, the TCS ranged from 0 to 15 and was the sum of the patient's daily RTSS over the previous 24 hours (composed of four ISSs, each rated as 0 = no symptom, 1 = mild symptom, 2 = moderate symptom or 3 = severe symptom) and the daily RMS score in which only the "strongest" type of medication used on a given day was taken into account (0 = no treatment, 1 = an oral H1 antihistamine, 2 = an intranasal corticosteroid, 3 = an oral corticosteroid). Schematically, and first looking at the symptom score component, a 1-point decrement in the aTCS can represent a downshift in one ISS from severe to moderate, or from moderate to mild, or from mild to no symptoms throughout the evaluation period. Alternatively, looking at the medication score component, a 1-point decrement in the aTCS can represent a downshift in daily intake from an oral corticosteroid to an intranasal corticosteroid, from an intranasal corticosteroid to an antihistamine or from an antihistamine to no medication throughout the evaluation period. In the present study, the decrement in the 300°IR group was 0.74. Schematically, a decrement of 0.74 means that a patient who would have suffered from a severely blocked nose every day of the year (thus scoring 3 points for that ISS) would only have had a moderately blocked nose for 9 months of the year (i.e. 0.74×12 months). Likewise, a patient who would have taken an antihistamine every day of the year (thus scoring 1 point towards the TCS) would have been medication-free for 9 months of the year.

It is noteworthy that the 300°IR tablet's beneficial effect increased over the 12-month treatment period, as has been observed with other AIT formulations (39-42). The mean aTCS in the 300°IR group fell from

7.84 at baseline to 3.62 after ~12 months of treatment. The relative LS mean difference in the aTCS vs. placebo increased from -8.5% at Month 3 to -16.6% at Month 12. This increase over time may be of value, given that AIT is a long-term treatment typically prescribed for 3 to 5 years. Further, another study of 12 months of treatment of the 300°IR HDM tablet showed that efficacy was maintained during a treatment-free follow-up year (25). We would also expect to see greater clinical efficacy in patients with more severe symptoms, as suggested by the increase in the 300°IR vs. placebo difference in the aTCS as the baseline aTCS rose. It is also noteworthy that the proportion of patients experiencing rhinitis exacerbations was significantly lower in the 300°IR group than in the placebo group.

The results for the secondary endpoints (such as the aCSMS and the six ISSs) also supported the findings for the primary endpoint. Interestingly, the greatest difference vs. placebo was observed for nasal congestion; the latter is typically reported in the literature to be the most bothersome feature of HDM-induced AR, and contributes strongly to poor QoL.(4) The 300°IR tablet was also effective (vs. placebo) for secondary endpoints related to AR control (e.g. PSCD) and QoL (e.g. RQLQ12+). In the field of respiratory allergy, QoL scores can serve as clinically relevant, supporting primary endpoints.(43, 44) The overall and domain-specific RQLQ12+ scores showed that improvement in QoL was significantly greater in the 300°IR tablet than in the placebo group. Consistently with the findings for clinical efficacy, the significant increase in IgE and IgG4 levels over the treatment period seen in the 300°IR group (but not in the placebo group) supports the tablet's immunologic activity.(45-50).

The use of a placebo run-in period (during which rescue/relief medication was authorized) enabled the selection of patients with truly moderate-to-severe AR symptoms. Although rescue/relief medication use during the primary evaluation period was low overall, it was significantly lower in the 300°IR group than in the placebo group (the LS mean average RMS was 0.30 in the placebo group and 0.21 in the 300°IR group). However, this low level of rescue/relief medication use was consistent with previous clinical studies of the 300°IR tablet.(25, 29, 30) It should be borne in mind that trial participants were instructed to take rescue/relief medication only when necessary, and so may have taken less medication than they would have outside the context of a clinical trial.

As expected from the literature data on AIT and despite the placebo run-in period, we observed a strong placebo effect; clinical benefit was observed in the placebo group over the 12-month treatment period as a whole and during the primary evaluation period.⁽⁵¹⁾ This benefit may have been due to improved care, the Hawthorne effect, and the patients' expectations. Hence, outside the context of a clinical trial (e.g. in routine clinical practice), we would expect the 300°IR tablet's treatment effect to be greater.

Consistently with previous observations, the 300°IR HDM tablet had a reassuring safety profile and was generally well tolerated. As expected, the TEAEs in the 300 IR group were primarily mild or moderate local reactions that arose early in the course of treatment and that resolved without specific management. There were no severe anaphylactic reactions. Two of the four epinephrine injections in the 300°IR group were administered for events (one local and one systemic) suspected to be drug-related. When considering the number of participants from the 300°IR group in the SS (800) and the mean number of days of treatment (297.5), this corresponds to two treatment-related epinephrine injections for ~240,000 administrations of the 300°IR sublingual tablet, or one per ~120,000 administrations. This value is in line with the literature data; in an analysis of epinephrine use in clinical trials of SLIT tablets (grass pollen, ragweed pollen, and HDM formulations), Nolte et al. reported that the number of epinephrine injections was 1.8 per 100,000 tablets (i.e. one per ~55,500 administrations). ^(52, 53)

The study had some limitations - most of which are inherent to placebo-controlled studies of AIT in which participants are exposed to confounding allergens and non-allergic irritants. Secondly, the duration of treatment was only 1 year; this is shorter than the period of several years typically recommended in clinical practice.⁽⁵⁴⁾ Nevertheless, many trials of HDM AIT have featured treatment periods of just a few months.⁽⁵⁵⁾ Thirdly, the proportion of patients withdrawing from the study during the first month of treatment was higher than expected; this emphasizes the need for physician-patient dialogue on what are often transient local administration site reactions. However, the frequencies of premature withdrawal due to an AE in the present study (12.4% in the 300 IR group and 2.1% in the placebo group) were similar to those observed in other studies of sublingual HDM tablets. ⁽¹⁶⁾

In conclusion, our present results confirmed that a 12-month course of treatment with a 300°IR sublingual HDM tablet was effective for the treatment of moderate-to-severe HDM-induced AR (with or without concomitant mild controlled asthma). The safety profile was consistent with the literature data on sublingual HDM AIT, with no newly identified or unexpected risks. HDM sensitivity is a chronic, burdensome disease that often results in daily use of several medications for often inadequate or partial control. A therapeutic agent capable of suppressing the patient's allergic process and offering lasting clinical benefit is clearly desirable for both the patient and the healthcare system. The 300°IR sublingual HDM tablet is a treatment option that minimizes the need for rescue/relief medication and provides effective symptom relief.

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AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the study conception and design and to data acquisition, analysis and/or interpretation. All authors contributed to drafting the article or revising it critically for important intellectual content, and all have given their final approval of the version submitted for publication.

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Figure Legends

FIG 1. Study design

FIG 2. Patient disposition

FIG 3. aTCS during treatment (FAS)

FIG 4. RQLQ12+ domain scores at the end of the treatment period (evaluable patients from the FAS)

FIG 5. Treatment-emergent adverse events suspected to be drug-related with incidence of at least 5% in the 300°IR HDM or placebo group (SS)

Tables

TABLE I. Baseline characteristics (FAS)

	300°IR N=711	Placebo N=765	Overall N=1,476
Gender [n (%)]			
Male	351 (49.4)	369 (48.2)	720 (48.8)
Female	360 (50.6)	396 (51.8)	756 (51.2)
Age (years)			
Mean (SD)	29.5 (13.07)	29.6 (12.58)	29.6 (12.81)
Median	27.0	29.0	28.0
Geographical region [n (%)]			
North America (USA & Canada)	212 (29.8)	240 (31.4)	452 (30.6)
Europe, Israel, Russia	499 (70.2)	525 (68.6)	1,024 (69.4)
Race [n (%)]			
White	660 (92.8)	701 (91.6)	1,361 (92.2)
Black or African American	25 (3.5)	37 (4.8)	62 (4.2)
American Indian or Alaska Native	0	1 (0.1)	1 (0.1)

	300°IR N=711	Placebo N=765	Overall N=1,476
Asian	21 (3.0)	20 (2.6)	41 (2.8)
Native Hawaiian or Other Pacific Islander	2 (0.3)	0	2 (0.1)
Multiple	2 (0.3)	3 (0.4)	5 (0.3)
Unknown	1 (0.1)	3 (0.4)	4 (0.3)
Duration of HDM-induced allergic rhinitis (years)			
Mean (SD)	11.38 (10.747)	11.40 (9.768)	11.39 (10.248)
Median	7.28	9.02	8.09
Range	0.8–58.9	0.4–50.2	0.4–58.9
Baseline sensitization status [n (%)]			
Monosensitized	397 (55.8)	413 (54.0)	810 (54.9)
Polysensitized	314 (44.2)	352 (46.0)	666 (45.1)
Average TCS at baseline			
Mean (SD)	7.84 (2.067)	7.71 (1.961)	7.77 (2.014)
95%CI	[7.69; 8.00]	[7.57; 7.85]	[7.67; 7.88]
Median	7.54	7.36	7.44
Range	3.8–14.4	4.4–14.0	3.8–14.4
Overall RQLQ12+ score at baseline			
Mean (SD)	2.64 (1.106)	2.64 (1.065)	2.64 (1.085)
Median	2.59	2.63	2.61
Range	0.1–5.7	0.2–5.8	0.1–5.8
Concomitant asthma [n (%)]			
Presence	273 (38.4)	282 (36.9)	555 (37.6)
Absence	438 (61.6)	483 (63.1)	921 (62.4)

715 CI: confidence interval; FAS: full analysis set; IR: index of reactivity; RQLQ12+: Standardized
716 Rhinoconjunctivitis Quality of Life Questionnaire, overall score (scale 0-6); SD: standard deviation; TCS: total
717 combined score (scale 0-15)
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TABLE II. Primary endpoint (aTCS) during the primary evaluation period (evaluable patients from the FAS^a)

Treatment	n ^a	LS mean ^b	Difference in LS means vs. Placebo			Relative LS mean difference ^d	
			Point estimate ^c	[95%CI]	p-value	%	[95%CI]
300°IR	586	3.62	-0.74	[-1.08; -0.38]	<0.0001	-16.9	[-24.0; -9.2]
Placebo	676	4.35					

CI: confidence interval; FAS: full analysis set; IR: index of reactivity; LS: least squares; n: number of patients with data; TCS: total combined score (scale 0-15)

^a Patients in the FAS with no efficacy evaluation during the primary evaluation period were not included in the primary analysis

^b LS mean: back-transformed LS mean obtained from an analysis of covariance of the square root of the aTCS during the primary evaluation period

^c Point estimate: LS mean difference between 300°IR and placebo

^d Relative LS mean difference: [(300°IR LS mean – placebo LS mean) / placebo LS mean] *100

All CIs were calculated using the bootstrap method with 10,000 replications

731 **TABLE III. Secondary endpoints (evaluatable patients from the FAS)**

	Treatment	n ^a	LS Mean ^b	Difference in LS means vs. placebo			Relative LS mean difference ^e
				Point estimate ^c	[95%CI]	p-value ^d	%
Average nasal congestion symptom score during the primary evaluation period	300°IR	586	0.85	-0.19	[-0.28; -0.10]	<0.0001	-18.3
	Placebo	676	1.04				
	Treatment	n ^f	LS Mean	Difference in LS means vs. placebo			Relative LS mean difference ^e
				Point estimate ^c	[95%CI]	p-value ^d	%
Overall RQLQ12+ score at the end of the treatment period	300°IR	625	1.42	-0.19	[-0.30; -0.09]	0.0004	-12.0
	Placebo	678	1.62				
	Treatment	n ^a	LS Mean ^b	Difference in LS means vs. placebo			Relative LS mean difference ^e
				Point estimate ^c	[95%CI]	p-value ^d	%
Average RMS during the primary evaluation period	300°IR	586	0.21	-0.09	[-0.14; -0.04]	0.0004	-29.7
	Placebo	676	0.30				
	Treatment	n ^a	LS Mean ^b	Difference in LS means vs. placebo			Relative LS mean difference ^e
				Point estimate ^c	[95%CI]	p-value ^d	%
Average CSMS during the primary evaluation period	300°IR	586	1.19	-0.26	[-0.38; -0.14]	<0.0001	-18.0
	Placebo	676	1.45				
	Treatment	n ^a	LS Mean ^b	Difference in LS means vs. placebo			Relative LS mean difference ^e
				Point estimate ^c	[95%CI]	p-value ^d	%
Average RCTSS during the primary evaluation period	300°IR	586	4.22	-0.81	[-1.24; -0.39]	0.0002	-16.1
	Placebo	676	5.04				

	Treatment	n ^a	Mean	[95%CI] of the mean	Median	p-value ^g	Q1	Q3
PSCD ₂₋₀ during the primary evaluation period	300 IR	586	31.82	[28.59; 35.06]	4.35	0.0082	0.00	74.07
	Placebo	676	25.44	[22.72; 28.15]	0.00		0.00	50.00

CI: confidence interval; CSMS: Combined Symptom and Medication Score (scale 0-6); FAS: full analysis set; IR: index of reactivity; LS: least squares; n: number of patients with data; Nasal congestion symptom score (scale 0-3) ; Q1: First quartile (25%); Q3: Third quartile (75%); RQLQ12+: Standardized Rhinoconjunctivitis Quality of Life Questionnaire, overall score (scale 0-6); RCTSS: rhinoconjunctivitis total symptom score (scale 0-18) ; RMS: rescue/relief medication score (scale 0-3); RTSS: rhinitis total symptom score (scale 0-12)

^a Patients in the FAS with no efficacy evaluation during the primary evaluation period were not included in the analysis

^b LS mean = back-transformed LS mean obtained from an analysis of covariance of the square root of the average score during the primary evaluation period

^c Point estimate = LS mean difference between 300°IR and placebo

^d Analysis of covariance

^e Relative LS mean difference: [(300°IR LS mean – placebo LS mean) / placebo LS mean] *100. CIs for differences in LS means and relative LS mean differences are calculated using the bootstrap method on 10,000 replications

^f Patients in the FAS with no evaluation of the RQLQ12+ during the primary evaluation period were not included in the analysis

^g Wilcoxon rank-sum test

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Table E1 Secondary and exploratory variables

Rhinitis total symptom score (RTSS, scale: 0-12)
Rescue medication score (RMS, scale: 0-3)
The rhinoconjunctivitis total symptom score (RCTSS, scale: 0-18) was the sum of the four rhinitis symptom scores and the two ocular symptom scores.
The combined symptom and medication score (CSMS, scale: 0-6) combined the RTSS and the RMS, which were given equal weightings. Hence, the CSMS was calculated as follows: $\text{CSMS} = \text{RTSS}/4 + \text{RMS}$
The six individual symptom scores (ISSs, each scored on a scale of 0-3): nasal pruritus, sneezing, rhinorrhoea, nasal congestion, ocular pruritus and tearing
Proportion of symptom-controlled days (PSCD), defined for each patient during an evaluation period as the proportion of days with RTSS ≤ 2 and no use of rescue/relief medication
Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ12+) overall and RQLQ12+domain scores (scale: 0 to 6)
Rhinitis exacerbation (proportion of patients with a daily TCS ≥ 5 , and at least one of the four rhinitis symptoms rated as severe)
Immunological markers: Dpte- and Dfar-specific serum IgE (kU/L) and IgG ₄ (mgA/L) levels

6 TABLE E2. Baseline characteristics by age class (FAS)

	Adolescents (N=312)		Adults (N=1,164)	
	300°IR N=155	Placebo N=157	300°IR N=556	Placebo N=608
Gender [n (%)]				
Male	91 (58.7)	99 (63.1)	260 (46.8)	270 (44.4)
Female	64 (41.3)	58 (36.9)	296 (53.2)	338 (55.6)
Age (years)				
Mean (SD)	14.1 (1.75)	14.2 (1.72)	33.8 (11.51)	33.6 (11.03)
Median	14.0	14.0	32.0	32.0
Geographical region [n (%)]				
North America (USA & Canada)	28 (18.1)	31 (19.7)	184 (33.1)	209 (34.4)
Europe, Israel, Russia	127 (81.9)	126 (80.3)	372 (66.9)	399 (65.6)
Race [n (%)]				
White	146 (94.2)	147 (93.6)	514 (92.4)	554 (91.1)
Black or African American	3 (1.9)	5 (3.2)	22 (4.0)	32 (5.3)
American Indian or Alaska Native	0	0	0	1 (0.2)
Asian	5 (3.2)	3 (1.9)	16 (2.9)	17 (2.8)
Native Hawaiian or Other Pacific Islander	0	0	2 (0.4)	0
Multiple	1 (0.6)	2 (1.3)	1 (0.2)	1 (0.2)
Unknown	0	0	1 (0.2)	3 (0.5)
Duration of HDM-induced allergic rhinitis (years)				
Mean (SD)	5.29 (3.552)	5.27 (3.387)	13.08 (11.446)	12.98 (10.243)
Median	4.70	4.37	9.46	10.87

Range	0.8–14.4	0.9–16.0	1.0–58.9	0.4–50.2
Baseline sensitization status				
[n (%)]				
Monosensitized	104 (67.1)	95 (60.5)	293 (52.7)	318 (52.3)
Polysensitized	51 (32.9)	62 (39.5)	263 (47.3)	290 (47.7)
Average TCS at baseline				
Mean (SD)	8.00 (1.978)	7.95 (1.979)	7.80 (2.091)	7.65 (1.954)
95%CI	[7.69; 8.31]	[7.64; 8.26]	[7.63; 7.97]	[7.49; 7.80]
Median	7.61	7.65	7.49	7.30
Range	3.8–14.0	4.9–14.0	4.0–14.4	4.4–14.0
Overall RQLQ12+ score at baseline				
Mean (SD)	2.32 (1.120)	2.31 (1.050)	2.73 (1.087)	2.73 (1.053)
Median	2.21	2.27	2.68	2.68
Range	0.1–5.4	0.3–5.0	0.3–5.7	0.2–5.8
Concomitant asthma [n (%)]				
Presence	80 (51.6)	76 (48.4)	193 (34.7)	206 (33.9)
Absence	75 (48.4)	81 (51.6)	363 (65.3)	402 (66.1)

CI: confidence interval; FAS: full analysis set; IR: index of reactivity; RQLQ12+: Standardized

Rhinoconjunctivitis Quality of Life Questionnaire, overall score (scale: 0-6); SD: standard deviation;

TCS: total combined score (scale: 0-15)

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Table E3 Positive SPT results at baseline for allergens with an incidence of at least 5% in the placebo group or 300 IR group (FAS)

	300°IR	Placebo	Overall
	N=711	N=765	N=1,476
	n (%)	n (%)	n (%)
<i>D. pteronyssinus</i> or <i>D. farinae</i>	711 (100)	765 (100)	1,476 (100)
<i>D. pteronyssinus</i>	696 (97.9)	750 (98.0)	1,446 (98.0)
<i>D. farinae</i>	689 (96.9)	732 (95.7)	1,421 (96.3)
Cat	141 (19.8)	200 (26.1)	341 (23.1)
Grass	135 (19.0)	141 (18.4)	276 (18.7)
Birch	93 (13.1)	89 (11.6)	182 (12.3)
Ragweed	65 (9.1)	66 (8.6)	131 (8.9)
Dog	51 (7.2)	64 (8.4)	115 (7.8)
Mugwort	59 (8.3)	56 (7.3)	115 (7.8)
Alder	42 (5.9)	43 (5.6)	85 (5.8)
Oak	21 (3.0)	41 (5.4)	62 (4.2)

D.: *Dermatophagoides*; FAS: full analysis set; IR: index of reactivity; n: number of patients with data; SPT: skin prick test. Note: a patient could have more than one positive SPT.

15 Table E4. Rhinoconjunctivitis symptom scores and a rescue medication score at baseline (FAS)

	300°IR n=711	Placebo n=765	Overall n=1,476
Average RTSS			
Mean (SD)	7.01 (1.936)	6.92 (1.880)	6.96 (1.907)
95%CI	[6.87; 7.15]	[6.79; 7.06]	[6.87; 7.06]
Median	6.68	6.59	6.63
Range	2.6–12.0	2.8–12.0	2.6–12.0
Average RMS			
Mean (SD)	0.83 (0.767)	0.79 (0.754)	0.81 (0.760)
95%CI	[0.78; 0.89]	[0.73; 0.84]	[0.77; 0.85]
Median	0.65	0.57	0.63
Range	0.0–3.0	0.0–3.0	0.0–3.0
Average ISS: Nasal pruritus			
Mean (SD)	1.63 (0.615)	1.60 (0.630)	1.61 (0.623)
95%CI	[1.58; 1.67]	[1.55; 1.64]	[1.58; 1.64]
Median	1.58	1.59	1.59
Range	0.0–3.0	0.0–3.0	0.0–3.0
Average ISS: Sneezing			
Mean (SD)	1.62 (0.629)	1.61 (0.608)	1.62 (0.618)
95%CI	[1.58; 1.67]	[1.57; 1.65]	[1.58; 1.65]
Median	1.59	1.58	1.58
Range	0.0–3.0	0.0–3.0	0.0–3.0

	300°IR n=711	Placebo n=765	Overall n=1,476
Average ISS: Rhinorrhoea			
Mean (SD)	1.84 (0.578)	1.82 (0.556)	1.83 (0.566)
95%CI	[1.79; 1.88]	[1.78; 1.86]	[1.80; 1.86]
Median	1.85	1.80	1.82
Range	0.0–3.0	0.0–3.0	0.0–3.0
Average ISS: Nasal congestion			
Mean (SD)	1.92 (0.604)	1.89 (0.612)	1.91 (0.608)
95%CI	[1.88; 1.96]	[1.85; 1.94]	[1.88; 1.94]
Median	1.96	1.92	1.93
Range	0.0–3.0	0.1–3.0	0.0–3.0
Average ISS: Ocular pruritus			
Mean (SD)	1.36 (0.756)	1.33 (0.752)	1.34 (0.754)
95%CI	[1.30; 1.41]	[1.27; 1.38]	[1.30; 1.38]
Median	1.32	1.29	1.31
Range	0.0–3.0	0.0–3.0	0.0–3.0
Average ISS: Tearing			
Mean (SD)	1.18 (0.784)	1.12 (0.770)	1.15 (0.777)
95%CI	[1.13; 1.24]	[1.07; 1.18]	[1.11; 1.19]
Median	1.12	1.08	1.11
Range	0.0–3.0	0.0–3.0	0.0–3.0

CI: confidence interval; FAS: full analysis set; IR: index of reactivity; ISS: individual
 rhinoconjunctivitis symptom score (scale 0-3); RMS: rescue/relief medication score (scale 0-3);
 RTSS: rhinitis total symptom score (scale 0-12); SD: standard deviation

Table E5. Average individual rhinoconjunctivitis symptom scores (ISSs) during the primary evaluation period (evaluative patients from the FAS)

Treatment	n ^a	LS mean ^b	Difference in LS means vs. Placebo			Relative LS mean difference ^d	
			Point estimate ^c	[95%CI]	p-value	%	[95%CI]
Average nasal pruritus							
300°IR	586	0.61	-0.15	[-0.23; -0.07]	0.0004	-19.7	[-28.9; -9.5]
Placebo	676	0.76					
Average sneezing							
300°IR	586	0.66	-0.16	[-0.24; -0.08]	0.0002	-19.5	[-28.2; -9.9]
Placebo	676	0.82					
Average rhinorrhoea							
300°IR	586	0.81	-0.16	[-0.25; -0.07]	0.0004	-16.5	[-24.7; -7.8]
Placebo	676	0.97					
Average nasal congestion							
300°IR	586	0.85	-0.19	[-0.28; -0.10]	<0.0001	-18.3	[-26.1; -9.7]
Placebo	676	1.04					
Average ocular pruritus							
300°IR	586	0.47	-0.09	[-0.16; -0.02]	0.0161	-15.4	[-26.2; -3.4]
Placebo	676	0.56					
Average tearing							
300°IR	586	0.34	-0.08	[-0.14; -0.02]	0.0138	-18.2	[-30.4; -4.1]
Placebo	676	0.42					

CI: confidence interval; FAS: full analysis set; IR: index of reactivity; ISS: individual rhinoconjunctivitis symptom score (scale 0-3), LS: least squares; n: number of patients with data

^a Patients in the FAS with no efficacy evaluation during the primary evaluation period were not included in the analysis

^b LS mean = back-transformed LS mean obtained from an analysis of covariance of the square root of the average ISS during the primary evaluation period

^c Point estimate = LS mean difference between 300°IR and placebo

^d Relative LS mean difference: [(300°IR LS mean – placebo LS mean) / placebo LS mean] *100

All CIs are calculated using the bootstrap method on 10,000 replications

Table E6. Rhinitis exacerbations (proportion of patients) for each evaluation period (FAS).

	300 IR	Placebo	p-value^a
	n(%)	n(%)	
Baseline			
Yes	570 (80.2)	597 (78.0)	0.3150
No	141 (19.8)	168 (22.0)	
Total	711 (100)	765 (100)	
Interim evaluation period 1 (Month 3)			
Yes	278 (39.9)	345 (46.1)	0.0167
No	419 (60.1)	403 (53.9)	
Total	697 ^b (100)	748 ^b (100)	
Interim evaluation period 2 (Month 6)			
Yes	193 (30.9)	270 (38.2)	0.0052
No	431 (69.1)	436 (61.8)	
Total	624 ^b (100)	706 ^b (100)	
Interim evaluation period 3 (Month 9)			
Yes	165 (28.0)	243 (35.6)	0.0037
No	424 (72.0)	439 (64.4)	
Total	589 ^b (100)	682 ^b (100)	
Primary evaluation period (Month 12)			
Yes	163 (27.8)	261 (38.6)	<0.0001
No	423 (72.2)	415 (61.4)	
Total	586 ^b (100)	676 ^b (100)	

CI: confidence interval; FAS: full analysis set; IR: index of reactivity; N: number of patients in each treatment

group; n: number of patients with data

^aChi-squared test

^bPatients in the FAS with no efficacy evaluation during the evaluation period were not included in the analysis

38 **Table E7. Serum *Dermatophagoides pteronyssinus*- and *Dermatophagoides farinae*-specific IgG4**
 39 **levels at baseline and at the end of the treatment period (FAS)**

Statistic		300°IR n=711	Placebo n=765
<i>Dermatophagoides pteronyssinus</i>-specific serum IgG₄			
Baseline (mg _A /L)	n	709	763
	Geometric mean	0.27	0.27
	[95%CI]	[0.26; 0.29]	[0.26; 0.29]
	Median	0.27	0.28
	Range	0.0–10.0	0.0–6.1
Endpoint (mg _A /L)	n	664	725
	Geometric mean	0.95	0.26
	[95%CI]	[0.86; 1.04]	[0.24; 0.28]
	Median	0.98	0.26
	Range	0.0–29.2	0.0–7.1
Fold-change from baseline	n	662	723
	Geometric mean	3.49	0.95
	[95%CI]	[3.20; 3.80]	[0.91; 0.99]
	Median	3.25	0.99
	Range	0.0–179.8	0.1–35.4
<i>Dermatophagoides farinae</i>-specific serum IgG₄			
Baseline (mg _A /L)	n	709	763
	Geometric mean	0.22	0.22
	[95%CI]	[0.20; 0.23]	[0.20; 0.23]
	Median	0.22	0.22
	Range	0.0–9.8	0.0–7.3
Endpoint (mg _A /L)	n	664	725

Statistic		300°IR n=711	Placebo n=765
	Geometric mean	0.89	0.22
	[95%CI]	[0.80; 0.98]	[0.21; 0.23]
	Median	0.91	0.22
	Range	0.0–30.0	0.0–8.5
Fold-change from baseline	n	662	723
	Geometric mean	4.12	1.01
	[95%CI]	[3.78; 4.19]	[0.98; 1.05]
	Median	3.70	1.00
	Range	0.1–166.8	0.1–94.1

CI: confidence interval; FAS: full analysis set; IR: index of reactivity

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Table E8. Serum *Dermatophagoides pteronyssinus*- and *Dermatophagoides farinae*-specific IgE levels at baseline and at the end of the treatment period (FAS)

Statistic		300°IR n=711	Placebo n=765
<i>Dermatophagoides pteronyssinus</i>-specific serum IgE			
Baseline (kU/L)	n	711	765
	Geometric mean	16.27	17.80
	[95%CI]	[14.91; 17.76]	[16.37; 19.34]
	Median	14.81	16.87
	Range	0.8–499.5	0.5–714.3
Endpoint (kU/L)	n	663	723
	Geometric mean	42.46	15.61
	[95%CI]	[38.20; 47.19]	[14.24; 17.12]
	Median	44.01	14.99
	Range	0.1–1366.4	0.1–893.2
Fold-change from baseline	n	663	723
	Geometric mean	2.62	0.88
	[95%CI]	[2.42; 2.84]	[0.85; 0.92]
	Median	2.54	0.89
	Range	0.0–158.4	0.0–7.5
<i>Dermatophagoides farinae</i>-specific serum IgE			
Baseline (kU/L)	n	711	765
	Geometric mean	16.20	17.92
	[95%CI]	[14.93; 17.58]	[16.58; 19.38]
	Median	15.43	16.74
	Range	1.2–600.0	0.5–992.5
Endpoint (kU/L)	n	663	723

Statistic		300°IR n=711	Placebo n=765
	Geometric mean	41.24	15.32
	[95%CI]	[37.16; 45.77]	[14.05; 16.70]
	Median	42.10	14.77
	Range	0.1–1225.4	0.1–811.9
Fold-change from baseline	n	663	723
	Geometric mean	2.53	0.86
	[95%CI]	[2.34; 2.74]	[0.82; 0.89]
	Median	2.49	0.86
	Range	0.0–126.6	0.0–6.8

CI: confidence interval; FAS: full analysis set; IR: index of reactivity

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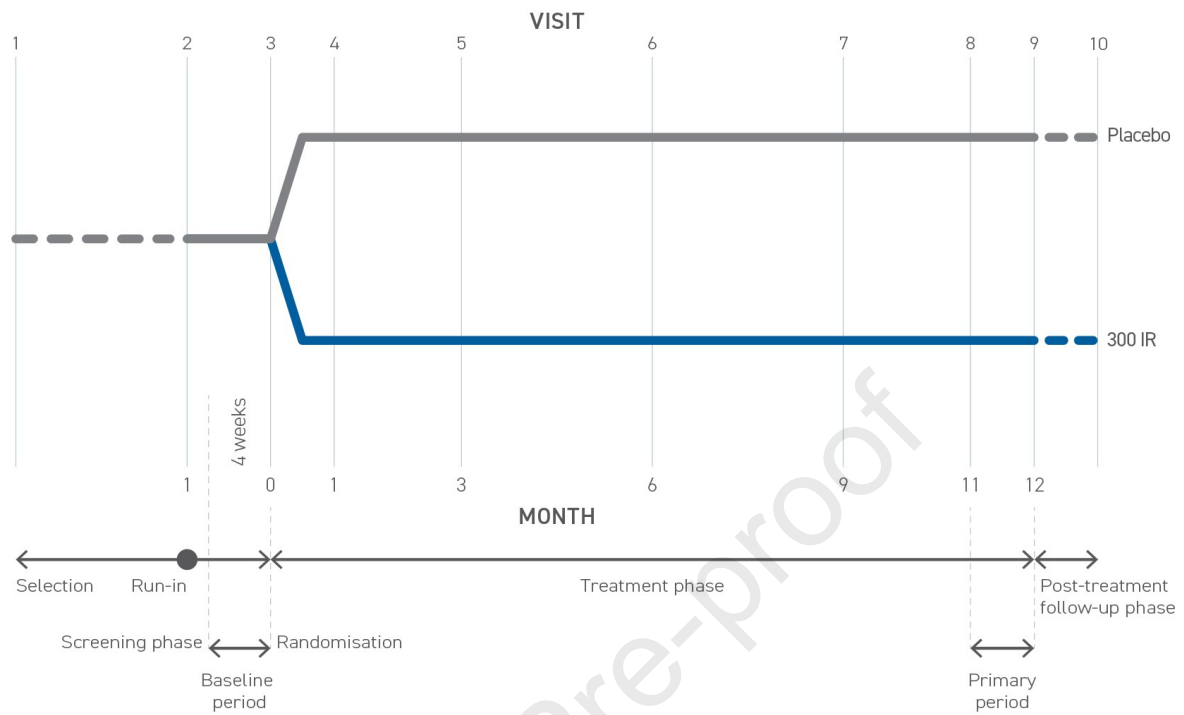
46

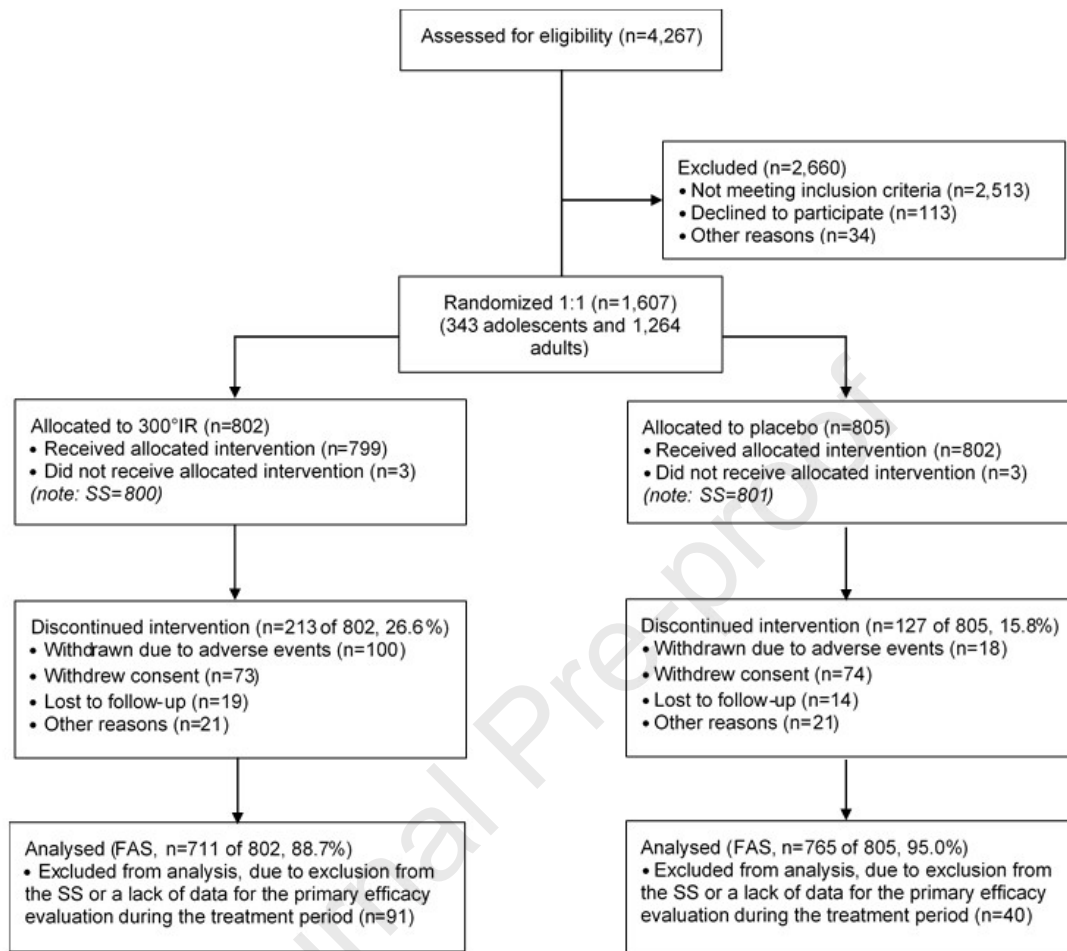
Table E9. Overview of TEAEs by age class (SS)

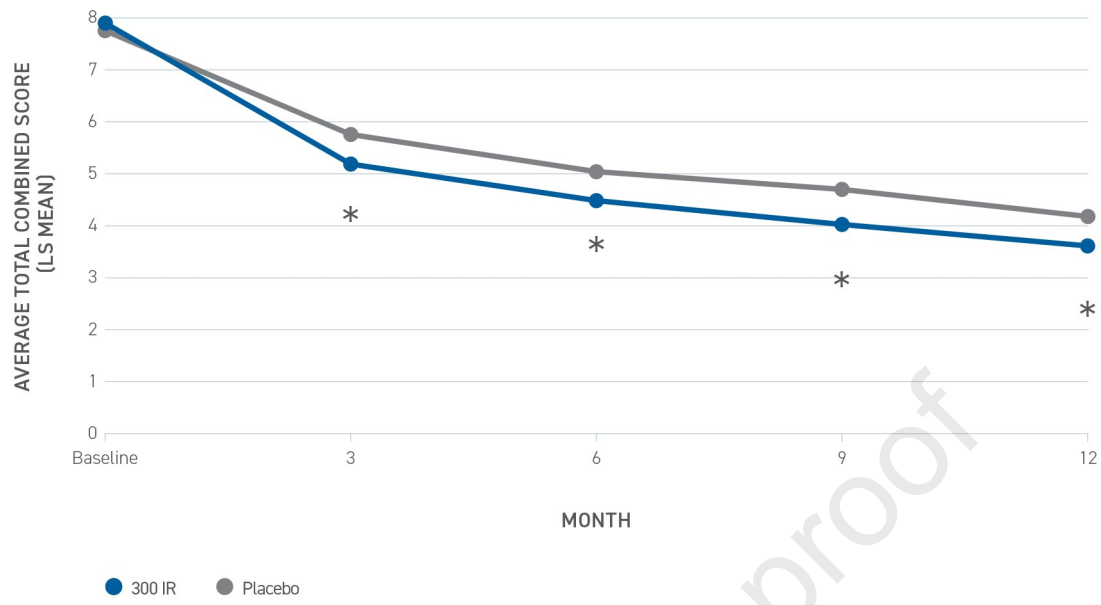
	Adolescents N=341		Adults N=1,260		Whole population N=1,601	
	300°IR N=178 n (%)	Placebo N=163 n (%)	300°IR N=622 n (%)	Placebo N=638 n (%)	300°IR N=800 n (%)	Placebo N=801 n (%)
TEAE	124 (69.7)	89 (54.6)	437 (70.3)	351 (55.0)	561 (70.1)	440 (54.9)
TEAE suspected to be drug-related	88 (49.4)	21 (12.9)	320 (51.4)	98 (15.4)	408 (51.0)	119 (14.9)
Serious TEAE	4 (2.2)	1 (0.6)	17 (2.7)	8 (1.3)	21 (2.6)	9 (1.1)
Serious TEAE suspected to be drug-related	1 (0.6)	0	1 (0.2)	0	2 (0.3)	0
TEAE leading to premature study withdrawal	23 (12.9)	2 (1.2)	74 (11.9)	15 (2.4)	97 (12.1)	17 (2.1)
TEAE leading to premature study withdrawal suspected to be drug-related	21 (11.8)	1 (0.6)	63 (10.1)	6 (0.9)	84 (10.5)	7 (0.9)

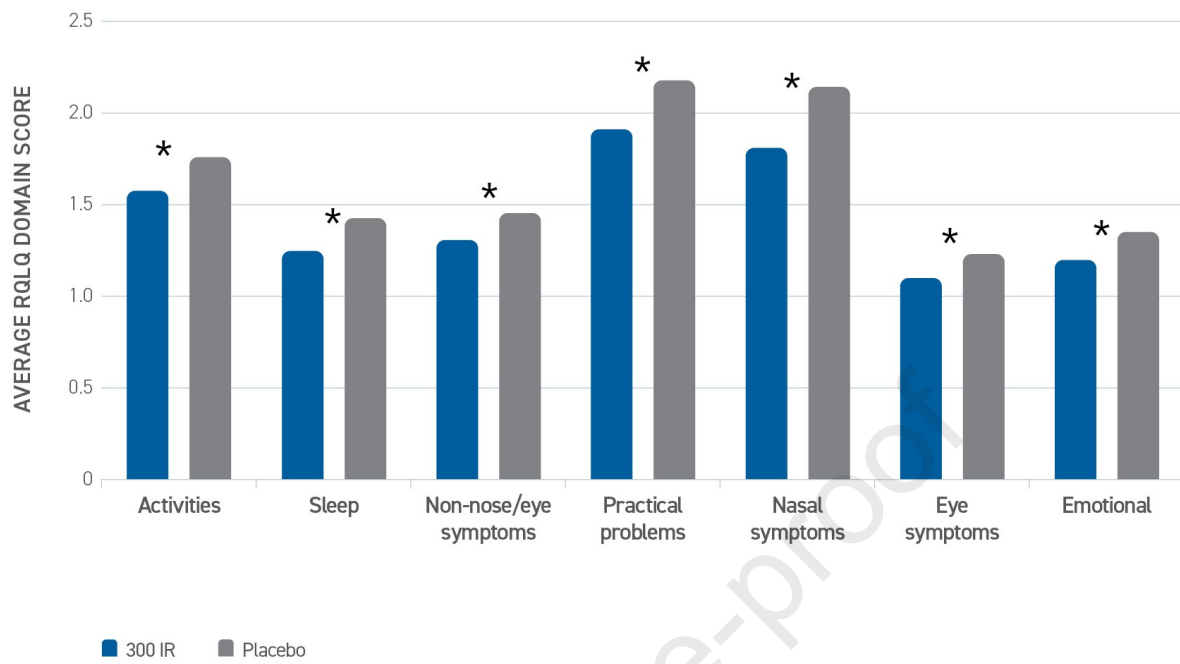
IR: index of reactivity; N: number of patients in each group; n: number of patients with at least one event; SS: safety set; TEAE: treatment-emergent adverse event. A patient could have more than one event.

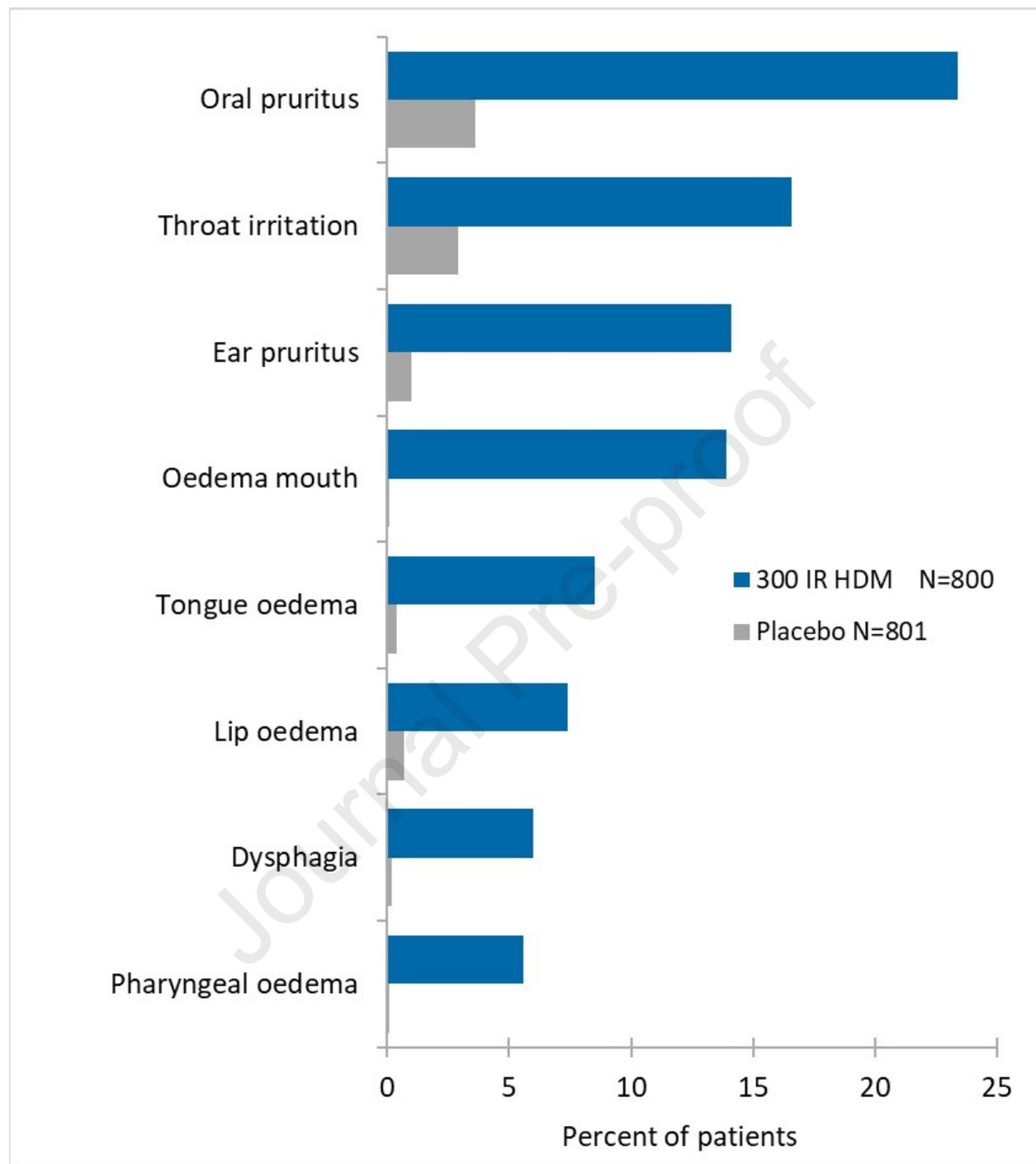
Note: two additional patients in the 300°IR group (1 adolescent and 1 adult) did not complete the treatment period or the study due to an AE, although the 300°IR tablet was not withdrawn by the investigators.











Online Repository

Supplemental safety data

Treatment-emergent adverse events

As expected, the most common TEAEs associated with the investigational product (IP) in the 300°IR group were mild or moderate application-site reactions typically associated with AIT (oral pruritus, throat irritation, ear pruritus, or mouth oedema) and resolved without specific management or discontinuation of the IP (Fig S1). No deaths occurred during the study. Thirty-five serious TEAEs were reported in 30 patients (21 in the 300°IR group and 9 in the placebo group) but only two serious pharyngeal disorders (both in the 300 IR group) were suspected to be related to the IP. In the context of sublingual AIT, these serious, severe laryngopharyngeal reactions were not unexpected, and occurred upon treatment initiation (on treatment day 1 or 2). There were no reports of severe anaphylactic reactions.

Serious TEAEs suspected to be related to the IP (in two patients in the 300°IR group)

- A 17-year-old female experienced a severe laryngopharyngeal reaction on treatment day 1, three minutes after taking the IP. The investigator administered an intramuscular epinephrine injection, inhaled salbutamol, and oral cetirizine. The AE had resolved about an hour later. The patient discontinued the study on the same day.
- A 25-year-old male experienced a severe pharyngeal reaction on treatment day 2 immediately after taking the IP at home. He took cetirizine tablets immediately, and the AE had resolved one hour later. The patient discontinued the study on the same day.

Epinephrine administration

All randomized participants received an epinephrine auto-injector for use in the event of a severe allergic reaction. Six patients (four in the 300°IR group and two in the placebo group) received epinephrine by self-injection or otherwise during the treatment period, and are described below. In the 300°IR group,

epinephrine administration was prompted by a severe pharyngeal disorder (as described above for the 17-year-old female patient), severe tongue oedema, moderate acute urticaria, and severe nasal congestion/fatigue. Only the first two cases were suspected to be treatment-related.

Cases of epinephrine administration in the 300°IR group

- As mentioned above, a 17-year-old female experienced a severe laryngopharyngeal reaction on treatment day 1, three minutes after taking the IP in the investigator's office. The investigator administered an intramuscular epinephrine injection, inhaled salbutamol, and oral cetirizine. The AE had resolved about an hour later. The investigator considered that the TEAE having prompted epinephrine injection was related to the IP. The patient permanently discontinued the IP on the same day and was withdrawn from the study on Day 122 (end of study).
- A 33-year-old female used her epinephrine auto-injector (on her own initiative) at home on treatment day 8, after developing severe tongue oedema. The investigator considered that the TEAE having prompted epinephrine injection was related to the IP. The patient permanently discontinued the IP on the same day and was withdrawn from the study on Day 10 (end of study).
- A 37-year-old female attended the emergency room on treatment day 95 after developing moderate acute urticaria. An emergency room physician administered intramuscular epinephrine. The investigator considered that the TEAE having prompted epinephrine injection was unrelated to the IP. The patient completed the study.
- A 26-year-old female used her epinephrine auto-injector (on her own initiative) at home on two separate occasions (for severe nasal congestion on treatment day 57, and for fatigue on treatment day 79). The investigator considered that both of these TEAEs were unrelated to the IP. The patient permanently discontinued the IP on Day 192 (lost to follow-up) and was withdrawn from the study on Day 382 (end of study).

Cases of epinephrine administration in the placebo group

- A 27-year-old female used her epinephrine auto-injector (on her own initiative) on treatment day 201, after developing a moderately severe allergic reaction of unknown aetiology. The

investigator considered that the TEAE having prompted epinephrine injection was unrelated to the IP. The patient completed the study.

- An 18-year-old female used her epinephrine auto-injector (on her own initiative) at home on treatment day 115, after developing a moderate severe allergic reaction to peanuts in food. The investigator considered that the TEAE having prompted epinephrine injection was unrelated to the IP. The patient completed the study.

Autoimmune disease

There were three cases of autoimmune disease (a case of coeliac disease in the 300°IR group and cases of polymyalgia rheumatica and rheumatoid arthritis in the placebo group, none of which was considered to be related to the IP), two cases of eosinophilic esophagitis (neither serious, and both in the 300°IR group) and three cases of laryngopharyngeal disorder (all in the 300°IR group). Both cases of eosinophilic esophagitis and two of the three cases of laryngopharyngeal disorder (the two cases mentioned above, associated with epinephrine administration) were suspected to be drug-related.

Supplemental efficacy data.

We assessed the 300°IR vs. placebo difference in the aTCS at Month 3, Month 6, Month 9 and Month 12 in the patients from the FAS who presented an average TCS at baseline greater than 6, 8, 10 and 12, respectively. A higher baseline aTCS was associated with a greater 300°IR vs. placebo difference.

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