Report on the Deliberation Results

January 26, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Actair House Dust Mite Sublingual Tablets 100 units (IR) Actair House Dust Mite Sublingual Tablets 300 units (IR)
[Non-proprietary name]	None
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	April 24, 2014

[Results of deliberation]
In the meeting held on January 21, 2015, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Develop and properly implement a risk management plan.
2. Take necessary measures, before market launch, to ensure that the product is prescribed and administered only by qualified physician(s) with adequate knowledge and experience in sublingual immunotherapy who can successfully manage and explain the risks associated with the product in a medical institution that allows such physicians to do so, and to ensure that the product is dispensed by pharmacists who have confirmed that the product has been prescribed by the physician(s) in an appropriate medical institution.

Review Report

January 9, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Actair House Dust Mite Sublingual Tablets 100 units (IR) (b) Actair House Dust Mite Sublingual Tablets 300 units (IR)
[Non-proprietary name]	None
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	April 24, 2014
[Dosage form/Strength]	(a) Sublingual tablets: Each tablet contains 50 units (IR [index of reactivity]) of *Dermatophagoides pteronyssinus* extract bulk powder and 50 units (IR) of *Dermatophagoides farinae* extract bulk powder. (b) Sublingual tablets: Each tablet contains 150 units (IR) of *Dermatophagoides pteronyssinus* extract bulk powder and 150 units (IR) of *Dermatophagoides farinae* extract bulk powder.
[Application classification]	Prescription drug (1) Drug with new active ingredients
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

Review Results

January 9, 2015

[Brand name] (a) Actair House Dust Mite Sublingual Tablets 100 units (IR)
(b) Actair House Dust Mite Sublingual Tablets 300 units (IR)
[Non-proprietary name] None
[Applicant] Shionogi & Co., Ltd.
[Date of application] April 24, 2014
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in desensitization therapy for house dust mite antigen-induced allergic rhinitis has been demonstrated. As for safety, desensitization therapy has a risk of inducing anaphylaxis because allergens are administered to sensitized patients on the therapy. The product should therefore be used only by physicians with adequate knowledge of the product and expertise and experience in desensitization therapy. In addition, measures should be taken (e.g., education and guidance for healthcare professionals and patients) to ensure proper safety measures against anaphylaxis. Furthermore, post-marketing surveillance is required to further investigate the long-term efficacy and safety of the product.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration specified below, with the following conditions:

[Indication]
Desensitization therapy for house dust mite antigen-induced allergic rhinitis

[Dosage and administration]
For adults and children ≥12 years old, the starting dose of Actair is 100 units (IR) administered sublingually once daily. The dose is increased by 100 units (IR) up to 300 units (IR) over a period of 3 days, in principle, or a longer period depending on the patient's condition. Following sublingual administration, the tablet(s) should be held under the tongue until it completely dissolved, and then swallowed. For the next 5 minutes, the patient should avoid gargling, eating, or drinking.

[Conditions for approval]
The applicant is required to:
1. Develop and properly implement a risk management plan.
2. Take necessary measures, before market launch, to ensure that the product is prescribed and administered only by qualified physician(s) with adequate knowledge and experience in sublingual immunotherapy who can successfully manage and explain the risks associated with the product in a medical institution that allows such physicians to do so, and to ensure that the product is dispensed

by pharmacists who have confirmed that the product has been prescribed by the physician(s) in an appropriate medical institution.

Review Report (1)

December 15, 2014

I. Product Submitted for Registration

[Brand name]	Actair Sublingual Tablets 100 IR Actair Sublingual Tablets 300 IR
[Non-proprietary name]	None
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	April 24, 2014
[Dosage form/Strength]	(a) Each sublingual tablet contains 50 IR of *Dermatophagoides pteronyssinus* extract bulk powder and 50 IR of *Dermatophagoides farinae* extract bulk powder. (b) Each sublingual tablet contains 150 IR of *Dermatophagoides pteronyssinus* extract bulk powder and 150 IR of *Dermatophagoides farinae* extract bulk powder.
[Proposed indication]	House dust mite antigen-induced allergic rhinitis (allergen immunotherapy)
[Proposed dosage and administration]	For adults and children ≥12 years old, the product is administered sublingually once daily before breakfast at 100 IR on Day 1, 200 IR on Day 2, and 300 IR from Day 3 onward as the maintenance dose.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

As described in the Japanese and foreign treatment guidelines, desensitization therapy is a therapeutic modality whereby appropriate amounts of causative allergens are continuously administered to enhance immunological tolerance against allergens. Long-term desensitization therapy can improve abnormal immunological reactions in patients, and thereby can achieve a cure or long-term remission of allergic diseases (Practical Guideline for the Management of Allergic Rhinitis in Japan 2013, WHO position paper: *Allergy*. 1998;53:1-42 [hereinafter referred to as “WHO position paper 1997”]).

House dust mites are major allergens in allergic disease. Of the various types of house dust mites, *D. pteronyssinus* and *D. farinae* (2 species of *Pyroglyphidae Dermatophagoides*) are common species of allergens. Actair is a tablet containing extract bulk powder of *D. pteronyssinus* and *D. farinae* in an

equal antigen activity ratio for sublingual immunotherapy (SLIT) of house dust mite antigen-induced allergic rhinitis. Actair was developed by Stallergenes S.A. in France.

In Japan, house dust mite extract products for subcutaneous immunotherapy (SCIT) have been approved (Allergen Extract for Subcutaneous Injection "Torii" House Dust 1:10, etc.). SCIT, however, causes injection pain and may induce serious adverse drug reactions such as anaphylactic shock. Actair for SLIT has therefore been developed. In Japan, SLIT products containing cedar pollen (Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle, etc.) were approved in 2014.

In other countries, a sublingual solution containing *D. pteronyssinus* and *D. farinae* extracts for desensitization therapy has been approved for the treatment of allergic rhinitis and bronchial asthma (Staloral [brand name] marketed by Stallergenes S.A.). As of April 2014, the solution is marketed in 21 countries in Europe and other regions. [redacted]

In Japan, the applicant, Shionogi & Co., Ltd., began to develop Actair in [redacted] 20[redacted] and filed the new drug application based on data from Japanese clinical studies.

Skin prick test was conducted in 30 patients sensitized to relevant mite antigens, to determine the index of reactivity (IR)[1] for Actair. As a result, 100 units (IR) was defined as the concentration resulting in a mean wheal diameter of 7 mm.

The proposed brand names "Actair Sublingual Tablets 100 IR" and "Actair Sublingual Tablets 300 IR" will be changed to "Actair House Dust Mite Sublingual Tablets 100 units (IR)" and "Actair House Dust Mite Sublingual Tablets 300 units (IR)," respectively, in order to prevent medical errors and accidents.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

[redacted][2][redacted][3][redacted][4][redacted][5][redacted]

[1] The Japanese Society of Allergology uses a Japan-specific allergen activity unit called Japanese allergy units (JAU): 100 units (IR) is equal to 19,000 JAU.
[2] Extracted primarily from the feces of *D. pteronyssinus*, one of the main allergens
[3] Extracted primarily from the bodies of *D. pteronyssinus*, one of the main allergens
[4] Extracted primarily from the feces of *D. farinae*, one of the main allergens
[5] Extracted primarily from the bodies of *D. farinae*, one of the main allergens

[redacted]

2.A.(1).2) Manufacturing process

[redacted]

2.A.(1).3) Control of drug substance

[redacted]

2.A.(1).4) Stability of drug substance

Table 1 shows the results of stability studies for each drug substance. [redacted]

Table 1. Stability studies of drug substance

Studies	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 commercial batches	5℃	Not controlled	[redacted]	[redacted] months
Accelerated	3 commercial batches	25℃	60%RH	[redacted]	6 months

[redacted]

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a tablet containing total allergenic activity of 100 units (IR) (50 units [IR] each of the 2 drug substances) or 300 units (IR) (150 units [IR] each of the 2 drug substances) of extract bulk powder. The drug product contains the following excipients: microcrystalline cellulose, croscarmellose sodium, light anhydrous silicic acid, magnesium stearate, and lactose hydrate.

2.A.(2).2) Manufacturing process

[redacted]

2.A.(2).3) Control of drug product

[redacted]

2.A.(2).4) Stability of drug product

The results of drug product stability studies are shown in Table 2. The photostability studies showed the drug product to be photostable.

Table 2. Stability studies of the drug product

Studies		Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	100 units (IR)	Commercial 3 batches	25°C	60% RH	Aluminum/Aluminum blister pack	36 months
	300 units (IR)					
Accelerated	100 units (IR)		40°C	75% RH		6 months
	300 units (IR)					

[redacted]

2.B Outline of the review by PMDA

Based on the submitted data and the following review, PMDA concludes that the quality of the drug substance and drug product is properly controlled.

2.B.(1) Protein content and Der p 2 or Der f 2 content

PMDA asked the applicant to explain the appropriateness of control methods for allergenic proteins.

The applicant explained as follows:

In *D. pteronyssinus* and *D. farinae*, the major allergens eliciting allergic reactions are Der p 1 and Der f 1 (glycoproteins found mainly in mite feces) and Der p 2 and Der f 2 (proteins found mainly in mite bodies). The content of other allergens is generally <1%, and their contribution to biological activity is low. Consequently, allergenic proteins are controlled by establishing specifications for the content of Der p 1 or Der f 1 for the drug substance and drug product. The specifications for the content of Der p 2 and Der f 2, the other major allergens, were not established for the drug substance or drug product. Nevertheless, the quality of the drug substance and drug product can be controlled by controlling total allergenic activity and the content of major allergens Der p 1 and Der f 1, for the following reasons: (1) total allergenic activity which indicates biological activity is the most important parameter for the efficacy of Actair; (2) biological activity has been reported to closely correlate with major allergen content (Van Ree R. *Allergy.* 1997;52:795-805 and Yasueda. *IgE practice in asthma*. 2008;2:2-5); and

(3) the biological activity of Der p 2 and Der f 2 can be deduced by subtracting the biological activity of Der p 1 and Der f 1 from total allergenic activity.

PMDA instructed the applicant to control the drug substance and drug product by establishing specifications not only for total allergenic activity and Der p 1 or Der f 1 content, but also for Der p 2 or Der f 2 content and protein content, for the following reasons: (1) the applicant explained that Der p 2 or Der f 2, mite body allergens, are major allergens eliciting allergic reactions; and (2) both the drug substance and the drug product contain many other potentially allergenic proteins, albeit in small amounts, besides Der p 1, Der f 1, Der p 2, and Der f 2. Therefore Der p 2 or Der f 2 content and protein content, as well as Der p 1 or Der f 1 content, may affect the efficacy and safety of Actair. Der p 2 and Der f 2 are thus critical control parameters for ensuring the quality profile of the drug substance and drug product.

The applicant replied that it would establish specifications for Der p 2 or Der f 2 content for the drug substance and specifications for protein content for the drug substance and drug product. PMDA accepted the applicant's reply.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

A secondary pharmacodynamic study was conducted to analyze airway inflammation using a mite antigen-induced asthma model.

Studies investigating primary pharmacodynamics, safety pharmacology, and pharmacodynamic drug interactions have not been performed for the following reasons: There is no standard animal model for evaluating the efficacy of desensitization therapy for allergic rhinitis; products containing mite antigens for desensitization therapy have been reported to be effective against allergic rhinitis (Corrado OJ et al. *Allergy.* 1989;44:108-115 and Pichler CE et al. *Allergy.* 1997;52:274-283); and allergenic proteins contained in the Actair are considered to be scarcely absorbed, without being metabolized, through the sublingual mucosa or digestive tract [see "3.(ii).A Summary of the submitted data"]. With respect to safety pharmacology, effects on the nervous system and general condition were investigated in a rat 26-week repeated subcutaneous dose study [see "3.(iii).A.(2).1) Twenty-six week repeated subcutaneous dose study in rats"].

3.(i).A.(1) Secondary pharmacodynamics (4.2.1.2-01)

3.(i).A.(1).1) Effects on airway inflammation in a mite antigen-induced asthma mouse model

The secondary pharmacodynamic study investigated the effects of allergen extract (a mixture containing extract bulk powder of *D. pteronyssinus* and *D. farinae* in an equal antigen activity ratio) on respiratory functions and airway inflammation. Mice received intraperitoneal administration of the allergen extract mixed with the aluminum hydroxide gel, and then were exposed to an aerosol containing the allergen

extract and lipopolysaccharides, which induced asthma-like symptoms. The allergen extract 2500 or 20,000 IR/kg/day was sublingually administered twice weekly for 8 weeks to the mice (asthma mouse model). The mice were exposed to the antigens for 2 days after the completion of exposure. Compared to the negative control group, both the 2500 and 20,000 IR/kg/day groups showed (1) improvements in Penh index, a respiratory function indicator, at 24 hours after antigen exposure, and (2) a suppression of eosinophil counts in bronchoalveolar lavage fluid and of the production of interleukin (IL)-5 and IL-13 in the lung tissue, both airway inflammation indicators, at 48 hours after antigen exposure.

3.(i).A.(2) Safety pharmacology

No safety pharmacology study has been performed. In a toxicity study that investigated 26-week repeated subcutaneous doses in rats (4.2.3.2-01), neurobehavioral and functional tests (including body temperature measurement) were performed. Following subcutaneous administration of the allergen extract 500, 1500, or 2500 IR/kg/day for 26 weeks, the rats showed no effects on general condition, the central nervous system, or the autonomic nervous system.

3.(i).B Outline of the review by PMDA

PMDA asked the applicant to explain the mechanism of action of SLIT in comparison with SCIT.

The applicant provided the following explanation based on literature:

SLIT and SCIT have much in common in their mechanism to induce immunological tolerance, e.g., (1) the uptake of administered antigens by antigen-presenting cells, (2) suppression of the functions of allergen-specific Type II helper T cell, (3) increased secretion of allergen-specific immunoglobulin (Ig) G4 and IgA, and (4) suppression of IgE production. Compared with SCIT, however, SLIT has been reported to more efficiently induce blood and mucus allergen-specific IgA (Moingeon P and Mascarell L. *Clin Dev Immunol*. 2012;ID: 623474 and Moingeon P. *J Allergy Clin Immunol*. 2013;1:228-241). Additionally, antigen-presenting cells in the oral mucosa exposed to SLIT have a greater ability to produce IL-10- and IL-12 and to induce suppressor T cells and Type I helper T cells specific to captured allergens (Moingeon P and Mascarell L. *Clin Dev Immunol*. 2012;ID: 623474), although whether these findings contribute to the efficacy of SLIT is unknown because of the lack of data comparing the efficacy of SLIT and SCIT.

PMDA considers as follows:

While the mechanism of action of Actair has yet to be fully elucidated, Actair is expected to be effective based on the literature. The omission of non-clinical pharmacological studies (other than the secondary pharmacodynamics study) is acceptable.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The literature on human pharmacokinetics of sublingually administered ^{123}I-labeled *Parietaria judaica* antigens (Bagnasco M et al. *J Allergy Clin Immunol*. 1997;100:122-129, Bagnasco M et al. *Clin Exp*

Allergy. 2001;31:54-60, and Passalacqua G et al. *Allergy.* 1998;53:477-484) or ^{123}I-labeled *D. pteronyssinus* antigen (Bagnasco M et al. *Int Arch Allergy Immunol.* 2005;138:197-202) suggests that allergenic proteins are scarcely absorbed, without being metabolized, through the sublingual mucosa or digestive tract. Furthermore, allergenic protein levels in blood are difficult to measure. Consequently, no studies on absorption, distribution, metabolism, or excretion have been conducted.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Repeated-dose toxicity studies and genotoxicity, reproduction toxicity, and local tolerance studies have been conducted as toxicology studies. The repeated-dose toxicity and reproduction toxicity studies used the allergen extract. The genotoxicity studies used *D. pteronyssinus* or *D. farinae* extract bulk powder. The local tolerance study used the same formulation administered in a clinical study (Study VO36).

3.(iii).A.(1) Single-dose toxicity

No single-dose toxicity study has been performed. A 26-week repeated oral dose study in rats (4.2.3.2-02) showed no deaths or effects on the general condition on Day 1 in rats given up to 2500 IR/kg/day of the allergen extract. The approximate lethal dose was thus considered to be >2500 IR/kg/day.

3.(iii).A.(2) Repeated-dose toxicity

As repeated-dose toxicity studies, 26-week subcutaneous and oral dose studies have been conducted using rats. Subcutaneous dosing is the administration route that achieves the highest levels of immunogenicity. A long-term repeated-dose toxicity study of sublingual dosing, the proposed clinical administration route, is difficult to conduct. Consequently, subcutaneous and oral studies have been conducted. Oral dosing caused no effect on the general condition. Major findings associated with subcutaneous dosing included elevated neutrophil counts, elevated total white leukocyte counts, increased spleen weight, and injection site changes (hyperplasia, hematoma, petechiae, inflammatory cell infiltration, etc.). The no observed adverse effect level (NOAEL) was determined to be 2500 IR/kg/day (15,000 IR/m^2/day) for both subcutaneous and oral administration. The NOAEL is 81 times the clinical dose for adults (300 IR/day, 185 IR/m^2/day) and 40 times the clinical dose for children (300 IR/day, 375 IR/m^2/day)[6] The principal components of the allergen extract are proteins and polypeptides; therefore toxicological findings attributable to the metabolic differences between rodents and non-rodent animals are unlikely to be seen. Additionally, a reproductive toxicity study in juvenile dogs (4.2.3.5-04) showed no toxicity findings associated with the allergen extract, suggesting no marked interspecies differences in toxicity findings between rodents and canines. Thus, no repeated-dose toxicity studies using non-rodent animals have been performed.

[6] The conversion assumes a body surface area of 1.62 m^2 for adults weighing 60 kg and 0.8 m^2 for children weighing 20 kg.

3.(iii).A.(2).1) Twenty-six week repeated subcutaneous dose study in rats (4.2.3.2-01)

Male and female SD rats received saline or 500, 1500, or 2500 IR/kg/day of the allergen extract administered subcutaneously for 26 weeks.[7] Rats receiving ≥500 IR/kg/day showed macroscopic findings at the injection site (hyperplasia, hematoma, petechiae, and induration). Rats receiving ≥1500 IR/kg/day showed increased spleen weight. Rats receiving 2500 IR/kg/day showed elevated neutrophil counts, elevated total leukocyte counts, and histopathological findings at the injection site (fiber formation accompanied by dermal edema, bleeding inside the site of inflammation, inflammatory cell infiltration, etc.). Furthermore, mite-specific IgG was detected in the serum of rats receiving ≥500 IR/kg/day. The increased spleen weight was considered to be potentially attributable to immunogenicity, but no histopathological changes related to the finding were observed. Additionally, the injection site inflammation is toxicologically irrelevant, since the proposed clinical route of administration is sublingual. Consequently, the NOAEL of the allergen extract was determined to be 2500 IR/kg/day.

3.(iii).A.(2).2) Twenty-six week repeated oral dose study in rats (4.2.3.2-02)

Male and female SD rats received D-mannitol solution or 500, 1500, or 2500 IR/kg/day of the allergen extract administered orally for 26 weeks. No abnormalities were found in general condition, body weight, food intake, estrous cycle, ophthalmoscopy, hematology, blood chemistry, blood coagulation tests, urinalysis, macroscopic necropsy findings, organ weight, or histopathological tests. Mite-specific IgG was detected in the serum of rats receiving ≥500 IR/kg/day. Based on the above, the NOAEL of the allergen extract was determined to be 2500 IR/kg/day.

3.(iii).A.(3) Genotoxicity (4.2.3.3-01 through 4.2.3.3-04)

A bacterial reverse mutation assays (Ames tests) and mouse lymphoma tk assays using *D. pteronyssinus* and *D. farinae* extract bulk powders have been conducted as genotoxicity studies.

The Ames tests were conducted with the plate or pre-incubation method. Incubation with both *D. pteronyssinus* and *D. farinae* extract bulk powders (incubated separately) increased the number of reverse mutant colonies of multiple strains with and without metabolic activation system. To investigate the effects of the amino acids and peptides included in the *D. pteronyssinus* and *D. farinae* extract bulk powders on this finding (increased mutant colonies), additional tests were conducted with the modified treat-and-wash method. The results were negative for all strains with both extract bulk powders. Thus no biological significance was found in the increased reverse mutant colonies of multiple strains incubated with the *D. pteronyssinus* and *D. farinae* extract bulk powders with the plate or pre-incubation method. The Ames tests demonstrated that neither *D. pteronyssinus* nor *D. farinae* extract bulk powders were genotoxic.

The mouse lymphoma tk assays revealed that neither *D. pteronyssinus* nor *D. farinae* extract bulk powders were genotoxic.

[7] The Irwin screen test was used to assess effects on the nervous system at baseline and Weeks 13 and 26 of administration.

No *in vivo* genotoxicity study has been performed for the following reasons: *D. pteronyssinus* and *D. farinae* extract bulk powders tested negative in the *in vitro* genotoxicity studies; genotoxic concerns are minimal for the compounds that may be included in the drug substance or manufacturing processes for the allergen extract; the allergenic proteins in *D. pteronyssinus* and *D. farinae* extract bulk powders are considered to be scarcely absorbed without being metabolized; and oral concentrations of the allergen extract used in clinical practice is unlikely to exceed the concentrations of the allergen extract investigated in the *in vitro* studies.

3.(iii).A.(4) Carcinogenicity

The genotoxicity studies suggested that the allergen extract is unlikely to be genotoxic in clinical use. No pre-cancerous lesions were observed in repeated-dose toxicity studies in rats (4.2.3.2-01 and 4.2.3.2-02). Consequently, no carcinogenicity study has been performed.

3.(iii).A.(5) Reproductive toxicity

Embryo-fetal development studies in rats and rabbits and toxicity studies in juvenile rats and juvenile dogs have been conducted. No study of fertility and early embryonic development to implantation has been performed, because the 26-week repeated subcutaneous dose study and 26-week repeated oral dose study in rats showed no effects of the allergen extract on male or female reproductive organs, and because the toxicity study in juvenile rats (4.2.3.5-03) showed no effects on fertility. No study of effects on pre- and postnatal development, including maternal function, has been performed, because the embryo-fetal development study in rats (4.2.3.5-01) showed no effects of the allergen extract on pregnant rats, embryos, or fetuses, and because the toxicity studies in juvenile rats and juvenile dogs (4.2.3.5-03 and 4.2.3.5-04) showed no effects on neonates.

3.(iii).A.(5).1) Embryo-fetal development study in rats (4.2.3.5-01)

Pregnant SD rats received D-Mannitol solution or 300, 1500, or 2500 IR/kg/day of the allergen extract administered orally from Days 6 to 17 of gestation. The allergen extract had no effects on pregnant rats. In the 2500 IR/kg/day group, hypodactylia (1 of 256 animals) and a lumbar vertebral defect (1 of 140 animals) were observed in embryos and fetuses, but these events appeared unlikely to be related to the allergen extract because they occur naturally in SD rats. Specifically, the incidence of lumbar vertebral defect was within the range of historical data at the study center; and the incidence of hypodactylia was within the range of historical data in the literature (Ema M et al. *Congenit Anom*. 2014;54(3):150-61.doi: 10.1111/cga.12050). The NOAEL of the allergen extract in pregnant rats, embryos, and fetuses was thus determined to be 2500 IR/kg/day.

3.(iii).A.(5).2) Embryo-fetal development study in rabbits (4.2.3.5-02)

Pregnant NZW rabbits received D-Mannitol solution or 300, 1500, or 2500 IR/kg/day of the allergen extract administered orally from Days 6 to 18 of gestation. In maternal rabbits receiving ≥1500 IR/kg/day, body weight increases tended to be suppressed during the treatment period. No effects on

embryos and fetuses were found. The maternal finding was not considered to be toxicologically significant because no effects on food intake and general condition were observed. The NOAEL of the allergen extract in pregnant rabbits, embryos, and fetuses was thus determined to be 2500 IR/kg/day.

3.(iii).A.(5).3) Toxicity study in juvenile rats (4.2.3.5-03)

Male and female juvenile rats received D-Mannitol solution or 300, 1500, or 2500 IR/kg/day of the allergen extract administered orally from Days 10 to 80 of birth. No effects on systemic toxicity or reproductive functions were observed. Rats receiving ≥1500 IR/kg/day showed a tendency of delayed eyelid opening before weaning (Day 17 of birth), but all rats showed eyelid opening after weaning (Day 21 of birth). A toxicity study in juvenile dogs showed no tendency of delayed eyelid opening, indicating that the delayed eye opening in the juvenile rats were not attributable to the allergen extract. The allergen extract had no other effects on preweaning and postweaning functions. The NOAEL of the allergen extract was thus determined to be 2500 IR/kg/day.

3.(iii).A.(5).4) Toxicity study in juvenile dogs (4.2.3.5-04)

Male and female juvenile beagles received D-Mannitol solution or 300, 1500, or 2500 IR/kg/day of the allergen extract administered orally from Days 1 to 28 of birth. Deaths or euthanasia due to exacerbated general condition occurred in 1 of 20 animals in the control group (Day 3 of birth), 5 of 20 animals in the 300 IR/kg/day group (Day 3 or 5), 4 of 20 animals in the 1500 IR/kg/day group (Days 2-4 of birth), and 4 of 20 animals in the 2500 IR/kg/day group (Days 2-4 of birth).[8] As maternal dogs of dead juveniles exhibited decreased activity, decreased lactation, and decreased food intake, the deaths and weakness were probably associated with the decreased lactation. The allergen extract had no effects on eyelid opening, ophthalmological findings, or any other parameters. The NOAEL of the allergen extract was thus determined to be 2500 IR/kg/day.

3.(iii).A.(6) Local tolerance (4.2.3.6-01)

The same allergen extract formulation used in Study VO36 at 100, 300, or 500 IR or placebo was administered to the buccal pouch of male and female hamsters for 4 weeks. The allergen extract did not irritate the oral cavity.

3.(iii).B Outline of the review by PMDA

PMDA concludes that, based on the submitted data, there are no specific toxicological concerns in the clinical use of Actair.

4. Clinical data

4.(i) Summary of clinical efficacy and safety

4.(i).A Summary of the submitted data

[8] After Day 5 of birth, euthanized neonates and dead neonates were replaced by those born to other maternal animals to secure 10 dogs/sex/group.

The applicant submitted the following efficacy and safety data on Actair: the results of a phase I clinical study (Study D1711 [5.3.5.1-01]) and a phase II/III study (Study D1731 [5.3.5.1-02]) in Japanese patients with perennial allergic rhinitis; and the results of a phase I study (Study VO36 [5.3.5.1-05]), a phase II study (Study VO67 [5.3.5.1-04]), and a phase II/III study (Study VO57 [5.3.5.1-03]) in non-Japanese patients with perennial allergic rhinitis.

4.(i).A.(1) Japanese phase I study (5.3.5.1-01, Study D1711 [[redacted] to [redacted] 20[redacted]])

A randomized double-blind placebo-controlled dose-escalation study was conducted to investigate the safety of Actair in patients with house dust mite antigen-induced perennial allergic rhinitis[9] (target sample size, 36 patients [12 per step]).

Patients received Actair 100, 300, or 500 units (IR) or placebo administered sublingually once daily before breakfast for 14 days, as specified in Table 3. The patients were instructed to hold the study drug under the tongue until it dissolved completely.

Table 3. Doses for Study D1711

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Days 9-14
100 IR	100	100	100	100	100	100	100	100	100
300 IR	100	200	300	300	300	300	300	300	300
500 IR	100	100	200	200	300	300	400	400	500
Placebo[a)]	0	0	0	0	0	0	0	0	0

Unit, IR

a) Placebo group: Patients receiving the same dose of placebo as the above dose groups (unless otherwise noted, the same applies below, main text included)

All 36 randomized patients (9 patients each in the 100 IR, 300 IR, 500 IR, and placebo groups) were included in the safety analysis. None of the patients discontinued the study.

Adverse events occurred in 7 of 9 patients (77.8%) in the 100 IR group, 6 of 9 patients (66.7%) in the 300 IR group, 9 of 9 patients (100%) in the 500 IR group, and 2 of 9 patients (22.2%) in the placebo group. Table 4 lists adverse events occurring in ≥ 2 patients in any group. No adverse events leading to deaths, serious adverse events, or study discontinuation occurred. Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) occurred in 5 of 9 patients (55.6%) in the 100 IR group, 6 of 9 patients (66.7%) in the 300 IR group, 8 of 9 patients (88.9%) in the 500 IR group, and 1 of 9 patients (11.1%) in the placebo group.

[9] Patients with perennial allergic rhinitis who meet all of the following criteria: (a) 20-39 years old; (b) disease duration of ≥ 2 years; (c) positive results for *D. pteronyssinus*- or *D. farinae*-specific IgE antibody quantification (CAP-RAST scores of ≥ 2); (d) positive nasal induction test with house dust disks

Table 4. Adverse events occurring in ≥ 2 patients in any group (safety analysis set)

Events	100 IR (n = 9)	300 IR (n = 9)	500 IR (n = 9)	Placebo (n = 9)
Oropharingeal discomfort	4 (44.4)	3 (33.3)	2 (22.2)	0
Oral hypoesthesia	2 (22.2)	2 (22.2)	1 (11.1)	0
Oral discomfort	2 (22.2)	1 (11.1)	0	0
Pruritus	2 (22.2)	0	0	0
Throat irritation	1 (11.1)	5 (55.6)	6 (66.7)	0
Ear pruritus	1 (11.1)	1 (11.1)	4 (44.4)	0
Stomatitis	1 (11.1)	0	3 (33.3)	0
Oedema mouth	0	5 (55.6)	3 (33.3)	0
Oral pruritus	0	2 (22.2)	2 (22.2)	0
Diarrhea	0	1 (11.1)	2 (22.2)	0
Alanine aminotransferase increased	0	1 (11.1)	2 (22.2)	0
Oropharingeal pain	0	0	5 (55.6)	0
Cough	0	0	2 (22.2)	0
Glossalgia	0	0	2 (22.2)	0
Lip swelling	0	0	2 (22.2)	0
Lip pruritus	0	0	2 (22.2)	0
Pyrexia	0	0	0	2 (22.2)

n (%)

4.(i).A.(2) Japanese phase II/III study (5.3.5.1-02, Study D1731 [[redacted] to [redacted]])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to investigate the efficacy and safety of Actair in patients with house dust mite antigen-induced perennial allergic rhinitis[10] (target sample size, 750 patients [250 per group]).

Patients received Actair 300 or 500 units (IR) or placebo administered sublingually once daily before breakfast[11] for 52 weeks, as specified in Table 5. The patients were instructed to swallow the study drug after holding it under the tongue until it dissolved completely, and to avoid gargling, eating, or drinking for about 5 minutes after administration. If symptoms of perennial allergic rhinitis worsened and was considered by the investigator or subinvestigator to require treatment,[12] rescue medications were used as follows: (1) The first step was administration of an oral or ophthalmic antihistamine (oral, fexofenadine hydrochloride; ophthalmic, olopatadine hydrochloride). (2) The second step was administration of a nasal corticosteroid (beclometasone dipropionate) to patients in whom continuing the study was difficult because of insufficient response to the first step therapy.[13] (3) The third step was co-administration of the antihistamine (used in the first step) and the corticosteroid (used in the second step) to patients in whom continuing the study was difficult because of insufficient response to the second step therapy.[14]

[10] Patients with perennial allergic rhinitis who met all of the following criteria: (a) 12-64 years old; (b) disease duration of ≥2 years; (c) positive results for *D. pteronyssinus*- or *D. farinae*-specific IgE antibody quantification (CAP-RAST scores of ≥2); (d) positive nasal induction test with house dust disks

[11] The study drug was administered before breakfast to ensure medication compliance and to allow patients to receive treatment for adverse drug reactions requiring emergency medical care.

[12] For patients with nasal symptoms (total nasal symptom score of ≥9 points/day) or ocular symptoms (total ocular symptom scores of ≥6 points/day)

[13] For patients with nasal symptoms (total nasal symptom score of ≥9 points/day)

[14] For patients with nasal symptoms (total nasal symptom score of ≥9 points/day) or ocular symptoms (total ocular symptom scores of ≥6 points/day)

Table 5. Doses for Study D1731

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Days 9-14	Day 15 to Week 52
300 IR	100	200	300	300	300	300	300	300	300	300
500 IR	100	100	200	200	300	300	400	400	500	500
Placebo	0	0	0	0	0	0	0	0	0	0

Unit, IR; Days 1-14, dose escalation period; Day 15 to Week 52, dose maintenance period

All 968 randomized patients (322 in the 300 IR group, 324 in the 500 IR group, and 322 in the placebo group) were included in the safety analysis. Of the 968 patients, 927 patients (315 in the 300 IR group, 296 in the 500 IR group, and 316 in the placebo group) were included in the full analysis set (FAS) and the efficacy analysis. Excluded were 41 patients who discontinued the study because of adverse events or other reasons and had no patient diary[15] records after the start of study treatment. Some patients discontinued the study: 35 of 322 patients (10.9%) in the 300 IR group, 49 of 324 patients (15.1%) in the 500 IR group, and 31 of 322 patients (9.6%) in the placebo group. The most common reason for discontinuation was adverse events: 14 of 322 patients (4.3%) in the 300 IR group, 29 of 324 patients (9.0%) in the 500 IR group, and 12 of 322 patients (3.7%) in the placebo group.

The primary efficacy endpoint was adjusted nasal symptom score,[16] i.e., total nasal symptom score of 4 symptoms (paroxysmal sneeze, nasal discharge, nasal congestion, and nasal pruritus)[17] adjusted for the use of rescue medications. Symptoms of perennial allergic rhinitis are known to worsen generally in autumn. The study was therefore designed to allow both “baseline total nasal symptom score” and “adjusted nasal symptom score after 1 year of treatment (the primary endpoint)” to be assessed in autumn.

Table 6 shows mean adjusted nasal symptom scores (primary efficacy endpoint) at Weeks 44 through 52. Statistically significant differences were found between the placebo group and the 300 or 500 IR, demonstrating the superiority of 300 and 500 IR over placebo.

[15] In accordance with the Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, patients assessed their paroxysmal sneeze, nasal discharge, and nasal congestion (each scored on a scale of 0 to 4) and nasal pruritus (scored on a scale of 0 to 3) and recorded the scores.

[16] The use of rescue medications might impact total nasal symptom score on the day of and the day after the use of rescue medications. Adjusted nasal symptom score were therefore determined as follows: (a) When no rescue medications were administered, adjusted nasal symptom score was considered the same as total nasal symptom score. (b) When rescue medications were administered, adjusted nasal symptom score on the day of rescue medication was determined to be the higher score of either “adjusted nasal symptom score on the day before rescue medication” or “total nasal symptom score on the day of rescue medication”, and adjusted nasal symptom score on the day after rescue medication was determined to be the higher score of either “adjusted nasal symptom score on the day of rescue medication” or “total nasal symptom score on the day after rescue medication.”

[17] Total nasal symptom score is the sum of the scores of paroxysmal sneeze, nasal discharge and nasal congestion (each scored on a scale of 0 to 4) and nasal pruritus (scored on a scale of 0 to 3).

Table 6. Mean adjusted nasal symptom scores from Week 44 to Week 52 (FAS)

	300 IR (n = 315)	500 IR (n = 296)	Placebo (n = 316)
Baseline	9.09 ± 2.04 (315)	9.04 ± 1.94 (296)	9.12 ± 2.02 (316)
Weeks 44-52	4.99 ± 2.42 (288)	5.23 ± 2.69 (276)	6.13 ± 2.77 (297)
Change from baseline	-4.12 ± 2.41 (288)	-3.75 ± 2.96 (276)	-3.02 ± 2.67 (297)
Difference from placebo group (95% confidence interval [CI]) [a], *P* value[a),b)]	-1.11 [-1.50, -0.72] *P* < 0.0001	-0.80 [-1.20, -0.40] *P* < 0.0001	

Mean ± standard deviation (SD) (number of subjects) was calculated among observed cases.
Observed cases mean patients in whom measurements needed for analysis were obtained without supplemental data for missing values.

a) A mixed effect model for repeated measures with an unstructured covariance structure for intrasubject analysis with the following explanatory variables: observation points, treatment groups, treatment group observation point interactions, baseline values, age, gender, autumn allergen multiple sensitization, rescue medication during a pre-treatment observation period, and previous medication of the primary disease.

b) Multiplicity adjustments were made by the Holm's method.

Table 7 shows the secondary efficacy endpoints.

Table 7. Secondary efficacy endpoints during the last 8 weeks of study (Weeks 44-52) (FAS)

	300 IR (n = 315)	500 IR (n = 296)	Placebo (n = 316)	Difference from placebo [95% CI][a)]	
				300 IR	500 IR
Mean total nasal symptom score	4.92 ± 2.35 (288)	5.13 ± 2.59 (276)	6.00 ± 2.67 (297)	-1.07 [-1.45, -0.69]	-0.78 [-1.16, -0.39]
Mean rescue medication score	0.03 ± 0.13 (288)	0.06 ± 0.20 (276)	0.07 ± 0.21 (297)	-0.03 [-0.06, 0.00]	-0.01 [-0.04, 0.02]
Mean combined score	0.63 ± 0.32 (288)	0.67 ± 0.37 (276)	0.78 ± 0.38 (297)	-0.15 [-0.20, -0.10]	-0.10 [-0.15, -0.05]
Mean ocular and nasal symptom score	6.38 ±3.34 (288)	6.68 ± 3.73 (276)	7.62 ± 3.71 (297)	-1.31 [-1.85, -0.77]	-0.88 [-1.43, -0.33]

Mean ± SD (number of subjects) was calculated among observed cases.
Observed cases mean patients with measurements needed for analysis without supplemental data for missing values.
Mean total nasal symptom score: A total daily score for paroxysmal sneeze, nasal discharge and nasal congestion (each scored on a scale of 0 to 4) and nasal pruritus (scored on a scale of 0 to 3) (minimum score, 0; maximum score, 15)
Mean rescue medication score: A total daily score for "no use of rescue medications (0)," "use of an oral or ophthalmic antihistamine alone (2)," "use of a nasal corticosteroid alone (2)," and "use of an oral or ophthalmic antihistamine plus a nasal corticosteroid (2)" (minimum score, 0; maximum score, 2)
Mean combined score: (Total nasal symptom score/4 + rescue medication score)/2 (minimum score, 0; maximum score, 2.875)
Mean ocular and nasal symptom score: A total daily score for paroxysmal sneeze, nasal discharge, nasal congestion, ocular pruritus, and lacrimation (each scored on a scale of 0 to 4) and nasal pruritus (scored on a scale of 0 to 3) (minimum score, 0; maximum score, 23)
a) See Note a) under Table 6.

Adverse events occurred in all groups: 284 of 322 patients (88.2%) in the 300 IR group, 294 of 324 patients (90.7%) in the 500 IR group, and 243 of 322 patients (75.5%) in the placebo group. Table 8 lists major adverse events. No deaths occurred. Serious adverse events occurred in 6 of 322 patients (1.9%) in the 300 IR group (appendicitis, gastroenteritis, bacterial pneumonia, cholelithiasis, hematuria, and induced abortion [1 patient each]), 5 of 324 patients (1.5%) in the 500 IR group (appendicitis/diverticulitis, coliform gastroenteritis, hepatitis B, inguinal hernia/cholelithiasis, and colonic polyp [1 patient each]), and 2 of 322 patients (0.6%) in the placebo group (forearm fracture and ligament injury [1 patient each]). All events were unrelated to the study drug. Adverse events leading to study discontinuation occurred in 14 of 322 patients (4.3%) in the 300 IR group, 29 of 324 patients (9.0%) in the 500 IR group, and 12 of 322 patients (3.7%) in the placebo group. A causal relationship to the study drug could not be ruled out for 7 patients in the 300 IR group (oedema mouth/wheezing/oral pain, cheilitis/cracked lip, urticaria, rash, gastrointestinal disorder, stomatitis, and upper abdominal pain [1 patient each]) and 21 patients in the 500 IR group (diarrhea, asthma, and abdominal pain [2 patients each] and upper abdominal pain, pharyngeal edema/upper abdominal pain, lip

swelling/dyspnoea/rash, abdominal discomfort, eczema, laryngeal edema, abdominal bloating/lip edema, palpitation, oedema mouth, chest pain/dyspnoea/nausea/dizziness, gastrointestinal disorder, gastroenteritis, lip edema/oedema mouth, indigestion, and dyspnea [1 patient each]).

Adverse drug reactions occurred in 215 of 322 patients (66.8%) in the 300 IR group, 237 of 324 patients (73.1%) in the 500 IR group, and 60 of 322 patients (18.6%) in the placebo group.

Table 8. Adverse events occurring at an incidence of ≥5% in any group (safety analysis set)

Events	300 IR (n = 322)	500 IR (n = 324)	Placebo (n = 322)
Nasopharyngitis	117 (36.3)	99 (30.6)	116 (36.0)
Oedema mouth	67 (20.8)	81 (25.0)	1 (0.3)
Throat irritation	67 (20.8)	66 (20.4)	12 (3.7)
Pharyngitis	55 (17.1)	60 (18.5)	58 (18.0)
Ear pruritus	45 (14.0)	44 (13.6)	3 (0.9)
Oral pruritus	36 (11.2)	51 (15.7)	7 (2.2)
Stomatitis	28 (8.7)	25 (7.7)	12 (3.7)
Gastroenteritis	20 (6.2)	21 (6.5)	17 (5.3)
Influenza	18 (5.6)	19 (5.9)	19 (5.9)
Acute sinusitis	18 (5.6)	18 (5.6)	20 (6.2)
Oropharingeal discomfort	17 (5.3)	23 (7.1)	4 (1.2)
Oral discomfort	14 (4.3)	20 (6.2)	4 (1.2)

n (%)

4.(i).A.(3) Foreign phase I study (5.3.5.1-05, Study VO36 [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled dose-escalation study was conducted to investigate the safety and tolerance of Actair in patients with house dust mite antigen-induced perennial allergic rhinitis[18] (target sample size, 32 patients [8 per step]).

Patients received Actair 100, 300, or 500 IR or placebo administered sublingually once daily for 10 days, as specified in Table 9.

Table 9. Doses for Study VO36

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Group 1	100	100	200	200	300	300	400	400	500	500
Group 2	100	200	300	400	500	500	500	500	500	500
Group 3	300	300	300	300	300	300	300	300	300	300
Group 4	500	500	500	500	500	500	500	500	500	500
Placebo[a)]	0	0	0	0	0	0	0	0	0	0

Unit, IR

a) Placebo group: Patients receiving placebo for each of the above dose groups (unless otherwise noted, the same applies below, main text included)

All 31 randomized patients (6 in Group 1, 6 in Group 2, 6 in Group 3, 5 in Group 4, and 8 in the placebo group) were included in the safety analysis. Some patients discontinued the study: 3 of 6 patients (50%) in Group 1, 1 of 6 patients (16.7%) in Group 2, 0 of 6 patients (0%) in Group 3, 3 of 5 patients (60%) in Group 4, and 3 of 8 patients (37.5%) in the placebo group. The reason for discontinuation was adverse events in all patients.

[18] Patients with perennial allergic rhinitis who met all of the following criteria: (a) 18-50 years old; (b) disease duration of ≥2 years; (c) positive prick tests for *D. pteronyssinus* or *D. farinae*; (d) positive results for *D. pteronyssinus*- or *D. farinae*-specific IgE antibodies

Adverse events occurred in all 6 patients (100%) in Group 1, all 6 patients (100%) in Group 2 (100%), all 6 patients (100%) in Group 3, all 5 patients (100%) in Group 4, and 4 of 8 patients (50.0%) in the placebo group. Table 10 lists adverse events occurring in ≥2 patients in any group. No deaths or serious adverse events occurred. Adverse events leading to study discontinuation occurred in 3 of 6 patients (50.0%) in Group 1, 1 of 6 patients (16.7%) in Group 2, 3 of 5 patients (60.0%) in Group 4, and 3 of 8 patients (37.5%) in the placebo group. A causal relationship to the study drug could not be ruled out for 1 patient in Group 2 (urticaria), 3 patients in Group 4 (facial edema in 2 patients and diarrhea in 1 patient), and 2 patients in the placebo group (decreased forced expiratory flow and asthma in 1 patient each).

Adverse drug reactions occurred in all 6 patients (100%) in Group 1, all 6 patients (100%) in Group 2, all 6 patients (100%) in Group 3, all 5 patients (100%) in Group 4, and 2 of 8 patients (25.0%) in the placebo group.

Table 10. Adverse events occurring in ≥2 patients in any group (safety analysis set)

Events	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)	Group 4 (n = 5)	Placebo (n = 8)
Oral pruritus	5 (83.3)	4 (66.7)	6 (100)	5 (100)	0
Throat irritation	4 (66.7)	2 (33.3)	5 (83.3)	2 (40.0)	1 (12.5)
Lip blister	0	3 (50.0)	0	0	0
Ear pruritus	2 (33.3)	2 (33.3)	2 (33.3)	2 (40.0)	0
Headache	2 (33.3)	1 (16.7)	1 (16.7)	0	2 (25.0)
Tongue blister	2 (33.3)	0	2 (33.3)	2 (40.0)	0
Gingival pruritus	0	0	3 (50.0)	1 (20.0)	0
Abdominal pain	0	0	0	2 (40.0)	0
Chest pain	0	0	1 (16.7)	3 (60.0)	1 (12.5)
Tongue edema	0	0	0	3 (60.0)	0
Ocular pruritus	2 (33.3)	0	0	0	0
Laryngeal discomfort	0	2 (33.3)	0	0	0
Facial edema	0	0	0	2 (40.0)	0

n (%)

The applicant explained as follows:

As compared with the other groups, Groups 3 and 4 (the groups without dose escalation) showed an increased number of adverse events on Day 1, or an increased number of patients who discontinued the study due to adverse drug reactions. Based on this, the dose for the 300 IR group should be initiated at 100 IR and increased by 100 IR daily up to 300 IR, and the dose for the 500 IR group should be initiated at 100 IR and increased by 100 IR every other day up to 500 IR.

4.(i).A.(4) Foreign phase II study (5.3.5.1-04, Study VO67 [20 to September 2012])

A randomized, double-blind, placebo-controlled parallel-group study was conducted to investigate the efficacy and safety of Actair in patients with house dust mite antigen-induced perennial allergic rhinitis,[19] using an antigen exposure room (target sample size, 336 patients [84 per group]).

[19] Patients with perennial allergic rhinitis who met all of the following criteria: (a) 18-55 years old; (b) disease duration of ≥1 year; (c) positive prick tests for *D. pteronyssinus* or *D. farinae* (wheal diameters ≥3 mm larger than negative control); (d) ≥0.7 kU/L of *D. pteronyssinus*- or *D. farinae*-specific IgE antibodies; (e) a total score for 4 nasal symptoms (nasal discharge, nasal congestion, nasal pruritus, and paroxysmal sneeze) of ≥ 6 points at ≥2 time points following 4-hour exposure to mite antigens at baseline (Visit 2)

As specified in Table 11, patients received Actair 100, 300, or 500 IR or placebo administered sublingually once daily before breakfast for 6 months. The patients were instructed to swallow the study drug after holding it under the tongue until it completely dissolved.

Table 11. Doses for Study VO67

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10 to Month 6
100 IR	100	100	100	100	100	100	100	100	100	100
300 IR	100	200	300	300	300	300	300	300	300	300
500 IR	100	100	200	200	300	300	400	400	500	500
Placebo	0	0	0	0	0	0	0	0	0	0

Unit, IR

All 355 randomized patients (89 in the 100 IR group, 86 in the 300 IR group, 93 in the 500 IR group, and 87 in the placebo group) were included in the FAS, safety analysis, and efficacy analysis. Some patients discontinued the study: 14 of 89 patients in the 100 IR group (15.7%), 18 of 86 patients in the 300 IR group (20.9%), 23 of 93 patients in the 500 IR group (24.7%), and 12 of 87 patients in the placebo group (13.8%). The most common reason for discontinuation was adverse events: 5 of 89 patients in the 100 IR group (5.6%), 5 of 86 patients in the 300 IR group (5.8%), and 11 of 93 patients in the 500 IR group (11.8%).

The primary efficacy endpoint was change in the area under time curve[20] of total nasal symptom scores[21] from baseline (0-4 hours of antigen exposure before the start of administration) to 6 months after the initiation of administration (0-4 hours of antigen exposure). Statistically significant differences were found between the 500 IR and placebo groups but not between the placebo group and the 100 or 300 IR group.

Table 12. Change from baseline to 6 months in the area under time curve of total nasal symptom scores (0-4 hours of antigen exposure) (FAS, LOCF)

	100 IR	300 IR	500 IR	Placebo
Baseline	1680.42 ± 457.82 (89)	1672.15 ± 522.21 (86)	1602.50 ± 497.62 (93)	1753.18 ± 576.91 (87)
At 6 months	960.60 ± 594.24 (75)	918.97 ± 608.25 (68)	851.04 ± 598.95 (70)	1104.60 ± 637.30 (75)
Change from baseline	-711.89 ± 628.47 (75)	-786.40 ± 621.42 (68)	-738.11 ± 689.82 (70)	-639.39 ± 729.70 (75)
Difference from placebo [95% CI][a], *P* value[a) b)]	-118.43 [-305.90, 69.04] -	-171.82 [-363.87, 20.24] *P* = 0.0793	-198.18 [-389.82, -6.55] *P* = 0.0427	

Mean ± SD (number of subjects)

a) Covariance analysis with treatment groups and baseline values as explanatory variables

b) Multiplicity adjustments were made by a step-down method whereby the 500 IR and placebo groups were compared first, the 300 IR and placebo groups compared next, and the 100 IR and placebo groups compared last.

Adverse events occurred in 86 of 89 patients (96.6%) in the 100 IR group, 78 of 86 patients (90.7%) in the 300 IR group, 87 of 93 patients (93.5%) in the 500 IR group, and 72 of 87 patients (82.8%) in the placebo group. Table 13 shows major adverse events. No deaths occurred. Serious adverse events

[20] During the 4 hours of antigen exposure, total nasal symptom score was recorded every 15 minutes for the first 2 hours and every 30 minutes for the last 2 hours. The area under time curve at each time point was calculated from the recorded scores.

[21] Total nasal symptom score is the sum of the scores of 4 nasal symptoms (nasal discharge, nasal congestion, nasal pruritus, and paroxysmal sneeze [each scored on a scale of 0 to 3]).

occurred in 1 of 89 patients (1.1%) in the 100 IR group (nephrolithiasis), 1 of 86 patients (1.2%) in the 300 IR group (schizoaffective disorder), 2 of 93 patients (2.2%) in the 500 IR group (meningitis and convulsion [1 patient each]). A causal relationship to the study drug was ruled out for all events. Adverse events leading to study discontinuation occurred in 4 of 89 patients (4.5%) in the 100 IR group, 5 of 86 patients (5.8%) in the 300 IR group, and 11 of 93 patients (11.8%) in the 500 IR group. A causal relationship to the study drug could not be ruled out for 3 patients in the 100 IR group (pharyngeal edema, asthma, and oral pruritus [1 patient each]), 3 patients in the 300 IR group (nausea/vomiting, chest pain, and lip edema/lip blister [1 patient each]), and 6 patients in the 500 IR group (oedema mouth [2 patients], and pharyngeal edema/tongue edema/oedema mouth, vomiting, indigestion/headache, and dyspnoea/cough [1 patient each]).

Adverse drug reactions occurred in 60 of 89 patients (67.4%) in the 100 IR group, 59 of 86 patients (68.6%) in the 300 IR group, 66 of 93 patients (71.0%) in the 500 IR group, and 38 of 87 patients (43.7%) in the placebo group.

Table 13. Adverse events with an incidence of ≥5% in any group (safety analysis set)

Events	100 IR (n = 89)	300 IR (n = 86)	500 IR (n = 93)	Placebo (n = 87)
Bronchospasm	30 (33.7)	18 (20.9)	20 (21.5)	26 (29.9)
Headache	29 (32.6)	22 (25.6)	29 (31.2)	38 (43.7)
Throat irritation	28 (31.5)	32 (37.2)	37 (39.8)	12 (13.8)
Upper respiratory infection	28 (31.5)	28 (32.6)	26 (28.0)	34 (39.1)
Oral pruritus	23 (25.8)	30 (34.9)	29 (31.2)	7 (8.0)
Ear pruritus	19 (21.3)	21 (24.4)	23 (24.7)	8 (9.2)
Oedema mouth	16 (18.0)	19 (22.1)	20 (21.5)	0
Cough	16 (18.0)	11 (12.8)	7 (7.5)	12 (13.8)
Nausea	12 (13.5)	8 (9.3)	7 (7.5)	4 (4.6)
Oropharingeal pain	7 (7.9)	7 (8.1)	8 (8.6)	5 (5.7)
Decreased forced expiratory flow	7 (7.9)	7 (8.1)	4 (4.3)	4 (4.6)
Ocular pruritus	7 (7.9)	4 (4.7)	6 (6.5)	6 (6.9)
Indigestion	7 (7.9)	4 (4.7)	4 (4.3)	0
Chest discomfort	7 (7.9)	4 (4.7)	3 (3.2)	3 (3.4)
Dyspnoea	6 (6.7)	3 (3.5)	13 (14.0)	7 (8.0)
Vomiting	6 (6.7)	3 (3.5)	3 (3.2)	2 (2.3)
Gastroesophageal reflux disease	5 (5.6)	3(3.5)	0	1 (1.1)
Pyrexia	5 (5.6)	1 (1.2)	1 (1.1)	0
Oral hypoesthesia	5 (5.6)	1 (1.2)	1 (1.1)	2 (2.3)
Diarrhea	4 (4.5)	5 (5.8)	5 (5.4)	1 (1.1)
Fatigue	4 (4.5)	5 (5.8)	1 (1.1)	3 (3.4)
Myalgia	4 (4.5)	2 (2.3)	4 (4.3)	5 (5.7)
Dry mouth	3 (3.4)	5 (5.8)	1 (1.1)	2 (2.3)
Lip pruritus	3 (3.4)	4 (4.7)	5 (5.4)	0
Mouth paresthesia	3 (3.4)	3 (3.5)	6 (6.5)	1 (1.1)
Pruritus	3 (3.4)	3 (3.5)	2 (2.2)	6 (6.9)
Pharyngitis	3 (3.4)	2 (2.3)	9 (9.7)	2 (2.3)
Rhinorrhea	3 (3.4)	1 (1.2)	1 (1.1)	5 (5.7)
Nasal congestion	2 (2.2)	6 (7.0)	5 (5.4)	3 (3.4)
Systemic pruritus	2 (2.2)	2 (2.3)	1 (1.1)	5 (5.7)
Lip edema	1 (1.1)	3 (3.5)	9 (9.7)	0
Aphthous stomatitis	1 (1.1)	3 (3.5)	5 (5.4)	1 (1.1)

n (%)

The applicant explained as follows:

The change from baseline to 6 months in the area under time curve of total nasal symptom scores (the primary endpoint) was smaller in the 100 IR group than in the 300 or 500 IR group, suggesting that the

100 IR dose did not sufficiently improve the symptoms. The Japanese phase II/III study (Study D1731) therefore investigated the efficacy of the 300 and 500 IR doses.

4.(i).A.(5) Foreign phase II/III study (5.3.5.1-03, Study VO57 [2007 to February 2010])

A randomized, double-blind, placebo-controlled parallel-group study was conducted to investigate the efficacy and safety of Actair in patients with house dust mite antigen-induced perennial allergic rhinitis[22] (target sample size, 486 patients [162 per group]).

Patients received Actair 300 or 500 IR or placebo administered sublingually once daily for 12 months (treatment period), as specified in Table 14. The patients were instructed to swallow the study drug after holding it under the tongue until it completely dissolved. To investigate the persistence of efficacy following the completion of treatment, patients underwent a 12-month post-treatment blind observation period after the completion of treatment. Rescue medications were administered when symptoms of perennial allergic rhinitis worsened: (1) The first step was administration of an oral or ophthalmic antihistamine (oral, cetirizine hydrochloride or loratadine; ophthalmic, levocabastine hydrochloride). (2) The second step was administration of nasal corticosteroid spray (mometasone furoate) to patients unresponsive to the first step therapy without improvement in symptoms. (3) The third step was administration of an oral corticosteroid (prednisone or prednisolone) to patients unresponsive to the second step therapy without improvement in symptoms, in consultation with physician.

Table 14. Doses for Study VO57

Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10 to Month 12
300 IR	100	200	300	300	300	300	300	300	300	300
500 IR	100	100	200	200	300	300	400	400	500	500
Placebo	0	0	0	0	0	0	0	0	0	0

Unit, IR; Days 1-8, dose escalation period; Day 9 to Month 12, dose maintenance period

An analysis set was established for both the treatment period and the post-treatment observation period. All 509 randomized patients (170 in the 300 IR group, 169 in the 500 IR group, and 170 in the placebo group) were included in the safety analysis for the treatment period. Of the 509 patients, 466 patients (153 in the 300 IR group, 150 in the 500 IR group, and 163 in the placebo group) were included in the efficacy analysis and FAS for the treatment period. Excluded were 43 patients who discontinued the study because of adverse events or other reasons and had no patient diary[23] records for the treatment period. All of the 427 patients who completed the treatment period (139 in the 300 IR group, 135 in the 500 IR group, and 153 in the placebo group) were included in the safety analysis for the post-treatment observation period. Of the 427 patients, 412 patients (134 in the 300 IR group, 132 in the 500 IR group, and 146 in the placebo group) were included in the efficacy analysis and FAS for the post-treatment observation period. Excluded were 15 patients without patient diary records for the post-treatment observation period. Some patients discontinued the study during the treatment period: 31 of 170 patients

[22] Patients with perennial allergic rhinitis who met all of the following criteria: (a) 18-50 years old; (b) disease duration of ≥1 year; (c) positive prick tests for *D. pteronyssinus* and/or *D. farinae* (wheal diameters of ≥3 mm); (d) ≥0.7 kU/L of *D. pteronyssinus*- and/or *D. farinae*-specific IgE antibodies; (e) mean total nasal symptom score of ≥5 during the 7-day baseline period.

[23] Patients scored each of paroxysmal sneeze, nasal discharge, nasal congestion, and nasal pruritus on a scale of 0 to 3 (4 grades) and recorded the scores.

(18.2%) in the 300 IR group, 34 of 169 patients (20.1%) in the 500 IR group, and 17 of 170 patients (10.0%) in the placebo group. The most common reason for discontinuation was adverse events: 17 of 170 patients (10.0%) in the 300 IR group, 20 of 169 patients (11.8%) in the 500 IR group, and 5 of 170 patients (2.9%) in the placebo group. Some patients discontinued the study during the post-treatment observation period: 6 of 139 patients (4.3%) in the 300 IR group, 12 of 135 patients (8.9%) in the 500 IR group, and 12 of 153 patients (7.8%) in the placebo group. The most common reason for discontinuation was consent withdrawal: 1 of 139 patients (0.7%) in the 300 IR group, 1 of 135 patients (0.7%) in the 500 IR group, and 4 of 153 patients (2.6%) in the placebo group.

Since symptoms of perennial allergic rhinitis are known to worsen generally in autumn, the primary endpoint was assessed over the 3-month period from October 1 to December 31.

Table 15 shows the results of the primary efficacy endpoint, i.e., mean adjusted nasal symptom scores[17] for the last 3 months of the treatment period. Statistically significant differences were found between the placebo group and the 300 or 500 IR group, showing the superiority of 300 and 500 IR over placebo. Table 15 also lists mean adjusted nasal symptom scores for the last 3 months of the post-treatment observation period.

Table 15. Mean adjusted nasal symptom scores for the last 3 months of post-treatment observation period (FAS, OC)

Treantment period FAS (primary endpoint)	300 IR (n = 153)	500 IR (n = 150)	Placebo (n = 163)
Baseline	6.93 ± 1.51	7.24 ± 1.66	6.79 ± 1.48
Last 3 months	3.14 ± 2.48	3.21 ± 2.40	3.81 ± 2.68
Change from baseline	-3.79 ± 2.32	-4.03 ± 2.62	-2.97 ± 2.80
Difference from placebo group [95% CI][a], *P* value[a) b)]	-0.69 [-1.25, -0.14] *P* = 0.0150	-0.78 [-1.34, -0.22] *P* = 0.0066	
Post-treatment observation period FAS	300 IR (n = 134)	500 IR (n = 132)	Placebo (n = 146)
Baseline	6.97 ± 1.52	7.23 ± 1.68	6.80 ± 1.50
Last 3 months	3.15 ± 2.37	3.09 ± 2.49	3.67 ± 2.63
Change from baseline	-3.82 ± 2.37	-4.13 ± 2.67	-3.12 ± 2.80
Difference from placebo group [95% CI][a)]	-0.62 [-1.20, -0.05]	-0.70 [-1.29, -0.11]	

Mean ± SD

a) Covariance analysis with treatment groups, center groups, age, gender, baseline values, asthma, and multiple sensitization as explanatory variables

b) Multiplicity adjustments were made by a step-down method whereby the 500 IR and placebo groups were compared first and the 300 IR and placebo groups compared next.

During the treatment period, adverse events occurred in 150 of 170 patients (88.2%) in the 300 IR group, 141 of 169 patients (83.4%) in the 500 IR group, and 136 of 170 patients (80.0%) in the placebo group. Table 16 summarizes the adverse events. No deaths occurred. Serious adverse events occurred in 6 of 170 patients (3.5%) in the 300 IR group (metrorrhagia, vaginal tear, pharyngeal edema, eczema, tubo-ovarian abscess, and injury/traffic accident [1 patient each]), 1 of 169 patients (0.6%) in the 500 IR group (respiratory distress), and 2 of 170 patients (1.2%) in the placebo group (urticaria and pituitary tumor [1 patient each]). A causal relationship to the study drug could not be ruled out for 2 patients in the 300 IR group (eczema and pharyngeal edema [1 patient each]), 1 patient in the 500 IR group (respiratory distress), and 1 patient in the placebo group (urticaria). Adverse events leading to study discontinuation were reported by 17 of 170 patients (10.0%) in the 300 IR group, 20 of 169 patients

(11.8%) in the 500 IR group, and 5 of 170 patients (2.9%) in the placebo group. A causal relationship to the study drug could not be ruled out for 14 patients in the 300 IR group (nausea, oral mucosa blister, and pharyngeal edema [2 patients each] and anxiety, oral pruritus, throat irritation, stomatitis/oedema mouth, tongue swelling, indigestion, laryngeal pain, and oedema mouth [1 patient each]), 18 patients in the 500 IR group (pharyngeal edema and indigestion [2 patients each] and abdominal pain, nausea, tongue swelling, esophageal discomfort, hypotension, laryngeal irritation, oedema mouth, asthma, rash, angina, respiratory distress, chest discomfort, headache, and acute sinusitis [1 patient each]), and 2 patients in the placebo group (nausea and urticarial [1 patient each]).

During the treatment period, adverse drug reactions occurred in 111 of 170 patients (65.3%) in the 300 IR group, 110 of 169 patients (65.1%) in the 500 IR group, and 38 of 170 patients (22.4%) in the placebo group.

Table 16. Adverse events with an incidence of ≥5% in any group (safety analysis set for treatment period)

Events	300 IR (n = 170)	500 IR (n = 169)	Placebo (n = 170)
Oral pruritus	51 (30.0)	43 (25.4)	8 (4.7)
Throat irritation	42 (24.7)	36 (21.3)	7 (4.1)
Nasopharyngitis	28 (16.5)	23 (13.6)	39 (22.9)
Headache	23 (13.5)	24 (14.2)	33 (19.4)
Oedema mouth	21 (12.4)	28 (16.6)	1 (0.6)
Pharyngitis	17 (10.0)	10 (5.9)	19 (11.2)
Influenza	15 (8.8)	14 (8.3)	16 (9.4)
Upper respiratory infection	11 (6.5)	5 (3.0)	9 (5.3)
Dyspnoea	9 (5.3)	2 (1.2)	6 (3.5)
Cough	7 (4.1)	16 (9.5)	18 (10.6)
Pharyngeal edema	6 (3.5)	11 (6.5)	0
Pharyngolaryngeal pain	6 (3.5)	7 (4.1)	12 (7.1)
Ear pruritus	4 (2.4)	13 (7.7)	1 (0.6)
Asthma	4 (2.4)	10 (5.9)	10 (5.9)
Eczema	4 (2.4)	3 (1.8)	9 (5.3)
Pyrexia	4 (2.4)	1 (0.6)	10 (5.9)

n (%)

The applicant's explanation:

The mean adjusted nasal symptom scores in Study VO57 during the last 3 months of the post-treatment observation period were better in the 300 and 500 IR groups than in the placebo group. Thus, the efficacy of Actair would persist for at least 1 year after the completion of treatment.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Efficacy

The applicant explained the efficacy of Actair as follows:

No established indicator exists for assessing the efficacy of desensitization therapy for allergic rhinitis. Clinical studies of desensitization therapy generally allow the use of rescue medications. According to European clinical development guidelines for allergen extract products, primary endpoints reflect the severity of symptoms and the use of rescue medications (Guidelines on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. EMEA CHMP/EWP/18504/2006, London, 20 November 2008). The primary endpoint for the Japanese phase II/III study (Study D1731) was therefore adjusted nasal symptom score, i.e., total nasal symptom score

(paroxysmal sneeze, nasal discharge, nasal congestion, and nasal pruritus) adjusted for the use of rescue medications. The half-life of rescue medications and other data suggest that rescue medications may impact total nasal symptom scores on the day and the day after administration. Thus total nasal symptom scores were adjusted, as described below. The conditions for use were defined to minimize differences in the use of rescue medications among the patients [see "4.(i).A.(2) Japanese phase II/III study"].

- When no rescue medications were administered, adjusted nasal symptom score was considered the same as total nasal symptom score.
- When rescue medications were administered, adjusted nasal symptom score on the day of rescue medication was determined to be the higher score of either "adjusted nasal symptom score on the day before rescue medication" or "total nasal symptom scores on the day of rescue medication", and adjusted nasal symptom score on the day after rescue medication was determined to be the higher score of either "adjusted nasal symptom score on the day of rescue medication" or "total nasal symptom score on the day after rescue medication."

A combined score in terms of symptom and rescue medication has been used as an assessment indicator reflecting the severity of symptoms and the use of rescue medications. However, adjusted nasal symptom score would be more appropriate because the combined score raises a concern about unbalanced scoring between symptom and rescue medication.

In the Japanese phase II/III study (Study D1731), statistically significant differences were found in mean adjusted symptom scores from Week 44 to Week 52 of administration between the placebo group and the 300 IR or 500 IR group. The foreign phase II/III study (Study VO57) demonstrated the superiority of Actair 300 and 500 IR over placebo in mean adjusted nasal symptom score, indicating the efficacy of Actair 300 and 500 IR in alleviating symptoms of allergic rhinitis. Both the Japanese and foreign phase II/III studies showed that 300 IR was comparable or superior to 500 IR in efficacy, suggesting that the efficacy of Actair generally reaches a plateau at 300 IR and above.

PMDA's conclusion on the efficacy of Actair:
Adjusted nasal symptom score, the primary endpoint of the Japanese phase II/III study (Study D1731), is not an established efficacy endpoint of desensitization therapy for allergic rhinitis. However, symptom scores, a component of adjusted nasal symptom score, have been a common indicator to assess the efficacy of treatment for allergic rhinitis. Additionally, the adopted method for adjusting total nasal symptom scores based on rescue medications is rational. Consequently, the efficacy of Actair may be adequately assessed based on this primary endpoint.

The Japanese phase II/III study (Study D1731) demonstrated the superiority of Actair 300 and 500 IR over placebo in adjusted nasal symptom score. As a secondary endpoint, the study used combined score of symptom and rescue medication (combined score has been used as primary endpoint in clinical studies of similar drug products). The secondary endpoint showed a trend similar to that for the primary

endpoint. The foreign phase II/III study (Study VO57) also demonstrated similar results. PMDA thus concluded that Actair 300 or 500 IR is effective in alleviating symptoms of allergic rhinitis.

4.(i).B.(2) Safety

The applicant explained adverse events considered to be mite antigen-induced allergic reactions, based on the combined data of the Japanese phase II/II study (Study D1731) and the foreign phase II/III study (Study VO57), as follows:

No deaths, anaphylaxis, or anaphylactic shock occurred in the clinical studies of Actair. The incidence of serious adverse events was 2.4% (12 of 492 patients) in the 300 IR group, 1.2% (6 of 493 patients) in the 500 IR group, and 0.8% (4 of 492 patients) in the placebo group. No marked differences were found between the Actair and placebo groups.

Table 17 summarizes the incidence of adverse events considered to be mite antigen-induced allergic reaction[24] based on the combined data of Japanese phase II/II study (Study D1731) and the foreign phase II/III study (Study VO57). Common mite antigen-induced allergic reactions were localized adverse reactions, including throat irritation (22.2% [109 of 492 patients] in the 300 IR group, 20.7% [102 of 493 patients] in the 500 IR group, and 3.9% [19 of 492 patients] in the placebo group), oedema mouth (17.9% [88 of 492 patients] in the 300 IR group, 22.1% [109 of 493 patients] in the 500 IR group, and 0.4% [2 of 492 patients] in the placebo group), and oral pruritus (17.7% [87 of 492 patients] in the 300 IR group, 19.1% [94 of 493 patients] in the 500 IR group, and 3.0% [15 of 492 patients] in the placebo group); and gastrointestinal adverse events, including gastroenteritis (5.1% [25 of 492 patients] in the 300 IR group, 5.5% [27 of 493 patients] in the 500 IR group, and 4.7% [23 of 492 patients] in the placebo group) and nausea (3.0% [15 of 492 patients] in the 300 IR group, 3.0% [15 of 493 patients] in the 500 IR group, and 1.4% [7 of 492 patients] in the placebo group). In all groups, the incidence of adverse events considered to be mite antigen-induced allergic reactions was higher during Weeks 1 and 2 than during Week 3 or later, with a particularly high incidence on Day 1 during Weeks 1 and 2.

[24] Atopic dermatitis, aphthous stomatitis, allergic cough, sneezing, pruritus, erosive gastritis, erosive esophagitis, hot flush, lymphadenitis, lymphedema, nausea, foreign body sensation, gastritis, gastroenteritis, gastrointestinal disorder, dry throat, throat tightness, throat irritation, pharyngeal inflammation, pharyngitis, pharyngeal hypoesthesia, pharyngeal erythema, pharyngeal dysesthesia, pharyngeal edema, diarrhea, cough, ocular pruritus, abnormal sensation in the eye, eye discomfort, eyelid edema, facial edema, elevated bronchial reactivity, bronchial obstruction, chest pain, chest discomfort, localized swelling, angioedema, respiratory distress, dyspnoea, flatulence, oral hypoesthesia, mouth paresthesia, palatal edema, thirst, oral pruritus, oropharingeal plaque, oropharingeal pain, oropharingeal discomfort, mouth hemorrhage, oral pain, mouth ulceration, oral discomfort, oral mucosa erosion, oral mucosa erythema, oral enanthema, oral mucosa blister, oedema mouth, lip pruritus, cracked lip, cheilitis, lip swelling, lip edema, stomatitis, dry mouth, laryngeal inflammation, laryngitis, laryngeal irritation, dyspnoea due to laryngeal disorder, laryngeal pain, laryngeal discomfort, laryngeal edema, erythema, pericoronitis, periodontitis, gingival pruritus, gingivitis, gingival pain, gingival edema, ear pruritus, ear pain, ear discomfort, eczema, duodenitis, indigestion, upper airway cough, upper abdominal pain, esophageal irritation, esophageal pain, esophageal discomfort, decreased appetite, blister, tongue pruritus, glossitis, swollen tongue, glossalgia, tongue ulcer, tongue edema, systemic pruritus, feeling of suffocation, erythema multiforme, sialitis, enlarged salivary gland, hyperesthesia, perennial allergy, perennial rhinitis, hypotension, palpitations, feeling hot, mucosal edema, reduced bowel movements, increased bowel movements, rash, voice disorder, pyrexia, rhinitis, nasal discomfort, nasal congestion, nasal obstruction, rhinorrhoea, tachycardia, abdominal pain, abdominal discomfort, abdominal bloating, irregular bowel movement, buccal mucosa roughness, taste abnormality, increased lacrimation, salivary hypersecretion, asthma, wheezing, vomiting, dysphagia, painful swallowing, prurigo, and urticaria

Table 17. Adverse events considered to be mite antigen-induced allergic reactions (combined data from Studies D1731 and VO57)

	Groups	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Days 9-14	Weeks 1-2	Weeks 3-4	Weeks 3-52
Dose	300 IR	100	200	300	300	300	300	300	300	300	100 → 300	300	300
	500 IR	100	100	200	200	300	300	400	400	500	100 → 500	500	500
	Placebo	0	0	0	0	0	0	0	0	0	0	0	0
Number of subjects	300 IR	492	492	492	491	491	491	491	491	489	492	488	488
	500 IR	493	492	492	492	491	491	491	491	488	493	481	481
	Placebo	492	492	491	491	491	490	490	490	487	492	487	487
Adverse events	300 IR	145 (29.5)	45 (9.1)	14 (2.8)	15 (3.1)	18 (3.7)	14 (2.9)	17 (3.5)	14 (2.9)	95 (19.4)	277 (56.3)	61 (12.5)	230 (47.1)
	500 IR	151 (30.6)	39 (7.9)	9 (1.8)	11 (2.2)	20 (4.1)	16 (3.3)	19 (3.9)	25 (5.1)	106 (21.7)	284 (57.6)	95 (19.8)	257 (53.4)
	Placebo	23 (4.7)	9 (1.8)	5 (1.0)	4 (0.8)	7 (1.4)	7 (1.4)	6 (1.2)	4 (0.8)	20 (4.1)	79 (16.1)	32 (6.6)	204 (41.9)
Serious adverse events	300 IR	0	0	0	0	0	0	0	0	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.4)
	500 IR	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)
	Placebo	0	0	0	0	0	0	0	0	0	0	0	1 (0.2)
Events leading to study discontinuation	300 IR	3 (0.6)	0	1 (0.2)	0	1 (0.2)	0	3 (0.6)	0	6 (1.2)	14 (2.8)	2 (0.4)	8 (1.6)
	500 IR	2 (0.4)	2 (0.4)	0	0	0	1 (0.2)	1 (0.2)	2 (0.4)	12 (2.5)	19 (3.9)	13 (2.7)	20 (4.2)
	Placebo	0	0	0	0	0	0	0	0	2 (0.4)	2 (0.4)	0	4 (0.8)
Adverse drug reactions	300 IR	144 (29.3)	44 (8.9)	12 (2.4)	13 (2.6)	14 (2.9)	12 (2.4)	16 (3.3)	14 (2.9)	89 (18.2)	270 (54.9)	50 (10.2)	128 (26.2)
	500 IR	151 (30.6)	39 (7.9)	9 (1.8)	10 (2.0)	17 (3.5)	13 (2.6)	17 (3.5)	23 (4.7)	98 (20.1)	276 (56.0)	81 (16.8)	152 (31.6)
	Placebo	21 (4.3)	9 (1.8)	4 (0.8)	3 (0.6)	3 (0.6)	5 (1.0)	5 (1.0)	2 (0.4)	10 (2.1)	58 (11.8)	7 (1.4)	40 (8.2)

n (%)

The combined data on adverse events considered to be mite antigen-induced allergic reactions showed no marked difference in the incidence of adverse events leading to study discontinuation between the 300 and 500 IR groups. However, the Japanese phase II/III study (Study D1731) demonstrated that the incidence of events leading to study discontinuation was higher in the 500 IR than in the 300 IR group (2.5% [8 of 322 patients] in the 300 IR group, 7.1% [23 of 324 patients] in the 500 IR group, and 0.9% [3 of 322 patients] in the placebo group). Furthermore, the incidence of "events requiring emergency treatment," as defined by the protocol of the Japanese phase II/III study (Study D1731),[25] was 1.9% (6 of 322 patients) in the 300 IR group, 3.7% (12 of 324 patients) in the 500 IR group, and 0.3% (1 of 322 patients) in the placebo group. The incidence of such adverse events during Weeks 1 and 2 was higher in the 500 IR group than in the other groups (0.6% [2 of 322 patients] in the 300 IR group, 3.1% [10 of 324 patients] in the 500 IR group, and 0% [0 of 322 patients] in the placebo group). The most common "adverse events requiring emergency treatment" were dyspnoea (0% [0 of 322 patients] in the 300 IR group, 1.2% [4 of 324 patients] in the 500 IR group, and 0% [0 of 322 patients] in the placebo group). These events eventually resolved. A causal relationship to the study drug could not be ruled out for any of them.

[25] Included were patients with skin symptoms (systemic dermal pruritus, erythema, or urticaria), respiratory symptoms (dyspnoea), ocular symptoms (visual abnormality), cardiovascular symptoms (palpitations, cold sweat), neurotic symptoms (disturbed consciousness), gastrointestinal symptoms (severe abdominal pain, diarrhea), patients with symptoms similar to these symptoms, and patients with these symptoms that required rescue medications (antihistamines and corticosteroids).

The above data suggests that Actair has an acceptable tolerability. The Japanese phase II/III study (Study D1731) showed that 300 IR was superior to 500 IR in safety. Actair may cause adverse events at the administration site or in the gastrointestinal tract. These adverse events will be mentioned in the package insert so that patients and healthcare professionals can be cautioned against the events.

PMDA considers as follows:
No anaphylaxis occurred in the clinical studies. In the post-marketing setting, however, anaphylaxis may occur in patients receiving Actair, for the following reasons: (1) In the clinical studies, patients receiving Actair showed higher incidences of adverse events considered to be mite antigen-induced allergic reactions than those receiving placebo. (2) The adverse events included symptoms that may be a predictor of anaphylaxis, such as dermal and respiratory symptoms. (3) Allergens are administered directly to patients on Actair therapy.

PMDA asked the applicant to explain the risk of anaphylaxis following SLIT based on data including the literature and to describe post-marketing safety measures for anaphylaxis.

The applicant explained as follows:
A total of 66 studies of SLIT demonstrated that the incidence of adverse events ranged from 12% to 21%, with the incidence of systemic reactions being 0.054% (169 of 314,959 injections) (Cox LS et al. *J Allergy Clin Immunol*. 2006;117:1021-1035). SLIT caused mild local reactions on the oral mucosa in 40% to 75% of patients and induced anaphylaxis in 11 patients (Calderon MA et al. *Allergy*. 2012;67:302-311). However, no deaths have been reported in these articles. On the other hand, SCIT has been reported to result in 1 death in every 2 to 2.5 million injections (Reid MJ et al. *J Allergy Clin Immunol*. 1993;92:6-15 and Bernstein DI et al. *J Allergy Clin Immunol*. 2004;113:1129-1136) and 1 case of systemic reaction including anaphylaxis in every 500 to 1000 injections (0.1%-0.2%) (Rank MA *et al*, *J Allergy Clin Immunol Pract.* 2014;2:131-135). SLIT and SCIT thus differ in safety in terms of fatal adverse drug reactions.

Safety measures against anaphylaxis proposed by the applicant:

- The warnings section of the package insert will include the following statements: (1) Actair should be used under the supervision of a physician with adequate knowledge of Actair and expertise and experience in desensitization therapy who belong to a medical institution capable of appropriately handling emergencies and who can instruct patients on the proper use of Actair. (2) Pharmacists should dispense Actair only after confirming that Actair has been prescribed by a qualified physician who meets the above requirements.
- In the clinical studies, adverse events occurred most frequently on Day 1 of administration. The Practical Guideline for the Management of Allergic Rhinitis 2013 recommends that patients be monitored for 20 to 30 minutes after the administration of SCIT. Therefore patients should receive the initial dose of Actair under the eye of a physician in a medical institution, and should be monitored for ≥ 30 minutes after the administration.

- Physicians will be instructed to avoid readministration of Actair to patients who experienced shock associated with Actair, because readministration may cause shock or anaphylaxis attributable to the nature of desensitization therapy.
- The package insert will indicate that Actair should be administered only after providing appropriate information to and obtaining consent from patients, on the risks of adverse drug reactions due to allergic reactions, anaphylaxis in particular, and on actions to be taken in the event of adverse drug reactions. Educational materials for physicians will explain symptoms that predict anaphylaxis and treatment for anaphylaxis. Educational materials for patients will instruct them to promptly visit a medical institution in the event of anaphylaxis, including its initial symptoms. Furthermore, patients will be instructed to carry a card which includes emergency contact information and precautions for anaphylaxis.
- Actair will be administered at home by patients themselves. Thus, the following management system will be established: All physicians who wish to use Actair will be required to complete Internet-based e-learning courses so that Actair is prescribed only by physicians who know well the importance of the proper use of SLIT and the importance of educating patients on actions to be taken in the event of adverse reactions. In addition, pharmacists will be required to dispense Actair after confirming that the drug has been prescribed by a physician qualified for Actair therapy.
- Should multiple SLIT products become commercially available, co-administration of Actair with other SLIT may potentiate allergic reactions. The package insert will state that the safety of Actair in combination with other SLIT has yet to be established.

PMDA considers as follows:

The published literature and other data suggest that the incidence of anaphylaxis may be lower for SLIT than for SCIT. However, anaphylaxis has been reported in patients receiving SLIT, and data allowing the comparison of SLIT and SCIT are limited because of insufficient evidence for SLIT (including SLIT using mite antigens). Actair thus has a risk of causing anaphylaxis. The risk should be well recognized to take proper safety measures. The applicant should ensure the proposed safety measures are taken, and should avoid informing patients and healthcare professionals that SLIT, compared with SCIT, has a low risk of fatal adverse drug reactions such as anaphylaxis. The applicant should also inform patients and healthcare professionals of the risk of anaphylaxis, including symptoms that predict anaphylaxis, through the package insert and information materials. Moreover, the post-marketing safety measures proposed by the applicant must be carefully reviewed through the Expert Discussions for the following reasons: (1) Actair will generally be administered by patients at home, and thus anaphylaxis may occur outside medical institutions. (2) Due to the convenient route of administration, many patients may wish to use Actair and physicians without experience in desensitization therapy may prescribe Actair in clinical settings; this requires the applicant to take appropriate safety control measures for Actair after the market launch.

4.(i).B.(3) Dosage and administration

4.(i).B.(3).1) Usual dosage and administration

The applicant provided the following rationale for the dosage regimen used in the Japanese phase II/III study (Study D1731):

The foreign phase I study (Study VO36) showed that the incidence of adverse drug reactions was higher in patients receiving a fixed dose of Actair from Day 1 throughout the study period. Actair should thus be administered in gradually increasing doses. In the foreign phase II study (Study VO67), the 100 IR group did not show much improvement in symptoms compared with the 300 and 500 IR groups.

The Japanese phase I study (Study D1711) and the foreign phase II/III study (Study VO57) revealed no marked differences between the Japanese and non-Japanese populations in the distribution of IgE antibodies specific to the 2 types of mite antigens or in the profile of adverse events. The rationale for the dosage regimen in the foreign clinical studies was used to design clinical studies in Japan. Accordingly, in the Japanese phase II/III study (Study D1731), the dose of Actair was gradually increased to the maintenance dose of 300 or 500 IR (from Day 15 to Week 52).

The Japanese phase II/III study (Study D1731) demonstrated the superiority of 300 and 500 IR over placebo and showed that the efficacy of 300 IR was similar to that of 500 IR. Both 300 and 500 IR were well-tolerated, but the incidence of adverse events leading to study discontinuation was higher in the 500 IR group than in the 300 IR group (4.3% [14 of 322 patients] in the 300 IR group, 9.0% [29 of 324 patients] in the 500 IR group, and 3.7% [12 of 322 patients] in the placebo group). The incidence of adverse events requiring emergency treatment was also higher in the 500 IR group than in the 300 IR group (1.9% [6 of 322 patients] in the 300 IR group, 3.7% [12 of 324 patients] in the 500 IR group, and 0.3% [1 of 322 patients] in the placebo group). The 300 IR dose was determined to be an appropriate maintenance dose. The proposed dosage and administration is as follows: 100 IR on Day 1, 200 IR on Day 2, and 300 IR from Day 3 onward as the maintenance dose.

The Actair tablet dissolves in the mouth. In order for Actair to be effective, mite extract components need to be placed and remain onto the sublingual mucosa for some time. In the foreign phase II study (Study VO67) and the foreign phase II/ III study (Study VO57), patients were instructed to swallow the study drug after holding it under the tongue until it dissolved completely. In the Japanese phase II/III study (Study D1731), the efficacy and safety of Actair were confirmed at the same dosage regimen. The precautions for dosage and administration section in the package insert will state that Actair should be swallowed with saliva after being held under the tongue until it dissolved completely and that gargling, eating, and drinking should be avoided for 5 minutes after the swallow.

The Japanese phase II/III study (Study D1731) indicated that the incidence of adverse events leading to study discontinuation and adverse events requiring emergency treatment was higher in the 500 IR group than in the 300 IR group. PMDA asked the applicant to explain the appropriateness of recommending the 300 IR maintenance dose for all patients, including patients with low body weight and children.

The applicant explained as follows:

Table 18 shows the incidence of adverse events by body weight in the Japanese phase II/III study (Study D1731). In the 300 IR group, patients with low body weight showed a higher incidence of adverse events considered to be mite antigen-induced allergic reactions. At Weeks 1 and 2 and from Week 3 onward, however, no marked differences by body weight were observed in the incidence of overall adverse events considered to be mite antigen-induced allergic reactions. In the foreign phase II/III study (Study VO57), no differences by body weight were observed in the incidence of adverse events or adverse events considered to be mite antigen-induced allergic reactions at Weeks 1 and 2 and from Week 3 onward, although no clear conclusion can be drawn because of the small number of subjects weighing <50 kg.

In the Japanese phase II/III study (Study D1731), the incidence of adverse events by age in the 300 IR group was 94.4% (34 of 36 patients) in patients ≥12 to <15 years old and 87.4% (250 of 286 patients) in those ≥15 years old. The incidence of adverse events considered to be mite antigen-induced allergic reactions was 80.6% (29 of 36 patients) in patients ≥12 to <15 years old and 75.2% (215 of 286 patients) in those ≥15 years old. In the 500 IR group, the incidence of adverse events was 91.4% (32 of 35 patients) in patients ≥12 to <15 years old and 90.7% (262 of 289 patients) in those ≥15 years old. The incidence of adverse events considered to be mite antigen-induced allergic reactions was 85.7% (30 of 35 patients) in patients ≥12 to <15 years old and 79.2% (229 of 289 patients) in those ≥15 years old.

Thus, body weight and age did not markedly impact the incidence of adverse events or adverse events considered to be mite antigen-induced allergic reactions. The maintenance dose of 300 IR is therefore considered to be appropriate for all patients, including children and patients with low body weight.

Table 18. Adverse events by body weight in the Japanese phase II/III study (Study D1731)

		Adverse events			Adverse events considered to be mite antigen-induced allergic reactions		
		300 IR (n = 322)	500 IR (n = 324)	Placebo (n = 322)	300 IR (n = 322)	500 IR (n = 324)	Placebo (n = 322)
Weeks 1-2	<50 kg	55/84 (65.5)	54/89 (60.7)	18/80 (22.5)	53/84 (63.1)	51/89 (57.3)	14/80 (17.5)
	≥50 kg and <60 kg	80/120 (66.7)	77/120 (64.2)	27/118 (22.9)	74/120 (61.7)	76/120 (63.3)	21/118 (17.8)
	≥60 kg and <70 kg	36/72 (50.0)	41/64 (64.1)	15/72 (20.8)	34/72 (47.2)	37/64 (57.8)	12/72 (16.7)
	≥70 kg	22/46 (47.8)	26/51 (51.0)	11/52 (21.2)	19/46 (41.3)	25/51 (49.0)	8/52 (15.4)
Weeks ≥3	<50 kg	70/84 (83.3)	67/85 (78.8)	60/79 (75.9)	46/84 (54.8)	44/85 (51.8)	36/79 (45.6)
	≥50 kg and <60 kg	89/118 (75.4)	96/117 (82.1)	74/115 (64.3)	51/118 (43.2)	70/117 (59.8)	43/115 (37.4)
	≥60 kg and <70 kg	49/70 (70.0)	52/62 (83.9)	56/72 (77.8)	29/70 (41.4)	30/62 (48.4)	27/72 (37.5)
	≥70 kg	36/46 (78.3)	44/49 (89.8)	37/51 (72.5)	22/46 (47.8)	33/49 (67.3)	17/51 (33.3)

n (%)

PMDA considers the proposed dosage and administration, as follows:

In the Japanese phase II/III study (Study D1731), the 300 IR dose was comparable or superior in efficacy to the 500 IR dose, and the incidence of events leading to study discontinuation or adverse events requiring emergency treatment was higher in the 500 IR group than in the 300 IR group. Selecting 300 IR for the maintenance dose is thus considered appropriate in view of the risk-benefit balance. As a general rule, the initial dose of 100 IR may be increased by 100 IR every day up to 300 IR, as was done in clinical studies. The Japanese phase II/III study (Study D1731), however, showed an increased incidence of adverse events considered to be mite antigen-induced allergic reactions during dose escalation even in the 300 IR group, and the age- or body weight-stratified subgroup analyses failed to rule out the potential for higher incidences of such events among children and patients with low body weight. In the foreign phase I study (Study VO36), adverse drug reactions leading to study discontinuation occurred in Group 2 with daily dose escalation, but did not occur in Group 1 with alternate-day dose escalation. The dosage and administration section should thus state that dose escalation period may be extended as needed based on the patient's condition.

In the Japanese phase II/III study (Study D1731), Actair was administered before breakfast so that adverse drug reactions requiring emergency treatment would be properly treated. Meanwhile, the efficacy of Actair was confirmed also in the foreign clinical studies in which the timing of administration was not specified. The dosage and administration section should not specify the timing of administration in order to allow patients to select the timing of administration depending on their lifestyle and condition. However, considering a possible occurrence of an adverse drug reaction requiring emergency treatment such as anaphylaxis, patients should be informed that Actair is preferably administered during the daytime and/or in the presence of another family member. Additionally, the dosage and administration section should specify that Actair should be swallowed after being held under the tongue until it completely dissolved, because this sublingual-swallow route for SLIT is documented in World Allergy Organization Position Paper 2009 (233-281).

The above view by PMDA will be discussed in the Expert Discussion.

4.(i).B.(3).2) Appropriate duration of treatment, timing to determine the lack of efficacy, and dosage and administration for re-administration

PMDA asked the applicant to discuss the appropriate duration of treatment and the timing to determine whether to continue Actair therapy in unresponsive patients.

The applicant explained as follows:

Table 19 shows the time course of mean adjusted nasal symptom scores in the Japanese phase II/III study (Study D1731). Differences between the Actair and placebo groups tended to become greater with time throughout the treatment period, suggesting that continuing treatment beyond 52 weeks may result in greater efficacy. Table 20 summarizes the percentage of days on which symptoms were successfully controlled in the Japanese phase II/III study (Study D1731). The stricter the symptom control criteria are, the smaller the difference between the Actair and placebo groups is. This suggests that 1 year of treatment may not be sufficient to achieve remission of allergic symptoms, the final objective of desensitization therapy.

Table 19. Time course of mean adjusted nasal symptom scores in the Japanese phase II/III study (Study D1731) (FAS)

Time	300 IR (n = 315)	500 IR (n = 296)	Placebo (n = 316)	Difference from placebo (95% CI)	
				300 IR	500 IR
Baseline	9.09 ± 2.04 (315)	9.04 ± 1.94 (296)	9.12 ± 2.02 (316)		
Weeks 8-10	6.49 ± 2.61 (315)	6.67 ± 2.54 (296)	7.09 ± 2.60 (316)	-0.59 [-0.940, 0.231]	-0.37 [-0.730,-0.009]
Weeks 24-26	5.36 ± 2.63 (301)	5.64 ± 2.53 (287)	6.35 ± 2.78 (303)	-0.96 [-1.347,-0.577]	-0.64 [-1.031,-0.251]
Weeks 44-52	4.99 ± 2.42 (288)	5.23 ± 2.69 (276)	6.13 ± 2.77 (297)	-1.11 [-1.504,-0.720]	-0.80 [-1.196,-0.401]

Mean ± SD (number of subjects)

Table 20. Percentage of days on which symptoms were controlled in the Japanese phase II/III study (Study D1731) (FAS)

Degree of symptom control	300 IR (n = 315)	500 IR (n = 296)	Placebo (n = 316)	Difference from placebo (95% CI)	
				300 IR	500 IR
Percentage of days on which both total nasal symptom scores and rescue medication score were 0	4.1 ± 11.12 (288)	5.6 ± 18.60 (276)	4.1 ± 14.74 (297)	-0.2 [-2.61, 2.21]	1.3 [-1.13, 3.75]
Percentage of days on which total nasal symptom scores was <1 and rescue medication score was 0	10.1 ± 20.01 (288)	10.2 ± 22.83 (276)	7.2 ± 18.94 (297)	2.7 [-0.60, 5.99]	2.6 [-0.74, 5.94]
Percentage of days on which total nasal symptom scores was <2 and rescue medication score was 0	21.2 ± 30.12 (288)	21.0 ± 31.38 (276)	14.5 ± 27.11 (297)	6.6 [1.89, 11.31]	6.3 [1.52, 11.07]

Mean ± SD (number of subjects)

A foreign study of mite antigen-specific SLIT administered for 3 to 5 years to adult patients with allergic rhinitis showed improvements in symptoms over time (Marogna M et al. *J Allergy Clin Immunol.* 2010;126:969-975). Based on this finding and other data, treatment of 3 to 5 years is recommended for SLIT (WHO Position Paper. Geneva January 27-29, 1997, Cox L et al. *J Allergy Clin Immunol*. 2011;127:S1-55, and Zuberbier T et al. *Allergy*. 2010;65:1525-1530). A 3-year foreign study of Gramineae pollen-specific SLIT reported that therapeutic effects persisted for 2 years after the end of

treatment (Durham SR et al. *J Allergy Clin Immunol*. 2012;129:717-725). A 1-year foreign phase II/III study (Study VO57) of Actair confirmed that therapeutic effects persisted for approximately 1 year after the end of treatment [see "4.(i).A.(5) Foreign phase II/III study"]. These results suggest that the therapeutic effects of Actair would persist after the end of treatment if the drug is administered for multiple years.

The efficacy of Actair is thus expected to appear 2 to 4 months after the start of administration and persist to a certain extent after 1 year of treatment. The above finding and the literature suggest that Actair therapy for ≥3 years would enhance and prolong treatment efficacy.

As for the timing to determine whether to continue Actair therapy in unresponsive patients, assessing symptoms every 6 to 12 months or every year is recommend during desensitization therapy (Zuberbier T et al. *Allergy*. 2010;65:1525-1530 and Cox L et al. *J Allergy Clin Immunol*. 2011;127:S1-55). Symptoms of house dust mite antigen-induced allergic rhinitis are generally known to vary seasonally. Therapeutic effects of immunotherapy should therefore be assessed in the same season. Thus physicians using Actair should evaluate the efficacy every year, and in case of lack of efficacy, should decide whether to continue treatment after re-evaluating antigens and considering the use of concomitant drugs. Accordingly, physicians will be advised to carefully consider whether to continue Actair therapy in patients unresponsive to ≥1 year of treatment.

PMDA asked the applicant to explain the dosage regimen for re-administration after short-term interruption due to safety and other reasons and for re-administration for a recurrence of symptoms after remission.

The applicant's response:
The protocol of the Japanese phase II/III study (Study D1731) stated that (1) during the dose escalation period (Days 1-14 of administration), the restarting dose should be the predefined dose for the day on which re-administration was started, and that (2) during the dose maintenance period (Day 15 to Week 52 of administration), the restarting dose should be the same as the dose administered before interruption. On the first day of re-administration, adverse drug reactions occurred in 3 of 23 patients (13.0%) who had interrupted treatment due to adverse drug reactions and in 13 of 361 patients (3.6%) who had interrupted treatment for reasons other than adverse drug reactions. Although the number of patients investigated was small, adverse drug reactions occurred more frequently in patients who resumed treatment after interruption due to adverse drug reactions. The duration of interruption did not tend to correlate with adverse drug reactions: On the first day of re-administration, adverse drug reactions occurred in 15 of 370 patients (4.1%) with a <7-day interruption and in 1 of 17 patients (5.9%) with a ≥7-day interruption. In Study D1731, the duration of interruption ranged from 1 to 27 days. In post-marketing settings, however, treatment may be resumed even after a longer interruption. Thus physicians must determine the restarting dose for individual patients depending on the duration of interruption, the

type and severity of the adverse drug reactions leading to interruption, and other factors. Treatment should be resumed under the supervision of a physician as in initial administration, as appropriate.

In a clinical study, patients who had a recurrence of house dust mite antigen-induced allergic rhinitis received re-administration of SLIT in escalating doses, as per initial administration. The study demonstrated the efficacy of re-administration of SLIT for recurrence of symptoms following remission (Marogna M et al. *J Allergy Clin Immunol.* 2010;126:969-975). This suggests that re-administration of Actair may also prove efficacy against a recurrence of symptoms. As explained above (in the discussion on appropriate duration of treatment and timing to determine the lack of efficacy), the efficacy of Actair may persist for some time after the end of treatment, suggesting that symptoms may recur after a long period of remission. Thus, in patients with a recurrence of symptoms, Actair therapy should be resumed in escalating doses, as per initial treatment.

PMDA considers as follows:
No convincing evidence is currently available for duration of treatment, timing to determine the lack of efficacy, and dosage regimen for re-administration, although such information is important for starting Actair therapy. Physicians are thus required to make decisions based on the condition of individual patients and other data. Healthcare professionals should therefore be informed of appropriate duration of treatment, timing to determine the lack of efficacy, and dosage regimen for re-administration, through educational materials etc. prepared based on the foreign and Japanese clinical practice guidelines. Desensitization therapy takes a long time, with the ultimate goal of achieving remission of allergic reactions. However, Actair has not been administered for >1 year in any clinical study. Post-marketing surveillance is needed to gather information on the long-term efficacy and safety, including the efficacy of continued treatment in unresponsive patients and the safety in patients who resumed treatment after interruption due to safety issues or other reasons.

4.(i).B.(4) Clinical positioning

Based on Japanese treatment guidelines, PMDA considers the clinical positioning of Actair as follows:
The core of allergic rhinitis treatments is pharmacotherapy using histamine H_1 receptor antagonists, leukotriene receptor antagonists, and nasal steroid sprays. Such symptomatic treatment may transiently improve symptoms, but if treatment is discontinued, symptoms will recur in a short period of time. In contrast, desensitization therapy reduces sensitivity towards causative antigens by repeatedly administering the causative antigens to patients, thus achieving long-term remission and cure. In Japan, only SCIT has been approved for mite-antigen desensitization therapy, while SLIT is expected to offer a more convenient desensitization therapy. The Japanese treatment guidelines (Japanese Rhinologic Society ed. Practical Guideline for the Management of Allergic Rhinitis in Japan 2013, Current state of sublingual immunotherapy) states that SLIT can be used as a basic treatment for allergic rhinitis regardless of severity and may prevent sensitization to new allergens. Actair is thus expected to be used in all types of patients with allergic rhinitis, regardless of co-administration of common drugs such as antihistamines, but SLIT has a risk of anaphylaxis. Healthcare professionals should therefore be advised

through the package insert etc. to determine whether to start Actair therapy based on the patient's symptoms, treatment history, and other factors, while weighing other therapeutic options.

No clear conclusion can be drawn on the positioning of SLIT relative to SCIT because of limited data for comparison between the formulations. The positioning of SLIT is important information for selecting treatment and should therefore be further discussed.

4.(i).B.(5) Efficacy

The proposed indication is "House dust mite antigen-induced allergic rhinitis (allergen immunotherapy)." However, no broad consensus exists over the term "allergen immunotherapy." PMDA considers that the wording for indication should be modified as follows:

[Indication] <u>Desensitization therapy for</u> house dust mite antigen-induced allergic rhinitis

(The revised part is underlined.)

Additionally, the package insert should state that the efficacy and safety of Actair have not been confirmed in patients with high titers of IgE specific to antigens other than mite antigens because of limited data on the efficacy and safety in such patients in the Japanese phase II/III study (Study D1731).

4.(i).B.(6) Post-marketing surveillance

As reviewed in "4.(i).B.(3).2) Appropriate duration of treatment, timing to determine the lack of efficacy, and dosage regimen for re-administration," PMDA considers that more information should be collected, through post-marketing surveillance and other sources, on the long-term efficacy and safety of Actair, including the efficacy of continued treatment in unresponsive patients and the safety of re-administration in patients who had discontinued therapy due to safety issues and other reasons.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there would be no problems with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-02). PMDA concluded that there would be no problems with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

The submitted data show that desensitization therapy with Actair is effective for house dust mite antigen-induced allergic rhinitis. Appropriate safety measures must be taken to ensure the safety of Actair since the product has a risk of serious systemic reactions such as anaphylaxis, as with other drugs for desensitization therapy. The applicant must therefore provide education and guidance to healthcare professionals and patients. Furthermore, the applicant should conduct long-term post-marketing surveillance to investigate the safety and efficacy of re-administration and to identify the appropriate timing to determine the lack of efficacy, and should provide the collected information to physicians and patients as it becomes available.

The product may be approved if Actair is not considered to have any problems based the Expert Discussion.

Review Report (2)

January 9, 2015

I. Product Submitted for Registration

[Brand name]	Actair House Dust Mite Sublingual Tablets 100 units (IR) Actair House Dust Mite Sublingual Tablets 300 units (IR)
[Non-proprietary name]	None
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	April 24, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the efficacy of Actair, as described in Review Report (1). Some expert advisors commented that Actair can be useful in desensitization therapy based on the clinical study results demonstrating the efficacy in alleviating symptoms of allergic rhinitis and the foreign publications on long-term SLIT using mite antigens.

(2) Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the dosage and administration of Actair, as described in Review Report (1). The expert advisors made the following comments:

- In principle the dosage of Actair should be increased over the course of 3 days. However, the duration of dose escalation should be adjusted as appropriate based on the patient's condition so that treatment can be adjusted based on the patient's response to Actair and the severity of adverse drug reactions.

- Information materials for healthcare professionals and patients should include concrete examples of patient conditions that may require an extension of dose escalation period.

Based on the review by the Expert Discussion, PMDA instructed the applicant to modify the wording for dosage and administration and to include the statement shown below in the precautions for dosage and administration. The applicant responded appropriately.

[Dosage and administration]

For adults and children ≥12 years old, ~~Actair is administered sublingually once daily before breakfast at 100 IR on Day 1, 200 IR on Day 2, and 300 IR from Day 3 onward as the maintenance dose.~~ the starting dose of Actair is 100 units (IR) administered sublingually once daily. The dose is increased by 100 units (IR) up to 300 units (IR) over a period of 3 days, in principle, or a longer period depending on the patient's condition. Following sublingual administration, the tablet(s) should be held under the tongue until it completely dissolved, and then swallowed. For the next 5 minutes, the patient should avoid gargling, eating, or drinking.

(The added part is underlined; the deleted part is struck through.)

[Precautions for dosage and administration]

Patients should be instructed to consult a physician about whether to increase the dose if an allergic reaction occurs outside the medical institution during the dose escalation period.

(3) Post-marketing safety measures and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the safety of Actair, including post-marketing safety measures, as described in Review Report (1). The expert advisors made the following comments:

- Actair therapy involves administering allergens directly to patients, and will be often administered outside a medical institution because it is SLIT. An appropriate safety management system should therefore be established before the market launch to address the risk of anaphylaxis.
- In particular, appropriate educational materials should be prepared so that patients and their families are aware of the risks (e.g., anaphylaxis) and benefits of Actair.

Based on the investigations in "4.(i).B.(2) Safety" and "4.(i).B.(6) Post-marketing surveillance" of Review Report (1) and the review during the Expert Discussion, PMDA concluded that the proposed risk management plan should include the safety and efficacy specifications listed in Table 21, and that the applicant should implement the additional pharmacovigilance activities and risk minimization activities listed in Table 22.

Table 21. Safety and efficacy specifications in the proposed risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Shock and anaphylaxis	• None	• None
Efficacy specifications		
• Confirm efficacy in long-term treatment and after the end of treatment		

Table 22. Summary of additional pharmacovigilance and risk minimization activities in the proposed risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (long-term use)	• Early post-marketing phase vigilance • Preparation and distribution of educational materials for healthcare professionals • Preparation and distribution of educational materials for patients • Establishment of management system to ensure proper use

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above-mentioned items.

The applicant's response:

A specified use-results survey will be conducted in 500 patients with house dust mite antigen-induced allergic rhinitis with an up to 4-year observation period, as shown in Table 23, to investigate (1) the safety of Actair in clinical settings with priority survey items of "shock" and "anaphylaxis," (2) the long-term efficacy of Actair, including the efficacy of continued treatment in unresponsive patients, and (3) the efficacy for up to 1 year after discontinuation due to improved symptoms.

Table 23. Outline of proposed plan for specified use-results survey

Objective	Confirm the long-term safety and efficacy (4 years) of Actair in clinical settings.
Survey method	Central registration
Population	Patients with house dust mite antigen-induced allergic rhinitis
Observation period	Up to 4 years
Target sample size	500 patients
Priority survey items	• Shock and anaphylaxis
Major survey items	• Patient characteristics • Past history/concurrent conditions • Severity of rhinitis • Administration of Actair • Concomitant drugs • Efficacy evaluation • Adverse events

PMDA concludes that the applicant should conduct the survey promptly and appropriately provide the survey results to healthcare professionals.

III. Overall Evaluation

Based on the above review, PMDA concludes that the product may be approved for the indication and the dosage and administration as shown below with the following conditions for approval. The re-examination period is 8 years because the product contains a new active ingredient. Neither the drug

substance nor the drug product is classified as a poisonous or powerful drug. The product is not classified as a biological or specified biological product.

[Indication]
Desensitization therapy for house dust mite antigen-induced allergic rhinitis

[Dosage and administration]
For adults and children ≥12 years old, the starting dose of Actair is 100 units (IR) administered sublingually once daily. The dose is increased by 100 units (IR) up to 300 units (IR) over a period of 3 days, in principle, or a longer period depending on the patient's condition. Following sublingual administration, the tablet(s) should be held under the tongue until it completely dissolved, and then swallowed. For the next 5 minutes, the patient should avoid gargling, eating, or drinking.

[Conditions for approval]
The applicant is required to:

1. Develop and properly implement a risk management plan.
2. Take necessary measures, before market launch, to ensure that the product is prescribed and administered only by qualified physician(s) with adequate knowledge and experience in sublingual immunotherapy who can successfully manage and explain the risks associated with the product in a medical institution that allows such physicians to do so, and to ensure that the product is dispensed by pharmacists who have confirmed that the product has been prescribed by the physician(s) in an appropriate medical institution.