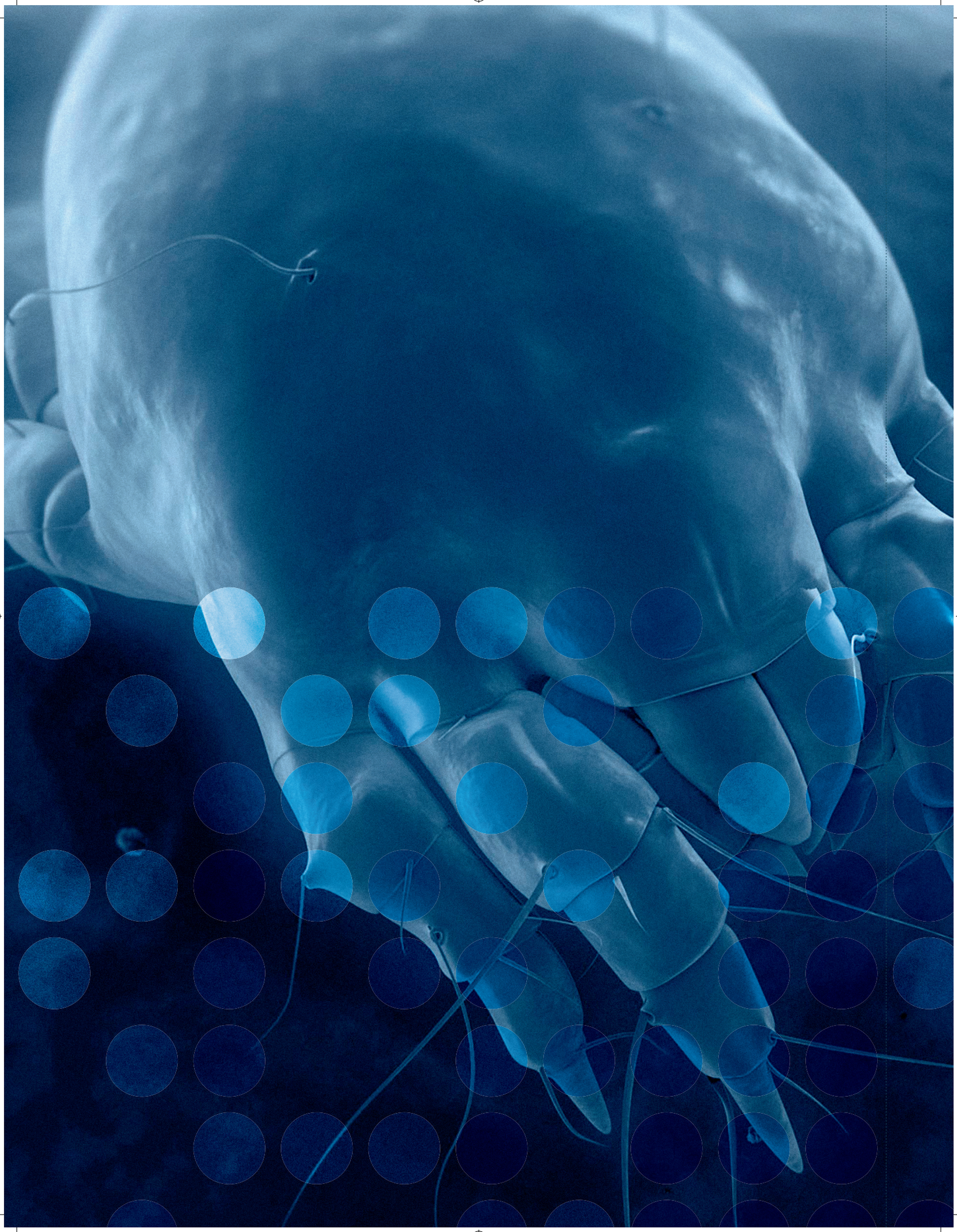
# ACARIZAX™
Reference Kit

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 1 10/10/2017 15.20

## THE HOUSE DUST MITE

The house dust mite (HDM) is a cosmopolitan pyroglyphid that lives in human habitation. HDM feed on organic detritus, such as flakes of shed human skin, and flourish in the stable environment of dwellings. HDM are a common cause of asthma and allergic symptoms worldwide. The mite's gut contains potent digestive enzymes (notably proteases) that persist in their faeces and are major inducers of allergic reactions including both upper and lower respiratory symptoms. The mite's exoskeleton can also contribute to allergic reactions. The European HDM *(Dermatophagoides pteronyssinus)* and the American HDM *(Dermatophagoides farinae)* are two different species, that are widespread and not necessarily confined to their respective continents. Relative humidity both outdoors and indoors is a critical factor for HDM prevalence, with lower levels in temperate high-altitude and cold sub-arctic regions and more infestations in damp homes.



# EXECUTIVE SUMMARY

## Respiratory allergic disease is a significant burden

- House dust mite (HDM) allergy is strongly implicated in the pathogenesis of respiratory allergic disease, among which a main manifestation is allergic rhinitis (AR).
- Many patients are unable to achieve adequate symptom control through allergen avoidance and pharmacotherapy and there is a need for additional treatment options.

## Allergy immunotherapy targets the underlying etiology of allergic disease

- Allergy immunotherapy (AIT) is the only treatment option for AR that addresses the underlying etiology of allergic disease by modifying the immunological response to the causative allergen.
- AIT provides clinically meaningful symptom relief, reduces the need for medication and improves quality of life for patients.
- Compared to subcutaneous immunotherapy (SCIT), sublingual immunotherapy (SLIT) is associated with fewer and less severe adverse events and offers improved convenience, including at-home administration.

## ACARIZAX™ is a fast-dissolving oral lyophilisate for sublingual administration

- ACARIZAX™ is a fast-dissolving freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *Dermatophagoides (D.) pteronyssinus* and *D. farinae*. Thus, the tablet contains all *D. pteronyssinus* and *D. farinae* allergens.
- A highly standardized production process ensures a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2.
- ACARIZAX™ (Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*) Sublingual Tablet) is indicated as allergy immunotherapy for the treatment of moderate to severe house dust mite-induced allergic rhinitis, with or without conjunctivitis, in adults 18 to 65 years of age confirmed by a positive skin prick test and/or *in vitro* testing for *D. farinae* or *D. pteronyssinus* IgE antibodies.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 6 10/10/2017 15.20

## ACARIZAX™ reduces symptoms and medication need in patients with HDM AR with or without allergic conjunctivitis and with or without AA

- ACARIZAX™ improves symptoms, reduces medication need and improves quality of life in patients with HDM AR.
- ACARIZAX™ provides an early onset of action which is maintained for a year-round effect.
- ACARIZAX™ is efficacious in patients regardless if they are mono sensitized to HDM or have additional multiple sensitizations.
- Treatment with ACARIZAX™ can be initiated at any time during the year.

## ACARIZAX™ is well-tolerated

- ACARIZAX™ is well-tolerated with most adverse events being mild-to-moderate local allergic reactions which tend to subside with continued treatment.
- No treatment-related serious adverse events were reported in the NA clinical trials with ACARIZAX™. Cases of systemic allergic reactions, including anaphylactic reactions, have been reported post-marketing and are considered a class effect.
- ACARIZAX™ is well-tolerated in patients with concomitant stable asthma.
- Treatment with ACARIZAX™ is suitable for at-home administration in patients with HDM respiratory allergic disease, providing that contraindications are adhered to.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 7 10/10/2017 15.20

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 8 10/10/2017 15.20

# 1. BACKGROUND

## 1.1. House dust mite-induced respiratory allergic disease

House dust mite (HDM) allergy is strongly implicated in the pathogenesis of respiratory allergic disease, among which a main manifestation is allergic rhinitis (AR). AR is common and has been previously estimated to affect approximately 20-25% of Canadians[1]. Evidence suggests that 75 percent of middle aged adult with asthma are allergic to one or more inhalant allergens as evidenced by allergy skin testing[2]. The most common allergens sensitization in Canada are dust mites, grass pollen, ragweed pollen, cat and birch pollen[3].

House dust mites, which are ubiquitous in human habitats, are one of the most common sources of indoor, perennial allergies and a significant cause of respiratory allergic disease[4, 5]. In Canada, over 50% of all allergic asthmatics are sensitive to house dust mites[6]. House dust mite sensitization rates in six different cities across Canada showed highest prevalence in Montreal with 43%, to 38% in mid country (Winnipeg,Man, Hamilton, Ont), to 39% West coast in Vancouver to a lower level at 32% in PEI from Atlantic provinces[3]. Approximately half of patients with HDM AR are reported to have concomitant HDM AA, whereas approximately 95% of patients with HDM AA are reported to have concomitant HDM AR[7]. Asthma severity appears increased in adults sensitized to HDM[8].

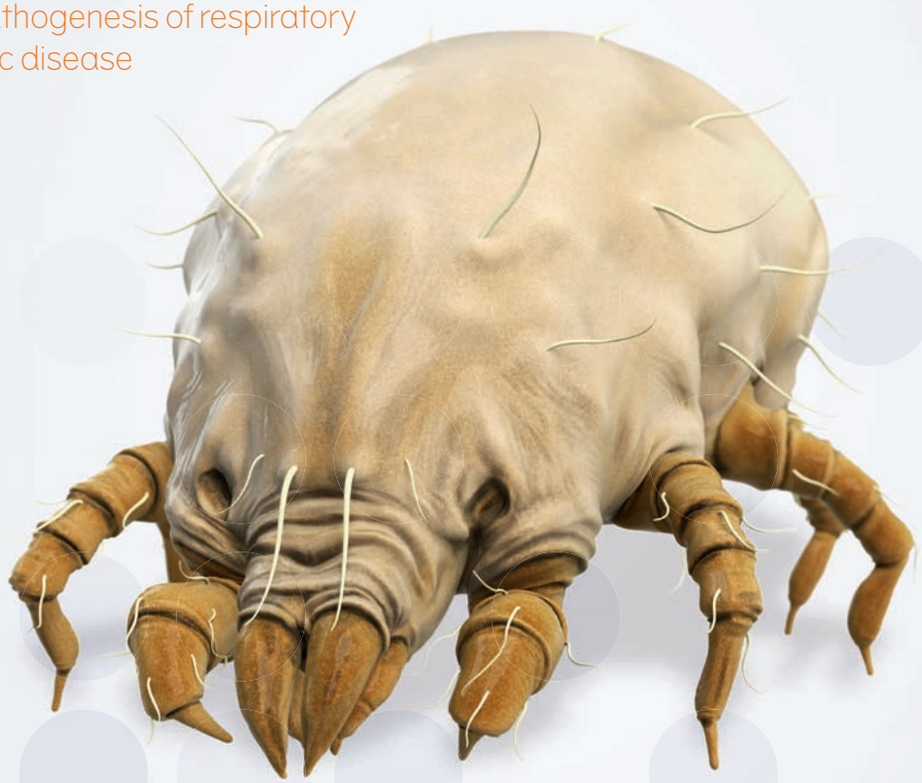
Disease management has largely focused on allergen avoidance and symptom relief through pharmacotherapy. However, the efficacy of HDM avoidance has been questioned and evidence suggests it is not possible to an extent that provides clinically relevant symptom relief[9-12]. Moreover, while pharmacotherapy (e.g. oral or topical antihistamines, intranasal or inhaled corticosteroids [ICS]) can help reduce symptoms, many of the standard treatments have not been specifically assessed for HDM allergy. Patients are often unable to achieve adequate symptom control and dissatisfaction with treatment can be high[13, 14]. As such, there is a need for additional treatment options to relieve the burden of HDM respiratory allergic disease.

Allergy immunotherapy (AIT) is the only treatment option for allergic diseases that addresses the underlying etiology of the disease by modifying the immunological response to the causative allergen. AIT has been shown to provide clinically meaningful symptom relief, reduce the need for medication and improve the quality of life of patients[9, 15]. In addition, it has the potential to alter the natural course of allergic disease, preventing the progression of AR, as well as providing a long-term clinical benefit even after cessation of treatment[9, 15]. Both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are effective in alleviating allergic symptoms and reducing the need for pharmacotherapy. However, sublingual administration is associated with fewer and less severe adverse events than SCIT and offers improved convenience, including the option of at-home administration without medical supervision after the first medically supervised intake[16].



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 10 10/10/2017 15.20

**House dust mite allergy**
is strongly implicated in
the pathogenesis of respiratory
allergic disease





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 11 10/10/2017 15.20

## 1.2. Mode of action of allergy immunotherapy

AIT involves repeated administration of the specific allergen in order to gradually induce immunological tolerance. Unlike pharmacotherapy, AIT modulates the underlying immunological response to the causative allergen and is the only current treatment option that can modify the natural course of respiratory allergic disease.

Several mechanisms by which AIT acts have been proposed although the precise process is not yet fully understood. However, current consensus is that the effect of repeated allergen administration is to stimulate the induction of distinct subsets of T-regulatory cells (Tregs), which over time results in the development of allergen tolerance. This is thought to involve AIT increasing the production of Tregs, inhibiting the T-helper 2 (Th2) cell response and thereby reducing interleukin (IL-4, IL-5, IL-13) release, IgE production and tissue eosinophilia. In addition, AIT is proposed to induce a deviation from a Th2 immune response towards a T-helper 1 (Th1) response, stimulating the release of immunoglobulin (Ig)G, IgG4 and IgA, and preventing binding between IgE and the allergen. These processes lead to lower activation of mast cells, and consequently less release of inflammatory mediators such as histamine. As a result, fewer allergic symptoms are produced (Figure 1.1)[17].

## 1.3. ACARIZAX™: sublingual tablet immunotherapy

ACARIZAX™ is a fast-dissolving oral lyophilisate (freeze-dried tablet) for sublingual administration. Each tablet contains 12 SQ-HDM extract, which is derived from the bodies and faecal particles of the two HDM species, *D. pteronyssinus* and *D. farinae* (Figure 1.2). SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract. The formulation of ACARIZAX™ is the same as that used for two equivalent SLIT-tablets approved in Canada: GRASTEK (grass SLIT-tablet) and RAGWITEK (ragweed SLIT-tablet).

## 1.4. Product quality: standardized and reproducible HDM allergen content

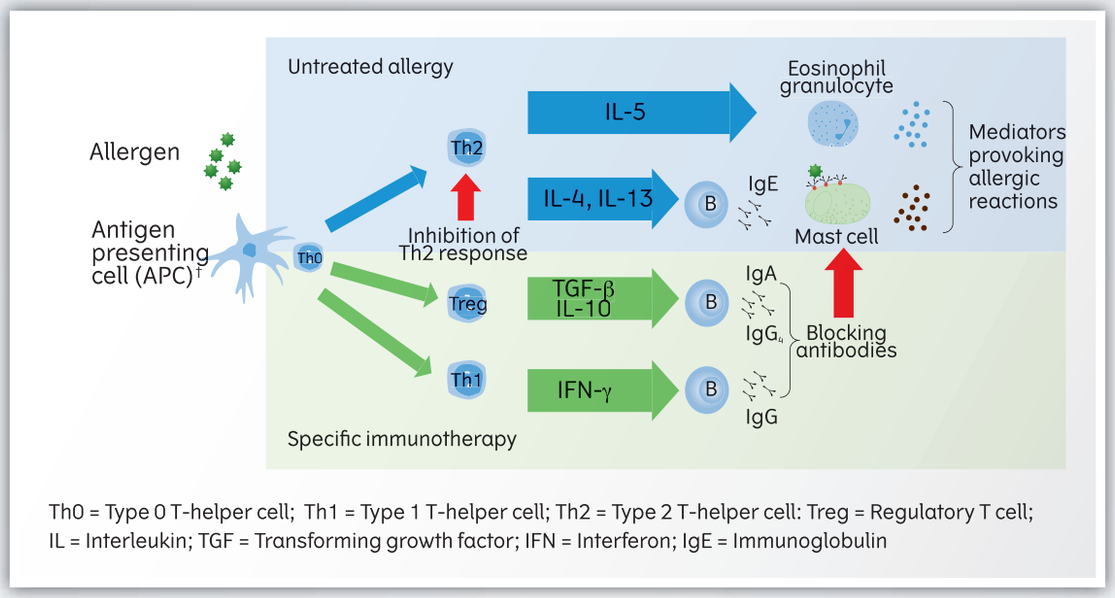
Products for HDM AIT are manufactured from aqueous extracts of raw materials produced by growing the most prevalent mite species, *D. pteronyssinus* and *D. farinae*, in pure cultures. Traditionally, raw materials have comprised either whole mite culture or purified fractions, such as faecal particles or mite bodies. Different raw materials and production processes are used for production of HDM allergen products, and products from different manufacturers can differ in composition and clinical performance[18, 19]. As noted in a recent international consensus statement, the efficacy and safety of AIT is dependent on extract quality[15].

More than 20 HDM allergens have been characterised and recognised by the I.U.I.S. Allergen Nomenclature Sub-committee (www.allergen.org); however, group 1 (Der f 1, Der p 1) and group 2 (Der f 2, Der p 2) allergens are of particular importance in terms of IgE production and potency[20]. The group 1 allergen is a cysteine protease, a digestive enzyme found in high amounts in faecal particles[21], and the group 2 allergen is a carrier protein found primarily in mite bodies[22].

ACARIZAX™ is formulated as a freeze-dried oral lyophilisate containing aqueous allergen extract in a gelatine matrix. Fractionation of the source material allows precise control of major allergen content (Der f 1, Der f 2, Der p 1 and Der p 2) and high reproducibility of the final product[23]. In the production process, shown in Figure 1.3, HDM species



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 12 10/10/2017 15.20




Th0 = Type 0 T-helper cell; Th1 = Type 1 T-helper cell; Th2 = Type 2 T-helper cell: Treg = Regulatory T cell; IL = Interleukin; TGF = Transforming growth factor; IFN = Interferon; IgE = Immunoglobulin

Figure 1.1. Mechanism of action of allergy immunotherapy

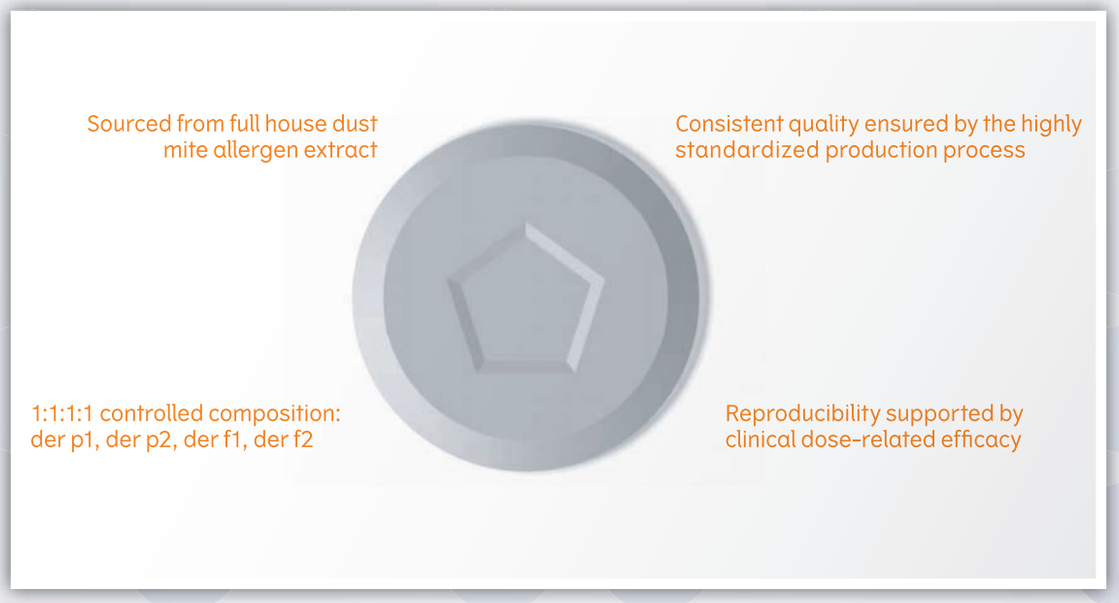



Figure 1.2. ACARIZAX™ – Tablet composition



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 13 10/10/2017 15.20

*D. pteronyssinus* and *D. farinae* are separately cultivated before being freeze-dried and mechanically separated into four different fractions (mite body and mite faecal particle fractions for *D. pteronyssinus* and *D. farinae*), each of which is rich in one of the four important allergens. Each of the four fractions is then processed (by extraction, separation and ultrafiltration) into an intermediate product which is stabilised as frozen droplets. For each HDM species, one drug substance is produced by mixing frozen droplets from mite bodies and faecal particles in a 1:1 ratio. The two drug substances based on *D. farinae* and *D. pteronyssinus* are then mixed in a 1:1 ratio, based on a standardised potency measure calculated as a combination of IgE-binding potency and assays for group 1 and 2 major allergens. Gelatine and mannitol are added as excipients to provide structure and form the tablet, which is dispensed into blister pockets, freeze-dried and sealed. Routine batch quality control throughout the process includes assessment of protein content, antigen profile, allergen profile and IgE binding potency content and ensures a high quality product with standardized allergen content.

## 1.5. Pharmacodynamics

ACARIZAX™ has been shown to induce a dose- and time dependent immunological response including increase in specific IgG4 antibodies that may compete with IgE in the binding of HDM allergens[24-27]. In clinical trials, an initial increase in HDM specific IgG4 was observed after 4 weeks of treatment, which continued with further treatment with ACARIZAX™ (Figure 1.4)[24]. For HDM-specific IgE, there was an initial increase at the first assessment after 4 weeks. This increase then appeared to reach a plateau followed by a decrease over time (Figure 1.5)[24]. These response patterns are in accordance with data for an equivalent approved grass SLIT-tablet (GRASTEK) with the same formulation as ACARIZAX™, for which a disease-modifying post-treatment effect has been demonstrated[28]. While the clinical implications of these immunological changes have not been fully established, they demonstrate that ACARIZAX™ has an immunomodulatory effect.

## 1.6. Pharmacokinetics

The active molecules of the allergens in ACARIZAX™ are primarily polypeptides and proteins. In sublingual administration, passive absorption through the oral mucosa does not occur. Studies suggest that the allergen is taken up through the oral mucosa by dendritic cells, with allergen not absorbed being hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract. There is no evidence to suggest that the allergens present in ACARIZAX™ are absorbed into the vascular system after sublingual administration to any significant extent. Consequently, no pharmacokinetic assessments have been conducted.

## 1.7. Toxicology

*In vitro* and *in vivo* studies have indicated that the HDM allergen extract has no genotoxic potential in humans. Studies in mice reported no reproductive toxicity. However, there are no clinical data on the use of ACARIZAX™ in pregnant or lactating women.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 14 10/10/2017 15.20

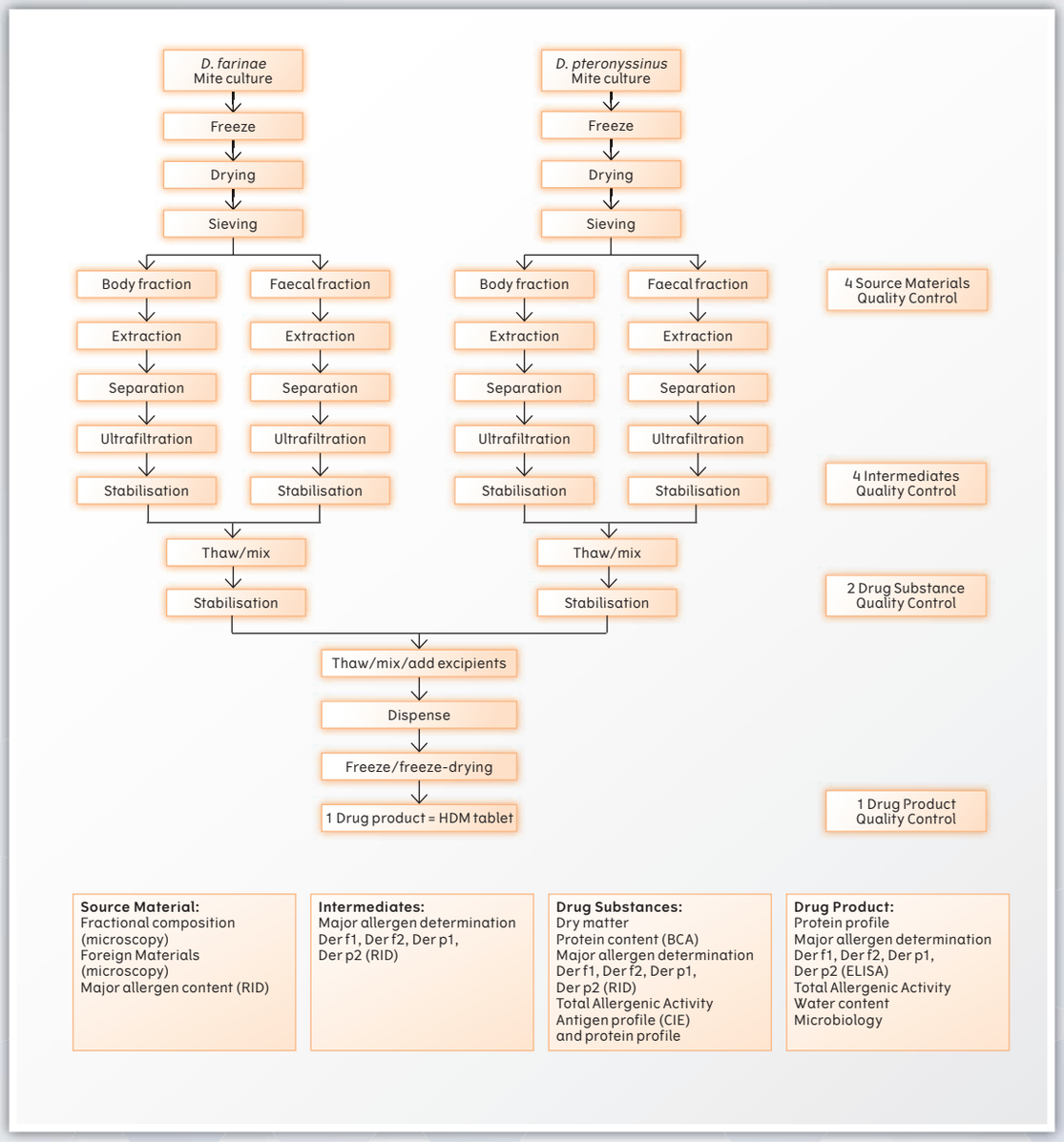



Figure 1.3. Production process for ACARIZAX™. Quality control processes are indicated below in the boxes[23]



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 15 10/10/2017 15.20

## 1.8. Choice of dose

Doses from 1 to 32 SQ-HDM were assessed in three phase I trials in patients with HDM-induced AA with or without rhinoconjunctivitis[29, 30]. Treatment-related adverse events, primarily local allergic reactions, were dose-dependent, with their occurrence considerably higher with 16 SQ-HDM compared to lower doses and the 32 SQ-HDM dose not being tolerated. Thus, 12 SQ-HDM (subsequently referred to as ACARIZAX™ in Canada) was chosen as the maximum dose with an acceptable tolerability profile. A phase 2 trial in a HDM environmental exposure chamber assessing both 6 and 12 SQ-HDM doses clearly showed that the 12 SQ-HDM dose provided the best risk-benefit profile[31]. This was further confirmed in the phase 3 in-field trials performed in Europe using both 6 and 12 SQ-HDM[26,27].

## Key conclusions

- HDM allergy is strongly implicated in the pathogenesis of respiratory allergic disease.
- Many patients are unable to achieve adequate symptom control through allergen avoidance and pharmacotherapy.
- AIT is the only treatment option that addresses the underlying etiology of allergic disease by modifying the immunological response to the causative allergen.
- AIT provides clinically meaningful symptom relief, reduces the need for medication and improves quality of life for patients.
- Compared to SCIT, SLIT is associated with fewer and less severe adverse events and offers improved convenience, including at-home administration.
- ACARIZAX™ is a fast-dissolving freeze-dried tablet with a 1:1 mixture of allergen extracts from the HDM species *D. pteronyssinus* and *D. farinae*. Thus, the tablet contains all known *D. pteronyssinus* and *D. farinae* allergens.
- A highly standardised production process ensures a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 16 10/10/2017 15.20

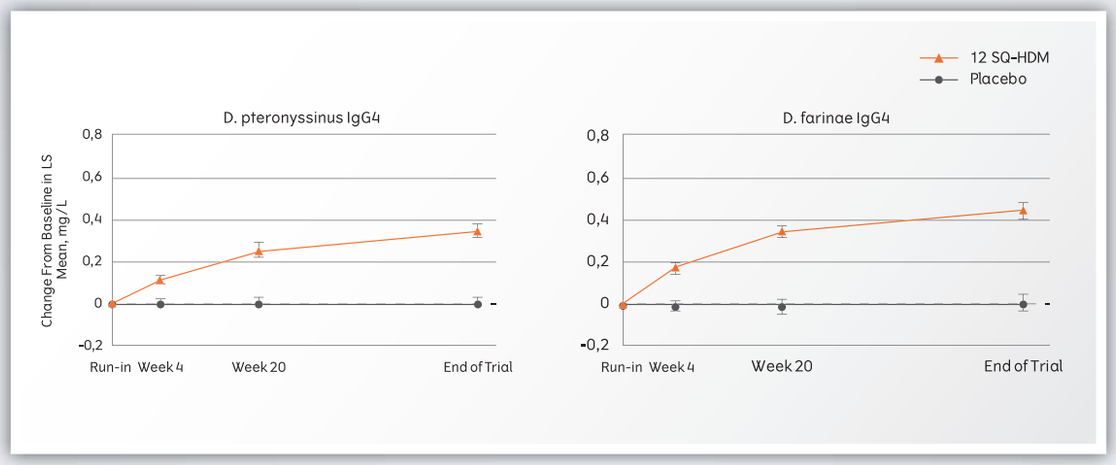



Figure 1.4. Increase in HDM specific IgG4 antibodies with ACARIZAX[24]

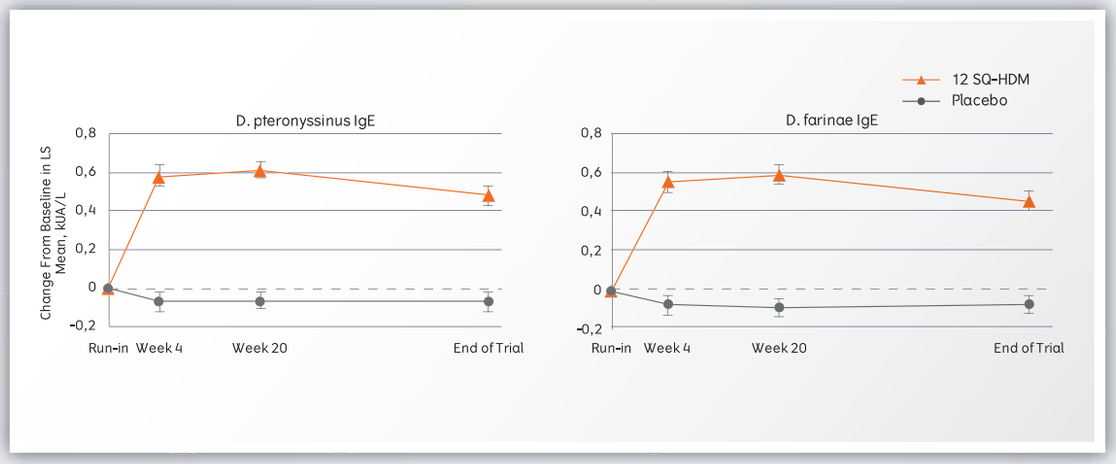



Figure 1.5. Increase in HDM specific IgE antibodies with ACARIZAX[24]



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 17 10/10/2017 15.20

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 18 10/10/2017 15.20

# 2. CLINICAL EFFICACY AND SAFETY

## 2.1. Overview of clinical trials supporting the ACARIZAX™ indication

The patient population in the ACARIZAX™ clinical program was well defined with clear inclusion and exclusion criteria (see table 2.1). Outcomes evaluated were standardized and clinically relevant, and were based on guidelines and scientific advice from regulatory agencies.

The phase II environmental exposure chamber trial (P003)evaluated both 6 and 12 SQ-HDM doses showing that the 12 SQ-HDM dose (i.e. ACARIZAX™) elicited a higher and faster immunological response than the 6 SQ-HDM dose, as well as a higher magnitude and faster onset of efficacy when assessed in a controlled HDM exposure setting [31]. Table 2.2 shows the Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS [including also the total ocular symptom score]) over the course of this 24 weeks trial. No safety observations gave rise to concern during this trial.

The phase III studies P001 and MT-06 assessed the therapeutic value of ACARIZAX™ in the treatment of patients with HDM AR with and without conjunctivitis and with and without asthma[24, 26]. In addition a third phase III study performed in Europe, MT-04, investigated both 6 and 12 SQ-HDM doses in a patient population with HDM AR and stable but not well controlled AA by daily use of 400-1200 mcg ICS[27]. It is important to note that HDM AA is not an approved indication for ACARIZAX™ in Canada as it is in Europe. However, tolerability data from the MT-04 trial was included in the Canadian label to support overall safety.

The P003, MT-06 and MT-04 studies evaluated both the 6 and 12 SQ-HDM dose, and results from these studies support the 12 SQ-HDM dose, marketed as ACARIZAX™ in Canada and Europe (ODACTRA in the United States), as the preferred dose.

**Over 3500 patients were enrolled**
in the Phase I-III trials in North America and Europe evaluating efficacy and safety of ACARIZAX™



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 20 10/10/2017 15.20

| Trial | Design | Patients | Primary endpoint | Secondary endpoints |
|---|---|---|---|---|
| Allergic rhinitis | | | | |
| Phase II Environmental Exposure Chamber trial (P003/ P07627) [31] | 24-week SC, R, DB, PC trial with 6 SQ-HDM and ACARIZAX™ | Age ≥18 years, Moderate-to-severe persistent HDM AR with or without AA (AR symptom score ≥6 within first 2 hours of screening allergen exposure challenge; positive skin prick test; serum IgE ≥0.7 kU/L; and $FEV_1$ ≥70% of predicted value | AR symptom score during hours 2–6 of environmental chamber challenge at week 24 | AR symptom score at weeks 8 and 16; conjunctivitis symptom score; total symptom score; asthma symptom score (exploratory); and RQLQ(S) |
| North America Phase III trial (P001/ P05607) [24] | 1-year MC, R, DB, PC trial with ACARIZAX™. All patients had access to standardised pharmacotherapy for AR and/or conjunctivitis. | Age ≥12 years, Moderate-to-severe persistent HDM AR with or without AA or conjunctivitis (AR symptom score ≥6 or ≥5 with one severe symptom on 5 of 7 days during run-in period); positive skin prick test; serum IgE ≥0.7 kU/L; and $FEV_1$ ≥80% of predicted value | Total combined rhinitis score during the last 8 weeks of treatment | AR symptom score; AR medication score; rhinoconjunctivitis symptom score; rhinoconjunctivitis medication score; combined rhinoconjunctivitis score; and AR/C symptoms assessed by VAS |
| European Phase III trial (MT-06) [26] | 1-year MC, R, DB, PC trial with 6 SQ-HDM and ACARIZAX™. All patients received standardised pharmacotherapy for AR and/or conjunctivitis. | Age 18-65 years, Moderate-to-severe persistent HDM AR with or without AA or conjunctivitis (AR symptom score ≥6 or ≥5 with one severe symptom during ≥8 days of baseline period and use of symptomatic medication for ≥8 days of baseline period); positive skin prick test; serum IgE ≥0.7 kU/L; and $FEV_1$ ≥70% of predicted value | Total combined rhinitis score during the last 8 weeks of treatment | AR symptom score; AR medication score; rhinoconjunctivitis symptom score; rhinoconjunctivitis medication score; combined rhinoconjunctivitis score; and RQLQ(S) |

AA=allergic asthma; AR=allergic rhinitis; AR/C=allergic rhinoconjuntivitis; DB = doubleblind; $FEV_1$ = forced expiratory volume in the first second; JRQLQ = Japanese Rhinoconjunctivitis Quality of Life Questionnaire; MC = multicentre; PC = placebo-controlled; R = randomized; RQLQ(S)= Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities; SC = single-centre; SLIT = sublingual immunotherapy, VAS= visual analog scale.

Table 2.1 Clinical development of ACARIZAX™ in allergic rhinitis



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 21 10/10/2017 15.20

## 2.2. Summary of efficacy in the North America Phase III trial (P001)

- The objective of this trial was to evaluate both the safety and efficacy of ACARIZAX™ in adults and adolescents with HDM-induced allergic rhinitis/conjunctivitis in North America.
- This study was a randomized, double-blind trial comparing the 12 SQ-HDM dose to placebo for up to 52 weeks. The study was conducted at 182 sites in the United States and Canada.
- A total of 1482 subjects were randomized to 12 SQ HDM SLIT-tablets (n = 741) or placebo (n = 741); median treatment duration was 271 days.
- For the primary outcome, total combined rhinitis score (TCRS) subjects treated with ACARIZAX™ had a significantly lower average TCRS during the efficacy assessment period compared to placebo (lower scores indicating fewer/less severe symptoms and/or less use of medication). Based on the primary analysis, patients treated with ACARIZAX™ had significant relief of nasal symptoms and reduction in standard allergy medication use as measured by a decrease in TCRS of 17.2% (95%CI, 9.7% to 25%) compared to placebo-treated subjects. This treatment difference was greater than the FDA predefined criteria of 15%. Results were similar in mono- and poly-sensitized subjects and in subjects with or without mild asthma.
- Significant differences were also shown between ACARIZAX™ and placebo treated subjects in total nasal symptom score (TNSS; $P < 0.001$), total conjunctivitis symptom score ($P < 0.001$), and improvement in least-square mean asthma disease symptom score ($P = 0.002$ for between treatment difference).

## 2.3. Summary of efficacy in the European Phase III trial (MT-06)

- This study was a randomized, double-blind trial comparing the 6 and 12 SQ-HDM dose to placebo for up to 52 weeks. The study was conducted at 100 sites in 12 European countries.
- The primary objective of this trial was to confirm the efficacy of 6 SQ-HDM (n = 336) and 12 SQ HDM (n = 318) compared to placebo (n = 338) in subjects with moderate-to-severe HDM AR despite pharmacotherapy, using the TCRS. The primary efficacy analysis was based on a multiple imputations method. This method is more conservative than the use of observed data as the analysis treats all subjects who discontinued the trial before the efficacy evaluation period as placebo subjects.
- Subjects randomized (full analysis set with multiple imputations [FAS-MI]) to 6 and 12 SQ HDM SLIT-tablets had a statistically significant decrease in the TCRS compared to those randomized to placebo of 1.07 and 1.09 respectively. The predefined clinical relevance criterion was defined as an absolute difference of 1 or more in TCRS meaning that the differences between the placebo and 6 SQ HDM and 12 SQ HDM SLIT-tablet groups were not only statistically significant but also clinically relevant.
- Efficacy was assessed at pre-defined intervals throughout the treatment period at weeks 4, 14, 24 and 34 in addition to during the last 8 weeks of treatment. Onset of effect was demonstrated at 14 weeks with a treatment effect that was maintained throughout the year with continued treatment (Figure 2.3).



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 22 10/10/2017 15.20

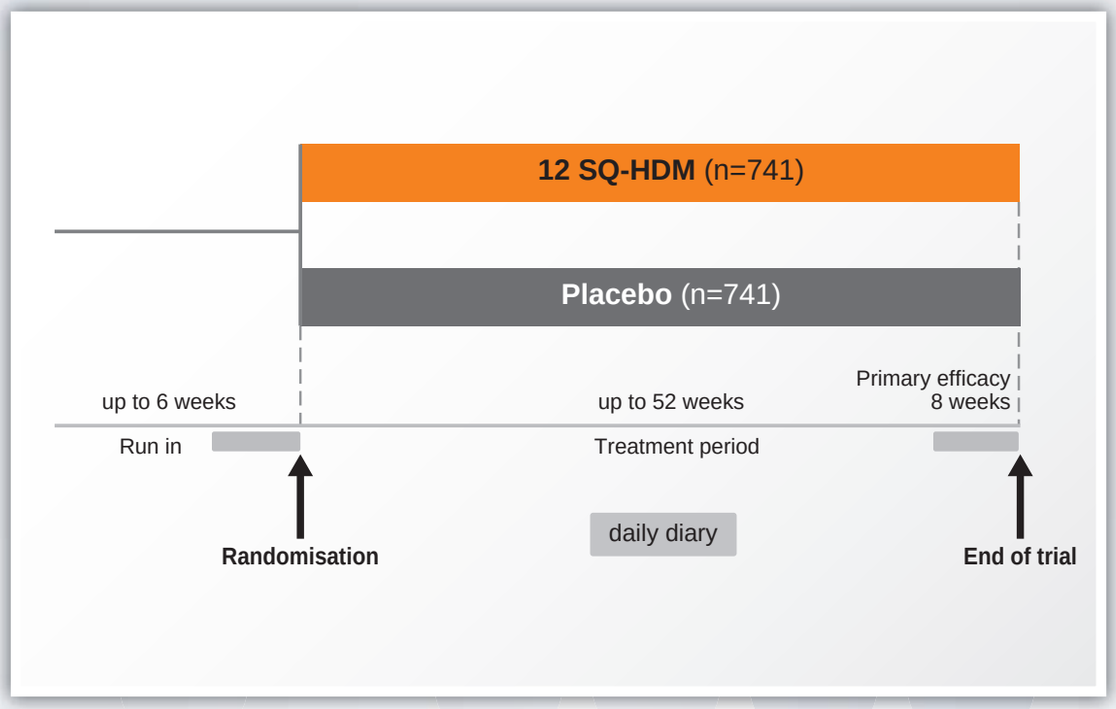



Figure 2.1. Trial design (P001/P05607) adapted from 24

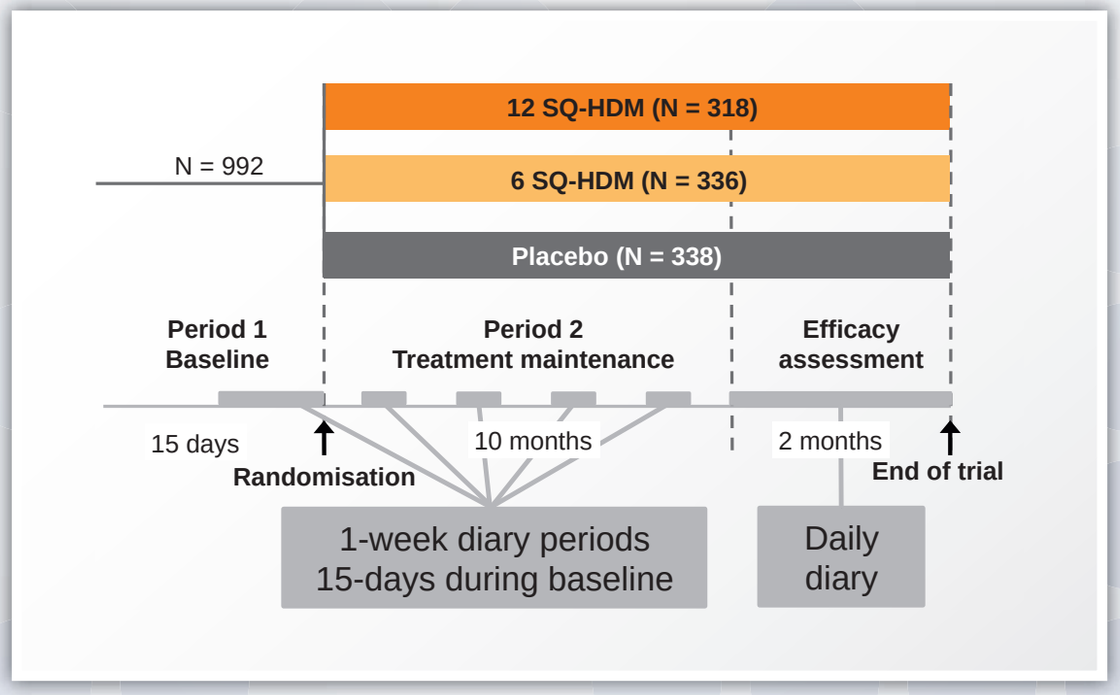



Figure 2.2. Trial design (MT-06) Adapted from 26



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 23 10/10/2017 15.20

- Statistically significant differences were also reported for several key secondary endpoints including AR symptom score, AR medication score, overall RQLQ score, and combined rhinoconjunctivitis score (secondary endpoints were assessed using FAS).
- Results from a post-hoc analysis aiming to illustrate the clinical relevance of the MT-06 primary outcome found that the estimated probability of experiencing a rhinitis exacerbation based on the outcomes during the 8-week assessment period was reduced from 11% in the placebo groups to 5% in the 12 SQ HDM SLIT-tablet group. A rhinitis exacerbation was defined as a day with a return to the level of AR symptoms required for study enrollment (i.e. AR symptom score ≥ 6 (or ≥ 5 if 1 symptom was severe).
  Additionally, and to reflect the clinical relevance in another way, the estimated probability for experiencing a mild day was estimated, showing an increase from 16% in the placebo group to 34% after treatment with ACARIZAX™ (P = 0.0009 vs placebo). A mild day was defined as having no AR symptoms >1 (i.e. symptom clearly present but minimal awareness and easily tolerated). These results are illustrated in Figure 2.4.

  Extrapolating these results to a full year, assuming similar conditions throughout the year as during the 8-weeks assessment period, this corresponds to 40 AR exacerbation days in the placebo group being reduced to 19 days with active treatment and the number of mild days being increased from 2 months in the placebo group to 4 months with active treatment. Both the differences in exacerbation days and mild days reached statistically significant differences[32].

## 2.4. Quality of life outcomes

The Rhinitis Quality of Life Questionnaire (RQLQ) was included in all 3 trials (P001, MT-06 and P003). The results consistently showed a statistically significantly higher improvement for patients treated with ACARIZAX™ across the 3 trials as compared to placebo. The significant improvement was seen both in the overall score as well as individual domains such as sleep, practical problems, and nasal symptoms, leading to an increase in the quality of life of AR patients[24, 26, 31].

## 2.5. Safety summary

Apart from three Phase I studies[29, 30], safety was assessed in 4 double-blind, placebo-controlled, randomized clinical studies, enrolling patients with HDM AR with or without conjunctivitis and with or without concomitant asthma, aged 18 through 65 years of age[24, 26, 27, 31]. Across the 4 clinical studies, 1,279 subjects received at least one dose of the 12 SQ HDM SLIT-tablet, of whom 1,104 (86%) completed at least 4 months of therapy. In these studies, 50% of subjects treated with the 12 SQ-HDM dose had mild to moderate asthma and 71% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, molds, and animal dander. The study population was 88% White, 6% African American, 4% Asian, and 55% female.

The most common adverse reactions reported in ≥10% of subjects treated with the 12 SQ-HDM SLIT-tablet were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore in the mouth, and taste alteration/food tastes different.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 24 10/10/2017 15.20

## Table 2.2: Summary of effect outcomes during HDM-allergen challenge (Trial P003) ACARIZAX™ Product Monograph

| Endpoint* | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™- Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value | Estimate | (95% CI) |
| **Primary endpoint** | | | | | | |
| **TNSS – Week 24** | (36) 3.83 | (34) 7.45 | -3.62 | <0.001 | -48.6% | (-60.2%, -35.3%) |
| **Secondary endpoints** | | | | | | |
| **TNSS – Week 8** | (40) 5.34 | (39) 6.71 | -1.37 | | -20.4% | (-33.3%, -6.8%) |
| **TNSS – Week 16** | (39) 4.82 | (38) 6.90 | -2.08 | | -30.1% | (-42.3%, -16.8%) |
| **TSS – Week 24** | (36) 4.43 | (34) 9.27 | -4.84 | | -52.2% | (-65.0%, -37.0%) |

TNSS=Total Nasal Symptom Score, endpoint score range: 0-12.; TSS=Total Symptom Score (TNSS + total ocular symptom score), endpoint score range 0-18; CI=Confidence Interval

* Parametric analysis using analysis of covariance for all endpoints: analysis via ANCOVA with treatment and baseline endpoint score as fixed effects. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the screening.

† Number of subjects in analyses. Subjects who discontinued the trial prior to the given time point were not included in the analyses.

‡ For all endpoints, the estimated group least squares mean is reported. Treatment difference was the difference between least squares means.

§ Difference relative to placebo was calculated based on the estimated group least squares means as: (ACARIZAX™- placebo)/placebo x 100%.

## Table 2.3: Summary of effect outcomes from North America Phase III trial (P001) ACARIZAX™ Product Monograph

| Endpoint | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™ - Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value | Estimate | (95% CI) |
| **Primary Endpoint** | | | | | | |
| **TCRS*** | (566) 4.10 | (620) 4.95 | -0.80 | <0.001 | -17.2% | (-25.0%, -9.7%) |
| **TCRS+** | (566) 3.16 | (620) 3.87 | -0.71 | <0.001 | -18.4% | (-31.0%, -6.5%) |
| **Secondary Endpoints** | | | | | | |
| **Rhinitis DSS*** | (566) 3.55 | (620) 4.20 | -0.60 | <0.001 | -15.5% | (-24.4%, -7.3%) |
| **Rhinitis DMS#** | (566) 0.65 | (620) 0.79 | -0.15 | 0.154¶ | -18.4% | (-41%, 4.3%) |
| **TCS*** | (566) 5.50 | (620) 6.60 | -1.10 | <0.001¤ | -16.7% | (-24.6%, -4.0%) |

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints using the Wilcoxon Rank Sum test.

\+ Longitudinal Data Analysis (LDA) model for TCRS.

\# Parametric analysis using a zero-inflated log-normal model for Rhinitis DMS endpoint. 337 (59.5%) and 336 (54.2%) subjects in the ACARIZAX™ and placebo treatment groups, respectively, did not utilize rescue medications.

† Number of subjects in analyses; subjects not evaluable for diary-based endpoints were not included in the analyses (ACARIZAX™ 23.5%; placebo 16.3%).

‡ For the non-parametric analyses, the estimated group medians are reported and treatment difference is the Hodges-Lehmann estimate.. For the LDA and zero-inflated log-normal models, the estimated group means are reported and treatment difference is the difference in estimated group means.

§ Difference relative to placebo was calculated based on the estimated group medians (for non-parametric analyses) or means (for LDA and zero-inflated log-normal model) as: (ACARIZAX™ – placebo)/placebo x 100%.

¶ Not statistically significant.

¤ This result cannot be considered confirmatory due to the pre-specified multiplicity control strategy, which involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 25 10/10/2017 15.20

The percentages of subjects in these studies who discontinued treatment because of an adverse reaction while exposed to 12 SQ HDM SLIT-tablets was 8.1% or placebo 3.0%. The most common adverse reactions (≥1.0%) that led to study discontinuation in subjects who received 12 SQ HDM SLIT-tablets were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%).

Serious adverse events were reported, 16 of 1,279 (1.3%) subjects receiving 12 SQ HDM SLIT-tablets and 23 of 1,277 (1.8%) subjects receiving placebo. No deaths were reported. Epinephrine use was reported in 5 of 1,279 (0.4%) subjects receiving 12 SQ HDM SLIT-tablets and 3 of 1,277 (0.2%) subjects receiving placebo. Of these subjects, one recipient reported a systemic allergic reaction and used epinephrine on the day of treatment initiation compared to 2 placebo recipients who reported anaphylaxis and used epinephrine 6 and 25 days after treatment initiation.

## 2.6. Conclusions

ACARIZAX™ represents a new generation of allergy immunotherapy approved for the treatment of adult patients with HDM-induced AR, with or without conjunctivitis. The efficacy of ACARIZAX™ was demonstrated in randomized controlled trials meeting strict regulatory requirements.

Results from these studies show that ACARIZAX™:

- improve disease control by providing symptom relief and decreased need for other anti-allergic medications
- has an early onset of effect that is sustained year-round
- has a favorable safety profile, and is well tolerated with the majority of treatment-related adverse events being local, mild or moderate reactions, similar to those seen with GRASTEK and RAGWITEK

Results from these efficacy studies suggest that patients suffering from HDM AR, with or without conjunctivitis and with or without asthma, also when inadequately controlled by pharmaco-therapy would benefit from ACARIZAX™ therapy. Data support the safe at-home administration of ACARIZAX™ in this patient population as long as appropriate precautions are adhered to (and first-dose administered under medical supervision.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 26 10/10/2017 15.20

Table 2.4: Summary of effect outcomes from European Phase III trial (MT-06) ACARIZAX™ Product Monograph

| Endpoint | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™ - Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value¤ | Estimate | (95% CI) |
| **Primary Endpoint** | | | | | | |
| **TCRS*** | (318) 5.71 | (338) 6.81 | -1.09 | 0.004 | -16.1% | (-25.8%, -5.7%) |
| **TCRS+** | (284) 4.92 | (298) 6.23 | -1.31 | <0.001 | -21.0% | (-31.2%, -9.4%) |
| **Secondary Endpoints** | | | | | | |
| **Rhinitis DSS*** | (318) 2.84 | (338) 3.31 | -0.47 | 0.01 | -14.1% | (-23.8%, -3.9%) |
| **Rhinitis DMS*#** | (318) 2.32 | (338) 2.86 | -0.54 | 0.045 | -18.9% | (-34.7%, -1.3%) |
| **TCS*¶** | (241) 7.91 | (257) 9.12 | -1.21 | 0.029 | -13.2% | (-23.7%, -1.5%) |

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Linear mixed effect (LME) model. Multiple imputation was performed for TCRS, rhinitis DSS, and rhinitis DMS.

\+ Longitudinal Data Analysis (LDA) model for TCRS analysed post hoc.

† Number of subjects in analyses; all randomized subjects were included in the LME analyses of TCRS, rhinitis DSS, and rhinitis DMS. All randomized subjects evaluable for diary-based endpoints were included in the LDA model for TCRS and in the LME analysis of TCS.

‡ Estimated group means are reported. Treatment difference is difference in estimated group means.

¤ The pre-specified multiplicity control strategy involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).

§ Difference relative to placebo was calculated based on the estimated group means as: (ACARIZAX™ – placebo)/placebo x 100%.

\# 45 (15.8%) and 29 (9.7%) subjects in the ACARIZAX™ and placebo treatment groups, respectively, did not utilize rescue medications.

¶ Subjects from Serbia and Croatia (48 [15.1%] and 46 [13.6%] subjects in the ACARIZAX™ and placebo treatment groups, respectively) were not included in the analysis of TCS because the preferred formulations of antihistamine eye drops were not available in these countries at the time the trial was conducted.

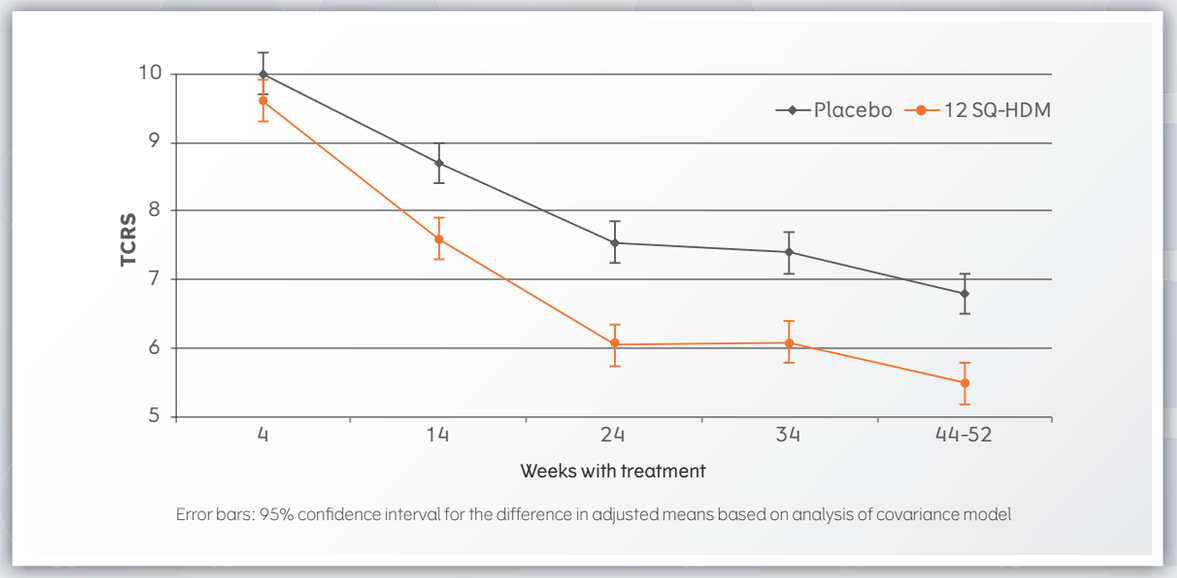



Figure 2.3: Effect over time in the MT-06 trial ACARIZAX Product Monograph



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 27 10/10/2017 15.20

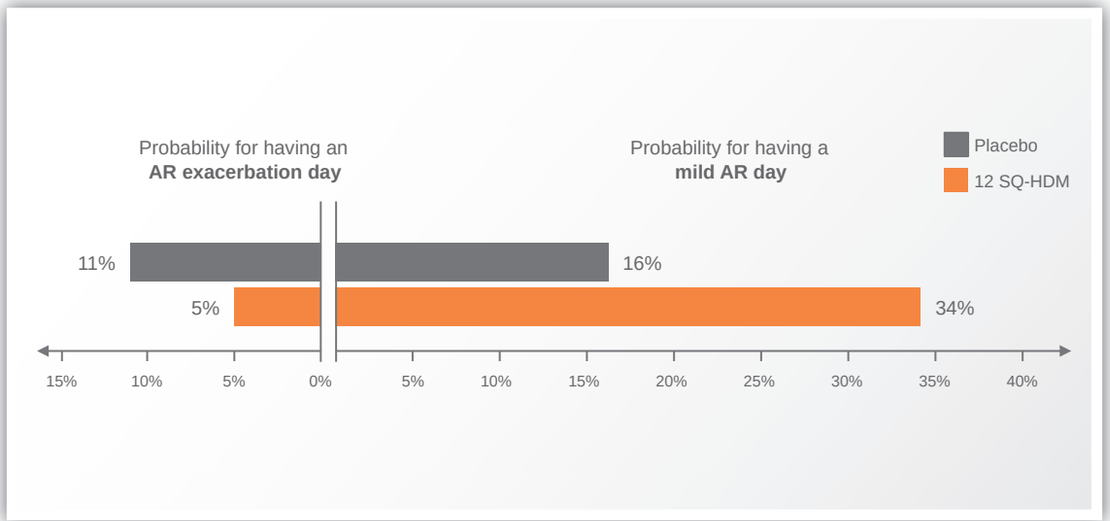



Figure 2.4. Post-hoc analysis on clinical relevance showing decreased probability for having AR exacerbation days and increased probability for having mild days following treatment with ACARIZAX™ (MT-06) [32]



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 28 10/10/2017 15.20

## 3. ACARIZAX™ PRODUCT MONOGRAPH

# 3. ACARIZAX™ PRODUCT MONOGRAPH

Standardized Allergen Extract, House Dust Mite (*D. farinae* and *D. pteronyssinus*)

# PART I:HEALTH PROFESSIONAL INFORMATION

## 3.1 SUMMARY OF PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Oral<br><br>Sublingual | Sublingual tablet /<br><br>12 SQ-HDM* | For a complete listing see Dosage Forms, Composition and Packaging section. |

* SQ-HDM is the dose unit for ACARIZAX™. SQ is a method for standardization on biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

## 3.2 DESCRIPTION

ACARIZAX™ (Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*) Sublingual Tablet) is an allergy immunotherapy tablet for the treatment of the signs and symptoms of house dust mite (HDM) allergy. It is formulated as an orally disintegrating tablet designed to rapidly dissolve within seconds under the tongue. The active substance is a standardized allergen extract derived from house dust mites. Each sublingual tablet has a strength of 12 SQ-HDM* [6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*]. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

## 3.3 INDICATIONS AND CLINICAL USE

ACARIZAX™ (Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*) Sublingual Tablet) is indicated as allergy immunotherapy for the treatment of moderate to severe house dust mite-induced allergic rhinitis, with or without conjunctivitis, in adults 18 to 65 years of age confirmed by a positive skin prick test and/or *in vitro* testing for *D. farinae* or *D. pteronyssinus* IgE antibodies.

Treatment with ACARIZAX™ should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.

### *Geriatrics (≥ 65 years of age):*

The safety and efficacy of immunotherapy with ACARIZAX™ in patients over 64 years of age have not been well-established (see **WARNINGS AND PRECAUTIONS/ Geriatrics**).

### *Pediatrics (<18 years of age):*

The safety and efficacy of immunotherapy with ACARIZAX™ for house dust mite-induced allergic rhinitis, with or without conjunctivitis, have not been well-established in patients under 18 years of age and not studied in patients under 12 years of age (see **WARNINGS AND PRECAUTIONS/ Pediatrics**).



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 30 10/10/2017 15.20

## 3.4 CONTRAINDICATIONS

ACARIZAX™ is contraindicated in patients who:

- are hypersensitive to any of the excipients in the formulation or components of the container. For a complete listing, see **Dosage Forms, Composition and Packaging.**
- have previously had a severe systemic allergic reaction to house dust mite immunotherapy.
- have unstable, severe asthma (FEV1 <70% of predicted value after adequate pharmacologic treatment in adults).
- are taking beta-blockers, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction.
- have active inflammatory conditions in the oral cavity, e.g., oral lichen planus with ulcerations, severe oral candidiasis, dental extraction (see **WARNINGS AND PRECAUTIONS/ Patients with Oral Conditions**).
- have a history of eosinophilic esophagitis.

## 3.5 WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

Treatment with ACARIZAX™ should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.

Systemic allergic reactions, including severe local allergic reactions, have been observed in patients receiving ACARIZAX™, and may require emergency administration of epinephrine, antihistamines, bronchodilators or systemic corticosteroids (see WARNINGS AND PRECAUTION/ Immune)

The first tablet of ACARIZAX™ must be taken at the physician's office under medical supervision and the patient must be monitored for 30 minutes.

### *General*

No data are available regarding the effect of vaccination in patients with ACARIZAX™ treatment. Vaccination may be given without interrupting treatment with ACARIZAX™ after medical evaluation of the patient's general condition.

Patients previously administered epinephrine used to treat a severe systemic allergic reaction, including anaphylactic shock, were not studied in clinical trials with ACARIZAX™. Effects of epinephrine may be potentiated in patients treated with tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

ACARIZAX™ should not be initiated in pregnant women.





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 31 10/10/2017 15.20

ACARIZAX™ should be used with caution in patients who have had severe systemic reactions to any house dust mite subcutaneous immunotherapy or severe local or systemic reactions to any house dust mite immunotherapy taken by mouth.

As with other immunotherapy treatments, patients treated with ACARIZAX™ may have local swelling which is severe or which may increase in severity over time. Because of the risk of upper airway compromise, treatment with ACARIZAX™ should be discontinued in these patients.

### *Carcinogenesis and Mutagenesis*

No carcinogenicity studies were conducted in animals with *D. farinae* and *D. pteronyssinus* extracts. Based on *in vitro* assays for mutagenicity and an in vivo assay for DNA damage, no evidence of genotoxic risk was associated with *D. farinae* and *D. pteronyssinus* extracts.

### *Gastrointestinal*

#### Eosinophilic esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. Discontinue ACARIZAX™ and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

### *Immune*

#### Severe Allergic Reactions

ACARIZAX™ can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, ACARIZAX™ can cause severe local reactions, including laryngopharyngeal swelling which may compromise breathing and be life-threatening. Signs and symptoms that may be associated with a systemic allergic reaction include syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, wheezing, bronchospasm, chest discomfort, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing and urticaria.

Systemic allergic reactions, including anaphylactic reactions and severe local allergic reactions, have occurred in clinical trial patients treated with ACARIZAX™ (see **ADVERSE REACTIONS**). The majority of these reactions occurred within minutes after receiving the first dose, but were also reported to occur after administration of subsequent doses. Treatment of severe allergic reactions may require the administration of epinephrine, antihistamines, inhaled bronchodilators and/or systemic corticosteroids.

The first dose of ACARIZAX™ should only be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction. Patients should be observed for 30 minutes after first time administration of ACARIZAX™. Immediately discontinue ACARIZAX™ in any patient developing clinical evidence of a severe systemic or severe local allergic reaction. In such cases, consider discontinuing treatment with ACARIZAX™ permanently. Patients should be informed and educated about the symptoms of a severe allergic reaction, and instructed to discontinue ACARIZAX™, seek immediate medical care and contact their physician should any of these symptoms occur after taking ACARIZAX™.

Patients who are prescribed epinephrine while receiwe upon use of auto-injectable epinephrine and to stop treatment with ACARIZAX™.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 32 10/10/2017 15.20

### *Patients with Oral Conditions*

In patients with oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush) or oral wounds, such as those following oral surgery, tooth loss or dental extraction, treatment with ACARIZAX™ should be interrupted to allow healing of the oral cavity.

### *Respiratory*

#### Patients with Asthma

Immunotherapy with ACARIZAX™ is contraindicated in patients who have unstable or severe asthma. During treatment with ACARIZAX™, instruct patients to stop treatment with ACARIZAX™ and contact their physician immediately if they have difficulty breathing or if asthma becomes inadequately controlled (see CONTRAINDICATIONS).

Initiation of treatment with ACARIZAX™ should be postponed in patients with uncontrolled asthma who are experiencing an acute respiratory tract infection until the infection has resolved.

### Special Populations

**Pregnant Women:** Immunotherapy with ACARIZAX™ should not be initiated during pregnancy because severe systemic reactions may be detrimental to the mother or fetus. No clinical data are available for the use of ACARIZAX™ during pregnancy. For animal studies refer to PART II TOXICOLOGY. Because ACARIZAX™ is not expected to be absorbed systemically following sublingual administration, maternal use is not expected to result in fetal exposure to the drug.

**Nursing Women:** No clinical data are available for the use of ACARIZAX™ during lactation. It is not known whether ACARIZAX™ is excreted in human milk.

**Pediatrics:** The safety and efficacy of immunotherapy with ACARIZAX™ for house dust mite-induced allergic rhinitis, with or without conjunctivitis, have not been well-established in patients under 18 years of age and not studied in patients under 12 years of age.

**Geriatrics (≥ 65 years of age):** The safety and efficacy of immunotherapy with ACARIZAX™ in patients over 64 years of age have not been well-established.

## 3.6 ADVERSE REACTIONS

### *Adverse Drug Reaction Overview*

Use of ACARIZAX™ has been associated with systemic allergic reactions (see **WARNINGS AND PRECAUTIONS/ Immune and "Serious Warnings and Precautions"** box).

In 4 clinical trials (P001, MT-06, MT-04, P003) with ACARIZAX™, treatment-related systemic allergic reactions were reported in 0.1% (1/1383) of adolescent and adult patients treated with ACARIZAX™ and no adolescent or adult patients treated with placebo. Signs and symptoms associated with a systemic allergic reaction may include sneezing, rhinorrhea, light-headedness, pruritus of the mouth, tongue and throat, edema of the lips and throat, throat irritation, dysphagia, dyspnea and chest tightness.





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 33 10/10/2017 15.20

The percentage of adolescent and adult patients who discontinued from the clinical trials because of a treatment-related adverse reaction while exposed to ACARIZAX™ or placebo was 6.6% (91/1383) and 0.8% (11/1397), respectively. The most common treatment-related adverse reactions that led to trial discontinuation in adolescent and adult patients who were exposed to ACARIZAX™ were throat irritation (23/1383 patients), oral pruritus (17/1383 patients), mouth swelling (15/1383 patients), ear pruritus (15/1383 patients), and swollen tongue (14/1383 patients).

In clinical trials with ACARIZAX™, epinephrine was administered 4 times in ACARIZAX™ treated adolescent and adult patients and 4 times in placebo treated adolescent and adult patients. In ACARIZAX™ treated patients, all four of the administrations were for treatment-related allergic events.

### *Clinical Trial Adverse Drug Reactions*

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### *Clinical Trial Experience*

The safety data described below are based on 4 clinical trials (P001, MT-06, MT-04, P003). In total, these trials randomized 95 adolescent patients 12 through 17 years of age and 1288 adult patients 18 years of age and older with house dust mite-induced allergic rhinitis and with or without asthma, including 95 adolescent patients and 1286 adult patients who were exposed to at least one dose of ACARIZAX™ (12 SQ-HDM). Of the patients treated with ACARIZAX™, approximately 50% had asthma and 71% were sensitized to other allergens in addition to house dust mites. The patient population was approximately 86% White and 46% male. The mean age of patients was about 34 years. Patient demographics in placebo treated patients were similar to the active group. (See **PART II: CLINICAL TRIALS/ Trial demographics and trial design** for detailed demographics).

In one trial (P001) that included active solicitation of pre-specified adverse reactions, 740 patients 12 years of age and older received at least one dose of ACARIZAX™. In this trial, the most common treatment-related adverse reactions reported in patients treated with ACARIZAX™ and at least twice that of placebo were: throat irritation (67.1% vs 22.0% placebo), oral pruritus (62.3% vs 14.3%), ear pruritus (50.7% vs 11.3%), lip swelling (17.9% vs 2.2%), swollen tongue (16.1% vs 2.2%), and glossodynia (15.4% vs 3.4%). The timing relative to drug exposure and the intensity of the most treatment-related common adverse reactions was evaluated. Most of these local allergic events were transient and recurrent symptoms generally resolved over time. The median duration when these adverse reactions occurred on the first day of treatment initiation ranged from 30 to 78 minutes. Typically, the adverse reactions began within the first 8 days after treatment initiation with ACARIZAX™. For many patients, these adverse reactions reoccurred with subsequent doses. The days of recurrence ranged from a median of 3 to 12 days. Of these adverse reactions, most were mild to moderate in intensity. The percentage of patients who reported an adverse reaction of severe intensity as determined by the investigator were: throat irritation (0.4% vs 0.0% placebo), oral pruritus (0.4% vs 0.0%), and ear pruritus (0.3% vs 0.0%).



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 34 10/10/2017 15.20

In a pool of the other three clinical trials (MT-06, MT-04, and P003) that did not include active solicitation of pre-specified adverse reactions, 641 patients 17 years of age and older received at least one dose of ACARIZAX™. In these trials, the most common treatment-related adverse reactions reported in patients treated with ACARIZAX™ and at least twice that of placebo were: oral pruritus (19.8% vs 2.4% placebo), throat irritation (15.0% vs 2.4%), mouth edema (8.9% vs 0.2%), and paresthesia oral (5.5% vs 0.3%). Of these adverse reactions, most were mild to moderate in intensity. The percentage of patients who reported an adverse reaction of severe intensity as determined by the investigator were: oral pruritus (0.3% vs 0.0% placebo), throat irritation (0.3% vs 0.0%), and mouth edema (0.3% vs 0.0%).

Solicited and unsolicited treatment-related adverse reactions reported in ≥1% of patients treated with ACARIZAX™ that also occurred more commonly than in placebo-treated patients in either P001 and/or the three pooled trials are shown in Table 1.

In addition to routine safety monitoring for the entire duration of P001, all patients received a report card containing a pre-specified list of adverse reactions (identified using asterisks in Table 1). Patients indicated daily on this card whether or not each of these reactions occurred within the first 60 minutes after dosing. These pre-specified adverse reactions were solicited during approximately the first 28 days after treatment initiation.

Table 1: Solicited* and Unsolicited Treatment-related Adverse Reactions Reported in ≥1% of Patients with House Dust Mite-Induced Allergic Rhinitis and/or Asthma Treated with ACARIZAX™ and Occurring More Commonly than Placebo in One or More Trial Populations

| | **Trial Population: (P001)** | | **Trial Population: Three Pooled Trials (MT-06, MT-04, P003)** | |
|---|---|---|---|---|
| | **ACARIZAX™ N=741 n (%)** | **PLACEBO N=741 n (%)** | **ACARIZAX™ N=642 n (%)** | **PLACEBO N=656 n (%)** |
| **Ear and Labyrinth Disorders** | **380 (51.3)** | **84 (11.3)** | **30 (4.7)** | **3 (0.5)** |
| Ear pruritus | 376 (50.7)* | 84 (11.3)* | 30 (4.7) | 3 (0.5) |
| **Eye Disorders** | **20 (2.7)** | **15 (2.0)** | **10 (1.6)** | **9 (1.4)** |
| Eye pruritus | 12 (1.6) | 9 (1.2) | 7 (1.1) | 4 (0.6) |
| **Gastrointestinal Disorders** | **552 (74.5)** | **216 (29.1)** | **275 (42.8)** | **42 (6.4)** |
| Oral pruritus | 462 (62.3)* | 106 (14.3)* | 127 (19.8) | 16 (2.4) |
| Lip swelling | 133 (17.9)* | 16 (2.2)* | 20 (3.1) | 1 (0.2) |
| Swollen tongue | 119 (16.1)* | 16 (2.2)* | 12 (1.9) | 1 (0.2) |
| Glossodynia | 114 (15.4)* | 25 (3.4)* | 14 (2.2) | 1 (0.2) |
| Nausea | 98 (13.2)* | 33 (4.5)* | 12 (1.9) | 1 (0.2) |
| Tongue ulceration | 94 (12.7)* | 16 (2.2)* | | |
| Abdominal pain upper | 81 (10.9)* | 32 (4.3)* | | |
| Palatal swelling | 79 (10.7)* | 10 (1.3)* | | |
| Mouth ulceration | 75 (10.1)* | 20 (2.7)* | | |
| Mouth swelling | 71 (9.6)* | 12 (1.6)* | 10 (1.6) | 0 (0.0) |





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 35 10/10/2017 15.20

| | | | | |
|---|---|---|---|---|
| Paresthesia oral | 68 (9.2) | 21 (2.8) | 35 (5.5) | 2 (0.3) |
| Tongue pruritus | 35 (4.7) | 7 (0.9) | 30 (4.7) | 6 (0.9) |
| Diarrhea | 34 (4.6)* | 13 (1.8)* | | |
| Stomatitis | 22 (3.0) | 11 (1.5) | 7 (1.1) | 2 (0.3) |
| Oral pain | 22 (3.0) | 5 (0.7) | | |
| Oral mucosal erythema | 16 (2.2) | 4 (0.5) | | |
| Vomiting | 15 (2.0)* | 4 (0.5)* | | |
| Dyspepsia | 14 (1.9) | 0 (0.0) | 7 (1.1) | 0 (0.0) |
| Lip edema | 12 (1.6)* | 1 (0.1)* | 16 (2.5) | 2 (0.3) |
| Tongue edema | 12 (1.6)* | 0 (0.0)* | 11 (1.7) | 0 (0.0) |
| Enlarged uvula | 12 (1.6)* | 0 (0.0)* | | |
| Dysphagia | 11 (1.5) | 0 (0.0) | | |
| Abdominal pain | 10 (1.3)* | 4 (0.5)* | | |
| Lip pruritus | 10 (1.3) | 2 (0.3) | 11 (1.7) | 0 (0.0) |
| Hypoesthesia oral | 8 (1.1) | 6 (0.8) | | |
| Gastrooesophageal reflux disease | 8 (1.1) | 0 (0.0) | | |
| Palatal edema | 8 (1.1)* | 0 (0.0)* | | |
| Mouth edema | | | 57 (8.9) | 1 (0.2) |
| Oral discomfort | | | 13 (2.0) | 2 (0.3) |
| **General Disorders and Administration Site Conditions** | **20 (2.7)** | **9 (1.2)** | **12 (1.9)** | **4 (0.6)** |
| Chest discomfort | 9 (1.2) | 2 (0.3) | | |
| **Injury, Poisoning and Procedural Complications** | | | **18 (2.8)** | **11 (1.7)** |
| Accidental overdose | | | 18 (2.8) | 11 (1.7) |
| **Nervous System Disorders** | **83 (11.2)** | **40 (5.4)** | **9 (1.4)** | **2 (0.3)** |
| Dysgeusia | 67 (9.0)* | 27 (3.6)* | | |
| Paresthesia | 9 (1.2) | 2 (0.3) | | |
| **Respiratory, Thoracic and Mediastinal Disorders** | **515 (69.5)** | **177 (23.9)** | **137 (21.3)** | **40 (6.1)** |
| Throat irritation | 497 (67.1)* | 163 (22.0)* | 96 (15.0) | 16 (2.4) |
| Pharyngeal edema | 106 (14.3)* | 20 (2.7)* | 14 (2.2) | 0 (0.0) |
| Pharyngeal erythema | 16 (2.2) | 3 (0.4) | | |
| Dry throat | 9 (1.2) | 2 (0.3) | | |
| Oropharyngeal pain | 9 (1.2) | 2 (0.3) | | |
| Sneezing | 9 (1.2) | 1 (0.1) | | |
| **Skin and Subcutaneous Tissue Disorders** | **25 (3.4)** | **16 (2.2)** | **11 (1.7)** | **10 (1.5)** |
| Urticaria | 12 (1.6) | 3 (0.4) | | |
| Pruritus | 10 (1.3) | 9 (1.2) | | |

Percentage reported in the table reflects the data collected over the entire trial duration.
*P001 solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy) were those reported by subjects within approximately 28 days of treatment initiation.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 36 10/10/2017 15.20

## Less Common Clinical Trial Adverse Reactions (< 1%)

**Blood and Lymphatic System Disorders:** lymphadenitis

**Cardiac Disorders:** palpitations

**Ear and Labyrinth disorders:** ear congestion, ear discomfort, tinnitus

**Eye Disorders:** eye irritation, eyelids pruritus, ocular hyperaemia, scintillating scotoma

**Gastrointestinal Disorders:** abdominal discomfort, abdominal distension, cheilitis, erosive duodenitis, gastritis, gingival edema, gingival pruritus, gingival swelling, glossitis, hypertrophy of tongue papillae, lip blister, lip disorder, lip pain, noninfective sialoadenitis, odynophagia, esophageal irritation, esophageal pain, esophageal spasm, esophagitis, oral disorder, oral mucosal erosion, oral mucosal blistering, oral mucosal discoloration, oral papule, palatal disorder, rectal hemorrhage, salivary gland enlargement, salivary hypersecretion, sensitivity of teeth, submaxillary gland enlargement, tongue blistering

**General Disorders and Administration Site Conditions:** asthenia, chest pain, fatigue, feeling hot, local swelling, malaise, mucosal dryness, sensation of foreign body, thirst

**Immune System Disorders:** hypersensitivity, oral allergy syndrome

**Infections and Infestations:** abscess oral, acute sinusitis, nasopharyngitis, oral candidiasis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection

**Injury, Poisoning and Procedural Complications:** tongue injury

**Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, body temperature increased, forced expiratory volume decreased

**Musculoskeletal and Connective Tissue Disorders:** back pain, musculoskeletal pain, neck pain

**Nervous System Disorders:** aphonia, hypoesthesia, somnolence, tremor

**Psychiatric Disorders:** anxiety

**Renal and Urinary Disorders:** micturition urgency

**Respiratory, Thoracic and Mediastinal Disorders:** bronchospasm, dry throat, dysphonia, dyspnea, laryngeal discomfort, laryngeal edema, nasal congestion, nasal obstruction, nasal edema, nasal pruritus, nasal ulcer, oropharyngeal discomfort, oropharyngeal swelling, pharyngeal disorder, pharyngeal hypoesthesia, pharyngeal ulceration, rhinorrhea, sinus congestion, sneezing, snoring, throat tightness, tonsillar hypertrophy, upper-airway cough syndrome

**Skin and Subcutaneous Tissue Disorders:** alopecia, eczema, rash, rash papular

**Vascular Disorders:** hot flush





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 37 10/10/2017 15.20

### Adverse Drug Reactions of Special Interest in Controlled Clinical Trials

- Hypersensitivity Reactions (systemic reactions): There were 4 patients (1 adolescent, 3 adult) with systemic allergic reactions who were exposed to ACARIZAX™ `. In 3 of the 4 patients, the systemic allergic reaction was attributed to triggers unrelated to ACARIZAX™ use.
- Serious and Severe Local Reactions and progression of oral reactions to the throat: There were no patients exposed to ACARIZAX™ who developed serious local allergic swellings or airway compromise. Severe reactions that affected the throat included mouth edema (n=2), throat tightness (n=1), pharyngeal edema (n=1), and tongue edema (n=1).
- Acute Asthma: There was 1 adult patient with a serious treatment-related asthma exacerbation who was exposed to ACARIZAX™ in the clinical development program.

#### *Post-Market Adverse Drug Reactions*

There is limited post-marketing data on ACARIZAX™.

## 3.7 DRUG INTERACTIONS

#### *Overview*

No potential drug interactions have been identified, and no drug interaction studies have been conducted in humans.

Co-administration with other immunotherapy has not been studied.

#### *Potential Drug-Drug Interactions*

Interactions with other drugs have not been established.

- See **CONTRAINDICATIONS** for potential drug-drug interactions with beta-blockers.
- See **WARNINGS AND PRECAUTIONS/General** for potential drug-drug interactions with MAOIs or Tricyclic anti-depressants.

### Drug-Food Interactions

Interactions with food have not been studied.

### Drug-Herb Interactions

Interactions with herbal products have not been studied.

### Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

### Drug-Lifestyle Interactions

If dizziness or fatigue is experienced by the patient they should be advised not to drive or operate machinery until these effects have passed.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 38 10/10/2017 15.20

## 3.8 DOSAGE AND ADMINISTRATION

### *Dosing Considerations*

- The first dose of ACARIZAX™ should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases.
- After receiving the first dose, the patient should be kept under observation for 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the first dose is adequately tolerated, subsequent doses may be taken at home.
- Treatment with ACARIZAX™ can be initiated at any time during the year.
- Onset of the clinical effect is to be expected 8-14 weeks after initiation.
- In patients with history of house dust mite allergy, methods of determining the presence of house dust mite specific IgE should also include prick testing and/or serum testing for specific IgE against *D. farinae* or *D. pteronyssinus*.

### *Recommended Dose and Dosage Adjustment*

- For house dust mite-induced allergic rhinitis (with or without conjunctivitis), the recommended dose of ACARIZAX™ is 1 sublingual tablet (12 SQ-HDM) daily.

### *Interruptions of Treatment*

Patients should not take more than one sublingual tablet daily. Advise patients who miss taking a dose of ACARIZAX™ to return to their normal schedules the next day. A review of subjects who experienced treatment interruptions from the controlled clinical studies did not reveal a risk to interrupting and restarting treatment with ACARIZAX™.

### *Administration*

- ACARIZAX™ is a sublingual tablet. The tablet should be taken from the blister unit after carefully removing the foil with dry hands.
- The tablet should be placed under the tongue immediately where it will rapidly dissolve within seconds.
- Do not take the tablet with food or beverage. Swallowing should be avoided for about 1 minute. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after handling the tablet.





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 39 10/10/2017 15.20

## 3.9 OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The risk of side effects may increase with doses above 12 SQ-HDM. In the event of an overdose; any adverse effects should be treated symptomatically.

In clinical trials, local reactions such as oral pruritus, oral pain, throat irritation, and severe vomiting were observed with daily doses of 24 or 32 SQ-HDM.

## 3.10 ACTION AND CLINICAL PHARMACOLOGY

### *Mechanism of Action*

The immune system is the target of immunotherapy. The aim is to prevent or suppress allergic symptoms through repeated administration of the allergen. The effect of sublingual immunotherapy is thought to be mediated through local and systemic immunomodulatory mechanisms (immune deviation) including changes in allergen specific antibodies and regulatory T-cells leading to long-term tolerance development.

### *Pharmacodynamics*

The immune system is the target for the pharmacodynamic effect. The aim is to induce an immune response against the allergen with which the patient is treated. ACARIZAX™ administered daily via the sublingual route induces a time and dose-dependent immune response in both house dust mites specific IgG4 and IgE. Data from studies of up to 52 weeks demonstrate that these immunological changes can be observed as early as approximately 28 days after treatment initiation and continue during treatment. The clinical significance of these findings has not been established.

### *Pharmacokinetics*

No pharmacokinetic studies in animals or clinical studies investigating the pharmacokinetic profile and metabolism of *D. farinae* and *D. pteronyssinus* extracts have been conducted.

## 3.11 STORAGE AND STABILITY

Store at room temperature (do not store above 25°C). Store in the original package until use to protect from moisture.

## 3.12 DOSAGE FORMS, COMPOSITION AND PACKAGING

### *Dosage Form*

ACARIZAX™ is a white to off-white circular sublingual tablet with a debossed pentagon on one side. ACARIZAX™ is a sublingual tablet designed to dissolve rapidly within seconds under the tongue.

### *Composition*

Each ACARIZAX™ tablet contains 12 SQ-HDM of standardized house dust mites allergen extract from *D. farinae* and *D. pteronyssinus*.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 40 10/10/2017 15.20

The active substance is a standardized allergen extract derived from house dust mites. ACARIZAX™ contains the following inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF. ACARIZAX™ is free of lactose.

### *Packaging*

ACARIZAX™ sublingual tablets are packaged in aluminum blister packs composed of a blister film and a lidding foil. The lidding foil has been designed to be peeled back from the blister film to allow the removal of the tablets.

The trade size is a box of 30 tablets (3 blisters packs with 10 tablets each).

# PART II: SCIENTIFIC INFORMATION

## 3.13 PHARMACEUTICAL INFORMATION

### *Drug Substance*

The potency of the two drug substances in SQ-HDM is based on the total allergenic activity and the content of two major allergens (group 1 and group 2).

**PROPER NAME:** Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*)

**MOLECULAR FORMULA AND MOLECULAR MASS:** Contains two drug substances, each of which consists of a complex mixture of proteins and other biologically derived substances extracted from two cultivated house dust mite species. Therefore, there is no molecular formula and no detailed structural information available.

**PHYSICOCHEMICAL PROPERTIES:** Light to dark brown non-sterile, non-adhesive frozen droplets that are soluble in a range of buffers and water.

### *Product Characteristics*

The drug substances (DS) are prepared by extraction of house dust mites, which are then purified by filtration and stabilized into frozen droplets before incorporation in the final dosage form. The characterization of the major allergenic components includes identification of the relevant allergen. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

## 3.14 CLINICAL TRIALS

The efficacy of ACARIZAX™ for the treatment of HDM-induced allergic rhinitis was investigated in two double-blind, placebo-controlled, randomized clinical field efficacy trials (Studies P001 and MT-06). Collectively, the trials were conducted with initation of treatment throughout the year. Subjects received ACARIZAX™ or placebo as a sublingual tablet daily for a duration of approximately 12 months.





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 41 10/10/2017 15.20

Table 4: Summary of patient demographics and trial design for ACARIZAX™ Allergic Rhinitis clinical trials

| Trial # | Trial design | Dosage<br>Duration | Number of subjects<br>N = total | Subject Population<br>Age Range (mean)<br>Male (%) / Female (%) |
|---|---|---|---|---|
| P001 | Phase III<br>R, MC, DB, PG, PC | 12 SQ-HDM QD<br>placebo<br>Up to approximately 12 months | 741<br>741<br>N = 1482 | 12 – 85 years (35)<br>608 (41) / 875 (59) |
| MT-06 | Phase III<br>R, MC, DB, PG, PC | 12 SQ-HDM QD<br>6 SQ-HDM QD<br>placebo<br>Approximately 12 months | 318<br>336<br>338<br>N = 992 | 18 - 66 years (32)<br>494 (50) / 498 (50) |

R = randomized; MC = multi-center; DB = double-blind; PG = parallel-group; PC = placebo-controlled
HDM = house dust mite;

### *Trial P001 (North American Field Efficacy Trial)*

P001 was a double-blind, placebo-controlled, randomized field efficacy trial conducted in the United States and Canada for a duration of up to 12 months, that compared the efficacy of ACARIZAX™ (N=741) compared to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects 12 through 85 years of age were enrolled if they had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE. Subjects were required to be symptomatic and were not taking symptom-relieving allergy medications at enrollment.

Subjects with mild to moderate asthma, defined as asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid, were enrolled in the trial.

In this trial, 31% of subjects had asthma, 48% had conjunctivitis, and 76% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, animal danders and molds. The subject population was 76% White, 11% African American, 7% Asian, and 59% female. The mean age of subjects was 35 years.

The efficacy of ACARIZAX™ in the treatment of HDM-induced allergic rhinitis was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the total combined rhinitis score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this trial were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the trial as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 42 10/10/2017 15.20

The primary endpoint was the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Other secondary endpoints in this trial included the average rhinitis DSS, the average rhinitis DMS, and the total combined score (TCS). The TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS, which was then averaged during approximately the last 8 weeks of treatment.

Subjects in this trial were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm.

Based on the primary analysis, patients treated with ACARIZAX™ had significant relief of nasal symptoms and reduction in standard allergy medication use as measured by a decrease in TCRS compared to placebo-treated subjects. Similar improvement was observed in patients treated with ACARIZAX™ for other key secondary endpoints. The results of this trial are shown in Table 5.

Table 5: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment (P001)

| Endpoint | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™ - Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value | Estimate | (95% CI) |
| **Primary Endpoint** | | | | | | |
| **TCRS*** | (566) 4.10 | (620) 4.95 | -0.80 | <0.001 | -17.2% | (-25.0%, -9.7%) |
| **TCRS+** | (566) 3.16 | (620) 3.87 | -0.71 | <0.001 | -18.4% | (-31.0%, -6.5%) |
| **Secondary Endpoints** | | | | | | |
| **Rhinitis DSS*** | (566) 3.55 | (620) 4.20 | -0.60 | <0.001 | -15.5% | (-24.4%, -7.3%) |
| **Rhinitis DMS#** | (566) 0.65 | (620) 0.79 | -0.15 | 0.154¶ | -18.4% | (-41%, 4.3%) |
| **TCS*** | (566) 5.50 | (620) 6.60 | -1.10 | <0.001¤ | -16.7% | (-24.6%, -4.0%) |

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints using the Wilcoxon Rank Sum test.

\+ Longitudinal Data Analysis (LDA) model for TCRS.

\# Parametric analysis using a zero-inflated log-normal model for Rhinitis DMS endpoint. 337 (59.5%) and 336 (54.2%) subjects in the ACARIZAX™ and placebo treatment groups, respectively, did not utilize rescue medications.

† Number of subjects in analyses; subjects not evaluable for diary-based endpoints were not included in the analyses (ACARIZAX™ 23.5%; placebo 16.3%).

‡ For the non-parametric analyses, the estimated group medians are reported and treatment difference is the Hodges-Lehmann estimate.. For the LDA and zero-inflated log-normal models, the estimated group means are reported and treatment difference is the difference in estimated group means.

§ Difference relative to placebo was calculated based on the estimated group medians (for non-parametric analyses) or means (for LDA and zero-inflated log-normal model) as: (ACARIZAX™ – placebo)/placebo x 100%.

¶ Not statistically significant.

¤ This result cannot be considered confirmatory due to the pre-specified multiplicity control strategy, which involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 43 10/10/2017 15.20

### *Trial MT-06 (European Field Efficacy Trial)*

This double-blind, placebo-controlled, randomized field efficacy trial evaluated adult subjects 18 through 66 years of age comparing ACARIZAX™ (N=318) and placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this trial had a history of symptomatic allergic rhinitis when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing. At trial entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the baseline period.

In this trial, 46% of subjects had asthma, 97% had conjunctivitis and 67% were polysensitized to other allergens in addition to HDM, including trees, grass, weeds, animal danders and molds. The trial population was 98% White, <1% African American, and <1% Asian; 50% of subjects were female. The mean age of subjects in this trial was 32 years. The primary efficacy endpoint was the average TCRS during the last 8 weeks of treatment. The mean Rhinitis DSS at baseline was 7.95 out of 12 for the treatment arm and 8.00 out of 12 total points for the placebo arm.

Based on the primary analysis, patients treated with ACARIZAX™ had significant relief of nasal symptoms and reduction in standard allergy medication use as measured by a decrease in TCRS compared to placebo-treated subjects. Similar improvement was observed in patients treated with ACARIZAX™ for other key secondary endpoints. The results of this trial are shown in Table 6.

Table 6: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment (MT-06)

| Endpoint | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™ - Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value¤ | Estimate | (95% CI) |
| **Primary Endpoint** | | | | | | |
| **TCRS*** | (318) 5.71 | (338) 6.81 | -1.09 | 0.004 | -16.1% | (-25.8%, -5.7%) |
| **TCRS+** | (284) 4.92 | (298) 6.23 | -1.31 | <0.001 | -21.0% | (-31.2%, -9.4%) |
| **Secondary Endpoints** | | | | | | |
| **Rhinitis DSS*** | (318) 2.84 | (338) 3.31 | -0.47 | 0.01 | -14.1% | (-23.8%, -3.9%) |
| **Rhinitis DMS*#** | (318) 2.32 | (338) 2.86 | -0.54 | 0.045 | -18.9% | (-34.7%, -1.3%) |
| **TCS*¶** | (241) 7.91 | (257) 9.12 | -1.21 | 0.029 | -13.2% | (-23.7%, -1.5%) |

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Linear mixed effect (LME) model. Multiple imputation was performed for TCRS, rhinitis DSS, and rhinitis DMS.

\+ Longitudinal Data Analysis (LDA) model for TCRS analysed post hoc.

† Number of subjects in analyses; all randomized subjects were included in the LME analyses of TCRS, rhinitis DSS, and rhinitis DMS. All randomized subjects evaluable for diary-based endpoints were included in the LDA model for TCRS and in the LME analysis of TCS.

‡ Estimated group means are reported. Treatment difference is difference in estimated group means.

¤ The pre-specified multiplicity control strategy involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).



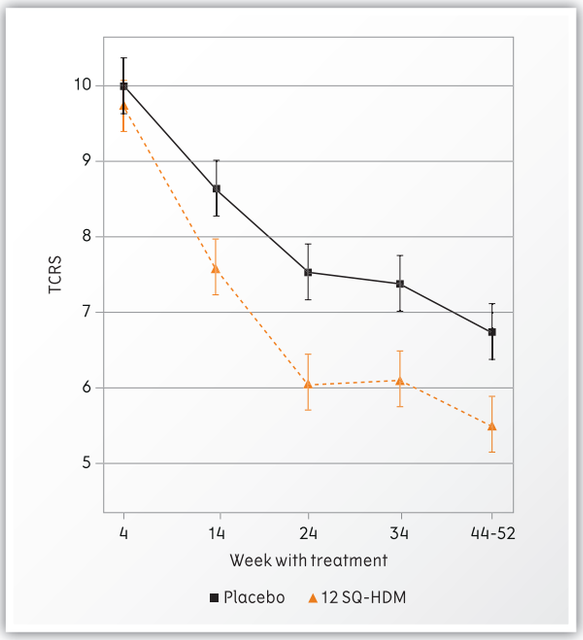
100295 ALK - ACARIZAX Reference Kit Canada K2.indd 44 10/10/2017 15.20

§ Difference relative to placebo was calculated based on the estimated group means as: (ACARIZAX™ – placebo)/placebo x 100%.

# 45 (15.8%) and 29 (9.7%) subjects in the ACARIZAX™ and placebo treatment groups, respectively, did not utilize rescue medications.

¶ Subjects from Serbia and Croatia (48 [15.1%] and 46 [13.6%] subjects in the ACARIZAX™ and placebo treatment groups, respectively) were not included in the analysis of TCS because the preferred formulations of antihistamine eye drops were not available in these countries at the time the trial was conducted.

Efficacy was assessed at pre-defined intervals throughout the treatment period at weeks 4, 14, 24 and 34 in addition to during the last 8 weeks of treatment (see Figure 2).




Error bars: 95% confidence interval for the difference in adjusted means based on analysis of covariance model.

Figure 2: Adjusted Means of the Total Combined Rhinitis Score (TCRS) Over Time (MT-06)

## 3.15 DETAILED PHARMACOLOGY

### Animal Pharmacology

No dedicated animal safety pharmacology studies were conducted with ACARIZAX™ (*D. farinae* and *D. pteronyssinus*). However, there were no overt central nervous system or respiratory effects noted for up to 6-months of dosing in the mouse based on routine clinical observations.

### Human Pharmacology

A double-blind, placebo-controlled, phase IIb, dose-finding, randomized environmental exposure chamber (EEC) trial evaluated adult subjects 18 through 58 years of age comparing ACARIZAX™ (N=42) and placebo (N=41) administered as a sublingual tablet daily for approximately 24 weeks. Subjects had a history of symptomatic allergic rhinitis with and without conjunctivitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE.





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 45 10/10/2017 15.20

In this trial, 23% of subjects had asthma, 87% had conjunctivitis, and 84% were polysensitized to other allergens in addition to HDM, including tree, grass, weeds, animal danders and molds. The subject population was 90% White, <1% African American, 8% Asian, and 43% female. The mean age of subjects was 27 years.

The primary endpoint was the average TNSS at Week 24. The Total Nasal Symptom Score (TNSS) represents the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints were the average TNSS at Weeks 8 and 16, and Total Symptom Score (TSS) at Week 24. Baseline TNSS following house dust mite EEC challenge prior to treatment was 7.74 out of 12 total points for ACARIZAX™ and 7.32 out of 12 total points for placebo. The results of the trial are shown in Table 7.

Table 7: Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (EEC Trial)

| Endpoint* | ACARIZAX™ (n)† Score‡ | Placebo (n)† Score‡ | Treatment Difference (ACARIZAX™- Placebo) | | Difference Relative to Placebo§ | |
|---|---|---|---|---|---|---|
| | | | Estimate | p-value | Estimate | (95% CI) |
| **Primary endpoint** | | | | | | |
| **TNSS – Week 24** | (36) 3.83 | (34) 7.45 | -3.62 | <0.001 | -48.6% | (-60.2%, -35.3%) |
| **Secondary endpoints** | | | | | | |
| **TNSS – Week 8** | (40) 5.34 | (39) 6.71 | -1.37 | | -20.4% | (-33.3%, -6.8%) |
| **TNSS – Week 16** | (39) 4.82 | (38) 6.90 | -2.08 | | -30.1% | (-42.3%, -16.8%) |
| **TSS – Week 24** | (36) 4.43 | (34) 9.27 | -4.84 | | -52.2% | (-65.0%, -37.0%) |

TNSS=Total Nasal Symptom Score, endpoint score range: 0-12.; TSS=Total Symptom Score (TNSS + total ocular symptom score), endpoint score range 0-18; CI=Confidence Interval

* Parametric analysis using analysis of covariance for all endpoints: analysis via ANCOVA with treatment and baseline endpoint score as fixed effects. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the screening.

† Number of subjects in analyses. Subjects who discontinued the trial prior to the given time point were not included in the analyses.

‡ For all endpoints, the estimated group least squares mean is reported. Treatment difference was the difference between least squares means.

§ Difference relative to placebo was calculated based on the estimated group least squares means as: (ACARIZAX™- placebo)/ placebo x 100%.

## 3.16 TOXICOLOGY

### *Animal Toxicology*

A general toxicity study in mice dosing HDM allergen extract (the active substance of ACARIZAX™) up to 14 SQ-HDM/day for 6 months did not reveal any significant treatment-related effects.

### *Carcinogenesis, Mutagenesis, Impairment of Fertility*

The carcinogenic potential of ACARIZAX™ has not been evaluated.

There were no clinically relevant positive findings in *in vitro* chromosome aberration assays, an *in vitro* bacterial mutagenesis assay and a combined Comet and micronucleus assay for mutagenicity in rats using HDM allergen extract (*D. farinae* and *D. pteronyssinus*).



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 46 10/10/2017 15.20

Mice administered HDM allergen extract by daily subcutaneous injections from the time of implantation through late gestation (gestational days 6 to 17) revealed no significant treatment related effects on post-implantation loss or prenatal development up to five times the human sublingual dose.

Fertility studies have not been performed with HDM allergen extract.

## 3.17 REFERENCES


1. J Allergy Clin Immunol. 2015 Aug 17. pii: S0091-6749(15)00935-5. doi: 10.1016/j.jaci.2015.06.036. (MT-06)
2. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, Kaur A, Zieglmayer P, Zieglmayer R, Lemell P, Horak F. Onset and Dose-related Efficacy of House Dust Mite Sublingual Immunotherapy Tablet in an Environmental Exposure Chamber. J Allergy Clin Immunol 2015, 135(6):1494-1501 (P003)
3. P001 Data on file


This leaflet was prepared by ALK-Abelló A/S.

Last Revised: April 25, 2017


™ Trademark of ALK-Abelló A/S.

© 2016 ALK-Abelló A/S. All rights reserved.







100295 ALK - ACARIZAX Reference Kit Canada K2.indd 47 10/10/2017 15.20

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 48 10/10/2017 15.20

# REFERENCES

## 4. REFERENCES


1. Keith PK, Desrosiers M, Laister T et al.: The burden of allergic rhinitis (AR) in Canada: perspectives of physicians and patients. Allergy, Asthma &Clinical Immunology 2012 8:7.
2. Agency for Healthcare Research and Quality. Draft comparative effectiveness review: The role of immunotherapy in the treatment of asthma. http://effectivehealthcare.ahrq.gov/ehc/products/644/2467/asthma-immunotherapy-draft-report-170424.pdf. Published Accessed June 21, 2017.
3. Chan-Yeung M, Anthonisen NR, Becklake MR et al. Geographical variations in the prevalence of atopic sensitization in six study sites across Canada. Allergy 2010;65(11):1404-13.
4. Compalati E, Ridolo E, Passalacqua G, Braido F, Villa E, Canonica GW. The link between allergic rhinitis and asthma: the united airways disease. Expert Rev Clin Immunol. 2010;6(3):413-423.
5. Feng CH, Miller MD, Simon RA. The united allergic airway: connections between allergic rhinitis, asthma, and chronic sinusitis. Am J Rhinol Allergy. 2012;26(3):187-190.
6. Asthma Society of Canada, 2017. Dust mites control in the home. https://asthma.ca/wp-content/uploads/2017/08/asthma_dust_mite_eng.pdf
7. Linneberg A, Henrik Nielsen N, Frolund L, et al. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The Copenhagen Allergy Study. Allergy. 2002;57(11):1048-1052.
8. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009;9:24.
9. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
10. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. Allergy 2008;63:646-59.
11. Valovirta E, Myrseth SE, Palkonen S. The voice of the patients: allergic rhinitis is not a trivial disease. Curr Opin Allergy Clin Immunol 2008;8:1-9.
12. Global Initiative for Asthma (GINA), Global strategy for asthma management and prevention. Updated 2015. Accessed October 2015. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_Aug11.pdf.
13. Canonica GW, Bousquet J, Mullol J, et al. A survey of the burden of allergic rhinitis in Europe. Allergy 2007;62 Suppl 85:17-25.
14. Chivato T, Valovirta E, Dahl R, et al. Allergy, living and learning: diagnosis and treatment of allergic respiratory diseases in Europe. J Investig Allergol Clin Immunol 2012;22:168-79.
15. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. J Allergy




100295 ALK - ACARIZAX Reference Kit Canada K2.indd 50 10/10/2017 15.20

Clin Immunol 2015;136:556-68.

16. Canonica GW, Cox L, Pawankar R, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014;7:6.

17. Calderón MA, Linneberg A, Kleine-Tebbe J, et al. Respiratory allergy caused by house dust mites: What do we really know? . J Allergy Clin Immunol. 2015;136:38-48.

18. Casset A, Mari A, Purohit A, et al. Varying allergen composition and content affects the in vivo allergenic activity of commercial Dermatophagoides pteronyssinus extracts. Int Arch Allergy Immunol. 2012;159:253-62.

19. Calderón MA, Larenas D, Kleine-Tebbe J, et al. European Academy of Allergy and Clinical Immunology task force report on 'dose-response relationship in allergen-specific immunotherapy'. Allergy 2011;66:1345-59.

20. Thomas WR, Hales BJ, Smith WA. House dust mite allergens in asthma and allergy. Trends Mol Med 2010; 16:321-8.

21. Chapman MD, Platts-Mills TA. Purification and characterization of the major allergen from Dermatophagoides pteronyssinus-antigen P1. J Immunol 1980; 125:587-92.

22. Heymann PW, Chapman MD, Aalberse RC, et al. Antigenic and structural analysis of group II allergens (Der f II and Der p II) from house dust mites (Dermatophagoides spp). J Allergy Clin Immunol 1989;83:1055-67.

23. Henmar H, Toft Frisenette SM, Grosch K, et al. Fractionation of Source Materials Leads to a High Reproducibility of the SQ House Dust Mite SLIT-Tablets. Int Arch Allergy Immunol 2016;169:23-32.

24. Nolte H, Bernstein DI, Nelson HS et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2016;138:1631-1638.

25. Hernandez, D; Mosbech, H; Dichmann, R; et al. SQ HDM SLIT-tablet induces significant immunomodulatory response; results from a DBPC phase III trial (MITRA). Allergy 014;69(Suppl. s99): Abstract 421.

26. Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized double-blind, placebo-controlled phase III trial. J Allergy Clin Immunol. 2016;137(2):444-451.

27. Virchow JC, Backer V, Kuna P, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma. A Randomized Clinical Trial. JAMA. 2016;315(16):1715-1725.

28. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129:717-725.

29. Corzo JL, Carrillo T, Pedemonte C, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. J Investig





100295 ALK - ACARIZAX Reference Kit Canada K2.indd 51 10/10/2017 15.20

Allergol Clin Immunol 2014;24:154-61.

30. Maloney J, Prenner BM, Bernstein DI, Lu S, Gawchik S, Berman G, Kaur A, Li Z, Nolte H. Safety of house dust mite sublingual immunotherapy standardized quality tablet in children allergic to house dust mites. Ann Allergy Asthma Immunol. 2016 Jan;116(1):59-65.

31. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 015;135:1494-501

32. Demoly P, Kleine-Tebbe J, Rehm D. Clinical benefits of treatment with SQ house dust mite sublingual tablet in house dust mite allergic rhinitis. Allergy. 2017 Mar 8.



100295 ALK - ACARIZAX Reference Kit Canada K2.indd 52 10/10/2017 15.20

## ADDITIONAL RELEVANT REFERENCES


Emminger, W; Smeenk, F; Guzik, T; et al. The SQ HDM SLIT-tablet is well-tolerated in respiratory allergic disease; results from 2 DBPC phase III trials (MERIT and MITRA). Allergy 2014;69(Suppl. s99):Abstract 417.

Nolte H, Plunkett G, Grosch K, Larsen JN, Lund K, Bollen M. Major allergen content consistency of SQ house dust mite sublingual immunotherapy tablets and relevance across geographic regions. Ann Allergy Asthma Immunol. 2016 Sep;117(3):298-303.

Durham SR, Creticos PS, Nelson HS, Li Z, Kaur A, Meltzer EO, Nolte H. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. J Allergy Clin Immunol. 2016 Oct;138(4):1081-1088.

Zieglmayer P, Nolte H, Nelson HS, Bernstein DI, Kaur A, Jacobi H, Lemell P, Schmutz R, Zieglmayer R, Horak F. Long-term effects of a house dust mite sublingual immunotherapy tablet in an environmental exposure chamber trial. Ann Allergy Asthma Immunol. 2016 Dec;117(6):690-696.

Nolte H, Casale TB, Lockey RF, Fogh BS, Kaur A, Lu S, Nelson HS. Epinephrine Use in Clinical Trials of Sublingual Immunotherapy Tablets. J Allergy Clin Immunol Pract. 2017 Jan - Feb;5(1):84-89.

Bernstein DI, Bardelas JA Jr, Svanholm Fogh B, Kaur A, Li Z, Nolte H. A practical guide to the sublingual immunotherapy tablet adverse event profile: implications for clinical practice. Postgrad Med. 2017 Mar 22:1-8

Okubo K, Masuyama K, Imai T et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite–induced allergic rhinitis. J Allergy Clin Immunol. 2017 Jun;139(6):1840-1848.

Calderón MA, Bousquet J, Canonica GW, Cardell LO, Fernandez de Rojas DH, Kleine-Tebbe J, Demoly P. Guideline recommendations on the use of allergen immunotherapy in house dust mite allergy: Time for a change? J Allergy Clin Immunol. 2017 Jul;140(1):41-52.






100295 ALK - ACARIZAX Reference Kit Canada K2.indd 53 10/10/2017 15.20

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 54 10/10/2017 15.20

# 5 SUPPORTIVE MATERIAL

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 56 10/10/2017 15.20

100295 ALK - ACARIZAX Reference Kit Canada K2.indd 57 10/10/2017 15.20