



Australian Government
Department of Health
Therapeutic Goods Administration

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

Proprietary Product Name: Actair initiation
treatment and Actair continuation treatment

Sponsor: Stallergenes Australia Pty Ltd

August 2017

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Common abbreviations

Abbreviation	Meaning
AASS	Average Adjusted Symptom Score
AE	Adverse Event
AHR	airway hyper responsiveness
AIHW	Australian Institute of Health and Welfare
AIT	Allergen Immunotherapy
AR	Allergic Rhinitis
AUC	Area under the curve
ANCOVA	Analysis of Covariance
ARMS	Average Rescue Medication Score
ARTSS	Average Rhinitis Total Symptom Score
Ch _{BL}	Change from Baseline
CI	Confidence Interval
D.far	<i>Dermatophagoides farina</i> (American house dust mite)
D.pte	<i>Dermatophagoides pteronyssinus</i> (European house dust mite)
DSMB	Data and Safety Monitoring Board
EMA/CHMP/EWP	European Medicines Agency's/Committee for Medicinal Products in Human Use/Efficacy Working Party
EoE	Eosinophilic esophagitis
EU	Europe
FAS	Full Analysis Set
FASY1	Full Analysis Set Year 1
FDA	Food and Drug Administration (USA)
FEV ₁	Forced Expiratory Volume in one second

Abbreviation	Meaning
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
HDM	House Dust Mites
ICH	International Conference on Harmonization
IFN γ	interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IR	Index of Reactivity
JRQLQ	Japanese Allergic Rhinitis Standard QOL Questionnaire
LOCF	Last Observation Carried Forward
LS	Least Squares
MMRM	Mixed-effects Model for Repeated Measures
NOAEL	no observed adverse effect level
PI	Product Information
PPSY1	Per Protocol set Year 1
PSCDs	Proportion of Symptom-Controlled Days
RMP	Risk Management Plan
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RTSS	Rhinitis Total Symptom Score
S-524101	Sublingual tablet of house dust mite extracts
SC	Subcutaneous
SCIT	Subcutaneous Immunotherapy
SL	Sublingual

Abbreviation	Meaning
SLIT	Sublingual Immunotherapy
SPT	Skin Prick Test
TEAE	Treatment Emergent Adverse Event
TGF- β	transforming growth factor- β
Th2	T helper 2 cells
VIT	venom immunotherapy

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation (new dosage form and new route of administration)
<i>Decision:</i>	Approved
<i>Date of decision:</i>	5 April 2016
<i>Date of entry onto ARTG</i>	15 April 2016
<i>Active ingredients:</i>	American house dust mite / European house dust mite
<i>Product names:</i>	Actair initiation treatment, Actair continuation treatment
<i>Sponsor's name and address:</i>	Stallergenes Australia Pty Ltd 4 Daydream Street, Building 2 Suite 2408 Warriewood NSW 2102
<i>Dose form:</i>	Tablet
<i>Strengths:</i>	100 IR, and 300 IR
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	3, 100 IR and 88, 300 IR tablets (initiation treatment) 3, 100 IR and 28, 300 IR tablets (initiation treatment) 3, 100 IR and 7, 300 IR tablets (initiation treatment) 30, 90 tablets (300 IR, continuation treatment))
<i>Approved therapeutic use:</i>	<i>Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy</i>
<i>Route of administration:</i>	Sublingual
<i>Dosage:</i>	The therapy is composed of an initiation treatment (including a 3 day dose escalation) and a continuation treatment. For full details of dosage please see the Product Information
<i>ARTG numbers:</i>	233470, 233471

Product background

This AusPAR describes the application by Stallergenes Australia Pty Ltd (the sponsor) to register Actair initiation treatment and Actair continuation treatment for the following indication:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents and children (above the age of 5) diagnosed with house dust mite allergy

This submission seeks to register a new dosage form and new route of administration (sublingual tablet) for a 50% mixture of allergens extracted from European house dust mites (*Dermatophagoides pteronyssinus* (D.pte)) and American house dust mites (*Dermatophagoides farina* (D.far)) with the names Actair initiation treatment and Actair continuation treatment. The products in this document are also referred to as Actair 100 IR and Actair 300 IR.

The active ingredients in Actair, European house dust mite and American house dust mite allergen extracts are currently included in the ARTG in the products Alustal house dust mites extract (AUST R 132680 and AUST R 132725) which are freeze dried allergen extracts for administration by subcutaneous injection.

The sponsor has established an in-house reference standard for the measurement of total allergenic activity (as required in the European (EU) pharmacopoeia). The potency unit used by the sponsor in this measurement is referred to as the Index of Reactivity or "IR". The titre of an allergen extracts is measured in a skin prick test (SPT) performed with the sponsor's SPT device (the Stallerpoint).

The clinical efficacy of subcutaneous immunotherapy (SCIT) is well established for allergic rhinitis.¹ Patients typically receive maintenance injections twice monthly or monthly for 3 to 5 years. Sublingual immunotherapy (SLIT) is an alternative to SCIT with similar efficacy and a favourable safety profile.² Patients self-administer a liquid or tablet under the tongue daily. As of 2009, approximately 45% of allergen immunotherapy (AIT) in Europe was SLIT.³

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 April 2016.

The related product Alustal house dust mites extract (AUST R 132680 and AUST R 132725) have been registered since 2006.

Overseas status

The product was approved in Japan (approved March 2015) and an application had been submitted in New Zealand and South Korea (but not yet approved) at the time of consideration of this submission.

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>>.

¹ Lin S. Y et al Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma: Comparative Effectiveness Review. Rockville (MD)2013.

² Canonica G. W et al Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009; 64: 1-59.

³ Cox L. and Jacobsen L. Comparison of allergen immunotherapy practice patterns in the United States and Europe. *Ann Allergy Asthma Immunol.* 2009; 103: 451-459; quiz 459-461, 495.

II. Quality findings

Drug substance (active ingredient)

The drug substances; European house dust mite and American house dust mite allergen extracts used in the new drug product formulation have previously been approved for Alustal house dust mites extract.

The drug substances used in formulation of drug product are both complex mixtures of antigens. Of these two major antigens predominate in the immune reaction to the mixtures and each has been characterised as follows.

- The drug substance for European house dust mite (D.pt) contains two relevant allergens Der p 1 and Der p 2
- The drug substance for American house dust mite (D.far) contains two relevant allergens Der f 1 and Der f 2.

Mites are identified visually based on morphological characters of taxonomic importance such as body size, characteristic shape and colour of body parts and hair organisation. Both drug substances contain a decontaminated (gamma-irradiated) freeze dried whole culture of mites, including mite bodies, faecal particles and spent culture medium, composed mainly of carbohydrates, proteins and glycoproteins, the latter including major and minor allergens as well as non-allergenic components.

Since mite faeces and bodies contain different allergens known to contribute to patient sensitization, D.far and D.pt drug substances used in House dust mites (HDM) sublingual tablets intended for allergen immunotherapy are made from material containing both bodies and faeces.^{4,5} Analyses of purified mite components have revealed that bodies and faeces contain different profiles of allergens:

- D.far; Der f 1 is preferentially found within mite faecal particles, whilst Der f 2 is synthesized in the epithelium of the anterior mid-gut, secreted in the lumen with digestive materials and concentrated in the faeces.^{6,7} In addition, whilst faecal particles contain group 4, 5, 7, 13, 21 and 23 allergens, mite bodies contain group 3, 14, and 20 allergens.^{8,9}
- D.pt; DS Der p 1 is preferentially found within mite faecal particles, whilst Der p 2 is associated with mite bodies, most particularly in the gut, and is present in lower quantities within faecal pellets. In addition, whilst faecal particles contain group 4, 5, 7, 13, 21 and 23 allergens, mite bodies contain group 3, 14, and 20 allergens.

The potency of the drug substances is measured using an assay for total allergenic activity which is quantified as index of reactivity (IR) units.¹⁰ Each drug substance D far and D.pt

⁴Batard T et al. Production and Proteomic Characterization of Pharmaceutical-Grade Dermatophagoides pteronyssinus and Dermatophagoides farina Extracts for Allergy Vaccines. *Int Arch Allergy Immunol* 2006; 140: 295-305

⁵Batard T et al. Molecular and Functional Characterization of natural Allergen products. *Arbciten aus dent Paul-Ehrlich-Institut 13th International Paul-Ehrlich-Seminar*, Washington, D.C. 2011 Verlag Chmielor.l

⁶ Jeong K.Y. et al. Localisation of Der f2 in the gut and fecal pellets of Dermatophagoides farina. *Allergy* 2002; 57: 729-731

⁷ Zhang Y-Y et al Morphology and three dimensional reconstruction of the digestive system of Dermatophagoides farina. *Int. Arch Allergy Immunol* 2008; 146:219-226

⁸ Tovey E.R. et al Mite faeces are a major source of house dust allergens *Nature Vol.* 1981; 289: 592-593

⁹ Park G-M et al Localization of a major allergen, Der p 2 in the gut and faecal pellets of Dermatophagoides pteronyssinus. *Clinical and Experimental Allergy*, 2000; 30: 1293-1297

¹⁰ The IR unit has been defined to measure the allergenicity of an allergen extract. The allergen extract contains 100 IR/mL when, on a skin prick-test using a Stallerpoint, it induces a wheal diameter of 7 mm in 30

contains at least a minimum amount measured in µg/mg of the allergen Der f 1 and Der p1 respectively.

The proposed specifications: control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Appropriate validation data have been submitted in support of the test procedures.

Drug product

Table 1 shows the composition of the 100 IR and 300 IR sublingual tablets.

Table 1: Composition of 100 IR and 300 IR sublingual tablets

Ingredient	Function	Reference to standards	Quantity (mg)	
			100 IR	300 IR
Drug Substances				
D.pte drug substance (sieved freeze-dried)	Drug substance	In-house	Quantity equivalent to	
			50 IR*	150 IR*
D.far drug substance (sieved freeze-dried)	Drug substance	In-house	Quantity equivalent to	
			50 IR*	150 IR*
Excipients				
Microcrystalline cellulose	Binder	USP-NF / JP / Ph. Eur.		
Croscarmellose sodium	Disintegrant	USP-NF / JP / Ph. Eur.		
Colloidal anhydrous silica	Glidant	USP-NF / JP / Ph. Eur.		
Magnesium stearate	Lubricant	USP-NF / JP / Ph. Eur.		
Lactose monohydrate	Filler	USP-NF / JP / Ph. Eur.		

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were reviewed and were acceptable.

patients sensitized to this allergen, (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive skin prick-test to either 9% codeine phosphate or 10 mg/mL histamine. The IR unit of Stallergenes is not comparable to the units used by other allergen manufacturers.

The results from stability studies conducted on House dust mite 100 IR and 300 IR sublingual tablets from commercial scale batches packaged in Alu/Alu blisters support a 24 month shelf-life when stored at or below 30°C.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The quality evaluators recommend that Actair 100 IR and 300 IR sublingual tablets should be approved.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was satisfactory. While some aspects of the primary pharmacology and pharmacodynamics were addressed using published literature the toxicity data was primarily gathered from Good Laboratory Practice (GLP) compliant laboratory studies. To this end, classical secondary pharmacodynamic, safety pharmacology and pharmacokinetic studies were not conducted owing to the nature of Actair and limited justification was also provided for omission of carcinogenicity and some reproductive toxicity studies.

Pharmacology

Primary pharmacology

One pharmacology study in the mouse model of dust mite asthma investigated the efficacy of D.ptc and D.far using the oral route. The 8 week study, which used allergens at 2,500 IR/kg and 20,000 IR/kg twice daily, demonstrated improved airway hyperresponsiveness (AHR) compared to the control group (in response to the bronchoconstrictor, methacholine at 100 mg/ml). While the effect of the allergens on AHR appeared dose-related, other noted improvements seen in the treatment groups, such as reduced eosinophil infiltration, reduced interleukin-5 (IL-5) and interleukin-13 (IL-13) cytokine responses and increased immunoglobulin (Ig) IgA in saliva did not demonstrate a dose-related response. The serum IgG1, IgG2a and IgE responses for both allergens were also broadly comparable between the two allergens compared to the vehicle control. The accompanying histopathology data indicated a slight attenuation of the perivascular and peribronchiolar inflammatory lesions of lung tissues compared to the control group. Taken together, the findings of the study suggest potential for D.ptc and D.far allergens to attenuate clinical signs associated with the murine model of chronic house dust mite induced asthma. However, the lack of an obvious dose response across multiple immunological and physiological parameters remained unaddressed.

In the response to TGA questions, the sponsor provided published data on the occurrence of dust mites in Australia, which reported that D.ptc was the most abundant species in all

locations^{11, 12}. *D. far* 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 pharmacodynamics

The sponsor also referenced published literature to demonstrate that oral tolerance can be achieved by antigen administration (feeding, oral or sublingual) in experimental animals. A study was used to show decreased specific IgE when mice fed β -lactoglobulin or whey proteins were challenged intraperitoneally.¹³ Furthermore, decreased IL-2 and interferon gamma (IFN γ) levels and increased IL-10 and transforming growth factor- β (TGF- β) levels were noted in the mice. A study by Lafont implied that oral allergen administration can suppress specific immediate hypersensitivity response to the same allergen in animals pre-sensitized to it.¹⁴ To this end, a study by Holt¹⁵ indicated that development of tolerance by sublingual allergen administration was independent of processes occurring in the gut as a result of swallowing the allergen; thus, suggesting that the process of sensitisation and tolerance can be achieved from different routes.

While the inflammatory processes initiated through allergen exposure have been elucidated to a large extent (Figure 1), the mechanisms underpinning allergen specific immunotherapy (AIT) remain largely uncharacterised. However, AIT has been utilised in a clinical setting for some time.¹⁶ In the case of subcutaneous immunotherapy (SCIT) it is proposed 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 IgA2.¹⁷ Furthermore, it is postulated that induction of regulatory cytokines, such as TGF- β and IL-10,¹⁸ potentiates a shift from T helper 2 cells (Th2) to a Tregs or Th1 response pattern. A similar mechanism in immune response is also postulated in sublingual immune therapy (Figure2).¹⁹

In the submitted pharmacology study, reduced IL-5 and IL-13 cytokine levels and stabilised IgE levels in the treatment groups compared to that of the vehicle control group are consistent with the current understanding of SLIT mediated immune response to allergens.

¹¹ Tovey ER et al. Domestic mite species and Der p 1 allergen levels in nine locations in Australia. *ACI Inter.* 2000; 12: 226-231.

¹² 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

¹³ Pecquet S et al Immunoglobulin E suppression and cytokine modulation in mice orally tolerized to β -lactoglobulin. *Immunology* 1999; 96: 278-285

¹⁴ Lafont s et al Abrogation by subsequent feeding of antibody response, including ige, in parenterally immunized mice *J. Exp Med* 1982; 155: 1573-1578

¹⁵ Holt P G et al Sublingual allergen administration. I. Selective suppression of IgE production in rats by high allergen doses *Clinical Allergy*, 1988, 18: 229-234

¹⁶ Bousquet PJ et al. Sub-lingual immunotherapy: World Allergy Organization position paper. *Allergy* 2009; 64: 1-59

¹⁷ Pilette C et al. Grass-pollen immunotherapy induces an allergen specific IgA2 antibody response associated with mucosal TGF-beta expression. *J Immunol* 2007; 178: 4658-4666

¹⁸ Jutel M, et al. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol.* 2003; 33: 1205-1214

¹⁹ Yousef A. et al. Allergen-specific subcutaneous immunotherapy in allergic asthma: immunologic mechanisms and improvement. *Libyan J Med* 2010; 5: 5303

Figure 1. Uptake of HDM allergen particles, immediate allergic reaction, and sustained inflammatory response are shown (From Calderon et al., 2015)²⁰.

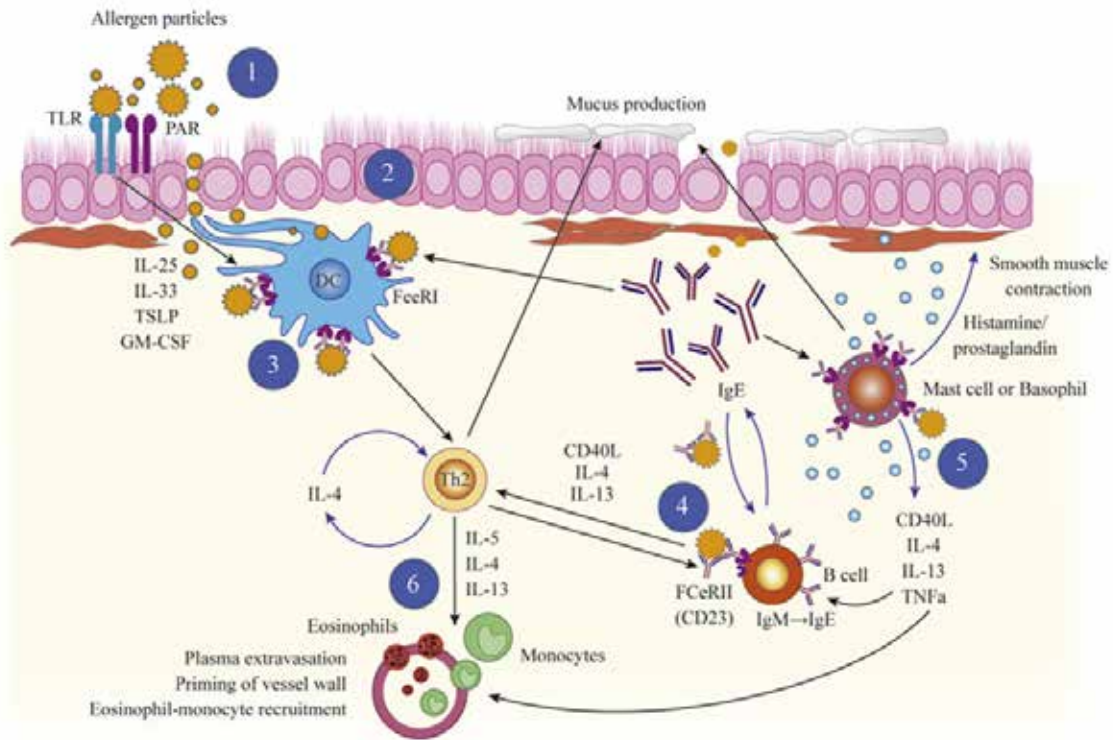
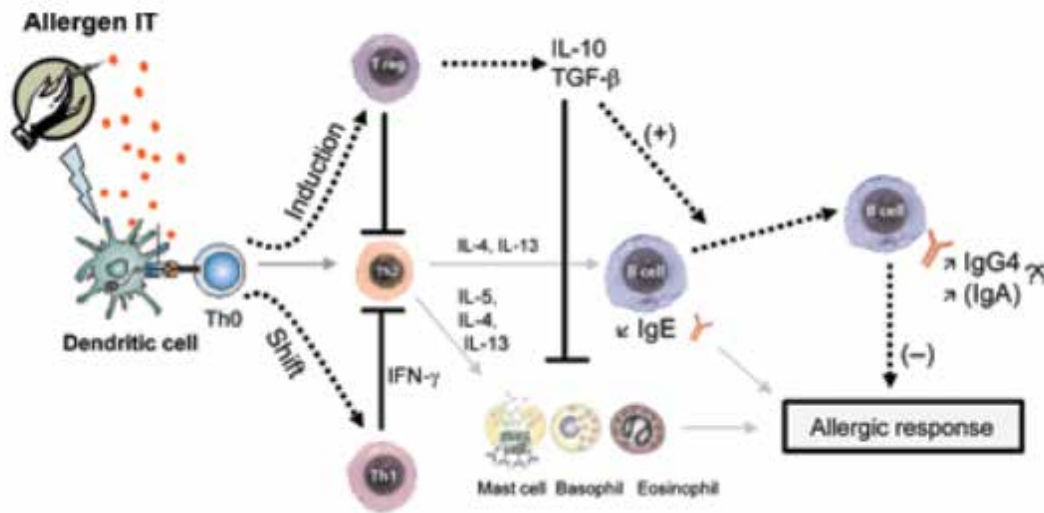


Figure 2 Schematic representation of the potential immune deviation leading to the beneficial effects of allergen immunotherapy (From Yousef et al., 2010).¹⁹



The sponsor however also identified the inadequacy of current animal models used to evaluate effects of AIT, specifically:

- The symptom scores or use of rescue medication, selected as primary and/or secondary endpoints in clinical trials are not applicable to animals to evaluate the treatment efficacy

²⁰ Calderon M.A. Respiratory allergy caused by house dust mites: What do we really know? *J Allergy Clin Immunol* 2015; 136, 38-

- Systemic immunological changes induced by SLIT do not necessarily correlate with clinical efficacy^{21,2,22}
- Biomarkers that are predictive of, or surrogate for, the clinical response to immunotherapy are not currently available in humans, and thus in sensitized animals.

Despite the noted shortcomings, the sponsor also measured specific IgG levels in serum during the repeat dose toxicity studies. While increases in mite-specific IgGs were detected in rats administered with D.ptc and D.far in these studies, consistent with the understood mechanisms of developing tolerance, no definitive dose relationship was observed.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic or safety pharmacology studies were submitted. The sponsor provided the following justification for the absence of such studies, which is acceptable:

- Secondary pharmacodynamic studies were not submitted because the use of allergen extracts for SLIT in humans has been broadly considered as a therapy with recognized efficacy and an acceptable level of safety, for more than 20 years²
- No or low tissue systemic absorption of the mite extracts is anticipated
- 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 justifying the conduct of dedicated safety pharmacology studies.

Furthermore, limited neuro-behavioural tests performed during the 26 week repeat dose toxicity study in rats also did not raise safety pharmacology issues up to the maximum dose of 2500 IR/kg/day.

Pharmacokinetics

The sponsor did not submit any pharmacokinetic studies citing the following justifications:

- Following administration by sublingual-swallow route, 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. As they are large molecules, they can hardly pass through the biomembrane by passive diffusion. Thus the extent of systemic absorption of the mite extracts is assumed to be very low or negligible.
- The pharmacological effect of the HDM sublingual tablet is not related to blood allergen levels based on our (the sponsor's) knowledge of SLIT mechanisms. The pharmacological effect is related to the capture of allergens by dendritic cells within the sublingual mucosa, and subsequent presentation to T-lymphocytes in the draining lymph nodes
- The mite allergen extracts consist of a multitude of constituents. Thus, standard pharmacokinetic measurements to substantiate the systemic exposure of mite extract components in animals would be technically difficult.

²¹ Scadding G and Durham SR. Mechanisms of sublingual immunotherapy. *Immunol Allergy Clin North Am.* 2011; 31: 191-209.

²² 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. *Clin Exp Allergy* 2012; 42: 1745-1755.

- Limited animal data are available in the literature documenting the pharmacokinetics of allergen preparations administered via local routes. Noteworthy, for the sublingual route, the choice of animals is limited to conduct relevant studies because, unlike humans, most laboratory animals have an oral lining epithelium that is keratinized.

Given the low risk of systemic exposure from allergenic extract through sublingual administration and the currently understood pharmacological mechanisms of allergic response, the absence of classical pharmacokinetic studies for Actair is acceptable.

Pharmacokinetic drug interactions

While pharmacokinetic drug interaction studies were not performed, the sponsor noted contraindications with known beta-blockers.^{23, 24}

Toxicology

Acute toxicity

The sponsor did not present any acute toxicity studies as, “repeat-dose studies (had been) conducted in rats at high dose-levels for 26 weeks by subcutaneous and oral routes”. Given the nature of the test article, long term administration and previous approval of the active ingredients for same indication²⁵, omission of acute toxicity studies is acceptable.

Repeat-dose toxicity

The sponsor presented data from three repeat dose toxicity studies in rats; one 14-day range finding study and two 26-week studies (one subcutaneous and one gavage). All studies were GLP compliant. Only one 26 week study utilised the oral route proposed for clinical application. No toxicokinetic or pharmacokinetic data for D.Pte or D.far were determined. Repeat dose studies were only performed on one rodent species and no non-rodent models were utilised. While data from non-rodent studies are also strongly preferred, given that D.Pte or D.far have been approved for use in combination subcutaneously for the same indication, absence of non-rodent repeat dose toxicity studies was not considered critical.

Relative exposure

Relative exposure calculations based on area under the curve (AUC) or C_{max} were not possible as it was not possible to determine pharmacokinetic and/or toxicokinetic data for Actair. Comparison of relative exposure for the major nonclinical studies was therefore estimated based on dose/body surface area as summarised in Table 2. Based on a maximum recommended clinical dose of 300 IR/day, a 6 IR/kg or 198 IR/m² dose of Actair was calculated for a 50 kg adult/day. The values at no observed adverse effect level (NOAEL) are highlighted in bold for each study; relative exposure at NOAELs was high for all repeat dose toxicity studies. However, the relative immunological potency of Actair in animals compared with humans was not assessed hence the accuracy of the relative exposures is uncertain.

²³ Walker SM, et al. Immunotherapy for allergic rhinitis. *Clin Exp Allergy*. 2011; 41:1177-1200

²⁴Bousquet J, et al. Review article – 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

²⁵ Alustal; ARTG #: 132725 and 132680

Table 2: Relative exposure in repeat dose toxicity and reproductive toxicity studies

Species	Study duration [study number]	Dose (IR/kg/day)	Dose (IR/m ²)	Exposure ratio [#]
Rat (SD)	14 days (repeat dose, SC) [20050324TR]	500	3000	15
		1500	9000	45
		2500	15000	76
	26 weeks (repeat dose, gavage) [32065 TCR]	500	3000	15
		1500	9000	45
		2500	15000	76
	26 weeks (repeat dose, SC) [20050326TRB]	500	3000	15
		1500	9000	45
		2500	15000	76
Human	steady state	6	198	-

= estimated based on body surface area assuming conversion factor of 6 for rat and 50 kg individual.
SC = subcutaneous; SD = Sprague Dawley

Major toxicities

Actair was well tolerated in all repeat dose toxicity studies, with NOAEL established at the high dose in all studies. This represented a relative exposure of 76 fold of that of the clinical dose (based on IR/m²). In the 26 week study with per oral administration, no major test article related, clinically relevant toxicities were identified. In this study, the most notable gross pathology was enlargement of ears which was also confirmed by presence of auricular chondropathy in the histopathological analysis. In the second 26 week subcutaneous administration study, with the exception of oedema at the site of test article, no other clinical signs were reported. Microscopic analysis showed neofibrosis with focal haemorrhage on the injection sites, often with a necrotic polymorphonuclear leucocyte core of cells.

Genotoxicity

The genotoxicity of Actair was investigated using bacterial reverse mutation assays and in vitro mammalian gene mutation assays. Of the eight genotoxicity studies, the two bacterial reverse mutation assays and one each of the micronucleus/ TK locus assays were GLP compliant. The concentrations used were adequate and the assays were validated with appropriate positive and negative controls.

The bacterial mutagenesis assays initially suggested positivity for mutagenic potential. Subsequent modifications to the mutagenic assay protocol suggested 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 and that D.Pte and D.far were unlikely to be mutagenic in the assay. Indeed, similar observations were noted with other sublingual allergen extracts where impurities gave rise to false positive genotoxicity from the bacterial reverse mutation assay.²⁶

While a statistically significant increase in mutation frequency was noted in two thymidine kinase locus assays, a biologically significant threshold was not achieved. No genotoxic effect was observed for D.Pte or D.far in the mammalian micronucleus assay.

²⁶ Extract of five grasses [Oralair](PM-2009-03500-3-2)

Taken together, genotoxicity assays were in line with relevant International Conference on Harmonization (ICH) guidelines and Actair appears unlikely to possess significant genotoxic potential.

Carcinogenicity

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

- The absence of histopathological lesions related to the mite extracts on tissues after oral and subcutaneous administration to rats over 26 weeks;
- The absence of in vitro genotoxicity;
- The assumed absence or minimal systemic exposure of the mite extracts after sublingual administration.

While the histopathological data from the repeat dose toxicity studies and the negative genotoxicity data are encouraging, given the proposed one year treatment for Actair and increased dose form compared to Alustal injection, submission of carcinogenicity studies would have been strongly preferred.

Reproductive toxicity

Reproductive toxicity studies only encompassed two embryofetal development studies in rats and rabbits and two juvenile development studies in rats and dogs. The studies were all GLP compliant. In the embryofetal development studies, rats were treated on GD6-17, and rabbits on GD6-18. No fertility or peri-postnatal study was conducted. It was possible to gather limited fertility data from the rat juvenile studies.

Actair did not appear to negatively impact embryofetal or juvenile development at the maximum dose (2500 IR/kg/day) in any of the tested species with regards to mortality, body weight gain, maternal clinical signs and litter values, including fetal body weight and sex ratios (See Table 3 below). Fetal malformations and variations were also within historical range for both species with the exception of incomplete frontal ossification in rats, which was greater than historical control at 2500 IR/kg/day.

Actair was also well tolerated in juvenile studies in doses up to 2500 IR/kg/day up to postnatal day 80 (in rats) and 28 (in dogs). In rats, no impact on mortality, clinical signs, body weight gain, long bone growth, cliff avoidance, tooth eruption and auditory canal opening were observed. Increased activity levels which were not statistically significant were noted at 2500 IR/kg/day and a delay in mean eye opening time was also noted for the same test group compared to the control group. No functional problems were however detected when tested for pupillary reflex and visual stimulus response. The biological significance of these observations remains unclear. Reproductive data suggest there was no impact on fertility following treatment at juvenile stages.

In beagles, a high rate of mortality was noted (generally within the first five days of treatment) in all treatment groups compared to controls (compared with ≥ 4 /test group compared to 1 in the control group). There was no dose relationship associated with the mortalities. The sponsor highlighted elevated postnatal mortality as a natural occurrence in beagles, and in the absence of any other adverse clinical signs, effects on body weight or ophthalmological parameters, the deaths were considered to be stochastic events rather than treatment related.

The potential transfer of Actair to offspring across the placenta or during lactation was not investigated, but is considered unlikely. Therefore, Actair was considered to be well tolerated in the two embryofetal and juvenile development studies with high exposure ratios compared to the proposed clinical dose.

Table 3: Relative exposure; reproductive toxicity studies

Species	Study	Dose (IR/kg/day)	Dose (IR/m ²)	Exposure ratio [#]
Rat (SD)	Embryofetal development (GD6-17)	300	1800	9
		1500	9000	45
		2500	15000	76
Rabbit (NZW)	Embryofetal development (GD6-18)	300	4500	23
		1500	22500	113
		2500	37500	189
Rat (SD)	Juvenile development	300	1800	9
		1500	9000	45
		2500	15000	76
Dog (Beagle)	Juvenile development	300	6000	30
		1500	30000	151
		2500	50000	252
Human	steady state	6	198	-

= estimated based on body surface area assuming conversion factor of 6 for rat, 15 for rabbit and 20 for dog and 50 kg individual.

Pregnancy classification

Antigen preparations for desensitisation are usually exempted from pregnancy classification²⁷. However, based on nonclinical data from the embryofetal development studies, the proposed B2 classification²⁸ is acceptable.

Local tolerance

One local tolerance study investigated effect of sublingual administration using the hamster cheek pouch model. The 28 day study, which used doses up to 500 IR/day showed no treatment related adverse histopathological or irritation observations. While weight loss was noted in all female treatment groups and acanthosis or hyperkeratosis was observed in cheek pouches of both sexes, no dose relationship was observed, and was thus considered not Actair related.

Paediatric use

Actair was well tolerated in juvenile development studies in rats and dogs up to 76 and 252 times the clinical dose, respectively (see Table 3). The animals were administered D.Pte and D.far allergen extracts orally from postnatal Day 10 to 80 in rats and 1 to 28 in dogs. Given the relative similarities in early immune system development in rodents, canines and humans²⁹, no significant safety concerns are anticipated with paediatric administration of Actair (for ages ≥ 5 years).

²⁷ Therapeutic goods exempt from pregnancy categorisation, Prescribing medicines in pregnancy database, 2011.

²⁸ Pregnancy classification Category B2 :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.

²⁹ Holsapple et al. Species comparison of anatomical and functional immune system development. *Birth Def Res* 2003; 68: 321-334

Nonclinical summary and conclusions

Summary

- A single study using the mouse model of dust mite-asthma was used to demonstrate clinical efficacy for Actair (PO) consistent with currently understood SLIT-mediated immune response to allergens.
- No specific secondary pharmacodynamic, safety pharmacology or pharmacokinetic studies were submitted.
- No acute toxicity studies were submitted.
- In three repeat dose toxicity studies in rats (up to 26 weeks), no Actair-related systemic toxicities were noted in doses up to 76 times the clinical exposure with oral administration.
- No Actair related genotoxic effects were noted in a panel of in vitro studies with potential exposures significantly greater than that of the proposed clinical dose. It was however noted that proteins, peptides, free amino acids and materials containing or capable of releasing amino acids contained within the extract were interfering with the assays and potentially giving rise to false positive readings (particularly in the bacterial reverse mutation study).
- No carcinogenicity studies were submitted, although warranted.
- No Actair-related toxicities were observed in embryofetal and juvenile development studies in rats, rabbits and dogs at exposures up to 76, 189 and 252 times greater than the clinical exposure, respectively.
- In a 28 day local toxicity study in hamsters, no local irritation was noted for doses up to 500 IR/day when administered to the hamster cheek pouch.

Conclusions and recommendation

A number of limitations were identified during the assessment:

- In most studies, including pivotal repeat dose toxicity studies and reproductive toxicity studies, gavage was utilised as route of administration. It is however a limited approximation of the proposed sublingual route of clinical administration.
- Repeat dose toxicity studies were only conducted in one rodent species, which potentially compromised the legitimacy of the safety data.
- No carcinogenicity studies were conducted using Actair, although warranted.
- No dedicated fertility and pre/postnatal development studies were performed using Actair.

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

The nonclinical evaluator also made recommendations relating to the risk management plan (RMP) and PI but these are beyond the scope of the 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

Clinical rationale

Allergic rhinitis (AR) is a chronic disorder of the upper airways that is caused by allergen exposure and the resulting IgE mediated inflammation of the nose and to a less extent, the eyes (allergic rhinoconjunctivitis). Symptoms include sneezing, runny nose, nasal itching and nasal congestion. Untreated or inadequately treated AR can cause sleep disturbance, daytime fatigue and somnolence as well as depressed mood, irritability, and behavioural problems. Patients affected by AR are also at increased risk for the development of asthma. AR is a worldwide disease affecting over 500 million people including approximately 3.1 million Australians.^{30, 31}

Current treatment options for AR are allergen avoidance, symptomatic pharmacotherapy, and allergen specific immunotherapy. However, mite avoidance measures are not generally effective. Symptomatic treatment options include antihistamines, intranasal corticosteroids, and leukotriene modifiers. These provide temporary relief from allergy symptoms but are not effective in all patients and are not disease modifying. In addition, pharmacotherapy may be associated with significant side effects such as sedative and anticholinergic effects for antihistamines, dryness and epistaxis for intranasal corticosteroids and neuropsychiatric reactions for leukotriene modifiers.

Allergen specific immunotherapy (AIT) is a therapeutic option for patients whose symptoms are not adequately controlled by avoidance measures or medications, those experiencing unacceptable adverse effects of medications, or those who wish to reduce the long term use of medications. The primary therapeutic goals of AIT include reducing symptoms, reducing medication use, and improving allergy related quality of life. The evidence is strong that AIT achieves these goals and can be disease modifying, with benefits persisting in many patients for several years after treatment discontinuation.^{1, 24,}

The clinical efficacy of SCIT is well established for rhinitis.¹ Patients typically receive injections twice monthly or monthly for 3 to 5 years. However, despite the documented benefits of SCIT, less than 5% of the US population with AR, asthma, or both receive this potentially disease modifying treatment. This limited uptake of SCIT is likely due to the risk of near fatal or fatal anaphylaxis as well as the discomfort and inconvenience of frequent injections.

Sublingual immunotherapy (SLIT) is an alternative to SCIT with similar efficacy and a favourable safety profile.² Patients self-administer a liquid or tablet under the tongue daily for periods ranging from 3 to 5 years. As of 2009, approximately 45% of AIT in Europe was SLIT.³

Contents of the clinical dossier

The clinical dossier comprised a development program consisting of a dose finding study and efficacy and tolerability studies.

³⁰ Bousquet J, et al Allergic Rhinitis and its Impact on Asthma (ARIA) *Allergy* 2008; 63: 8-160

³¹ AIHW 2011 Allergic rhinitis ('hay fever') in Australia *AIHW 2011* Cat No ACM 23

The submission contained the following clinical information:

- No Pharmacokinetic/Pharmacodynamic studies
- 7 studies in Section 5.3.51 Controlled trials. These studies comprised
- 1 x clinical pharmacology Study (V067.10) that provided dose finding and pharmacodynamic data
- 2 x pivotal efficacy/safety Studies (V057.07, and 1207D1731)
- 1 x other study in children (V064.08)
- 3 x other safety and tolerability Studies (V036.04F, 1109D1711 and V073.13).

The 5 studies numbered VOXX were conducted by the sponsor of the product Stallergenes S.A. while the other 2 studies were conducted by the Japanese partner company Shionogi and Co Ltd.

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission included paediatric efficacy and safety data.

Guidelines

EU Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases. CHMP/EWP/ 18504/ 2006.

Good clinical practice

The clinical study reports (CSR) state that all studies were conducted and written informed consent obtained in accordance with the ethical principles of the 5th Declaration of Helsinki and any amendments (World Medical Association General Assembly, Tokyo 2004) that were in place when the study started, the ICH and Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95, and the explanatory notes and comments, CPMP/768/97), the European Union's Commission Directives (2001/20/EC, 04 April 2001 and 2005/28/EC, 08 April 2005) as well as the requirements of national drug and data protection laws and other applicable regulatory requirements.

For the studies conducted in Japan the CSR states that the studies were conducted in compliance with the Ministry of Health, Labour, and Welfare Ordinance No. 24 (Feb 29, 2008) Standards for Implementation of Clinical Studies on Drugs (Good Clinical Practice [GCP]).

Pharmacokinetics

Studies providing pharmacokinetic data

In line with the EU Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases:

“Pharmacokinetic studies are not possible for products of specific immunotherapy. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product.”

Evaluator's conclusions on pharmacokinetics

No data relevant to PK was provided in the submission. This is accepted given the nature of the product.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic studies were provided in the clinical evaluation report. Table 4 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 4: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary Aim
Primary Pharmacology	Effect on Immunological markers	VO67.10	Dose Ranging
		VO57.07	Efficacy & Safety in adults
		VO36.04F	Safety
		VO64.08	Efficacy & Safety in Children
		VO73.13	Safety
		1109D1711	Safety
		1207D1731	Efficacy & Safety in Adults

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

For detail of the evaluation of the pharmacodynamics please see Attachment 2.

Evaluator's conclusions on pharmacodynamics

The sponsor has made efforts to document the effect of treatment on the immunological markers in each of the clinical studies as required by the EU guideline. The results are confused by the inconsistency in the reporting in the submission with the tendency to overstate the results from the individual studies in the summaries. The results however tend to suggest an immunological activity of the doses of HDM tablets in patients with HDM associated allergic rhinitis.

Dosage selection for the pivotal studies

Comment: The dose selection of 300 IR or 500 IR is not clearly explained in the study reports or the summaries.

The sponsor has established an in-house reference standard for the measurement of total allergenic activity (as required in the EU guideline and EU pharmacopoeia). The potency unit used by the sponsor in this measurement is referred to as the index of reactivity or "IR". The titre of an allergen extracts corresponds to 100 IR/mL when, in a skin prick test

(SPT) performed with the sponsor's SPT device (the Stallerpoint); in 30 subjects sensitised to the allergen in question, the extract produces a wheal measuring 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick test with 9% codeine phosphate or 10 mg/mL histamine dihydrochloride.

The selection of doses was based on previous experience with sublingual immunotherapy (sublingual solution, Staloral) reported in the literature. Clinical data with this formulation indicated that doses of SLIT with HDM extracts up to 300 IR/day have been well tolerated.

In the Phase I Study V036.04 incremental doses of SLIT with HDM extracts up to 500 IR and immediate repeated high dose administration of SLIT 300 IR and 500 IR was studied. Three out of five patients included in the immediate 500 IR dose withdrew due to adverse events (AEs) related to treatment indicating that this dose was not considered acceptable. No patients withdrew from the dose escalation to 500 IR suggesting that a longer escalation phase was better tolerated.

A dose response in efficacy was observed across the 100 IR to 500 IR dose range in Study V067.10.

In the pivotal efficacy studies 2 doses were tested 300 IR and 500 IR. In the study in children only the 300 IR dose was tested. The 300 IR dose was chosen as the recommended dose as it was the minimum effective dose in the studies.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies

Study V057.07

A randomised, double blind, placebo controlled multi-national Phase II / III Study of the safety and efficacy of two doses of SLIT administered as allergen based tablets once daily to adult patients suffering from house dust mite allergic rhinitis.

Study 1207D1731

A Phase II/III Study of sublingual tablet of house dust mite extracts (S-524101) in patients with perennial allergic rhinitis.

Other efficacy studies

Study V064.08

A randomised, double blind, placebo controlled, multinational, Phase III Trial to assess the efficacy and safety of 300 IR SLIT administered as allergen based tablets once daily to adolescents and children above the age of 5 years, suffering from house dust mite allergic rhinitis.

For the details of the evaluation of the above studies please see Attachment 2.

Evaluator's conclusions on efficacy

The efficacy of HDM allergen extract is dependent on the results of 2 pivotal studies; V057.07 which included only adults (18 to 50 years) and Study 1207D1731 which included both adults and adolescents aged 12 to 65 years. In these studies there was statistically significant superiority for both the 300 IR and 500 IR tablets compared to placebo. The difference between the 2 treatments groups was not statistically significant.

The dedicated paediatric Study VO64.08 (5 to 17 years) found no difference between 300 IR and placebo. The study was stopped after the end of the first year of treatment due to the subjects not being sufficiently symptomatic to enable assessment of the efficacy of HDM tablets.

The sponsor claims that the efficacy of the product in children and adolescents is demonstrated from the results of Study 1207D1731. The mean age was 30 ± 11 years and the median age was 30 years. The breakdown of the ages cohorts presented in the study report is as follows.

Table 5: Study 1207D1731: Age cohorts

Age cohort	300 IR N (%)	500 IR N (%)	Placebo N (%)
12 to <18	57 (18.1)	55 (18.6)	59 (18.7)
18 to <51	245 (77.8)	228 (77.0)	245 (77.5)
51 to <65	13 (4.1)	13 (4.4)	12 (3.8)

Source: Study 1207D1731 CSR Table 11.2-1

A subgroup analysis in the adolescents (aged 12 to < 18 years) was referenced in the summary of clinical efficacy. ~~This is not included in the study report.~~ A conclusion of a statistically significant difference between 500 IR and 300 IR compared to placebo is given. The treatment effect of the 500 IR group was estimated as the difference in least squares (LS) means of - 1.88 (95% CI: -2.84, -0.93), corresponding to a relative LS mean difference compared to placebo of -24.8% and the treatment effect of the 300 IR group was estimated as the difference in LS mean of -2.04 (95% CI: -3.01, -1.08), corresponding to a relative LS mean difference compared to placebo of -26.9%.

There were no children (aged 5 to 12 years) in this study and so the efficacy in this population has not been established.

The EU guideline is clear about the need to establish the efficacy in children and adolescents:

“The efficacy of products for specific immunotherapy has to be evaluated in special trials in the paediatric population and not in combined trials with paediatric population and adults. Adolescents and adults can be investigated as a combined population.”

Study VO64.08 does establish the safety of the product in children and adolescents. It would have been preferable to have been able to fully evaluate the subgroup analysis for the full study outcomes but the change in average adjusted symptom score (AASS) has been shown to be statistically significant for the adolescent population. The efficacy has not been established.

There is also a concern about the dose which was used in the studies. The doses selected for study were 300 IR and 500 IR. The selection of these doses is not explained other than as an extrapolation from another sublingual solution product Staloral made by the same sponsor. No details are given about Staloral other than to say in one section of the clinical overview that it is extemporaneously compounded and has been used for decades in Australia and in another part that it contains the same antigens as Actair and that it has been used by over 432,000 patients. It is unclear whether the product has been evaluated for efficacy and safety and how the doses recommended were determined. There is some justification for the choice of 300 IR over 500 IR. Both doses are effective but the 300 IR has a better safety profile than the 500 IR but it is not proven that this is the minimum effective dose. The 100 IR dose is clearly less effective but no doses between 100 IR and 300 IR were tested.

Safety

Studies providing safety data

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by specifically monitoring for, or asking about any adverse events using a non-leading question at each visit.
- AEs of particular interest, including anaphylactic shock/severe anaphylactic reactions, severe laryngopharyngeal disorders and autoimmune disorders, were assessed by review of the AE database.
- Laboratory tests, including Haematology: haemoglobin, haematocrit, red blood cells (RBC), platelets, white blood cells (WBC), differential counts (neutrophils, basophils, eosinophils, monocytes, lymphocytes). Biochemistry: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, gamma glutamyltransferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, urea, and creatinine, were performed at enrolment, end of treatment phase and end of observation phase.
- Physical examination; including vital signs (systolic and diastolic blood pressure (BP) and pulse rate) were assessed at each study visit.

Dose-response and non-pivotal efficacy studies

The dose response and safety and tolerability studies summaries were provided. They provided the same data as for the pivotal studies above.

Patient exposure

2,407 patients were exposed to HDM extract tablet or placebo: 1,571 (1,182 adults, 261 adolescents and 128 children) were exposed to HDM tablet as shown in Tables 6 and 7.

Table 6: Exposure to HDM extract and placebo in clinical studies

Rhinitis program		Duration	Active (n)	Placebo (n)	Total
Population	Study				
Adults	VO36.04F	10 days	23	8	31
	VO57.07	12 months	339	170	509
	VO67.10	6 months	268	87	355
	1109D1711	14 days	27	9	36
Adults and adolescents	1207D1731	12 months	646	322	968
Subpopulation: adolescents ≥ 12 and < 18 years old	1207D1731	12 months	121	60	181
Subpopulation: Adults ≥ 18 and < 65 years old	1207D1731	12 months	525	262	787
Adolescents	VO73.13	10 days	27	10	37
Adolescents and children	VO64.08	12 months	241	230	471
Subpopulation: children ≥ 5 and ≤ 11 years old	VO64.08	12 months	128	118	246
Subpopulation: adolescents ≥ 12 and ≤ 17 years old	VO64.08	12 months	113	112	225
Total			1,571	836	2,407

n = Number of patients exposed Source: Module 2.7.4 Table 2.7.4-7 (amended) (Study VO36.04F CSR Table 12.1; Study VO57.07 CSR Table 14.1.1/1a; Study VO67.10 CSR Table 14.1.1.1b; Study 1109D1711 CSR Table 12.1-1; Study 1207D1731 CSR Table 1-2 and Table 1-3.3; Study VO73.13 CSR Table 14.1.1-2; Study VO64.08 CSR Table 14.1.1.5a and Table 14.1.2.1.1a)

Table 7: Maximum dose patients received

Rhinitis program		Maximum dose							
		100 IR (n)	200 IR (n)	300 IR (n)	400 IR (n)	500 IR (n)	800 IR (n)	1,000 IR (n)	1,500 IR (n)
Adults	VO36.04F	-	1	7	-	15	-	-	-
	VO57.07	1	-	170	-	168	-	-	-
	VO67.10	92	-	86	-	90	-	-	-
	1109D1711	9	-	9	-	9	-	-	-
Adults and adolescents	1207D1731	-	1	322	3	320	-	-	-
Adolescents	VO73.13	-	-	-	-	9	-	9	9
Children and adolescents	VO64.08	1	1	239	-	-	-	-	-
Total		103	3	833	3	611	0	9	9

IR = Index of Reactivity; n = Number of patients exposed Source: Module 2.7.4 Table 2.7.4-8 (Study VO36.04F CSR Table 12.1; Study VO57.07 CSR Listing 16.2.5/5a; Study VO67.10 CSR Listing 16.2.1.3b; Study 1109D1711 CSR Section 12.1; Study 1207D1731 CSR Listing 1-1.1, Study VO73.13 CSR Listing 16.2.5-1, Study VO64.08 CSR Listing 16.2.5.1a)

For further details relating to the evaluation of the safety aspects please see Attachment 2.

Post-marketing data

Not applicable as the product is not commercially available in any country.

Evaluator's conclusions on safety

Overall the safety of Actair is consistent in the clinical studies. No systemic toxicity has been seen and there were no reports of anaphylactic shock, anaphylaxis or use of adrenaline. The most frequent adverse events were application site reactions such as oral pruritus and throat irritation. Most were mild or moderate severity and were generally reported in the first weeks of treatment but in some cases were significant and led to some patients discontinuing therapy.

The safety profiles in children and adolescents were similar to that seen in adults.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of Actair in the proposed usage are:

- Statistically significant efficacy compared to placebo in improving symptoms of HDM allergy. 500 IR and 300 IR were equally efficacious in adults and adolescents with no difference between the treatments
- Efficacy at the end of 12 months of treatment in adults is maintained over a treatment free follow up year.

First round assessment of risks

The risks of Actair in the proposed usage are:

- Application site adverse reactions are very common
- Efficacy in children (aged 5 to 11 years) has not been demonstrated.

First round assessment of benefit-risk balance

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

First Round Recommendation Regarding Authorisation

Based on the clinical data presented it is recommended that Actair be approved but for the modified indication of only for adults and adolescents aged > 12 years.

Clinical Questions

No questions relating to matters other than the PI and CMI were raised in this evaluation.

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

No new clinical information was submitted in response to questions. Accordingly, the risks of Actair are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Actair are unchanged from those identified the first round assessment of risks..

Second round assessment of benefit-risk balance

The benefit-risk balance of Actair, given the proposed indications for use in adults and adolescents aged > 12 years, is favourable.

Second round recommendation regarding authorisation

Authorisation is recommended, given the proposed indications for use in adults and adolescents aged > 12 years.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan AUS-RMP version 1 which was reviewed by the Risk Management Plan (RMP) evaluator.

Safety specification

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

Table 8: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Severe laryngopharyngeal reactions
Important potential risks	Severe anaphylactic reactions/ anaphylactic shock Autoimmune disorders
Missing information	Lack of clinical data on: <ul style="list-style-type: none"> · Exposure during pregnancy · Patients older than 65 years · Patients less than 5 years

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance³² to monitor all the safety concerns. This includes documentation of the reported cases using specific forms for the important identified risk of 'severe laryngopharyngeal reactions' and the important potential risk 'severe anaphylactic reactions/anaphylactic shock'. No additional pharmacovigilance has been proposed.

³² Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities³³ to mitigate all the safety concerns. No additional risk minimisation is considered necessary by the sponsor.

Reconciliation of issues outlined in the RMP report

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

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

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>Safety considerations may be raised by the non-clinical and clinical evaluators through the TGA's consolidated 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>No additional safety concerns were raised by the nonclinical and clinical evaluators that impact upon the RMP</p> <p>Additional information:</p> <p>Since the time of submission of the Australian dossier, the product Actair has received market authorization in Japan on 26 March 2015. A copy of the English translation of the approved Japanese SmPC is provided. The approved indication is "<i>Desensitization therapy for allergic rhinitis due to mite antigens</i>" with approval for use in Adults and Children from 12 years of age and over".</p>	<p>The sponsor's response is satisfactory. The evaluator has noted the additional regulatory information provided by the sponsor regarding the recent market authorisation granted in Japan.</p>
<p>The sponsor should include the date on which the AUS-RMP was finalised in the document. If available, data lock point should also be included.</p>	<p>The data lock point date of 14 January 2015 has been included as well as the date of release of this version 1.0 of the RMP, being the 22 July 2015.</p>	<p>The sponsor's response is satisfactory. To distinguish the updated version from the original version, the new version should be version 2.0</p>

³³ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>The sponsor has advised that patients with severe, uncontrolled or unstable asthma, concomitant use of beta blockers, and patients with severe immune deficiency or malignancies have been excluded from its clinical trials. As the draft PI document already includes these patient groups under 'contraindications', it is acceptable that no further measures are planned for these safety concerns. Nonetheless, they should still be included in the list of safety concerns.</p>	<p>The above recommendations have been incorporated into the Summary of Safety concerns, Section Part II: Module SVIII. Other consequential changes throughout the RMP have also been made. Please refer to the annotated copy of the RMP provided in the response.</p>	<p>The evaluator has noted the relevant updates to the 'Summary of the safety concerns' in the AUS-RMP. The sponsor's response is satisfactory.</p>
<p>The sponsor has advised that 'there are no data on possible risks of simultaneous immunotherapy with other allergens during treatment with Actair'. This should also be included as missing information.</p>	<p>The above recommendation has been incorporated in Section Part II: Module SVIII - Summary of Safety concerns, under Missing Information. Other consequential changes throughout the RMP have also been made. Please refer to the annotated copy of the RMP provided.</p>	<p>The evaluator has noted the relevant update to the 'Summary of the safety concerns' in the AUS-RMP. The sponsor's response is satisfactory.</p>
<p>The pharmacovigilance and risk minimisation sections should be updated accordingly to provide plans for managing these safety issues.</p>	<p>The relevant sections of the RMP have been updated as a consequence of the changes referred to above. Please refer to the annotated copy of the RMP provided.</p>	<p>The sponsor's response is satisfactory.</p>
<p>The sponsor is expected to analyse all the reported events of 'severe laryngopharyngeal reactions' and 'severe anaphylactic reactions/anaphylactic shock' in the PSURs. Specific consideration should be given to patient history of previous systemic reactions to allergen immunotherapy and concomitant use of simultaneous immunotherapy with other allergens.³⁴</p>	<p>The relevant sections of the RMP have been updated as a consequence of the changes referred to above and those sections impacting on the above comments. Please refer to the annotated copy of the RMP provided.</p>	<p>The evaluator has noted the updates to the 'Pharmacovigilance plan' in the AUS-RMP. The sponsor's response is satisfactory.</p>

³⁴ Please see the pharmacovigilance plan regarding the use of specific forms the documentation of the reported of 'severe laryngopharyngeal reactions' and the important potential risk 'severe anaphylactic reactions/anaphylactic shock'

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>The sponsor is required to provide clarification on the following wording: 'Four cases of overdose up to 1000 IR for up to 28 days have been reported in patients receiving HDM sublingual tablets: one patient receiving 100 IR, one receiving 300 IR and 2 receiving 500 IR.' It appears that receiving 100 IR and 300 IR are not overdose and none of the cases received 1000 IR.</p>	<p>In the Actair DSURs Actair(referred to as STG320) for the periods 2010-2011 and 2011-2012 the following overdoses were reported as occurred in the active arm of the V067.10 study:</p> <p>Patient [information redacted] (group: 500 IR): After the initiation treatment phase of 8 days, the patient continued taking twice the full dose per day during 21 days by mistake.</p> <p>Patient [information redacted] (group: 500 IR) After the initiation treatment phase of 8 days, the patient took 80 tablets over a 20 day period (from Day 9 to Day 29) instead of 20 tablets (1 tablet daily). Number of tablets taken each day was unknown and patient was unable to confirm on which days additional tablets were taken.</p> <p>Patient [information redacted] (group: 300 IR) This patient continued by mistake taking 2 tablets daily instead of 1 tablet daily during 1 week from Day 9 to Day 15 after the initiation treatment phase of 8 days.</p> <p>Patient [information redacted] (group: 100 IR) For an unknown reason between Day 37 and Day 64, during 9 days (unspecified days) the patient took 2 tablets daily instead of 1 daily.</p>	<p>The sponsor's response is satisfactory. Routine risk minimisation through PI and CMI as proposed by the sponsor is considered sufficient at this stage.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>The evaluator has noted the following advice in the draft PI: 'Clinical experience on immunotherapy with Actair in patients older than 65 years is lacking.' This is considered routine risk minimisation through labelling. The sponsor should include this labelling advice in the relevant part of 'V.1 Risk minimisation measures by safety concern' in the RMP.</p>	<p>The relevant section of the RMP has been updated to include the reference to labelling and the inclusion of the information within the PI. Please refer to the annotated copy of the RMP provided.</p>	<p>The evaluator has noted the update to the 'Risk minimisation measures by safety concern' in the AUS-RMP. The sponsor's response is satisfactory.</p>
<p>As the product comes in two different strengths, the sponsor should explain what measures are in place to avoid mixing up of different strengths.</p>	<p>The two different strengths are presented in separate blisters each of which is labelled specifically with the tablet strength i.e. 100 IR or 300 IR, therefore there is no possibility of getting the two different strengths mixed up. Furthermore, the 100 IR tablets are used only on days 1 and 2, while the 300 IR tablets are used from days 3 onwards. This is also clearly marked on the blister labels. Finally each tablet is marked individually such that the 100 IR tablet is marked with 100 and the 300 IR tablet is marked with 300.</p>	<p>The sponsor's response is satisfactory.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<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 follows:</p> <p>Considering the product is administered chronically in home settings after the first dose, the CMI should provide advice on situations when treatment might have to be withheld or patients must consult the doctor before continuing treatment. Examples of such situations are oropharyngeal infection or inflammation, asthma exacerbation.</p> <p>The following advice on resuming treatment after interruption should be added: 'If you interrupted the treatment for longer than 7 days, you should ask your doctor before restart treatment.'</p>	<p>The CMI has been updated to include the recommendations suggested by the TGA. The amendments to the CMI are as follows. The page numbers refer to the annotated CMI.</p> <p>(i) Page 4, under the section If you stop taking Actair: the following text has been added: "If you interrupt treatment for longer than 7 days, you should ask your doctor before restarting treatment".</p> <p>(ii) Page 4, under the section While you are receiving Actair: the following text has been added: "If you experience any infection or inflammation in the mouth or if you experience an increase in symptoms related to asthma or allergies, ask your doctor for advice before continuing treatment with Actair".</p> <p>The annotated and clean copies of the CMI are provided.</p>	<p>The sponsor's response is noted. The recommendations on CMI remain for Delegate's consideration.</p>

Summary of recommendations

The sponsor has adequately addressed most of the issues identified in the first round RMP evaluation report.

The only outstanding issue is:

To distinguish the updated version from the original version 1.0, the new version should be version 2.0.

The AUS-RMP version 1 evaluated during the first round was superseded by an updated AUS-RMP version 1 dated 23 July 2015 (data lock point 14 January 2015).

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

ACSOM advice was not sought for this submission.

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 AUS-RMP version 2.0 dated 23 July 2015 (data lock point 14 January 2015) 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:

Quality

The drug substances are extracts of the house dust mites *Dermatophagoides farinae* (D.far) and *Dermatophagoides pteronyssinus* (D.pt), which have been purified, freeze dried and sieved then compounded in HDM sublingual tablets. Both drug substances contain a decontaminated (gamma irradiated) freeze dried whole culture of mites, including mite bodies, faecal particles and spent culture medium, composed mainly of carbohydrates, proteins and glycoproteins, the latter including major and minor allergens as well as non-allergenic components.

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The quality evaluator(s) recommend that Actair 100 IR and 300 IR sublingual tablets should be approved.

Nonclinical

A single study using the mouse model of dust mite-asthma was used to demonstrate clinical efficacy for Actair (PO) consistent with currently understood SLIT mediated immune response to allergens. No specific secondary pharmacodynamic, safety pharmacology or pharmacokinetic studies were submitted. No acute toxicity studies were submitted. In three repeat dose toxicity studies in rats (up to 26 weeks), no Actair-related systemic toxicities were noted in doses up to 76 times the clinical exposure with PO administration. No Actair-related genotoxic effects were noted in a panel of in vitro studies with potential exposures significantly greater than that of the proposed clinical dose. No Actair-related toxicities were observed in embryofetal and juvenile development studies in rats, rabbits and dogs at exposures significantly greater than the proposed clinical dose. In a 28-day local toxicity study in hamsters, no local irritation was noted for doses up to 500 IR/day when administered to the hamster cheek pouch.

A number of limitations were identified during the assessment:

- In most studies, including pivotal repeat dose toxicity studies and reproductive toxicity studies, gavage was utilised as route of administration. It is however a limited approximation of the proposed sublingual route of clinical administration.
- Repeat dose toxicity studies were only conducted in one rodent species, which potentially compromised the legitimacy of the safety data.
- No carcinogenicity studies were conducted using Actair, although warranted.
- No dedicated fertility and pre/postnatal development studies were performed using Actair.

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

Clinical

Pharmacology

No PK studies were conducted. During specific immunotherapy plasma concentrations of the active substance are usually not measurable.

As recommended in the EU guideline,³⁵ an alternative to classical PD studies is to evaluate the changes in immunological markers in order to document the effect of treatment on the immune system. Therefore changes in the D.pte and D.far specific serum IgE and IgG4 were evaluated in the efficacy and safety clinical trials. In addition the cutaneous reactivity to allergen solutions of D.pte and D.far was assessed by SPT. The cutaneous reactivity to allergen solutions of D.pte and D.far is reflected in the diameter of the wheal induced by the SPT and provides evidence of sensitisation to these allergens. In the studies with a treatment period of 6 to 12 months the ratio (end of treatment period/baseline) of D.pte and D.far specific serum IgE was generally higher in the active groups than in the placebo groups as shown in Table 10. Serum IgG4 was consistently higher in the active groups than in the placebo groups as shown in Table 11. In the longer studies with a treatment periods of 6 to 12 months, the decrease from baseline in mean SPT wheal diameter was larger in the active groups than in the placebo groups, as shown in Table 12. Conclusions on pharmacodynamics are confounded by inconsistent reporting in the submission. The results tend to suggest immunological activity of the doses of HDM tablets in patients with HDM associated allergic rhinitis.

Table 10: Endpoint/Baseline ratio of the *D. pteronyssinus* and *D. farinae* specific serum IgE (primary analysis set)

Study	Allergen	Geometric mean ratio			
		500 IR	300 IR	100 IR	Placebo
VO57.07	<i>D. pte</i>	1.51	1.44		0.91
	<i>D. far</i>	1.24	1.29		0.89
VO64.08	<i>D. pte</i>		1.31		0.97
	<i>D. far</i>		1.37		0.98
VO67.10	<i>D. pte</i>	7.99	8.31	6.21	2.30
	<i>D. far</i>	6.58	6.61	5.46	1.75
1207D1731	<i>D. pte</i>	1.91	1.85		0.82
	<i>D. far</i>	1.82	1.77		0.83

D far= *Dermatophagoides farinae*; *D pte*= *Dermatophagoides pteronyssinus*; IR= Index of Reactivity

Source: Module 2.7.2 Table 2.7.2-5 (Study VO57.07 CSR Table 14.2.2/11a; Study VO64.08 CSR 14.2.4.2.1.1a and 14.2.4.2.1.2a; Study VO67.10 CSR Table 14.2.69b; Study 1207D1731 CSR Table 2-5)

³⁵ CHMP/EWP/ 18504/ 2006 Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases.

Table 11: Endpoint/Baseline ratio of the *D. pteronyssinus* and *D. farinae* specific serum IgG₄ (primary analysis set)

Study	Allergen	Geometric mean ratio			
		500 IR	300 IR	100 IR	Placebo
VO57.07	<i>D. pte</i>	2.98	2.38		1.13
	<i>D. far</i>	5.08	4.41		1.56
VO64.08	<i>D. pte</i>		2.25		1.02
	<i>D. far</i>		2.26		0.99
VO67.10	<i>D. pte</i>	2.19	1.86	1.38	0.83
	<i>D. far</i>	3.59	3.03	2.27	1.22
1207D1731	<i>D. pte</i>	3.13	2.58		0.88
	<i>D. far</i>	3.68	3.11		0.98

D far= *Dermatophagoides farinae*; *D pte*= *Dermatophagoides pteronyssinus*; IR= Index of Reactivity

Source: Module 2.7.2 Table 2.7.2-6 (Study VO57.07 CSR Table 14.2.2/11a; Study VO64.08 CSR 14.2.4.2.1.1a and 14.2.4.2.1.2a; Study VO67.10 CSR Table 14.2.69b; Study 1207D1731 CSR Table 2-5)

Table 12: Endpoint change from Baseline of the SPT wheal diameter (mm) for the primary period (primary analysis set)

Study	Allergen	Mean (SD) (mm)			
		500 IR	300 IR	100 IR	Placebo
VO57.07	<i>D. pte</i>	-1.68 (3.159)	-1.64 (2.498)		-0.82 (2.804)
	<i>D. far</i>	-1.85 (2.969)	-1.55 (2.445)		-0.76 (3.052)
VO64.08	<i>D. pte</i>		-2.50 (3.430)		-1.21 (3.207)
	<i>D. far</i>		-2.29 (3.340)		-1.22 (4.042)
VO67.10	<i>D. pte</i>	-0.29 (2.747)	-0.69 (3.246)	-0.55 (3.729)	0.54 (3.563)
	<i>D. far</i>	-0.38 (3.306)	-1.37 (3.956)	-0.10 (2.414)	0.30 (2.669)

D far= *Dermatophagoides farinae*; *D pte*= *Dermatophagoides pteronyssinus*; IR= Index of Reactivity; mm= millimetre; SD= Standard Deviation; SPT= Skin Prick Test

Source: Module 2.7.2 Table 2.7.2-7 (Study VO57.07 CSR Table 14.2.2/10.2.2a; Study VO64.08 CSR 14.2.4.1.2.1a and 14.2.4.1.2.2a; Study VO67.10 CSR Table 14.2.72b)

Dose selection

In the Phase I Study V036.04 incremental doses of SLIT with HDM extracts up to 500 IR and immediate repeated high dose administration of SLIT 300 IR and 500 IR was studied. Three out of 5 patients included in the immediate 500 IR dose withdrew due to AEs related to treatment indicating that this dose was not considered acceptable. No patients withdrew from the dose escalation to 500 IR suggesting that a longer escalation phase was better tolerated.

Study V067.10 provided dose finding and pharmacodynamic data. This was a randomised, double blind, placebo controlled, parallel group, multi-centre study conducted in 8 centres in Canada from December 2010 to September 2012 using an environmental exposure chamber model. The primary objective was to assess the effect of 100 IR, 300 IR and 500 IR sublingual HDM tablets change from baseline of the AUC of the rhinitis total symptom score ((RTSS): rhinorrhoea, nasal congestion, nasal pruritus, sneezing) during the 4 hours of allergen challenge. Male and female outpatients aged 18 to 55 years with a history of HDM related allergic rhinitis for at least 1 year. Diagnosis was confirmed by positive SPT to *D.pte* and *D.far* (wheal diameter > 3 mm) and HDM specific serum IgE levels ≥ 0.7 kU/L. Patients also to have RTSS ≥ 6 at least 2 time points during the 4 hour allergen challenge session at the qualifying allergen challenge. Patients were randomised to sublingual tablets of 100 IR, 300 IR and 500 IR or placebo taken sublingually at the same time every day. Patients on the 300 IR and 500 IR doses had an 8 day dose escalation phase starting at 100 IR and in increments of 100 IR. All groups were treated for 6 months with a treatment free period of 6 months. The primary efficacy variable and several secondary variables were derived from the patient self-scoring of nasal (rhinorrhoea, nasal congestion, nasal pruritus, sneezing) and non-nasal symptoms (ocular itching, tearing, ocular redness, ear/palate pruritus) using a 4 point scale

(from 0 = absent to 3 = severe) during the 4 hours of each allergen challenge. Change in RTSS from baseline to the end of treatment period is summarised in Table 13. The 33.2% relative improvement differed significantly between the 500 IR group and the placebo group ($p = 0.0427$). The difference between the 300 IR and placebo group did not reach statistical significance but there was evidence of a dose effect with relative LS mean difference of 28.8% and 19.8% between the 300 IR and 100 IR groups and placebo, respectively.

In the pivotal efficacy studies 2 doses were tested 300 IR and 500 IR. In the study in children only the 300 IR dose was tested. The 300 IR dose was chosen as the recommended dose as it was the minimum effective dose in the studies and had a better safety profile.

Table 13: Study V067.10: ANCOVA of the change from baseline to the end-of-treatment period in $AUC_{RTSS,0-4h}$ ($Ch_{BL}AUC_{RTSS,0-4h}$); full analysis set

Treatment	n	Difference vs. placebo				
		LS Mean (SE)	LS Mean difference	[95% CI]	p-value	Relative LS Mean difference
500 IR	70	-795.58 (69.877)	-198.18	[-389.82;-6.55]	0.0427	33.2%
300 IR	68	-769.21 (70.659)	-171.82	[-363.87;20.24]	0.0793	28.8%
100 IR	75	-715.83 (67.261)	-118.43	[-305.90;69.04]	-	19.8%
Placebo	75	-597.40 (67.401)				

AUC = Area under the curve; Ch_{BL} = Change from baseline; CI = Confidence interval; FAS = Full Analysis Set; IR = Index of reactivity; LS = Least squares; n = Number of patients at Visit 7 for whom data is available; RTSS = Rhinitis Total Symptom Score; SE = Standard error. Relative LS mean difference = (LS mean difference from Placebo / LS mean Placebo) \times 100.
Source: Study V067.10 CSR Table 11-9 (Table 14.2.2b).

Efficacy

Study V057.07

Study V057.07 is described in the clinical evaluation report (see Attachment 2). Study V057.07 is a pivotal, randomised, double blind, placebo controlled, multicentre, multinational study of SLIT HDM tablets administered once daily in adult patients with HDM allergic rhinitis. The study was conducted in 48 centres in 7 European countries from October 2007 to February 2010.

The primary objective was to assess efficacy based on average adjusted symptom score (AASS) during the increased symptom period in autumn (primary period of Year 1). The AASS was derived from the daily (non-missing) Rhinitis Total Symptom Score (RTSS) based on the severity of four rhinitis symptoms (sneezing, rhinorrhoea, nasal pruritus and nasal congestion) each graded on a 4 point scale and adjusted for the daily rescue medication usage during the evaluation period.

The study included healthy male or female (non-childbearing potential) outpatients aged 18 to 50 years (inclusive) with history of HDM related rhinitis for at least 1 year with diagnosis confirmed by positive SPT to HDM with wheal diameter > 3 mm and specific IgE level of ≥ 0.7 kU/L and baseline average rhinitis total symptom score (ARTSS) of ≥ 5 on a scale ranging from 0 (no symptoms) to 12 (severe symptoms).

Patients presenting with the following conditions were not included in the study: Asthma requiring treatment other than beta-2 agonists or with $FEV_1^{36} < 80\%$ of predicted (Note: Patients with Global Initiative for Asthma [GINA] Step 1 asthma were eligible); Patients treated with systemic, nasal or inhaled steroids (whatever the indication) within 4 weeks before Visit 1 or patients treated with long acting systemic steroids within 12 weeks

³⁶ FEV_1 Forced expiratory volume (FEV) measures how much air a person can exhale during the first second of a forced breath..

before Visit 1 or Visit 2: Co-sensitisation leading to clinically relevant allergic rhinitis, sinusitis, conjunctivitis or asthma likely to significantly change the symptoms of the patient throughout the study; Patients who had received allergy specific immunotherapy for house dust mites in the preceding 10 years.

Patients were randomised to 1 of the 3 treatment groups, HDM allergen extracts 300 IR, HDM allergen extracts 500 IR or placebo. During the 8 day Incremental Phase, the dose was escalated from 100 IR to the randomised dose. During the incremental phase patients took 2 sublingual tablets daily. After completion of the Incremental Phase, patients took one tablet daily until the end of the Treatment Phase (Year1).

Allowed rescue medications were:

- Step 1: Antihistamine (oral form and/or eye drops); (oral: cetirizine 10 mg, loratadine 10 mg; eye drops: levocabastine 0.5 mg/mL)
- Step 2: Nasal corticosteroids if the symptoms did not alleviate (mometasone 50 µg / dose)
- Step 3: If the patient needed oral corticosteroid (Step 3) to manage the rhinitis, the patient was to consult the investigator (prednisone 5 mg, prednisolone 5 mg).

509 patients were randomised. In the 500 IR group 135 of 169 (79.9%) completed month 12, in the 300 IR group 139 of 170 (81.8%) completed month 12 and in the placebo group 153 of 170 (90%) completed month 12. In Year 2 in the 500 IR group 123 of 135 (91.1%) completed 24 months, in the 300 IR group 133 of 139 (95.7%) completed month 24 and in the placebo group 141 of 153 (92.2%) completed month 24. Adverse events were the most frequent cause for premature discontinuation in the 500 IR and 300 IR groups to 12 months. The number of patients with at least 1 major protocol deviation was similar in the treatment groups.

At study entry, demographic characteristics were similar across the three treatment groups. Patient ages were within the range specified in the inclusion criteria. The population was balanced between men and women and most were Caucasian.

Results for the primary efficacy outcome

Average adjusted symptom score (AASS) during the period from 1 October 2008 to 31 December 2008 assessed in full analysis set Year 1 (FASY1) population is summarised in Table 14. There was a statistically significant difference in AASS between the 500 IR group and the placebo group ($p = 0.0066$). The treatment effect was estimated as the difference in LS means of -0.78 (95% CI [-1.34, -0.22]), corresponding to a relative LS mean difference compared to placebo of -20.2%. There was a statistically significant difference in AASS between the 300 IR group and the placebo group ($p = 0.0150$) with a difference in LS means of -0.69 (95% CI [-1.25, -0.14]), corresponding to a relative LS mean difference versus placebo of -17.9%. The difference between active treatment groups was not statistically significant ($p = 0.7638$).

Table 14: Study VO57.07: Primary efficacy variable: ANCOVA of AASS for the Year 1 primary period - FASY1

Treatment	n	LS Mean		
500 IR	136	3.09		
300 IR	141	3.18		
Placebo	153	3.87		
Difference in LS Means				
Comparison	Point Estimate	[95% CI]	P-value	Relative LS Mean
500 IR vs. Placebo	-0.78	[-1.34, -0.22]	0.0066	-20.2
300 IR vs. Placebo	-0.69	[-1.25, -0.14]	0.0150	-17.9
500 IR vs. 300 IR	-0.09	[-0.66, 0.49]	0.7638	

AASS = Average Adjusted Symptom Score; ANCOVA = Analysis of Covariance; CI = Confidence Interval; FAS = Full Analysis Set; IR = Index of Reactivity; LS = Least Square; n = Number of patients valid for ANCOVA.

Relative LS Mean difference: $([Active - Placebo] / Placebo) * 100$ or $([500 IR - 300 IR] / 300 IR) * 100$.

Source: Study VO57.07 CSR Table 11-11 (Table 14.2.1/1.1a)

The robustness of the primary analysis using FASY1 was demonstrated by the consistency of the sensitivity analysis (with last observation carried forward (LOCF) imputation of missing AASS, use of randomisation factor as covariate and a linear mixed model of AASS measurements during the first year).

Results for other efficacy outcomes

- Per Protocol (PP) population; primary efficacy outcome

For the per protocol set Year 1 (PPSY1), there was a statistically significant difference between 300 IR and placebo ($p = 0.0468$) with a corresponding LS mean difference versus placebo of -15.9%. The difference between the 500 IR and placebo groups did not reach statistical significance ($p = 0.0541$). The corresponding LS mean difference versus placebo was -15.7%. The difference between the 2 active groups was not statistically significant.

- Year 1 Complementary Period

A complementary analysis was performed using the same model as described for the primary efficacy analysis for the AASS and calculated using the daily record card data for the Year 1 Complementary Period (1 October 2008 to 30 November 2008).

There was a statistically significant difference in AASS for both 500 IR ($p = 0.0059$) and 300 IR ($p = 0.0212$) compared to placebo for the Year 1 Complementary Period in the FASY1. The treatment effect was estimated as the difference in LS means of -0.80 (95% CI [-1.36, -0.23]) for 500 IR and -0.66 (95% CI [-1.22, -0.10]) for 300 IR, corresponding to a relative LS mean difference versus placebo of -20.5% for 500 IR and -17.0% for 300 IR. The difference between the active treatment groups was not statistically significant ($p = 0.6409$).

- Average adjusted symptom score (AASS) for the Year 2 period

Efficacy was maintained during the treatment free follow up phase of approximately 12 months. In the Year 2 primary period (1 October 2009 to 31 December 2009) there was a statistically significant difference compared to placebo in AASS for both 500 IR group ($p = 0.0206$) and the 300 IR group ($p = 0.0342$). For the 500 IR group, the treatment effect was estimated as the difference in LS means of -0.70 (95% CI [-1.29, -0.11]), corresponding to a relative LS mean difference compared to placebo of -19.1%. For the 300 IR group, there was a difference in LS means of -0.62 (95% CI [-1.20, -0.05]), corresponding to a relative LS mean difference versus placebo of -17.0%. The difference between the active treatment groups was not statistically significant ($p = 0.8024$).

- Average Rescue Medication Score (ARMS)

In both Year 1 and Year 2, ARMS were modest (LS means of 0.23 and 0.19 in the 500 IR group, 0.33 and 0.22 in the 300 IR group and 0.32 and 0.28 in the placebo group). There were no statistically significant differences between active groups and placebo for both the Year 1 and Year 2 Primary Periods.

- Average Rhinoconjunctivitis Symptom Scores (ARSS)

The ARSS for each of the 5 individual symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, and ocular itching) were consistently lower in the active treatment groups compared to placebo during both the Year 1 and Year 2 primary period but did not show statistical significance for all symptoms.

During the Year 1 Primary Period, the analysis of covariance (ANCOVAs) of the 5 individual symptom scores showed that there were statistically significant differences for 500 IR versus placebo for sneezing, nasal pruritus and ocular itching and for 300 IR versus placebo for sneezing, nasal pruritus, and nasal congestion. Similar results were observed for the 5 individual symptoms during the Year 1 Complementary Period.

- Mean Proportion of Symptom Controlled Days (PSCD)

Three proportion of symptom controlled days (PSCDs) were defined: PSCD₀₋₀, PSCD₁₋₀ and PSCD₂₋₀ corresponding to RTSS ≤ 0, 1 and 2, respectively, and RMS = 0, and without use of rescue medication. The mean PSCD was consistently higher in the 500 IR and 300 IR groups compared to placebo group during both the Year 1 and Year 2 primary periods. Similar results were observed for the Year 1 and Year 2 Complementary Periods.

- Patient quality of life

Patient quality of life was assessed using the self-administered rhinoconjunctivitis quality of life questionnaire (RQLQ). At endpoint of Year 1, the difference in overall RQLQ score between the 500 IR and placebo groups was not statistically significantly (difference in LS means: -0.15, 95%CI [-0.37, 0.06], p = 0.1666. Although not a pre-specified outcome variable, there were some statistically significant differences in the individual domains (nasal symptoms and emotional). There was a statistically significant difference between the 300 IR and placebo group for all domains. At the end of Year 2, there was a no statistically significant difference between the active treatment groups and placebo either overall or for individual domains

Skin prick tests (SPTs) were performed at Visit 1 (Screening) or Visit 2 (Month 0), Visit 9 (Month 12) and Visit 14 (Month 24). A SPT was considered 'Positive' when the wheal diameter was > 3 mm. For Year 1 at endpoint, the mean wheal diameters after SPT with both D.ptc and D.far for patients in the actively treated groups were statistically significantly smaller than those of patients in the placebo group. These differences were maintained for Year 2 for both active groups compared to placebo for both D.ptc and D.far.

HDM-specific serum IgG4 increased in both active treatment groups between Visit 1 and Visit 9 (Month 12) and remained elevated at Visit 14 (that is, 1 Year post-treatment). In the placebo group, levels of D.far-specific serum IgG4 were modestly elevated and those of D.ptc were essentially unchanged. Over the study period, HDM specific serum IgE was little changed across the 3 treatment groups.

Study 1207D1731

Study 1207D1731 is described in the clinical evaluation report (see Attachment 2). Study 1207D1731 is a randomised, double blind, placebo controlled, multicentre, of SLIT HDM tablets administered once daily in adolescent and adult patients with HDM perennial allergic rhinitis. The study was conducted at 50 centres in Japan from October 2012 to December 2013. An English translation of the Japanese study report was provided.

The primary objective was to evaluate the efficacy of S-524101 [HDM extract] in comparison to placebo. The primary efficacy outcome was the Average Adjusted Symptom Score (AASS,) during the last 8 weeks of the treatment phase.

The study included healthy male or female patients aged between 12 and 65 years with at least 2 years of allergic rhinitis symptoms and a score of 2 or higher on a quantitative IgE (CAP-RAST) specific to D.ptc and/or D.far antigens performed at screening and with a positive nasal provocation test using an allergen disc for house dust. At enrolment patients had to have an ARTSS (sneezing, rhinorrhoea, nasal congestion and nasal pruritus, range 0 to 15) of ≥ 6 /day for 7 days.

Patients were randomised to 1 of the 3 treatment groups: 300 IR group, 500 IR group, and placebo group. The treatment period was 52 weeks. 2 tablets were administered once daily in the 8 day dose escalation period and 1 tablet was administered daily in the maintenance period.

Rescue medication was used in the same step wise fashion as for study VO57.07. The allowed medications were: Oral antihistamine: Allegra; Antihistamine eye drop: Patanol; Nasal corticosteroid: Aldecin AQ Nasal.

A total of 968 patients were randomised. In the 300 IR group; 287 of 322 patients completed 52 weeks, in the 500 IR group; 274 of 323 patients and in the placebo group; 292 of 323 patients completed the study.

The baseline demographic data was balanced between the treatment groups. The average age was about 30 ± 11 years; approximately 55% female and 45% male; with mean BMI about 21 kg/m^2 .

Results for the primary efficacy outcome

AASS during the last 8 weeks (Week 44 to Week 52) are summarised in Table 15. The least squares mean of the AASS was 5.00 in the 300 IR group, 5.32 in the 500 IR group, and 6.11 in the placebo group. The differences between each S-524101 (HDM extract) group and the placebo group were -1.11 for the 300 IR group and -0.80 for the 500 IR group. The differences versus the placebo group were statistically significant for both active groups ($p < 0.0001$ for both groups). The relative LS mean differences in the AASS versus placebo were -18.2% for the 300 IR group and -13.1% for the 500 IR group.

Table 15: Study 1207D1731: Average adjusted symptom score during the last 8 weeks (Week 44 to Week 52) (mixed effects model for repeated measures (MMRM)) (FAS)

	300 IR N=315	500 IR N=296	Placebo N=316
LS Mean (SE)	5.00 (0.213)	5.32 (0.216)	6.11 (0.212)
Difference of LS Mean (SE)	-1.11 (0.200)	-0.80 (0.203)	
95% CI for Difference	-1.504, -0.720	-1.196, -0.401	
P-value	<0.0001	<0.0001	
Adjusted P-value (Holm method)	<0.0001	<0.0001	
Relative LS Mean Difference (%)	-18.2	-13.1	

The model has the terms for treatment group, time, treatment-by-time as fixed effects and baseline value, age, gender, sensitisation status with autumn allergies, rescue medication use during pre-treatment period and prior drug for target disease as covariate.

CI: Confidence interval, LS: Least squares, SE: Standard error.

Relative LS Mean difference: $\{(Active - Placebo) / Placebo\} \times 100$.

Source: Study 1207D1731 CSR Table 11.4-1

Results for other efficacy outcomes

Average Adjusted Symptom Score at each time point (full analysis set (FAS))

In the 300 IR group the AASS was statistically significantly improved after the first protocol defined diary entries at Week 8 to 10 compared to placebo group ($p = 0.0012$). The difference between this dose and placebo was also statistically significant throughout

the subsequent evaluation periods. In the 500 IR group, the AASS was statistically significantly improved after Week 8 to Week 10 as compared with the placebo group ($p = 0.0448$); however, the intergroup difference was not statistically significant from Week 16 to Week 18. The difference between this dose and the placebo was again statistically significant after Week 24 to Week 26 and remained significant throughout the subsequent evaluation periods.

Average Rhinitis Total Symptom Score (ARTSS) (FAS)

The LS mean of the ARTSS during the primary evaluation period (Week 44 to Week 52) was 4.96 in the 300 IR group and 5.25 in the 500 IR group, statistically significantly different from the placebo group (6.03, $p < 0.0001$ for both active groups).

Average Rescue Medication Score (ARMS)

The LS mean of the ARMS during the primary evaluation period (Week 44 to Week 52) was 0.04 in the 300 IR group, 0.07 in the 500 IR group, and 0.07 in the placebo group. The difference between the 300 IR group and the placebo group was statistically significant ($p = 0.0280$).

Individual Rhinoconjunctivitis Symptom Scores

During the primary evaluation period, the LS means of the individual nasal symptom scores (sneezing, rhinorrhoea, nasal congestion, and nasal pruritus) in the 300 and 500 IR groups were statistically significantly different from the placebo group. Of the individual ocular symptom scores (itchy eyes and watery eyes), the score of watery eyes for the 300 IR group was statistically significantly lower than that in the placebo group ($p = 0.0113$).

Proportion of symptom controlled days (PSCD)

The PSCD₂₋₀ (proportion of days with a RTSS of < 2 and a rescue medication score of 0) in the 300 and 500 IR groups were statistically significantly different from the placebo group ($p = 0.0061$ and $p = 0.0098$).

Patient Quality of Life

In all of the primary domains of the Japanese Allergic Rhinitis Standard QOL Questionnaire (JRQLQ), the differences between the 300 IR group and the placebo group were statistically significant ($p = 0.0124$ for nasal and eye symptoms, $p = 0.0041$ for QOL related questionnaires, $p = 0.0310$ for general state). There was no statistically significant difference between the 500 IR group and the placebo group in any domain.

In 4 (usual daily activities, outdoor activities, social functioning, physical problems) of the secondary JRQLQ domains, the differences between the 300 IR group and the placebo group were statistically significant ($p = 0.0049$ for usual daily activities, $p = 0.0030$ for outdoor activities, $p = 0.0038$ for social functioning, $p = 0.0234$ for physical problems). There was no statistically significant difference between the 500 IR group and the placebo group in any domain.

House dust mite specific IgE and IgG4 antibodies, and total IgE antibodies

The levels of IgG4 antibodies specific to D.ptc and D.far antigens at baseline and Week 52 (Visit 17) were compared. There was little change from baseline in the placebo group, while the levels of mite specific IgG4 antibodies increased 2.580 and 3.105 times in the 300 IR group, and 3.130 and 3.678 times in the 500 IR group, respectively. The levels of IgE antibodies specific to these mite antigens also increased 1.850 and 1.774 times in the 300 IR group and 1.914 and 1.819 times in the 500 IR group, respectively. Likewise, the levels of total IgE antibodies increased 1.417 times in the 300 IR group and 1.519 times in the 500 IR group. The differences from the placebo group were statistically significant for both active groups in all the comparisons between active groups and placebo group ($p < 0.0001$ for both active groups).

Study V064.08

Study V064.08 is described in the clinical evaluation report (see Attachment 2). This is a randomised, double blind, placebo controlled, parallel group study to assess the efficacy and safety of 300 IR SLIT administered as allergen based tablets once daily to adolescents and children above the age of 5 years with HDM Allergic Rhinitis. The study was conducted at 62 centres in 9 European countries from October 2009 to September 2011.

A primary objective was to determine if sublingual tablet of HDM allergen extracts administered sublingually at a dosage of 300 IR to children and adolescents during approximately 12 months was significantly better than placebo in relieving HDM allergic rhinitis symptoms, assessed by the AASS. Sustained clinical efficacy of 300 IR sublingual tablet of HDM allergen extracts on the AASS after 2 and 3 treatment years and post treatment long term efficacy (disease modifying effect) of 300 IR sublingual tablets of HDM allergen extracts on the AASS after one and two treatment free years, were also primary objectives.

After its first meeting (4 July 2011) to review the efficacy and safety data from Year 1, the data and safety monitoring board (DSMB) provided the recommendation of not pursuing the study into the following years, considering the patients were not symptomatic enough to enable differentiation between active treatment and placebo. There were no safety concerns. The sponsor decided to stop the study for futility in the Year 2 treatment free period following treatment for 1 year.

The study included male or female patients aged 5 to 17 years (inclusive) with a history of HDM related allergic rhinitis for at least 1 year, requiring regular intake of symptomatic treatments. Diagnosis was confirmed by positive SPT to D.ptc or D.far with wheal diameter > 3 mm and specific IgE level ≥ 0.7 kU/L. Patients had to have a baseline ARTSS ≥ 5 (7 day daily record card with at least 4 days of valid data).

The primary efficacy outcome was AASS during the primary treatment period (Year 1). The AASS was derived from the daily (non-missing) Rhinitis Total Symptom Score (RTSS) based on the severity of four rhinitis symptoms (sneezing, rhinorrhoea, nasal pruritus and nasal congestion) each graded on a 4 point scale and adjusted for the daily (non-missing) rescue medication usage during the evaluation period.

Patients were randomised to 1 of the 2 treatment groups (300 IR group or placebo) and treatment was continued for 12 months. A two day incremental dose was used for initiation of treatment. The study was designed with an 8month treatment free period and then a 6 month treatment period (Year 2) and a 6 month treatment free period and a 6 month treatment period in Year 3.

Rescue medication was the same stepwise regimen as for the previous studies. The allowed medications were:

- Step 1: Antihistamine (oral: cetirizine, levocetirizine, loratadine, desloratadine or eye drops: levocabastine, olopatidine, azelastine)
- Step 2: Nasal corticosteroid if the symptoms did not alleviate - mometasone, fluticasone, beclometasone, budesonide
- Step 3: If the patient needed oral corticosteroid (prednisolone, methylprednisolone) to manage the rhinitis, the patient was to consult the Investigator.

A total of 471 patients were randomised. In the 300 IR group 211 of 241(87.6%) completed 1 year and in placebo group 215 of 230 (93.5) completed 1 year. Adverse event and consent withdrawn by patient were the most common reasons for withdrawal during Year 1 treatment.

The number of patients with at least 1 major protocol deviation was similar in the two treatment groups (57 in the 300 IR group and 58 in the placebo group). Co-sensitisation was the most common (10%) reason for exclusion from the per protocol population.

The mean age of patients was 11.1 years old, with 53.0% of the population aged 5 to 11 and 47.0% of patients aged 12 to 17. More males (64.8%) were included than females (35.2%). Almost all patients were Caucasian. Demographic characteristics were balanced across treatment groups.

Results for primary efficacy endpoint

For the primary efficacy endpoint, AASS during the primary treatment period (1 October to 30 November 2010) in Year 1 in FAS, no statistically significant difference ($p = 0.96$) was observed between the 300 IR and placebo groups. This is shown in Table 16.

Table 16: Study VO64.08: ANCOVA of the AASS during Year 1 primary period; FASY1

Treatment	n	LS Mean	Difference in LS Means			Relative LS Mean difference (%)
			Point estimate	95% CI	p-value	
300 IR	222	2.85	0.01	[-0.41 ; 0.43]	0.9621	0.36
Placebo	221	2.84				

AAdSS = Average Adjusted Symptom Score; AdSS = Adjusted Symptom Score; ANCOVA = Analysis of Covariance; CI = Confidence Interval; FAS = Full Analysis Set; IR = Index of Reactivity; LS = Least Squares.

Year 1 Primary Period = From 1 October 2010 to 30 November 2010.

AAdSS is the average of the daily non-missing AdSS during the considered Period.

Relative LS Mean difference = $100 \times ((\text{LS Mean of 300 IR} - \text{LS Mean of placebo}) / \text{LS Mean of placebo})$.

Source: Study VO64.08 CSR Table 11-11 (Table 14.2.1.1a)

To be eligible, all patients were to have a minimum level of symptoms during baseline while they were not allowed to take any rescue medication, that is, ARTSS of at least 5 out of a possible score of 12. The mean ARTSS at baseline was 6.84 in the 300 IR group and 6.65 in the placebo group. Over the treatment year, the AASS continuously decreased in the placebo group. After 3 months of treatment, the LS mean was 3.51 and after 12 months of treatment it was 2.65, leaving little room for improvement.

Results for other efficacy outcomes

Average Adjusted Symptom Score in the Per Protocol Set

There was no statistically significant difference ($p = 0.7434$) between the 300 IR and the placebo group.

Relationship between efficacy and disease activity

An assessment of the treatment effect as a function of disease severity during the Year 1 primary period was performed. Centres pooled according to geographical zone were ranked according to the mean AASS in the placebo group. In each tertile, AASS means were similar in the 300 IR and placebo group.

Mean daily Adjusted Symptom Score (ASS)

The mean daily ASS curves for the 300 IR and Placebo groups overlapped over time.

Average Rhinitis Total Symptom Score (ARTSS)

The results on the ARTSS during the Year 1 primary period were consistent with those obtained with the AASS.

Average Rhinoconjunctivitis Symptom Score (ARSS)

During the Year 1 primary period, all individual symptom scores were similar in the 2 groups.

Average Rescue Medication Score (ARMS)

There was no statistically significant difference between 300 IR group and placebo group on the ARMS for Year 1 Primary Period.

Proportion of Symptom-Controlled Days (PSCDs)

The mean PSCD were similar in both treatment groups.

Quality of Life (RQOLQ)

Between baseline and Month 12, the overall RQOLQ score and each domain score changed in similar proportions in both treatment groups; no statistically significant difference was evidenced.

Asthma Evaluation

In the asthmatic patients (about 60% of study population), no statistically significant difference was shown between the 300 IR group and the placebo group for any of the lower airway symptom scores over the last period of evaluation during Year 1.

Skin prick and immunological markers

The geometric means of D.ptc and D.far skin prick test wheal diameters decreased in both treatment groups from baseline to Year 1 endpoint.

The average geometric means of D.ptc and D.far specific serum IgE were slightly increased in the 300 IR group at the end of the Year 1 treatment period and went back close to their baseline level at the end of the Year 2 treatment free period while they remained stable in the placebo group.

CER conclusions on efficacy

The efficacy of HDM allergen extract is dependent on the results of two pivotal studies; Study VO57.07 which included only adults (18 to 50 years) and Study 1207D1731 which included both adults and adolescents aged 12 to 65 years. In these studies there was a statistically significant superiority for both the 300 IR and 500 IR tablets compared to placebo. The difference between the 2 treatments groups was not statistically significant.

In Study 1207D1731, a subgroup analysis was performed for the 12 to < 18 age cohort. The treatment effect of the 500 IR group was estimated as the difference in LS means of -1.88 (95% CI: -2.84, -0.93), corresponding to a relative LS mean difference compared to placebo of -24.8% and the treatment effect of the 300 IR group was estimated as the difference in LS mean of -2.04 (p5% CI: -3.01, -1.08), corresponding to a relative LS mean difference compared to placebo of -26.9%.

The dedicated paediatric study VO64.08 (5 to 17 years) found no difference between 300 IR and placebo. The study was stopped after the end of the first year of treatment due to the subjects not being sufficiently symptomatic to enable assessment of the efficacy of HDM tablets. There were no children (aged 5 to 12 years) in Study 1207D1731 and so the efficacy in this population (children aged 5 to 12 years) has not been established.

The clinical evaluator also had concerns about the 300 IR and 500 IR doses selected for study. There is some justification for the choice of 300 IR over 500 IR. Both doses are effective but the 300 IR has a better safety profile than the 500 IR but it is not proven that this is the minimum effective dose. The 100 IR dose is clearly less effective but no doses between 100 IR and 300 IR were tested.

Safety

2,407 patients were exposed to HDM tablet or placebo: 1,571 (1,182 adults, 261 adolescents and 128 children) were exposed to HDM tablet. 833 patients received a maximum dose of 300 IR and 611 patients received 500 IR.

Adverse events are reported for individual studies without analysis across studies.

In study V057.07 a total of 1,883 treatment emergent adverse events were reported by 427 patients in Year 1. The proportion of patients reporting at least 1 treatment emergent adverse event (TEAE) was 83.4% of patients in the 500 IR group, 88.2% in the 300 IR group and 80.0% in the placebo group. A summary of TEAEs is shown in Table 17. Drug related TEAE and TEAE leading to premature withdrawal were more common in 500 IR and 300 IR groups compared to placebo. There were low numbers drug related serious TEAE and no TEAE deaths. The most commonly reported TEAEs were oral pruritus, mouth oedema, nasopharyngitis, and throat irritation³⁷. Application site reactions (for example oral pruritus, mouth oedema, tongue oedema, throat irritation, and pharyngeal oedema) were more commonly reported by patients in the active treatment groups compared to those receiving placebo. Asthma, cough, dyspnoea, and wheeze were reported by a similar percentage of patients in the active and placebo groups. TEAE considered treatment related most frequently occurred in the first week of treatment.

Table 17: Study V057.07: Year 1: summary of treatment emergent adverse events (safety set)

Description	500 IR		300 IR		Placebo	
	N=169		N=170		N=170	
	n	%	n	%	n	%
At least 1 TEAE	141	83.4	150	88.2	136	80.0
At least 1 drug-related TEAE	110	65.1	111	65.3	38	22.4
At least 1 serious TEAE	1	0.6	6	3.5	2	1.2
At least 1 drug-related serious TEAE	1	0.6	2	1.2	1	0.6
TEAE leading to premature withdrawal	20	11.8	17	10.0	5	2.9
TEAE leading to death	0	0.0	0	0.0	0	0.0

IR = Index of Reactivity; N = Number of patients per treatment group; n = number of patients with TEAE; TEAE = Treatment-Emergent Adverse Event

Source: Module 2.7.4 Tab e2.7.4-17 (Study V057.07 CSR Table 14.3.1/1a)

In Study 1207D1731, a total of 3,008 AEs were reported by 821 patients. The proportion of patients reporting at least 1 AE ranged from 75.5% in the placebo group to 90.7% in the 500 IR group. A summary of adverse events is shown in Table 18. Drug related AE and TEAE leading to premature withdrawal were more common in 500 IR group compared to other groups and more common in 300 IR group compared to placebo. No drug related serious AE or AE associated deaths were reported. Among the most commonly reported AEs mouth oedema, throat irritation, oral pruritus and ear pruritus were reported by a higher percentage of patients in the active groups than in the placebo group. Asthma or asthma related symptoms (cough, dyspnoea, wheezing) were reported in fewer than 3% of patients per treatment group. AEs occurred most frequently during the dose escalation period (Day 1 to Day 14) in all groups.

³⁷ Clarification: the percentage of nasopharyngitis in the placebo groups was higher (22.9%) than in the active groups (13.6 % and 16.5%). For the mouth oedema, the incidence was higher in the active groups (16.6% and 12.4%) versus the placebo group (0.6%). This is the reason why the mouth oedema was reported as the most commonly reported event.

Table 18: Study 1207D1731: Summary of adverse events (safety set)

Description	500 IR N=324		300 IR N=322		Placebo N=322	
	n	%	n	%	n	%
At least 1 AE	294	90.7	284	88.2	243	75.5
At least 1 drug-related AE	237	73.1	215	66.8	60	18.6
At least 1 serious AE	5	1.5	6	1.9	2	0.6
At least 1 drug-related serious AE	0	0.0	0	0.0	0	0.0
AE leading to premature withdrawal	29	9.0	14	4.3	12	3.7
Adverse event leading to death	0	0.0	0	0.0	0	0.0

AE = Adverse Event; IR = Index of Reactivity; N = Number of patients per treatment group; n = number of patients with AE
Source: Module 2.7.4 Table 2.7.4-39 (Study 1207D1731 CSR Table 3-1.1.1 and Table 3-1.1.2)

In Study V064.08, a total of 1,210 TEAEs were reported by 337 patients during Year 1. The proportion of patients reporting at least 1 TEAE was 75.1% in the 300 IR group and 67.8% in the placebo group. The incidence of TEAEs was higher in children aged 5 to 11 for both treatment groups (79.7% in the 300 IR group and 76.3% in the Placebo group) than in adolescents aged 12 to 17 (69.9% and 58.9%, respectively). A summary of TEAE is shown in Table 19. Drug related TEAE and TEAE leading to withdrawal were more frequent in the 300 IR group compared to placebo. No drug related serious AE or AE associated deaths were reported. Among the most commonly reported TEAEs, oral pruritus, throat irritation, and tongue oedema were reported by a higher percentage of patients in the active group than in the placebo group.

Table 19: Study V064.08: Summary of treatment emergent adverse events (safety set)

Description	300 IR N=241		Placebo N=230	
	n	%	n	%
At least 1 TEAE	181	75.1	156	67.8
At least 1 drug-related TEAE	92	38.2	21	9.1
At least 1 serious TEAE	7	2.9	7	3.0
At least 1 drug-related serious TEAE	0	0.0	0	0.0
At least 1 TEAE leading to withdrawal	16	6.6	4	1.7
At least 1 TEAE leading death	0	0.0	0	0.0

IR = Index of Reactivity; N = Number of patients per treatment group; n = number of patients; TEAE = Treatment-Emergent Adverse Event

Source: Module 2.7.4 Table 2.7.4-23 (Study V064.08 CSR Table 14.3.1.1.1a)

In all the completed studies standard haematological and biochemical tests were performed at start and at the end of treatment. While in most studies, out of range values (either above or below the laboratory reference ranges) were found in individuals, none were considered clinically relevant.

In all the studies, vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) were recorded at each study visit as part of the physical examination. There were no relevant changes over time and no relevant differences observed between the active and placebo groups.

The clinical evaluator's conclusions on safety

Overall the safety of Actair is consistent in the clinical studies. No systemic toxicity has been seen and there were no reports of anaphylactic shock, anaphylaxis or use of adrenaline. The most frequent adverse events were application site reactions such as oral pruritus and throat irritation. Most were mild or moderate severity and were generally reported in the first weeks of treatment but in some cases were significant and led to some patients discontinuing therapy.

The safety profile in children and adolescents were similar to that seen in adults.

Clinical evaluator's recommendation

The benefits of Actair in the proposed usage are:

- Statistically significant efficacy compared to placebo in improving symptoms of HDM allergy. 500 IR and 300 IR were equally efficacious in adults and adolescents with no difference between the treatments
- Efficacy at the end of 12 months of treatment in adults is maintained over a treatment free follow up year.

The risks of Actair in the proposed usage are:

- Application site adverse reactions are very common
- Efficacy in children (aged 5 to 11 years) has not been demonstrated.

The clinical evaluator recommends that Actair be approved but for the modified indication of only for adults and adolescents aged > 12 years.

Safety data submitted after CER

In July to August 2015 the sponsor contacted TGA to advise:

"The FDA has made a recommendation that the following information be added as a 'precaution' to the PI for all sublingual immunotherapy products³⁸:

"Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. During treatment with [Oralair],³⁹ if severe or persistent gastroesophageal symptoms including dysphagia or chest pain occur, [Oralair] should be interrupted and the patient evaluated by their physician. Treatment should only be resumed upon instruction of the physician."

Additional, Eosinophilic esophagitis – should also be added to the 'adverse effects' section of the PI. The sponsor informed the TGA 'that they had submitted the application for a change to Oralair, which is the sublingual tablet formulation consisting of allergens from pollen of 5 grass species (AUST R 167565 & 167566). That application includes the safety related amendment for the "Eosinophilic esophagitis.

The sponsor requested the advice of the TGA as to whether the above safety related information could be included into the Actair PI while it is proceeding through its evaluation as a new product.

The sponsor submitted published case reports from literature as support for the eosinophilic esophagitis statements.^{40,41} These case reports did not involve Stallergenes SLIT allergens.

The sponsor at this time additionally proposed changes to the 'contraindications' sections of PI supported by an EAACI position paper.⁴²

³⁸ Document citing this information

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/pediatricadvisorycommittee/ucm570095.pdf page 4

³⁹ ORALAIR is a grass pollen SLIT product registered in USA (and Australia by the sponsor of Actair).

⁴⁰ Antico A. and Rossella F. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. *J Allergy Clin Immunol.* 2014; 133:1482-1484

⁴¹ Miehle S. Alpan O, Schröder S, Straumann A. Induction of eosinophilic esophagitis by sublingual pollen immunotherapy. *Case Rep Gastroenterol.* 2013; 7: 363-368.

⁴² Pitsios C, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015; DOI10.1111/all.12638.

Risk management plan

The sponsor has adequately addressed substantive issues identified in the first round RMP evaluation report. ACSOM advice was not sought for this submission.

Risk-benefit analysis

This submission type was not an extension of indications but as a major variation to Alustal house dust mites extract (AUST R 132680 and AUST R 132725). The Alustal indications are:

Alustal treatment is indicated for patients with Type 1 allergy (Gell and Coombs classification), particularly presenting as seasonal or perennial rhinitis, conjunctivitis, rhinoconjunctivitis with or without associated asthma.

The Actair indications are currently proposed as:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

The Delegate considered the Actair Indications represent a similar population to the Alustal indications, except for the age limitation, and the proposed Actair indications are preferable.

Efficacy of Actair was not demonstrated in Study V064.08 and efficacy has not been established in children 5 to 12 years of age. The sponsor has accepted indications for use in adults and adolescents over 12 years. The sponsor does not propose to present Study V064.08 in the 'Clinical Trials' Section of PI whereas the Delegate views some discussion as appropriate in this section of PI.

As noted above the sponsor has advised that a precaution concerning eosinophilic esophagitis had been introduced into the US PI for a related SLIT product "Oralair". There are a small number of published case reports of eosinophilic esophagitis developing after commencement of SLIT.

The Delegate considered the benefit-risk profile of Actair is largely unchanged and accepted the proposed precaution in the PI. The US PI for Oralair also includes as a contraindication "A history of eosinophilic esophagitis". The ACPM was requested to advise whether history of eosinophilic esophagitis should be included under 'Contraindications' in the Actair PI.

The sponsor at a late stage of the evaluation proposed amendments to some 'Contraindications' based on a recently published EAACI position paper on clinical contraindications to allergen immunotherapy. In relation to beta blockers the EAACI position paper concludes: "*There is good evidence that anaphylaxis is not more frequent in patients receiving β -blockers. On the other hand, these patients may be at increased risk of more severe systemic reactions and that emergency treatment could be ineffective. Based on the risk/benefit ratio, there is no contraindication for VIT⁴³ in patients treated with beta blockers, and a relative contraindication for AIT with inhalant allergens. When feasible, beta blockers should be substituted in patients on AIT, with an alternative. If beta blockers are required and no effective substitute is available, patients should be evaluated carefully, based on an individual risk-benefit assessment (Table 2). Strength of recommendation: C*".⁴²

The ACPM was asked to comment on whether the deletion of the 'contraindication' "beta blocker co-medication" and inclusion of the new precaution is appropriate.

⁴³ VIT = venom immunotherapy

Modification of the 'contraindication' "in Immune deficiency or auto-immune disorders" is proposed to "Immune deficiency diseases or active forms of auto-immune disorder".

In relation to autoimmune disorders the EAACI position paper concludes '*Caution should be exercised when prescribing AIT to patients with an autoimmune disorder. Due to a lack of available data, there is a relative contraindication in autoimmune disorders in remission and an absolute contraindication in active forms. Strength of recommendation: D.*'

In relation to acquired immune deficiencies the EAACI position paper concludes "(i) HIV infection is a relative contraindication for AIT; AIT can be performed on an individual basis. Strength of recommendation: D. (ii) All current published cases refer to patients under HAART. No evidence exists that AIT is safe for untreated HIV-infected patients, so in these cases it should be avoided. Any Category C stage disease (CDC 1993 Classification) is considered an absolute contraindication. Strength of recommendation: NR."

The ACPM was asked to comment on whether the modified 'contraindication' "Immune deficiency diseases or active forms of auto-immune disorder" is appropriate.

Delegate's considerations

The Delegate considered the Actair indications represent a similar population to the Alustal indications, except for the age limitation, and the proposed Actair indications are preferable.

Efficacy of Actair was not demonstrated in Study V064.08 and efficacy has not been established in children 5 to 12 years of age. The sponsor has accepted indications for use in adults and adolescents over 12 years. The sponsor does not propose to present Study V064.08 under 'Clinical Trials' Section of PI whereas the Delegate saw some discussion as appropriate in this section of PI.

There are a small number of published case reports of eosinophilic esophagitis developing after commencement of sublingual immunotherapy. The Delegate accepted the proposed Precaution concerning eosinophilic esophagitis in PI as appropriate. The US PI for a related sublingual allergen extract includes a contraindication "History of eosinophilic oesophagitis".

The sponsor at a late stage of the evaluation has proposed amendments to some Contraindications based on a recently published EAACI position paper on clinical contraindications to allergen immunotherapy.

Deletion of the beta blocker co-medication is proposed together with new precautionary statements.

Amendment of a contraindication in immune deficiency and auto-immune disorders is proposed.

Proposed action

The Delegate had no reason to say, at this time, that the application for (the product) should not be approved for registration

Request for ACPM advice

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

1. Do Actair Indications represent a similar population to the ALUSTAL indications, except for the age limitation, and are the proposed Actair indications are preferable?
2. Should Study V064.08 efficacy results be summarised under 'Clinical Trials' Section of PI.

3. In view of published case reports of eosinophilic esophagitis associated with sublingual immunotherapy products, should “History of eosinophilic oesophagitis” be included as a Contraindication in PI?
4. Is the deletion of the Contraindication “beta blocker co-medication” and inclusion of the new precaution appropriate based on the EAACI position paper?
5. Is the amended Contraindication “Immune deficiency diseases or active forms of auto-immune disorder” appropriate based on the EAACI position paper?

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

Introduction

Stallergenes Australia Pty Ltd, submitted Actair sublingual tablets for registration as a variation to the approved subcutaneous injectable Alustal products in November 2014. The submission seeks to register a new dosage form (tablets) and route of administration (sublingual) of a 50% mixture of allergen extracts from European and American house dust mite. The presentations for Actair are an Initiation treatment (composite pack containing 100 IR and 300 IR tablets) and a Maintenance treatment pack containing 300 IR tablets.

Indication

The initial indication proposed was:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults, adolescents and children 5 years and over diagnosed with house dust mite allergy.

In accordance with the Delegate’s recommendations, the sponsor agreed to remove the indication for children and restrict the product for use in adults and adolescents.

Therefore the indication has been amended and is now:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

Dosage and Administration

No change has been made to the dosage and administration other than changes coinciding with the amended indication; that is, removal of reference to children 5 years and over.

Overseas status

Approval received in Japan on 26 March 2015. Submissions made in NZ in February 2015 and Korea in June 2015 and both are still in evaluation. The Indications in all submissions are essentially similar to those in Australia.

Serious ADR’s and PSUR

There are no new serious ADR’s to add, and the product has not yet been marketed therefore there is no PSUR.

The sponsor also raised issues regarding changes to the PI as requested in the clinical evaluation but discussion of these is beyond the scope of the AusPAR.

Response to the Delegate’s specific advice sought from ACPM

1. *Do Actair indications represent a similar population to the Alustal indications, except for the age limitation and are the proposed Actair indications preferable?*

The Alustal indications are broad as they cover a wide range of allergens in one PI (11 different Allergens or mixes). Hence the Alustal indications as stated on the ARTG and PI are:

Treatment of patients with Type 1 allergy (Gells and Coombs classification), particularly presenting as seasonal or perennial rhinitis, conjunctivitis with or without asthma.

Within the Alustal range there are three presentations which include HDM allergens. There is the mix of both American and European HDM, which is the equivalent of the Actair allergen mix, and there are the individual preparations for American HDM and European HDM.

HDM allergy is considered to be a perennial condition associated with symptoms of rhinitis and/or conjunctivitis. Hence the Alustal indication does include patients diagnosed to be allergic to HDM, and therefore the Actair indication can be seen to represent a subset of the broad population indicated by Alustal. As the Actair indication is specific for one type of allergy; HDM allergy, the Actair indication is preferable to the broader Alustal indication. The Actair indication is:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

Furthermore it should be noted that a similar product Oralair which is a sublingual tablet for the treatment of grass pollen allergies has a similar indication to the one proposed for Actair:

Treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.

2. *Should study VO64.08 efficacy results be summarised under clinical trials section of the PI.*

The company agrees with the Delegate's proposal to include the following text into the PI.

Clinical experience in children: Study 3; During a European, multinational, randomized, double blind, placebo controlled study, 471 patients from 5 to 17 years old received either the 300 IR dose (n = 241) of sublingual tablet of house dust mites allergen extract or placebo (n = 230) daily for 12 months. The patients were not sufficiently symptomatic to enable assessment of the efficacy of Actair.

3. *In view of published case reports of eosinophilic esophagitis associated with sublingual immunotherapy products should "History of eosinophilic oesophagitis" be included as a contraindication in the PI.*

At this stage, the company does believe it is not necessary to include a contraindication for patients with a history of eosinophilic esophagitis (EoE) at the time of starting AIT. This decision is based on a review of the available published information and the extensive post marketing experience, where it has been shown that patients with a past history of EoE are able to get benefit from AIT without additional risk. Furthermore, eosinophilia is a common finding in clinical practice of allergy. Therefore, excluding patients from AIT on the basis of past history of EoE would exclude a large number of patients who may derive potential benefit for AIT. Below is a brief summary of the consolidated information from the literature and post marketing experience.

"Eosinophilic esophagitis (EoE) is considered an extrinsic eosinophilic disorder and patients typically present with severe or persistent dysphagia or chest pain and are referred to a gastroenterologist. The reported incidence of EoE in the general population ranges from 1/70 000 to 4/1000. The aetiologies of EoE are not fully identified, but an

association between EoE and food allergies is recognised, suggesting that food antigens may be a possible cause.⁴⁴ Environmental allergens have also been implicated as possible contributors in the evolution of the disease, as described in a case of EoE exacerbation during the pollen season.⁴⁵ It is noteworthy that most patients developing EoE have underlying allergic disease suggesting a strong allergic component of this disease. The literature suggests that EoE is not associated with an increased risk of developing premalignant or malignant lesions and is not associated with a decreased life expectancy.⁴⁶

In the literature, two case reports were published suggesting a possible association between SLIT and EoE. These two cases are presented hereafter:

- Miehlike et al 2013⁴⁷ described a 44 year old female with a medical history of pollinosis who developed a complete manifestation of EoE (esophageal biopsy with peak eosinophils 164 per high power field) 4 weeks after initiation of SLIT using specific soluble allergens (hazelnut, birch, alder). After discontinuation of SLIT, EoE resolved completely within 4 weeks without any other medical intervention. During a 12 month follow-up, the patient remained free of any esophageal symptoms. The authors suggested that oral immunotherapy for food allergy and SLIT for seasonal aeroallergens could be triggers for EoE in predisposed individuals.
- Antico & Fante 2014⁴⁸ described a 23 year old male with a medical history of allergic rhinoconjunctivitis to grass and HDM with secondary asthma. The patient was given HDM SLIT tablets for a year. The treatment was well tolerated. During the subsequent year, grass SLIT tablets were added to the HDM SLIT treatment. Approximately one month later, the patient began to experience a mild sensation of retrosternal constriction, which worsened over the next days with retrosternal pain and dysphagia related to tablet and food ingestion. Gastroesophageal reflux was suspected and treated with proton pump inhibitors, prokinetic agents, antacids, and alginate without any improvement. Grass SLIT was discontinued with resolution of the clinical symptoms in a couple of weeks. Following a reassessment of allergy diagnosis, the patient restarted grass SLIT. After a relapse of symptoms on Day 7, he underwent an oesophago-gastroduodenoscopy with biopsy which was consistent with EoE. Then, grass SLIT was withdrawn and clinical symptoms resolved. Biopsy specimens taken from the oesophagus soon after the end of the pollen season showed complete healing of mucosa with no signs of inflammation and no eosinophils. Of note, HDM SLIT was continued without any problem for this patient. Nevertheless, the authors suggested that EoE should be considered in all patients receiving SLIT who complain of dysphagia or other gastroesophageal symptoms.

[Information redacted].

In the meantime a possible role of allergen immunotherapy suggesting some benefit was reported in 4 patients with EoE:

- Castilano & Zacharias (2013)⁴⁹ described a 30 year old man with topical steroid-refractory EoE and positive skin prick test reactions against dust mites, cockroaches, common weeds, and trees who received SCIT to these allergens over 3 years. No

⁴⁴ Philpott et al., 2014 Risk factors for eosinophilic esophagitis. *Clin. Exp. Allergy*. 44(8):1012-1019.

⁴⁵ Fogg et al., 2003 Pollen and eosinophilic esophagitis. *The J. Allergy Clin. Immunol.* 112(4):796-797

⁴⁶ Miehlike, 2014 Clinical features of eosinophilic esophagitis. *Dig. Dis* 32(1-2):61-67

⁴⁷ Miehlike et al 2013. Induction of Eosinophilic Esophagitis by Sublingual Pollen Immunotherapy. *Case Rep Gastroenterol* 2013;7:363-368

⁴⁸ Antico A and Fante R. Esophageal hypereosinophilia induced by grass sublingual immunotherapy. *J Allergy Clin Immunol* 2014; 1: 29-30

⁴⁹ Castilano & Zacharias (2013) Immunotherapy as treatment for aeroallergen triggered eosinophilic esophagitis. *Annals of Allergy, Asthma & Immunology*. 2013;111(Suppl 5):A62

relapse of symptoms was reported and complete resolution of eosinophilic infiltration was observed.

- Ramirez & Jacobs 2013⁵⁰ described a 4 year old boy with dust mite induced chronic rhinitis and EoE who received SCIT to American and European HDM. Resolution of eosinophilic infiltration was observed within 2 years after the start of allergen immunotherapy.
- De Swert et al.2013⁵¹ described a 10 year old boy with pollen allergy and eosinophilic gastrointestinal disease who received SCIT to birch and grass pollen allergens over 3 years. Three years after the start of treatment, only minor nonspecific signs of inflammation in the esophagus were observed and the stomach biopsy specimen appeared normal.
- Perez et al 2012⁵² described a 65 year old man with EoE complaining of an increase of his symptoms of allergic rhinitis and asthma who received SCIT for airborne allergens over 5 years. At the end of the 5 year treatment with AIT, symptoms of EoE were resolved.

Based on the above, the company maintains that the following proposed text under the precautions section, presents suitable information in regard to the risks associated with EoE:

“Cases of eosinophilic oesophagitis have been reported in association with sublingual immunotherapy. During treatment with Actair, if severe or persistent gastroesophageal symptoms including dysphagia or chest pain occur, Actair should be interrupted and the patient referred to a gastroenterologist for investigation. Treatment should only be resumed upon instruction of the physician.”

This position is consistent with other AIT products marketed in Europe, and specifically Grazax and Acarizax which includes a paragraph about EoE only in the section “Special warnings and precautions for use” in the SmPC and no statement under contraindications.

As mentioned above, to include “History of EoE” as a contraindication will potentially exclude a large population of patients that may be assisted by AIT. The company will continue to monitor the potential occurrences of EoE upon AIT and update the PI accordingly.

4. *Is the deletion of the contraindication “beta blocker co medication and inclusion of the new precaution appropriate based on the EAACI Position paper?”*

Stallergenes submits that the EAACI position paper is a suitable basis for making the proposed changes to the PI in relation to beta blocker co-medication. The EAACI position paper represents an extensive review of the literature on clinical contraindications to AIT. Clinical recommendations were based on the category and strength of the published evidence for each medical condition. The authors concluded that there is good evidence that anaphylaxis is not more frequent in patients receiving beta blockers. However, these patients may be at increased risk of more severe systemic reactions and emergency treatment could be ineffective. Based on the risk/benefit ratio, there is no contraindication for Venom Immunotherapy when treated with beta blockers and a relative contraindication for AIT with inhalant allergens. Where feasible, beta blockers should be

⁵⁰ Ramirez & Jacobs 2013 Eosinophilic esophagitis treated with immunotherapy to dust mites. J Allergy Clin Immunol. 2013 Aug;132(2):503-504.

⁵¹ De Swert et al.2013 Eosinophilic gastrointestinal disease suggestive of pathogenesis-related class 10 (PR-10) protein allergy resolved after immunotherapy. Journal of Allergy and Clinical Immunology. 2013;131(2):600-602.e603.

⁵² Perez et al 2012 Allergen specific immunotherapy as a treatment for eosinophilic esophagitis. World Allergy Organization Journal. 2012 5 Suppl. 2 (S146).

substituted with an alternative in patients on AIT. If there is no effective substitute patients should be evaluated on an individual risk-benefit basis.

As can be seen, the co-medication with beta blockers should be assessed on a risk-benefit basis. The company has chosen to follow the general advice given by the position paper and therefore remove co-medication with beta blockers as a contraindication for all of its AIT medications. By doing this and including the appropriate text in the precautions section, it allows the physician to assess the patient and their needs appropriately.

Therefore as proposed and included in the PI, the following text has been included in the precautions section while the contraindication to beta blockers has been removed.

“Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of adrenaline used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of adrenaline. Substitute treatment may be considered. If beta-blockers are required and no effective substitute is available, patients should be evaluated carefully, based on an individual risk/benefit assessment.”

This position is consistent with other AIT products; such as the ALK products Grastek/Grazax (Timothy grass pollen tablets; Ragwitek (ragweed pollen tablet) and Acarizax (mites tablet). “tek” refers to the US product; “ax” refers to the EU product. ALK does not have any products registered in Australia.

5. *Is the amended Contraindication Immune deficiency diseases or active forms of autoimmune disorder appropriate based on the EAACI position paper?*

[Information redacted]

The potential of specific immunotherapy to induce immunological adverse reactions due to its action on the immune system was first reported in the literature in 1978. In such cases of AIDs, the diagnosis may often take years to be established. Thus it is very difficult to attribute the occurrence of AID to specific AIT rather than other factors as described in the literature.

The EAACI guidelines conclude that AIT should be terminated in the case of development of an AID and that AIT is contraindicated in patients with active AID. Caution should be exercised when prescribing AIT to patients with an AID. Due to a lack of available data, there is a relative contraindication in AID in remission and an absolute contraindication in active forms.

Therefore, on the basis of this review and the extensive post marketing experience of over 20 years, Stallergenes has proposed to revise the PI of all their sublingual products in the following manner:

In the section “Contraindications”, the wording “Autoimmune diseases, immune complex diseases or immune deficiency diseases” has been modified into “Immune deficiency diseases or active forms of autoimmune disorder”

The proposed amendment is more specific and in keeping with the general findings in the literature and provides the physician with a more targeted diagnosis for consideration, rather than the broad and general descriptions previously included. The company has backed up the above changes with appropriate PV activities/monitoring.

Furthermore, this position is consistent with other products of AIT marketed in Europe, and specifically Acarizax where the PI includes a Contra-indication for “patients with active or poorly controlled Auto-immune disease ...”

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:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Actair 100 IR and 300 IR- sublingual tablets containing 100 IR and 300 IR of American House Dust Mite and European House Dust Mite allergen extracts to have an overall positive benefit-risk profile for the Delegate's amended indication;

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

In making this recommendation the ACPM was of the view that children between 5 and 11 years of age should be excluded from the indication as efficacy has not been established in the population.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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

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

- Under 'precautions', remove the words "A few" from "A few cases of eosinophilic oesophagitis...." as this implies very low risk. The ACPM proposed the following alternative wording: "Eosinophilic oesophagitis has been reported in association with sublingual immunotherapy".

Specific Advice

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

1. *Do Actair indications represent a similar population to the ALUSTAL indications, except for the age limitation, and are the proposed Actair indications preferable?*

The ACPM noted that the sponsor had agreed to the wording of the indication as proposed by the Delegate and also the removal of use in children between 5 and 11 years old. The ACPM considered that efficacy had not been established in Study V064.08 in children less than 12 years of age and noted that the sponsor does not intend to include this trial in the Clinical Trials section of the PI. The ACPM advised that the Actair population represents a subpopulation of the Alustal population and that the wording is appropriate for that product.

2. *Should Study V064.08 efficacy results be summarised under 'Clinical Trials' Section of PI.*

The ACPM was of the view that the efficacy results for Study V064.08 should be summarised under 'Clinical trials' and considered the Delegate's wording regarding clinical experience in children to be appropriate.

3. *In view of published case reports of eosinophilic esophagitis associated with sublingual immunotherapy products, should "History of eosinophilic oesophagitis" be included as a Contraindication in PI?*

The ACPM was of the view that there is no evidence that eosinophilic oesophagitis related to one allergen is associated with risk of eosinophilic oesophagitis to another. The ACPM therefore advised that "History of eosinophilic oesophagitis" should be included under

'precautions'. The ACPM noted the sponsor's proposed wording for the precaution in its pre-ACPM response and advised that "A few" should be omitted from "Few cases..." as it could imply very low risk. The ACPM considered that the size of the risk is not known and proposed the following alternate wording "Eosinophilic oesophagitis has been reported in association with sublingual immunotherapy". The sponsor should also be requested to provide references.

4. *Is the deletion of the Contraindication "beta blocker co-medication" and inclusion of the new precaution appropriate based on the EAACI position paper?*

The ACPM accepted that anaphylaxis is not more frequent in patients receiving beta blockers. However, these patients may be at risk of more severe systemic reactions and emergency treatment could be ineffective. The ACPM advised the deletion of the contraindication and proposed wording of the new precaution were appropriate.

5. *Is the amended Contraindication "Immune deficiency diseases (ID) or active forms of auto-immune disorder (AID)" appropriate based on the EAACI position paper?*

The ACPM noted that the EAACI paper talked only about acquired ID which if well treated is not a contraindication. Although data are limited it recommended absolute and relative contraindications respectively for active AID and AID in remission. However, the ACPM noted that the FDA had recommended similar wording for Oralair and a request for a similar amendment has been submitted to the TGA. Overall, the ACPM was satisfied with the sponsor's amendments to the wording under 'contraindications'.

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 these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actair Initiation Treatment 100 IR and 300 IR sublingual tablets blister pack and Actair Continuation Treatment 300 IR sublingual tablets blister pack indicated for:

Treatment of house dust mite allergic rhinitis with or without conjunctivitis in adults and adolescents over 12 years diagnosed with house dust mite allergy.

Specific conditions of registration applying to these goods

The Actair Initiation Treatment and Continuation Treatment Risk Management Plan (RMP), Implement AUS-RMP version 2.0 dated 23 July 2015 (data lock point 14 January 2015) and any future updates as a condition of registration.

Attachment 1. Product Information

The PI for Actair Initiation Treatment and Continuation Treatment 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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