Public Assessment Report

Scientific discussion

ACARIZAX 12 SQ-HDM oral lyophilisate
Allergen extract from house dust mite

DE/H/1947/001/DC

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This module reflects the scientific discussion for the approval of ACARIZAX12 SQ-HDM oral lyophilisate. The procedure was finalised on 30 Aug 2015. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, European Member States have granted a marketing authorisation for ACARIZAX 12 SQ-HDM oral lyophilisate, from ALK-Abelló A/S. ACARIZAX contains standardised allergen extract from the house dust mites Dermatophagoides pteronyssinus and Dermatophagoides farinae 12 SQ-HDM per oral lyophilisate. SQ-HDM is the dose unit for ACARIZAX. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

The product is indicated in adult patients (18-65 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with at least one of the following conditions:

• persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication
• house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Patients' asthma status should be carefully evaluated before the initiation of treatment.

A comprehensive description of the posology is given in the SmPC.

“The marketing authorisation has been granted pursuant to Article 8 and 28 of Directive 2001/83/EC.”

The HDM oral lyophilisate has been developed to treat the two main clinical manifestations of house dust mite (HDM) respiratory allergic disease: HDM-allergic rhinitis (AR) and HDM-allergic asthma (AA). Symptoms related to HDM allergy arise when sensitised patients are exposed to airborne fragments of mite bodies and faeces. HDM allergy classifies as perennial allergy, meaning that patients have persistent symptoms all year but of varying intensity (Bousquet et al. 2008).

Almost all adult patients with HDM respiratory allergy suffer from HDM AR and approximately half also suffer from HDM AA. Accordingly, almost all patients suffering from HDM AA also suffer from HDM AR (Knudsen et al. 2009; Linneberg et al. 2002). In addition, HDM allergy-related conjunctivitis is a common co-morbid allergic manifestation in a sub-set of patients (Bousquet et al. 2008; Ibanez et al. 2013).

The objective of allergy immunotherapy (AIT) is to treat the underlying immune-mechanism of the allergic disease resulting in an effect on clinical manifestations of the disease. AIT is a treatment option for allergy that is complementary to pharmacotherapy and with a distinct mechanism of action. AIT is performed by repeated sublingual (SLIT) or subcutaneous (SCIT) administration of specific allergens to an allergic person in order to gradually induce immunological tolerance towards the respective allergens. AIT modulates the basic immunological mechanism of the allergic disease and is the only known treatment option with the potential to provide long-term, post-treatment benefits and alter the natural course of allergic disease (Bousquet et al. 2008).

International treatment guidelines recommend an overall treatment period for AIT of 3 years (Bousquet et al. 2008). Subcutaneously administered AIT is performed by a physician at the physician's office. Treatment entails mostly an up-dosing period with frequent (at least weekly) visits over the first few months, followed by a period of up to bimonthly administrations of a maintenance dose. In contrast, SLIT is self-administered by the patient.
outside a healthcare setting, a feature that is made possible by the lower risk of severe systemic allergic reactions with SLIT compared to SCIT (Dretzke et al. 2013). Most commonly, daily administration is used for SLIT. The HDM oral lyophilisate ACARIZAX is developed for SLIT.

There are no conditions pursuant to Article 21a or 22 of Directive 2001/83/EC in section V

II. QUALITY ASPECTS

II.1 Introduction

ACARIZAX is a sublingual immunotherapy (SLIT) tablet presented as an oral lyophilisate for sublingual use. The active substances are extracts from the two house-dust mite species Dermatophagoides farinae and Dermatophagoides pteronyssinus. The lyophilisate is designed to rapidly disintegrate in the mouth. The lyophilisates are presented in aluminium blisters.

II.2 Drug Substance

Two drug substances are used for the manufacture of ACARIZAX which are produced by extraction of the source materials D. farinae mites and D. pteronyssinus mites, respectively. Each source material is separated into a body and a faecal fraction which is used for preparation of extracts. These fractions are combined in the drug substance in order to have consistent group 1 and group 2 allergen contents. Additionally, total allergenic activity is determined by a quantitative IgE competitive immunoassay using a serum pool obtained from patients allergic to house dust mite and In-House References of each drug-substance according to the EMA guideline on allergen products: production and quality issues (EMEA/CHMP/BWP/304831/2007). The standardization of the drug substances is based on three quality parameters: group 1 allergen content, group 2 allergen content and total allergenic activity. These parameters are weighted equally to determine the amount of dry weight of drug substance equaling a potency of 1 DU. This is equivalent to 1 SQ-HDM as the final labeling unit of the drug product. The manufacturing process and development are sufficiently described and appropriate process controls are in place. The specification includes identity testing (allergen- and protein profiles in comparison to current in-house reference preparations), determination of total allergenic activity as described above, major allergen content of group 1 and group 2 allergens quantification, protein content determination, appearance, and testing for microbial contamination. The theoretical protein content as well as the dry weight potency per DU are calculated in order to ensure that the protein content per DU is between 50 – 150 % of a stated amount as required by the Ph. Eur. monograph for allergen products.

Stability studies were performed according to ICH-guidelines and support the claimed shelf life of the drug substances of 36 months.

II.3 Medicinal Product

The HDM sublingual immunotherapy (SLIT) tablet ACARIZAX is an oral lyophilisate for sublingual use designed to rapidly disintegrate in the mouth.
The manufacturing, testing and packaging of the tablets is performed by Catalent UK Swindon Zydis® using the Zydis® technology. The two DSs are weighed out using equal amounts of DU from each of the HDM species.

The development of the drug product was based on the experiences which were made during development of GRAZAX® which is identically formulated as ACARIZAX®. A detailed description of the drug product manufacturing process development is provided.

The specification for the drug product includes the parameters appearance, disintegration, water content, uniformity of mass, protein profile, total allergenic activity, major allergen content of group 1 allergens, major allergen content of group 2 allergen- microbial testing.

Stability data for the drug product are provided covering the proposed shelf life of 36 months for batches which were produced using drug substances derived from a pilot scale manufacturing process. A stability study has been started for material from three batches derived from the current manufacturing process. Data are provided for time point 6 months at 25°C and accelerated conditions (i.e. 40°C/75%RH). The data are in support of the claimed shelf life. The stability studies are performed according to ICH guidelines Q1A and Q5C, respectively. Thus, the proposed shelf life is considered acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Not applicable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Most people all over the world are exposed naturally to inhaled allergens e.g. from house dust mites, pollen, animals etc. As native allergen extracts (e.g. HDM allergen extract) constitutes of these native allergens, an abridged toxicological testing programme has been applied. This is line with the regulatory recommendations given for allergen-specific immunotherapy.

For a number of years mice have been the species of choice in research of allergy and were consequently selected as one of the suitable species. The fact that mice in certain respects (e.g. re-production studies) have specific disadvantages (e.g. very small-size pups and limited possibilities for sequential blood sampling) has been considered as an acceptable limitation. Although mouse models can display some of the hallmarks of human rhinitis or asthma, no comprehensive mouse model of HDM-induced allergy and asthma mimicking all aspects of the human diseases is currently available. Hence, an animal species showing only some of the elements of tolerance induction seen in man has been selected for the non-clinical testing. Further, no comprehensive model mimicking rhinitis or asthma has been established in other species than mice. For these reasons, the in vivo non-clinical testing of ACARIZAX has involved testing in mice only. This approach is acceptable with regard to the concept of 3R (replacement, reduction and refinement) of animal testing, and no further information would be expected from studies in additional species.
III.2 Pharmacology

No pharmacological studies have been performed for ACARIZAX in animals or in vitro. The applicant referenced clinical and experimental studies to justify this fact. As no standardized and validated animal model for specific immunotherapy exists, formal pharmacodynamic studies on allergens for this application are generally not deemed necessary. In line, the CHMP/EWP/18504/2006 “Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases” does not request separate pharmacodynamic studies in humans but requests the determination of immunological parameters e.g. IgG4 in other clinical studies. The assessment of immunological parameters was included in clinical trials for ACARIZAX.

III.3 Pharmacokinetics

Allergens are proteins, which will be digested in the gastro-intestinal system and will be catabolised rapidly into peptides and amino acids. Thus, no systemic absorption of intact allergen is expected for sublingually applied extracts and hence no non-clinical pharmacokinetic studies have been conducted. The applicant justified the lack of data. Since standardized and validated animal models for specific immunotherapy do not exist this is acceptable. Moreover, based on CHMP/EWP/18504/2006 “Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases” pharmacokinetic studies are not possible for products of specific immunotherapy as during specific immunotherapy plasma concentrations of the active substance are usually not measurable, due to the nature of the product.

III.4 Toxicology

House dust mite allergen extracts from Dermatophagoides pteronyssinus (Der pte) and Dermatophagoides farinae (Der far) should be considered as biologic substances with regard to non-clinical testing and most people all over the world are exposed naturally to allergens from house dust mites. Therefore a reduced testing programme has been performed.

For testing of genotoxicity, the HDM allergen extract has been evaluated in two in-vitro assays (Ames test in bacteria and chromosome aberration assay in human lymphocytes). A questionable finding in the chromosome aberration test was further investigated according to the current guidelines in two in-vivo tests in rats (combined Comet (liver and stomach) and bone marrow micronucleus test), showing no genotoxic effects under in-vivo conditions. Moreover, it has to be noticed, that the concentrations used in the in-vitro chromosome aberration test were very high. Despite the recommended maximum concentration of 5.0 mg/ml for this test in former guidelines, the maximum concentration in the new ICH S2 (R1) “guideline on genotoxicity testing and data interpretation for pharmaceuticals intended for human use” (in effect since June 2012) is lowered to 0.5mg/ml due to the high rate of positive findings in the in-vitro mammalian cell tests without confirmation by the following in-vivo tests. However, in concentrations up to 1500 µg the performed chromosomal aberration test was negative. Thus, it is concluded that the HDM allergen extract does not pose any genotoxic risk for human patients.
Furthermore, the HDM extract has been tested in mice in a 26 week repeated dose toxicity study. 14 DU, the highest dosage tested, did not show any adverse effects and is thus considered as the “No observed adverse effect level (NOAEL).

In addition, an embryo-foetal development study was conducted. The NOAEL was determined to be 1800 DU/kg for both maternal toxicity and embryo-foetal development.

In conclusion, in the toxicological studies exposures to doses up to several thousand-fold higher than maximal exposure in the patient, revealed no findings indicating a risk for the human patients exposed to therapeutic dose. The toxicological testing was performed in accordance with the requirements laid down in current guidelines.

**III.5 Ecotoxicity/environmental risk assessment (ERA)**
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ACARIZAX is not expected to pose a risk to the environment.

**III.6 Discussion on the non-clinical aspects**
The HDM allergen extract was well tolerated in mice at doses up to several thousand-fold higher than maximal exposure in the patient. Hence, on the basis of the non-clinical studies and the existing clinical knowledge, it is concluded that the mixture of extracts from Dermatophagoides farinae and Dermatophagoides pteronyssinus is safe for the sublingual formulation and for the intended clinical use without any restrictions in the labelling.

**IV. CLINICAL ASPECTS**

**IV.1 Introduction**
The clinical development programme for the HDM oral lyophilisate comprised of four phase I trials, two phase II trials and two phase III trials. All efficacy trials were randomised, double-blind, placebo-controlled trials conducted in the target patient group. Two efficacy trials had a primary endpoint related to HDM AR and two efficacy trials had a primary endpoint related to HDM AA. Safety was evaluated throughout the spectrum of the intended target population, which are adults with persistent moderate-to-severe HDM AR despite the use of AR pharmacotherapy and adults with HDM AA not well controlled by ICS and associated with mild to severe house dust mite allergic rhinitis.

**IV.2 Pharmacokinetics**
No pharmacokinetic studies were conducted. In accordance with European Medicines Agency (EMA) “Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases (CHMP/EWP/18504/2006) classical pharmacokinetic studies are not possible for products of allergy immunotherapy. Due to the nature of the product (proteins which will be rapidly catabolised to peptides and amino acids) plasma levels of the active substance are not measurable.
IV.3 Pharmacodynamics

Formal pharmacodynamic studies are not possible for allergen products. However, to show the effect of allergy immunotherapy on the immune system, in accordance with “Guideline on the clinical development on products for specific immunotherapy for the treatment of allergic diseases” (CHMP/EWP/18504/2006) immunological changes and/ or modifications of the end-organ specific response should be measured.

For ACARIZAX immunological parameters were assessed in various clinical trials from phase I through phase III. Immunological response in IgG4, IgE and IgE blocking factor has been shown for all active treatments compared to placebo. A dose-response could be shown in most of the studies. Thus, the applicant could show that treatment with ACARIZAX modified the response of the immune system.

Due to the nature of the product (proteins which will be rapidly catabolised to peptides and amino acids) plasma concentrations of the active substance are not measurable. Hence the non-performance of interaction studies is acceptable.

IV.4 Clinical efficacy

The applicant has shown efficacy of the 12 SQ-HDM oral lyophilisate in two pivotal phase III studies (MT-04 and MT-06) and two supportive phase II studies (MT-02 and P003). All four studies were successfully completed; the primary endpoints were met and secondary endpoints supported the efficacy. In general, with 6 SQ-HDM as well as with 12 SQ-HDM superiority of efficacy compared to placebo could be shown. Overall, treatment with 12 SQ-HDM resulted in a better efficacy; a statistically significant effect compared to placebo was demonstrated in more endpoints and numerical effects were in majority favourable over the results for 6 SQ-HDM.

Two studies assessed allergic asthma as a primary endpoint (MT-02 and MT-04) and two studies assessed allergic rhinitis as the primary endpoint (MT-06 and P003). It should be noticed that for study MT-02 a post-hoc subgroup analysis had been performed for patients with allergic rhinitis, in which efficacy in AR has been analysed. Hence those data derived from study MT-02 are considered also as supportive for the treatment of AR.

In conclusion, for each indication data from one pivotal study (MT-04 for AA and MT-06 for AR) and from at least one supportive study (MT-02 for AA and AR and P003 for AR) are provided.

Formally, even if planned as phase II/III study MT-02 has been accepted only as a supportive study as in this study only doses up to 6 SQ-HDM were investigated. Hence, EMA “Points to consider on application with 1. Metaanalyses; 2. One pivotal study” (CPMP/EWP/2330/99) was applied for both indications. The minimum requirement is generally one controlled study with statistically compelling and clinically relevant results.

Dose-finding

All evidence from the clinical development programme points towards an at least similar or even higher magnitude of effect of the 12 SQ-HDM dose compared to the 6 SQ-HDM dose. The lack of the dose of 12 SQ-HDM in the dose range study, performed in the asthma indication, and a lack of investigation of lower dosages in the indication of allergic rhinitis have been noticed. However, in combination the whole programme shows that 1 and 3 SQ-
HDM doses are probably below the effective dose range, that the 12 SQ-HDM dose has a slightly higher efficacy than the 6 SQ-HDM dose and that 16 SQ-HDM does not have a suitable tolerability profile for at home administration. Thus, the decision to continue the development in the phase III studies with 6 SQ-HDM and 12 SQ-HDM doses was acceptable. As a conclusion, taking daily at-home administration in account, the dosages up to 12 SQ-HDM seem to have the best safety profile and lacks in dose range studies were accepted regarding that the product showed an appropriate risk-benefit ratio in the pivotal studies with 12 SQ-HDM. Thus, the efficacy data observed in MT-02 with 6 SQ-HDM were considered as strongly supportive also for 12 SQ-HDM.

**Efficacy for the treatment of Allergic Rhinitis:**

**MT-06**
The subjects were treated with 12 SQ-HDM, 6 SQ-HDM or placebo on a daily basis for approximately 13 months. The efficacy assessment period started after 01 October 2012 at the earliest to avoid interference of symptoms caused by grass pollen allergy in the assessment period.

The objective of the main efficacy study MT-06 (AR) was a reduction of the total combined rhinitis score (TCRS) during the last 8 weeks of treatment. The TCRS is the sum of the allergic rhinitis daily symptom score (DSS) and the allergic rhinitis daily medication score (DMS); thus it combines symptoms and pharmacotherapy use. The AR DSS consisted of four categories (runny nose, blocked nose, sneezing and itchy nose). For each of these categories a score between 0 and 3 was determined pending on the symptom severity. The AR DMS consisted of two categories - for the use of oral antihistamines and nasal steroids.

In MT-06 equal weight was given to symptoms and medication use.

<table>
<thead>
<tr>
<th></th>
<th>AR symptoms score (also referred to as total nasal symptoms score, TNSS)</th>
<th>AR medication score</th>
<th>Total combined rhinitis score (TCRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Runny nose</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0-3</td>
<td>0-3</td>
<td>0-3</td>
</tr>
<tr>
<td>Oral antihistamine</td>
<td>0-4</td>
<td>0-4</td>
<td>0-4</td>
</tr>
<tr>
<td>Nasal steroid</td>
<td>0-6</td>
<td>0-6</td>
<td>0-24</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0-12</strong></td>
<td><strong>0-12</strong></td>
<td><strong>0-24</strong></td>
</tr>
</tbody>
</table>

The minimal clinically relevant difference was pre-specified to a reduction of an absolute value of 1 in the TCRS. Two clinical scenarios for a reduction of 1 were given as examples, one purely in terms of the medication score and one purely in terms of the symptom score:

If a difference of 1 is merely expressed as medication intake it will reflect 3 months less therapy per year for a patient who is taking antihistamines on a daily basis. Such a decrease of symptom medication use is an advantage and could be considered as clinically relevant from the patient’s perspective.

If a difference of 1 is merely expressed as symptoms, it will reflect a change of one severity class in one symptom, e.g. blocked nose from severity level “severe” to “moderate”. It has to be acknowledged that the patients’ benefit can be presumed for the whole year for perennial allergy. Thus, even if the reduction of one severity level in only one symptom is considered a slight difference, annualised this is a clinically relevant benefit for the patient. Therefore, overall a reduction of 1 in the TCRS was regarded as clinically relevant.
This effect size was met for the primary endpoint in all analyses for the 12 SQ-HDM dose (Full Analysis Set-with multiple Imputations (FAS-MI): 1.09; Per Protocol (PP): 1.36), all being statistically significant with at least a p-value of 0.004. These data were supported by all key secondary endpoints for the 12 SQ-HDM oral lyophilisate (rhinitis daily symptom score, rhinitis daily medication score, overall rhinitis quality of life questionnaire score and combined rhinoconjunctivitis scores in the efficacy evaluation period, all statistically significant different). In addition, all other secondary endpoints were at least numerically in favour of 12 SQ-HDM compared to placebo. 3 out of 8 were also statistically significant better than placebo. Moreover, the post-hoc analysis on days with a rhinitis exacerbation (meaning days with a symptom score of 6 or of 5 with 1 symptom being severe) revealed that the number of days with such exacerbations was halved in the 12 SQ-HDM group. This can also be rated as a clear clinically relevant effect for the patients.

**P003**

Study P003 was designed as dose-response study in patients with allergic rhinitis/rhinoconjunctivitis with or without mild asthma. The trial was conducted in an environmental exposure chamber (EEC) investigating the efficacy of doses of 6 SQ-HDM and 12 SQ-HDM. The primary endpoint was the reduction of the total nasal symptom score (TNSS) measured after 24 weeks of treatment in the EEC. The TNSS comprised four nasal symptoms (runny nose, blocked nose, sneezing and itchy nose), all scored separately on a 0-3 scale (no, mild, moderate or severe symptoms). A clear reduction of the TNSS was seen after 24 weeks of treatment in both dose groups. A clearly better efficacy was shown for the 12 SQ-HDM dose with a faster onset of efficacy and a distinct higher efficacy after 24 weeks of treatment (6 SQ-HDM: reduction of 1.98 in TNSS (27%); 12 SQ-HDM: reduction of 3.62 in TNSS (49%), both statistically significant). The TNSS was lower for the active groups than for the placebo group at all time points following initiation of treatment (week 8, 16, 24) with the HDM oral lyophilisate. The difference between active and placebo increased with time for both doses, and a clear dose response was observed for both onset and magnitude of the effect. For 12 SQ-HDM the difference to placebo was statistically significant already after 8 weeks of treatment.

**MT-02**

Study MT-02 was designed as dose-response study in patients with asthma controlled with ICS. Doses up to 6 SQ-HDM were examined. AR was assessed as a secondary endpoint. No significant effect was shown in the FAS, however in a subgroup of patients who reported AR symptoms and/or AR medication use during the baseline period (81% of the FAS) an effect could be detected. As this subgroup analysis was performed post-hoc, it was only being rated as supportive. The effect of the HDM oral lyophilisate on AR for this subgroup was analysed through the total combined rhinitis score (TCRS) over the 4-week efficacy assessment period. The TCRS is defined as the sum of the rhinitis symptom and the allergic medication scores, thus it combines symptoms and pharmacotherapy use. The subgroup analyses revealed a statistically significant difference between 6 SQ-HDM and placebo at the end of treatment of 0.78 for the TCRS (28.5%; p-value 0.036). No statistically significant differences to placebo were observed for 1 and 3 SQ-HDM.

**Efficacy for the treatment of Allergic Asthma:**

**MT-04**

The primary endpoint chosen for the main efficacy study MT-04 was “time to first asthma exacerbation”. Prior to study conduct the applicant searched for scientific advice by the EMA
and national authorities, to discuss the acceptability of this endpoint as up to now experience with studies regarding allergen immuno-therapy in allergic asthma was very limited. The Committee for Medicinal Products for Human Use (CHMP) considered the chosen primary endpoint as acceptable but advised the applicant to determine the improvement which will be judged as clinically relevant in advance, with respect to the patient’s benefit. A clinically relevant effect size of a hazard ratio (HR) of 0.70 or below (corresponding to a risk reduction of 30% or above) was pre-specified in the protocol. The applicant chose this value based on the opinion of experts in the field of asthma and in comparison with the effect size of other asthma and/or COPD treatments measured as first asthma exacerbation in comparable patient groups. The justification of the applicant is acknowledged.

As AIT needs some time for the modification of the immune-system, the HDM oral lyophilisate was given as add-on therapy to patients’ standard controller medication for 7 – 12 month. After this period, the inhaled corticosteroid (ICS) was reduced to 50% of the applied dose for 3 month. If no asthma exacerbation occurred during this period the ICS was completely withdrawn. In order to deal with a potential bias, patients who dropped out before the ICS reduction phase were included in the primary analysis as if they were following the same distribution, with respect to first asthma exacerbation, as the observed placebo group during ICS reduction. In this analysis the 12 SQ-HDM oral lyophilisate showed a HR of 0.69 and thus met the criterion for clinical relevance. The 6 SQ-HDM dose missed this value slightly (0.72) but in both groups the effect was statistically significant. The analysis in the FAS showed a slightly better difference between active and placebo, with hazard ratio below 0.70 for both 12 SQ-HDM and 6 SQ-HDM compared to placebo (0.66 and 0.69, respectively, both statistically significant).

From a statistical point of view there were concerns regarding the application of a marketing authorisation with only one pivotal study as the primary endpoint ‘time to first moderate or severe asthma exacerbation’ was used for the first time in an AIT efficacy study for allergic asthma. This was especially due to the add-on treatment phase without measuring asthma exacerbations. Measuring phase started with the first reduction of ICS. However, the applicant provided additional analyses, e.g. data of asthma exacerbations for the entire study period after randomization, to support the validity of study results. Moreover, additional non-pivotal trials support the efficacy in asthma. Thus, even if from a methodological point of view a second pivotal study would have been the preferred option to substantiate the treatment effect, the lack of a second pivotal trial was accepted from the clinical point of view as in the totality of results the treatment effect with regard to asthma was shown.

Regarding the clinical relevance of the primary endpoint it should be noted that reducing the risk for having an asthma exacerbation under ICS reduction means that it is for some patients possible to reduce the ICS dose while asthma control remains the same (patients that do not exacerbate under ICS reduction) or that they have the possibility to come through a period with sub-optimal controller treatment (which are known to be prevalent among asthma patients in real-life situations for various reasons) without exacerbation. This increased protection against asthma exacerbations can be considered as clinically relevant for the patient.

Two out of the four defined key secondary endpoints showed statistically significant results to support the primary endpoint. The time to first asthma exacerbation with deterioration in asthma symptoms was significantly reduced by 12 SQ-HDM (HR=0.64) compared to placebo. Also IgG4 was significantly increased by 12 SQ-HDM for both HDM species. However, in the remaining two key secondary endpoints analyses of asthma control questionnaire (ACQ) and asthma quality of life questionnaire (AQLQ) (both adjusted for ICS use) no statistically significant differences between groups were shown. This was due to the fact, that the majority of subjects in all groups reported minimal important difference (MID)
improvements in both ACQ and AQLQ from baseline to visit 13 (end of trial). The placebo effect of treatment is clearly shown by these questionnaires which measure mostly subjective impressions of the patients.

As the study was powered on the primary efficacy parameter and it is not possible to power a study on both the primary endpoint and every other endpoint, secondary endpoints can be only considered of supportive nature and may fail statistically significance.

As stabilisation of disease is a target of AIT, secondary endpoints including measurements of lung function and symptom scores were proposed by the CHMP. To show the clinical relevance, additional endpoints as asthma control, quality of life and number of patients with exacerbation were proposed. Endpoints suggested by the CHMP for MT-04 were in majority considered as secondary endpoints. The results of two endpoints related to asthma exacerbations supported the primary analysis in particular for the 12 SQ-HDM dose. Statistically significant risk reductions (estimated by HR) were found for asthma exacerbations with increased use of SABA (short acting beta-agonist) and asthma exacerbations with deterioration in lung function.

By the measurement of lung function alone a clinical significant effect was only shown in the diurnal variability of PEF for 6 SQ-HDM. No other statistically significant change could be shown. As the HDM oral lyophilisate was taken as add-on treatment to the asthma control medication of the patients and patients should be controlled as such that a FEV1 of ≥ 70% of predicted value was achieved (requirement for inclusion) it is not astonishing that lung function parameters in periods with asthma control medication and until the first asthma exacerbation in the period with ICS reduction showed no great differences. The mean value at randomisation for the entire trial population was actually a FEV1 of 92.7% of predicted value. This shows that there was only little room for improvement from the beginning of the trial. FEV1 was measured at all trial site visits, and asthma treatment could be adjusted in case of any relevant changes in FEV1. Therefore a significant difference in FEV1 between the treatment groups could not be expected.

Also during the period when ICS was reduced, subjects who exacerbated were to adjust their asthma treatment (e.g. increase ICS dose again). Thus, any deterioration in asthma symptoms or lung function would be counteracted by ICS treatment, and the effect on their post exacerbation FEV1 measurements at subsequent trial visits would be diminished.

Regarding the lung function parameters in conjunction with the first asthma exacerbation, fewer exacerbations with deterioration in lung function occurred in the active groups versus the placebo group.

The secondary endpoints related to asthma symptoms and medication use showed mostly only a numerical improvement in favour for the HDM oral lyophilisate. These data showed in addition that the effect may also be evident prior to ICS reduction.

MT-02
Study MT-02 was designed as a dose-response study in patients with asthma controlled with ICS and was considered supportive for the indication AA.

Patients were adjusted to ICS treatment to achieve asthma control before start of AIT treatment. After 40 weeks of treatment with HDM oral lyophilisate, the dose of ICS was stepwise reduced. Reduction of ICS with retained asthma control was examined as the primary endpoint. Best efficacy was demonstrated for the highest dosage (6 SQ-HDM). The primary endpoint was met and the efficacy of 6 SQ-HDM was statistically significant compared to placebo (difference in reduction of ICS -81.4 µg/day, p= 0.0036 (FAS (N = 604)). The study showed a high placebo effect when comparing ICS doses needed for asthma control during baseline period and after treatment. Nevertheless, the difference to placebo in the 6 SQ-HDM group showed a benefit for treated patients. This benefit was clearly
pronounced in the subgroup of patients with higher daily ICS dose and less asthma control at baseline (difference to placebo in reduction of ICS -327 µg/day, p<0.0001 (N = 108)). As this subgroup analysis was performed post hoc, the results were only rated as supportive. The study dose was below the dose for which a marketing authorisation was intended (12 SQ-HDM). For this reason the study was considered as supportive only. However, it has to be emphasised that even with a dose of 6 SQ-HDM efficacy could be shown, especially for subgroups of patients with more pronounced symptoms. Moreover, the ability to reduce the ICS dose and to retain the same asthma control is a clear clinically relevant benefit for the patient. Reduction in ICS was also regarded as clinically relevant effect by the CHMP. Thus, overall the study results are assessed as supportive for the efficacy of ACARIZAX.

Analysis across trials
Clinical efficacy across trials was compared and discussed in terms of changes in TCRS, AR symptoms and medication score, RQLQ, ACQ and AQLQ.

One major difference between the studies in AR was that study MT-06 focussed on subjects with more severe AR. Hence the difference between active treatment and placebo, measured in absolute values, was higher in study MT-06 compared to MT-02 subgroup analysis. However the difference expressed in percentage was lower in study MT-06 compared to MT-02 subgroup analysis. This is caused by the fact that efficacy expressed in percentage value depends on the absolute symptom score for the placebo arm. Hence, the same difference in absolute value will give a higher difference in percentage value if the absolute scoring value in the placebo group decreases and vice versa.

Data of MT-02 and MT-04 cannot be compared directly, as different endpoints were used. However, it is acknowledged that the complementary nature of the trial designs provides independent substantiation of the effect.

All in all, the compiled clinical data reveal a clinically relevant effect of the 12 SQ-HDM oral lyophilisate and were regarded as sufficient for efficacy analysis.

It is acknowledged that AIT belongs to long term strategies and aims to have a persistent effect on the clinical outcome due to changes in the immune system. It is hypothesised that AIT can prevent the allergic march. However, from a positive outcome in one clinical indication (e.g. allergic rhinitis) it cannot be automatically concluded that the treatment is also efficacious for another clinical outcome of the disease (e.g. allergic asthma). For this reason it is acknowledged that some studies were investigating asthma and others allergic rhinitis in the primary endpoints, as evidence for efficacy was needed for both indications. This requirement was fulfilled with one pivotal phase III trial for each indication. Nevertheless, as AIT is designed to modulate the immune system and efficacy of the treatment is driven by changes in the immune system, efficacy in both indications was regarded as supportive for each other.

Conclusion
Relevant efficacy has been shown by the applicant for the 12 SQ-HDM oral lyophilisate for both claimed indications. The parameters assessed in the primary endpoints reflect clinically relevant outcomes. It is expected that the benefit for the patient will be present around the whole year. The proven efficacy is accepted as a clinically relevant effect for patients with HDM allergic rhinitis and asthma.

IV.5 Clinical safety
The safety evaluation is based on four completed phase I trials, two completed phase II trials and two completed phase III trials. In addition, interim safety data on serious adverse events (SAEs) and adverse events (AEs) leading to premature discontinuation were presented for the three ongoing trials with a data lock point (DLP) of 30 May 2014.

In total 734 patients received the 12 SQ-HDM dose, thereof 567 patients for ≥ 24 weeks. 891 patients received the 6 SQ-HDM dose, thereof 732 patients ≥ 24 weeks. 145 and 137 patients received doses of 3 SQ-HDM and 1 SQ-HDM, respectively, for ≥ 24 weeks. Other doses and shorter duration were in addition applied to a small number of patients.

Studies MT-02, MT-04 and P003 included patients without upper age limit. In study MT-06 an upper age limit of 65 years was defined. Subjects up to an age of 74 years were treated with 12 SQ-HDM during phase II and III studies.

Paediatric patients were included into studies MT-03 and P008, and adolescents were included into study MT-02.

Dose-dependence was observed for:
- the overall rate of subjects experiencing AEs
- the rate of subjects experiencing IMP (Investigational medicinal product)-related AEs
- the proportion of IMP-related events
- severity regarding percentages of subjects
- the average number (related and not-related) of AEs per subject (1.38 and 0.25 in 12 SQ-HDM and placebo, respectively, for IMP-related AEs)
- the proportion of subjects reporting most frequent events (≥ 1.5% of subjects) (related and not related)

Dose-dependence was not observed for:
- severity regarding percentages of events
- rate of serious AEs
- outcome of AEs

The highest percentage of subject withdrawals due to an AE was found in the 12 SQ-HDM group (6%), but the dose response was not regular. The same was true for AEs leading to temporary interruption of IMP administration.

The majority of the most frequent events (≥ 1.5% of subjects) were mild (72% in the 12 SQ-HDM group reported by 54% of the subjects). While the proportion of subjects reporting at least one moderate (28% of subjects) or severe (4% of subjects) AE was highest in the 12 SQ-HDM group, the dose response was not regular. Discontinuation or interruption of IMP occurred more frequently due to mild than to moderate or severe AEs.

**Significant adverse events:**
A single event of adrenaline use occurred in the 12 SQ-HDM group. Within 5 minutes after the first administration of IMP the patient experienced a laryngeal oedema which was not considered to compromise the airway and was rated mild and of no vital risk. Nevertheless the patient was treated with adrenaline, in addition to methylprednisolone and desloratadine. The symptoms abated after 30 min. The subject continued and completed the trial with mild oral pruritus as the only subsequent AE.

One case each occurred for idiopathic thrombocytopenia purpura (SAE, not recovered) and eosinophilic esophagitis in study MT-06, and arthralgia (SAE, not recovered) in study MT-04. Eosinophilic esophagitis is considered as a potential risk for AIT (class effect). The other two events are considered as single case event.
Serious adverse events:
A total of 6 IMP related SAEs (out of 65 SAEs occurred in 57 subjects (2%) of the completed phase II and III trials) occurred.

Only one asthma exacerbation was observed in the asthma trial (MT-04), classified as SAE. However, a viral infection might be a triggering factor. Laryngeal oedema is considered as an expected side effect of AIT. The patients with SAEs arthralgia and mild idiopathic thrombocytopenia purpura did not recover.

Overall only a small number of serious adverse events occurred not revealing a special risk.

Asthma
In Study MT-02 a dose-dependent higher number of asthma exacerbations occurred in the active treatment groups compared to placebo. Analyses of study MT-04 did not indicate relevant inhomogeneities between treatment groups for patients entering the ICS reduction phase, neither regarding documented baseline data nor regarding the treatment duration or the prescribed ICS dose. The additional analysis of asthma exacerbations, albeit not statistically significant, was in support of the primary analysis.

In regard to the chosen imputation strategy and the effects of patient drop-outs on the primary endpoint one has to assume that those patients that drop out during the treatment phase with controller medication were not more prone to experience asthma exacerbations than those that did not drop out. In Study MT-04 the standardized MedDRA query (SMQ) ‘asthma/bronchospasm’ identified 12 subjects (27%) in the placebo group, 13 subjects (27%) in the 6 DU group and 6 subjects (17%) in the 12 DU group.

Events of impaired lung function appeared to be connected both to asthma exacerbation leading to discontinuation during the ICS reduction/withdrawal period and to reporting of AEs of asthma. There were no indications of any increased risk for subjects treated with the HDM SLIT-tablet compared with those treated with placebo.

Since AIT has been known to pose a risk on some patients with uncontrolled asthma, in study MT-04 safety data for two sub-populations (“uncontrolled asthma” (n=232 (28%); uncontrolled according to GINA at randomisation) and “low FEV₁” (n=129 (15%) at least one episode of FEV₁ < 70% during the trial) were summarised.
There were no substantial differences regarding the proportion of patients entering the ICS reduction period compared with the total population and regarding withdrawals from the trial for both sub-groups. However, in both sub-groups more patients discontinued after having
experienced an asthma exacerbation compared to the total population (12% in “uncontrolled asthma”, 21% in “low FEV₁” and 9% in total population).

In addition differences compared to the total population were seen for the proportion of subjects reporting AEs being higher in the “low FEV₁” sub-population (84% compared with 72% in total population) and for the PT “asthma” being substantially higher for the “low FEV₁” (21% compared with 7% in total population).

**Safety in children**

From the data provided on AEs in children there are differences seen in the number of adverse events observed in children compared to those observed in adults, e.g. for local side reactions having in most PTs a higher frequency in children than in adults. However, the applicant considers that the safety and tolerability profile of 12 SQ-HDM is similar in children compared to adults. Therefore the applicant was requested to demonstrate in detail the safety and tolerability profile (adverse events) for 12 SQ-HDM, derived from studies in children compared to adults. As a consequence of the low number of children included into clinical trials it is clearly stated that the product is not indicated in children.

**Conclusion**

The safety evaluations demonstrated a favourable safety profile of ACARIZAX 12 SQ-HDM. The adverse events reported were in regard to the number of events as well as to the type of events in normal range for AIT treatment.

There was a dose response in the IMP-related AEs observed, but the events were mostly rated as mild in intensity and rarely leading to discontinuation. However the proportion of subjects discontinuing the trial due to an AE was higher in the 12 SQ-HDM group than in the other groups.

The AEs and SAEs reported as related to treatment (any dose) were isolated events managed by standard medical therapy except for one case: One subject from the 12 SQ-HDM group received adrenaline during the trial. This subject recovered and subsequently continued the trial without any significant AEs.

A total of six SAEs were assessed as (probably) related. Details for all 6 cases have been provided.

### IV.6 Risk Management Plan

A risk management plan has been developed to ensure that ACARIZAX is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for ACARIZAX, including the appropriate precautions to be followed by healthcare professionals and patients. Further information can be found in the summary of the risk management plan.

### IV.7 Discussion on the clinical aspects

All four studies were successfully completed; the primary endpoints were met and secondary endpoints supported the efficacy. In general, with 6 SQ-HDM as well as with 12 SQ-HDM superiority of efficacy compared to placebo was shown. Overall, treatment with 12 SQ-HDM resulted in a better efficacy. Statistically significant effect compared to placebo was demonstrated in more endpoints and numerical effects were in majority favourable over the results for 6 SQ-HDM.
For 12 SQ-HDM tablet the MT-06 (AR) trial came out positive with a statistically significant and clinically relevant reduction of the total combined rhinitis score (TCRS) (difference to placebo: FAS-MI: -1.09). A reduction of one point in the TCRS seems to be perceivable by the patient (e.g. reduction of one severity class or 3 month less antihistamines for a patient who needed this medication all year round) and thus is clinically relevant. Further, for the 12 SQ-HDM tablet, a statistically significant effect was confirmed for all key secondary endpoints.

The MT-04 trial (AA) was designed and powered as an ICS reduction/withdrawal trial with “time to first asthma exacerbation after ICS reduction” as primary endpoint. For the primary endpoint a clinically relevant effect size of a hazard ratio of 0.70 or below (corresponding to a risk reduction of 30% or above) was pre-specified as clinically relevant with respect to patient’s benefit. The HR for experiencing an asthma exacerbation for the 12 SQ-HDM tablet versus placebo was 0.69 in the FAS with imputations and thus the value for clinical relevance was met. Reducing the risk for having an asthma exacerbation under ICS reduction means that for some patients it will be possible to reduce the ICS dose while asthma control remains the same (patients that do not exacerbate under ICS reduction) or that they have the possibility to come through a period with sub-optimal controller treatment (which are known to be prevalent among asthma patients in real-life situations for various reasons) without exacerbation. Two secondary endpoints (asthma exacerbations with increased use of SABA and asthma exacerbations with deterioration in lung function) supported the primary analysis in particular for the 12 SQ-HDM dose. Regarding lung function, a significant effect was only shown in the diurnal variability of PEF for 6 SQ-HDM. However, as the HDM tablet was applied as add on treatment to the asthma control medication of the patients and patients asthma should be controlled as such that the FEV1 of ≥ 70% of predicted value was achieved, it is comprehensible that lung function parameters in periods with asthma control medication and before first asthma exacerbation in the period with ICS reduction showed no great differences. The ability to reduce the ICS dose and retaining the same asthma control is a clear clinically relevant benefit for the patient.

All trials demonstrated an immunological effect of the HDM allergy immunotherapy tablet. The immunological data indicated a dose response with numerically higher inductions of specific IgE and IgG4 in the 12 DU group compared to the 6 DU group and thus showed a modulation of the immune-system.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The objective of Allergen Immunotherapy (AIT) is to modify the ‘allergic’ response of the immune-system resulting in effects on clinical manifestations of the disease. The sublingual route was selected to provide a product with a safety profile allowing for at-home administration which improves convenience for patients (including treatment option for those having fear of injections or whose time schedule did not allow frequent visits to a physician over a treatment period of several years).

The quality of drug substances and the drug product are adequate.

The clinical development programme for the HDM SLIT-tablet has been discussed at several scientific advice meetings by the CHMP and national authorities between 2004 and 2014. The main topics discussed have been clinical trial design and choice of primary endpoint in AA and the adequacy of the clinical development programme as a whole. The development programme followed the current state of the art.

ACARIZAX is indicated in adult patients (18-65 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with at least one of the following conditions:

- persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication
- house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Patients' asthma status should be carefully evaluated before the initiation of treatment.

From a positive outcome in one clinical indication (e.g. allergic rhinitis) it cannot be automatically concluded that the treatment is also efficacious for another clinical outcome of the disease (e.g. allergic asthma). For this reason it is acknowledged that some studies were investigating allergic asthma (AA) as a primary endpoint (MT-02 and MT-04) and others allergic rhinitis (AR) in the primary endpoints (P003 and MT-06), as evidence for efficacy in both indications. Nevertheless, as AIT is designed to modulate the immune system and efficacy of the treatment is driven by changes in the immune system, efficacy in both indications can be regarded as supportive for each other.

Paediatric patients were included into studies MT-03 and P008, and adolescents were included into study MT-02.

Two clinical studies in children are planned in accordance with the Opinion of the Paediatric Committee on a Paediatric Investigation Plan and/or a Waiver adopted under Article 18 of Regulation (EC) No. 1901/2006, for Dermatophagoides pteronyssinus / Dermatophagoides farinae (EMEA-001258-PIP01-11). The initiation and completion of both studies have been deferred in the EMEA-001258-PIP01-11 decision. The due date of completion of the PIP is December 2028.

For 12 SQ-HDM tablet the MT-06 (AR) trial came out positive with a statistically significant and clinically relevant reduction of the total combined rhinitis score (TCRS) (difference to placebo: FAS-MI: -1.09). The minimal clinically relevant difference was pre-specified to a reduction of an absolute value of 1 in the TCRS. In accordance with literature data, the minimal difference which a patient can perceive can be used for determination of a minimal important difference. A reduction of one point in the TCRS seems to be perceivable by the patient (e.g. reduction of one severity class or 3 month less antihistamines for a patient who needed this medication all year round) and thus is clinically relevant.

Further, for the 12 SQ-HDM tablet, a statistically significant effect was confirmed for all key secondary endpoints with statistically significant reductions of the rhinitis daily symptom
score, rhinitis daily medication score, overall rhinitis quality of life questionnaire score and combined rhinoconjunctivitis scores in the efficacy evaluation period compared to placebo. In addition, all other secondary endpoints were at least numerically in favour for the 12 SQ-HDM, 3 out of 8 were statistically significant better than placebo. Moreover, the post-hoc analysis on days with a rhinitis exacerbation (meaning days with a symptom score of 6 or of 5 with 1 symptom being severe) revealed that the number of days with such exacerbations was halved in the 12 SQ-HDM group. This can also be rated as a clear clinically relevant effect for the patient.

Study P003 performed in an environmental exposure chamber supported the efficacy of the 12 SQ-HDM tablet. After 24 weeks of treatment in comparison with the placebo group a nearly 50% reduction in the total nasal symptom score during allergen exposition in the chamber was achieved. The difference between active and placebo increased with time and was already statistically significant after 8 weeks of treatment.

The MT-04 trial was designed and powered as an ICS reduction/withdrawal trial with “time to first asthma exacerbation after ICS reduction” as primary endpoint. The applicant received scientific advice by the CHMP. ALK has chosen a new primary endpoint for their phase III study in AA (time to first asthma exacerbation). For the primary endpoint a clinically relevant effect size of a hazard ratio of 0.70 or below (corresponding to a risk reduction of 30% or above) was pre-specified as clinically relevant with respect to patient’s benefit. This value was chosen based on the opinion of experts in the field of asthma and in comparison with the effect size of other asthma and/or COPD treatments. The HR for experiencing an asthma exacerbation for the 12 SQ-HDM tablet versus placebo was 0.69 in the FAS with imputations and thus the value for clinical relevance was met.

Reducing the risk for having an asthma exacerbation under ICS reduction means that for some patients it will be possible to reduce the ICS dose while asthma control remains the same (patients that do not exacerbate under ICS reduction) or that they have the possibility to come through a period with sub-optimal controller treatment (which are known to be prevalent among asthma patients in real-life situations for various reasons) without exacerbation. This increased protection against asthma exacerbations is considered as clinically relevant for the patient.

Two secondary endpoints (asthma exacerbations with increased use of SABA and asthma exacerbations with deterioration in lung function) supported the primary analysis in particular for the 12 SQ-HDM dose. Regarding lung function, a significant effect was only shown in the diurnal variability of PEF for 6 SQ-HDM. However, as the HDM tablet was applied as add on treatment to the asthma control medication of the patients and patients asthma should be controlled as such that the FEV$_1$ of $\geq 70\%$ of predicted value was achieved, it is comprehensible that lung function parameters in periods with asthma control medication and before first asthma exacerbation in the phase with ICS reduction showed no great differences. Nevertheless, regarding the lung function parameters in conjunction with the first asthma exacerbation, fewer exacerbations with deterioration in lung function occurred in the active groups versus the placebo group. The secondary endpoints related to asthma symptoms and medication use showed mostly only a numerical improvement in favour for the HDM tablet. These data showed in addition that the effect may also be evident prior to ICS reduction (assessed at the end of the period with asthma control medication). In addition, the treatment revealed a high placebo effect, precluding a statistically significant effect in the questionnaires for asthma control (ACQ) and asthma related quality of life (AQLQ) since values improved in all groups (including placebo group). Thus, data of ACQ and AQLQ cannot support the efficacy of the HDM tablet.

However, efficacy in asthma was also supported by study MT-02 measuring reduction of ICS while maintaining asthma control as primary endpoint. Best efficacy was demonstrated for the
highest dosage (6-SQ-HDM). Also this study showed a high placebo effect, however
difference to placebo was statistically significant. The ability to reduce the ICS dose and to
retain the same asthma control is a clear clinically relevant benefit for the patient.
All trials demonstrated an immunological effect of the HDM allergy immunotherapy tablet. 
The immunological data indicated a dose response with numerically higher inductions of
specific IgE and IgG4 in the 12 SQ-HDM group compared to the 6 SQ-HDM group and thus
showed a modulation of the immune-system.

The safety evaluations demonstrated a safety profile of the HDM allergy immunotherapy
tablet in both administered doses compatible with at-home administration. There was a dose
response in the IMP-related AEs, but the events were mostly rated as mild in intensity also for
the 12 SQ-HDM tablet dose. The AEs and SAEs reported as related to treatment (any dose)
were isolated events managed by standard medical therapy except for one case: One subject
from the 12 SQ-HDM group received adrenaline during the trial, however, for laryngeal
oedema which was not considered to compromise the airway and was rated as mild in
intensity. Thus, the need to treat this AE with adrenaline seems questionable. This subject
recovered and subsequently continued the trial without any significant AEs.

The AEs were only rarely leading to discontinuation. About 4% of subjects discontinued
prematurely from one of the phase II and III trials due to AEs. While the dose response was
not straight-forward, the highest proportion was observed in the 12 SQ-HDM group (6%)
compared with 3% in the placebo group. The majority of these AEs leading to premature
discontinuation were moderate in intensity; however 22% of patients who discontinued in the
12 SQ-HDM group did this also due to mild AEs. A total of six SAEs were assessed as
(probably) related. Details for all 6 cases have been provided. There was no apparent signal
for specific treatment-related events reported as serious or rated as severe.

AIT in general bears the risk of systemic allergic reactions up to an anaphylactic shock.
However, the allergic side reactions were of lower intensity, and systemic allergic reactions
occurred less common in sublingual AIT compared to subcutaneous application. Only one
allergic reaction requiring treatment with adrenalin occurred during the trials. From the
experience gained in sublingual immunotherapy in general an anaphylactic shock as side
effect is unlikely.

The applicant proposed a period of 30 minutes for medical observation after first intake, and
he could show that based on the safety data obtained in the clinical trials and in accordance
with international guidelines this period of observation is sufficient.

In conclusion, the clinically relevant efficacy shown in two pivotal phase III studies and
supported by clinically relevant efficacy shown in two phase II trials outweighs the risk of
suffering an allergic reaction of mostly mild intensity. Thus, a favourable benefit-risk profile
was demonstrated for the HDM allergy immunotherapy tablet 12 SQ-HDM in adult subjects
with HDM allergic rhinitis and/or only partly controlled asthma.
LIST OF REFERENCES


Dretzke et al. 2013).

