Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	(a) Miticure House Dust Mite Sublingual Tablets 3,300 JAU; (b) Miticure House Dust Mite Sublingual Tablets 10,000 JAU
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Date of application]	January 26, 2015

[Results of deliberation]

In the meeting held on August 31, 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 a risk management plan and implement it appropriately.
2. Take necessary measures in the marketing of the product to ensure that the product is prescribed and used only by physicians with sufficient knowledge and experience of sublingual desensitization therapy; that the product is used only under the supervision of physicians at medical institutions where they can adequately manage and explain the associated risks; and that the product is dispensed at pharmacies only after the prescribing physician and medical institution are identified.

Review Report

August 18, 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) Miticure House Dust Mite Sublingual Tablets 3,300 JAU; (b) Miticure House Dust Mite Sublingual Tablets 10,000 JAU
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Date of application]	January 26, 2015
[Dosage form/Strength]	(a) Sublingual tablets, each containing 1650 JAU (1 DU) each of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts; (b) Sublingual tablets, each containing 5000 JAU (3 DU) each of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Items warranting special mention]	Product subjected to prior assessment consultation
[Reviewing office]	Office of New Drug IV

Review Results

August 18, 2015

[Brand name]	(a) Miticure House Dust Mite Sublingual Tablets 3,300 JAU; (b) Miticure House Dust Mite Sublingual Tablets 10,000 JAU
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Date of application]	January 26, 2015

[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 allergic rhinitis induced by mite allergens has been demonstrated. The product requires the following safety considerations. Desensitization therapy may cause anaphylaxis because it involves the administration of allergens to sensitized patients. Therefore, the product should be used only by physicians with adequate knowledge of the product as well as sufficient knowledge and experience of desensitization therapy, and measures, such as education and instruction of healthcare providers and patients, should be taken to ensure that patients are adequately protected from anaphylaxis. In addition, PMDA considers that the long-term efficacy and safety of the product should be evaluated through post-marketing surveillance and other relevant programs.

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

[Indication] Desensitization therapy for allergic rhinitis induced by mite allergens

[Dosage and administration] The usual dosage of Miticure for adults and children aged ≥12 years is one 3300-JAU tablet administered sublingually once-daily during the first week of treatment and one 10,000-JAU tablet sublingually once-daily from the second week onward. The tablet should be placed under the tongue until dissolved for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan and implement it appropriately.
2. Take necessary measures in the marketing of the product to ensure that the product is prescribed and used only by physicians with sufficient knowledge and experience of sublingual desensitization therapy; that the product is used only under the supervision of physicians at medical institutions where they can adequately manage and explain the associated risks; and that the

product is dispensed at pharmacies only after the prescribing physician and medical institution are identified.

Review Report (1)

July 16, 2015

I. Product Submitted for Registration

[Brand name]	(a) Miticure House Dust Mite Sublingual Tablets 3,300 JAU; (b) Miticure House Dust Mite Sublingual Tablets 10,000 JAU; (c) Miticure House Dust Mite Sublingual Tablets 20,000 JAU
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Date of application]	January 26, 2015
[Dosage form/Strength]	(a) Sublingual tablets, each containing 1650 JAU (1 DU) each of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts; (b) Sublingual tablets, each containing 5000 JAU (3 DU) each of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts; (c) Sublingual tablets, each containing 10,000 JAU (6 DU) each of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* extracts
[Proposed indication]	Desensitization therapy for the following allergic disorder induced by mite allergens: Allergic rhinitis
[Proposed dosage and administration]	1. Loading dose period (Week 1) The usual dosage is one 3300-JAU tablet administered sublingually once daily in the first week of treatment (loading dose period). The tablet should be placed under the tongue until dissolved for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes. 2. Maintenance dose period (from Week 2 onward) After the loading dose period, the usual maintenance dosage is one 10,000-JAU tablet administered sublingually once daily. The tablet should be placed under the tongue until dissolved for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes. The dose may be increased to one 20,000-JAU tablet once daily according to the severity of symptoms, only after the 10,000-JAU tablet has been administered for at least 1 week.

II. Summary of the Submitted Data and Outline of the Review by the 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.

According to clinical guidelines and other relevant references in and out of Japan, desensitization therapy aims to enhance the immune tolerance to the causative allergen by continuous administration of causative allergen at an appropriate dose, and long-term desensitization therapy is expected to reduce the patient's abnormal immune responses, thereby effecting a cure or long-term remission of allergic diseases (*Practical Guidelines for the Management of Allergic Rhinitis in Japan 2013*; WHO position paper: *Allergy.* 1998;53:1-42).

The Miticure House Dust Mite Sublingual Tablet (hereinafter referred to as Miticure) is a sublingual immunotherapy (SLIT) product discovered by ALK-Abelló A/S in Denmark, indicated for allergic rhinitis induced by mite allergens. Each tablet contains extracts prepared from 2 house dust mites (HDMs), *Dermatophagoides farinae* (*D. farinae*) and *Dermatophagoides pteronyssinus* (*D. pteronyssinus*), in an antigenicity ratio of 1:1.

In Japan, marketing approval has been granted for desensitization therapy products containing mite allergens including SLIT products consisting of *D. farinae* and *D. pteronyssinus* extracts, such as Actair House Dust Mite Sublingual Tablets 100 units (IR), and for subcutaneous immunotherapy (SCIT) products consisting of *D. farinae* and *D. pteronyssinus* extracts, such as Allergen Extract Mites Subcutaneous Injections for Treatment "Torii" 10,000 JAU/mL. Miticure has been developed as a new SLIT product.

[redacted]

In Japan, the clinical development of Miticure was started in [redacted] 20[redacted] by the applicant, Torii Pharmaceutical Co., Ltd., which has filed the present new drug application based on Japanese clinical study results and other relevant data. Because the proposed dosage and administration were revised during review for marketing approval, the applicant withdrew the new drug application for 20,000 JAU tablets [see "4.(i).B.(3) Dosage and administration"].

Two units of potency are used for Miticure: "Development Unit" (DU) and Japanese Allergy Unit (JAU), with 1 DU being equivalent to 1650 JAU. Here, 1 DU-F (potency of *D. farinae* extract) and 1 DU-P (potency of *D. pteronyssinus* extract) represent the potency of 1 DU of the reference *D. farinae* and *D. pteronyssinus* extracts, respectively, and 1 DU is defined as the sum of 0.5 DU-F and 0.5 DU-P. The

JAU is a unique unit of allergenic potency established by the Japanese Society of Allergology based on intradermal testing of allergic patients. According to the JAU definition, a house dust mite extract containing 22.2 to 66.7 μg/mL of Der f 1[1] and Der p 1[2] combined can be labeled as having a potency of 100,000 JAU/mL.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substances

2.A.(1).1) Characterization

[redacted]

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

[redacted]

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

[redacted]

[1] One of the major mite fecal allergens extracted from the house dust mite *D. farinae*.
[2] One of the major mite fecal allergens extracted from the house dust mite *D. pteronyssinus.*
[3] One of the major mite body allergens extracted from the house dust mite *D. farinae*.
[4] One of the major mite body allergens extracted from the house dust mite *D. pteronyssinus.*

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

Table 1 summarizes the stability study that was performed for each of the drug substances, *D. farinae* and *D. pteronyssinus* extracts.

Table 1. Stability study of the drug substances

Study	Primary batch	Temperature	Storage container	Storage period
Long-term	3 pilot batches	−20 ± 5°C	[redacted]	[redacted] months

[redacted]

2.A.(2) Drug product

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

The drug product is a tablet, each containing 3300 JAU (1 DU each of the drug substances), or 10,000 JAU (3 DU each of the drug substances). The drug product also contains gelatin, D-mannitol, and sodium hydroxide as excipients.

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

[redacted]

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

[redacted][5]

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

Table 2 summarizes the stability studies of the drug product.

Table 2. Stability studies of the drug product

Study	Formulation	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3300 JAU	3 pilot batches	25°C	60% RH	Aluminum blister pack	24 months
Accelerated			40°C	75% RH		6 months
Long-term	10,000 JAU	3 pilot batches	25°C	60% RH	Aluminum blister pack	24 months
Accelerated			40°C	75% RH		6 months

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored in an aluminum blister pack at room temperature.

[5] [redacted]

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substances and the drug product is adequately controlled.

Drug product specifications (protein profile)

[redacted] Therefore, the applicant considers that protein profiles should not be used for identification of the drug product. [redacted]

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

No primary or secondary pharmacodynamic, safety pharmacology, or pharmacodynamic drug interaction studies have been conducted for the application of Miticure.

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

The applicant provided the following reasons for not conducting non-clinical pharmacology studies:

Primary pharmacodynamic studies were not conducted for the following reasons: (a) the efficacy of sublingual or subcutaneous immunotherapy using house dust mite (HDM) allergen extract products that have identical active ingredients with those of Miticure on mite allergen-induced allergic rhinitis and bronchial asthma has been demonstrated outside Japan (Eifan AO et al. *Expert Opin Biol Ther*. 2013;13:1543-1556; Canonica GW et al. *WAO Journal.* 2009;November:233-281; Abramson MJ et al. *Cochrane Database Syst Rev.* 2010;CD001186); and (b) the detailed mechanism of action of desensitization therapy has not been elucidated at this point, nor are any appropriate animal models available r efficacy evaluation.

No new secondary pharmacodynamic or safety pharmacology studies were conducted for the following reasons: neither the repeated-dose sublingual toxicology study using a mixture of extracts of *D. farinae* and *D. pteronyssinus* in an antigenicity ratio of 1:1 (hereinafter referred to as "*D. farinae* + *D.*

pteronyssinus") [see "3.(iii).A.(2) Repeat-dose toxicity"] nor the general pharmacology study with an already-approved HDM allergen extract product (see the new drug application data for "Allergen Scratch Extract 'Torii' Mite") indicated safety concerns.

No pharmacodynamic drug interaction studies were conducted for the following reasons: although there was a report that co-administration of a β-blocker with an allergen extract product caused stronger allergic reactions (Bousquet J et al. *Allergy.* 1998;53:1-42), there have been no other reports that an allergen extract product may affect the actions of allergy drugs possibly co-administered with the extract, suggesting that there are no special concerns regarding pharmacodynamic interactions.

PMDA accepted the above explanation by the applicant, and has concluded that it is acceptable that no non-clinical pharmacology studies including primary pharmacodynamic studies have been conducted.

3.(ii) Summary of pharmacokinetic studies

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

No absorption, distribution, metabolism, excretion, or pharmacokinetic drug interaction studies have been conducted for the application of Miticure.

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

The applicant provided the following reasons for not conducting non-clinical pharmacokinetic studies: In clinical use, Miticure is intended to be placed under the tongue until dissolved before being swallowed. In general, the absorption of proteins and peptides through the oral mucosa is based on passive diffusion depending on the molecular weight and charge state (Rojanasakul Y et al. *Pharm Res.* 1992;9:1029-1034), and the threshold for absorbable molecular weight is estimated to be 0.5 to 1.0 kDa (Merkle HP et al. *J Control Release.* 1992;21:155-164). It is reported that following sublingual administration of ^{123}I-labelled Der p 2 (15 kDa)[6] to humans, unchanged Der p 2 was not detected in plasma (Bagnasco M et al. *Int Arch Allergy Immunol.* 2005;138:197-202), and following sublingual administration of ^{125}I-labelled Cry j 1 (41 kDa and 46 kDa), a major allergen in Japanese cedar pollen, to rats, no radioactivity was detected in the trichloroacetic acid (TCA) insoluble fraction[7] of plasma (see the Review Report of "Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle" dated September 24, 2013). From these results, unchanged Der f 1,[8] Der p 1 (25 kDa)[9], and Der f 2 (15 kDa)[10] are also unlikely to be transferred from sublingual region into blood. Proteins absorbed into blood or tissues are degraded quickly by peptidases and other enzymes, and thus Der f 1, Der f 2, Der p 1, and Der p 2, after being placed under the tongue and then swallowed, are thought to be quickly degraded by gastric fluid and other digestive fluids.

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[6] One of the major mite body allergens extracted from the house dust mite *D. pteronyssinus.*

[7] Of the ^{125}I-labelled Cry j 1 administered, proteins including the unchanged compound are contained in the insoluble fractions, while low molecular weight substances and iodine ions are contained in the soluble fractions.

[8] One of the major mite fecal allergens extracted from the house dust mite *D. farinae*.

[9] One of the major mite fecal allergens extracted from the house dust mite *D. pteronyssinus.*

[10] One of the major mite body allergens extracted from the house dust mite *D. farinae*.

It has been suggested that allergens typically bind to oral mucosal epithelial cells after sublingual administration, and are then taken up by antigen-presenting cells (Langerhans cells in the mucosa or myeloid dendritic cells in the lamina propria) (Moingeon P et al. *Allergy.* 2006;61:151-165). Subsequently, the allergens are processed within the antigen-presenting cells, and are presented as peptides on the cell surface, while antigen-presenting cells move to lymph nodes near the sublingual region (e.g., submandibular lymph nodes), and present antigens to naïve T cells, thereby causing immunoreactions (Calderon MA et al. *Allergy.* 2012;67:302-311). The findings that high levels of radioactivity were distributed in the submandibular lymph nodes after ^{125}I-labelled Cry j 1 was sublingually administered to rats (see the Review Report of "Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle" dated September 24, 2013) suggest that the sublingually administered allergens are transferred to cervical lymph nodes (submandibular lymph nodes).

Based on the above discussions, the pharmacokinetics of Der f 1, Der f 2, Der p 1, and Der p 2 can be examined in the published literature; therefore, no non-clinical pharmacokinetic studies were conducted.

PMDA has concluded that it is acceptable that no non-clinical pharmacokinetic studies have been conducted because the transfer of major allergens to blood is considered extremely limited when Miticure is administered sublingually, and that there are no particular problems involving non-clinical pharmacokinetics in the clinical use of Miticure.

3.(iii) Summary of toxicology studies

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

The following studies were newly conducted as toxicology studies of *D. farinae* + *D. pteronyssinus*: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, a reproductive and developmental toxicity study, and a local tolerance study. Acute toxicity was also evaluated in repeated-dose toxicity studies and a combined *in vivo* rat micronucleus and comet assay. Non-rodent repeated-dose toxicity and embryo-fetal development studies were not conducted because subcutaneous immunotherapy (SCIT) products using HDM allergen extracts containing identical active ingredients as *D. farinae* + *D. pteronyssinus* have already been approved overseas, therefore, the overall safety profile in humans has been elucidated. Further, there is little concern regarding the genotoxicity of *D. farinae* + *D. pteronyssinus*. Humans are exposed to HDM allergens on an everyday basis, and no adverse drug reactions indicative of carcinogenicity have been reported in clinical studies or treatments with HDM products performed in or out of Japan; therefore, no carcinogenicity studies were conducted.

3.(iii).A.(1) Single-dose toxicity (4.2.3.2.1, 4.2.3.3.2.1)

A single dose of *D. farinae* + *D. pteronyssinus* (0 [purified water], 0.9, 3.5, or 14 Development Unit [DU]/body) was administered sublingually[11] to male and female CD-1 mice. No deaths occurred, and no changes associated with *D. farinae* + *D. pteronyssinus* treatment were observed. The approximate lethal dose was determined to be >14 DU/body (467 DU/kg[12]).

Oral doses of *D. farinae* + *D. pteronyssinus* (0 [purified water], 250, 500, or 1002 mg/kg/day) were administered to male Wistar rats for 3 days. No deaths occurred, and no changes associated with *D. farinae* and *D. pteronyssinus* treatment were observed. The approximate lethal dose was determined to be >1002 mg/kg/day (19,539 DU/kg/day[13]).

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

Twenty-six week sublingual administration study in mice (4.2.3.2.1)

Repeated doses of *D. farinae* + *D. pteronyssinus* (0 [purified water], 0.9, 3.5, or 14 DU/body/day) were administered sublingually[11] to male and female CD-1 mice for 26 weeks. No deaths occurred, and no effects of *D. farinae* and *D. pteronyssinus* were observed in relation to clinical signs, body weight, food consumption, laboratory test values, pathological examination results including reproductive organs, and other factors. From the results, the no observed adverse effect level (NOAEL) was determined to be 14 DU/body/day (467 DU/kg/day[12]), which is estimated to be more than 1100- to 1900-fold the maximum dose level used in the phase II/III study, 12 DU/body/day (0.24-0.4 DU/kg/day[14]).

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1-4.2.3.3.1.3, 4.2.3.3.2.1)

As genotoxicity studies, a bacterial reverse mutation assay, a chromosomal aberration assay using human peripheral lymphocytes, and a combined *in vivo* rat micronucleus and comet assay were performed. Test results were negative for the bacterial reverse mutation assay and combined *in vivo* rat micronucleus and comet assay. While test results were positive for the chromosomal aberration assay, an additional test using 3 different batches yielded negative test results in all batches. Although the cause of the initial positive test results has not been identified, *D. farinae* + *D. pteronyssinus* is considered unlikely to induce chromosomal aberrations based on its physical properties and other characteristics. On the basis of the above discussions and findings, the applicant considers that *D. farinae* + *D. pteronyssinus* is unlikely to cause genotoxicity in humans.

3.(iii).A.(4) Reproductive and developmental toxicity

An embryo-fetal development study was conducted in mice to evaluate reproductive and developmental toxicity. No study was conducted for fertility and early embryonic development to implantation because

[11] Because the maximum feasible sublingual dose in the mouse is 5 μL/body and the highest concentration that can be prepared of *D. farinae* + *D. pteronyssinus* is 1400 DU/mL, *D. farinae* + *D. pteronyssinus* was administered at 14 DU/body/day divided into 2 doses, 5 to 20 minutes apart.

[12] Calculated by assuming a mouse body weight of 30 g.

[13] [redacted]

[14] Calculated by assuming a human body weight range of 30 to 50 kg.

no histopathological changes have been observed in reproductive organs in the 26-week sublingual administration study in mice. No studies to ascertain possible effects on pre- and postnatal development including maternal function were conducted because no increase in pregnancy-related adverse events caused by exposure to HDM allergens or by desensitization therapy has been reported in the epidemiological information on women who received desensitization therapy during pregnancy or in the children born to the treated mothers (Metzger WJ et al. *J Allergy Clin Immunol.* 1978;61:268-272; Shaikh WA. *Clin Exp Allergy.* 1993;23:857-860; and Shaikh WA. *Allergy*. 2012;67:741-743) or in post-marketing safety reports on HDM SCIT products overseas. Non-rodent embryo-fetal development studies were not conducted because embryo-fetal development toxicity was not observed in the mouse embryo-fetal development study in addition to the above information on humans.

Embryo-fetal development study in mice (4.2.3.5.2.2)

Repeated doses of 0 (purified water), 450, 900, or 1800 DU/kg/day of *D. farinae* + *D. pteronyssinus* were subcutaneously administered to pregnant CD-1 mice from gestation day 6 to 17. No maternal deaths occurred, and no effects of *D. farinae* + *D. pteronyssinus* were observed on clinical signs, body weight, food consumption, necropsy findings, number of corpora lutea, or number of implantations in maternal animals. In embryos and fetuses, higher late resorption rate was observed in the 450 and 900 DU/kg groups, and lower fetal body weight in the 900 DU/kg group; but none of these changes were observed in the 1800 DU/kg group, and thus the observed changes were not dose-dependent; therefore, these findings were determined to be incidental. No effects of *D. farinae* + *D. pteronyssinus* were observed on the number of surviving fetuses, sex ratio, findings of the placenta, and appearance of the external surface, internal organs, and skeletal systems. A lower number of sacrococcygeal vertebrae (mean, 11.86) was observed as a potential ossification abnormality in the 1800 DU/kg group, however, it was determined to be unrelated to *D. farinae* + *D. pteronyssinus* because the value was within the historical range of the laboratory (lower limit, 11.61). Based on the above discussions and findings, the NOAELs for the maternal animal, embryo, and fetus were determined to be 1800 DU/kg/day, which is approximately 7500-fold the maximum dose level (0.24 DU/kg/day) used in the phase II/III study.

3.(iii).A.(5) Local tolerance

Oral mucosa irritation study in rabbits (4.2.3.6.2)

Repeated doses of *D. farinae* + *D. pteronyssinus* (0 [placebo tablet[15]], 12, or 24 DU/body/day) were sublingually administered[16] to male NZW rabbits for 7 days. No irritation was observed in the sublingual mucosa in any of the treatment groups, and no abnormalities were detected in the gross observation or histopathological examination. From the above results, *D. farinae* + *D. pteronyssinus* was determined to be non-irritating to the oral mucosa.

[15] A tablet containing gelatin, mannitol, and sodium hydroxide.

[16] Under inhalation anesthesia, 2 tablets each of placebo, 6 DU, or 12 DU of Miticure 10,000 JAU or Miticure 20,000 JAU were placed under the tongue for 10 minutes.

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

Based on the submitted data, PMDA concluded that there are no specific toxicological concerns with the clinical use of Miticure.

4. Clinical data

4.(i) Summary of clinical efficacy and safety

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

As the evaluation data for the efficacy and safety of Miticure, the results of the Japanese phase I study (5.3.3.2-1, Study 203-1-1) in patients with house dust mite (HDM)-induced allergic asthma, and Japanese phase II/III study (5.3.5.1-1, Study 203-3-2) in patients with HDM-induced allergic rhinitis were submitted.

4.(i).A.(1) Japanese phase I study (5.3.3.2-1, Study 203-1-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled study was conducted in adult patients with mild or moderate[17] HDM-induced allergic asthma[18] (target sample size, 48 subject [12 subjects per cohort; 9 for active drug and 3 for placebo]) to investigate the safety of Miticure.

In this study, subjects received once-daily sublingual doses of 3, 6, or 12 Development Unit (DU) of Miticure , or placebo for 14 days, or in the dose-escalation group, 3 DU on Days 1 to 3, 6 DU on Days 4 to 7, and 12 DU on Days 8 to 14. The subjects were instructed to place the administered Miticure or placebo under the tongue for 1 minute before swallowing; and refrain from gargling, eating, or drinking for the following 5 minutes after swallowing.

All 48 randomized subjects were included in the safety analysis population (9 subjects in the 3-DU group, 9 subjects in the 6-DU group, and 9 subjects in the 12-DU group, 9 subjects in the dose-escalation group, and 12 subjects in the placebo group). No subjects discontinued the treatment.

The incidence of adverse events was 77.8% (7 of 9 subjects) in the 3-DU group, 88.9% (8 of 9 subjects) in the 6-DU group, 66.7% (6 of 9 subjects) in the 12-DU group, 88.9% (8 of 9 subjects) in the dose-escalation group, and 25.0% (3 of 12 subjects) in the placebo group. Table 3 shows the main adverse events. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation. Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) occurred in 5 of 9 subjects (55.6%) in the 3-DU group, 8 of 9 subjects (88.9%) in the 6-DU group, 6 of 9 subjects (66.7%) in the 12-DU group, 8 of 9 subjects (88.9%) in the dose-escalation group, and 2 of 12 subjects (16.7%) in the placebo group.

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[17] Patients were classified into mild-intermittent, mild-persistent, or moderate-persistent categories based on the severity classification of asthma (*Japanese Guidelines for the Diagnosis and Treatment of Allergic Diseases 2010*). Subjects were assigned so that mild and moderate patients were distributed as evenly as possible across the cohorts.

[18] Patients meeting the following requirements: (1) HDM-specific IgE antibodies in serum (*D. farinae* + *D. pteronyssinus*) are ≥ Class 3; and (2) tested positive in HDM-induced allergen scratch test.

Table 3. Adverse events that occurred in ≥2 subjects in any group (safety analysis population)

Event	3-DU group (9 subjects)	6-DU group (9 subjects)	12-DU group (9 subjects)	Dose-escalation group (9 subjects)	Placebo group (12 subjects)
Throat irritation	2 (22.2)	6 (66.7)	3 (33.3)	6 (66.7)	1 (8.3)
Ear pruritus	2 (22.2)	1 (11.1)	1 (11.1)	2 (22.2)	0
Upper respiratory tract inflammation	2 (22.2)	0	0	0	0
Oedema mouth	1 (11.1)	4 (44.4)	1 (11.1)	4 (44.4)	0
Oropharyngeal discomfort	1 (11.1)	2 (22.2)	1 (11.1)	3 (33.3)	0
Oral pruritus	1 (11.1)	0	1 (11.1)	7 (77.8)	0
Paraesthesia oral	0	3 (33.3)	6 (66.7)	3 (33.3)	1 (8.3)
Abdominal discomfort	0	2 (22.2)	0	0	0
Lip pruritus	0	1 (11.1)	0	3 (33.3)	0

Number of subjects (%)

The applicant explained that no difference in safety profile was observed between the dose-escalation group and fixed dose groups (3-DU, 6-DU, and 12-DU groups) in the above Japanese phase I study (Study 203-1-1), and the foreign clinical study[19] was conducted at fixed dose levels throughout the study period. However, the applicant decided to include a dose-escalation period in the Japanese phase II/III study (Study 203-3-2) as a safety precaution, given that dose escalation regimens have been used for SLIT products already approved in Japan to reduce the occurrence and severity of anaphylaxis and other allergic symptoms. [redacted][20][redacted][21][redacted]

4.(i).A.(2) Japanese phase II/III study (5.3.5.1-1, Study 203-3-2 [redacted 20 to redacted 20])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients aged ≥12 years with HDM-induced allergic rhinitis[22] (target sample size, 900; 300 subjects per group) to investigate the efficacy and safety of Miticure.

[19] Studies MT-02, MT-04, and MT-06.

[20] A randomized, double-blind, placebo-controlled, dose-escalation study (5.3.3.2-2) conducted overseas in patients with HDM-induced allergic asthma (n = 71), who received once-daily sublingual doses of 1, 2, 4, 8, 16, or 32 DU of Miticure, or placebo for 28 days.

[21] A randomized, double-blind, placebo-controlled, parallel-group study (5.3.5.4-3) conducted overseas in patients with HDM-induced allergic asthma (n = 604), who received once-daily sublingual doses of 1, 3, or 6 DU of Miticure, or placebo for 52 weeks.

[22] Patients with HDM-induced allergic rhinitis who met the following requirements: (1) HDM-specific IgE antibodies in serum (*D. farinae* + *D. pteronyssinus*) are ≥ Class 3; (2) tested positive in HDM or house-dust nasal provocation test; and (3) allergic rhinitis daily symptom score of ≥7 on ≥7 days during the 14-day period after the start of monitoring. However, patients whose condition was complicated by bronchial asthma or who had a treatment history of bronchial asthma or had an asthma attack within 2 years prior to the start of observation were excluded.

In this study, subjects received once-daily sublingual doses of Miticure 6 DU (2 DU at Week 1, and 6 DU at Week 2 and thereafter), 12 DU (2 DU at Week 1, 6 DU at Week 2, and 12 DU at Week 3 and thereafter), or placebo for 52 weeks. Subjects were instructed to place the study drug under the tongue for 1 minute before swallowing; and refrain from gargling, eating, or drinking for the following 5 minutes after swallowing. When intolerable symptoms (as a general rule, at least one severe nasal symptom[23] or at least one severe eye symptom[24]) developed between the first day of treatment and the end of the study, subjects were allowed to take the following rescue medications: fluticasone propionate nasal drops for nasal congestion; and olopatadine hydrochloride eye drops for eye symptoms. If these agents failed to alleviate the symptoms and intolerable symptoms continued to persist, or sneezing, nasal discharge, or itching sensation was intolerable, the use of loratadine was allowed.

All 946 randomized subjects (313 subjects in the 6-DU group, 314 subjects in the 12-DU group, and 319 subjects in the placebo group) were included in the safety analysis population, from which 95 subjects[25] were excluded and the remaining 851 subjects (285 subjects in the 6-DU group, 281 subjects in the 12-DU group, and 285 subjects in the placebo group) were included in the full analysis set (FAS)[26] and the efficacy analysis population. Rates of treatment discontinuation were 8.6% (27 of 313 subjects) in the 6-DU group, 10.5% (33 of 314 subjects) in the 12-DU group, and 10.7% (34 of 319 subjects) in the placebo group.

The primary efficacy endpoint for this study was the total nasal symptom medication score (TNSMS), which is the sum of the daily nasal symptom score[27] and daily medication score[28] for allergic rhinitis.

Table 4 shows TNSMS in the period from Week 44 to Week 52, the primary efficacy endpoint. The results showed that both the 6-DU and 12-DU groups differed significantly from the placebo group, demonstrating the superiority of Miticure at 6-DU and 12-DU over placebo.

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[23] Nasal discharge, nasal congestion, sneezing, and itching sensation.

[24] Itchy eyes and teary eyes.

[25] Subjects who discontinued study treatment in the following periods except for any of the14-day periods following each observation day at Weeks 4, 12, 20, 28, and 36, or except for Weeks 44 to 52; discontinued prior to Weeks 44 to 52; or had <80% of data entry in the electronic patient diary (28 subjects in the 6-DU, 33 subjects in the 12-DU, and 34 subjects in the placebo groups).

[26] Subjects who received the study drug, and had ≥80% of data entry (data for ≥45 days) for symptom score and medication score in the period from Week 44 to Week 52, regardless of compliance with the protocol.

[27] The total scores of nasal symptoms (nasal discharge, nasal congestion, sneezing, and itching sensation), each evaluated in a scale of 0 to 3, with 3 the most severe.

[28] The total scores of medication in a scale with the per-dose score and the maximum daily score defined as 4 and 4, respectively, for loratadine and 4 and 8, respectively, for fluticasone propionate nasal drops.

Table 4. TNSMS in the period from Week 44 to Week 52 (FAS, observed case [OC])

	6-DU group	12-DU group	Placebo group
Baseline[a)]	8.53 ± 1.27 (285)	8.49 ± 1.27 (281)	8.42 ± 1.32 (285)
Week 44-Week 52	4.64 ± 3.22 (285)	4.73 ± 3.04 (281)	5.52 ± 3.07 (285)
Change	−3.89 ± 3.11 (285)	−3.75 ± 2.99 (281)	−2.90 ± 3.02 (285)
Difference from the placebo group [95% confidence interval (CI)],[b)] *P*-value[b), c)]	−1.15 [−1.65, −0.64] *P* < 0.0001	−0.99 [−1.50, −0.48] *P* = 0.0001	
Difference from the 6-DU group [95% CI],[b)] *P*-value[b), c)]		0.16 [−0.32, 0.63] *P* = 0.5179	

Mean ± standard deviation (number of subjects)

a) Baseline daily nasal symptom score for allergic rhinitis (mean score for the 14 days following Visit 1)

b) Based on a linear mixed-effects model, with the square root of TNSMS in the period from Weeks 44 to Week 52 as the outcome variable, the treatment group and the square root of baseline values as fixed effects, and medical institution as a random effect.

c) Multiplicity adjustment based on the Fisher's least significant difference method was performed (overall null hypothesis, *P* < 0.0001).

Table 5 shows the secondary efficacy endpoints. The percentage of subjects who used rescue medications during the study period was 66.8% (209 of 313 subjects) in the 6-DU group, 67.8% (213 of 314 subjects) in the 12-DU group, and 72.1% (230 of 319 subjects) in the placebo group.

Table 5. Secondary endpoints in the period from Week 44 to Week 52 (FAS, OC)

	6-DU group (285 subjects)	12-DU group (281 subjects)	Placebo group (285 subjects)	Difference from the placebo group [95% CI]	
				6-DU group	12-DU group
Change from baseline in the daily symptom score for allergic rhinitis	−4.27 ± 2.60	−4.09 ± 2.55	−3.36 ± 2.40	−1.05 [−1.49, −0.61]	−0.87 [−1.32, −0.43]
Daily medication score for allergic rhinitis	0.38 ± 1.15	0.34 ± 0.96	0.46 ± 1.24	−0.04 [−0.10, 0.02]	−0.05 [−0.11, 0.01]
Change from baseline in the daily symptom score for allergic conjunctivitis	−1.43 ± 1.53	−1.36 ± 1.40	−1.10 ± 1.41	−0.30 [−0.48, −0.12]	−0.29 [−0.47, −0.10]
Daily medication score for allergic conjunctivitis	0.14 ± 0.51	0.14 ± 0.41	0.21 ± 0.51	−0.03 [−0.06, −0.01]	−0.03 [−0.05, 0.00]
Percentage of subjects who had no rhinitis symptoms for ≥1 day (%)	38.9	34.2	26.7	12.3 [3.9, 20.5]	7.5 [−0.7, 15.8]
Percentage of subjects who had no conjunctivitis symptoms for ≥1 day (%)	72.3	72.6	64.2	8.1 [−0.3, 16.4]	8.4 [0.1, 16.5]

Mean, or mean ±standard deviation (SD)

The incidence of adverse events was 89.5% (280 of 313 subjects) in the 6-DU group, 90.4% (284 of 314 subjects) in the 12-DU group, and 80.3% (256 of 319 subjects) in the placebo group. Table 6 shows main adverse events.

Table 6. Adverse events that occurred with an incidence of ≥5% in any group (safety analysis population)

Event	6-DU group (313 subjects)	12-DU group (314 subjects)	Placebo group (319 subjects)
Nasopharyngitis	112 (35.8)	102 (32.5)	107 (33.5)
Pharyngitis	62 (19.8)	91 (29.0)	62 (19.4)
Oedema mouth	50 (16.0)	57 (18.2)	0
Throat irritation	44 (14.1)	37 (11.8)	3 (0.9)
Oral pruritus	37 (11.8)	55 (17.5)	4 (1.3)
Oropharyngeal discomfort	35 (11.2)	38 (12.1)	5 (1.6)
Oral discomfort	33 (10.5)	32 (10.2)	3 (0.9)
Paraesthesia oral	27 (8.6)	33 (10.5)	4 (1.3)
Influenza	25 (8.0)	26 (8.3)	26 (8.2)
Upper respiratory tract inflammation	24 (7.7)	15 (4.8)	19 (6.0)
Gastroenteritis	20 (6.4)	20 (6.4)	21 (6.6)
Stomatitis	20 (6.4)	20 (6.4)	17 (5.3)
Bronchitis	19 (6.1)	8 (2.5)	14 (4.4)
Ear pruritus	17 (5.4)	28 (8.9)	1 (0.3)
Acute sinusitis	16 (5.1)	15 (4.8)	18 (5.6)
Headache	13 (4.2)	18 (5.7)	20 (6.3)
Eczema	12 (3.8)	13 (4.1)	18 (5.6)

Number of subjects (%)

No deaths occurred. The incidence of serious adverse events was 1.6% (5 of 313 subjects) in the 6-DU group (tooth hypoplasia, ulna fracture, tonsillitis, haemorrhoid operation, and appendicitis in 1 subject each), 1.6% (5 of 314 subjects) in the 12-DU group (gastroenteritis, ovarian neoplasm, breast cancer, sudden hearing loss, and incisional hernia in 1 subject each), 0.9% (3 of 319 subjects) in the placebo group (contusion/haematoma evacuation, anaphylactic reaction, and gastric cancer in 1 subject each), A causal relationship to the study drug was ruled out for all the serious adverse events, and for all cases, outcomes were reported as either "recovered" or "improved."

Adverse events leading to treatment discontinuation occurred in 2.2% (7 of 313 subjects) in the 6-DU group, 1.9% (6 of 314 subjects) in the 12-DU group, and 2.8% (9 of 319 subjects) in the placebo group. A causal relationship to the study drug could not be ruled out for the events in the following subjects: 5 subjects in the 6-DU group (lip oedema, oedema mouth, asthma, sensation of foreign body/headache, nausea [1 subject each]), 4 subjects in the 12-DU group (drug eruption, chest discomfort, tongue pruritus/nausea, dyspepsia/feeling abnormal [1 subject each]), and 4 subjects in the placebo group (urticaria [2 subjects]; photosensitivity reaction, dermatitis atopic [1 subject each]). The outcomes were reported as either "recovered" or "improved" except for 1 subject in the placebo group (urticaria).

The incidence of adverse drug reactions was 63.6% (199 of 313 subjects) in the 6-DU group, 63.7% (200 of 314 subjects) in the 12-DU group, and 16.9% (54 of 319 subjects) in the placebo group.

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

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

The applicant explained the efficacy of Miticure as follows:

The European guideline for clinical development of allergen extract products recommends that the primary endpoints should represent both symptom severity and rescue medication use (Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. EMEA CHMP/EWP/18504/2006, London, 20 November 2008). Based on the recommendation of the guideline, the primary efficacy endpoint for the Japanese phase II/III study (Study 203-3-2) was defined as TNSMS, which is the sum of the daily nasal symptom score and daily medication score for allergic rhinitis. Table 7 shows the results of paired comparison test. The observed differences in TNSMS in the period from Week 44 to Week 52 between both the 6-DU and 12-DU groups and the placebo group were statistically significant. The primary analysis for the study was to be performed after primary variables were square-root transformed to achieve a better fit to a normal distribution. Untransformed data also showed similar trends as the primary analysis results (Table 7).

Table 7. TNSMS in the period from Weeks 44 to Week 52 (FAS, OC)

	6-DU group	12-DU group	Placebo group
Baseline[a)]	8.53 ± 1.27 (285)	8.49 ± 1.27 (281)	8.42 ± 1.32 (285)
Week 44-Week 52	4.64 ± 3.22 (285)	4.73 ± 3.04 (281)	5.52 ± 3.07 (285)
Change	−3.89 ± 3.11 (285)	−3.75 ± 2.99 (281)	−2.90 ± 3.02 (285)
Difference from the placebo group [95% CI],[b)] *P*-value[b), c)]	−1.15 [−1.65, −0.64] *P* < 0.0001	−0.99 [−1.50, −0.48] *P* = 0.0001	
Difference from the placebo group [95% CI],[d)] *P*-value[d)]	−0.94 [−1.42, −0.46] *P* = 0.0001	−0.85 [−1.33, −0.37] *P* = 0.0006	

Mean ± SD (number of subjects)

a) Baseline daily nasal symptom score for allergic rhinitis (mean score for the 14 days following Visit 1, the first monitoring visit day)

b) Based on a linear mixed-effects model, with the square root of TNSMS for Weeks 44 to 52 as the outcome variable, the treatment group and the square root of baseline values as fixed effects, and medical institution as a random effect.

c) Multiplicity adjustment based on the Fisher's least significant difference method was performed (overall null hypothesis, $P < 0.0001$).

d) Based on a linear mixed-effects model, with TNSMS in the period from Week 44 to Week 52 as the outcome variable, treatment group and baseline values as fixed effects, and medical institution as a random effect.

Another analysis was performed using an adjusted nasal symptom score method (Grouin JM et al. *Clin Exp Allergy.* 2011;41:1282-1288), which was proposed as a new efficacy endpoint evaluation method for desensitization therapy taking into account both symptom severity and rescue medication use. In this method, the daily symptom scores for the day of rescue medication treatment and for the following day are replaced by the score for the day prior to the rescue medication treatment. The results showed that the difference from placebo was −1.10 [−1.55, −0.64] for the 6-DU group, and −0.91 [−1.37, −0.44] for the 12-DU group, suggesting that they were consistent with the results for the primary endpoint, TNSMS.

The efficacy of 6 DU and 12 DU was also investigated in the foreign phase III study (Study MT-06).[29] Table 8 shows the results for the primary endpoints. Although there are differences in study design, such as the presence or absence of a dose-escalation period, the results showed that both the 6-DU and 12-DU groups were different from the placebo group significantly, similarly to the Japanese phase II/III study (Study 203-3-2).

From the above results, it is considered that the efficacy of Miticure at 6 DU and 12 DU for the relief of allergic rhinitis symptoms was demonstrated.

Table 8. TNSMS in the period from Weeks 44 to Week 52 in Study MT-06 (FAS, MI[a)])

	6-DU group	12-DU group	Placebo group
Baseline[b)]	8.03 ± 1.65 (338)	7.95 ± 1.68 (318)	8.00 ± 1.64 (338)
Week 44-Week 52	6.76 ± 4.61 (338)	6.68 ± 4.50 (318)	7.81 ± 4.63 (338)
Change	−1.26 ± 4.66 (338)	−1.28 ± 4.90 (318)	−0.19 ± 4.67 (338)
Difference from the placebo group [95% CI],[c)] *P*-value[c), d)]	−1.07 [−1.80, −0.34] *P* = 0.004	−1.09 [−1.84, −0.35] *P* = 0.004	
Difference from the 6-DU group [95% CI],[c)] *P*-value[c), d)]		−0.03 [−0.76, 0.70] *P* = 0.941	

Mean ± SD (number of subjects)

a) Multiple imputation; using observed data of the placebo group.

b) Baseline of daily nasal symptom score for allergic rhinitis (mean score for the 15 days following Visit 1, the first monitoring visit day)

c) Based on a linear mixed-effects model, with the square root of TNSMS in the period from Week 44 to Week 52 as the outcome variable, the treatment group and the square root of baseline values as fixed effects, and country as a random effect.

d) Fisher's least significant difference method (overall null hypothesis, $P = 0.003$).

[29] A randomized, double-blind, placebo-controlled, parallel-group study (5.3.5.1-2) conducted overseas in patients with HDM-induced allergic rhinitis (n = 992). In this study, subjects received once-daily sublingual doses of 6 DU or 12 DU of Miticure, or placebo for 52 weeks.

The ultimate goal of desensitization therapy is to achieve the remission of allergic symptoms through long-term treatment. The period-by-period results for TNSMS and daily nasal symptom score for allergic rhinitis in the Japanese phase II/III (Study 203-3-2) showed that the difference between the 6-DU and placebo groups, and the 12-DU and placebo groups tended to increase over time as shown in Table 9.

Table 9. The difference between the Miticure and placebo groups by period (Study 203-3-2, OC)

Endpoint	Dose group	Difference from placebo [95% CI][a]					
		Weeks 4-6 (304/307/316)[b]	Weeks 12-14 (299/295/307)[b]	Weeks 20-22 (297/291/302)[b]	Weeks 28-30 (294/288/294)[b]	Weeks 36-38 (293/282/293)[b]	Weeks 44-52 (286/281/286)[b]
TNSMS	6 DU	−0.33 [−0.76, 0.10]	−0.64 [−1.15, −0.13]	−0.71 [−1.27, −0.16]	−0.78 [−1.33, −0.22]	−1.12 [−1.66, −0.59]	−1.14 [−1.64, −0.64]
	12 DU	−0.42 [−0.84, 0.01]	−0.77 [−1.28, −0.25]	−0.56 [−1.12, 0.00]	−0.54 [−1.10, 0.03]	−0.85 [−1.39, −0.30]	−1.00 [−1.50, −0.49]
Daily symptom score for allergic rhinitis	6 DU	−0.26 [−0.58, 0.06]	−0.62 [−1.04, −0.21]	−0.61 [−1.03, −0.18]	−0.74 [−1.19, −0.29]	−0.99 [−1.45, −0.53]	−1.05 [−1.49, −0.61]
	12 DU	−0.28 [−0.60, 0.04]	−0.74 [−1.16, −0.33]	−0.48 [−0.91, −0.05]	−0.53 [−0.98, −0.08]	−0.72 [−1.19, −0.25]	−0.88 [−1.33, −0.44]

a) Based on a linear mixed-effects model, with TNSMS in the period from Week 44 to Week 52 as the outcome variable, the treatment group and the square root of baseline values as fixed effects, and medical institution as a random effect.
b) Number of subjects (6 DU/12 DU/placebo)

The efficacy of long-term treatment has been reported in the following studies: in a 10-year clinical study of SCIT using mite allergens in patients with allergic rhinitis, improvement in rhinitis symptoms was observed in a treatment-duration dependent manner (Ohashi Y et al. *Scand J Immunol.* 1998;47:167-178); in a 3-year clinical study of SCIT using mite allergens in adult patients with mite allergen-induced allergic rhinitis or asthma, rhinitis symptoms and asthma symptoms improved increasingly over time compared to pre-treatment (Pichler CE et al. *Allergy.* 1997;52:274-283; and Pichler CE et al. *Allergy.* 2001;56:301-306). The above discussions suggest that a higher efficacy may be achieved after long-term treatment (≥1 year) with Miticure.

Based on the applicant's explanation, PMDA has concluded that the efficacy of the product at 6 DU and 12 DU for the improvement in allergic rhinitis symptoms was demonstrated.

Desensitization therapy requires long-term treatment, and its ultimate goal is the remission of allergic symptoms. However, the treatment experience with Miticure in clinical studies has not exceeded 1 year. Therefore, through post-marketing surveillance and other relevant programs, it is necessary to gather more information on long-term efficacy including efficacy in continuous treatment in subjects whose response had been inadequate.

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

The applicant explained the occurrence of adverse events attributable to allergy-related reactions to mite allergens in clinical studies of Miticure, based on the Japanese phase II/III study in patients with allergic

rhinitis (Study 203-3-2), Japanese phase II/III study in patients with allergic asthma (Study 203-3-1),[30] and other relevant information.

In clinical studies of Miticure conducted in and out of Japan, subjects who received Miticure neither died nor experienced anaphylaxis or anaphylactic shock. The incidence of serious adverse events did not differ markedly among treatment groups in the Japanese phase II/III study (Study 203-3-2) [see "4.(i).A Summary of the submitted data"]. The incidence of serious adverse events was also similar among treatment groups in the other Japanese phase II/III study (Study 203-3-1): 2.6% (7 of 274 subjects) in the 6-DU group, 3.6% (10 of 276 subjects) in the 12-DU group, and 4.0% (11 of 274 subjects) in the placebo group. In the foreign phase III study (Study MT-06) in patients with allergic rhinitis, a subject in the 12-DU group experienced mild laryngeal oedema and received adrenaline, but there was no life-threatening risk, and this patient continued treatment with Miticure.

The occurrence of anaphylaxis-related symptoms[31] and adverse events attributable to allergy-related reactions to mite allergens[32] in the Japanese phase II/III study (Study 203-3-2) was as shown in Table 10, and major events among allergy-related reactions are listed in Table 11. The occurrence of anaphylaxis-related symptoms and allergy-related reactions was fairly similar between the 6-DU and 12-DU groups, and the incidence of allergy-related reactions tended to be higher in the maintenance dose period than in the dose-escalation period in all treatment groups. Similar trends were observed in the other Japanese phase II/III study (Study 203-3-1).

[30] A randomized, double-blind, placebo-controlled, parallel-group study (5.3.5.4-1) conducted in Japan in patients with HDM-induced allergic asthma (n = 826). In this study, the dosage and administration were the same as those of the Japanese phase II/III study (Study 203-3-2); subjects received once-daily sublingual doses of 6 DU or 12 DU of Miticure, or placebo for 52 weeks.

[31] Adverse events defined based on the "Manuals for management of individual serious adverse drug reactions: Anaphylaxis" (Ministry of Health, Labour and Welfare, March 2008), by referring to MedDRA Preferred Terms: pruritus, pruritus generalised, urticaria, erythema, erythema multiforme, abdominal pain, abdominal pain lower, abdominal pain upper, nausea, vomiting, visual impairment, visual acuity reduced, eye disorder, dysphonia, sneezing, throat irritation, larynx irritation, choking sensation, and dyspnoea.

[32] Palpitations, tachycardia, ear discomfort, ear pruritus, eyelid oedema, abdominal discomfort, abdominal pain, abdominal pain upper, cheilitis, diarrhoea, gingivitis, glossitis, glossodynia, lip oedema, lip pain, lip swelling, nausea, odynophagia, oedema mouth, oesophagitis, oral discomfort, oral mucosal blistering, oral pain, stomatitis, submaxillary gland enlargement, swollen tongue, tongue disorder, tongue oedema, vomiting, oral pruritus, palatal oedema, hypoaesthesia oral, paraesthesia oral, oral mucosa erosion, oral mucosal erythema, gingival erythema, tongue pigmentation, tongue pruritus, lip pruritus, chest discomfort, chest pain, feeling abnormal, local swelling, thirst, sensation of foreign body, anaphylactic reaction, food allergy, dizziness, dysgeusia, hypogeusia, asthma, choking sensation, cough, dysphonia, pharyngeal oedema, throat irritation, throat tightness, wheezing, nasal discomfort, pharyngeal erythema, larynx irritation, oropharyngeal discomfort, oropharyngeal pain, drug eruption, pruritus, rash, urticaria, pruritus generalised, and hot flush.

Table 10. The occurrence of anaphylaxis-related symptoms and allergy-related reactions by period (Study 203-3-2, safety analysis population)

Treatment group	6-DU group			12-DU group			Placebo group		
Period	Dose escalation 1 (2 DU)	Dose escalation 2 (6 DU)	Mainte-nance dose (6 DU)	Dose escalation 1 (2 DU)	Dose escalation 2 (6 DU)	Mainte-nance dose (12 DU)	Dose escalation 1 (0 DU)	Dose escalation 2 (0 DU)	Mainte-nance dose (0 DU)
Number of subjects	313	311	308	314	313	311	319	319	318
Anaphylaxis-related symptoms									
Any adverse event	26 (8.3)	24 (7.7)	32 (10.4)	24 (7.6)	12 (3.8)	37 (11.9)	2 (0.6)	1 (0.3)	19 (6.0)
Serious adverse events	0	0	0	0	0	0	0	0	0
Adverse events leading to study discontinuation	0	0	1 (0.3)	1 (0.3)	0	0	0	0	2 (0.6)
Adverse drug reactions	23 (7.3)	22 (7.1)	16 (5.2)	24 (7.6)	12 (3.8)	22 (7.1)	2 (0.6)	0	9 (2.8)
Allergy-related reactions									
Any adverse event	90 (28.8)	93 (29.9)	132 (42.9)	92 (29.3)	95 (30.4)	135 (43.4)	16 (5.0)	9 (2.8)	66 (20.8)
Serious adverse events	0	0	0	0	0	0	0	0	1 (0.3)
Adverse events leading to study discontinuation	0	2 (0.6)	5 (1.6)	2 (0.6)	1 (0.3)	1 (0.3)	0	0	4 (1.3)
Adverse drug reactions	85 (27.2)	90 (28.9)	104 (33.8)	91 (29.0)	91 (29.1)	107 (34.4)	14 (4.4)	3 (0.9)	20 (6.3)

Number of subjects (%)
Dose-escalation period 1, from the first day of treatment to 1 day before the start of dose escalation, which was 1 week after the start of treatment; dose-escalation period 2, from 1 week after the start of treatment to 1 day before the start of the maintenance period, which is 2 weeks after the start of treatment.

Table 11. Adverse events attributable to allergy-related reactions that occurred with an incidence of ≥5% in any group or any period (Study 203-3-2, safety analysis population)

Treatment group	6-DU group			12-DU group			Placebo group		
Period	Dose escalation 1 (2 DU)	Dose escalation 2 (6 DU)	Maintenance dose (6 DU)	Dose escalation 1 (2 DU)	Dose escalation 2 (6 DU)	Maintenance dose (12 DU)	Dose escalation 1 (0 DU)	Dose escalation 2 (0 DU)	Maintenance dose (0 DU)
Number of subjects	313	311	308	314	313	311	319	319	318
Oedema mouth	3 (1.0)	21 (6.8)	30 (9.7)	5 (1.6)	28 (8.9)	26 (8.4)	0	0	0
Oral pruritus	16 (5.1)	12 (3.9)	11 (3.6)	20 (6.4)	16 (5.1)	25 (8.0)	3 (0.9)	0	1 (0.3)
Paraesthesia oral	12 (3.8)	10 (3.2)	10 (3.2)	18 (5.7)	8 (2.6)	8 (2.6)	2 (0.6)	0	2 (0.6)
Stomatitis	2 (0.6)	1 (0.3)	17 (5.5)	2 (0.6)	2 (0.6)	18 (5.8)	2 (0.6)	3 (0.9)	15 (4.7)
Throat irritation	23 (7.3)	18 (5.8)	6 (1.9)	21 (6.7)	10 (3.2)	8 (2.6)	2 (0.6)	0	1 (0.3)
Oropharyngeal discomfort	15 (4.8)	9 (2.9)	11 (3.6)	9 (2.9)	9 (2.9)	20 (6.4)	1 (0.3)	1 (0.3)	3 (0.9)

Number of subjects (%)
Dose-escalation period 1, from the first day of treatment to 1 day before the start of dose escalation, which was 1 week after the start of treatment; dose-escalation period 2, from 1 week after the start of treatment to 1 day before the start of the maintenance dose period, which was 2 weeks after the start of treatment.

The above results are interpreted as indicating that the tolerability of Miticure at both 6 DU and 12 DU is acceptable, although attention should be paid to possible local reactions at the administration site. SLIT is considered to have a lower risk of serious systemic adverse drug reactions such as anaphylaxis than SCIT, and serious systemic adverse drug reactions such as anaphylaxis have not occurred in foreign clinical studies of Miticure. However, given that SLIT consists of allergen administration, the risk of serious systemic adverse drug reactions such as anaphylaxis in the post-marketing setting cannot be ruled out. In addition, a SLIT product is likely to raise expectations in healthcare professionals in clinical settings, that it offers ease of use and greater safety than SCIT products. Therefore, a system for post-marketing safety management will be established to raise awareness about the risk of anaphylaxis through the package insert and other relevant materials, as with an already approved SLIT product, Cedartolen Sublingual Drops.

Desensitization therapy requires long-term medication with a possible scenario of temporary treatment interruption and subsequent resumption. Therefore, PMDA asked the applicant to discuss the safety of treatment resumption after interruption, whether or not there should be any changes associated with the duration of interruption, the dose levels before and after interruption, or other factors.

The applicant explained as follows:
In the Miticure groups of the Japanese phase II/III study (Study 203-3-2), the incidence of treatment interruption was 14.7% (46 of 313 subjects) in the 6-DU group and 16.6% (52 of 314 subjects) in the 12-DU group, and the incidence of interruption due to adverse events was 12.1% (38 of 313 subjects) in the 6-DU group and 13.1% (41 of 314 subjects) in the 12-DU group. In cases in which treatment was interrupted because of adverse events, the occurrence of adverse events after treatment resumption was analyzed in terms of the duration of treatment interruption. The proportion of subjects who experienced adverse drug reactions within 1 week of treatment resumption was 13.8% (4 of 29 subjects[33]) in the 6-DU group and 9.7% (3 of 31 subjects[33]) in the 12-DU group when treatment was interrupted for <7 days, and was 9.1% (1 of 11 subjects[33]) in the 6-DU group and 15.4% (2 of 13 subjects[33]) in the 12-DU group when treatment was interrupted for ≥7 days, with no evident correlation between the duration of treatment interruption and the occurrence of adverse drug reactions. No association was found between the occurrence of adverse drug reactions and the dose levels before and after interruption.

The above results showed that the safety of treatment resumption following interruption was not affected by the duration of treatment interruption or other factors, and there appears to be no need to specify the doses when resuming treatment. However, in the post-marketing setting, some patients may resume treatment after a more prolonged interruption. Therefore, patients will be advised, through appropriate materials provided, to seek medical consultation about treatment resumption after interruption.

PMDA considers as follows:
Although anaphylaxis did not occur in the clinical studies of Miticure, adverse events attributable to allergy-related reactions to mite allergens occurred frequently in subjects who received Miticure, and these adverse events included skin and respiratory symptoms, which are possible prodromes of anaphylaxis. The nature of treatment with Miticure consisting of direct administration of allergens suggests that anaphylaxis potentially occurs in the post marketing setting, as explained by the applicant. Therefore, the risk of anaphylaxis should be taken into consideration to ensure Miticure is managed safely, and it is important to take safety measures by appropriately providing information on the risk of anaphylaxis through the package insert and other relevant materials, as with already approved SLIT products. In addition, Miticure is intended mainly for home use by patients, and consequently anaphylaxis and related events may occur outside medical institutions. Furthermore, as explained by the

[33] Events occurring in subjects who had 2 treatment interruptions (≥7-day and <7-day periods) were included in both interruption categories.

applicant, the ease of use and other features of Miticure may lead to its use by physicians with no experience of desensitization therapy. Therefore, a system for safety management that takes these factors into account should be established as with already approved SLIT products.

While desensitization therapy requires long-term treatment, the experience with Miticure in clinical studies has not exceeded 1 year of treatment duration, and there are limited data on resumption of Miticure following interruption. Therefore, through post-marketing surveillance and other relevant programs, it is necessary to gather more information on efficacy and safety in long-term use, including safety when resuming Miticure after treatment has been interrupted for safety reasons. Because dosage and administration at resumption have not been established at this point, these need to be determined by physicians based on the condition of individual patients. Therefore, the information on the dosage and administration should also be appropriately provided to healthcare professionals in clinical settings using materials, taking into consideration the information in treatment guidelines in and out of Japan.

The above conclusion by PMDA and specific safety measures proposed by the applicant will be discussed at the Expert Discussion.

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

The proposed dosage and administration was that the dose may be increased to 12 DU according to the severity of symptoms. After PMDA pointed out that the efficacy of Miticure was similar between 6 DU and 12 DU in the Japanese phase II/III study (Study 203-3-2), and that clinical study data justifying a dose increase to 12 DU according to the severity of symptoms have not been obtained, the proposed dose level of 12 DU (20,000 JAU) was withdrawn.

The applicant provided the following explanation for setting a uniform dose level of 6 DU for Miticure in the maintenance dose period for all patients including children aged ≥12 years.

The results of the Japanese phase II/III study (Study 203-3-2) showed that the difference from the placebo group in TNSMS in the period from Week 44 to Week 52 was −1.08 in the 6-DU group and −0.99 in the 12-DU group for the subgroup of subjects aged ≥12 years and <18 years, suggesting that the trend is similar to that of the entire population [see “4.(i).A.(2) Japanese phase II/III study”].

Table 12 shows the occurrence of allergy-related reactions by age in the Japanese phase II/III study (Study 203-3-2). The results showed that there was no trend towards an increased incidence of allergy-related reactions in subjects aged ≥12 years and ≤17 years compared with subjects aged ≥18 years in either the dose-escalation or maintenance dose period. Based on the above discussions, it is considered appropriate to select 6 DU of Miticure as the dose level in the maintenance dose period for all patients, including children aged ≥12 years.

Table 12. Occurrence of allergy-related reactions by age (Study 203-3-2, safety analysis population)

Treatment group	6-DU group						12-DU group					
Period	Dose escalation 1 (2 DU)		Dose escalation 2 (6 DU)		Maintenance dose (6 DU)		Dose escalation 1 (2 DU)		Dose escalation 2 (6 DU)		Maintenance dose (12 DU)	
Age (year)	12-17	≥18	12-17	≥18	12-17	≥18	12-17	≥18	12-17	≥18	12-17	≥18
Number of subjects	96	217	96	215	94	214	107	207	106	207	106	205
Any adverse event	23 (24.0)	67 (30.9)	38 (39.6)	55 (25.6)	39 (41.5)	93 (43.5)	27 (25.2)	65 (31.4)	43 (40.6)	52 (25.1)	48 (45.3)	87 (42.4)
Serious adverse events	0	0	0	0	0	0	0	0	0	0	0	0
Adverse events leading to study discontinuation	0	0	1 (1.0)	1 (0.5)	1 (1.1)	4 (1.9)	1 (0.9)	1 (0.5)	1 (0.9)	0	0	1 (0.5)
Adverse drug reactions	20 (20.8)	65 (30.0)	37 (38.5)	53 (24.7)	31 (33.0)	73 (34.1)	27 (25.2)	64 (30.9)	42 (39.6)	49 (23.7)	36 (34.0)	71 (34.6)

Number of subjects (%)

PMDA considers that it is acceptable to include a 1-week period in which once-daily doses of 2 DU (3300 JAU) of Miticure are administered, followed by a maintenance dose period, from Week 2 onward, in which once-daily doses of 6 DU (10,000 JAU) are administered, as in the dosage and administration in the Japanese phase II/III study (Study 203-3-2).

Based on the submitted data, PMDA considers there should be no particular problem with using 6 DU for children aged ≥12 years, the same dose level for adults in the maintenance dose period; however, the efficacy and safety of Miticure for children aged <12 years have not been evaluated in the Japanese phase II/III study (Study 203-3-2). Therefore, it is considered appropriate to specify that the product is indicated for adults and children aged ≥12 years in the dosage and administration section.

[Dosage and administration]

~~1. Dose escalation period (Week 1)~~

The usual dosage of Miticure House Dust Mite Sublingual Tablets for adults and children aged ≥12 years is a once-daily 3300-JAU tablet ~~for~~ during the first week of treatment ~~(dose escalation period). The tablet should be held under the tongue for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes.~~

~~2. Maintenance period (from Week 2 onward)~~

~~After the dose escalation period, the usual maintenance dose of~~ and a once-daily 10,000-JAU tablet ~~is administered~~ from the second week onward. The tablet should be placed under the tongue for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes. ~~The dose may be increased to a once-daily 20,000-JAU tablet according to the severity of symptoms, only after the 10,000-JAU tablet has been administered for at least 1 week.~~

(Underlined parts are additions to, and struck-through parts are deletions from the proposed dosage and administration)

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

PMDA considers as follows:

Desensitization therapy is defined as a treatment to reduce sensitivity to a causative antigen by continuous administration of the causative antigen, thereby producing cure or long-term remission of allergic diseases, according to the treatment guidelines in Japan (The Japanese Rhinologic Society eds. *Practical Guidelines for the Management of Allergic Rhinitis in Japan 2013: Sublingual Immunotherapy; Practice and Management*). The guidelines also state that SLIT can be used as a basic treatment method regardless of the severity of allergic rhinitis symptoms in view of its preventive effect on new allergen sensitization. Therefore, it is assumed that Miticure is indicated for patients with allergic rhinitis in general, and it is expected that it can be used regardless of concomitant use of antihistamines and other common drugs. However, SLIT is a therapy for which the risk of anaphylaxis exists; therefore, it is considered appropriate to provide a caution in the package insert and other relevant materials that the use of Miticure should be determined according to the symptoms and treatment history of the patient, taking into consideration the possible use of other treatment methods. While the clinical positioning of Miticure is considered to be the same as already-approved SLIT products, the difference in efficacy and safety between Miticure and these products is unknown at this point.

4.(i).B.(5) Indication

PMDA has concluded that it is appropriate to modify the indication of Miticure as follows on the basis of discussions in the sections [“4.(i).B.(1) Efficacy” and “4.(i).B.(4) Clinical positioning”].

[Indication] Desensitization therapy for ~~the following~~ allergic ~~disorder~~ rhinitis induced by mite allergens~~: allergic rhinitis~~

(Underlined parts are additions to, and struck-through parts are deletions from the proposed indication)

In the Japanese phase II/III study (Study 203-3-2), data on the efficacy and safety of Miticure in patients with high non-mite-allergen-specific IgE antibody titers are limited; therefore, it is considered appropriate to provide information in the package insert and other relevant materials that the efficacy and safety of Miticure in these patients have not been evaluated.

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

PMDA considers that, as discussed in the sections [“4.(i).B.(1) Efficacy” and “4.(i).B.(2) Safety”], it is necessary to gather more information on the efficacy and safety of long-term treatment exceeding 1 year, including efficacy in continuous treatment in subjects whose response has been inadequate, and safety when resuming Miticure after treatment has been interrupted for safety reasons, through post-marketing surveillance and other relevant programs.

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

The inspections are currently underway. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently underway. The results and PMDA's conclusion will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of Miticure in desensitization therapy in patients with mite allergen-induced allergic rhinitis has been demonstrated. With regard to the safety of the product, appropriate safety measures must be taken against the risk of anaphylaxis and other serious systemic reactions, as with already approved SLIT products. Thus, it is essential to educate and provide guidance to healthcare professionals and patients. After market launch, long-term post-marketing surveillance should be conducted long enough to investigate the appropriate timing for determining lack of efficacy, and safety and efficacy at resumption of treatment after interruption. The information collected should be successively provided to physicians and patients.

PMDA considers that Miticure may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

August 17, 2015

I. Product Submitted for Registration

[Brand name]	(a) Miticure House Dust Mite Sublingual Tablets 3,300 JAU;
	(b) Miticure House Dust Mite Sublingual Tablets 10,000 JAU
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Date of application]	January 26, 2015

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described 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 and safety

The PMDA's conclusion regarding the efficacy and safety of Miticure House Dust Mite Sublingual Tablets (hereinafter referred to as Miticure), as described in the Review Report (1), was supported by the expert advisors, who also raised the following comments:

- The ultimate goal of desensitization therapy is to achieve the remission of allergic symptoms. However, the treatment experience with Miticure in clinical studies has not exceeded 1 year. Therefore, through post-marketing surveillance and other relevant programs, it is necessary to gather more information on long-term efficacy.
- In the Japanese phase II/III study (Study 203-3-2), the primary variables had a high interindividual variability, which may have been caused by subjects with inadequate responses to the product. Desensitization therapy including the one with Miticure requires long-term treatment, and patients, their families, and healthcare providers should take safety measures to guard against the risk of anaphylaxis and other measures. Given that some patients have inadequate responses to the therapy, it is important to thoroughly consider the timing for evaluating the therapeutic effect through post-marketing surveillance or other relevant programs to avoid injudicious use of Miticure in patients with inadequate responses to it.
- Given that the nature of desensitization therapy, which consists of direct administration of allergens, including the one with the product, and that the product, a sublingual immunotherapy (SLIT) product, is likely to be administered outside medical institutions, it is essential to establish an appropriate system for safety management with the risk of anaphylaxis in mind, as with already approved SLIT products.

- It is particularly important to ensure that healthcare providers caution patients by using an information leaflet so that patients and their families understand the risks and benefits of the therapy including the risk of anaphylaxis before using Miticure.

Taking account of the comments from the Expert Discussion, PMDA asked the applicant to explain the timing for evaluating the effect of Miticure on remission of allergic symptoms and for determining whether to continue treatment with Miticure.

The applicant responded as follows:
In the Japanese phase II/III study (Study 203-3-2), the number of days on which patient symptoms were controlled in the period from Week 44 to Week 52 was as shown in Table 13. However, when control of symptoms is defined more conservatively, the results showed that the Miticure groups had a greater number of days without rhinitis symptoms compared with the placebo group, and further, the trends of the greater number of days with symptoms controlled (the number of days with a total nasal symptom medication score [TNSMS] of 0) over time as shown in Table 14, suggests that the difference between the Miticure groups and placebo group tended to increase across the entire treatment period.

Table 13. Number of days on which symptoms were controlled in the period from Week 44 to Week 52 in the Japanese phase II/III study (Study 203-3-2) (FAS)

Definition of symptom control	6-DU group (313 subjects)	12-DU group (314 subjects)	Placebo group (319 subjects)	Difference from placebo [95% CI]	
				6-DU group	12-DU group
Number of days with TNSMS of 0 (Number of days without rhinitis symptoms)	8.3 ± 15.8 (285)	6.5 ± 14.3 (281)	3.8 ± 10.4 (285)	4.5 [2.3, 6.7]	2.7 [0.7, 4.8]
Number of days with an allergic rhinitis daily symptom score of ≤1 and daily medication score of 0	12.2 ± 18.3 (285)	10.9 ± 17.4 (281)	6.6 ± 13.1 (285)	5.6 [3.0, 8.2]	4.3 [1.7, 6.8]
Number of days with an allergic rhinitis daily symptom score of ≤2 and daily medication score of 0	16.6 ± 20.5 (285)	15.6 ± 19.9 (281)	10.8 ± 16.4 (285)	5.8 [2.8, 8.9]	4.8 [1.8, 7.8]

Mean ± SD (number of subjects)

Table 14. Number of days on which TNSMS was 0 over time in the Japanese phase II/III study (Study 203-3-2) (FAS)

Time point after the start of treatment	6-DU group (313 subjects)	12-DU group (314 subjects)	Placebo group (319 subjects)	Difference from placebo [95% CI]	
				6-DU group	12-DU group
Baseline	0.0 ± 0.2 (285)	0.0 ± 0.1 (281)	0.0 ± 0.1 (285)	0.0 [−0.0, 0.0]	0.0 [−0.0, 0.0]
Week 12-Week 14	0.5 ± 2.1 (284)	0.7 ± 2.5 (281)	0.3 ± 1.5 (283)	0.2 [−0.1, 0.5]	0.4 [0.1, 0.7]
Week 20-Week 22	0.6 ± 2.0 (285)	0.7 ± 2.3 (281)	0.4 ± 1.9 (285)	0.2 [−0.1, 0.5]	0.3 [−0.1, 0.6]
Week 28-Week 30	0.9 ± 2.9 (285)	0.8 ± 2.5 (281)	0.5 ± 2.0 (285)	0.4 [0.0, 0.8]	0.3 [−0.1, 0.7]
Week 36-Week 38	1.8 ± 3.8 (285)	1.3 ± 3.3 (281)	0.8 ± 2.6 (285)	0.9 [0.4, 1.4]	0.5 [0.0, 1.0]
Week 44-Week 52	8.3 ± 15.8 (285)	6.5 ± 14.3 (281)	3.8 ± 10.4 (285)	4.5 [2.3, 6.7]	2.7 [0.7, 4.8]

Mean ± SD (number of subjects)

It is generally well known that mite allergen-induced allergic rhinitis symptoms are susceptible to seasonal changes (Bousquet J et al. *J Allergy Clin Immunol.* 2001;108:S147-334), and in patients sensitized with multiple allergens including pollens other than mite allergens, the therapeutic effect of Miticure is more likely to be affected by seasonal factors; therefore, it is important to perform evaluations in the same seasons to accurately determine the therapeutic effect. Thus, after the start of treatment with Miticure, the efficacy should be evaluated about 1 year later, as a general principle. If an adequate response is not observed, treatment discontinuation should also be considered after re-

examining causal antigens and considering the concomitant use of other drugs. Based on the above, a caution will be provided to make a careful decision as to whether treatment should be continued in patients with inadequate responses after 1 year of treatment with Miticure.

PMDA considers as follows:

Information on the timing for determining whether to continue Miticure in patients with inadequate responses is of great importance in implementing treatment with Miticure. However, at this point, knowledge on the timing for evaluating the therapeutic effect of desensitization therapy has not been established for any drugs, including the product. Therefore, it is important to provide information to healthcare professionals in clinical settings using an information leaflet on the timing for determining whether to continue Miticure, taking into account the information from treatment guidelines in and out of Japan, to avoid injudicious use of Miticure in patients with inadequate responses. Further, although the ultimate goal of desensitization therapy is to achieve the remission of allergic symptoms, the treatment experience with Miticure in clinical studies has not exceeded 1 year. Therefore, through post-marketing surveillance and other relevant programs, it is necessary to gather more information on long-term efficacy, including the timing for evaluating the efficacy of Miticure and for determining whether to continue Miticure in patients with inadequate responses [see " (2) Risk management plan (draft)"]. It is also considered necessary to take appropriate safety measures against the risk of anaphylaxis and other serious systemic reactions, as with already approved SLIT products.

(2) Risk management plan (draft)

Based on the discussions in the sections [see "4.(i).B.(2) Safety" of the Review Report (1)] and the Expert Discussion [see "(1) Efficacy and safety"], PMDA concluded that the applicant should establish safety and efficacy specifications as shown in Table 15 and implement additional pharmacovigilance and risk minimization activities as shown in Table 16 in the risk management plan (draft) of Miticure at this point.

Table 15. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis	• None	• None
Efficacy specifications		
• Efficacy in long-term use and after completion of treatment		

Table 16. Outline of additional pharmacovigilance and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey (long-term use)	• Early post-marketing phase vigilance • Creation and distribution of information materials for healthcare providers • Creation and distribution of information materials for patients • Construction of management system for proper use of the product

Therefore, PMDA instructed the applicant to implement post-marketing surveillance to review the above issues.

The applicant responded as follows:

A specified drug use-results survey will be implemented in patients with mite allergen-induced allergic rhinitis with a target sample size of 500 and a maximum observation period of 4 years (3 years as the treatment period) as shown in Table 17. The survey will primarily focus on shock and anaphylaxis (including anaphylaxis-related symptoms) to evaluate the safety of Miticure under actual use conditions. Long-term efficacy and the timing for determining whether to continue Miticure in patients with inadequate responses will also be studied, and if treatment is discontinued after improvement of symptoms, the efficacy up to 1 year after treatment discontinuation will be evaluated.

Table 17. Outline of specified drug use-results survey (draft)

Objectives	To evaluate safety and efficacy of Miticure under long-term use conditions
Survey method	Central registry system
Target patient	Patients with mite allergen-induced allergic rhinitis
Observation period	Maximum of 4 years (3 years as a treatment period)
Planned number of patients	500 patients
Focused survey items	Shock and anaphylaxis (including anaphylaxis-related symptoms)
Main survey items	Patient characteristics (severity, disease duration, medical history, complications, history of allergies, etc.) Treatment status of Miticure Concomitant drugs Safety evaluation Efficacy evaluation

PMDA considers that the survey should be conducted as promptly as possible, and the results should be appropriately provided to healthcare professionals in clinical settings.

(3) Other

The applicant also noted as follows:

There were concerns over the negative effect of desensitization therapy on patients with malignant tumors or systemic diseases that affect the immune system due to the therapy's possible effect on the immune system; however, recently published studies have accumulated negative results for these risks (Bozek A et al. *Int Arch Allergy Immunol.* 2014;163:307-312; Linneberg A et al. *J Allergy Clin Immunol.* 2012;129:413-419; Steiner U et al. *World Allergy Organization Journal*. 2009;2:57-58; and Randhawa IS et al. *Ann Allergy Asthma Immunol.* 2007;98:495-497). Accordingly, it is considered appropriate to provide a caution in the Careful Administration section of the package insert, rather than to make Miticure contraindicated in such patients.

PMDA has concluded that the applicant's proposed actions above are acceptable based on the information available as of today including the latest information, and the conclusion was supported by the expert advisors. However, post-marketing safety information on desensitization therapy concerning the patients mentioned above should be gathered further, including by literature review.

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 was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem 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 took place in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5.1-1). As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of 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. Because Miticure is a drug with a new active ingredient, 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.

[Indication]	Desensitization therapy for allergic rhinitis induced by mite allergens
[Dosage and administration]	The usual dosage of Miticure for adults and children aged ≥12 years is one 3300-JAU tablet administered sublingually once-daily during the first week of treatment and one 10,000-JAU tablet sublingually once-daily from the second week onward. The tablet should be placed under the tongue for 1 minute before being swallowed, and the patient should refrain from eating, drinking, or gargling during the subsequent 5 minutes.
[Conditions for approval]	The applicant is required to: 1. Develop a risk management plan and implement it appropriately. 2. Take necessary measures in the marketing of the product to ensure that the product is prescribed and used only by physicians with sufficient knowledge and experience of sublingual desensitization therapy; that the product is used only under the supervision of physicians at medical institutions where they can

adequately manage and explain the associated risks; and that the product is dispensed at pharmacies only after the prescribing physician and medical institution are identified.