



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for: American house dust mite extract/ European house dust mite extract

Proprietary Product Name: Acarizax

Sponsor: Seqirus Pty Ltd

October 2017

About the Therapeutic Goods Administration (TGA)

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- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
AA	Allergic Asthma
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AIT	Allergy Immunotherapy
ALK	ALK-Abelló A/S
ALT	Alanine Aminotransferase
AQLQ(S)	Asthma Quality of Life Questionnaire
ACS	Asthma Control Scores
AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
CER	Clinical Evaluation Report
CI	Confidence Interval
<i>D. farinae</i>	<i>Dermatophagoides farinae</i>
<i>D. pteronyssinus</i>	<i>Dermatophagoides pteronyssinus</i>
DMS	Daily Medication Score
DSS	Daily Symptom Score
DU	Development Unit
EMA	European Medicines Agency
EoE	Eosinophilic Esophagitis
FAS	Full Analysis Set
FAS-MI	Full Analysis Set with Multiple imputation
FEV ₁	Forced Expiratory Volume in one second
HDM	House Dust Mite

Abbreviation	Meaning
HDMSLIT-tablet	House Dust Mite Sublingual Immunotherapy Tablet
HR	Hazard Ratio
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgE	Immunoglobulin E
IL-10	Interleukin 10
IMP	Investigational Medicinal Product
IT	Immunotherapy
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
GPV	Global Pharmacovigilance, ALK
LFT	Liver Function Tests
MID	Minimal Important Difference
NNH	Number Needed to Harm
NNT	Number Needed to Treat
PO	Per Oral
PP	Per Protocol Set
RQLQ	Rhinitis Quality of Life Questionnaire
SABA	Short-Acting Beta-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCIT	Subcutaneous Immunotherapy
SE	Standard Error

Abbreviation	Meaning
SLIT	Sublingual Immunotherapy
SOC	System Organ Class
SPT	Skin Prick Test
SS	Safety Set
TACA	Total Allergen Centaur Assay
TCRS	Total Combined Rhinitis Score; the sum of the DSS and the DMS averaged over the last 8 weeks of treatment
TH1	T helper cell type 1
TH2	T helper cell type 2
Treg	regulatory T cell

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	21 July 2016
<i>Date of entry onto ARTG</i>	1 August 2016
<i>Active ingredients:</i>	American house dust mite extract European house dust mite extract
<i>Product name:</i>	Acarizax
<i>Sponsor's name and address:</i>	Seqirus Pty Ltd ¹ 63 Poplar Rd Parkville VIC 3052
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	12 SQ-HDM (6 SQ-HDM American house dust mite extract and 6 SQ-HDM European house dust mite extract)
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	10, 30 and 90 oral tablets
<i>Approved therapeutic use:</i>	<i>Acarizax is indicated for the treatment of adults diagnosed with:</i> <ul style="list-style-type: none"><i>House dust mite (HDM) allergic rhinitis not well controlled despite use of symptom relieving medication or</i><i>HDM allergic asthma not well controlled by inhaled corticosteroids and associated with HDM allergic rhinitis. Patients' asthma status should be carefully evaluated before the initiation of treatment.</i>
<i>Route of administration:</i>	sublingual
<i>Dosage:</i>	One oral lyophilisate tablet per day for adults. The first dose should be taken under medical supervision. Acarizax is not recommended for children below 18 years of age. For further details please see the Product Information.
<i>ARTG number:</i>	250392

¹ At the time of the submission the sponsor was bioCSL Pty Ltd, however prior to approval the sponsor changed to Seqirus Pty Ltd, 63 Poplar Road, Parkville VIC 3052.

Product background

This AusPAR describes the application by bioCSL Pty Ltd¹ (the sponsor) to register Acarizax² American house dust mite extract and European house dust mite extract lyophilisate sublingual tablets for the following indication:

Acarizax is indicated in adults diagnosed with house dust mite sensitisation with at least one of the following conditions:

- *persistent moderate to severe HDM-allergic rhinitis despite use of symptom-relieving medication*
- *HDM-allergic asthma not well controlled by inhaled corticosteroids. Patients' asthma status should be carefully evaluated before the initiation of treatment.*

The application is for an allergen extract as an add on treatment for adult subjects with allergy to house dust mites (HDM) where it is associated with allergic asthma (AA) not controlled with inhaled corticosteroid and/or associated with allergic rhinitis (AR).

Both AA and AR are significant health burdens in Australia, and current symptomatic therapy is often insufficient to adequately treat symptoms in individuals with moderate or severe disease. Approximately 15% of Australians have AR, and approximately 10% have current asthma.

Asthma is a complex chronic disease with a pathogenesis that is incompletely understood. There is underlying immunological dysregulation in asthma, which can be identified in situ within the lung, adjacent lymph nodes and also in the circulating lymphocyte compartment.

Allergic rhinitis (AR) is the clinical manifestation of allergic disease in the nose. Many of the clinical symptoms of AR can be directly attributed to an abnormal immunological response to allergen/s and to the release of mast cell and basophil mediators. AR and asthma often co-exist, and there is some evidence of a naso-pulmonary axis, by which control of AR symptoms leads to clinical improvement in asthma. AR often co-exists with allergic conjunctivitis (which is not a disease indication in the current application).

The sponsor states that immunotherapy (IT) is a treatment option for allergy that is complementary to pharmacotherapy and with a distinct mechanism of action. Immunotherapy is performed by repeated subcutaneous or sublingual administration of specific allergens to an allergic person in order to gradually induce immunological tolerance towards the allergens. They state that considerations for initiating IT include disease severity, lack of efficacy of pharmacotherapy, side effects of pharmacotherapy, patient preference and the presence of more than one manifestation of the underlying allergic disease. They state that IT can modulate the basic immunologic 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.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 1 August 2016.

At the time this application was submitted there were several other products on the ARTG containing European and American house dust mite extracts. These included Alustal House Dust mites extract suspension for injection (ARTG 132725, 132680)

² At the time of the submission the proposed name for the product was Mitizax, during the course of the submission the name was changed to Acarizax.

At the time the TGA considered this application; a similar application had been approved in the European Union under the decentralised procedure (reference member state was Germany, approved August 2015) and was under consideration in Switzerland (submitted February 2015) and the USA (submitted February 2016).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

The house dust mite (HDM) drug substances are allergen extracts derived from two species of cultivated HDM, *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) and *Dermatophagoides farinae* (*D. farinae*). Each drug substance is a mixture of proteins and other natural substances; therefore, no detailed structural information is available.

Physical and chemical properties

The drug substances (DS) consist of frozen aqueous droplets of allergen extracts. The biological potency of the two drug substances is given in development units (DU³). Each batch of DS for a species is standardised against the in-house reference for each species. During the standardisation, the DU potency is assigned to the DS based on total allergenic activity and the content of two major allergens (group 1 and group 2 allergens).

Drug product

The drug product specifications for the HDM SLIT-tablet, 12 SQ-HDM per tablet control appearance, disintegration, water content, uniformity of mass, protein profile, identity, potency, microbiological examination and test for specified microorganisms.

All analytical procedures are validated. There were no issues related to specification.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data: The photostability study demonstrated that no special labelling on the packaging is needed in order to avoid exposure to light. The proposed shelf life is 36 months when stored below 25°C. Stability studies have been conducted in accordance with relevant ICH guidelines.

Potency by total allergen centaur assay

The total allergen centaur assay (TACA) measures the total allergenic activity of *D. farinae* or *D. pteronyssinus* allergens. TACA is a quantitative IgE competitive immunoassay.

³ The potency of the HDM SLIT-tablet is defined in development units (DU). The DU is based on a standardised amount of allergens from each species.

Biopharmaceutics

None: tablet.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Acarizax (standardised allergen extract from house dust mites *Dermatophagoides* sp.), sublingual immunotherapy tablet.

Conditions of registration

1. It is a condition of registration that all batches of Acarizax (standardised allergen extract from house dust mites *Dermatophagoides* sp.), sublingual immunotherapy tablet imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. The Sponsor must provide:
 - a. an Annual Product Report, using the template available on the TGA website (<https://www.tga.gov.au/form/annual-product-report-biological-prescription-medicines>), on the above product listing batch details and quantities released during the previous year (including export products). A justification should be supplied for the release of any batches which do not meet specifications or undergo unacceptable temperature deviations during shipping. The annual report should be submitted by an agreed due date.
 - b. samples, reference materials, certificates of analysis and related documentation when requested by the Laboratories Branch of the TGA for post market monitoring.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was adequate. Aspects of primary pharmacology and pharmacodynamics were addressed using largely published literature and a limited number of in-house studies. One good laboratory practice (GLP) compliant repeat dose toxicity study was conducted in mice. Classical secondary pharmacodynamic, safety pharmacology and pharmacokinetic studies were not conducted owing to the nature of Acarizax, and justification was provided for omission of carcinogenicity studies, some reproductive toxicity studies, and use of a single rodent species in repeat dose toxicity studies (see below).

Pharmacology

No primary pharmacology studies were submitted for assessment. Instead, the sponsor presented numerous published articles which alluded to the efficacy, safety and mechanism of action of HDM extracts in the context of sublingual immunotherapy (SLIT). In addition, articles discussing suitable animal models for nonclinical analysis of HDM extracts were also presented. The collective findings of these studies formed the basis of the pharmacological component of the dossier.

Published data on the occurrence of dust mites in Australia reported that *D. pteronyssinus* was the most abundant species in all locations.^{4, 5} *D. farinae* was found in some locations, but its abundance was low. *Euroglyptus maynei* was also identified. Although average dust mite allergen levels were higher in humid regions, high allergen levels were measured in some homes in dry inland regions.

Primary pharmacology

While the inflammatory processes initiated through allergen exposure have been elucidated to a large extent (Figure 1), the mechanisms underpinning allergy immunotherapy (AIT) remain poorly characterised. In the case of subcutaneous immunotherapy (SCIT) it is postulated that 'allergenic tolerance' is mediated through the induction of FOXP3+ CD25+ regulatory T cells (Tregs) specific to such allergens and induction of 'blocking' antibodies such as IgG4 and Immunoglobulin A (IgA) IgA2.⁶ Furthermore, it is proposed that induction of regulatory cytokines, such as TGF- β and Interleukin 10 (IL-10) potentiates a shift from T helper cell type 2 (TH2) to a regulatory T cell (Treg) or T helper cell type 1 (TH1) response pattern. A similar mechanism in immune response is also postulated in sublingual immune therapy (SLIT) (Figure2).

Supporting this hypothesis, the sponsor presented studies from Smith et al., 2004, showing increased allergen-specific IgG and IgE following chronic treatment. In this study, increased IgG levels appeared to correlate with longer treatment durations. In addition investigations from Ippoliti et al. 2003, Pajno et al. 2000 and Silvestri et al., 2002 suggested attenuated local and systemic inflammatory mediators.^{7,8,9} To this end, Ippoliti et al. demonstrated that SLIT modulates the synthesis of Th2 cytokines accompanied by a reduction of IL-13. Furthermore, the study suggested reduced activation of T lymphocytes due to reduction of prolactin levels. While the study from Pajno et al. offered limited insight towards mechanisms underlying SLIT, it did suggest reduced efficacy of SLIT compared to subcutaneous immunotherapy in children with asthma. A study by Silvestri et al. in contrast did not show any significant increase in IgE following SLIT of *D. pteronyssinus* or *D. farinae* extract exposure. Though not a double blind study, Silvestri et al. did demonstrate an overall reduction of rhinoconjunctivitis and asthma symptom scores accompanied by a reduction in use of medication by the study subjects. The sponsor also referenced studies from Bohle et al., 2007; Fanta et al., 1999; O'Hehir et al., 2009 which implicated T cell tolerance in SLIT.^{10, 11, 12} The study by Bohle et al. demonstrated that SLIT induces regulatory T-cell suppression through IL-10 during the early phase and immune deviation of allergen-specific T cells during the later phase of therapy. Fanta et al. also

⁴ Colloff MJ et al House dust mite acarofauna and Der p 1 equivalent in Australia: the relative importance of Dermatophagoides pteronyssinus and Euroglyptus maynei. *Clin Exp Allergy* 1991; 21: 225-230.

⁵ Tovey ER et al. Domestic mite species and Der p 1 allergen levels in nine locations in Australia. *ACI Inter.* 2000; 12: 226-231.

⁶ Pilette C, et al. Grass-pollen immunotherapy induces an allergenspecific IgA2 antibody response associated with mucosal TGF-beta expression. *J Immunol.* 2007;178:4658-4666

⁷ Ippoliti F et al. Immunomodulation during sublingual therapy in allergic children. *Pediatr Allergy Immunol* 2003; 14, 216-221

⁸ Pajno G B et al. Clinical and immunologic effects of long-term sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, placebo-controlled study. *Allergy* 2000; 55: 842-849.

⁹ Silvestri M et al. Changes in inflammatory and clinical parameters and in bronchial hyperreactivity asthmatic children sensitized to house dust mites following sublingual immunotherapy. *J Investig Allergol Clin Immunol* 2002; 12: 52-59

¹⁰ Bohle, B., et al. Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. *J Allergy Clin Immunol* 2007; 120: 707-713

¹¹ Fanta, C. et al. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. *Int Arch Allergy Immunol* 1999; 120: 218-224.

¹² O'Hehir, R.E. et al.. House dust mite sublingual immunotherapy: the role for transforming growth factor-beta and functional regulatory T cells. *Am J Respir Crit Care Med* 2009; 180: 936-947.

observed increases in allergen specific IgG, IgG4 and IgE following SLIT treatment with grass pollen extract. The study postulated that successful allergen immunotherapy is likely to be associated with changes at the T cell level rather than with alterations in quantity or distribution of antibodies.

Figure 1: Uptake of HDM allergen particles, immediate allergic reaction, and sustained inflammatory response are shown (From Calderon et al., 2015¹³).

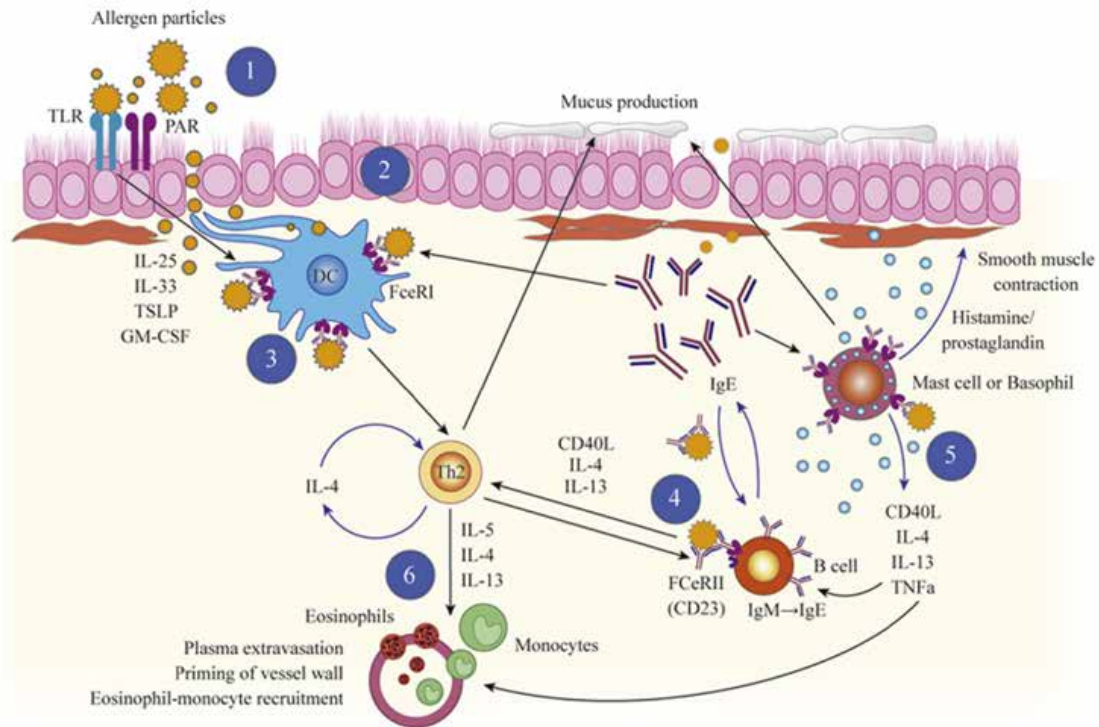
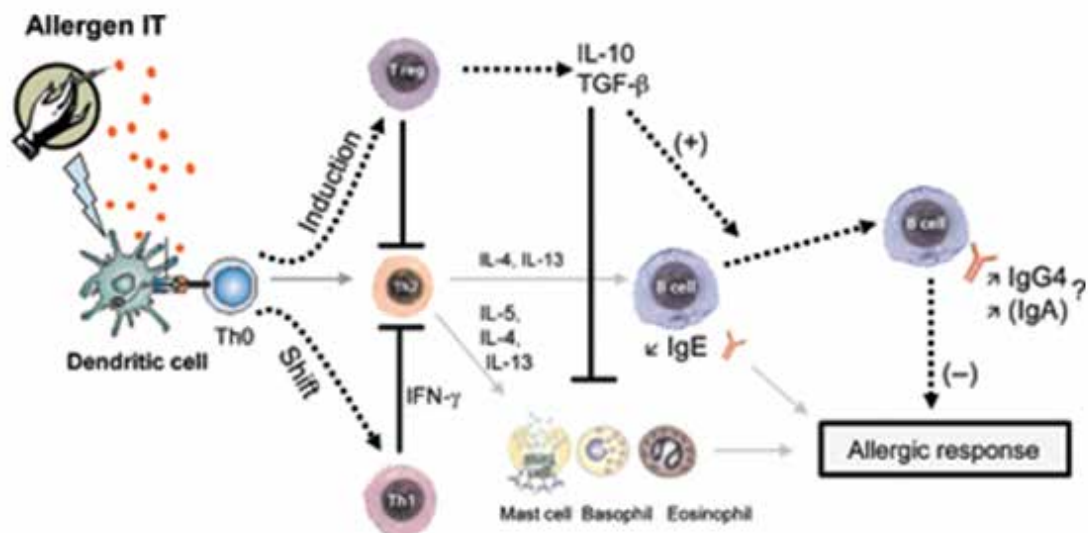


Figure 2: Schematic representation of the potential immune deviation leading to the beneficial effects of allergen immunotherapy (From Yousef et al., 2010)¹⁴



¹³ Calderon M.A. Respiratory allergy caused by house dust mites: What do we really know? *J Allergy Clin Immunol* 2015; 136, 38

¹⁴ Yousef A. et al. Allergen-specific subcutaneous immunotherapy in allergic asthma: immunologic mechanisms and improvement. *Libyan J Med* 2010; 5: 5303

The sponsor also presented numerous published clinical studies as evidence of SLIT efficacy, both as a short and long-term treatment.^{15, 16, 17, 18, 19, 20, 8, 21, 9, 22, 23, 24} Bousquet et al. demonstrated improved respiratory function, bronchial hyperreactivity and quality of life when HDM related asthma is treated with *D. pteronyssinus* and *D. farinae* extracts. Di Rienzo et al. showed clinical efficacy in reducing asthma up to 4 to 5 years following cessation of SLIT treatment with *D. pteronyssinus* and *D. farinae* extracts. The findings of Guez et al. were ambiguous with respect to clinical benefit when treated with same allergen extract. The authors however indicated allergen avoidance measures undertaken by the subjects as a likely source of the ambiguity. Marcucci et al demonstrated changes in local parameters such as eosinophil cationic protein, tryptase and IgE commensurate with improved clinical outcomes in a 12 month SLIT study using major mite allergen Group 1 and half of the major mite allergen Group 2. Potential efficacy of HDM allergen SLIT treatment was also demonstrated by Mortemousque et al. as a preventative treatment for perennial conjunctivitis caused by HDM. Mungan et al. demonstrated decreased rhinitis symptoms with unchanged asthma scores in patients treated with *D. pteronyssinus* and *D. farinae* extracts. A review by Passalacqua et al. concluded, based on publications up to November 2003, that the use of SLIT was a viable alternative to subcutaneous immunotherapy, particularly in paediatric patients. As previously mentioned, Silvestri et al. showed an overall reduction of rhinoconjunctivitis and asthma symptom scores. Tari et al. reported increased IgG1, IgG4 and IgE levels compared to controls when treating asthma and rhinitis patients with SLIT accompanied by notable clinical improvement. The study by Tonnel et al. revealed that SLIT treatment of chronic rhinitis resulted in better efficacy compared to placebo. Wilson et al. conducted a review of clinical trials and literature up to 2006 and concluded that SLIT is a safe treatment, which significantly reduces symptoms and medication requirements in allergic rhinitis. The study further emphasised that the difference between SCIT and SLIT was unclear and optimising allergen dosage and patient selection was required.

The sponsor submitted additional published articles, which support the clinical safety of SLIT.^{25, 26, 27, 8, 21, 24} A review of eight double blind, placebo controlled trials by Andre et al., 2000, did not reveal any serious adverse effects. A study Di Rienzo et al., 1999 also did

¹⁵ Bousquet, J et al. WHO Position Paper. Allergen immunotherapy: Therapeutic vaccines for allergic diseases. *Allergy* 1998; 53: 1-42.

¹⁶ Di Rienzo, V. et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003; 33: 206-210.

¹⁷ Guez S. et al. House-dust-mite sublingual-swallow immunotherapy (SLIT) in perennial rhinitis: a double-blind, placebo-controlled study. *Allergy* 2000; 55: 369-375.

¹⁸ Marcucci, F. et al. 2003. Effects on inflammation parameters of a double-blind, placebo controlled one-year course of SLIT in children monosensitized to mites. *Allergy* 2003; 58: 657-662.

¹⁹ Mortemousque B. et al. House-dust mite sublingual swallow immunotherapy in perennial conjunctivitis: a double-blind, placebo-controlled study. *Clin Exp Allergy* 2003; 33: 464-469.

²⁰ Mungan, D. et al. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma--a placebo controlled study. *Ann Allergy Asthma Immunol* 1999; 82: 485-490.

²¹ Passalacqua G. et al. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2004; 93: 3-12.

²² Tari MG. et al. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. *Allergol Immunopathol* 1990; 18: 277-284.

²³ Tonnel AB et al. Allergic rhinitis due to house dust mites: evaluation of the efficacy of specific sublingual immunotherapy. *Allergy* 2004; 59: 491-497.

²⁴ Wilson DR et al. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2006CD002893

²⁵ Almagro E. et al. Estudio multicéntrico de farmacovigilancia de inmunoterapia sublingual en pacientes alérgicos. *Allergol Immunopathol* 1995; 23: 153-159.

²⁶ Andre c. et al. Safety of sublingual-swallow immunotherapy in children and adults. *Int Arch Allergy Immunol* 2000; 121: 229-234.

²⁷ Di Rienzo V. et al. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. *Allergy* 1999; 54: 1110-1113.

not show adverse effects in paediatric patients (aged 2 to 15) when treated with SLIT.²⁷ Though no serious adverse effects were noted, the study by Pajno et al., 2003 reported rhino-conjunctivitis, urticarial and wheezing in 10% paediatric patients, which could potentially be attributed to SLIT treatment.⁸ While most studies supplied by the sponsor were completed more than 10 years prior to submission, recent safety reviews based on clinical trials also concur with previous findings; that is systemic reactions are rare and side effects mostly consist of mild, self-limiting local reactions.²⁸ The latter review does however caution that since data on important outcomes such as exacerbations, quality of life and use of different unvalidated symptom and medication scores are incomplete and that further analysis using validated scales and important outcomes for patients and decision makers are needed. The study by Normansell et al 2015²⁹ also notes that while limited adverse events have been documented, the preferential recruitment of patients with intermittent or mild asthma for clinical trials precludes safety conclusions regarding SLIT treatment of those with moderate or severe asthma is difficult. It is however noted that subjects with a broader severity of HDM allergic asthma than previously investigated were recruited for the Acarizax clinical trials where the safety profile of Acarizax was demonstrated.

While the majority of the supplied studies pertaining to efficacy and safety were of clinical origin, the sponsor also presented unpublished in-house data as well as published animal model studies in evaluating the efficacy and safety of SLIT. The studies included mouse^{30, 31, 32, 33, 34, 35, 36, 37, 38, 39}, rat⁴⁰ and guinea pig models;⁴¹ some of which appeared to be in-house reports and study summaries from the sponsor.^{32, 34, 35} While the animal models are in broad alignment with efficacy and safety data associated with the clinical studies, in the absence of an established mechanism of action, efficacy and safety data that can be extrapolated from animal models is limited. In addition, symptom scores or use of

²⁸ Senna G, et al. Safety and tolerability of sublingual immunotherapy in clinical trials and real life. *Curr Opin Allergy Clin Immunol*. 2013; 13: 656-662.

²⁹ Normansell R, et al. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. 2015; 28: 8: CD011293.

³⁰ Brimnes, J et al. Sublingual immunotherapy reduces allergic symptoms in a mouse model of rhinitis. *Clin Exp Allergy* 2007; 37: 488-497.

³¹ Cates, E.C. et al. Intranasal exposure of mice to house dust mite elicits allergic airway inflammation via a GM-CSF-mediated mechanism. *J Immunol* 2004; 173: 6384-6392.

³² Hagner-Benes, S. Investigation of prophylactic SLIT (High dose). 1-5. 2014. Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Medical Faculty, Philipps University of Marburg, Germany.

³³ Kildsgaard, J. et al. Sublingual immunotherapy in sensitized mice. *Ann Allergy Asthma Immunol*, 2007; 98: 366-372.

³⁴ Rask, C., Brimnes, J. & Lund, K. Internal Report: Pharmacodynamic data of HDM SLIT in mice. Report Number 198903, 1-21. 2011. ALK, Denmark

³⁵ Rask, C., et al. Sublingual immunotherapy with house dust mite extract prevents the development of allergic inflammation and asthma in a mouse model. *J Allergy Clinical Immunol* 2010; 125, AB263. 2010. Oral poster presentation at AAAAI 2010, New Orleans, LA, US.

³⁶ Sato, M.N. et al. Oral tolerance induced to house dust mite extract in naive and sensitized mice: evaluation of immunoglobulin G anti-immunoglobulin E autoantibodies and IgG-IgE complexes. *Immunology* 1998; 95: 193-199.

³⁷ Tategaki, A., et al. A high-molecular-weight mite antigen (HM1) fraction aggravates airway hyperresponsiveness of allergic mice to house dusts and whole mite cultures. *Int Arch Allergy Immunol* 2002; 129: 204-211.

³⁸ Tourdot, S. et al. mouse model of chronic house dust mite-induced asthma for evaluation of therapeutic vaccines. *Allergy* 2010; 65: 132-133.

³⁹ Yu, H.Q. et al. Sublingual immunotherapy efficacy of Dermatophagoides farinae vaccine in a murine asthma model. *Int Arch Allergy Immunol* 2010; 152: 41-48.

⁴⁰ Xie Q-m et al. Oral administration of allergen extracts from Dermatophagoides farinae desensitizes specific allergen-induced inflammation and airway hyperresponsiveness in rats. *International Immunopharmacology* 2008; 8: 1639-1645.

⁴¹ Hsiue, T.R., Lei, H.Y., Hsieh, A.L., Wang, T.Y., Chang, H.Y. & Chen, C.R. 1997. Mite-induced allergic airway inflammation in guinea pigs. *Int Arch Allergy Immunol*, 112, 295-302

rescue medication, selected as primary and/or secondary endpoints in clinical trials are not necessarily superimposable on animal models to evaluate treatment efficacy; systemic immunological changes induced by SLIT do not always correlate with clinical efficacy^{42, 43, 44} and biomarkers that are predictive of, or surrogate, for the clinical response to immunotherapy are not currently available in humans, and thus in sensitized animals. These limitations are however countered by the relatively large body of clinical data demonstrating tangible efficacy accompanied by safety history.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic or safety pharmacology studies were submitted. While no specific justification was provided by the sponsor, given that:

- c. Use of allergen extracts for SLIT in humans has been broadly considered as a therapy with recognized efficacy and an acceptable level of safety over a long period⁴⁵
- d. No or low tissue systemic absorption of the mite extracts is anticipated and
- e. The freeze-dried mite allergen extracts have been used in humans for SLIT in the form of sublingual drops for many years without relevant safety concern.

The absence of such studies was considered acceptable.

Pharmacokinetics

The sponsor did not submit any pharmacokinetic studies. However, the sponsor presented published studies that noted limited systemic exposure to the allergen was achieved following SLIT.^{46, 47, 48;49, 50} The proteolytic digestion in the gastrointestinal tract is assumed to be the predominant fate of mite extracts, since they consist mostly of proteins and glycoproteins, however the occurrence of systemic effects suggests that some allergen may be absorbed.⁴⁸

The sponsor also cited that sublingually administered antigens are intercepted by local antigen-presenting cells.⁵¹ Thus it is unlikely that the pharmacological effect of SLIT is related to the blood allergen level per se, but rather the number of immune cells recruited for AIT; which may vary individually.

⁴² Greiner AN, et al. Allergic rhinitis. *Lancet*. 2011; 378: 2112-2122.

⁴³ Canonica GW, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Org J*. 2014; 7:

⁴⁴ Bonvalet M, et al. Allergen-specific CD4+ T cell responses in peripheral blood do not predict the early onset of clinical efficacy during grass pollen sublingual immunotherapy. *Clinical and Experimental Allergy* 2012; 42: 1745-1755.

⁴⁵ Canonica GW, et al. Sub-lingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Org J*. 2014; 7:

⁴⁶ Bagnasco, M., et al. Pharmacokinetics of Der p 2 allergen and derived monomeric allergoid in allergic volunteers. *Int Arch Allergy Immunol* 2005; 138: 197-202.

⁴⁷ Bagnasco, M., et al. Absorption and distribution kinetics of the major *Parietaria judaica* allergen (Par j 1) administered by noninjectable routes in healthy human beings. *J Allergy Clin Immunol* 1997; 100: 122-129.

⁴⁸ Bagnasco, M. et al. Allergen biodistribution in humans. *Chem Immunol Allergy* 2003; 82: 33-43.

⁴⁹ Bagnasco, M., et al. 2001. Pharmacokinetics of an allergen and a monomeric allergoid for oromucosal immunotherapy in allergic volunteers. *Clin Exp Allergy* 2001; 31: 54-60.

⁵⁰ Dirks CG et al Does absorption across the buccal mucosa explain early onset of food-induced allergic systemic reactions? *J Allergy Clin Immunol* 2005; 115: 1321-1323.

⁵¹ Van Wilssem, E.J., et al Dendritic cells of the oral mucosa and the induction of oral tolerance. A local affair. *Immunology* 1994; 83: 128-132

In addition, since mite allergens are composed of different constituents, classical pharmacokinetic measurements to determine systemic exposure would also be difficult.

Taking these factors into consideration, the absence of pharmacokinetic studies was considered acceptable.

Pharmacokinetic drug interactions

The sponsor did not provide any pharmacokinetic drug interaction studies. It is however noted that β -blocker therapy is generally considered a contraindication during AIT due to the risk of refractory anaphylaxis.⁵² The labels for all three pollen allergen extract sublingual tablet products approved in the USA, Grastek, Oralair and Ragwitek, which are prescribed with auto-injectable adrenaline, all contain precautions with respect to drugs which may potentiate or antagonise the effects of adrenaline, namely α and β -adrenergic blockers, ergot alkaloids, tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and some antihistamines.

The Precautions section of the proposed PI for Acarizax states “Severe systemic allergic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.”

Toxicology

Acute toxicity

The sponsor did not present any acute toxicity studies. While no justification was provided for the absence of acute toxicity studies, given the nature of the test article, long term administration and previous approval of the active ingredients for same indication, omission of acute toxicity studies did not significantly impede assessment of the application.

Repeat-dose toxicity

The sponsor submitted data from one 26 week repeat dose toxicity study in mice. The study was GLP compliant and utilised the clinical route of administration. No toxicokinetic or pharmacokinetic data for *D. pteronyssinus* and *D. farinae* extract were determined. The repeat dose study was conducted in mice, and no non-rodent models were utilised. The sponsor justified testing solely in mice on the basis of published data indicating that mice were responsive to SLIT,³⁰ however SLIT has also been reported to be efficacious in rats⁴⁰ and dogs.⁵³

Relative exposure

In the absence of pharmacokinetic and/or toxicokinetic data relative exposure calculations based on AUC or C_{max} were not possible. Therefore, relative exposure for the repeat dose toxicity study was estimated based on dose/body surface area (Table 3). Based on a maximum recommended daily dose of 12 SQ-HDM (equivalent to 12 DU/day), a 0.24 SQ-HDM/kg/day or 7.94 SQ-HDM/m²/day was estimated for a 50 kg adult

⁵² M T Krishna and A P Huissoon. Clinical immunology review series: an approach to desensitization. *Clin Exp Immunol*. 2011 Feb; 163(2): 131–146.

⁵³ De Boer D *et al* Multicentre open trial demonstrates efficacy of sublingual immunotherapy in canine atopic dermatitis. *Vet Dermatol* 2012; 23: 65

(conversion factor of 33). Furthermore, since the daily dose in the repeat dose toxicity study was not indicated in (SQ-HDM or DU)/kg/day format, the average weight of mice prior to treatment was used to determine the daily dose in kg/day (26.64 g; all groups, both sexes), and the body surface area conversion factor used was 3.

Table 3: Relative exposure, repeat dose toxicity studies

Species	Study duration	Dose (SQ-HDM/kg/day)	Dose (SQ-HDM/m ² /day)	Exposure ratio
Mouse (CD-1)	26 weeks (repeat dose, SL) [VPQ0001]	34	102	13
		132	396	50
		526	1578	199
Human	steady state	0.24	7.94	–

Major toxicities

Acarizax was well tolerated in the repeat dose toxicity study. This represented a relative exposure 199-fold of that of the clinical dose (based on SQ-HDM/m²/day). In the 26 week study with per oral (PO) administration, no major test article related, clinically relevant toxicities were identified. Histopathological finding of note included a high incidence of bursal and follicular cysts in ovaries, which were also present in controls groups and did not demonstrate any dose relationship.

Genotoxicity

The genotoxicity of Acarizax was investigated using bacterial reverse mutation assays, in vitro chromosomal aberration assays and a combined comet assay. All studies were GLP compliant, all studies used adequate concentrations and the assays were validated with appropriate positive and negative controls.

The bacterial mutagenesis assays suggested positivity for mutagenic potential. However, the positive results were likely due to proteins, peptides, free amino acids and materials containing or capable of releasing amino acids which can interfere with the assay.

Similarly, while statistically significant increases in chromosomal aberrations were noted; given the absence of mutagenic potential in the AMES test and historical clinical use of the *D. pteronyssinus* and *D. farinae* allergen mixture as SCITs, it was concluded that the test article is unlikely to possess genotoxic potential at the clinical dose.

Taken together, genotoxicity assays were in line with relevant international conference on harmonisation (ICH) guidelines and Acarizax appears unlikely to possess significant genotoxic potential.

Carcinogenicity

No carcinogenicity studies were submitted by the sponsor citing the following justifications:

Histopathological examination of the sublingual region of mice in the 26 week repeated dose toxicity study showed no neoplastic changes at doses up to 14 DU/day (that is approximately 1,900 fold higher than the maximum human therapeutic dose for a 50 kg person).

In vitro and in vivo preclinical genotoxicity data concludes that the relatively low exposure to specific immunotherapeutic product prepared from the HDM allergen extract does not pose any genotoxic risk for patients.

The absence of any adverse genotoxic or carcinogenic effect(s) is supported by approximately 30 years of clinical experience with products containing HDM allergen extracts.

For sublingually administered allergy immunotherapy products, studies have shown that only limited absorption of the allergen through the oral mucosa occurs.^{47, 48, 46} Therefore, no systemic absorption of sublingually applied allergen is expected to any significant extent.

The inherent properties of the product (naturally occurring proteins) makes it very unlikely that any interaction with intra-cellular DNA should occur.

Although many naturally occurring materials have the potential for genotoxicity and/or carcinogenicity, despite most of the world's population being exposed to HDM allergens on a daily basis throughout their lives, there is no recorded evidence of any adverse health conditions related to genotoxic and/or carcinogenic potential.

While the 26 week toxicity study in mice did not indicate neoplasia, a treatment period of 1 to 2 years would be required to detect carcinogenic potential in mice. However, in view of the negative genotoxicity, lack of evidence of carcinogenicity with human exposure to the allergens naturally, and relatively small dose of allergen, the lack of carcinogenicity studies is acceptable.

Reproductive toxicity

Reproductive toxicity investigations were restricted to one embryofetal development study in mice. The SC route was selected as it delivered a higher dose. No dedicated nonclinical fertility study was submitted. Histopathological assessment performed as part of the repeat dose toxicity study showed no effects on the reproductive organs.

Acarizax did not appear to negatively impact embryofetal development at the maximum dose (1,800 DU/kg/day) with regards to mortality, body weight gain, maternal clinical signs and litter values, including foetal body weight and sex ratios. Foetal malformations and variations were also within historical range. Acarizax was well tolerated in the embryofetal development study with a high exposure ratio compared to the proposed clinical dose.

No nonclinical peri-postnatal study was submitted, and transfer of Acarizax or Acarizax-induced antibodies to offspring via milk was not investigated in animals. It is known that antibodies of the classes shown to be induced by Acarizax in humans are transferred to offspring by lactation.

Relative exposure**Table 4: Relative exposure, reproductive studies**

Species	Study	Dose (SQ-HDM/kg/d ay)	Dose (SQ-HDM/m ² /d ay)	Exposure ratio#
Mouse (CD-1)	Embryofetal development	450	1350	170
		900	2700	340
		1800	5400	680
Human	steady state	0.24	7.94	-

= estimated based on body surface area assuming conversion factor of 3 for mouse and 33 (for 50 kg human individual). Total human daily dose is 12 SQ-HDM.

Pregnancy classification

Antigen preparations for desensitisation are exempted from pregnancy classification.⁵⁴ The sponsor has however proposed a pregnancy classification of B2⁵⁵, which is acceptable.

Local tolerance studies

No local tolerance studies were submitted. Local tolerance was investigated histologically in the sublingual region and GI tract in the mouse repeat dose toxicity study and no treatment related reactions were observed.

Paediatric use

While Acarizax application is indicated for adults only, the sponsor presented published and clinical development data suggesting safety and efficacy in paediatric patient groups.²¹

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for Acarizax detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

However, the attention of the RMP evaluator is drawn to the fact that the labels for the three pollen allergen extract sublingual tablet products approved in the USA, Grastek, Oralair and Ragwitek, which are prescribed with auto-injectable adrenaline, all contain precautions with respect to drugs which may potentiate or antagonise the effects of adrenaline, namely α and β -adrenergic blockers, ergot alkaloids, tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and some antihistamines (see also PI comments regarding the precautions statements).⁵⁶

⁵⁴ Therapeutic goods exempt from pregnancy categorisation, Prescribing medicines in pregnancy database, 2011

⁵⁵ Pregnancy category B2 is defined as 'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.'

⁵⁶ These issues were considered by the Sponsor and the PI was amended accordingly.

Nonclinical summary and conclusions

- The nonclinical dossier contained adequate published data and minimal GLP compliant toxicology studies necessary for satisfactory assessment of Acarizax.
- Published studies in mouse, rat and guinea pig models and limited in-house mouse studies were used to demonstrate efficacy for dust mite allergens consistent with currently understood SLIT-mediated immune response to allergens.
- No specific secondary pharmacodynamics, safety pharmacology or pharmacokinetic studies were submitted.
- No single dose toxicity studies were submitted.
- One repeat dose toxicity study was submitted, a 26 week study in mice; no Acarizax related systemic toxicities were noted in doses up to 199 times the clinical dose adjusted for body surface area with sublingual administration.
- No Acarizax related genotoxic effects were noted at in a panel of in vitro and in vivo studies which included exposures which were likely to be significantly higher than that of the proposed clinical dose. It was however noted that in the bacterial reverse mutation study proteins, peptides, free amino acids and materials containing or capable of releasing amino acids contained within the extract had the potential to interfere with the assay and potentially give false positive readings.
- The sponsor provided adequate justification for the absence of carcinogenicity studies.
- No Acarizax related toxicities were observed in one mouse embryofetal development study at SC doses up to 680 times greater than the clinical dose, adjusted for body surface area. No fertility or peri-postnatal studies were submitted.
- No other nonclinical studies were submitted.

Conclusions and recommendation

A number of limitations were identified during the nonclinical assessment:

- Primary pharmacology was based on published literature and a limited number of in-house studies, and the exact mechanisms of action have not been elucidated.
- A Repeat dose toxicity study was conducted in one rodent species (mice), which limits the strength of the safety data.
- Adequate justification was provided for the absence of carcinogenicity studies.
- No dedicated fertility and pre/postnatal development studies were performed using Acarizax, and embryofetal development was only investigated in one species (mice).

- The clinical formulation also uses standard and high-molecular weight fish gelatine as an excipient, a possible hazard for individuals with fish allergies; and clinical comment is sought on this matter.⁵⁷

While some studies necessary for a robust nonclinical evaluation were lacking, given the longstanding clinical experience with dust mite allergen extracts utilised in this study, there are no nonclinical objections to the registration of Acarizax.

The nonclinical evaluator also made recommendations related to the PI but presentation of these is beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The current application is for add on treatment for adult subjects with allergy to HDM where it is associated with allergic asthma and/or AR, not well controlled with standard therapy. The step wise approach to pharmacotherapy in patients with asthma is recommended by the Global Initiative for Asthma (GINA),⁵⁸ American Thoracic Society (ATS)⁵⁹ and locally by National Asthma Council of Australia (NAS)⁶⁰ and involves addition of therapy with the goal of achieving symptom control. Thus, use of add on therapy for moderate or severe persistent disease not well controlled by inhaled corticosteroid (ICS) is consistent with current guidelines.

Both allergic asthma and AR are significant health burdens in Australia, and current symptomatic therapy is often insufficient to adequately treat symptoms in individuals with moderate or severe disease. In several westernized countries, asthma is reported to affect over 20% of children and 10% of adults. Approximately 15% of Australians have allergic rhinitis,⁶¹ and approximately 10% have current asthma.⁶²

Asthma is a complex chronic disease with a pathogenesis that is incompletely understood. There is underlying immunological dysregulation in asthma, which can be identified in situ within the lung, adjacent lymph nodes and also in the circulating lymphocyte compartment. A significant proportion of subjects with asthma have associated atopic

⁵⁷ Fish derived gelatine is a potential allergen for a small proportion of food allergic individuals. However, the allergenic potential of commercial food-grade fish gelatine has been evaluated in a randomised, double-blind, placebo-controlled oral challenge study conducted in clinically fish-allergic individuals. (Hansen K et al A randomized, double blind, placebo controlled oral challenge study to evaluate the allergenicity of commercial, food-grade fish gelatine. *Food and Chemical Toxicology* 2004; 42, 2037-2044.) The results from this clinical trial, as well as the knowledge that fish allergens are removed during the fish gelatine production and that the drug product only contains a small amount of fish gelatine, provide assurance that the allergenic risk associated with fish gelatine is minimal to patients who take the HDM Tablet.

⁵⁸ Reddel HK, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J.* 2015; 46: 622-639.

⁵⁹ Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009; 180: 59-99.

⁶⁰ Australia NACo. Australian Asthma Handbook 2015. Available from: <http://www.nationalasthma.org.au/handbook>

⁶¹ Welfare. AloHa. Allergic rhinitis ('hay fever') in Australia. In: AIHW,; editor. Canberra:2011

⁶² Monitoring. ACfA. Asthma in Australia 2011: with a focus chapter on chronic obstructive pulmonary disease. In: AIHW,; editor. AIHW Asthma Series Canberra: 2011.

predisposition and susceptibility to production of IgE (allergy) antibodies to non-pathogenic ubiquitous environmental allergens, particularly those found in the air and inhaled (aeroallergens). Allergen recognition, production of IgE, and release of mast cell and basophil mediators on allergen recognition signalled through IgE does not directly contribute to all the clinical or histological manifestations of asthma (reviewed in Fahy, 2015⁶³).

Allergic rhinitis (AR) is the clinical manifestation of allergic disease in the nose. It can be acute and seasonal, or chronic and perennial, depending upon the allergen/s to which the individual is sensitised. It is characterised by a cluster of symptoms, chiefly rhinorrhoea, sneezing, nasal blockage and itch and histologically by mucosal oedema and tissue infiltration with eosinophils, lymphocytes and to a lesser extent neutrophils. Many of the clinical symptoms of AR can be directly attributed to an abnormal immunological response to allergen/s and to the release of mast cell and basophil mediators. AR and asthma often co-exist, and there is some evidence of a naso-pulmonary axis, by which control of AR symptoms leads to clinical improvement in asthma.⁶⁴ AR often co-exists with allergic conjunctivitis (which is not a disease indication in the current application).

House dust mite is probably the most prevalent aeroallergen in the Australian context associated with respiratory allergy, although good population based prevalence data is lacking. There is evidence from meta-analysis that IT directed at relevant aeroallergens, can improve symptom control in both AR^{65, 66} and in asthma⁶⁷ where relevant aeroallergen sensitisation has been demonstrated. However, a recent Cochrane review of SLIT for the treatment of asthma, found high heterogeneity of investigational medicinal product (IMP) and outcomes measures and poor quality studies, and were unable to recommend SLIT for mild or moderate asthma on the basis of the 52 studies reviewed. There were too few studies in severe asthma to make any recommendations.⁶⁸

Burden of disease

The sponsor states that the overall estimated prevalence of AR in adult subjects in Europe is 22%. They state that a large proportion of patients with Asthma and AR are inadequately controlled by pharmacotherapy^{69, 70, 71} The sponsor states that although use of ICS have greatly improved asthma control, studies suggest that the more than half of asthma patients did not achieve control of their asthma with standard of care.⁷² More than half of all AR patients have moderate/severe AR, and for a substantial proportion, their disease is persistent.^{73;69} The stated frequency of HDM sensitisation in individuals from Europe with asthma is approximately 50%. An Australian study specifically investigated

⁶³ Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol* 2015; 15: 57-65.

⁶⁴ Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. *N Engl J Med*. 2015; 372: 456-463.

⁶⁵ Compalati E, et al. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GAZLEN meta-analysis. *Allergy*. 2009; 64: 1570-1579.

⁶⁶ Wilson DR, et al. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev*. 2003; CD002893

⁶⁷ Tao L, et al. Efficacy of sublingual immunotherapy for allergic asthma: retrospective meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J*. 2014; 8:1 92-205.

⁶⁸ Normansell R, et al. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. 2015; 8: CD011293

⁶⁹ Canonica G W et al A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007; 62: 17-25

⁷⁰ Chivato T et al Allergy, Living and Learning: Diagnosis and Treatment of Allergic Respiratory Diseases in Europe *J Investig Allergol Clin Immunol* 2012; 22: 168-179.

⁷¹ Ibero M et al. Diagnosis and treatment of allergic rhinitis in children: Results of the PETRA study. *Allergol Immunopathol (Madr)*. 2012; 40: 138-143

⁷² Partridge M R et al. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulmonary Medicine* 2006; 6: 13

⁷³ Bousquet J et al. Severity and impairment of allergic rhinitis in patients consulting in primary care *J Allergy Clin Immunol* 2006; 117: 158-162.

the link between HDM AR and bronchial symptoms, showing occurrence of bronchial symptoms in 34% of the patients with HDM AR compared with 9% in the control group⁷⁴.

Mechanism of action: The sponsors state that IT is a treatment option for allergy that is complementary to pharmacotherapy and with a distinct mechanism of action. IT is performed by repeated subcutaneous or sublingual administration of specific allergens to an allergic person in order to gradually induce immunological tolerance towards the allergens. They state that considerations for initiating IT include disease severity, lack of efficacy of pharmacotherapy, side effects of pharmacotherapy, patient preference and the presence of more than one manifestation of the underlying allergic disease. They state that IT can modulate the basic immunologic 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.⁷⁵

Delivery: The sponsor's rationale for delivery of HDM-IT via the sublingual (SL) route in tablet form is convenience, ability for home self-medication, safety and efficacy. Their stated aim of oromucosal administration of allergens is to reduce the risk of systemic reactions. The sublingual route is therefore proposed over subcutaneous injections to provide a product with a safety profile allowing for at-home administration, thereby improving the quality of life for patients.

Contents of the clinical dossier

The dossier documents a clinical development programme of pharmacodynamics, tolerability, dose finding, safety and efficacy. It does not contain traditional pharmacology studies due to the nature of immunotherapy, consistent with the European Medicines Agency (EMA) guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. It contains 2 pivotal studies, which relate to each of the proposed indications, HDM driven asthma and allergic rhinitis.

The submission contained the following clinical information:

- No clinical pharmacology studies
- 1 human study for bio-analytical methods (for determination of in-house reference).
- 2 pivotal efficacy studies.
- 2 tolerability/safety dose-finding studies.
- 4 other efficacy/safety studies.
- Synopsis (only) of ongoing 2 studies in Japan and US to meet regulatory requirement for product registration in other regions.
- Literature references.
- Overall Quality Summary.

The submission also contained; nonclinical overview, nonclinical summary, clinical overview, clinical summary (biopharmaceutical studies and analytical methods, clinical efficacy, clinical safety, synopsis of individual studies, notes to evaluators and literature references.

⁷⁴ Downie S. R. et al. Association between nasal and bronchial symptoms in subjects with persistent allergic rhinitis. *Allergy* 2004; 59: 320-326.

⁷⁵ Bousquet J et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA2LEN* and AllerGen**). *Allergy* 2008; 63: 8-160.

Paediatric data

The submission included some paediatric efficacy and safety data; however the current proposed indications are for adults only. The paediatric data represents only a small proportion of the total subjects exposed to the IMP. The sponsor has in place a paediatric development programme (albeit with a very long current time line). The spectrum and prevalence of HDM disease in the paediatric population is such that there would be likely significant value in this IMP for the paediatric population with HDM driven asthma and allergic rhinitis.

Good clinical practice

The clinical studies in the submission are all compliant with the CPMP/ICH/135/95 guidelines on Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

There are no pharmacokinetic studies.

Evaluator's conclusions on pharmacokinetics

Overall the absence of pharmacokinetic data to support this application is acceptable and within the EMA guidelines for IT. There is however insufficient evidence supplied that supports the sponsors and external reviewer's statement that no intact allergen is absorbed systemically. The studies presented to support this are with purified single component allergen only, and not whole allergen extract. In addition only one supplied reference used HDM, the remainder used plant based aeroallergen (paretaria), which have very different physical properties to HDM allergen. The study provides to support the sponsors view, even though it is only single purified Derp1 and not whole extract does show systemic absorption of allergoid and of peptides. Given the allergenic properties of HDM are primarily mediated via recognition of its peptides (both linear and conformational); it is quite possible that systemic absorption in the GIT of relevant immunogenic HDM peptides does occur.⁷⁶ Indeed, that would be the obvious explanation for the uncommon but reported cases of systemic allergic reactions and systemic anaphylaxis to HDM sublingual IT (in drop formulation) and to the tablet SLIT AE in the synopsis studies. A class effect with similar reports (post marketing) has been noted for the grass pollen tablet Grazax.

Therefore complete lack of systemic absorption should not be the stated reason for not supplying pharmacological studies in the dossier and should be substantiated, or removed.⁷⁷

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies were provided. Table 5 below outlines the studies relating to each pharmacodynamic topic.

⁷⁶ Clarification the potential clinical relevance remains to be investigated

⁷⁷ Upon consideration of the Evaluator's comment the PI was amended accordingly by the Sponsor.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on HDM-specific IgG4	MT-02§‡ P-003§ MT-04§ MT-06§
	Effect on HDM-specific IgE	MT-01§ TO-203§ MT-03
		MT-02§‡
		P-003§ MT-04§
		MT-06§
Secondary Pharmacology	Effect on HDM IgE blocking (IgE inhibition assay)	MT-01 TO-203 MT-03
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	TO-203 (adult male)
	Effect of ethnicity	No Studies
	Effect of age	MT-03 (children only)
PD Interactions		N/A
Population PD and PK-PD analyses	Healthy subjects	No studies
	Target population	MT-01 (some of subjects) TO-203 (some of subjects) MT-02 (some of subjects) P-003 MT-04 MT-06

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

None of the pharmacodynamic studies had significant deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The nature of the IMP precludes the use of traditional pharmacodynamic or pharmacokinetic studies and the dossier contains a rationale for not undertaking or providing these studies, and this rationale is consistent with the relevant EMA guidelines. This guideline recommends the use of immune system markers such as specific IgG levels, T cell responses and/or cytokine production. The current studies under consideration provide HDM specific IgG4 and IgE responses.

Overall the studies support the contention that the IMP at the dose of 12 SQ daily, when taken for periods longer than a month's duration have significant immunomodulatory effects which are sustained across the 12 to 18 month treatment period.

Dosage selection for the pivotal studies

The pivotal studies (MT-04 AA and MT-06 AR) both used two doses of HDM-SLIT tablet: 6 and 12 DU once daily. The current application is for the higher dose, 12 SQ/DU.⁷⁸

Classic Phase I tolerability and dose studies were not possible due to the nature of allergen immunotherapy, such that an individual must be sensitised to the allergen in order for tolerability and safety to be assessed.

Initial tolerability and dose finding was therefore carried out on HDM allergic individuals with mild to moderate asthma with or without AR (MT-01). Doses in the range from 1 to 32 SQ-HDM were tested. 16 SQ-HDM was concluded to be the maximum tolerable dose, but the number of IMP related AEs was considerably higher than at the lower doses. The 32 SQ-HDM dose group was discontinued after only 2 doses, as a single subject suffered immediate symptoms (vomiting) following administration of the 32 SQ/DU dose. As AEs were higher in 16 SQ-HDM compared to lower doses, this dose was also evaluated to have a tolerability profile that could potentially impair compliance in a setting of daily and was not pursued as a possible dose in further efficacy and safety Phase II and III studies.

Phase II safety, dose finding and tolerability studies used dosages ranging from 1-12 SQ-HDM. In Study MT-02 (with an allergic asthma (AA) primary endpoint) the highest dose used was 6 SQ/DU and this was evaluated as being associated with higher efficacy (endpoint; lowest dose of ICS after 1 year of HDM-SLIT tablet) than the lower two doses (1 and 3). Based upon this result, investigators pursued 6 DU and 12 DU as the doses of interest for maximum efficacy and reasonable tolerability and safety for the two pivotal studies.

Secondary endpoint immunological data from the Phase II studies also suggested that a higher dose (6 DU or above) was associated with greater immunomodulation.

Based upon the data and studies provided, the two doses for the two pivotal studies, 6 and 12 DU appear to be a reasonable choice.

Efficacy HDM asthma

Pivotal efficacy studies; HDM asthma

MITRA Study MT-04

No other pivotal asthma study is provided.

⁷⁸ During development the term development units (DU) has been used. 12 DU is equal to 12 SQ-HDM.

Other efficacy studies***Study MT-02***

For the full details of the evaluation of these studies please see Attachment 2.

Evaluator's conclusions on clinical efficacy for asthma

One pivotal Phase III and one Phase II study were provided by the sponsor for evaluation. The design and conduct of the two studies is adequate for the proposed purpose of IMP registration, and the trials were conducted in accordance with international and TGA relevant guidelines, with appropriate primary efficacy end points.

The pre-determined primary efficacy endpoints for both studies were met, and a likely clinically significant difference between the 12 SQ HDM SLIT-tablet and placebo was shown.⁷⁹ Overall these studies suggest that HDM tablet is efficacious as an add-on therapy for adults with moderate to severe asthma, which is not well controlled on current optimised ICS, where a clinical history of sensitization and exacerbation of asthma on exposure to HDM, and evidence of HDM IgE sensitization is demonstrated.

Efficacy; HDM allergic rhinitis**Pivotal efficacy studies HDM allergic rhinitis*****Study MT-06***

No other pivotal AR study is provided.

Other efficacy studies***Study P-003******Study MT-02***

For the full details of the evaluation of these studies please see Attachment 2.

Evaluator's conclusions on clinical efficacy for HDM allergic rhinitis

One pivotal Phase III study, one Phase II study with predetermined statistical analysis plan (SAP) and one Phase II study subject to post-hoc analysis of a subgroup with AR symptoms at baseline were available for review.

Overall, the studies with pre-determined study endpoints all met their predetermined primary efficacy endpoints. The endpoints chosen were in line with EMA and allergic rhinitis and its impact on asthma (ARIA) guidelines for primary efficacy endpoints in AR studies, and are likely to represent clinically relevant effects. This suggests that adults with moderate to severe AR not well controlled on existing therapy may benefit from treatment with Acarizax, where the clinical history is consistent with HDM driven AR and evidence of IgE sensitisation to HDM is demonstrated.

⁷⁹ Clarification the 12 SQ HDM SLIT-tablet was used in study MT-04, but not in Study MT-02.

Safety

Studies providing safety data

Pivotal efficacy studies (asthma and allergic rhinitis)

The following studies provided evaluable safety data: MT-06 (pivotal AR study) and MT-04 (pivotal asthma study). As the type and methodology for collecting and assessing safety data was very similar for the two indications and between the two studies, the indications will be considered together.

Dose-response and non-pivotal efficacy studies

- Study MT-02
- Study P003
- Studies TO-203 AR and TO-203 AA
- Studies P001 (AR) and P009 (AR)

Other studies evaluable for safety only

- Study MT-01
- Study MT-03
- Study P008
- TO-203-ph1

For further details with regard to the evaluation of these studies from a safety aspect please see Attachment 2.

Patient exposure

Table 6: Exposure to HDM-SLIT tablet and clinical studies

Study type/ Indication/ duration	Controlled studies (n)		Uncontrolled studies	Total HDM SLIT Tablet exposure
	HDM SLIT Tablet	Placebo	HDM	
Clinical pharmacology				
ASTHMA			NA	
Pivotal (MT-04)	557	277		557
Phase II (MT-02)	461	143		461
Phase I (MT-01, MT-03, TO-203)	54	17		
	54	18		
	36	12		
Subtotal	1162	467		1162

Study type/ Indication/ duration	Controlled studies (n)		Uncontrolled studies	Total HDM SLIT Tablet exposure
	HDM SLIT Tablet	Placebo	HDM	
Indication 1				
AR			NA	
Pivotal (MT-06)	654	338		654
Phase II (P003)	83	41		83
Phase I (P008)	130	65		130
Subtotal Indication 2	867	444		867
TOTAL	2029	972		2029

There is only one proposed dose for this current application: 12 DU/SQ.

Table 7: Exposure by duration to 12 DU across all studies

Study type/Indication	Proposed maximum dose: 12 DU daily				
	< 4 weeks.	4 -12 weeks	12-24 weeks	> 24 weeks	Unknown
Clinical pharmacology					
Asthma					
Placebo controlled	18	12 65		282	
Subtotal Indication 1	18	77	0	282	
Allergic Rhinitis					
Placebo controlled			42	318	
Subtotal Indication 2	0	0	42	318	
TOTAL	18	77	42	600	12

Evaluator's conclusions on safety

AEs related to IMP were common. The overall rate of subjects experiencing AEs was dose-dependent, with highest rates of AEs and highest rates of study discontinuation related to the 12 DU/SQ dose. Rates of serious adverse events (SAEs) were low, and did not appear

to be dose related. Most AEs recovered without any treatment. The investigational medicinal product (IMP) did not appear to significantly contribute to overall rates of asthma exacerbations, although a few cases of severe asthma exacerbation did appear IMP related. Adrenaline was required to treat one IMP related AE in the pivotal studies and a further 3 cases outlined in the ongoing studies. In additional study discontinuation reports from ongoing studies provided signals for a possible association with Meniere's disease and study discontinuation due to elevated liver enzymes.⁸⁰ One case of eosinophilic esophagitis (EoE) was reported from the pivotal studies and a further case from the ongoing studies.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Acarizax in the proposed usage are:

- Reduced risk of moderate to severe asthma exacerbation after at least 7 months of daily IMP by 31%. Based upon an absolute risk reduction of moderate to severe exacerbation from 30% in placebo to 21% in 12 DU group, this equates to number needed to treat (NNT) = 11.1
- At least a 1.09 reduction in overall symptom and medication score for AR from 14 weeks of therapy.
- A 50% reduction in the risk of having an allergic rhinitis exacerbation and twice the probability of having days without more than minimal awareness of AR symptoms.

First round assessment of risks

The risks of Acarizax in the proposed usage of 12 SQ daily are:

- There were 42% and 52% of participants in the two pivotal studies with possible or probable IMP related AEs, compared with 14% and 15% in the placebo group's respectively. On an event basis, the number needed to harm (NNH) overall for an AE was 2.5.
- The majority of these AEs were mild to moderate and self-resolving and related to local AEs at the site of IMP application (mouth and throat).
- The risk of SAEs was low and no deaths were reported.

First round assessment of benefit-risk balance

The benefit-risk balance of Acarizax, given the proposed usage, is favourable.

First round recommendation regarding authorisation

The recommendation is to approve the submission subject to changes to the PI and CMI and specific post marketing surveillance requirements.

⁸⁰ Clarification after review of the sponsor's response to clinical questions the clinical evaluator was satisfied that the single case of Meniere's disease did not represent a safety signal, however there were ongoing concerns related to liver dysfunction.

Clinical questions

Safety

1. Given the high rate of mild to moderate IMP related AEs, especially local AEs, and rates of study discontinuation related to these AEs, it would be useful to understand why no dose escalation regime was trailed in the presented Phase II and III studies in the dossier. It appears that both ongoing TO-203 AR and AA studies include dose escalation arms, presumably for the aim of reducing early local AEs, and improving overall IMP tolerability.
2. The safety signals appearing from the ongoing TO-203 AR and AA and the P-001 study discontinuations which are considered possibly IMP related are Meniere's disease and liver function abnormalities. These are somewhat concerning, and differ from the result presented for the Phase II and III studies which comprise this dossier. What are the plans for interrogating these possible safety concerns?

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

The second round benefit risk assessment is not significantly altered from the first round.

The overall benefits of Acarizax in the proposed usage at 12 DU daily are:

- Reduced risk of moderate –severe asthma exacerbation after at least 7 months of daily IMP by 31%. Based upon an absolute risk reduction of moderate to severe exacerbation from 30% in placebo to 21% in 12 DU group, this equates to NNT = 11.1
- At least 1.09 reduction in overall symptom and medication score for AR from 14 weeks of therapy.
- A 50% reduction in the risk of having an allergic rhinitis exacerbation and twice the probability of having days without more than minimal awareness of AR symptoms.

Second round assessment of risks

The second round benefit risk assessment is not significantly altered from the first round. Clarification of the safety signal for Meniere's disease⁸¹ and inclusion by the sponsor of some precautions around the use and surveillance for emerging eosinophilic esophagitis (EoE) with the HDM SLIT-tablet use makes the overall risk lower than the first round assessment.

⁸¹ The second round clinical evaluator was satisfied that the single case of Meniere's disease did not represent a safety signal.

Overall the risks of Acarizax in the proposed usage of 12 SQ-HDM daily are:

- There were 42% and 52% of participants in the two pivotal studies with possible or probable IMP related AEs, compared with 14 and 15% in the placebo group's respectively. On an event basis, the number needed to harm (NNH) overall for an AE was 2.5.
- The majority of these AEs were mild to moderate and self-resolving and related to local AEs at the site of IMP application (mouth and throat).
- The risk of SAEs was low and no deaths were reported.

Second round assessment of benefit-risk balance

The overall risk benefit analysis for Acarizax, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

The recommendation is to approve the submission subject to the additional changes to PI and CMI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1.0 (dated 25 September 2014, DLP 30 May 2014) and Australian Specific Annex edition 1.0 (dated June 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8: Ongoing safety concerns

Ongoing safety concerns	
Important identified risks	Acute worsening of asthma symptoms (exacerbation)
Important potential risks	Local allergic swelling with potential to compromise airway Serious systemic allergic reactions, including anaphylactic reactions Anaphylactic shock
Missing information	Use in children (off-label use) Use in pregnant or lactating women Use in asthma patients against the proposed contraindications and warnings and precautions for use (off-label use)

Pharmacovigilance plan

Routine pharmacovigilance is proposed to monitor all the specified safety concerns. No additional pharmacovigilance activities are proposed in the EU RMP or the ASA.

According to the ASA the sponsor 'operates in accordance with the current TGA guidelines for the pharmacovigilance responsibilities of sponsors'.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities only are required to mitigate the specified safety concerns.

Reconciliation of issues outlined in the RMP report

Table 9 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 9: Reconciliation of issues outlined in the first round RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p>Seqirus provides assurance that all safety considerations raised by the nonclinical and clinical evaluator's and the responses to any such items include consideration of the RMP.</p>	<p>The sponsor's response is noted.</p>
<p>Cases of eosinophilic oesophagitis have been reported in association with Acarizax treatment. 'Eosinophilic oesophagitis' should be included as a safety concern in the RMP/ASA with an appropriate pharmacovigilance and risk minimisation plan.</p>	<p>As per the response to the clinical evaluation report (CER), EoE has been included as an important potential risk in the current EU RMP version 3.</p> <p>As per the response to CER the 'precautions' section of the proposed PI has consequently been amended as follows:</p> <p>Isolated cases of eosinophilic</p>	<p>This is acceptable from an RMP perspective. PI amendments are subject to final determination by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>oesophagitis have been reported in association with Acarizax treatment. Initiation of Acarizax in patients with known eosinophilic oesophagitis should be carefully considered, and the possibility of exacerbating existing disease should be assessed. In patients with severe or persisting gastro-oesophageal symptoms such as dysphagia, abdominal pain or dyspepsia, medical attention must be sought.</p> <p>Eosinophilic oesophagitis will be monitored via routine pharmacovigilance activities, including ongoing signal detection and management, review of data from scientific literature and presentation of frequencies and relevant cases in PSURs. This is done in order to monitor risk factors and severity, and to identify any potential new safety signals. Any new safety issues identified in relation to this risk will be actioned accordingly.</p>	
<p>In an effort to further characterise the important identified and potential risks it is recommended that targeted questionnaires (as a routine pharmacovigilance activity) are employed for adverse event reports relating to cases of severe allergic reaction including severe acute exacerbation of asthma.</p>	<p>ALK Abelló (ALK) acknowledge the importance of collecting detailed information on adverse events reported post marketing, and is committed to obtain as much relevant information as possible for all cases reported, including cases related to important risks.</p> <p>ALK specialises in allergy immunotherapy and treatment of systemic allergic reactions, and currently has no products on the market outside this therapeutic area. Case report forms used for post marketing reporting and to obtain follow up information are therefore tailored to capture relevant details of known adverse effects of immunotherapy, including systemic allergic reactions and associated risk</p>	<p>The sponsor's response is noted and is considered acceptable in the context of this RMP evaluation.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>factors. Furthermore, all personnel handling AE reporting and follow up requests post marketing are trained within the therapeutic area.</p> <p>In addition to information on case source, reporter information, patient information, information about suspected products, concomitant medication and adverse event details, the standard case report form includes specific questions regarding:</p> <ul style="list-style-type: none"> · Use of AE treatment including <ul style="list-style-type: none"> – Antihistamine – Steroid – β2-Agonist – adrenaline · Relevant medical history, including specification of <ul style="list-style-type: none"> – Allergic rhinitis – Allergic conjunctivitis – Asthma – Verified allergies <p>ALK contend that the standard case report forms used for collection of spontaneous post marketing data sufficiently captures information relevant for cases of severe allergic reactions including severe acute exacerbation of asthma. Consequently, ALK maintains that additional targeted questionnaires are unnecessary.</p>	
<p>Other immunotherapy products contraindicate use in patients treated with beta-blockers due to their potential to interfere with treatment for anaphylaxis. It is recommended a similar contraindication is applied to</p>	<p>Concomitant administration of beta-blockers and immunotherapy are often contraindicated in immunotherapy guidelines because blockage of β-adreno receptors is undesirable during adrenaline administration which may be indicated in the</p>	<p>The sponsor's response is noted. There is no objection from an RMP perspective to the proposed PI statement regarding</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Acarizax.	<p>event of a serious systemic allergic reaction.</p> <p>ALK does not agree that concomitant treatment with beta-blockers is an absolute contraindication as the risk is associated with the use of adrenaline and not directly related to the HDM SLIT-tablet. The recently published European Academy of Allergy and Clinical Immunology (EAACI) position paper on contraindications furthermore supports that beta-blockers is considered a relative contraindication.⁸²</p> <p>Subsequently, Seqirus proposes to describe concomitant treatment with beta-blockers in the PI under 'precautions', specifically:</p> <p>Severe systemic allergic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.</p>	<p>beta-blockers.</p> <p>However the recommendation regarding the related contraindication is maintained for final determination by the Delegate.</p>
<p>Other immunotherapy products contraindicate use in patients with severe immune deficiency or autoimmune disease. It is recommended that a similar contraindication is applied or at least advice regarding use in these groups is added.</p>	<p>The EU RMP (v3.0) includes use in patients with severe immune deficiency or autoimmune disease. Given this and given the evaluator's comment, the proposed PI has been amended as follows:</p> <p>Acarizax is contraindicated:</p> <p>in patients with a known hypersensitivity to the any of the excipients in patients with forced expiratory volume in one second</p>	<p>This is acceptable from an RMP perspective. PI amendments are subject to final determination by the Delegate.</p>

⁸² Pitsios,C., et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>(FEV1) < 70% of predicted value (after adequate pharmacological treatment) at initiation of treatment</p> <p>in patients who have experienced a severe asthma exacerbation within the last 3 months</p> <p>in patients with active or poorly controlled autoimmune diseases, immune defects, immunodeficiency's, immunosuppression or malignant neoplastic disease</p> <p>Concurrently, the following amendment is also proposed to the 'precautions section of the AU PI for alignment with the current EU SPC (approved late 2015):</p> <p>Limited data is available on treatment with allergy immunotherapy in patients with autoimmune diseases in remission. Acarizax should therefore be prescribed with caution in these patients.</p>	
<p>The draft contraindications define some asthma parameters but should specifically contraindicate use in patients with 'unstable and/or severe asthma' as well as patients with defined FEV1 < 70% and in patients who have experienced an exacerbation within the last 3 months.</p>	<p>Asthma is a known risk factor for anaphylaxis^{83, 84, 85} and has previously been known to constitute a risk in AIT despite AIT having also been used to treat asthma.⁸⁶</p> <p>The safety profile of the population of subjects not well controlled by medium-to-high dose ICS (corresponding to doses recommended at GINA treatment</p>	<p>The sponsor's response is acceptable from an RMP perspective however this recommendation is subject to final determination by the Delegate.</p>

⁸³ Lieberman P, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126: 477-480.

⁸⁴ Muraro A, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014; 69: 1026-1045.

⁸⁵ Simons FE, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011; 127: 587-593.

⁸⁶ GINA Executive Committee. Global Initiative for Asthma; Global Strategy for Asthma Management and Prevention. National Heart, Lung and Blood Institute, National Institute of Health, Bethesda, Maryland, USA; 2012.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>steps 3-4) for the pivotal Phase III trial MT-04 population was investigated through analysis of a range of AEs that could potentially be related to asthma. There was no evidence of any increase in reporting rate of asthma events for the actively treated groups compared with placebo.</p> <p>In other AIT labels, terms like uncontrolled or severe asthma have been listed as a general contraindication. Translation of the baseline asthma control questionnaire (ACQ) scores into GINA criteria for asthma control by a pre-specified translation algorithm revealed that 232 subjects in MT-04 (28%) were uncontrolled by GINA terminology at randomisation, evenly distributed over the three treatment groups. There was no evidence of active treatment affecting this group any differently with respect to AEs than the entire trial population.</p> <p>This shows that use of the term 'uncontrolled asthma' is not appropriate for identifying patients in whom treatment with the HDM SLIT-tablet cannot safely be initiated. The same applies to 'severe asthma' and 'unstable asthma' that also are unspecific terms that may be interpreted differently from physician to physician. Consequently, unstable and/or severe asthma has not been added to the 'contraindications' section of the proposed PI to avoid potential confusion through the use of these non-specific terms.</p> <p>However the proposed AU PI includes contraindications reflecting the exclusion criteria that specifically address the elements of asthma that are</p>	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>considered to pose a risk for the patients, namely:</p> <p>Lung function (that is in patients with FEV1 < 70% of predicted value (after adequate pharmacological treatment) at initiation of treatment)</p> <p>Recent exacerbations (that is in patients who have experienced a severe asthma exacerbation within the last 3 months)</p>	
...(cont'd)	<p>In addition to the proposed Contraindications, for alignment with the EU RMP (v3.0), it is proposed that the current text regarding postponement of initiation of treatment with the HDM SLIT-tablet in patients with asthma and an acute respiratory tract infection is relocated from the 'precautions' section of the PI to the 'contraindications' section (see below).</p> <p>Other measures are described in the 'precautions' section of the PI, to avoid treating patients with currently unstable asthma at risk for a severe allergic reaction. Among the issues addressed here are instructions to seek medical attention upon deterioration in asthma, and information on the HDM SLIT-tablet in relation to potential changes in asthma pharmacotherapy.</p> <p>'Contraindications'</p> <p>Acarizax is contraindicated:</p> <p>in patients with a known hypersensitivity to the any of the excipients</p> <p>in patients with FEV1 <70% of predicted value (after adequate pharmacological treatment) at initiation of treatment</p> <p>in patients who have experienced a</p>	See above

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p>severe asthma exacerbation within the last 3 months</p> <p>in patients with asthma experiencing an acute respiratory tract infection, initiation of Acarizax treatment should be postponed until the infection has resolved</p> <p>'Precautions'</p> <p>In patients with asthma and experiencing an acute respiratory tract infection, initiation of Acarizax treatment should be postponed until the infection has resolved.</p>	
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as appropriate to reflect changes made to the PI resulting from the evaluation process.</p>	<p>In accordance with the Evaluator's recommendations, Seqirus provides assurance that the CMI has been amended to reflect the changes made to the PI.</p> <p>A copy of the proposed amended PI and CMI is provided (all changes tracked).</p>	<p>This is acceptable from an RMP perspective. CMI changes are subject to final determination by the Delegate.</p>

Key changes to the updated RMP

The EU-RMP Version 1.0 (dated 25 September 2014, DLP 30 May 2014) and Australian Specific Annex edition 1.0 (dated June 2015) has been superseded by:

EU-RMP Version 3.0 (dated 8 July 2015, DLP 30 May 2014) and Australian Specific Annex edition 2.0 (dated February 2016).

Table 10: Summary of key changes between EU RMP v1.0/ASA edition 1.0 and EU RMP v3.0/ASA edition 2.0

Summary of key changes between EU RMP v1.0/ASA edition 1.0 and EU RMP v3.0/ASA edition 2.0	
Safety specification	<p>New important potential risk: Eosinophilic oesophagitis</p> <p>New items of missing information:</p> <p>Elderly (off-label use)</p> <p>Race/ethnicity other than Caucasian</p> <p>Patients with endocrine disorders</p> <p>Patients with cardiac disease</p> <p>Long term safety</p>
Pharmacovigilance activities	No significant material change
Risk minimisation activities	Some PI changes made in response to the new RMP version and to the TGA's evaluation reports.
ASA	<p>Revised to address recommendations in RMP evaluation report</p> <p>Revised to reflect EU RMP v3.0</p>

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Summary of recommendations

It is considered that the sponsor's response to the TGA S31 Request has adequately addressed all of the issues identified in the RMP evaluation report.

There are recommendations for the Delegate's consideration:

- The sponsor has disagreed with the following recommendation which remains for the Delegate's consideration:
Other immunotherapy products contraindicate use in patients treated with beta-blockers due to their potential to interfere with treatment for anaphylaxis. It is recommended a similar contraindication is applied to Acarizax.
- The Delegate is also advised that the sponsor has amended the PI in response to the RMP evaluation report. These changes remain subject to final Delegate approval.

Suggested wording for conditions of registration***RMP***

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP Version 3.0 (dated 8 July 2015, DLP 30 May 2014) and Australian Specific Annex edition 2.0 (dated February 2016) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

The stated frequency of HDM sensitisation in individuals from Europe with asthma is approximately 50%. An Australian study specifically investigated the link between HDM AR and bronchial symptoms, showing occurrence of bronchial symptoms in 34% of the patients with HDM AR compared with 9% in the control group.

There is evidence from meta-analysis that immunotherapy (IT) directed at relevant aeroallergens, can improve symptom control in both AR and in asthma where relevant aeroallergen sensitisation has been demonstrated. However, a recent Cochrane review of SLIT for the treatment of asthma, found high heterogeneity of medicinal products and outcomes measures and poor quality studies, and were unable to recommend SLIT for mild or moderate asthma on the basis of the 52 studies reviewed.

Quality

There are no objections on quality grounds to the approval of Acarizax (standardised allergen extract from house dust mites *Dermatophagoides* sp.), sublingual immunotherapy tablet.

The HDM drug substances are allergen extracts derived from two species of cultivated HDM, *D. pteronyssinus* and *D. farinae*. Each DS is a mixture of proteins and other natural substances.

Each batch of drug substance for a species is standardised against the in-house reference (IHR) for each species. During the standardisation, the development unit (DU) potency is assigned to the drug substance based on total allergenic activity and the content of two major allergens (group 1 and group 2 allergens).

Active ingredient manufacture is performed at ALK-Abello in Denmark.

Nonclinical

The nonclinical dossier contained adequate published data and minimal GLP compliant toxicology studies necessary for satisfactory assessment of Acarizax. Published - studies in mouse, rat and guinea pig models and limited in-house mouse studies were used to demonstrate efficacy for dust mite allergens consistent with currently understood SLIT-mediated immune response to allergens. One repeat-dose toxicity study was submitted, a 26-week study in mice; no Acarizax-related systemic toxicities were noted in doses up to 199-times the clinical exposure with sublingual administration.

Limitations identified in the assessment were:

- A Repeat dose toxicity study was conducted in one rodent species, which limits the strength - of the safety data.

- No carcinogenicity studies were conducted using Acarizax.⁸⁷
- No dedicated fertility and pre/postnatal development studies were performed using Acarizax, and embryofetal development was only investigated in one species.

Given the longstanding clinical experience with dust mite allergen extracts utilised in this study, there are no nonclinical objections to the registration of Acarizax.

Clinical

Pharmacokinetics

No pharmacokinetic studies were submitted. The sponsor has provided a the rationale that the effect of IT is not mediated via systemic uptake of the allergen, but local uptake in the oral and sublingual mucosa by resident antigen presenting cells. Overall the absence of pharmacokinetic data to support this application is accepted in the CER and within the EMA guidelines for IT.

Pharmacodynamics

Primary pharmacology studies measured effect immunological effects of the product in humans, measured by serum HDM specific IgG4 and HDM specific IgE. The results are summarised in Table 11 below. The studies were not mechanistic studies but dose finding, safety and tolerability, or efficacy and safety studies with measurement of immunological parameters.

Table 11: Results from primary pharmacodynamic studies

Study Number	Summary of results
MT-01	<p>PD results:</p> <p>Significant change in HDM-IgE was observed over this short 28 day period. A non-significant change from baseline to end of treatment in specific IgE-blocking factor was observed for all doses of HDM-SLIT however there was a trend to greater effect in the higher doses, particularly in 4 to 16 DU. The effect plateaued at 4DU and higher.</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory; however it was not primarily a mechanistic study, but a dose finding study with immunological parameters. The short duration of the study makes any meaningful interpretation of the PD data difficult.</p>
TO-203 PH1	<p>PD results:</p> <p>No changes in HDM-IgE were noted in any group over this short time period of 14 days</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory; however it was not primarily a mechanistic study, but a safety and tolerability study with immunological parameters. The very short duration of the study (2 weeks) makes any meaningful interpretation of the PD data</p>

⁸⁷ Clarification; the sponsor provided justifications were accepted by the TGA

Study Number	Summary of results
	<p>difficult. It would not be unexpected not to see changes in immunological parameters at this early stage. The study was limited to males.</p>
MT-03	<p>PD results:</p> <p>Some statistically significant changes were observed over this short study. There was a general trend for elevation of HDM-IgE and IgE blocking with increasing doses compared with placebo, which appeared to plateau at doses of 6 DU or higher.</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory, however the study group of interest was children, who are not included in this current application and the study itself was not primarily a mechanistic study, but a safety and tolerability study with immunological parameters.</p>
Study MT-02	<p>PD results:</p> <p>Overall the results from the sub-cohort that were available for analysis of immunological parameters showed statistically significant changes in all immunological parameters under investigation, for all doses at 2, 6 and 12 months compared with baseline, and compared with placebo. In all active treatment arms there was maximal change (increase) in the IgE response at the 2 month measurement with a gradual decrease over the remainder of the study.</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory, however the study group of interest was only a sub-cohort of the whole population and the study itself was not primarily a mechanistic study, but a safety and tolerability study with immunological parameters. The longer time course allowed for demonstration of a sustained effect in promotion of HDM-IgG4 and persistence of a serum inhibitory effect on HDM-IgE binding for the study duration (1 year).</p>
P-003	<p>PD results:</p> <p>The difference from placebo was statistically significant for all assessed parameters (HDM-IgE and IgG4) at 8 weeks of therapy compared with baseline and placebo. There was dose effect observed with larger differences for 12 SQ-HDM than for 6 SQ-HDM.</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory, however and the study itself was not primarily a mechanistic study, but an efficacy and safety with immunological parameters. It is unclear why the immunological parameters were only assessed at one time point (8 weeks) and not at end of study (24 weeks). Inhibition assays were not performed.</p>
MT-04	<p>PD results:</p> <p>HDM-IgE increased after 4 weeks of treatment in both 12 SQ-HDM and 6 SQ-HDM but not placebo groups. From 20 weeks until end of therapy (13 to 18 months) the HDM-IgE slowly declined in active</p>

Study Number	Summary of results
	<p>groups, but remained significantly above baseline and placebo for the whole time course. HDM- IgG4 was significantly increased in all actively treated groups after 4 weeks of treatment and reached maximum peak at study end. HDM-IgG4 was statistically higher in the 12SQ-HDM than for 6 SQ-HDM at all-time points after baseline. Inhibition assays were not performed</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory; however the study itself was not primarily a mechanistic study, but an efficacy and safety with immunological parameters. Clear and sustained effects were shown in both immunological parameters assessed and indicated a superior effect in the 12 SQ compared with 6 SQ doses. This is consistent with the current application for the 12SQ dose.</p>
MT-06	<p>PD results:</p> <p>HDM-IgE increased from 4 weeks of treatment in both 12 SQ-HDM and 6 SQ-HDM but not placebo groups. From 24 weeks until end of therapy (52 weeks) the HDM-IgE slowly declined in active groups, but remained significantly above baseline and placebo for the whole time course. HDM-IgG4 was significantly increased in all actively treated groups after 4 weeks of treatment and reached maximum peak at study end. HDM-IgG4 was statistically higher in the 12 SQ-HDM than for 6 SQ-HDM at all-time points after baseline. Inhibition assays were not performed.</p> <p>Evaluator's comments:</p> <p>The study design, conduct and analysis were satisfactory, however the immunological analysis was only performed on a small sub-cohort (59 subjects, all from German based centres) and the study itself was not primarily a mechanistic study, but an efficacy and safety with immunological parameters. Clear and sustained effects were shown in both immunological parameters assessed and indicated a superior effect in the 12 SQ compared with 6 SQ doses. This is consistent with the current application for the 12SQ dose.</p>

The longer duration (12 months +) and pivotal AR and AA studies contained in this dossier provide good evidence of a immunomodulatory effect of the HDM-SLIT tablet, with consistent elevation of both species HDM-IgG4, particularly at the 6 and 12 SQ dose. The two pivotal efficacy studies (MT-04 (AA) and MT-06 (AR)) provide evidence that the 12 SQ dose was superior to the 6 SQ dose in terms of magnitude of increase in IgG4 from baseline.

HDM-IgE levels were consistently elevated at doses of 1 SQ and greater than across all studies provided with duration longer than 4 weeks. No consistent effects were observed in studies of less duration. Elevation of HDM-IgE was generally maximal at around 4 to 8 weeks in the larger studies with longer follow-up, but remained significantly elevated compared with baseline, and compared with placebo throughout the 12 to 18 months of therapy in the three studies of this duration (MT-04, MT-06, and MT-02).

Effect on HDM-IgE blocking (IgE inhibition assay) was a secondary pharmacological measurement performed in several tolerability, dose finding and safety studies. Findings across the studies were inconsistent, particularly in the shorter duration studies. A significant and sustained serum IgE blocking effect was observed in MT-02 for 1,3 and 6 DU at 6 and 12 month time points, however only a sub-cohort of the study was analysed.

Efficacy

Two efficacy and safety studies were pivotal MT-04 and MT-06.

Study MT-04

Study MT-04: MITRA trial is described in the clinical evaluation report (Please see Attachment 2). This is a Phase III, multicentre (109 sites in 13 European countries), randomised, parallel group, double blind, placebo controlled study. It was conducted August 2011 to April 2013. The study was designed to determine whether, after a period of stabilization of asthma on a single ICS and short acting beta-agonist (SABA), treatment for 7 to 12 months on HDM-SLIT would improve the time to first moderate or severe asthma exacerbation, once ICS were withdrawn in adults with asthma not well controlled on appropriate ICS therapy.

The study inclusion criteria were subjects age > 18 years, clinical evidence of HDM driven asthma (for at least one year) and HDM AR, Sensitization to *D. pteronyssinus* and/or *D. farinae* by both positive skin prick test (SPT) and sIgE (> 0.70 kU/L). Use of an appropriate amount of ICS (including combination products) in accordance with the GINA Guideline step 2-4 for at least 6 months within past year and documented reversible airways obstruction. Major exclusion criteria included FEV1 < 70% of predicted value, no hospitalisations (> 12 hour stay) due to an asthma exacerbation within the last 3 months, no current or previous use of any listed immunosuppressive, no inflammatory conditions in the oral cavity with severe symptoms, no history of systemic allergic reaction with cardiorespiratory symptoms and no relevant chronic disease.

The study treatment was daily HDM tablets 6DU, and HDM tablet 12DU, or placebo. Tablets were self-administered on a daily basis through two treatment periods, Period 1 (7 to 12 months) and treatment Period 2 (6 months whilst ICS were being withdrawn).⁸⁸

Efficacy variables were: Asthma exacerbations; time to first exacerbation, moderate and severe exacerbations, change in asthma control (measured by asthma control questionnaire (ACQ)), and change in asthma quality of life questionnaire AQLQ(S). Moderate and severe exacerbations are defined in the clinical evaluation report (see Attachment 2 section 7.1.1.4).

The primary efficacy outcome was difference in time to first moderate or severe asthma exacerbation during Period 3 (ICS reduction/withdrawal), after a Period of 7 to 12 months of study treatment, between subjects on HDM SLIT tablet (6DU and 12DU) and those on placebo.

A total of 834 patients were randomised (1:1:1) to placebo, 6DU or 12DU; with group distribution: Placebo (N = 277), 6DU (N = 275), 12DU (N = 282). A total of 26% of participants withdrew/discontinued during the course of the study, and this was evenly distributed across the three groups with a total of 693 out of 834 subjects completing the trial. Withdrawal due to AE was higher in the 12DU group (25) than in the 6DU group (12) or placebo (8).

All patients had HDM driven asthma, of a median 10 years duration and HDM associated AR. Approximately one third of subjects were mono sensitised to HDM, and the remainder were poly sensitised. The study population was almost exclusively Caucasian (98%). The median age was 31, with an equal distribution of males and females. ICS dose, forced expiratory volume in one second (FEV1), and asthma control scores (AQS) were very similar across the three groups at baselines. All were requiring between 200 to 1,200 µg of ICS per day for asthma control, indicating they had at least moderate asthma.

⁸⁸ Clarification: during the second 6 month treatment period ICS were reduced by 50% in the first 3 months followed by complete withdrawal for the second 3 months.

Approximately 70% had partially controlled and 30% uncontrolled asthma, by GINA definition at randomisation.

The primary efficacy analysis was based on Full analysis set with multiple imputation for missing data. For the primary efficacy outcome, the hazard ratio for time to moderate or severe asthma exacerbation after a fixed treatment period with 12 or 6 DU HDM tablet over the study period compared with placebo was 0.69 (95% CI-0.50-0.96) and 0.72 (95% CI 0.52-0.99] respectively. This is a positive clinical effect, just within predefined study criteria for clinically effectiveness with a 30% reduction in time to first asthma exacerbation. Full analysis set (FAS) observed analysis was consistent with this effect. Per protocol set (PP) analysis was not significant (hazard ratio (HR)-12DU versus placebo, 0.73 (p = 0.0867), HR- 6DU versus placebo, 0.70 (p = 0.0547).

In terms of stated key secondary clinical efficacy outcomes:

- Time to first asthma exacerbation with deterioration in asthma symptoms; there was a significantly reduced risk of having an asthma exacerbation with deterioration in asthma symptoms in the HDM-Tab 12DU (HR = 0.64, p = 0.0312) but not 6DU group compared with placebo.
- Proportion of subjects with minimal important difference (MID) change in ACQ (controlled for change in ICS); there were no significant differences between the groups in the proportion of subjects with improvement, although more subjects in the active groups (46% for 6DU and 50% for 12DU) had a MID improvement in ACQ score than in placebo (43%) at study end.
- Proportion of subjects with MID change in AQLQ(S) (controlled for change in ICS); there were no significant differences between the groups in the proportion of subjects with improvement, although more subjects in the active groups (55% for 6DU and 55% for 12DU) had a MID improvement in AQLQ(S) score than in placebo (47%) at study end.

There was no significant effect on symptom scores or quality of life when ICS at baseline was adjusted for. The clinical evaluator comments that, in general the results of the secondary analysis are consistent with the primary efficacy results, particularly related to asthma exacerbations.

Study MT-06

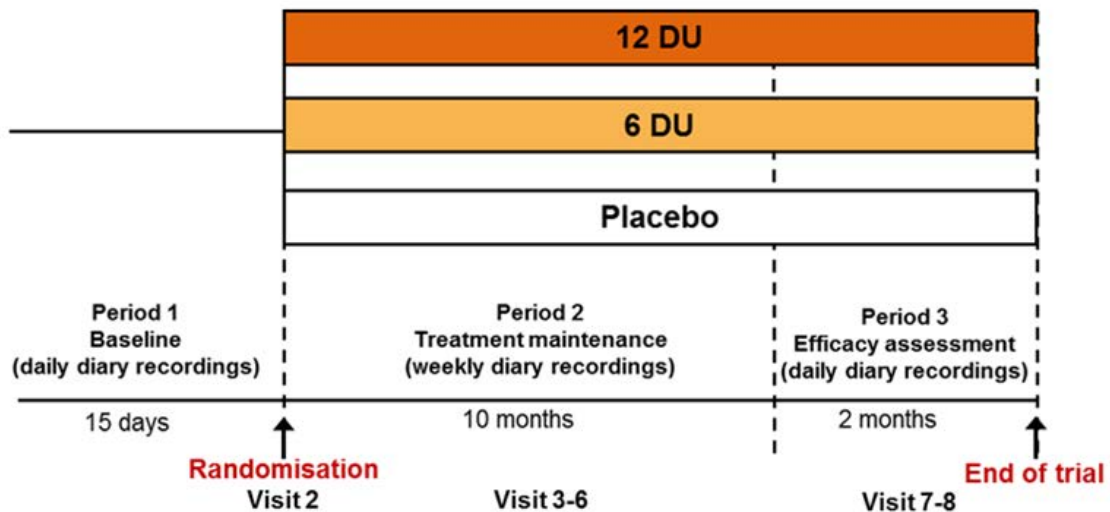
Study MT-06 is described in the clinical evaluation report (please see Attachment 2). This is a Phase III, multicentre (100 sites in European countries), randomised, parallel group, double blind, placebo controlled study. It was conducted October 2011 to April 2013. The study was designed to assess the efficacy and safety of HDM tablet in the treatment of HDM-AR in adults with inadequately controlled AR symptoms on standard treatment. Study was commenced out of grass and birch pollen season to avoid potential confounders. Subjects were required to have pre-existing HDM-AR symptoms for more than one year and not be controlled on current therapy.

Trial design is shown in Figure 3. A 15 day baseline with daily diary recording was followed by a 10 month treatment maintenance phase with weekly diary recording and a 2 month efficacy assessment with daily diary recording.

Study inclusion criteria were age 18 to 65 years, with history consistent with moderate to severe persistent HDM AR (with or without asthma) for at least one year, with AR symptoms despite symptomatic treatment. Diagnosed sensitization to *D. pteronyssinus* and/or *D. farinae* by both positive SPT and sIgE (> 0.70 kU/L). Major exclusion included moderate to severe asthma; defined as a requirement of more than 400 µg of budesonide for any co-existing asthma, and an FEV1 of < 70% predicted on adequate treatment and any uncontrolled asthma within 3 months of screening. Potential participants were

excluded if there was history of symptomatic seasonal allergic rhinoconjunctivitis and/or asthma caused by an allergen to which the subject is regularly exposed within the 8 week efficacy evaluation period or to AR due to animal hair/dander or mould to which they were regularly exposed.

Figure 3: Study MT-06 trial design



The study treatment was daily HDM tablets 6DU, and HDM tablet 12DU, or placebo. The total duration of treatment was 12 months. Standard AR and ARC therapy was provided to all subjects at randomization to be used throughout the study period in order to standardize all patients' treatment: Oral antihistamine tablets (desloratadine tablets, 5 mg), Nasal corticosteroid spray (budesonide 64 µg/dose), eye drops (azelastine 0.05%).

The main efficacy variables were combined AR symptom score and medication score (by electronic diary) described in the clinical evaluation report (see Attachment 2). The primary efficacy outcome was the average total combined rhinitis score (TCRS) during the last 8 weeks of treatment. The TCRS was the sum of the allergic rhinitis daily symptom score (DSS) and the allergic rhinitis daily medication score (DMS) averaged over the last 8 weeks of treatment.

Overall 992 subjects were randomised. There was 88% retention to the study end. The randomised/completed for each group were; placebo (338/ 296), 6DU (336/ 297), 12DU (318/ 284), respectively. The per protocol data set was 805.

Baseline characteristics between active and placebo groups were not significantly different. There were an appropriate mix of mono and poly aeroallergen sensitized patients (approx. 1:2). Median length of HDM-AR at screening was 7 years. 46% had HDM-asthma. There were roughly equal numbers of males and females, with a median age of 30 years. 98% were Caucasian.

Results for the primary outcome are shown in Table 12. In the full analysis set with multiple imputation (FAS-MI) data set there was an absolute difference of 1.09 (95% CI; 0.35-1.84) in the adjusted mean total combined rhinitis score (TCRS) between placebo and the 12DU HDM tablet group, and an absolute difference of 1.09 (95% CI 0.34-1.80) between the placebo and 6DU group. Both were significant differences at $p < 0.004$. The clinical evaluator comments that these differences are likely to be clinically meaningful.

Table 12: Primary efficacy outcome MT-06

Panel 9-2 Result of the analyses of the TCRS during the efficacy evaluation period

Analysis set	Treatment group	N	Adjusted mean TCRS [95% CI]	Absolute difference [95% CI]	Relative difference [95% CI]	p-value
FAS-MI (N=992)	Global*	992	-	-	-	0.003
	Placebo	338	6.81 [6.48;7.13]	-	-	-
	6 DU	336	5.74 [5.42;6.05]	1.07 [0.34;1.80]	-	0.004
	12 DU	318	5.71 [5.40;6.02]	1.09 [0.35;1.84]	-	0.004
FAS with observations (N=879)	Placebo	298	6.76 [5.94;7.63]	-	-	-
	6 DU	297	5.58 [4.81;6.40]	1.18 [0.45;1.91]	17.5% [7.0%;26.9%]	0.002
	12 DU	284	5.53 [4.77;6.35]	1.22 [0.49;1.96]	18.1% [7.7%;27.6%]	0.001
PP (N=805)	Placebo	272	6.74 [5.86;7.67]	-	-	-
	6 DU	269	5.53 [4.73;6.41]	1.20 [0.44;1.96]	17.9% [6.9%;27.7%]	0.002
	12 DU	264	5.38 [4.58;6.24]	1.36 [0.60;2.12]	20.2% [9.4%;29.8%]	0.001
FAS-LOCF (N=950)	Placebo	326	6.87 [6.12;7.66]	-	-	-
	6 DU	323	5.86 [5.14;6.61]	1.01 [0.29;1.74]	14.8% [4.4%;24.1%]	0.007
	12 DU	301	5.69 [4.99;6.43]	1.18 [0.46;1.90]	17.2% [7.1%;26.4%]	0.001

N = number of subjects included in the analysis; FAS = full analysis set; FAS-MI = FAS with imputation; FAS-LOCF = FAS with imputation of missing data using the method of LOCF; PP = per protocol dataset; CI = confidence interval.

*: Global refers to the global null hypothesis of no difference between the mean TCRS between the 3 treatment groups
Cross-reference: [Table 9.1.1](#), [Table 9.1.2](#), [Table 9.1.3](#), and [Table 9.1.4](#). [Figure 28](#) illustrates graphically the adjusted means of the TCRS for the FAS (with 95% CI) during the efficacy evaluation period in the 3 different treatment groups and [Figure 29](#) illustrates the absolute difference between the 2 active groups and placebo.

For secondary efficacy outcomes, in general positive effects were observed for rhinitis but not for conjunctivitis or combined rhino-conjunctivitis.

Study MT-02

Study MT-02 (Asthma). This Phase II study involved 604 subjects > 14 years with mild to moderate HDM asthma requiring < 800 µg of budesonide on randomisation and associated HDM-AR. This was a randomised, parallel group, double blind, placebo controlled, multi-centre trial (European sites) with 3 doses of active treatment (1, 3 and 6 DU) conducted from 2006 to 2008. Duration of study was approximately 12 months.

604 subjects were randomised and 532 (88%) completed the study. Baseline characteristics did not differ significantly between groups. There were equal numbers of males and female, an almost entirely Caucasian population (98%). The median age was 29. Six percent were less than 17 years. Subjects had a median duration of asthma and AR of 12 years.

The primary efficacy endpoint was predefined as reduction in ICS use at study end. Outcome was significant with ICS reduction of 81.4 µg/day observed for the 6 DU group compared with the placebo group (95% confidence interval, 26.7 to 136.1 µg/day; p = 0.0036). No significant reduction was observed for the lower two doses (1DU and 3DU).

Safety

A total of 318 subjects received the proposed 12DU/SQ-HDM dose for > 24 weeks in placebo controlled asthma studies and 282 subjects received this dose for > 24 weeks in AR studies. The clinical evaluator comments that safety assessment is based on small numbers of adults and with little safety data for treatment periods longer than 12 months.

In pivotal studies the a summary of adverse events is provided in Table 13 below

Table 13: Summary of adverse events

	All AE n/events	% AE Placebo group	% AE 6DU** group	% AE 12DU** group	Severe AE n/events	SAE n/events	Study DIS. *** Placebo/6 / 12DU(n)	Not recover ed (n)
MT-04 n = 834	599/2084	63%	74%	79%	45/57	28/32	8/12/25	68
MT-06 n = 992	579/1686	46%	63%	67%	*28/31	12/12	7/10/13	33

*- one of the AEs was not classified by the investigators or sponsors as severe, but on reading the details provided, this has been misclassified in the reviewers opinion and added to the numbers. **Both pivotal studies used both 6 and 12DU doses of daily HDM-tab. *** study discontinuation due to AE

In both pivotal studies, more participants in the 6DU or 12 DU groups reported AE and discontinued due to AE. In MT-04, 30 subjects (4%) discontinued due to 57 treatment related AEs, where 4 were from the placebo, 9 from the 6DU and 17 from the 12 DU groups respectively. In MT-06, 30 subjects (3%) discontinued the trial due to 50 AEs, where 1, 9, and 12 subjects from placebo, 6DU and 12DU groups, respectively, discontinued due to treatment related AEs. There were no deaths across the pivotal studies.

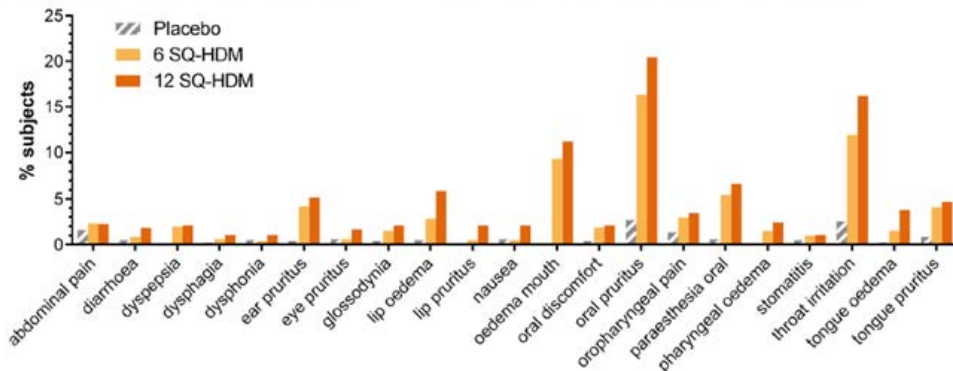
Rate of SAE were low (1 to 3% of study population). The clinical evaluator identifies 9 severe treatment related AE's in MT-06, of which 3 were in the 6DU group, 6 were in the 12DU group, and none were receiving placebo. In MT-04 there were 7, 2 and 3 from the 12DU, 6DU and placebo groups respectively. In MT-04 subjects being treated for asthma had higher rates of SAEs and higher treatment related study discontinuations than those in MT-06, where the target disease was AR. There were no reports of systemic anaphylaxis requiring adrenaline; however adrenaline was required for 1 IMP related episode of laryngeal oedema.

In the four studies (MT-04, MT-06, MT-02 and P003), 51%, 44% and 15% of participants exposed to 12DU, 6DU or placebo HDM-tab, respectively, had at least one possible/probable treatment related AE reported. The majority of AEs were mild (71 to 85% of events) or moderate (14 to 25% of events) in severity.

The most frequent treatment related AEs were reasonably consistent across the two pivotal studies, and the other two Phase II studies (MT-02, P-003). Oral pruritus (20%), throat irritation (16%), and mouth oedema (11%) were most frequently in the 12 SQ-HDM group). Other reported local effects included oral paraesthesia, lip oedema, oropharyngeal pain, tongue oedema, ear pruritus and lip pruritus as shown in Figure 4 and Table 14. These events showed dose dependence.

Figure 4: Overview of frequent AEs

A graphical overview of the frequencies of the most frequent events with dose dependence as listed above is shown in [Panel 12](#) for placebo and the two efficacious active doses, 6 and 12 SQ-HDM.



Most frequent defined as $\geq 1.5\%$ of the subjects in the 12 SQ-HDM group in pool 4. In the MedDRA version used for MT-02, the PT Paraesthesia oral belonged to the Nervous system disorders SOC. In this table the frequencies have been merged under the gastrointestinal disorders SOC in accordance with the MedDRA versions used for the more recently conducted trials. Pool 4: MT-02 (adults), P003, MT-04, MT-06.

Cross-reference: section 2.7.4.7 [Appendix, Table 27](#).

Table 14: AE pivotal studies by SOC

	SOC	Placebo MT04	Placebo MT06	Active MT04	Active MT06	% AE active groups	% all AE
All events		323	327	1064	1359	2423	3073
Ear and labyrinth disorders	All	2	2	19	48	2.8%	2.3%
	Ear pruritus	2	1	19	40		
Eye disorders	All	3	22	11	20	1.3%	1.8%
	Conjunctivitis allergic	3	4	11	4		
	Pruritus	-	3	-	9		
	Abdominal pain upper	2	0	10	6		
	Diarrhoea	4	0	13	3		
	Dyspepsia	8	0	14	7		
	Glossodynia	0	2	0	22		
	Lip oedema	1	2	13	17	1.2%	1.1%
	Lip pruritus	0	3	8	8		
	Lip swelling	4	0	11	18	1.2%	1.1%
	Nausea	2	1	9	4		
	Oedema mouth	0	1	61	68	5.3%	4.2%
	Oral pruritus	8	8	123	172	12.2%	10.1%
	Oral discomfort	0	0	0	21		
Paraesthesia oral	0	2	35	71	4.4%	3.5%	
Infections and infestations	Swollen tongue	0	1	12	10		
	Tongue pruritus	1	6	29	45	3.1%	2.6%
	All	213	135	477	286	32%	36%
	Acute tonsillitis	2	2	10	8		
	Acute sinusitis	-	2	-	12		
	Bronchitis	22	8	43	22	2.7%	3.1%
	Gastroenteritis	9	4	11	3		
	Influenza	9	4	20	13		
	Pharyngitis /nasopharyngitis	13	55	48	108	6.4%	7.3%
	Respiratory tract infection	10	3	26	10	1.5%	1.6%
	Rhinitis	4	2	16	3		
	Sinusitis	7	7	19	12	1.3%	1.5%
	Tonsillitis	5	4	10	7		
	Upper respiratory tract infection	31	9	55	22	3.2%	3.8%
Viral infection	8	3	32	13	1.9%	1.8%	
Injury, poisoning and procedural complications	All	12	12	21	16	1.5%	2.0%
	Accidental overdose	12	2	21	6		
Musculoskeletal and connective tissue disorders	All	4	4	11	18	1.2%	1.2%
	Back pain	4	2	11	10		
Nervous system disorders	All	13	13	23	38	2.5%	2.8%
	Headache	13	11	23	17		
Respiratory, thoracic and mediastinal disorders	All	58	66	164	272	18%	18.2%
	Asthma	28	6	46	25	2.9%	
	Cough	9	5	16	11	1.1%	
	Oropharyngeal pain	6	3	19	15	1.4%	
	Pharyngeal oedema	-	0	-	18		
	Rhinitis allergic	10	5	21	11	1.3%	
	Nasal discomfort	-	13	-	9		
Throat irritation	5	14	62	120	7.5%	6.5%	
Skin and subcutaneous tissue disorders	All	-	14	-	50	2.0%	2.1%
	Pruritus	-	5	-	12		

AEs related to the application site (mouth and throat symptoms) were relatively common and constant over the first 4 weeks of daily treatment. This tapered from week 16 of the study in all groups, to be less than 5% in both 12DU and 6DU by study end and 0 by week 40 in the placebo group.

The majority of the most frequent AEs in MT-04 started within 20 minutes following the first intake of IMP. For the 3 most common AEs, the overall median onset in minutes was 1 minute for oral pruritus, 1 minute for throat irritation, and 2 minutes for oedema mouth.

Asthma exacerbations related to IMP were an AE of special interest in both pivotal studies.

Overall, in MT-04; 38 subjects (14%) in placebo, 33 subjects (12%) in 6 SQ-HDM and 28 subjects (10%) in 12 SQ-HDM groups reported AEs that could be considered related to asthma. The majority of these events were considered unlikely to be related to the IMP. In MT-04 there were two study discontinuations due to severe asthma exacerbations considered likely to be related to IMP.

In MT-04 analysis of those individuals who had FEV1 < 70% at any point during the study, or who satisfied the GINA criteria for uncontrolled asthma were assessed for evidence of increased risk of asthma exacerbations compared with the remainder of the cohort. There was no difference reported, however the uncontrolled asthma cohort only comprised of 232 subjects.

Onset of eosinophilic oesophagitis (EoE) during MT-06 was observed in one participant receiving IMP. This did not result in study discontinuation; however the subject continued to have evidence of EoE and was considered not resolved at end of study. Development of EoE on a SLIT study would normally be an indication for discontinuation.

In the first round the clinical evaluator identified safety signals possible related to IMP for Meniere's disease and liver function abnormalities in ongoing studies for which only SAEs and study discontinuations were provided. The second round clinical evaluator accepts the single case of Meniere's disease does not represent a safety signal. The second round clinical evaluator notes that cases of liver function abnormalities SAE and AE leading to discontinuation were all reported in study TO-203 AA. The evaluator considers there is a lack of clarity around data related to liver dysfunction in TO 203 AA. The second round clinical evaluator comments "*On balance, taking into account known biological plausibility, it is an unlikely safety signal; but more convincing data on the identified case would be helpful*".

Clinical evaluation benefit-risk assessment and recommendation regarding authorisation

The overall benefits of Acarizax in the proposed usage at 12DU daily are:

- Reduced risk of moderate to severe asthma exacerbation after at least 7 months of daily investigational medicinal product (IMP) by 31%. Based upon an absolute risk reduction of moderate-severe exacerbation from 30% in placebo to 21% in 12 DU group, this equates to number needed to treat (NNT) = 11.1
- At least a 1.09 reduction in overall symptom and medication score for AR from 14 weeks of therapy.
- A 50% reduction in the risk of having an allergic rhinitis exacerbation and twice the probability of having days without more than minimal awareness of AR symptoms.

The clinical evaluator's recommendation is to approve the submission subject to the additional changes to PI and CMI and clarification of whether any safety signal exists for liver dysfunction.⁸⁹

⁸⁹ Clarification; the Delegate was satisfied by later communication with the sponsor that a safety signal for liver dysfunction did not exist.

Risk management plan

Outstanding issues

The sponsor has disagreed with a contraindication to use in patients treated with beta-blockers. This remains subject to final determination by the Delegate.

Other aspects of PI have been amended in response to the RMP evaluation report (eosinophilic oesophagitis, autoimmune disease, contraindication in asthma). These changes are subject to final Delegate approval.

Risk-benefit analysis

Delegate's considerations

The clinical studies safety data was limited to 642 adult subjects who received 12 SQ-HDM in Phase II/III studies.

The Sponsor, in a response to second round clinical evaluation, has provided further information on liver function abnormalities SAE and AE leading to discontinuation in clinical trial TO-203-3-1 (AA) which is included in papers for consideration by the ACPM.

This study (TO-203-3-1(AA)) was sponsored by Torii Pharmaceuticals in Japan. Six subjects reported liver function abnormalities leading to either SAEs or discontinuation of the trial. From these 6 subjects, 3 reported SAEs (subjects [information redacted]) and 4 reported non-serious AEs leading to trial discontinuation (subject [information redacted]); 1 subject [information redacted] reported both SAEs and non-serious AEs leading to trial discontinuation. Subjects [three subjects information redacted] received active treatment.

Information was presented in a table and with case narratives. For subjects who received active treatment:

- Subject [information redacted], 22 year old male, 12 SQ-HDM, hepatic function abnormal, alanine aminotransferase (ALT) elevation, aspartate aminotransferase (AST) elevation, SAE, day of onset 82, day of discontinuation 90, recovered Day 131. The investigator judged highly likely due to viral infection-not related to IMP.
- Subject [information redacted], 34 year old female, 12 SQ-HDM, liver disorder, ALT increase, day of onset 309, discontinuation due to moderate worsening of asthma, recovered liver disorder day 345. The investigator evaluated the event as not related to IMP based on mechanism of action of IMP. Furthermore the patient had previously been treated with subcutaneous HDM IT for several decades.
- Subject [information redacted], 52 year old female, 6 SQ-HDM, AST increased, ALT increased, ALP increased, non-serious AE, day of onset 274, day of discontinuation 277, recovered day 309. The events were assessed as not related to IMP by the investigator. As the events were non-serious no alternative aetiology was reported and no further information is reported.

No signals related to liver function abnormalities were identified in any other Phase II or Phase III trials.

ALK evaluates that the 3 reported cases related to liver function abnormalities following the administration of the active treatment do not represent a safety signal for the HDM SLIT-tablet. No clear temporal relationship to intake of IMP exists in the cases, and as mentioned by the evaluator, based on biological plausibility, liver function abnormalities is an unlikely safety signal. Should additional events be reported in clinical trials or post-

marketing, these will be evaluated and if signal are identified these will be described in PSURs and actioned accordingly. The Delegate considers the 3 cases of liver function abnormalities reported in TO-203-3-1 (AA) do not represent a safety signal.

The second round clinical evaluator maintains that a requirement for sensitization to be specifically demonstrated via SPT or specific IgE is appropriate in the 'indications' section of PI. The sponsor notes that the 'dosage and administration' section states that patients should have a confirmed clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) prior to treatment. The sponsor proposes no further changes to indications and notes this is consistent with the approved indications for Actair SLIT tablets.

The sponsor has introduced editorial amendment of proposed indications in the response to second round evaluations, which includes deletion of "*despite use of symptom relieving medications*" from the house dust mite allergic rhinitis indication. This differs from the population studied in the pivotal Study MT-06. The clinical evaluator has also noted that patients in study MT-04 and MT-02 had both HDM -AA and HDM-AR. Efficacy of this product for patients with asthma only has not been assessed.

Pivotal efficacy and safety studies and Phase II study P-003 were undertaken in adults. Phase II study MT-02 allowed adolescents > 14 years but only 6% of enrolled subjects were less than 17 years of age. MT-02 involved active treatment doses of 1, 3 and 6 DU. The 'dosage and administration' section of PI includes an appropriate statement '*Acarizax is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.*' In contrast, the Delegate considers the proposed "Paediatric use" statement in PI is unacceptable as it refers to 212 subjects between 5 and 17 years of age and states no differences in safety, tolerability and effectiveness were observed between these subjects and subjects > 18 years.

The 'dosage and administration' section of PI includes a statement '*International treatment guidelines refer to a treatment period of immunotherapy to achieve disease modification.*' The Delegate considers this statement is unacceptable in Acarizax PI because of the limited duration of submitted clinical studies with Acarizax. A recent Cochrane review of SLIT for the treatment of asthma, found high heterogeneity of medicinal products and outcomes measures and poor quality studies, and were unable to recommend SLIT for mild or moderate asthma on the basis of the studies reviewed.

Proposed action

The Delegate had no reason to say, at this time, that the application for Acarizax should not be approved for registration, subject to ACPM advice on issues identified above and finalisation of PI.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the ACPM consider the limited clinical studies safety data at the proposed dose in Phase II/III studies are adequate to support registration?
2. Taking account of the sponsor response to second round clinical evaluation report, on whether the 3 cases of liver function abnormalities reported in TO-203-3-1 (AA) represent a safety signal.
3. The indications proposed by the sponsor in response to second round evaluation reports, taking account of the clinical evaluator's recommendation to require sensitization to be specifically demonstrated via SPT or specific IgE.

4. The indications proposed by the sponsor in response to second round evaluation reports, taking account of difference in population form that in pivotal clinical studies. That is, HDM-AR despite use of symptom relieving medication and both HDM-AA and HDM-AR.
5. The limited numbers of children and adolescents included in the clinical development of Acarizax.
6. The inclusion under 'dosage and administration' of the sentence '*International treatment guidelines refer to a treatment period of immunotherapy to achieve disease modification.*'

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Seqirus (formerly known as bioCSL) welcomes the Delegate's proposed recommendation to register Acarizax (allergen extract from the house dust mites *Dermatophagoides* sp.).

Subsequent to the review of the Delegate's overview (dated 03 May 2016), this response seeks to address several items identified by Seqirus as requiring further clarification and also to address the Delegate's recommendations regarding the proposed PI.

Of note, late in the afternoon on 13 May 2016, Seqirus received final comments from the nonclinical evaluator regarding Seqirus' response to the second round nonclinical evaluation report (NCER). The final NCER dated 13 May 2016 includes 2 proposed amendments to the PI. Seqirus' responses to these are included.

Product overview

Acarizax is a 12 SQ-HDM once daily, sublingual immunotherapy (SLIT), oral lyophilisate tablet. It contains standardised allergen extracts from house dust mite (HDM) species *Dermatophagoides* (*D. pteronyssinus* and *D. farinae*). It has been developed to treat HDM respiratory allergic disease as there is currently an unmet clinical need in relation to a convenient, oral dosage form to treat patients with the following conditions:

- house dust mite (HDM) allergic rhinitis (AR) or
- HDM allergic asthma (AA) not well controlled by inhaled corticosteroids associated with HDM allergic rhinitis.

The ALK clinical development program for Acarizax includes 2 pivotal Phase III studies:

- MT-04 (MITRA): This study investigated the safety and efficacy in subjects with HDM allergic asthma not well controlled by ICS. The primary endpoint for this trial was the time to the first moderate or severe asthma exacerbation during the ICS reduction period. The 12 SQ-HDM dose demonstrated statistical significance compared to placebo for time to first asthma exacerbation ($p = 0.027$). The 12 SQ-HDM dose also met the pre-specified criterion for clinical relevance compared to placebo (that is $HR \leq 0.70$).
- MT-06 (MERIT): This study investigated the safety and efficacy in subjects with persistent moderate to severe HDM allergic rhinitis despite the use of symptom relieving medication. The primary endpoint for this trial was the average daily total combined rhinitis score (TCRS) evaluated during the last 8 weeks of treatment. The TCRS was the sum of the rhinitis symptoms score and the rhinitis medication score (maximum total possible score 24). The 12 SQ-HDM demonstrated a statistically significant reduction in TCRS compared to placebo ($p = 0.004$). The 12 SQ-HDM dose also met the pre-specified criterion for clinical relevance (that is the absolute

difference in the TCRS between both active groups and placebo was ≥ 1) commencing from 14 weeks of treatment and continuing for the duration of the trial.

The safety of Acarizax has been demonstrated in the Phase II and Phase III clinical trials in which 642 patients received the proposed 12 SQ-HDM dose. During evaluation, both the clinical evaluator and the Delegate have commented that the safety assessment is based on small numbers of subjects. Seqirus notes that, in the pooled Phase II/III safety analysis of the recently approved Actair (allergen extract from HDM *Dermatophagoides* sp.) (AUST R 233470 and 233471), only 492 subjects were administered the approved dose of 300 IR.⁹⁰

Overall, the Acarizax safety data demonstrates that the 12 SQ-HDM has an excellent safety profile that is favourable in terms of local tolerability compared to SCIT products and supports at home sublingual administration.

- In the pooled Phase II/III Acarizax studies, the majority of subjects in all treatment groups experienced treatment emergent adverse events (TEAE) that were mild to moderate in intensity.
- The most common TEAEs included oral pruritus, nasopharyngitis, throat irritation, and oedema mouth (reported by 20%, 16%, 15% and 10% of subjects). In the pooled Phase II/III studies, time to onset from first administration for oral pruritus, throat irritation and oedema mouth was typically fast (approximately 2 minutes after first administration).
- No long term concerns with regard to Acarizax were observed following 12 months of once daily treatment.

As mentioned in the Delegate's overview;

- There were no reports of anaphylaxis requiring adrenaline.
- Two cases of laryngeal oedema were reported. Importantly, of these, only 1 occurred following administration with the 12 SQ-HDM dose and this was reported by the investigator as a case of 'very mild laryngeal oedema'. This occurred after the first administration which was performed under medical supervision and was treated with adrenaline. The subject completed the trial with mild oral pruritus as the only subsequently reported AE.
- One event of eosinophilic oesophagitis (EoE) was reported in the Acarizax clinical trials (MT-06) with a dose lower than that proposed for registration. The event was assessed as related to the IMP by the investigator. As noted in the recently approved Actair PI (AUST R 233470 and 233471)⁹⁰ EoE is a suspected class effect of sublingual immunotherapy.
- Three cases of liver dysfunction were reported in a Phase III clinical study (TO-203-3-1, AA). The Delegate concludes that these 3 cases do not represent a safety signal. Seqirus concurs with the Delegate's assessment.

Body of request for ACPM Advice – items for clarification

The Delegate's overview notes that, whilst there is evidence from meta-analysis that immunotherapy directed at relevant aeroallergens can improve symptom control in both AR and in asthma where relevant aeroallergen sensitisation has been demonstrated, a recent Cochrane review of SLIT for the treatment of asthma found high heterogeneity of medicinal products and outcomes measures and poor quality studies, and were unable to recommend SLIT for mild to moderate asthma on the basis of the 52 studies reviewed.

⁹⁰ Actair PI: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01698-1&d=2016051216114622483>

As per Seqirus' response to the D150 Nonclinical Evaluation Report (NCER),⁹¹ the safety profile of Acarizax (SLIT) in subjects with a broader severity of HDM allergic asthma than previously investigated has been demonstrated. The conclusion of the Cochrane review⁹² (that is that safety conclusions regarding SLIT treatment of those with moderate or severe asthma is difficult due to the preferential recruitment of patients with intermittent or mild asthma for clinical trials) is therefore out dated. This was acknowledged by the nonclinical evaluator in the second round nonclinical evaluation report.

The Delegate's overview notes that there were no nonclinical objections to the registration of Acarizax. However the overview states that a limitation of the nonclinical development program was that a repeat dose toxicity study was conducted in one rodent species, which potentially compromised the legitimacy of the safety data.

As per Seqirus' response to the D150 NCER,⁹³ there is currently no comprehensive mouse or non-rodent model of HDM induced allergy and asthma mimicking all aspects of the human disease. However, mouse models can display some hallmarks of human rhinitis and asthma. Given this, and understanding the associated limitations, after careful consideration, mice were selected the species of choice for in vivo testing. This was discussed with and endorsed by the Paul-Ehrlich-Institut (PEI), Germany.

Indications

The Delegate's overview notes that Seqirus has introduced minor editorial amendments to the proposed indication in the second round response to the clinical evaluation report which differ from the population studied in the pivotal study MT- 06. In consideration of the Delegate's comments, Seqirus has amended the indication to reflect the population studied in MT-06; that is to:

HDM allergic asthma not well controlled by inhaled corticosteroids associated with HDM allergic rhinitis.

The Delegate's overview notes the clinical evaluator's recommendation regarding the inclusion of diagnosis via skin prick or specific IgE test in the indication. The indication section has been amended to include the word 'diagnosed'. Reference to sensitization (specific IgE or skin prick test) is included in the 'dosage and administration' section of the PI. This is consistent with the recently approved Actair PI (allergen extract from HDM *Dermatophagoides* sp.) (AUST R 233470 and 233471)5.

The proposed amended indication subsequently reads:

Acarizax is indicated for the treatment of adults diagnosed with:

- *house dust mite (HDM) allergic rhinitis or*
- *HDM allergic asthma not well controlled by inhaled corticosteroids associated with HDM allergic rhinitis.*

Patients' asthma status should be carefully evaluated before the initiation of treatment.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

⁹¹ D150 NCER EFMO ASSESSMENT (p8 of 24), Item 9, submitted 07 April 2016

⁹² Normansell R, Kew KM, Bridgman AL; Sublingual immunotherapy for asthma; Cochrane Database Syst Rev. 2015 Aug 28,

⁹³ D150 NCER EFMO, CONCLUSIONS RECOMMENDATIONS (p5 of 24); Item 6, submitted 07 April 2016

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Acarizax oral lyophilisate tablets containing 12 SQ-HDM standardised allergen extract of American house dust mite extract and European house dust mite extract to have an overall positive benefit–risk profile for the amended indication:

Acarixax is indicated for the treatment of adults diagnosed with:

- *Persistent moderate to severe house dust mite (HDM) allergic rhinitis not well controlled despite use of symptom-relieving medication or*
- *HDM allergic asthma not well controlled by inhaled corticosteroids associated with HDM allergic rhinitis.*

In making this recommendation the ACPM

- Advised that the clinical study had '*persistent moderate to severe house dust mite allergic rhinitis not well controlled despite use of symptom relieving medication*' and this should be added to the indication wording for house dust mite allergic rhinitis.
- Advised that treatment should be initiated under the guidance of a clinician experienced in allergen immunotherapy.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Monitoring of liver function abnormalities and eosinophilic oesophagitis should be included in the RMP/ASA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to PI and CMI and specifically advised on the inclusion of the following:

- Treatment with Acarizax should be initiated under the guidance of a clinician experienced in allergen immunotherapy.
- Precautions regarding eosinophilic oesophagitis, immune deficiency and autoimmune diseases should be included in the PI and modelled similarly to Actair.
- Specify the use of allergen sensitivity testing prior to treatment under dosage and administration.
- Include the paediatric data in the clinical trials section of the PI.
- The reported liver function abnormalities seen in Study TO-203-3-1 should be included in the PI.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Does the ACPM consider the limited clinical studies safety data at the proposed dose in Phase II/III studies are adequate to support registration?*

The ACPM noted that the safety data set is of similar size to that for the Actair sublingual tablet and that post marketing experience is reassuring. The ACPM advised that SLIT is considered to have very reassuring safety record and therefore there are adequate safety data to support registration.

2. *Taking account of the sponsor response to second round clinical evaluation report, do the 3 cases of liver function abnormalities reported in TO-203-3-1 (AA) represent a safety signal?*

The ACPM noted that concern about liver function tests (LFTs) is limited to one study and that there is no plausible mechanism. The ACPM advised that whilst these elevated LFTs do not preclude registration the three cases of reported liver function abnormalities might represent a safety signal and should therefore be included in RMP as well as the PI.

3. *Do the indications proposed by the sponsor in response to second round evaluation reports, take account of clinical evaluation report recommendation to require sensitization to be specifically demonstrated via SPT or specific IgE?*

The ACPM advised that the PI should specify the use of allergen sensitivity testing prior to treatment with Acarizax.

4. *Do the indications proposed by the sponsor in response to second round evaluation reports take account of difference in population from that in pivotal clinical studies, that is HDM-AR despite use of symptom relieving medication and both HDM-AA and HDM-AR?*

The ACPM recommended that allergic rhinitis indication should include the words “*persistent moderate to severe house dust mite allergic rhinitis not well controlled despite use of symptom-relieving medication*” as initially proposed and in accordance with enrolment into Study MT-06.

5. *Should the limited numbers of children and adolescents be included in the clinical development of Acarizax?*

The ACPM noted the proposed PI includes a statement that Acarizax has been administered to 212 subjects between 5 and 17 years of age and no overall differences in safety, tolerability and/or effectiveness were observed between these subjects and subjects ≥ 18 years of age. The ACPM also noted that SLIT is widely used in children, especially given that the alternative requires regular subcutaneous injections. The ACPM advised that although use in children is not being requested the paediatric data could be included in the clinical trials section of the PI.

6. *Does the inclusion under ‘dosage and administration’ of the sentence ‘International treatment guidelines’ refer to a treatment period of immunotherapy to achieve disease modification?*

The ACPM noted that unlike pharmacological treatments, the objective of allergen immunotherapy is for treatment effects to continue after treatment interruption. The ACPM noted that no data were provided of symptom control after the completion of the study intervention. The ACPM was of the view that the International Treatment Guidelines might be useful to prescribers in the absence of long term trial data on whether treatment should continue beyond 12 to 18 months.

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACPM advised that treatment should be initiated under the guidance of a clinician experienced in allergen immunotherapy.

The ACPM also advised that precautions regarding eosinophilic oesophagitis, immune deficiency and autoimmune diseases should be included in the PI and modelled similarly to Actair.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Acarizax standardised allergen extract from house dust mites *D. pteronyssinus* and *D. farinae* 12 SQ-HDM oral lyophilisate tablet, indicated for:

Acarizax is indicated for the treatment of adults diagnosed with:

- *house dust mite (HDM) allergic rhinitis not well controlled despite use of symptom relieving medication or*
- *HDM allergic asthma not well controlled by inhaled corticosteroids and associated with HDM allergic rhinitis.*

Patients' asthma status should be carefully evaluated before the initiation of treatment.

Specific conditions of registration applying to these goods in Australia

1. The standardised allergen extract from house dust mites *D. pteronyssinus* and *D. farinae* 12 SQ-HDM oral lyophilisate tablet (Acarizax) Risk Management Plan (RMP), EU-RMP Version 1.0 (dated 25 September 2014, DLP 30 May 2014) and Australian Specific Annex edition 1.0 (dated June 2015), included with submission PM-2015- 01531-1-2, and any subsequent revisions, as agreed with the TGA will be implemented.
2. Batch Release Testing and Compliance with Certified Product Details (CPD)
It is a condition of registration that all batches of Acarizax (standardised allergen extract from house dust mites *Dermatophagoides* sp.), sublingual immunotherapy tablet imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
1. The Sponsor must provide:
 - a. an Annual Product Report, using the template available on the TGA website (<https://www.tga.gov.au/form/annual-product-report-biological-prescription-medicines>), on the above product listing batch details and quantities released during the previous year (including export products). A justification should be supplied for the release of any batches which do not meet specifications or undergo unacceptable temperature deviations during shipping. The annual report should be submitted by an agreed due date.
 - b. samples, reference materials, certificates of analysis and related documentation when requested by the Laboratories Branch of the TGA for Post Market Monitoring.

Attachment 1. Product Information

The PI for Acarizax approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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