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300 IR HDM tablet: a sublingual immunotherapy tablet for the treatment of house dust mite-associated allergic rhinitis

Short title: 300 IR HDM SLIT tablet

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Summary

Introduction: The once-daily 300 index of reactivity (IR) house dust mite (HDM) tablet (Actair®; Stallergenes Greer, Antony, France/Shionogi & Co. Ltd., Osaka, Japan) is the first sublingual immunotherapy (SLIT) tablet to be approved for the treatment of HDM-induced allergic rhinitis.

Areas covered: This drug profile reviews the current body of evidence on the efficacy, safety and tolerability of the 300 IR HDM tablet, its pharmacodynamics, and its role in clinical practice.

Expert commentary: Data from its clinical development program demonstrate favorable efficacy and safety in adults and adolescents with HDM-induced allergic rhinitis, irrespective of mono- or polysensitization status, or the presence of comorbid mild asthma. The 300 IR HDM tablet is effective from as early as 2 months after treatment initiation, providing allergic symptom control and a reduction in the need for symptomatic medication, while improving health-related quality of life. Clinical efficacy is maintained for 1 year after treatment is stopped.

Key words: allergy immunotherapy, allergic rhinitis, clinical trial, efficacy, house dust mite allergy, safety, sublingual immunotherapy

1. Introduction

Allergic rhinitis (AR) is one of the most common chronic diseases [1], estimated to affect over 500 million people worldwide [2,3]. Despite advances in understanding of the pathophysiology of AR and its pharmacological treatment, the prevalence of this condition is increasing worldwide [4].

The disease burden of poorly controlled AR is considerable. The symptoms of AR have a significant negative impact on allergic patients' health-related quality of life, affecting sleep, mood, daily activities, physical and mental status, and social functioning [5-8]. As a consequence, AR is associated with significant direct healthcare costs and indirect socio-economic costs, through absenteeism and loss of workplace productivity [9], with these costs increasing with disease severity and the presence of comorbidities [10,11].

AR is a chronic and progressive disease. There is a well-established link between AR and the development of asthma [12,13], and an estimated 30% of patients with AR also suffer from asthma [2,5]. It is suggested that AR should be considered both a predictor and a major risk factor for asthma [14]. The house dust mite (HDM) is a common allergen source that is strongly associated with AR and asthma [15], with the two species, *Dermatophagoides pteronyssinus* and *D. farinae*, being responsible for more than 90% of HDM-induced allergies worldwide [16,17]. Current estimates suggest that 1–2% of the world's population might be affected by HDM-induced allergies [14]. In a cross-sectional, population-based survey in Europe, HDM sensitization was detected in 49% of adult patients with a clinical diagnosis of AR [18].

HDM-induced allergy commonly starts very early in life and persists throughout adolescence and adulthood [19]. HDM are often present year-round, triggering persistent symptoms, although recent data suggest that their allergen load may present seasonal variations [20-22]. Following exposure to HDM allergens, allergic individuals experience an IgE-mediated inflammatory response that is characterized by symptoms including rhinorrhea, nasal obstruction, nasal itching, and sneezing

[2,23,24]. Longitudinal studies on birth cohorts have shown sequential events leading to upper and lower respiratory allergies [25,26].

Current disease-management options for HDM-induced AR are limited and include specific allergen avoidance, symptomatic pharmacotherapy and allergy immunotherapy (AIT). The effectiveness of HDM avoidance is limited, because HDM are difficult to reduce drastically and impossible to eradicate completely and durably. The clinical efficacy of pharmacotherapy is well documented; however, symptom relief does not extend beyond the end of treatment [27] and some patients are resistant to the use of pharmacotherapy. AIT targets the underlying immunological mechanisms of allergic disease, and is the only treatment that provides disease-modifying effects in AR and allergic asthma [28].

AIT administered subcutaneously (subcutaneous immunotherapy [SCIT]) has demonstrated efficacy in the treatment of patients with HDM-induced AR and allergic asthma [29,30]. However, SCIT has a number of drawbacks, including the need for multiple injections over a period of years, and the possibility of serious systemic side effects or life-threatening anaphylaxis, particularly in patients with asthma. Sublingual immunotherapy (SLIT) involving local absorption of allergens under the tongue, offers improved convenience and safety over SCIT, is easy to administer at home, and does not require injections [30,31].

The 300 index of reactivity (IR) HDM tablet (Actair®; Stallergenes Greer, Antony, France/Shionogi & Co. Ltd., Osaka, Japan) is the first SLIT tablet approved for the treatment of HDM-associated allergic rhinitis. This paper reviews the current body of evidence on the efficacy and safety of the 300 IR HDM tablet.

2. Overview of available sublingual immunotherapies for house dust mite allergic rhinitis

SLIT formulations for HDM-induced AR include both aqueous or glycerinated allergen extracts ('SLIT drops' e.g. Staloral®; Stallergenes Greer, Antony, France) and tablets, which are administered under the tongue and then swallowed after a few minutes or once disintegrated, respectively [30]. HDM SLIT drops have been available in recent decades as named-patient products in several countries [32], but three HDM SLIT tablet therapies are currently marketed: the 300 IR HDM tablet [33], which was approved by regulatory authorities in Japan in March 2015 and Australia in April 2016, and the SQ HDM SLIT tablet (Acarizax®; ALK-Abelló, Hørsholm, Denmark /Miticure®; Torii Pharmaceutical Co. Ltd., Tokyo, Japan/MK-8237; Merck, Kenilworth, NJ, USA) [34,35], which received marketing approvals in the EU and Japan in August and September 2015, respectively [35] and a carbamylated monomeric allergoid tablet (Lais®; Lofarma S.p.A, Milan, Italy) approved by several regulatory agencies on a named-patient basis.

2.1. Introduction to the 300 IR HDM tablet

The 300 IR HDM tablet has been approved in Japan as AIT for HDM-induced AR, confirmed by specific IgE antibody or skin-prick testing, in patients aged >12 years [36], and in Australia as AIT for confirmed HDM-induced AR with or without conjunctivitis in adolescents and adults aged >12 years [37]. Local prescribing information should be consulted for specific details [36,37]. The 300 IR daily dose of SLIT has been established as offering optimum efficacy and tolerability for the treatment of AR induced by a variety of allergen extracts, including HDM [38]. IR is a unit of measure for the immunological reactivity of an allergen extract, which is not comparable to the units used by other allergen manufacturers. An 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 patients sensitized to this allergen (geometric mean) [37]. 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 dihydrochloride [37].

300 IR HDM tablet therapy should be initiated under the supervision of a physician with experience in the management of respiratory allergic diseases, and if treating adolescents aged >12 years, they should also have sufficient training and experience in this age group [37]. According to the product information, the tablet is placed under the tongue in an empty mouth until complete disintegration has occurred, and then swallowed. Patients should avoid taking food or beverages, or gargling, for 5 min after swallowing [36,37]. Patients should be monitored for at least 30 min, and if the first dose is well tolerated, then subsequent doses may be administered at home. Initiation requires a dose-escalation period of 100 IR per day up to 300 IR (over 3 days), after which a 300 IR tablet is taken daily until end of treatment [36,37]. Efficacy has been demonstrated over 1 year of treatment, with clinical benefits being shown within the first few months of treatment and maintained during the subsequent treatment-free year [39,40]. The recommended duration of AIT by international consensus is 3 to 5 years.

2.1.1. Contraindications and special patient populations

HDM tablets are contraindicated in patients with a history of shock associated with 300 IR HDM tablet therapy, or those with hypersensitivity to any of the inactive ingredients in the product; severe, unstable or uncontrolled bronchial asthma; oral inflammations (e.g. oral lichen planus, ulcerations or mycosis); or rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption [36,37].

Treatment of patients with immune deficiency diseases or active forms of autoimmune disorder, or malignant diseases (e.g. cancer), is contraindicated and should be prescribed with caution in patients with autoimmune diseases in remission [36,37,41]. Treatment should also be considered carefully in patients taking tricyclic antidepressants, monoamine oxidase inhibitors or β -blockers[37], and concomitant systemic corticosteroid use may render the 300 IR HDM tablet ineffective [36].

In cases of oral lesions, treatment should either be stopped and only resumed once complete healing has occurred [37] or be used with caution, after assessing whether absorption of the 300 IR

HDM tablet may be impaired and whether continued treatment may irritate the site of injury or infection [36]. Treatment should also be interrupted if severe or persistent gastroesophageal symptoms, including dysphagia or chest pain, occur [37].

As for any other AIT product, initiating 300 IR HDM tablet therapy during pregnancy should be avoided) [37,41] and only considered if benefits clearly outweigh risks (Japan) [36]. Ongoing 300 IR HDM tablet treatment may be continued with close medical supervision if pregnancy occurs, or during breastfeeding (Australia) [37]. It is not recommended to start 300 IR HDM tablet use while breastfeeding [36,37].

2.1.2. Excipients (inactive drug additives)

The excipients used are D-mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate and lactose monohydrate [36,37].

2.2. Other SLIT tablet medications approved for the treatment of house dust mite allergy

The SQ HDM SLIT tablet contains a 1:1 mixture of allergen extracts from the HDM species *D. pteronyssinus* and *D. farinae*, standardized to ensure a 1:1:1:1 ratio of the major allergens Der p 1, Der f 1, Der p 2, and Der f 2 [35]. A description of its efficacy and safety may be found in reference [35].

Both the 300 IR HDM tablet and SQ HDM SLIT tablet are significantly more effective than placebo at reducing the symptoms of HDM-induced AR during 1 year of treatment [34,39] and the 300 IR HDM tablet has demonstrated maintenance of these beneficial effects during the subsequent treatment-free year [39].

3. Chemistry of the 300 IR HDM tablet

D. pteronyssinus and *D. farinae* are the most prevalent species of *Dermatophagoides* mites worldwide, and are the most involved in the pathogenesis of HDM allergy [42]. In a study of 1,302

adults and children aged 5–17 years from North America, Europe and Japan with HDM-induced AR, all had IgEs specific to allergens found in the bodies and feces of *D. pteronyssinus* and/or *D. farinae*. Of these patients, >70% and >80% were sensitized to group 1 and 2 allergens, respectively, and 20–47% also had IgEs specific to allergens from groups 4, 5, 7, 13, 15, 21 and 23 [16]. Characterization of the group 1 and 2 allergens has suggested possible mechanisms contributing to the allergic response in atopic individuals. Der p 1 and Der f 1 have cysteine protease activity and can degrade tight junctions in lung epithelia, leading to the release of proinflammatory cytokines from bronchial epithelial cells, mast cells and basophils [14,43]. They can also cleave CD23 from activated B cells and CD25 from T cells, inducing a Th2 response [14,43]. Der p 2 and Der f 2 can act as Th2 adjuvants through structural and functional homology with the Toll-like receptor protein complex MD-2 [14,44]. The synergistic effects of these and other HDM allergens may promote IgE synthesis and contribute to allergic inflammation [14].

Therefore, to mimic conditions of natural exposure and sensitization, the active substance within the 300 IR HDM tablet consists of standardized allergen extracts from whole bodies and feces of *D. pteronyssinus* and *D. farinae*, which have been purified, freeze-dried and sieved, and mixed in a 1:1 ratio according to allergenic activity (IR/mg) [33,36,37]. In keeping with European Medicines Agency guidance on the manufacturing and quality control of allergen products [45], the allergen extracts are prepared from HDM cultured in specific, defined media that approximates the human stratum corneum, but is free from animal-derived material and other allergens [42,46]. The allergen content of these mites has been shown to be comparable to that of mites grown using shed human skin flakes [46]. Immunological activity and major allergen content are monitored throughout the production process to ensure the consistency, efficacy and safety of the final product [47]. Using an enzyme-linked immunosorbent assay (INDOOR Biotechnologies, Charlottesville, VA, USA), one 300 IR HDM tablet contains 8–19 µg Der p 1 and 39–79 µg Der f 1 [39,48].

4. Pharmacodynamics and mechanism of action

The exact mechanism of action of HDM allergen extracts administered during SLIT is not yet completely known. However, effects on both humoral and cellular immune responses are consistently observed and likely contribute to allergen-specific tolerance/immunosuppression and the alleviation of HDM-induced allergic symptoms. These include downregulation of allergen-specific CD4⁺ Th2 responses, the induction of Th1 and IL-10-producing CD4⁺ regulatory T cell responses, a decrease in the recruitment and activation of proinflammatory cells (basophils, mast cells and eosinophils) in target mucosae, and an increase in blocking anti-inflammatory IgG4 and IgA antibodies [49]. IgE neosensitization to allergens for which the immune system is naive before treatment has not been observed with SLIT using HDM allergen extracts [50].

The evaluation in a murine model of chronic house dust mite allergy confirmed that the Actair drug substance associating *D pteronyssinus* and *D farinae* extracts is more efficacious than each individual extract in decreasing airway inflammation.[51].

As recommended in current guidelines, no formal pharmacodynamic studies can be performed for AIT, and an alternative is to evaluate the changes on immunological markers (e.g. changes in allergen-specific IgE and IgG4 titers) in order to document the effect of treatment on the immune system [52,53].

The effect of the 300 IR HDM tablet on immunological changes has been investigated in a Phase 2/3 study (VO57.07) in adults with confirmed HDM-induced AR (N=509) [50]. In patients treated for 6–12 months, the ratios (end of treatment:baseline) of HDM-specific serum IgE and IgG4 were higher with the 300 IR HDM tablet than placebo. After 1 year of SLIT, HDM-specific IgE and IgG4 titers increased by 1.5- and 4.0-fold, respectively, in the 300 IR HDM tablet group, but not with placebo.. In all patients, HDM-specific IgG4 titers remained elevated at the end of the follow-up year [39].

5. Pharmacokinetics and metabolism

Given the sublingual route of administration of the 300 IR HDM tablet, the native allergens, mainly proteins and glycoproteins, are not expected to be absorbed into the vascular system [49,53-55].

Therefore, no studies were conducted in humans to investigate the pharmacokinetic profile and metabolism of the 300 IR HDM tablet [37].

6. Clinical efficacy of the 300 IR HDM tablet

The efficacy of the 300 IR HDM tablet for the treatment of HDM-induced AR was assessed in four double-blind, placebo-controlled clinical trials: 3 natural-field studies (VO57.07 study in adults VO64.08 study in children and adolescents [37,39,56] and 1207D1731 study in children, adolescents and adults conducted in Japan [36,37,40]) and one environmental exposure chamber study VO67.10 in adults [48]. In natural-field studies the 300 IR HDM tablet was significantly more effective than placebo at reducing the symptoms of HDM-induced AR. Across all Phase 1–3 clinical trials, a total of 1,571 participants (128 children, 261 adolescents and 1,182 adults) received at least one dose of HDM tablet (either 500, 300 or 100 IR) and 836 (118 children, 182 adolescents and 536 adults) received placebo (**Table 1**).

6.1. Phase 2: VO67.10 environmental exposure chamber study [48]

VO67.10, conducted in Canada, investigated the efficacy and dose-dependent effect of three doses of HDM tablet (500, 300 and 100 IR) in adults aged 18–55 years with confirmed HDM-induced AR (N=355) . Patients received an HDM or placebo tablet once-daily for 6 months, and recorded their rhinitis symptoms during 4-hour HDM allergen challenges in an environmental exposure chamber at randomization and months 1, 2, 4 and 6. The primary efficacy measure was the change from baseline to end of treatment in the area under the curve of the Rhinitis Total Symptom Score during

the four hours of the allergen challenge ($Ch_{BL}AUC_{RTSS\ 0-4h}$). Secondary efficacy measures included the change from baseline in area under the curve of RTSS during the last 2 hours of exposure ($Ch_{BL}AUC_{RTSS\ 2-4h}$), which is calculated when the symptoms are stabilized and better reflect the real-life exposure [48].

LS mean differences versus placebo for $Ch_{BL}AUC_{RTSS\ 0-4h}$ indicated a dose-dependent effect with improvements in symptom severity of 33% (500 IR), 29% (300 IR) and 20% (100 IR) (**Table 2**). The corresponding relative reductions over the last 2 hours of allergen challenge were 42%, 41% and 31%, respectively, indicating a greater effect size, compared with the outcomes for $Ch_{BL}AUC_{RTSS\ 0-4h}$. Both the 500 and 300 IR HDM tablet doses were more efficacious than placebo for $Ch_{BL}AUC_{RTSS\ 0-4h}$ ($p=0.043$ and $p=0.079$, respectively) and $Ch_{BL}AUC_{RTSS\ 2-4h}$ ($p=0.032$ and $p=0.038$, respectively), confirming the treatment effect. The 500 IR dose was associated with the greatest reduction in symptom score, but showed no statistically significant difference versus the 300 IR dose [48].

6.2. Phase 2/3: aVO57.07 efficacy and safety study in adults [39,50]

VO57.07 study, conducted in Europe, assessed the efficacy, safety and onset of action of 2 doses of HDM tablet (500 and 300 IR) in adults aged 18–50 years with confirmed HDM-induced AR (N=509), treated for 1 year and followed up for the subsequent immunotherapy-free year [39]. In total, 30% of patients had associated intermittent asthma and 51% were polysensitized to HDM allergens and at least one other seasonal or perennial aeroallergen (alder, birch, cypress, hazel, olive, plane, 5-grass pollen mix, mugwort, ragweed, *Alternaria* spp., *Parietaria* spp., cat, dog, cockroach, *Cladosporium* spp. and *Aspergillus* spp.) [39]. The primary efficacy measure was the Average Adjusted Symptom Score (AAAdSS), and secondary efficacy measures included Average Rhinitis Total Symptom Score (ARTSS), individual Average Rhinitis Symptom Scores (ARSSs), Average Rescue Medication Score (ARMS), and the patient's global evaluation of treatment efficacy, evaluated using a 5-point Likert scale (from marked worsening to marked improvement) and noted relative to the

previous year [39]. For the primary efficacy assessment, AAdSS was measured from 1 October to 31 December of each study year.

Over the 1-year treatment period, least-squares (LS) mean AAdSS was significantly lower in patients receiving the HDM tablet, compared with placebo (500 IR: -20.2%, $p=0.0066$; 300 IR: -17.9%, $p=0.0150$), irrespective of comorbid mild asthma or sensitization status, and with no significant difference between active-treatment groups [39] (Table 2). LS mean ARTSS improved significantly by 17.4% (500 IR) and 18.5% (300 IR) versus placebo ($p<0.05$ for both). Significant reductions ($p<0.05$) in individual LS mean ARSSs versus placebo were found for sneezing (-21.4%), nasal pruritus (-21.1%) and ocular itching (-27.5%) in the 500 IR group, and sneezing (-19.0%), nasal pruritus (-21.2%) and nasal congestion (-20.7%) in patients receiving the 300 IR HDM tablet [39]. Rescue medication use was low and the ARMS did not significantly differ between all treatment arms. Patients' global evaluation of treatment success was significantly higher in the 500 and 300 IR groups (73.1% and 80.5%), compared with placebo (59.6%) ($p=0.0206$ and 0.0001 , respectively) [39]. Onset of action, defined as the first period during which the difference in AAdSS between HDM tablet and placebo groups was significant, was from 4 months after initiation of HDM tablet therapy onwards [39].

Throughout the subsequent treatment-free year, the significant improvements in LS mean AAdSS (Table 2), ARTSS and the individual ARSS of nasal congestion achieved by patients using the 300 IR HDM tablet were maintained [39].

6.3. Phase 3: VO64.08 efficacy and safety study in children and adolescents [37,56]

VO64.08 study, conducted in EU was designed to assess the efficacy and safety of once-daily 300 IR HDM tablet therapy over 1 treatment year in children and adolescents aged 5–17 years with confirmed HDM-induced AR ($N=471$) [37,56]. Following the first treatment year, patients were to enter an 8-month treatment-free period, then treatment was to be restarted for 6 months (Year 2 treatment phase), followed by a 6-month, Year 2 treatment-free period. A similar 6-month

treatment phase was planned for Year 3, followed by a 22-month treatment-free follow-up period (Years 4 and 5). The primary efficacy measure was the AAdSS.

Results from Year 1 showed no statistically significant difference between the 300 IR and placebo groups. Based on these results, the Data and Safety Monitoring Board of independent external experts noted that the adolescents and children enrolled were not sufficiently symptomatic to enable assessment of the efficacy of the investigational product, and the study was early terminated [37].

6.4. Phase 2b/3: 1207D1731 efficacy and safety (Japanese study in adolescents and adults) [36,37,40]

1207D1731 study, conducted in Japan, evaluated the efficacy of two doses of the HDM tablet (500 and 300 IR) in adolescents and adults aged 12–64 years with confirmed HDM-induced AR (N=968), treated once-daily for 1 year and then followed up for 1 week post-treatment [36,37,40].

Approximately 70% of patients were polysensitized to HDM and at least one other allergen [40]. The primary efficacy measure was the AAdSS, evaluated for the last 8 weeks (weeks 44–52) of the 1-year treatment period. Secondary efficacy measures included ARTSS, ARMS, Average Combined Score (ACS), the Japanese Allergic Rhinitis Standard QoL Questionnaire (JRQLQ) and the patient's global evaluation of treatment efficacy. Onset of action, defined as the first of two consecutive time points with a statistically significant difference in AAdSS versus placebo, was also assessed.

LS mean AAdSS was significantly lower with HDM tablet therapy versus placebo (-13.1% and -18.2% for the 500 and 300 IR doses, respectively; $p < 0.0001$ for both), with no significant difference between active-treatment groups (**Table 2**) [36,37,40]. The onset of action for the 300 IR HDM tablet was observed from as early as the second month after treatment initiation [40].

In keeping with the AAdSS results, 300 IR HDM tablet therapy was associated with significantly decreased LS mean ARTSS (-17.7%) and ARMS (-41.6%), compared with placebo (all $p < 0.05$) [37].

Values of ARMS were modest, reflecting low consumption of symptomatic medication during the

study. Patient-reported outcomes with the 300 IR HDM tablet versus placebo also showed benefits: scores of all 3 primary domains and scores of 4 of the 6 secondary domains of the JRQLQ were significantly better at the end of treatment (all $p < 0.05$), and 22.2% of patients in the 300 IR HDM tablet group reported a marked improvement in treatment efficacy, compared with 9.7% in the placebo group [37].

6.5 Clinical subanalyses

6.5.1. HDM tablet efficacy in adolescent patients: 1207D1731 subgroup analysis [37,57]

In total, 181 patients randomized to treatment in study 1207D1731 were adolescents aged 12–17 years (500 IR dose: $n=61$, 300 IR dose: $n=60$, placebo: $n=60$), of whom 171 were analyzed for efficacy. In this subset, statistically significant improvements in AAdSS versus placebo were observed ($p=0.0001$ and $p < 0.0001$ for the 500 and 300 IR doses, respectively) [57]. Over the final 8 weeks of treatment, LS mean differences in AAdSS versus placebo were -1.88 [95% confidence interval (CI): $-2.837, -0.931$] and -2.04 (95% CI: $-3.007, -1.081$), corresponding to relative reductions of -24.8% and -26.9% for the 500 and 300 IR groups, respectively. These results were consistent with those obtained in the overall population [37,57]. Each of the four individual nasal symptom scores were significantly lower in the 300 IR group compared with placebo ($p < 0.05$), as per the overall population. The relative differences from placebo were -26.3% (total score), -20.7% (sneezing), -27.7% (rhinorrhea), -21.1% (nasal pruritus) and -34.6% (nasal congestion).

6.5.2. HDM tablet efficacy in mono- and polysensitized patients: 1207D1731 subgroup analysis [58]

Of the 968 patients randomized to treatment in study 1207D1731, 300 patients (31%) were monosensitized to HDM allergens (500 IR dose: $n=98$, 300 IR dose: $n=102$, placebo: $n=100$) and 668 (69%) were polysensitized to HDM and at least one other allergen (500 IR dose: $n=226$, 300 IR dose: $n=220$, placebo: $n=222$). LS mean AAdSS over the last 8 weeks of treatment was significantly improved compared with placebo for the 300 IR HDM tablet in monosensitized patients (5.28, 4.97

and 5.90 for the 500 IR, 300 IR and placebo groups, respectively ($p=0.0066$ for the 300 IR HDM tablet), and for both HDM tablet doses in polysensitized patients (5.22, 4.91 and 6.10 for the 500 IR, 300 IR and placebo groups, respectively; $p=0.0005$ and $p<0.0001$ for the 500 and 300 IR HDM tablets). Moreover, in the subsets of patients having any specific IgE level of cosensitized allergens (highest IgE level being 2, 3 or 4), the LS mean AAdSS for the 300 IR HDM tablet was significantly lower than that for placebo [58].

6.5.3. Evaluation of the onset of action: natural field studies [33,39,40]

Significant beneficial effects with the 300 IR HDM tablet versus placebo were shown from as early as 2 months after the initiation of treatment in study 1207D1731 [between-group difference of -0.59 (95% CI: -0.94, -0.23); $p=0.0012$], and as 4 months in study VO57.07 [between-group difference of -0.80 (95% CI: -1.35, -0.24); $p=0.005$].

6.5.4 Relationship between allergic disease severity and efficacy: VO57.07 subgroup analysis [59]

Post hoc analyses were performed to evaluate the relationship between allergic disease severity and efficacy. Centers pooled by geographical zones were ranked according to mean AAdSS in the placebo group. During the treatment period, the overall treatment effect, estimated as the difference in LS mean AAdSS values, was -0.69 (95% CI: -1.25, -0.14); $p=0.0150$, i.e. a relative difference of -17.9% from placebo. For the low-, medium- and high-severity tertiles ($n=98$, 94 and 102, respectively), the relative differences in this score for patients receiving 300 IR HDM tablet versus placebo were +10.3%, -7.2% and -39.3 %, respectively. During the treatment-free year, corresponding scores were -5.6%, -4.8% and -29.9% for the low-, medium- and high-severity tertiles ($n= 74$, 108 and 87), respectively. These results showed that the more severe the disease, the greater the treatment effect [59].

7. Safety and tolerability of the 300 IR house dust mite tablet

Across the clinical development program, the 300 IR HDM tablet had a favorable safety profile and was well tolerated in patients with HDM-induced AR, with or without asthma requiring therapies consistent with Global Initiative for Asthma (GINA) treatment step 1. In general, adverse events (AEs) were mild or moderate in severity, with the most commonly reported being application-site reactions (e.g. oral pruritus, mouth edema). Summary of treatment-associated adverse events with an incidence <2% in adults and adolescents receiving the 300 IR HDM tablet in clinical trials is presented in **Table 3**[37]. The safety of the HDM tablet has been assessed in 7 double-blind, placebo-controlled clinical trials in patients with HDM-induced AR, randomized to doses ranging from 100–1500 IR: VO36.04F (Phase I study in adults) [60], VO57.07 [39], VO67.10 [48], VO64.08 [37,56], VO73.13 (Phase I high-dose study in adolescents)[61] , 1109D1711 (Phase I study in adults in Japan) and 1207D1731 [36,37,40] (**Table 1**) [62]. The tolerability of the 500 IR dose was less favorable than that of the 300 IR dose with respect to the rate of treatment-emergent AEs (TEAEs) leading to premature study withdrawal. It was considered that for the AR indication, the benefit/risk ratio was in favour of the 300IR.[48].

7.1. Pooled safety analysis of 7 clinical trials of the HDM tablet (all doses) [62]

The pooled safety population comprised 2,407 patients with HDM-induced AR (1,718 adults, 443 adolescents and 246 children), of whom 26% (n=627) had intermittent mild asthma at enrollment. In total, 1,571 participants (128 children, 261 adolescents and 1,182 adults) received at least one dose of active treatment, and 836 (118 children, 182 adolescents and 536 adults) received placebo [62].

Drug-related, TEAEs were reported by 64% and 20% of patients treated with the HDM tablet or placebo, respectively, and were generally consistent with mild or moderate application-site reactions, such as throat irritation (23%), oral pruritus (17%), mouth edema (14%) and ear pruritus (12%). Most occurred during the initial 4 weeks of HDM tablet administration and resolved within days without requiring additional treatment. The proportions of patients with drug-related TEAEs

were similar, irrespective of asthma status (HDM tablet: 59% vs 66% and placebo: 19% vs 20% for patients with vs without asthma) [62]. Serious drug-related TEAEs (n=4) occurred in 3 patients receiving the HDM tablet (eczema, pharyngeal edema and dyspnea) and 1 patient receiving placebo (urticaria) in study VO57.07 [39,62]. TEAEs leading to premature discontinuation were more common with the HDM tablet (8%, n=123) than placebo (3%, n=24), and were mainly application-site reactions (e.g. mouth or lip edema). Across Phase 1–3 clinical trials of the HDM tablet (all doses), no deaths or Intensive Care Unit admissions were reported, and there were no reports of ‘anaphylactic shock’ or ‘anaphylaxis’, or the use of epinephrine [62].

7.2 Pooled safety analysis in children and adolescents

The safety profile of the HDM tablet in the pediatric population was consistent with that observed in adults and was generally similar in children (aged 5–11 years) and adolescents (aged 12–17 years) [37]. A total of 345 adolescents comprised the safety set, including 150 (43%) with mild intermittent asthma at enrolment [63]. The most commonly reported AEs during active treatment in the adolescents were mild or moderate application-site reactions such as throat irritation (13.9%), oral pruritus (9.8%) or mouth edema (8.7%). These AEs occurred during the first day of treatment in almost 20% of patients and within the first month in about 50% of them [63]. None of the serious AEs reported in 11 subjects (300 IR: n=5, placebo: n=6) were considered drug-related. 18 subjects [300 IR: n=12 (6.9%) and placebo: n=6 (3.5%)] withdrew due to an AE, mainly as a result of application-site reactions (e.g. upper abdominal pain, tongue edema). There were no reports of anaphylaxis and no use of epinephrine [63]. Percentages of adolescents reporting at least one AE during active treatment or those reporting adverse drug reactions (ADRs) were similar in patients with or without asthma [with asthma: 77% (AEs) and 50% (ADRs); without asthma: 78% (AEs) and 56% (ADRs)]. In both asthmatic and non-asthmatic subjects, the most frequent adverse reactions were those reported at the application site, and these were of similar incidences [63].

8. Regulatory affairs

Following marketing approval in March 2015, the 300 IR HDM tablet was launched in Japan in November 2015 and was subsequently licensed as therapy for HDM-induced AR in Australia in April 2016. Marketing authorisation is currently being sought in other regions.

9. Conclusion

Patients with HDM-induced AR have limited treatment options. HDM allergy avoidance is recommended, but the evidence for its effectiveness is controversial, and while pharmacotherapy is effective, allergic symptoms reappear when treatment is stopped. AIT is the only treatment with proven disease-modifying effects in AR [27].

The 300 IR HDM tablet is a once-daily SLIT that can significantly improve allergic symptoms, and reduce the need for symptomatic medication, versus placebo in adults, adolescents and children with HDM-induced AR, irrespective of sensitization status or the presence of comorbid mild allergic asthma. Importantly, its efficacy has been shown to persist for 1 year following discontinuation of treatment. It has an excellent safety profile in this population and can be conveniently administered at home after the first dose.

10. Expert commentary

The manufacturer of the 300 IR HDM tablet is firmly committed to improving the health of allergic patients, and has long-standing expertise and considerable research experience in AIT. The global clinical development program in allergic rhinitis has confirmed that 300 IR is the optimum clinically effective dose for AIT [64], and this dose is used across all their HDM SLIT portfolio, including HDM SLIT drops, which are the most widely used product of this type and for this indication worldwide, and the 300 IR HDM tablet, which was granted its first local marketing authorisation in Japan in

March 2015. Use of rescue medications was low in all trials of the HDM tablet, because they were allowed only when symptoms were intolerable or interfered with daily activities, in order to evaluate AR symptoms correctly. For ethical reasons, rescue medications cannot be prohibited in AIT trials lasting more than 1 year. Furthermore, rescue medication use tends to be greater in placebo groups than in active-treatment groups, which dampens the active versus placebo symptom score difference and leads to underestimation of the relative clinical impact of AIT products. The 300 IR HDM tablet represents an important development in the treatment of HDM-induced AR in both adults and adolescents [64,65], and is the only HDM SLIT tablet product that demonstrates sustained efficacy and benefits to patients following cessation of treatment.

11. Five-year view

In light of its demonstrated efficacy and favorable safety profile in treating patients with HDM-induced AR, the 300 IR HDM tablet also has the potential to be of benefit to patients with HDM-associated allergic asthma. Phase 1 dose-ranging clinical studies have indicated that the HDM tablet, in doses up to 2,000 IR, is well tolerated in adults, adolescents and children with HDM-associated mild to moderate allergic asthma [66-68]. No safety findings have been detected with doses up to 1,500 IR in patients with asthma that is controlled or partly controlled by therapies consistent with GINA treatment steps 2, 3 or 4 [37]. A Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-ranging clinical trial (VO72.12) in adults aged 18–50 years with HDM-associated allergic asthma (N=386) has been completed in 11 EU countries, to assess the efficacy and safety of three dosages of the HDM tablet (1000, 500 and 100 IR) for the treatment of allergic asthma [69].

This Phase 2 showed that the compound was active with clear evidence of a dose response based on its immunological activity, but missed its primary endpoint [69].

Evidence and findings from postmarketing surveillance studies and further randomized controlled trials in the US are likely to address several unmet needs, including the long-term efficacy of the HDM tablet beyond several years of treatment.

12. Key issues

- The 300 index of reactivity (IR) HDM tablet (Actair®; Stallergenes Greer, Antony, France/Shionogi & Co. Ltd., Osaka, Japan) is a once-daily sublingual immunotherapy tablet that is effective in controlling the symptoms of house dust mite (HDM)-induced allergic rhinitis, reducing the need for symptomatic medication and improving health-related quality of life with an onset of action as early as 2 months.
- It is effective in adults and adolescents with HDM-induced allergic rhinitis, irrespective of mono- or polysensitization status, or the presence of comorbid mild asthma. Clinical efficacy is maintained for 1 year after treatment is stopped.
- Data from the 300 IR HDM tablet clinical development program demonstrate its favorable safety profile in allergic patients, even those receiving doses of up to 2,000 IR.
- Future research is expected to further confirm the broad benefits of the 300 IR HDM tablet in patients with HDM-induced allergic rhinitis, and will investigate its utility for the treatment of HDM-associated allergic asthma.

13. Information resources

- For more information, please refer to the citations in the reference list marked as * ('of interest') or ** ('of considerable interest'), as well as the Stallergenes Greer website (<http://stallergenesgreer.com>).

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Declaration of Interests

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14. References

Reference annotations

* Of interest

** Of considerable interest

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15. List of abbreviations

AAdSS, Average Adjusted Symptom Score

AE, adverse event

AIT, allergy immunotherapy

AR, allergic rhinitis

AUC, area under the curve

Ch_{BL} AUC, change from baseline of the area under the curve

GINA, Global Initiative for Asthma

HDM, house dust mite(s)

IR, Index of Reactivity

JRQLQ, Japanese Allergic Rhinitis Standard Quality of Life Questionnaire

LS, least squares

MedDRA, Medical Dictionary for Regulatory Activities

RTSS, Rhinitis Total Symptom Score

SCIT, subcutaneous immunotherapy

SLIT, sublingual immunotherapy

SOC, System Organ Class

TEAE, treatment-emergent adverse event

WAO, World Allergy Organization

ACCEPTED MANUSCRIPT

16. Tables

Table 1. Summary of house dust mite sublingual immunotherapy tablet Phase 1–3 clinical trials and design.

Study Phase	Design and objectives	Location	Population	Treatment	Exposed patients (n)	Treatment duration	Ref.
VO36.04F Phase 1 2005	Single-center, randomized, double- blind, placebo-controlled Safety	France	Patients with HDM- induced AR Age 18–50 years	500 IR 300 IR 100 IR Placebo Total	15 7 1* 8 31	10 days	[60]
VO57.07 Phase 2/3 2010	Multinational, randomized, double- blind, placebo-controlled Efficacy, safety	7 EU countries: Czech Republic, France, Germany, The Netherlands, Poland, Slovakia, Spain	Patients with HDM- induced AR Age 18–50 years	500 IR 300 IR Placebo Total	169 170 170 509	12 months + 12 months follow-up without treatment	[39,50]
VO67.10 Phase 2 2012	Single-center, randomized, double- blind, placebo-controlled Efficacy, safety	Canada (environmental exposure chamber)	Patients with HDM- induced AR Age 18–55 years	500 IR 300 IR 100 IR Placebo Total	93 86 89 87 355	6 months + 2-week period without treatment	[48]
VO64.08 Phase 3 2011	Multinational, randomized, double- blind, placebo-controlled Efficacy, safety	9 EU countries: Denmark, France, Germany, Hungary, Ireland, Romania, Slovakia, Spain, Ukraine	Patients with HDM- induced AR Age 5–17 years	300 IR Placebo Total	241 230 471	12 months + 8 months follow-up without treatment	[37,56]

V073.13	Single-center, Phase 1 2013	Canada	Patients with HDM- induced AR Age 12–17 years	1500 IR 1000 IR 500 IR Placebo Total	9 9 9 10 37	10 days	[61]
1109D1711	Single-center, Phase 1 2011	Japan	Patients with HDM- induced AR Age 20–39 years	500 IR 300 IR 100 IR Placebo Total	9 9 9 9 36	14 days	Data not published
1207D1731	Multicenter, randomized, Phase 2b/3 2013	Japan	Patients with HDM- induced AR Age 12–64 years	500 IR 300 IR Placebo Total	324 322 322 968	12 months + 1 week follow-up without treatment	[36,37,40]
	Safety						
	Efficacy						

AR, allergic rhinitis; HDM, house dust mite; IR, index of reactivity. * actually this patient received a minimum dose of 200IR

Table 2. Summary of house dust mite sublingual immunotherapy tablet efficacy from key Phase 2-3 clinical trials.

Study Phase	Primary variable	Treatment	Primary analysis set (n)	LS mean difference vs placebo			
				LS mean	Absolute point estimate (95% CI)	Relative point estimate	P value vs placebo
VO57.07 EU study in adults 2/3 [39,50]	AAdSS*	Year 1 (on-treatment)	500 IR 136	3.09	-0.78 (-1.34, -0.22)	-20.2%	0.0066
			300 IR 141	3.18	-0.69 (-1.25, -0.14)	-17.9%	0.0150
			Placebo 153	3.87			
		Year 2 (treatment-free)	500 IR 120	2.97	-0.70 (-1.29, -0.11)	-19.1%	0.0206
			300 IR 132	3.04	-0.62 (-1.20, -0.05)	-17.0%	0.0342
			Placebo 137	3.67			
VO67.10 Environmental exposure chamber study in adults 2 [48]	Ch _{BL} AUC _{RTSS 0-4h}	500 IR 70	500 IR 70	-795.58	-198.18 (-389.82, -6.55)	33.2%	0.0427
			300 IR 68	-769.21	-171.82 (-363.87, 20.24)	28.8%	0.0793
			100 IR 75	-715.83	-118.43 (-305.90, 69.04)	19.8%	-
			Placebo 75	-597.40			
1207D1731 Japanese study in adolescents and adults 2b/3	AAdSS**	500 IR 296	500 IR 296	5.32	-0.80 (-1.20, -0.40)	-13.1%	<0.0001
			300 IR 315	5.00	-1.11 (-1.50, -0.72)	-18.2%	<0.0001
			Placebo 316	6.11			

[36,37,40]

AAdSS, Average Adjusted Symptom Score: a subject-specific score calculated as the average over the evaluation period of daily Adjusted Symptom Scores (which are calculated by adjusting the daily Rhinitis Total Symptom Score for rescue medication use), *ranged from 0 to 12, **ranged from 0 to 15; CI, confidence interval; IR, index of reactivity; LS, least squares; NS, not significant; $Ch_{BL}AUC_{RTSS\ 0-4h}$, change from baseline of the area under the curve of the Rhinitis Total Symptom Score during the 4 hours of the allergen challenge.

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Table 3: Summary of treatment-associated adverse events with an incidence <2% in adults and adolescents receiving the 300 IR HDM tablet in clinical trials (n=492) [37].

MedDRA SOC	Frequency (%)	
	Common (≥1/100 and <1/10)	Uncommon (≥1/1,000 and <1/100)
Cardiac disorders		Tachycardia
Ear and labyrinth disorders	Ear pain	
Eye disorders	Conjunctivitis	Eye edema, blepharospasm, lacrimation increased
Gastrointestinal disorders	Glossitis, oral mucosal blistering, oral hypoesthesia, gastritis, cheilitis	Oral pain, tongue pruritus, dysphagia, glossodynia, vomiting, gingivitis, gastrointestinal disorder, palatal edema, dry mouth, lip pruritus, breath odor, chapped lips, frequent bowel movements, irritable bowel syndrome, gingival pain, mouth ulceration, odynophagia, esophageal discomfort, salivary gland enlargement, salivary hypersecretion
General disorders and administration site conditions		Chest discomfort, lump feeling in throat, chest pain, asthenia, malaise
Infections and infestations		Periodontitis
Investigations	Gamma glutamyltransferase increased	Alanine aminotransferase increased, lymphocyte morphology abnormal, aspartate aminotransferase increased, basophil count increased, blood bilirubin increased, blood uric acid increased
Musculoskeletal and connective tissue disorders		Muscle spasms
Nervous system disorders		Somnolence

Psychiatric disorders		Anxiety
Respiratory, thoracic and mediastinal disorders	Dry throat	Laryngeal edema, wheezing, asthma, oropharyngeal pain, pharyngolaryngeal pain, sneezing, rhinorrhea, nasal discomfort, nasal congestion, throat tightness
Skin and subcutaneous tissue disorders	Pruritus, urticaria	Rash, angioedema, blister

Within each frequency category, treatment-related adverse events are presented in order of decreasing incidence. In addition to the adverse events listed above, patients in study VO67.10 who received the 300 IR HDM tablet (n=59) reported lip blister, bronchospasm, sinus congestion, AR, ear discomfort, eye pruritus, ocular hyperemia, paresthesia and pharyngitis (all common). Overall, the safety profile in the pediatric population is similar to that of adults. Malaise was reported at a higher frequency in the pediatric population than in adults (common). Additionally, the following reactions were reported in children and adolescents who received the 300 IR HDM tablet (n=239): enterocolitis, oral disorder, seborrhea, bronchitis, candida infections and ear disorder (all uncommon).

AR, allergic rhinitis; HDM, house dust mite; MedDRA, Medical Dictionary for Regulatory Activities; SOC, System Organ Class.