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Allergen immunotherapy in house dust mite-associated allergic rhinitis: efficacy of the 300 IR mite tablet

Ludger Klimek · Randolf Brehler · Ingrid Casper · Felix Klimek · Jan Hagemann · Mandy Cuevas · Karl-Christian Bergmann

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Abstract
Background A perennial house dust mite-associated allergic rhinitis has a major impact on the quality of life of patients and is associated with a high socioeconomic burden. The most common symptoms of allergic rhinitis include a runny nose and nasal congestion, sneezing, itching of nose, mouth and/or throat, and/or ocular symptoms. Affected patients often develop allergic bronchial asthma. Therapy options for allergic rhinitis include allergen avoidance, symptomatic treatment, and allergen immunotherapy. Allergen immunotherapy is the only disease-modifying treatment that can permanently alleviate the symptoms of allergic rhinitis. In July 2021, a new sublingual mite tablet was approved in Germany.
Methods This review summarizes clinical studies on the 300 IR (index of reactivity) mite tablet in adolescents and adults with house dust mite-associated allergic rhinitis and presents the results.
Results In the phase II and phase III studies considered here, different dosages of the mite tablet were investigated. The 300 IR mite tablet showed the best benefit–risk profile and has been approved in Europe, Japan, South Korea, Australia, and New Zealand for the treatment of house dust mite-associated allergic rhinitis.
Conclusion Allergen immunotherapy with the 300 IR mite tablet is an effective treatment that relieves allergic symptoms, reduces the need for symptomatic medication, and improves the quality of life in both adults and adolescents with house dust mite-associated allergic rhinitis. At the same time, treatment with the 300 IR mite tablet is well tolerated. Mild to moderate reactions at the application site subside after a few days.

Keywords House mites · Allergic rhinitis · Allergic asthma · Allergen immunotherapy · Mite tablet

L. Klimek · I. Casper · F. Klimek
Center for Rhinology and Allergology, Wiesbaden, Germany

R. Brehler
Clinic for Skin Diseases, Münster University Hospital, Muenster, Germany

J. Hagemann
Department of Otorhinolaryngology, Mainz University Medical Center, Mainz, Germany

M. Cuevas
Clinic and Polyclinic for Otorhinolaryngology, Carl Gustav Carus University Hospital, TU Dresden, Dresden, Germany

Prof. Dr. K.-C. Bergmann (✉)
Institute for Allergy Research, Charité—Universitätsmedizin Berlin, Berlin, Germany

Allergology and Immunology, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany
karl-christian.bergmann@charite.de;
karlchristianbergmann@gmail.com

Abbreviations

AAdSS	average adjusted symptom score
ADR	adverse drug reaction
AE	adverse event
AIT	allergen immunotherapy
AR	allergic rhinitis
ATCS	average total combined score
ARMS	average rescue medication score
ARCTSS	average rhinoconjunctivitis rotal symptom score
D. far.	Dermatophagoides farinae
D. pter.	Dermatophagoides pteronyssinus
EEC	environmental exposure challenge chamber
HDM	house dust mite
IR	index of reactivity

RDBPC randomized, double-blind, placebo-controlled
RQLQ Rhinoconjunctivitis Quality of Life Questionnaire
SCIT subcutaneous immunotherapy
SLIT sublingual immunotherapy

Introduction

House dust mites (HDM), especially the two species *Dermatophagoides pteronyssinus* (*D. pter.*) and *Dermatophagoides farinae* (*D. far.*) are among the most common sources of indoor allergens [1–3]. Allergic patients react with symptoms of perennial allergic rhinitis (AR), such as nasal congestion, runny nose, sneezing, itching in the nose, mouth, or throat, or watery eyes [4]. Year-round AR has a significant impact on health-related quality of life and is associated with a high socioeconomic burden [5–9]. The risk of developing asthma is higher in patients with AR than in the general population, and higher in patients with HDM allergy than in patients with other inhalant allergies [10, 11].

Therapeutic options for HDM-AR include abstinence measures, symptomatic treatment, and allergen immunotherapy (AIT). We have reported on avoidance measures as a therapy elsewhere in this issue [12] and various pharmacologic therapeutic options are recommended in the literature [5–7, 13]. Of these, AIT is the only treatment that has a disease-modifying effect because it targets the immunologic mechanisms underlying allergic disease. It is available in the form of subcutaneous injections (SCIT) and sublingual solutions and tablets (SLIT) [5–7, 13–15].

Recently, the new sublingual mite tablet Orylmyte® (Stallergenes GmbH, 47475 Kamp-Lintfort, Deutschland; in Austria: Actair®) was approved and has been available on the market since then. This review summarizes the clinical studies of the 300 IR mite tablet in adolescents and adults with HDM-AR and presents the results of immunological investigations.

The 300 IR mite tablet

Orylmyte® was approved in 2021 as an AIT for patients 12 years of age and older with established moderate-to-severe HDM-AR [16]. The tablet, with an allergen activity of 300 IR (IR = index of reactivity), contains a standardized 1:1 mixture of freeze-dried allergen extracts obtained from bodies and feces of *D. pter.* and *D. far.*. The tablet contains a broad repertoire of major and minor allergens and thus represents the conditions of natural exposure very well [1, 17]. In particular, it contains the major allergens of group 1 (per 300 IR tablet a total of approximately 75 µg group 1 allergens: approx. 14–17 µg Der p 1 and approx. 53–68 µg Der f 1 [18]), group 2 (per 300 IR tablet a total of approx. 25 µg Der p 2 + Der f 2 [19]) and also Der p 23 [18, 20]. Der p 23 has been identified only recently as a major allergen [1, 21] which is

Table 1 Randomized, double-blind, placebo-controlled phase II, II/III, and III clinical trials evaluating the efficacy and safety of HDM tablet

Type of study	Number and origin of patients	Patients	Treatment duration	Primary endpoint	Results
RDBPC Phase II [27]	$n = 355$ Canada	Adults (18–55 years) with HDM-AR with or without asthma	6 months	CH_{BL} $AUC_{RTSS\ 0–4\ h}$ after 6 months	*Dose-dependent effect:* 300 IR and 500 IR more effective than placebo *Higher dropout rate at 500 IR*
RDBPC Phase II/III [28]	$n = 509$ Europe	Adults (18–50 years) with HDM-AR with or without asthma	1 year +1 year follow-up	AAdSS during the last 3 months of each year	*Efficacy during treatment:* –18 and –20% vs. placebo in the 300 IR and 500 IR groups, respectively ($p < 0.05$ and 0.01). *Therapy-sustaining effect in the follow-up period:* –17 and –19% vs. placebo in the 300 IR and 500 IR groups, respectively ($p < 0.05$)
RDBPC Phase II/III [29]	$n = 968$ Japan	Teenagers and Adults (12–64 years) with HDM-AR with or without asthma	1 year	AAdSS during the last 8 weeks of Treatment	*Efficacy:* –18 and –13% vs. placebo in the 300 IR and 500 IR groups, respectively ($p < 0.001$). *Onset of action in week 8–10* *Higher dropout rate at 500 IR*
RDBPC Phase III [30]	$n = 438$ Japan	Children/Teenagers (5–16 years) with HDM-AR with or without asthma	1 year	AAdSS during the last 4 weeks of treatment	*Efficacy:* –13% vs. placebo ($p < 0.0005$)
RDBPC Phase III [18]	$n = 1607$ Canada Europe Israel Russia USA	Adolescents and adults (12–65 years) with HDM-AR with or without asthma	1 year	ATCS during the last 4 weeks of treatment	*Efficacy:* Total population: –17% vs. placebo ($p < 0.0001$) European subgroup (ACSMS): –22% vs. placebo ($p < 0.0001$) [31]

AAdSS average Adjusted Symptom Score, *ACSMS* average combined symptom and medication score, *AR* allergic rhinitis, *ATCS* average Total Combined Score, CH_{BL} $AUCRTSS_{0–4}$ Change from Baseline in Area Under the Curve of Rhinitis Total Symptom Score during 4 h of allergen challenge, *HDM* house dust mites, *RDBPC* randomized, double-blind, placebo-controlled

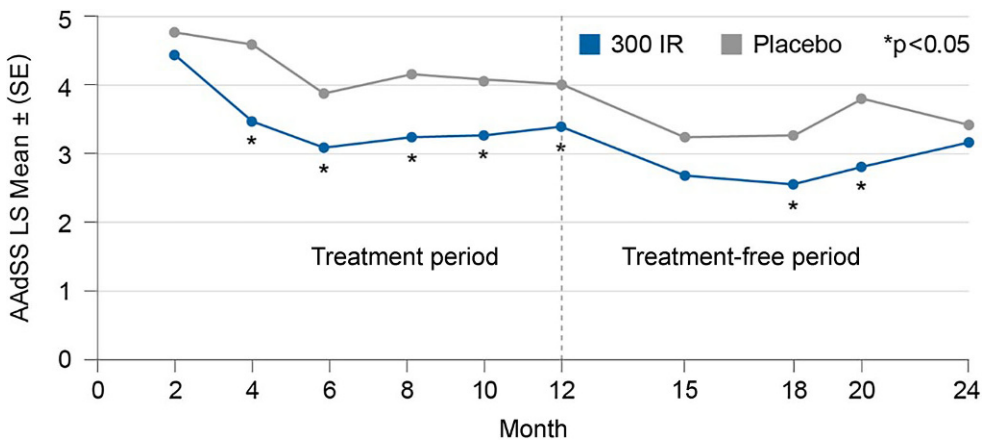

Fig. 1 The 12-month treatment with the 300 IR mite tablet was effective, and the effect of the treatment was maintained in the subsequent therapy-free year [28]

particularly associated with the occurrence of allergic asthma [22–25].

Orylmyte® is a compressed sublingual tablet that releases allergens constantly over 2–3 min. This promotes allergen uptake by mucosal allergen-presenting cells (i.e. Langerhans cells), while reducing sudden activation of local proinflammatory cells (i.e., mast cells) [26].

Clinical development: efficacy of the 300 IR mite tablet

The 300 IR mite tablet is approved in many European countries as well as in Japan, South Korea, Australia, and New Zealand for the treatment of HDM-AR in adolescents and adults. Approval is also available in Japan, Australia, and South Korea for the treatment of children ≥ 5 years of age. The approvals are based on an extensive global clinical development program with multiple randomized, double-blind, placebo-controlled trials (RDBPC; Table 1).

Phase II study in the allergen exposure chamber

Phase I dose-escalation studies were initially conducted with doses ranging from 100 IR to 2000 IR, in which HDM tablets were well tolerated by patients with HDM-induced AR or asthma [32–34]. Three of these dosages were further evaluated in a phase II study in an allergen exposure chamber („environmental exposure challenge chamber“) with adults aged 18–55 years for dose finding: a total of 355 patients received daily SLIT with 100 IR, 300 IR, 500 IR, or placebo over a 6-month period, with standardized 4 h HDM allergen provocations at baseline and at 1, 2, 4, and 6 months [27]. The results showed a dose-dependent effect: while the efficacy of 100 IR was not significantly different from placebo, 300 IR and 500 IR were comparable, however with a higher dropout rate for 500 IR [27].

Phase II/III studies

Phase II/III studies in adolescents and adults were conducted for 300 IR and 500 IR doses, evaluating efficacy under natural allergen exposure in field studies.

These studies included a European phase II/III field study of 509 adults with HDM-AR aged 18–50 years [28]. 30% of patients had concomitant asthma, and 52% were polysensitized. Patients received a 300 IR or 500 IR HDM tablet or placebo once daily. Patients were treated for 1 year in seven European countries and then followed up for an additional year without treatment. The primary endpoint was the average adjusted symptom score[1] (AAdSS; Average Adjusted Symptom Score); secondary endpoints included symptom and medication individual scores. Treatment resulted in a comparable significant reduction in AAdSS versus placebo in patients receiving the 300 IR or 500 IR HDM tablet once daily. The effect of treatment in this study began at approximately 4 months after initiation of therapy and continued throughout the treatment period. The efficacy was maintained as a treatment-sustained effect in the treatment-free follow-up year: AAdSS continued to be significantly lower in patients treated with HDM tablet in the first year than in patients receiving placebo (Fig. 1). Efficacy results were not affected by the presence of asthma or sensitization status [28].

In another 1-year phase II/III field study, doses of 300 IR and 500 IR were evaluated in 968 adolescents and adults aged 12–64 years in Japan [29]. The primary endpoint here was also AAdSS. The results were comparable to those of the European study, with a significant reduction in AAdSS compared with placebo in patients treated with 300 IR and 500 IR. The difference between the two active treatment groups was not statistically significant. The onset of action in this study was evident after 8–10 weeks and persisted for the

[1] A symptom score adjusted for the use of on-demand medication.

300 IR mite tablet throughout the observation period [29].

Overall, once-daily maintenance therapy at 300 IR proved to be the therapy with the most favorable benefit–risk profile in the phase II and II/III clinical trials and was therefore chosen for further clinical development.

Global phase III study

With 1607 patients from 13 countries, the pivotal global phase III trial was the largest RDBPC study ever conducted to investigate AIT in HDM-AR [18]. The efficacy and safety of 12 months of treatment with 300 IR in adults ($n = 1264$) and adolescents ($n = 343$) with HDM-AR were investigated. Thirty-eight percent of patients had concomitant asthma, and 45% were polysensitized. The primary endpoint was the average total combined score (aTCS). Secondary efficacy endpoints included another combined symptom-medication score, symptom and medication individual scores, and quality of life.

The primary endpoint and all predefined secondary endpoints were met with statistically significant differences versus placebo. The results of important endpoints are shown in the overview (Table 2; [18]).

Regarding on-demand medication, 27% of patients treated with the 300 IR mite tablet were able to discontinue it completely, 24% were able to discontinue oral antihistamines, and 30% were able to discontinue intranasal corticosteroids [35].

AR-related quality of life, as measured by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score, was significantly improved overall, as well as in all 7 individual domains (activities, sleep, general discomfort, practical problems, nasal as well as ocular symptoms, and emotional well-being) in patients treated with the 300 IR mite tablet compared with placebo (Fig. 2; [18]).

A post hoc analysis of this global phase III study showed an improvement in both combined symptom-medication scores (ACSMS, average combined symptom and medication score) in the European subgroup. The ACSMS also decreased significantly by 21.7% in patients treated with 300 IR compared to placebo ($p < 0.0001$) [31]. Treatment effects of this magnitude are perceived by patients as a noticeable improvement in AR [31].

Table 2 Results of the global phase III study—primary endpoint and key secondary endpoints

Endpoint	LS mean (300 IR vs placebo)	Absolute difference vs. placebo	Relative difference vs. placebo (in %)
Primary endpoint			
ATCS (unequally weighted score—weighting 80 symptoms/20 medication)	3.62 vs. 4.35	−0.74	−16.9***
Important secondary endpoints			
ACSMS (equally weighted score 50/50)	1.19 vs. 1.45	−0.26	−18.0***
ARCTSS	4.22 vs. 5.04	−0.81	−16.1**
ARMS	0.21 vs. 0.30	−0.09	−29.7**
Individual symptom scores			
Sneeze	0.66 vs. 0.82	−0.16	−19.5**
Running nose	0.81 vs. 0.97	−0.16	−16.5**
Itchy nose	0.61 vs. 0.76	−0.15	−19.7**
Blocked nose	0.85 vs. 1.04	−0.19	−18.3***
Eye itching	0.47 vs. 0.56	−0.09	−15.4*
Eye tears	0.34 vs. 0.42	−0.08	−18.2*

Lower values mean better results. Number of evaluable patients in the 300 IR vs. placebo groups: 586 vs. 676
ACSMS Average Combined Symptom-Medication Score, *ARMS* Average Rescue Medication Score, *ARSS* Average Individual Symptom Scores, *ARTSS* Average Rhinitis Total Symptom Score, *aTCS* Average Total Combined Score, *LS* Least Squares
*$p < 0.05$, **$p < 0.001$, ***$p < 0.0001$

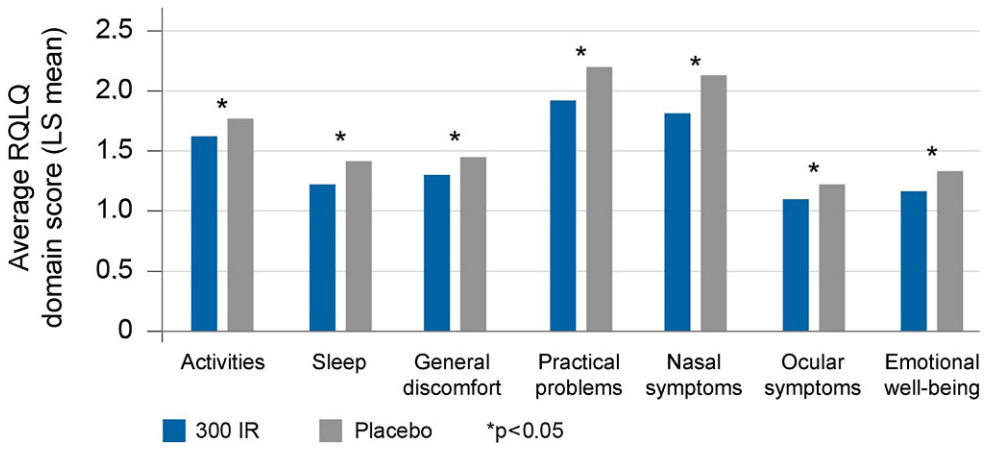

Fig. 2 Improved quality of life in all domains of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) under treatment with Orylmyte®

Clinical development: safety and tolerability of the 300 IR mite tablet

In the clinical development program studies, SLIT with the 300 IR mite tablet was well tolerated by patients with HDM-AR without or with mild asthma. In general, adverse events (AEs) were mild to moderate in intensity and occurred mostly in the first few days of treatment. Application site reactions, such as oral itching, throat irritation, or mouth swelling, were the most commonly reported reactions [36].

In the phase II study, which took place under controlled conditions in the allergen exposure chamber, AEs were reported by 90.7% of patients receiving 300 IR mite tablet and by 82.8% of patients in the placebo arm [27]. In 68.6% and 43.7% of patients, respectively, AEs were classified as adverse drug reactions (ADRs), i.e. AEs in which the association with the study medication was judged to be "possible." Most commonly reported were application site reactions (throat irritation, oral itching, ear itching, mouth swelling). No cases of serious ADRs or anaphylaxis were reported. In addition, this study showed that AIT with 300 IR mite tablet had no adverse respiratory effects: AEs such as asthma and asthma-related symptoms (e.g., cough, dyspnea, or wheezing) occurred with comparable frequency in the 300 IR group and the placebo-treated group.

In two studies conducted in Europe [28] and Japan [29], the safety profile was comparable: the proportion of patients for whom at least one AE was documented was 88.2% in the 300 IR group and 75.5–80.0% in the placebo group. In 66.8% (300 IR) and 18.6% (placebo) of patients, AEs were potentially related to study medication [29] (in [28] corresponding rates are not given). AEs such as asthma, cough, dyspnea, and wheezing were reported with similar frequency by patients in both the active and placebo groups [28].

In the global study [18], 51.0% of patients in the 300 IR group and 14.9% in the placebo group reported at least one ADR. As expected, the most common ADRs in patients treated with 300 IR in this study were also mild to moderate local reactions at the application site, such as oral itching, throat irritation, ear itching, and mouth swelling. Adolescents and adults tolerated the treatment comparably well. The incidence and distribution of ADRs was similar in both age groups, with 49.4% of adolescents and 51.4% of adults reporting at least one ADR. Concomitant asthma did not affect the safety profile of 300 IR mite tablet.

Overall, 57% of the 1583 adults and adolescents with HDM-induced AR treated with the 300 IR mite tablet in the clinical development program reported adverse events. The safety profile in children was similar to that in adults and adolescents. Of 270 children treated with the 300 IR dosage in clinical trials, a total of 50% reported adverse events [16, 36].

Confirming the good tolerability profile observed in clinical trials are data from more than 4 years of routine post-approval use in Japan, South Korea, Australia, and New Zealand with nearly 90,000 exposed patients: The most commonly reported ADRs were local application site reactions of mild to moderate intensity [36]. This was also shown in an observational study in Japan [37].

The safety data described for the 300 IR mite tablet strengthen the existing evidence base on the beneficial safety profile of SLIT. Sublingual formulations are almost always associated with mild or moderate reactions at the application site and very rarely with severe systemic allergic reactions. This may be due to specific features associated with sublingual allergen uptake and processing that reduce the induction of proinflammatory immune responses [38, 39].

Immunomodulation by the 300 IR mite tablet

The exact mechanism of action of AIT has not been definitively determined, but it is well established that an important immunologic response to AIT is the activation of antibodies that block the allergen antibody-mediated immune response. The activated antibodies are mainly IgG and IgA antibodies, which are able to prevent the binding of IgE-allergen complexes to B cells and dendritic cells. This mechanism contributes decisively to the treatment success of AIT [40, 41].

A crucial feature in the effect of SLIT is the oral uptake of the allergen via the oral mucosa. It has already been shown that ingestion of HDM allergen extracts by SLIT has an effect on both humoral and cellular immune responses, resulting in tolerance to the allergen and subsequently improvement of allergic symptoms [2, 6, 14, 39, 42].

In the European phase II/III study [28]. HDM-specific IgG_4 titers (for Der p 1, Der p 2, Der f 1, and Der f 2) increased 2- to 4-fold in patients treated with the 300 IR mite tablet, an effect not observed in the placebo group [19]. Of note, treatment was not associated with a significant risk of IgE new sensitization to allergens contained in the tablet or used in the mite culture medium [19].

An up to 4-fold increase in *D. pter.*- and *D. far.*-specific IgG_4 titers was also observed in the global phase III study [18]. In a more extensive analysis, humoral responses to a large group of HDM allergens (focus: *D. pter.*) were specifically studied in a subgroup of patients (300 IR mite tablet versus placebo) [20]: Der p 1, Der p 2 and Der p 23 were the mite allergens with the highest sensitization rates (83, 92, and 82% of patients, respectively). In particular, after one year of therapy, an increase in Der p 1, Der p 2 and Der p 23-specific IgG and IgG_4 was observed in patients treated with the 300 IR tablet. The increase in Der p 23-specific IgG antibodies by therapy demon-

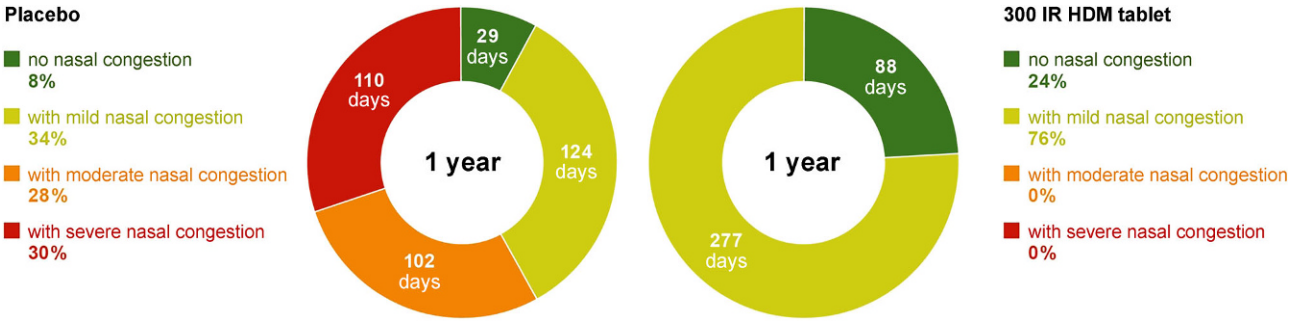

Fig. 3 Exemplary representation of the clinically relevant benefit using the symptom "blocked nose" as an example (assumption: patient with ACSMS0–6 = 1.45. No change in other symptoms: itchy nose, sneezing, runny nose, and taking on-demand medication)

strates the sufficient content of biologically active Der p 23 in the tablet to elicit an immune response.

Until now, especially allergens of groups 1 and 2 (Der p 1/Der f 1 and Der p 2/Der f 2) were considered as the HDM allergens with the greatest clinical relevance. In contrast, the allergen Der p 23 has only in recent years been identified as a major allergen that is strongly associated with asthma compared to other allergens [22–25]. Parental AR and early contact with *D. pter.* allergens promote IgE polysensitization to various *D. pter.* molecules, which in turn predicts the risk for mite-induced AR and for current or future asthma [25]. Thus, the strong IgG responses to Der p 23 may be of particular benefit to appropriately sensitized or allergic patients [20].

The 300 IR mite tablet in practice

Evidence from the extensive clinical development program: In patients with confirmed HDM allergy, AIT with the 300 IR mite tablet alleviated AR symptoms, with onset of action approximately 2 months after treatment initiation [29]. The decrease in symptoms was maintained during the 1-year AIT treatment period as well as during the remainder of the AIT-free year [28]. Although only clinical trial data for 12 months of treatment are available to date, daily, year-round therapy for 3 years is recommended according to the treatment guidelines to achieve ongoing treatment effects [16]. When treated with the 300 IR mite tablet, patients should benefit from a noticeable improvement in AR. On the ACSMS scale of 0 to 6, each of the four nasal symptoms considered scored a maximum severity of 0.75 points. A change of 0.25 points corresponds to a decrease of one symptom by one severity level, which also corresponds to the minimum clinically relevant benefit [43]. A model calculation based on an ANCOVA analysis shows what the decrease in a symptom, such as nasal congestion, by one severity level actually means [31]. This is based on the efficacy results of the global pivotal study [18]. Thus, hypothetically, a patient with average-severe HDM-AR (ACSMS = 1.45) will experience no more days of moderate or severe nasal congestion with the 300 IR mite tablet therapy over 1 year vs. 102 and 110 days, respectively, with placebo[2] (Fig. 3; [31]).

Treatment with 300 IR mite tablet is generally well tolerated, with mild to moderate reactions at the application site being the most commonly reported side effects. These occur quite predominantly in the first few days to about a week after the start of treatment and usually subside after a few days.

The first 300 IR mite tablet is taken under medical supervision, after which therapy can be safely and conveniently administered at home [16]. Thus, AIT with the 300 IR mite tablet is an effective and well-tolerated therapy that relieves allergic symptoms, reduces the need for symptomatic medication, and improves quality of life in adults and adolescents with HDM-induced AR, regardless of sensitization status or concomitant mild asthma.

Observational studies will provide further results on the efficacy and tolerability of 300 IR mite tablet therapy in clinical practice in Europe.

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[2] Assumption: patient with ACSMS0–6 = 1.45. No change in other symptoms: itchy nose, sneezing, runny nose, and taking on-demand medication.

two years, outside the submitted work. I. Casper, F. Klimek and J. Hagemann declare that they have no competing interests.

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