Report on the Deliberation Results

November 26, 2013
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	(a) Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle (b) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle (c) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack
[Non-proprietary name]	None
[Applicant]	Torii Pharmaceutical Co., Ltd.
[Dates of application]	(a) and (b) December 25, 2012 (c) March 22, 2013

[Results of deliberation]
In the meeting held on November 18, 2013, 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 for the product is 6 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]
Prior to marketing of the product, the applicant is required to take necessary measures to ensure that the product is prescribed and administered only by physicians with adequate knowledge of and experience with sublingual hyposensitization therapy; that the product is administered only under the supervision of physicians capable of adequately managing and explaining the associated risks at medical institutions that allow such physicians to do so; and that the product is dispensed at pharmacies only after the prescribing physician and medical institution are confirmed to meet such requirements.

Review Report

September 24, 2013
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) Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle (b) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle (c) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack
[Non-proprietary name]	None
[Name of applicant]	Torii Pharmaceutical Co., Ltd.
[Dates of application]	(a) and (b) December 25, 2012 (c) March 22, 2013
[Dosage form/Strength]	(a) Sublingual liquid containing 0.2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 10 mL bottle (b) Sublingual liquid containing 2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 10 mL bottle (c) Sublingual liquid containing 0.2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 1 mL pack
[Application classification]	Prescription drug (3) Drug(s) with a new route of administration
[Items warranting special mention]	A prior assessment consultation for drugs was undertaken for the product.
[Reviewing office]	Office of New Drug IV

Review Results

September 24, 2013

[Brand name] (a) Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle
(b) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle
(c) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack
[Non-proprietary name] None
[Name of applicant] Torii Pharmaceutical Co., Ltd.
[Dates of application] (a) and (b) December 25, 2012
(c) March 22, 2013

[Results of review]
It is concluded that the submitted data adequately demonstrates the efficacy of the product used in the treatment of Japanese cedar pollinosis (hyposensitization therapy). With regard to the safety of the product, hyposensitization therapy involves the administration of allergens to sensitized patients, which may lead to the risk of anaphylaxis. For this reason, it is necessary to implement a system whereby the product is used only by physicians with adequate knowledge of the product and adequate knowledge of and experience with hyposensitization therapy, and to educate and guide healthcare professionals and patients to ensure appropriate safety measures against anaphylaxis. Additionally, a long-term post-marketing surveillance must be undertaken to investigate the achievement and maintenance of remission after long-term treatment; the duration of treatment required to achieve sustained remission; the timeframe required to determine lack of efficacy; and the efficacy and safety of resumption of treatment.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indications and dosage and administration indicated below, with the following conditions for approval:

[Indication] Japanese cedar pollinosis (hyposensitization therapy)
[Dosage and administration] 1. Dose escalation period (Weeks 1-2)
The usual dosage of Cedartolen for adults and children ≥12 years of age for the first 2 weeks of administration (dose escalation period) is described in the dosing schedule shown below. The specified dose should be administered as sublingual drops once daily and be held under the tongue for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

Week 1 (dose escalation period)		Week 2 (dose escalation period)	
Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle		Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle	
Day 1	0.2 mL	Day 1	0.2 mL
Day 2	0.2 mL	Day 2	0.2 mL
Day 3	0.4 mL	Day 3	0.4 mL
Day 4	0.4 mL	Day 4	0.4 mL
Day 5	0.6 mL	Day 5	0.6 mL
Day 6	0.8 mL	Day 6	0.8 mL
Day 7	1 mL	Day 7	1 mL

2. Dose maintenance period (From Week 3 onward)
During the dose maintenance period following the dose escalation period, the entire contents (1 mL) of a Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack is placed under the

	tongue once daily and held in place for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.
[Conditions for approval]	Prior to marketing of the product, the applicant is required to take necessary measures to ensure that the product is prescribed and administered only by physicians with adequate knowledge of and experience with sublingual hyposensitization therapy; that the product is administered only under the supervision of physicians capable of adequately managing and explaining the associated risks at medical institutions that allow such physicians to do so; and that the product is dispensed at pharmacies only after the prescribing physician and medical institution are confirmed to meet such requirements.

Review Report (1)

August 6, 2013

I. Product Submitted for Registration

[Brand name] (a) Cedartolen Sublingual Drop 200 JAU/mL
(b) Cedartolen Sublingual Drop 2,000 JAU/mL
(c) Cedartolen Sublingual Drop 2,000 JAU/mL 1 mL
(as propose in the application)

[Non-proprietary name] None

[Name of applicant] Torii Pharmaceutical Co., Ltd.

[Dates of application] (a) and (b) December 25, 2012
(c) March 22, 2013

[Dosage form/Strength] (a) Sublingual liquid containing 0.2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 10 mL bottle
(b) Sublingual liquid containing 2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 10 mL bottle
(c) Sublingual liquid containing 0.2 mL of 10,000 JAU/mL of the standardized Japanese cedar pollen extract in a 1 mL pack

[Proposed indication] Japanese cedar pollinosis (allergen immunotherapy)

[Proposed dosage and administration]

1. Dose escalation period (Weeks 1-2)

The usual dosage of Cedartolen for the first 2 weeks of administration (dose escalation period) is described in the dosing schedule shown below. The specified dose should be administered as sublingual drops once daily and be held under the tongue for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

Week 1 (dose escalation period)		Week 2 (dose escalation period)	
200 JAU/mL product		2,000 JAU/mL product	
Day 1	0.2 mL	Day 1	0.2 mL
Day 2	0.2 mL	Day 2	0.2 mL
Day 3	0.4 mL	Day 3	0.4 mL
Day 4	0.4 mL	Day 4	0.4 mL
Day 5	0.6 mL	Day 5	0.6 mL
Day 6	0.8 mL	Day 6	0.8 mL
Day 7	1 mL	Day 7	1 mL

2. Dose maintenance period (From Week 3 onward)

During the dose maintenance period following the dose escalation period, 1 mL of 2,000 JAU/mL product is placed under the tongue once daily and held in place for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

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.

The proposed allergen product (this term is collectively used for the three proposed products) is a sublingual liquid formulation containing 10,000 JAU[1]/mL of the standardized Japanese cedar pollen extract extracted and prepared from Japanese cedar pollen (hereinafter referred to as "standardized Japanese cedar pollen extract"). In Japan, Allergen Therapy Extract "Torii" Cedar Pollen 1:100, Allergen Therapy Extract "Torii" Cedar Pollen 1:1,000, Allergen Therapy Extract "Torii" Cedar Pollen 1:10,000, and Allergen Therapy Extract "Torii" Cedar Pollen 1:100,000, which are formulations for subcutaneous injection that contain the standardized Japanese cedar pollen extract as the active ingredient, have been commercially available since January 1969. Moreover, Therapeutic Standardized Allergen Extract for Subcutaneous Injection "Torii" Cedar Pollen 2000 JAU/mL and Therapeutic Standardized Allergen Extract for Subcutaneous Injection "Torii" Cedar Pollen 200 JAU/mL, in which the amount of the antigen is standardized, have been commercially available since January 2000 (hereinafter collectively referred to as the "existing Japanese cedar pollen extracts"). The proposed allergen product was developed for sublingual administration by improving the manufacturing processes of formulations for subcutaneous injection.

Japanese cedar pollinosis is the collective term for allergic symptoms caused by the pollen of Japanese cedar (*Cryptomeria japonica* D. Don). Exposure to Japanese cedar pollen induces the following Type I allergic symptoms: nasal symptoms including sneezing, nasal discharge, and nasal congestion; ocular symptoms including eye itching and teary eye; pharyngeal symptoms including itchy throat; and dermal symptoms including systemic itching and dry skin. While the mechanism of action of hyposensitization therapy has yet to be elucidated, the administration of an allergen to a sensitized patient appears to elicit various immunological mechanisms that suppress the onset of allergic symptoms induced by the allergen, including suppressed production of IgE antibodies to the allergen (including suppressor T-cell induction and allergen-induced anergy), altered local infiltrating lymphocyte subfractions, and elevated production of blocking antibodies, making it possible to cure allergic diseases or to achieve sustained remission (Practical Guideline for the Management of Allergic Rhinitis in Japan 2009, WHO position paper: Bousquet J et al. *J Allergy Clin Immunol.* 1998;102:558-62 [hereinafter referred to as "WHO position paper 1998"]). Hyposensitization therapy has been administered in the form of subcutaneous immunotherapy (SCIT), but this approach has not been generally taken in Japan due to the risk of serious adverse reactions including anaphylaxis; prolonged injection-site pain; and long-term periodic hospital visits, resulting in a small number of patients receiving the therapy. In recent years, sublingual immunotherapy (SLIT) has emerged, primarily in Europe, as a mode of administration intended to overcome issues associated with SCIT. SLIT products have already been approved outside of Japan for use in the treatment of allergies caused by Gramineae pollen and dust mites. In Japan, several clinical studies of SLIT have been conducted in patients with Japanese cedar pollinosis using the existing Japanese cedar pollen extracts (Okubo K et al. *Allergology International.* 2008;57:265-275, Horiguchi S et al. *Int Arch Allergy Immunol.* 2008;146:76-84, Sakaguchi M et al. Research project supported by the Health and Labour Sciences Research Grants: Development of new immunotherapy for Japanese cedar pollinosis and dust mite allergies, FY 2006-2008 Comprehensive Research Reports. 2009;54-64, Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2009 Partial Research Report. 2010;12-14, Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2010 Partial Research Report. 2011;9-11). The reports indicate the efficacy and safety of SLIT.

Given the above background, clinical development of the proposed allergen product in Japan began in July 2010. The applicant has filed a marketing application based on Japanese clinical studies, claiming that the efficacy and safety of the proposed allergen product has been confirmed in the treatment of Japanese cedar pollinosis. As of August 2013, the product is not being developed outside of Japan.

[1] The Japanese Society of Allergology's Allergen Committee defines 10,000 JAU as an extract containing 7.3 to 21 μg of Cry j 1, the main allergen, per 1 mL (Yasueda, et al. *Japanese Journal of Allergology*, 1996;45:416-421).

To prevent medical errors, the brand names of the proposed allergen product have been changed from Cedartolen Sublingual Drop 200 JAU/mL, Cedartolen Sublingual Drop 2,000 JAU/mL, and Cedartolen Sublingual Drop 2,000 JAU/mL 1 mL, which were initially proposed in the application, to Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle, Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle, and Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack, respectively.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The drug substance is an extract of Japanese cedar pollen which is similar to the drug substance of the existing Japanese cedar pollen extracts. In light of the change in the route of administration from subcutaneous injection to sublingual administration, the manufacturing process has been modified and improved by taking into account yields and operability.

2.A.(1).1) General properties

The drug substance is a clear, light yellow liquid containing allergens such as Cry j 1[2] and Cryj 2[3] extracted from Japanese cedar (*Cryptomeria japonica* D. Don) pollen. The following attributes have been investigated: description, identification ([redacted]), pH, assay (Cry j 1), assay (Cry j 2), safety, purity ([redacted]), protein content, total allergenic activity, SDS-polyacrylamide gel electrophoresis (SDS-PAGE), extract profile by high-performance liquid chromatography (HPLC), ultraviolet-visible spectrophotometry, polysaccharides, and inorganic components.

The drug substance lacks a defined chemical structure.

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

[redacted] The specifications for Japanese cedar pollen include description (color and shape), description (microscopy), purity, loss on drying, total ash, and acid-insoluble ash. Inorganic components ([redacted]) were added to the specifications during the application review process. The drug substance is manufactured using only Japanese cedar pollen meeting the specifications through the preparation step comprising extraction, separation, and clarifying filtration. The drug substance preparation step is defined as a critical process step.

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

The specifications for the drug substance include content (Cry j 1), description (appearance), identification ([redacted]), pH, and assay ([redacted]). Identification ([redacted]), protein content, content (Cry j 2), and assay ([redacted]) were also included in the drug substance specifications in the course of the review.

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

Table 1 shows the results of a stability study for the drug substance. The results of photostability testing indicate that the drug substance is photostable.

Table 1. Stability study for the drug substance

Study name	Primary batch	Temperature	Storage container	Storage period
Long-term	3 pilot batches	-20°C	Air-tight stainless steel container	18 months

[2] Glycoprotein, one of the major allergens of Japanese cedar pollen
[3] Protein, one of the major allergens of Japanese cedar pollen

Based on the above results, a shelf life of 18 months has been proposed for the drug substance when stored at -25°C to -15°C in an air-tight container. The long-term study is currently underway and will proceed for 36 months.

2.A.(2) Drug product

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

The drug product contains 50% glycerin solution as an excipient and is supplied in 10 mL bottles containing Japanese cedar pollen allergen extract at concentrations of 200 JAU/mL and 2000 JAU/mL for use during the dose escalation period (hereinafter referred to as "bottle product") and in a 1 mL pack containing Japanese cedar pollen allergen extract at a concentration of 2000 JAU/mL for use during the dose maintenance period (hereinafter referred to as "aluminum laminated product").

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

The bottle and aluminum-laminated products are produced by the following manufacturing steps: mixing of multiple batches of the drug substance; preparing and filtering whereby the drug substance is weighed and diluted to adjust the potency of the drug solution to the indicated value; and filling. Each step, i.e., drug substance mixing, drug solution preparation and filtration, and aluminum lamination filling, is considered critical. Process control items and values have been established.

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

The specifications for the drug product include content (Cry j 1), description (appearance), pH, uniformity of dosage units for single-dose packages, [4] microbial limit, and assay ([redacted]). Identification ([redacted]), [5] content (Cry j 2), and assay ([redacted]) were added to the specifications in the course of the review.

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

Table 2 shows the results of stability tests for the drug product. The results demonstrate that the drug product is photostable.

Table 2. Stability study for the drug product

Study name	Drug product	Primary batch	Temperature	Relative humidity	Storage container	Storage period
Long-term	2000 JAU/mL 1 mL	3 pilot batches	5°C	–	Aluminum-laminated pack	18 months
Accelerated		3 pilot batches	25°C	60%RH		3 months
Long-term	2000 JAU/mL 10 mL	3 pilot batches	5°C	–	Bottle	18 months
Accelerated		3 pilot batches	25°C	60%RH		3 months
Long-term	200 JAU/mL 10 mL	3 pilot batches	5°C	–		18 months
Accelerated		3 pilot batches	25°C	60%RH		6 months

Based on the above, a shelf life of 18 months has been proposed for the drug product when stored at 2°C to 8°C in an air-tight container. The long-term studies are currently underway and will proceed for 36 months.

2.B Outline of the review by PMDA

2.B.(1) Control of Cry j 1 content

[redacted]

[4] Established only for aluminum-laminated products.
[5] Because no band was detected for the 200 JAU/mL 10 mL product, established for the 2000 JAU/mL 10 mL and 1 mL products.

[redacted]

PMDA accepted the applicant's response.

2.B.(2) Site of Japanese cedar pollen collection

The raw material for the drug product is specified simply as domestically-grown Japanese cedar. PMDA asked the applicant to explain the potential impact of different growth environment factors for Japanese cedar on the quality of the Japanese cedar pollen, such as collection site and time.

The applicant responded as follows:

[redacted] Furthermore, a clinical study of SLIT was conducted in the Chubu region using Japanese cedar pollen extract manufactured from the pollen collected in the Kanto and Tohoku regions, reports on the study indicate the therapeutic efficacy of SLIT (Yuta A et al. *Japanese Journal of Allergology.* 2009;58:124-132, Fujieda S et al. Research project supported by the Health and Labour Sciences Research Grants: Prevention and treatment of immunologic and allergic diseases, Comprehensive Research Report. 2009;183-186), suggesting that regional differences in pollen collection do not affect the efficacy of the drug product. [redacted]

PMDA accepted the applicant's response.

2.B.(3) Specifications for drug substance and drug product

PMDA asked the applicant to explain the components considered to be contained in the drug substance and what steps are taken to ensure appropriate control of these components.

The applicant responded as follows:

Japanese cedar pollen is considered to contain a wide variety of substances besides the major allergens Cry j 1 and Cry j 2, including allergen proteins, non-allergen proteins, lipids, saccharides, and inorganic substances. Serum samples from145 patients with Japanese cedar pollinosis were tested for

allergen-specific serum IgE, and 92% of the patients showed the specific IgE reactivity to both Cry j 1 and Cry j 2, while <5% of the patients showed the specific IgE reactivity to only one of the two allergens (Hashimoto M et al. *Clin Exp Allergy.* 1995;25:848-852). Although other reports have documented proteins that could potentially be allergens (Fujimura T et al. *Clin Exp Allergy.* 2005;35:234-243, Kawamoto S et al. *Clin Exp Allergy.* 2002;32:1064-1070, Ibrahim AR et al. *Biosci Biotechnol Biochem.* 2010;74:504-509, Ibrahim AR et al. *Int Arch Allergy Immunol.* 2010;152:207-218), no conclusive evidence indicates any of these proteins are involved in allergic symptoms. To ensure efficacy, the applicant considers it is crucial to control the two major allergens, Cry j 1 and Cry j 2. The applicant has included Cry j 1 and Cry j 2 in the specifications for the drug substance and Cry j 1 in those for the drug product. [redacted]

The applicant has not included the content of organic substances in the specifications. However, the main component is flavonoids which are found in plants in general and the flavonoid intake following administration of 1 mL of 2000 JAU/mL formulation does not exceed the flavonoid content of common edible plants, suggesting no major safety concerns. Based on the above, the applicant claims that the components of the drug substance are appropriately controlled.

In addition to the above, PMDA considers it appropriate to include Cry j 2 in the specifications for the drug product because Cry j 2 is the major allergen as with Cry j 1 and an important ingredient affecting the efficacy and safety of the drug product. PMDA requested the applicant to take action on this matter. The applicant agreed to it.

Based on the above, PMDA has concluded that the quality of the drug substance and drug product is properly controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

No new primary pharmacodynamic, secondary pharmacodynamic, safety pharmacology, or pharmacodynamic drug interaction studies have been conducted for this application.

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

The applicant provided the following rationales for refraining from any new non-clinical pharmacology studies for sublingual administration as part of the product application.

Primary pharmacodynamic studies were not conducted for the following reasons: (a) Outside of Japan, the efficacy of SLIT with various allergens has been demonstrated and the therapy has been used in clinical settings. Also, clinical studies conducted in Japan using the existing Japanese cedar pollen extracts have confirmed the efficacy of SLIT (Okubo K et al. *Allergology International.* 2008;57:265-275, Horiguchi S et al. *Int Arch Allergy Immunol.* 2008;146:76-84, Sakaguchi M et al. Research project supported by the Health and Labour Sciences Research Grants: Development of new immunotherapy for Japanese cedar pollinosis and dust mite allergies, FY 2006-2008 Comprehensive Research Reports. 2009;54-64, Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2009 Partial Research Report. 2010;12-14, Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2010 Partial Research Report. 2011;9-11, and others); (b) the efficacy of SCIT with the existing Japanese cedar pollen extracts has been demonstrated and has been approved for commercial introduction in Japan; and (c) the mechanism of action of hyposensitization therapy has not been elucidated in detail, thereby making it difficult at present to generate an animal model with which efficacy can be evaluated appropriately.

Secondary pharmacodynamic and safety pharmacology studies were not conducted for the following reasons: (a) A pharmacokinetic study using Cry j 1, one of the major allergens in the proposed allergen product, showed that following sublingual administration of a single dose of ^{125}I-labeled Cry j 1 to rats, the radioactivity level in the plasma remained lower over time when compared to that following a single subcutaneous injection. The peak plasma radioactivity was about one twentieth that following the single subcutaneous injection, suggesting that the level of systemic exposure for SLIT is lower when compared to that for SCIT [see "3.(ii) Summary of pharmacokinetic studies"]; (b) adverse reactions can be anticipated based on the clinical use of SCIT with the existing Japanese cedar pollen extracts; and (c) toxicology studies of the standardized Japanese cedar pollen extract, including a 26-week repeated-dose oral and subcutaneous toxicology study in rats, have shown no secondary pharmacological effects or signs of effects posing safety concerns [see "3.(iii) Summary of toxicology studies"].

No pharmacodynamic drug interaction studies were conducted for the following reasons: Co-administering a β blocker with a Japanese cedar pollen extract product is known to induce stronger allergic reactions, but no reports document exacerbated adverse reactions resulting from the concomitant use of a β blocker in patients receiving SCIT with the existing Japanese cedar pollen extracts, suggesting the absence of major concerns for pharmacodynamic interactions.

PMDA asked the applicant to explain the mechanism of action of SLIT compared to that of SCIT, based on the information currently available.

The applicant provided the following explanation, citing published reports:
While the mechanism of action of hyposensitization therapy has not been fully elucidated, the uptake of allergens by dendritic cells (antigen-presenting cells [APCs]) is considered to be important for both SLIT and SCIT, as the starting point of effective therapy. The expression of the receptor IgE (FcεRI) on dendritic cells in the oral mucosa as the administration site for SLIT is higher than that on dendritic cells in the skin as the administration site for SCIT, suggesting that the uptake of allergens observed after SLIT is more efficient than that after SCIT, leading to induction of immunological tolerance associated with IL-10 production (Cappella A et al. *Hum Vaccin Immunother.* 2012;8:1499-1512).

Furthermore, in both SLIT and SCIT, the allergen uptake by APCs is followed by the suppression of increases in Th2 cells, increase of Th1 cells, induction of regulatory T cells, and the increase in antigen-specific IgG and IgA, resulting in remission of allergy symptoms. The mechanism for achieving immunological tolerance as the ultimate goal is presumably the same between the two therapy (World Allergy Organization [WAO] Position Paper 2009;233-281 ["WAO position paper 2009" hereinafter], Cappella A et al. *Hum Vaccin Immunother.* 2012;8:1499-1512, Bahceciler NN et al. *Immunotherapy.* 2011;3:747-756, Allam JP et al. *Curr Opin Allergy Clin Immunol.* 2011;11:571-578, Soyer OU et al. *Immunol Allergy Clin N Am.* 2011;31:175-190).

PMDA accepted the above explanation by the applicant and concluded that because there are no marked differences in the pharmacological actions elicited by SCIT and SLIT, it is acceptable that no new non-clinical pharmacology studies on sublingual administration have been conducted.

3.(ii) Summary of pharmacokinetic studies

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

The results of sublingual and subcutaneous administration studies in rats to investigate absorption, distribution, metabolism, and excretion were submitted. Additionally, as a toxicokinetic study, the results of a subcutaneous and oral administration study in rats were submitted. [redacted] In studies utilizing radiolabeled Cry j 1 (^{125}I-labeled Cry j 1), radioactivity levels in plasma, blood and tissue were measured using either a gamma well counter (lower limit of quantification, twice the background value) or whole-body autoradiography. Radioactivity levels in metabolites were measured by HPLC.

Unless otherwise specified, pharmacokinetic parameters are shown as either the mean or mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2.1)

Table 3 shows chronological changes in plasma radioactivity following a single subcutaneous injection or single sublingual administration[6] of 7.5 µg of ^{125}I-labeled Cry j 1 to male rats (n = 3/group). For the sublingual administration group, plasma radioactivity increased over time up to 4 hours after administration (last measurement). For the subcutaneous administration group, plasma radioactivity peaked at 2 hours after administration, then decreased over time, to 22% and 3% of the peak concentration at 24 and 168 hours after administration, respectively. Plasma radioactivity at 4 hours after sublingual administration (last measurement) was about one twentieth that of the peak plasma radioactivity following subcutaneous injection.

Table 3. Plasma radioactivity following single sublingual or subcutaneous administration of ^{125}I-labeled Cry j 1 to rats (pg eq. of Cry j 1/mL)

Measurements	Sublingual group	Subcutaneous group
15 minutes	ND	3130.09 ± 354.31
30 minutes	309.93 ± 64.71	6400.52 ± 1402.46
1 hour	660.73 ± 132.61	19247.94 ± 5958.38
2 hours	966.12 ± 265.84	31013.14 ± 4101.66
4 hours	1595.07 ± 551.09	26488.06 ± 1998.92
6 hours	–	23630.30 ± 2511.73
8 hours	–	17970.69 ± 2152.36
10 hours	–	14133.86 ± 1269.87
24 hours	–	6850.49 ± 1231.43
48 hours	–	4495.27 ± 1592.70
72 hours	–	3250.11 ± 636.63
96 hours	–	2189.21 ± 343.13
120 hours	–	1775.05 ± 231.79
144 hours	–	1351.13 ± 363.28
168 hours	–	1029.30 ± 316.67

Mean ± SD
ND, not detected (below the lower limit of quantification); n = 3 per group

Additionally, the ratio of plasma radioactivity for the trichloroacetic acid (TCA) insoluble fractions[7] for the sublingual group could not be determined because the plasma radioactivity was below the lower limit of quantification at all time points. However, plasma radioactivity for the subcutaneous group was 41.9 ± 7.3% at 15 minutes after administration, 17.6 ± 3.0% at 30 minutes after administration, 5.4 ± 0.7% to 9.5 ± 1.1% at 1 to 10 hours after administration, and 52.7 ± 12.0% to 93.9 ± 8.1% at 24 to 168 hours after administration. Based on the above, the applicant asserted that many low molecular weight substances originating from ^{125}I-labeled Cry j 1 existed in the plasma soon after administration, and attributed the fact that the ratio of radioactivity for the TCA insoluble fraction increased at ≥24 hours after subcutaneous administration to high molecular weight biological compounds incorporating free ^{125}I.

3.(ii).A.(1).2) Repeat-dose studies (Toxicokinetics) (4.2.3.2.1, 5)

Oral doses of 1 mL/kg of the standardized Japanese cedar pollen extract ([redacted] µg Cry j 1/kg) were administered to rats (n = 5/sex) once daily for 26 weeks. As a result, the serum concentration of Cry j 1 was below the lower limit of quantification (1.00 ng/mL) at all time points.

Subcutaneous doses of 0.2 or 1 mL/kg of the standardized Japanese cedar pollen extract ([redacted] and [redacted] µg of Cry j 1/kg, respectively) were administered to rats (n = 5 /sex/group) once daily for 26 weeks. The serum concentration of Cry j 1 was below the lower limit of quantification (1.00 ng/mL) at all time points in both groups, except for 1 and 2 hours after administration for 1 of the 5 females at Week 26 in the 1 mL/kg group (1.52 and 1.01 ng/mL, respectively).

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[6] Sublingual administration was performed by ligating the esophagus, and for the humane treatment of animals, radioactivity levels in the plasma for the sublingual group were measured up to four hours after administration.

[7] Proteins including unchanged ^{125}I-labeld Cry j 1 were included in the insoluble fractions, while iodine ions and low molecular weight substances originating from ^{125}I-labeld Cry j 1 were included in the soluble fractions.

3.(ii).A.(2) Distribution (4.2.2.2.1)

A single dose of 7.5 μg of ^{125}I-labeled Cry j 1 was administered sublingually to male rats (n = 3).[8] Radioactivity in the submandibular lymph node, bladder and intestinal tract peaked 2 hours after administration. Radioactivity in other tissues and plasma and whole blood peaked 4 hours after administration (last measurement). At 4 hours after administration, radioactivity was highest in the lung, followed in descending order by the thyroid, trachea, submandibular lymph node, stomach, kidney, bladder, plasma, and whole blood.

A single dose of 7.5 μg of ^{125}I-labeled Cry j 1 was administered subcutaneously to male rats (n = 3). Radioactivity was detected throughout the body by 30 minutes after administration, peaking in the thyroid 24 hours after administration and peaking in other tissues, plasma, and whole blood 2 hours after administration. At 2 hours after administration, radioactivity was highest in the thyroid, followed in descending order by the stomach, plasma, whole blood, skin, kidney, trachea, and bladder. In all tissues, radioactivity was eliminated over time by 168 hours after administration.

Additionally, the radioactivity was measured in the TCA insoluble fraction of each tissue. In the sublingual group, the radioactivity found in the TCA insoluble fraction of the lung was high (101.8 ± 1.7% of the total radioactivity recovered) 4 hours after administration, but this was attributed to breathing in ^{125}I-labeled Cry j 1 along with the saliva that resulted in aspiration into the lungs. The radioactivity found in the TCA insoluble fractions of other tissues ranged from 19.0 ± 3.6% to 61.8 ± 20.5%. In the subcutaneous group, no marked differences in radioactivity levels were found among various tissues for up to 24 hours after administration. The radioactivity found in the TCA insoluble fractions of the tissues 24 hours after administration ranged from 42.6 ± 3.9% to 74.6 ± 2.0% of the total radioactivity recovered. At 168 hours after administration, the radioactivity found in the TCA insoluble fractions of all the tissues tested, except the submandibular gland in which radioactivity was undetectable, ranged from 72.2 ± 7.0% to 90.9 ± 3.4% of the total radioactivity recovered.

A single dose of 7.5 μg of ^{125}I-labeled Cry j 1 was administered sublingually or subcutaneously to male rats (n = 1/group/time point), after which radioactivity was measured by whole-body autoradiography. The distribution of radioactivity was almost consistent with the radioactivity levels measured in respective tissues. For the sublingual group, radioactivity at 4 hours after administration was highest in the nasal cavity, followed in descending order by the trachea, lung, and thyroid. For the subcutaneous group, radioactivity at 2 hours after administration was highest in the thyroid, followed in descending order by gastric contents, injection site, small intestinal contents, skin, trachea, small intestine, and stomach. At 168 hours after administration, no radioactivity was detected except in the thyroid, skin, and large intestinal contents.

Based on the above, the applicant explained that although the mechanism of action of SLIT has not been clarified in detail, the transfer of allergens to the cervical lymph nodes (e.g. submandibular lymph nodes) may be involved in the mechanism of action of SLIT for the following reasons: (1) the ratio of tissue radioactivity to plasma radioactivity following sublingual administration remained higher than that following subcutaneous administration; and (2) it has been reported that allergens captured by dendritic cells in the oral mucosa (administration site) transfer to neighboring lymph nodes (including submandibular lymph nodes) and elicit immunoreactions (Moingeon P et al. *Allergy.* 2006;61:151-165).

3.(ii).A.(3) Metabolism (4.2.2.2.1)

A single dose of 7.5 μg of ^{125}I-labeled Cry j 1 was administered subcutaneously to male rats (n = 3), and plasma samples collected at 30 minutes and 2, 24, and 168 hours after administration were analyzed by gel-filtration HPLC and reverse-phase HPLC. At all time points after administration, no peak matching the dissolution time for ^{125}I-labeled Cry j 1 was observed in the plasma, and radioactive peaks inferred to be iodine ions and radioactive peaks having the same dissolution time as iodotyrosine were mainly detected. The ratio of each peak to the total radioactivity detected was 53.9% to 57.8% and 8.6% to 13.1%, respectively, at 30 minutes after administration; 87.5% to 89.8%

[8] Sublingual administration was performed by ligating the esophagus, and for the humane treatment of animals, radioactivity levels in the plasma, blood and tissues were measured up to four hours after administration.

and 3.2% to 4.2%, respectively, at 2 hours after administration; and no radioactive peaks having the same dissolution time as iodotyrosine were detected at 24 hours after administration. The radioactive peak inferred to be iodine ion was 36.4% to 52.4%.

Based on the above, the applicant explained that ^{125}I-labeled Cry j 1 is rapidly metabolized after administration, similarly to other foreign proteins.

3.(ii).A.(4) Excretion (4.2.2.2.1)

A single dose of 7.5 μg of ^{125}I-labeled Cry j 1 was administered subcutaneously to male rats (n = 3), and urinary and fecal excretion rates (the ratio of excretion of radioactivity to the administered dose) up to 168 hours after administration was 74.4 ± 5.2% and 6.3 ± 1.4%, respectively. The rate of residual radioactivity in the body was 11.8 ± 2.3%. The ratio of urinary radioactivity in TCA insoluble fractions was 4.9 ± 0.6% to 8.7 ± 1.2%.

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

PMDA has asked the applicant to discuss the pharmacokinetics of Cry j 2, since both Cry j 1 and Cry j 2 have been identified as the major allergens in Japanese cedar pollen, but the applicant addressed only the pharmacokinetics of Cry j 1.

The applicant explained as follows:

There is no homology in the amino acid sequence between Cry j 1 and Cry j 2, but they consist of comparable numbers of amino acids, with no marked differences in molecular weight (Cry j 1, 41 kDa and 46 kDa; Cry j 2, 45 kDa) or isoelectric points (Cry j 1, pI 8.9 and pI 9.2; Cry j 2, pI 9.5) (Yasueda H et al. *J Allergy Clin Immunol.* 1983;71:77-86, Sakaguchi M et al. *Allergy.* 1990;45:309-312). The following 2 findings suggest that, as with Cry j 1, Cry j 2 is unlikely to be distributed into circulating blood from the sublingual region without being subjected to degradation, indicating that the 2 compounds exhibit similar *in vivo* kinetics: (a) Typically, the absorption of proteins and peptides through the oral mucosa is based on passive diffusion and dependent on the molecular weight and charge state (Rojanasakul Y et al. *Pharm Res.* 1992;9:1029-1034), but the threshold of molecular weight of absorbable moleculesis considered to be 500 to 1000 Da (Merkle HP et al. *J Control Release.* 1992;21:155-164). (b) Studies have found that following sublingual administration to humans of ^{123}I-labeled Par j 1 (10 kDa), one of the main allergens of pollen from the spreading pellitory (*Parietaria judaica*), or ^{123}I-labeled Der p 2 (15 kDa), one of the main allergens generated by the European house dust mite (*Dermatophagoides pteronyssinus*), the unchanged allergenic protein was not detected in plasma (Bagnasco M et al. *J Allergy Clin Immunol.* 1997;100:122-129, Bagnasco M et al. *Int Arch Allergy Immunol.* 2005;138:197-202).

PMDA accepted the above explanation by the applicant and concluded that, based on the submitted data, there are no particular non-clinical pharmacokinetic concerns with the clinical use of the proposed allergen product.

3.(iii) Summary of toxicology studies

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

Single-dose toxicity, repeat-dose toxicity, genotoxicity, and local tolerance studies were conducted. Subcutaneous dose studies were conducted in order to investigate systemic exposure higher than that in sublingual administration (proposed clinical route of administration). Moreover, oral dose studies were conducted because the dosage regimen changed from “is placed under the tongue and held in place for 2 minutes before spitting out” to “is placed under the tongue and held in place for 2 minutes before swallowing” during development.

3.(iii).A.(1) Single-dose toxicity (Reference data 4.2.3.1.1)

A single dose of 0 (vehicle, 5 mL/kg of 50% glycerin/sodium chloride solution), 25,000 JAU/kg (2.5 mL/kg of 10,000 JAU/mL), or 50,000 JAU/kg (5 mL/kg of 10,000 JAU/mL) of the standardized Japanese cedar pollen extract[9] was administered subcutaneously to male and female SD rats. The

[9] The drug substance of the existing Japanese cedar pollen extracts was used.

approximate lethal dose was determined to be >50,000 JAU/kg. Clinical signs observed were urinary occult blood, decreased locomotor activity, scab, and alopecia likely to be due to glycerin (vehicle).

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

As repeat-dose toxicity studies, 26-week oral and subcutaneous studies were conducted in rats. Both studies indicated that findings were attributable to the irritant effects of the vehicle. The maximum dose for the repeat-dose toxicity studies was set to about 300 times (10,000 JAU/kg/day) the proposed maximum clinical dose (1 mL/day of 2000 JAU/mL; about 33 JAU/kg/day with an arbitrary human body weight of 60 kg). The no observed adverse effect level (NOAEL) for the rat oral dose study was 10,000 JAU/kg/day (1 mL/kg/day with 10,000 JAU/mL). NOAELs for rat subcutaneous dose study were <2000 JAU/kg/day (local toxicity, <0.2 mL/kg/day with 10,000 JAU/mL) and 10,000 JAU/kg/day (systemic toxicity; 1 mL/kg/day with 10,000 JAU/mL). The safety margin calculated based on the proposed maximum clinical dose was approximately 300-fold for the rat oral dose study and about 300-fold (systemic toxicity) for the rat subcutaneous dose study. The toxicokinetic study showed that serum levels of Cry j 1, one of the major allergens in the standardized Japanese cedar pollen extract, were below the lower limit of quantification at most time points, and thus the safety margin based on Cry j 1exposure has not been calculated.

3.(iii).A.(2).1) Twenty-six week oral dose study in rats (4.2.3.2.1)

Male and female SD rats received oral doses of 0 (1 mL/kg/day of saline), 0 (vehicle, 1 mL/kg/day of 50% glycerin/sodium chloride solution), 200 JAU/kg/day (1 mL/kg/day of 200 JAU/mL), 2000 JAU/kg/day (1 mL/kg/day of 2000 JAU/mL), or 10,000 JAU/kg/day (1 mL/kg/day of 10,000 JAU/mL) of the standardized Japanese cedar pollen extract for 26 weeks. No changes indicative of systemic toxicity were observed. Histopathological examinations in the vehicle and 10,000 JAU/kg/day groups confirmed hyperplasia of the squamous cell border of the anterior stomach and increased globular leukocytes in the glandular stomach, but these findings disappeared after 4 weeks of drug withdrawal. These changes were considered to be attributed to the irritant effect of the vehicle and to be clinically insignificant, since they were observed at 60 times the clinical dose on a body weight basis (1 mL/kg/day of vehicle to humans weighing 60 kg) and unaccompanied by bleeding or ulcer. Based on the above, the NOAEL in the study was determined to be 10,000 JAU/kg/day.

3.(iii).A.(2).2) Twenty-six week subcutaneous dose study in rats (4.2.3.2.5)

Male and female SD rats received subcutaneous doses of 0 (1 mL/kg/day of saline), 0 (vehicle, 1 mL/kg/day of 50% glycerin/sodium chloride solution), 2000 JAU/kg/day (0.2 mL/kg/day of 10,000 JAU/mL), or 10,000 JAU/kg/day (1 mL/kg/day of 10,000 JAU/mL) of the standardized Japanese cedar pollen extract for 26 weeks, and no changes indicative of systemic toxicity were observed. The changes observed at the injection site that were attributable to the vehicle were injection-site scab; subcutaneous dark reddish spots, bleeding, fibrosis, inflammatory cell infiltration, degeneration/necrosis, and edema at the injection site; and thickening, scab, and ulceration of the epidermis at the injection site. The changes observed at the administration site that were attributable to the standardized Japanese cedar pollen extract were the higher frequency and degree of subcutaneous inflammatory cell infiltration and edema. These changes were deemed not clinically significant because the proposed allergen product is administered by the sublingual route in clinical use. Based on the above, the NOAEL in the study was determined to be <2000 JAU/kg/day for local toxicity and 10,000 JAU/kg/day for systemic toxicity.

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

As genotoxicity studies, a bacterial reverse mutation test, a chromosomal aberration assay in Chinese hamster lung fibroblast cell lines (CHL/IU cells) and a rat micronucleus assay were performed. The standardized Japanese cedar pollen extract was found to be non-genotoxic.

3.(iii).A.(4) Carcinogenicity and reproductive and developmental toxicity

No carcinogenicity or reproductive and developmental toxicity studies have been performed because Japanese cedar pollen exists in nature; people are normally exposed to large quantities during the pollen season. Clinical use of SCIT with the existing Japanese cedar pollen extracts has shown no adverse reactions suggesting carcinogenicity, reproductive, or developmental toxicity. The level of

systemic exposure of the standardized Japanese cedar pollen extract for SLIT does not exceed that for SCIT.

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

3.(iii).A.(5).1) One-week sublingual dose study in rabbits (4.2.3.6.2)

Male NZW rabbits received sublingual repeated doses of 0 (0.2 mL/body/day of saline), 0 (vehicle, 0.2 mL/body/day of 50% glycerin/sodium chloride solution), or 400 JAU/body/day (0.2 mL/body/day of 2000 JAU/mL) of the standardized Japanese cedar pollen extract once daily for 1 week. The administered dose was being held under the tongue for 20 minutes. The results indicated no sublingual irritation with the standardized Japanese cedar pollen extract.

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

PMDA concluded that, based on the submitted data, there are no specific toxicological concerns with the clinical use of the proposed allergen product.

4. Clinical data

4.(i) Summary of clinical efficacy and safety

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

As the results of efficacy and safety studies on the proposed allergen product, the results of a phase III clinical study on Japanese cedar pollinosis patients (194-3-1 Study 5.3.5.1.1) were submitted.

4.(i).A.(1) Phase III clinical study in patients with Japanese cedar pollinosis (5.3.5.1.1: 194-3-1 Study, [redacted])

A randomized, placebo-controlled, double-blind, parallel-group comparative study was conducted in patients with Japanese cedar pollinosis[10] (target sample size of 440; 220 subjects per group) to investigate the efficacy and safety of the proposed allergen product.

The dosage regimen was designed by referring to multiple reports of Japanese clinical studies on SLIT using the existing Japanese cedar pollen extracts (Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2009 Partial Research Report. 2010; 12-14, and other reports) as follows: The dose escalation period consisted of Weeks 1 and 2 of administration. The dose maintenance period was from Week 3 and onward. As shown in Table 4, either the proposed allergen product or placebo was administered sublingually once daily, and the subjects were instructed to hold the administered dose under the tongue for 2 minutes before swallowing and to refrain from gargling, eating, or drinking for 5 minutes after swallowing. The longest dosing period was to be 83 weeks, consisting of 2 weeks of dose escalation followed by up to about 81 weeks of dose maintenance.[11] Unbearable symptoms (as a general rule, 4+ for any of the nasal symptoms or 3+ for one of the ocular symptoms) were treatable using the following rescue medications: in general, tramazoline hydrochloride nasal solution (Towk Nasal Solution 0.118% or Tramazoline Nasal Solution 0.118% “AFP”) was usable for nasal congestion and ketotifen fumarate ophthalmic solution (Zaditen Ophthalmic Solution 0.05%) was usable for ocular symptoms. If these agents failed to alleviate symptoms or if sneezing or nasal discharge was intolerable, the daily dose of fexofenadine hydrochloride (allegra 60 mg Tablets) was allowed to be taken. It has been reported that high levels of allergen exposure exacerbate patients’ hypersensitivity, elevating the risk for anaphylaxis (Calderón MA et al. *Allergy.* 2012;67:302-311). Thus, to ensure a certain length of dosing in each subject prior to the peak season of Japanese cedar pollen dispersal (time period for efficacy assessment), the dosing of the proposed allergen product was scheduled to start during the period from October 1, 2010 to as a general rule December 15, 2010, i.e., before the pollen season. Actually in the study, the initiation of

[10] Inclusion criteria: (a) Aged ≥12 and <65 years at the time of giving informed consent; (b) ≥ Class 3 by Japanese cedar pollen specific IgE antibody assay on Day 1 of observation; (c) During 2009 or 2010 pollen seasons, the score and duration for at least one of the following nasal symptoms was ≥2+ and at least 1 week, respectively: sneezing (6-10 times during the day), nasal discharge (6-10 times during the day) or nasal congestion (severe nasal congestion and occasional mouth breathing during the day); (d) [redacted].

[11] All of the subjects were to be given the last dose by April 30, 2012.

administration ranged from October 2 to December 14, 2010.

Table 4. Dosage regimen for phase III clinical study

Week 1, Dose Escalation Period		Week 2, Dose Escalation Period		≥ Week 3, Dose Maintenance Period
200 JAU/mL product		2000 JAU/mL product		2000 JAU/mL product
Day 1	0.2 mL (40 JAU)	Day 1	0.2 mL (400 JAU)	1 mL (2000 JAU)
Day 2	0.2 mL (40 JAU)	Day 2	0.2 mL (400 JAU)	
Day 3	0.4 mL (80 JAU)	Day 3	0.4 mL (800 JAU)	
Day 4	0.4 mL (80 JAU)	Day 4	0.4 mL (800 JAU)	
Day 5	0.6 mL (120 JAU)	Day 5	0.6 mL (1200 JAU)	
Day 6	0.8 mL (160 JAU)	Day 6	0.8 mL (1600 JAU)	
Day 7	1 mL (200 JAU)	Day 7	1 mL (2000 JAU)	

Dosage (potency)

All 531 randomized subjects (266 subjects in the proposed allergen product group and 265 subjects in the placebo group) were included in the safety analysis and received the investigational product, while 482 subjects in whom efficacy was assessed during the second season[12] (241 subjects in the proposed allergen product group and 241 subjects in the placebo group) were included in the full analysis set (FAS) and the efficacy analysis. In the study, 8.6% (23 of 266 subjects) of the proposed allergen product group discontinued study treatment, while 9.1% (24 of 265 subjects) of the placebo group discontinued study treatment. The main reason for discontinuation was personal matters: 3.8% (10 of 266 subjects) of the proposed allergen product group and 5.3% (14 of 265 subjects) of the placebo group.

There are no established indicators for assessing the efficacy of hyposensitization therapy for allergic rhinitis. However, the European guideline for clinical development of allergen extract products recommends that the primary endpoints should reflect both the degree of symptoms and use of rescue medications (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 endpoint for efficacy in this study was the total nasal symptom medication score (TNSMS)[13] which consists of the following two scores: the sum of the total nasal symptom score (TNSS) taking into account the severity of the major symptoms of Japanese cedar pollinosis (i.e., sneezing, nasal discharge, nasal congestion); and the medication score calculated based on the use of rescue medications.

Table 5 shows TNSMS for a total of three weeks (the 7 days of peak symptom period[14] plus 7 days each before and after the peak period) during the second season (March 19 to March 31, 2012,[15] Period A) (primary efficacy endpoint),[16] and a statistically significant difference was observed between the proposed allergen product and placebo groups, demonstrating the superiority of the proposed allergen product over the placebo.

[12] Pre-pollen and pollen periods (January 8 to April 30, 2012)

[13] The sum of the total nasal symptom score (TNSS) and the medication score (maximum score of 18 points). TNSS was calculated by assessing each of the three nasal symptoms (sneezing, nasal discharge, nasal congestion) with a score of 0 to 4 points and totaling the three individual scores. The medication score was calculated by adding 3 points for using fexofenadine hydrochloride tablet, 3 points for using tramazoline hydrochloride nasal solution and 0 points for using neither of the two rescue medications. Since TNSS consisted of three symptoms (4 points per symptom for a total of 12 points), the score for each rescue medication was set at 3 points (total of 6 points) by weighing the balance between TNSS and medication scores.

[14] During the pre-pollen and pollen periods (January 8 to April 30), the 7-day cumulative TNSMS was calculated by adding the results of daily TNSMS for any consecutive 7-day period in the entire study period. The 7-day period with the highest cumulative score for each season was defined as the peak symptom period (First season, March 14 to March 20, 2011; Second season, March 26 to April 1, 2012).

[15] Based on the pre-defined rule "To avoid the impact of Japanese cypress pollen, the last day of assesment is to be March 31 even if it is not the last day of the period," the last day of assessment was March 31, resulting in a total of 13 days of assessment.

[16] Based on the results of the onsite GCP inspection, the applicant considered that it would be difficult to ensure that the level of quality for the data collected by handwritten patient journals is comparable with that for the data collected electronically, and submitted the results of analysis by excluding all the data entered into the EDC (electronic data capture) based on handwritten patient journals.

Table 5. Mean TNSMS at Period A[a)] during the second season (FAS)

Proposed allergen product group	Placebo group	Inter-group difference (95% confidence interval [CI]), *P* value [b)]
4.00 ± 2.99 (241)	5.71 ± 3.70 (241)	-1.71 [-2.31, -1.11], $P < 0.0001$

Mean ± SD (number of subjects)
a) Peak symptom period plus 7 days each before and after the peak period (March 19 to March 31, 2012); b) t-test

Table 6 shows the analysis results of secondary efficacy endpoints at Period A during the first and second seasons.

Table 6. Secondary endpoints at Period A during the first and second seasons[a)] (FAS)

	First season			Second season		
	Proposed allergen product group (n = 261)	Placebo group (n = 256)	Inter-group difference [95% CI]	Proposed allergen product group (n = 241)	Placebo group (n = 241)	Inter-group difference [95% CI]
Total nasal symptom medication score (TNSMS)	7.04 ± 3.62	8.61 ± 4.01	-1.57 [-2.23, -0.91]	–	–	–
Total nasal ocular symptom medication score (TNOSMS)	9.86 ± 5.30	12.35 ± 5.92	-2.49 [-3.46, -1.52]	5.62 ± 4.51	8.10 ± 5.46	-2.49 [-3.38, -1.59]
Total ocular symptom medication score (TOSMS)	2.82 ± 1.97	3.75 ± 2.36	-0.92 [-1.30, -0.55]	1.62 ± 1.81	2.40 ± 2.18	-0.78 [-1.14, -0.42]
Total nasal ocular symptom score (TNOSS)	8.69 ± 3.80	10.30 ± 3.87	-1.61 [-2.27, -0.95]	5.19 ± 3.53	7.13 ± 3.99	-1.94 [-2.62, -1.27]
Total nasal symptom score (TNSS)	6.32 ± 2.66	7.34 ± 2.68	-1.03 [-1.49, -0.57]	3.77 ± 2.40	5.13 ± 2.78	-1.37 [-1.83, -0.90]
Total ocular symptom score (TOSS)	2.38 ± 1.36	2.95 ± 1.50	-0.58 [-0.82, -0.33]	1.42 ± 1.34	2.00 ± 1.52	-0.58 [-0.83, -0.32]
Number of days without rescue medications	16.1 ± 6.6	12.8 ± 8.0	3.2 [2.0, 4.5]	11.0 ± 3.0	9.5 ± 4.3	1.5 [0.9, 2.2]
Number of “Well Days”	3.7 ± 5.6	2.1 ± 4.4	1.6 [0.7, 2.5]	5.7 ± 4.9	3.5 ± 4.3	2.2 [1.4, 3.0]
Number of days with severe symptoms	7.2 ± 7.1	10.9 ± 8.1	-3.6 [-4.9, -2.3]	1.4 ± 3.1	3.4 ± 4.4	-2.0 [-2.7, -1.3]

Mean ± SD
Total nasal symptom medication score (TNSMS): total of three nasal symptom scores (sneezing, nasal discharge, nasal congestion) and medication scores (fexofenadine hydrochloride tablet and tramazoline hydrochloride nasal solution)
Total nasal ocular symptom medication score (TNOSMS): total of three nasal symptom scores, two ocular symptom scores (eye itching and teary eye), and medication scores (fexofenadine hydrochloride tablet, tramazoline hydrochloride nasal solution, ketotifen fumarate ophthalmic solution)
Total ocular symptom medication score (TOSMS): total of two ocular symptom scores and medication score (ketotifen fumarate ophthalmic solution)
Total nasal ocular symptom score (TNOSS): total of three nasal and two ocular symptom scores
Total nasal symptom score (TNSS): total of three nasal symptom scores
Total ocular symptom score (TOSS): total of two ocular symptoms scores
a) Peak symptom period and one week before and after (First season, March 7-March 27, 2011, Second season, March 19-March 31, 2012)

Figure 1 shows TNSMS over time during the first and second seasons.

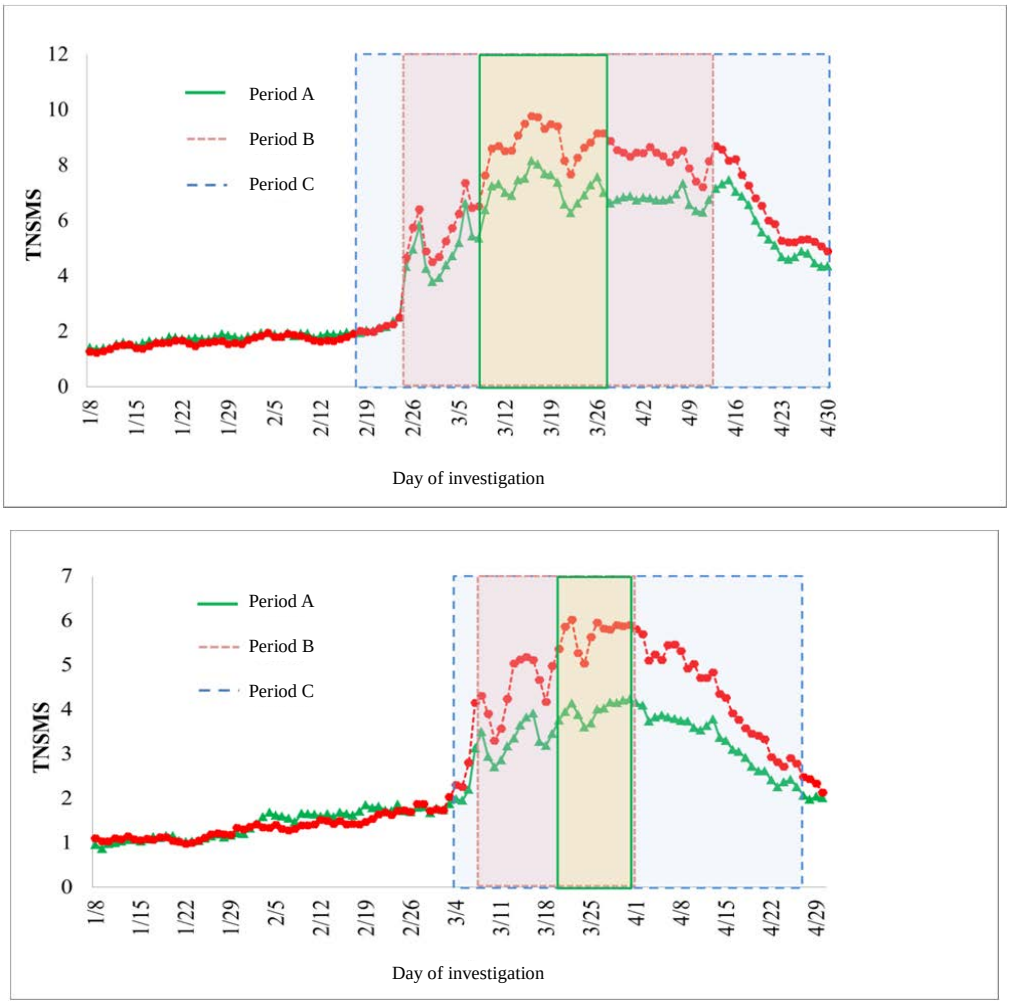

Figure 1. Mean TNSMS throughout the assessment period
(Top, First season; Bottom, Second season; ▲, Proposed allergen product group; ●, Placebo group)

Period A: peak symptom period and one week before and after (First season, March 7 to March 27, 2011; Second season, March 19-March 31, 2012)
Period B: peak pollen period (First season, February 25 to April 12, 2011; Second season, March 6 to March 31, 2012)
Period C: whole pollen season (First season, February 17 to April 30, 2011; Second season, March 3 to April 27, 2012)

Adverse events were reported by 79.7% (212 of 266 subjects) in the proposed allergen product group and 71.3% (189 of 265 subjects) in the placebo group. Table 7 lists the major events. No deaths were reported. Serious adverse events were documented in 2.6% for the proposed allergen product group (7 of 266 subjects, soft tissue neoplasm, herpes zoster, clavicular fracture, oropharyngeal cancer, cervical dysplasia, pneumonia mycoplasmal, diverticulitis [1 subject each]) and 2.3% for the placebo group (6 of 265 subjects, intracranial hypotension, breast cancer, diverticulitis, colon cancer, anal fissure, benign mediastinal neoplasm [1 subject each]), but the causal relationship to the investigational products was ruled out for all events. Adverse events leading to treatment discontinuation occurred in 1.9% for the proposed allergen product group (5 of 266 subjects, toxic skin eruption, periodontal disease, Meniere's disease, migraine, oropharyngeal cancer [1 subject each]) and in 1.1% for the placebo group (3 of 265 subjects, uveitis, breast cancer, colon cancer [1 subject each]). Of these, the causal relationship of toxic skin eruption to the investigational product for the proposed allergen product group could not be ruled out. Adverse events leading to treatment withdrawal were reported in 4.1% for the proposed allergen product group (11 of 266 subjects, oedema mouth [2 subjects], dental caries, edema, gastroenteritis norovirus/soft tissue neoplasm, swelling face, throat irritation/dysphonia/herpes zoster, urticaria, clavicular fracture, stomatitis, oedema peripheral [1 subject each]) and 0.8% for the placebo group (2 of 265 subjects, cellulitis/intracranial hypotension

and urticaria/ paraesthesia oral [1 subject each]), and as for outcomes, the placebo subject with intracranial hypotension improved, and the other events resolved.

Adverse drug reactions[17] were reported by 13.5% in the proposed allergen product group (36 of 266 subjects) and 5.3% in the placebo group (14 of 265 subjects). The reaction reported with incidence of ≥2% for either group was oedema mouth (3.8%, 10 of 266 subjects in the proposed allergen product group).

Table 7. Adverse events with incidence of ≥2% (safety analysis population)

Adverse events	Proposed allergen product group (n = 266)	Placebo group (n = 265)
Nasopharyngitis	113 (42.5)	104 (39.2)
Upper respiratory tract inflammation	34 (12.8)	31 (11.7)
Influenza	17 (6.4)	15 (5.7)
Headache	14 (5.3)	21 (7.9)
Pharyngitis	13 (4.9)	14 (5.3)
Dental caries	12 (4.5)	11 (4.2)
Oedema mouth	10 (3.8)	0
Back pain	9 (3.4)	8 (3.0)
Gastroenteritis	7 (2.6)	6 (2.3)
Stomatitis	7 (2.6)	3 (1.1)
Coughing	6 (2.3)	4 (1.5)
Eczema	6 (2.3)	4 (1.5)
Rhinorrhoea	6 (2.3)	4 (1.5)
Diarrhea	6 (2.3)	3 (1.1)
Gingivitis	6 (2.3)	1 (0.4)
Rash	5 (1.9)	6 (2.3)
Oropharyngeal pain	2 (0.8)	6 (2.3)

n (%)

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

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

It has been reported that, as a method to assess efficacy reflecting both the severity of symptoms and the use of rescue medications in hyposensitization therapy for allergic rhinitis, nasal symptom scores were calculated by substituting symptom scores for the day of use of rescue medications and for the following day with scores for the previous day of the rescue therapy (Grouin JM et.al. *Clin Exp Allergy.* 2011;41:1282-1288). PMDA asked the applicant to perform the same analysis using the results of the Phase III study and to compare the results to that of TNSMS analysis.

The applicant explained as follows:
As shown in Table 8, statistically significant differences was observed between the placebo and proposed allergen product groups in nasal symptom scores calculated by the method of Grouin and others, and that this finding matched the results of TNSMS analysis.

Table 8. Mean TNSMS and mean nasal symptom scores, taking account of the use of rescue medication at Period A[a)] during the second season (FAS)

	Proposed allergen product group	Placebo group	Inter-group difference [95% CI], *P* value
TNSMS	4.00 ± 2.99 (241)	5.71 ± 3.70 (241)	-1.71 [-2.31, -1.11], $P < 0.0001$
Nasal symptom score, taking account of the use of rescue medication	3.85 ± 2.53 (241)	5.40 ± 3.04 (241)	-1.55 [-2.05, -1.05], $P < 0.0001$

Mean ± SD (number of subjects)
a) Peak symptom period plus 7 days each before and after the peak period (March 19 to March 31, 2012)

[17] The causal relationship of adverse events to investigational products was assessed in three grades (Related, Possibly related, Not related), and adverse events with a causal relationship of other than "Not related"were defined as adverse drug reactions.

Since the ultimate therapeutic goal of hyposensitization therapy is the remission of allergic symptoms, PMDA asked the applicant to compare the percentages of subjects achieving remission between the proposed allergen product and placebo groups in the Phase III clinical study.

The applicant responded as follows:
No definition for remission of Japanese cedar pollinosis has been established. However, the Practical Guideline for the Management of Allergic Rhinitis in Japan 2013 advises targeting "a state wherein symptoms are either non-existent or very mild, activities of daily living are not impaired, and no or minimal medication is required." Cutoff values were established for each efficacy endpoint, which generally corresponded to the scores for a state in which subjects are able to perform daily living activities without discomfort. Table 9 shows the results for subgroup analysis. For the first season, the percentage of patients with a score of <3 on TNSMS (an indicator most closely matching the definition of remission from a clinical perspective) for the proposed allergen product and placebo groups was 11.9% and 7.0%, respectively. The percentage of patients who experienced only "well days" (defined as nasal and ocular symptoms scores of either "-" or "1+" without the use of rescue medications throughout the assessment period) for the proposed allergen product and placebo groups was 2.3% and 1.6%, respectively. No marked differences were found between the two groups. The results were attributable to be the short treatment period and large quantities of Japanese cedar pollen dispersal. However, for the second season, the percentage of patients with a score of <3 on TNSMS for the proposed allergen product and placebo groups was 44.4% and 25.3%, respectively, and the percentage of patients who experienced only "well days" for the proposed allergen product and placebo groups was 17.0% and 8.3%, respectively. Hence, for the second season, remission was achieved in a certain number of patients treated with the proposed allergen product.

Table 9. Summary of remission based on each assessment criterion (peak symptom period plus 7 days each before and after the peak period [a total of 3 weeks])

Cutoff values for each assessment score		First season		Second season	
		Proposed allergen product group (n = 261)	Placebo group (n = 256)	Proposed allergen product group (n = 241)	Placebo group (n = 241)
TNSMS	< 3 points	31 (11.9)	18 (7.0)	107 (44.4)	61 (25.3)
	< 4 points	52 (19.9)	31 (12.1)	147 (61.0)	95 (39.4)
TNOSMS	< 5 points	45 (17.2)	24 (9.4)	132 (54.8)	84 (34.9)
	< 6 points	63 (24.1)	37 (14.5)	155 (64.3)	109 (45.2)
TOSMS	< 2 points	100 (38.3)	66 (25.8)	166 (68.9)	131 (54.4)
	< 3 points	168 (64.4)	115 (44.9)	207 (85.9)	171 (71.0)
TNSS	< 3 points	31 (11.9)	18 (7.0)	107 (44.4)	61 (25.3)
	< 4 points	52 (19.9)	31 (12.1)	148 (61.4)	98 (40.7)
TOSS	< 2 points	108 (41.4)	71 (27.7)	168 (69.7)	134 (55.6)
	< 3 points	188 (72.0)	128 (50.0)	212 (88.0)	177 (73.4)
Number of patients who experienced only "Well Days"		6 (2.3)	4 (1.6)	41 (17.0)	20 (8.3)
Number of patients who experienced only days with severe symptoms		73 (28.0)	52 (20.3)	177 (73.4)	120 (49.8)

n (%)

PMDA asked the applicant to explain the difference in efficacy between SLIT and SCIT.

The applicant responded as follows:
While no studies comparing SLIT and SCIT in patients with Japanese cedar pollinosis have been performed, several studies document the efficacy of both SLIT and SCIT with other allergens in allergic rhinitis and asthma patients (Calderón MA et al. *Cochran Database Syst Rev 2007* CD001936, Abramson MJ et al. *Cochran Database Syst Rev 2010* CD001186, Wilson DR et al. *Cochran Database Syst Rev 2003* CD002893, Radulovic S et al. *Allery.* 2011;66:740-752, Bona DD et al. *J Allergy Clin Immunol.* 2012;130:1097-1107). Clinical studies that directly compare SLIT and SCIT do not document clear differences in efficacy (Calderón MA et al. *Allergy.* 2012;67:302-311, Quirino T et al. *Clin Exp Allergy.* 1996;26:1253-1261, Khinchi MS et al. *Allergy.* 2004;59:45-53). A meta-analysis of 36 double-blind placebo-controlled comparative studies of seasonal allergic rhinitis associated with Gramineae pollen (10 SLIT studies [solutions], 12 SLIT studies [tablets], 14 SCIT studies) showed the

superiority of both SCIT and SLIT (solutions and tablets) over the placebo, but suggested that SCIT achieved greater clinical benefits than SLIT (Bona DD et al. *J Allergy Clin Immunol.* 2012;130:1097-1107).

Based on the above, while the efficacy of both SLIT and SCIT has been demonstrated, no clear conclusion has been drawn on the difference in efficacy. Due to the limited amount of data for SLIT in particular, more evidence need to be gathered.

PMDA considers as follows:
Based on the above, the results of the Phase III clinical study demonstrate the efficacy of the proposed allergen product in alleviating allergic symptoms associated with Japanese cedar pollen. Hyposensitization therapy requires long-term treatment, and its ultimate goal is the remission of allergic symptoms. Thus, post-marketing surveillance is required to collect information regarding the rate at which remission is achieved following long-term treatment with the proposed allergen product and the rate at which remission is sustained after the completion of therapy. Furthermore, it is appropriate to consider the conduct ofa post-marketing clinical study, thereby providing definitive evidence to the medical practice. At this point of time, it is difficult to reach a definitive conclusion concerning differences in efficacy between SLIT and SCIT. However, since post-marketing information could represent an important factor in selecting the optimal therapy, further investigation is recommended.

4.(i).B.(2) Dosage and administration

4.(i).B.(2).1) Usual dosage and administration

The applicant gave the following justification for the dosage regimen employed for the Phase III clinical study:
The dose escalation period was established for the Phase III clinical study because (1) many Japanese clinical studies incorporated a dose escalation period in which subjects receive small initial doses followed by maintenance doses to ensure safety; and (2) outside of Japan, dosage regimens for some SLIT products include a dose escalation period. According to the report by Horiguchi and others (Horiguchi S. et al. *Int Arch Allergy Immunol.* 2008;146:76-84), no specific safety problems were noted when the initial dose was set at 0.2 mL of 20 JAU/mL (4 JAU) and the dose was increased to 2000 JAU (1 mL of 2000 JAU/mL) over a period of 3 weeks in increments of 0.2 mL in order to avoid exceeding a 2-fold increase in the dose escalation rate. Moreover, at a potency of >200 JAU/mL, the relative loss of Cry j 1 content was high due to adhesion to the container or degradation, making it technically challenging to manufacture the proposed allergen product within the specifications. In the Phase III clinical study, the initial dose was set at 0.2 mL of 200 JAU/mL (40 JAU) and the dose was increased to the maintenance dose over a period of 2 weeks without exceeding a 2-fold increase in the dose escalation rate. The optimal dose of allergens in hyposensitization therapy should be the highest dose that can show clear clinical efficacy without inducing unacceptable adverse drug reactions, such as anaphylaxis (WHO position paper 1998). Okamoto and others reported that administration of a maintenance dose of 1 mL of 2000 JAU/mL once daily caused no unacceptable adverse drug reactions, and decreased symptom scores (Okamoto Y et al. Research project supported by the Health and Labour Sciences Research Grants: Efficacy of sublingual immunotherapy for Japanese cedar pollinosis and methods to predict efficacy, FY 2009 Partial Research Report. 2010;12-14). Furthermore, 2000 JAU/mL is the highest potency and the highest concentration for the proposed allergen product for which the current manufacturing process can achieve and ensure availability. Based on the above considerations, the dose during the maintenance period in the Phase III clinical study was set at 1 mL of 2000 JAU/mL for a once-daily dose.

The dosing regimen established for the proposed allergen product—holding the dose under the tongue for 2 minutes after administration, followed by swallowing—is based on the following findings: As the main dosing regimen for SLIT, the WAO Position Paper 2009 recommends that the allergen extract be kept under the tongue for 1 to 2 minutes, and then swallowed; Japanese clinical studies suggest the efficacy of the sublingual-spit method in which the allergen extract is held under the tongue for 2 minutes before being spitted out, while the sublingual-swallow method has been employed in all SLIT products approved in Europe; and the sublingual-swallow method reduces burdens upon the patient and improves the patient's convenience. The subsequent regimen for the

proposed allergen product is to refrain from gargling, eating, or drinking for 5 minutes after swallowing the product. This is considered because the dosage and administration for SLIT with Gramineae pollen (timothy grass, *Phleum pretens*) extracts approved in Europe state that the patient should refrain from drinking and eating for 5 minutes after dosing, since allergens, attached to oral mucosal epithelial cells after sublingual administration, should be held under the tongue for a certain period of time for uptake by dendritic cells under the oral mucosa.

PMDA considers as follows:
In addition to the lack of examination on dose-response relationships, the optimal dose of the proposed allergen product has not been adequately investigated, but the situation is inevitable in light of technical limitations on formulation development. The Phase III clinical study confirmed the efficacy of the proposed allergen product in the treatment of Japanese cedar pollinosis and suggested no major safety concerns. Thus, the following dosage regimen of the product are acceptable: The treatment should be started with the initial dose of 0.2 mL of 200 JAU/mL and increased to 1 mL of 2000 JAU/mL over a period of 2 weeks. From the third week of administration onward, the dose of 1 mL of 2000 JAU/mL is administered sublingually once daily as the maintenance dose. Based on the results of the Phase III clinical study, PMDA has also concluded that the following dosage regimen presents no specific problems: the proposed allergen product should be held under the tongue for about 2 minutes, then be swallowed. It is necessary to refrain from gargling, eating, or drinking for 5 minutes after swallowing the proposed allergen product.

No specific age limitations have been specified in the proposed dosage and administration. However, since the Phase III clinical study did not investigate the efficacy or safety of the proposed allergen product in children <12 years of age, it would be appropriate to set the scope to adults and children ≥12 years of age and to clearly state in the "Pediatric Use" section of the package insert that the safety of the product in children <12 years of age has not been established. In light of the increasing number of children with Japanese cedar pollinosis, it will be necessary to develop the proposed allergen product for use in children <12 years of age.

Based on the above, PMDA considers it appropirate to specify the following dosage and administration for the proposed allergen product (Underline: changes from the proposed dosage and administration).

[Dosage and administration]

1. Dose escalation period (Weeks 1-2)
The usual dosage of Cedartolen <u>for adults and children ≥12 years of age</u> for the first 2 weeks of administration (dose escalation period) is described in the dosing schedule shown below. The specified dose should be administered as sublingual drops once daily and be held under the tongue for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

Week 1 (dose escalation period)		Week 2 (dose escalation period)	
<u>Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle</u>		<u>Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle</u>	
Day 1	0.2 mL	Day 1	0.2 mL
Day 2	0.2 mL	Day 2	0.2 mL
Day 3	0.4 mL	Day 3	0.4 mL
Day 4	0.4 mL	Day 4	0.4 mL
Day 5	0.6 mL	Day 5	0.6 mL
Day 6	0.8 mL	Day 6	0.8 mL
Day 7	1 mL	Day 7	1 mL

2. Dose maintenance period (From Week 3 onward)
During the dose maintenance period after the completion of the dose escalation period, <u>using Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack,</u> 1 mL of the product is placed under the tongue once daily and held in place for 2 minutes before being

swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

4.(i).B.(2).2) Appropriate duration of treatment, timeframe required to determine lack of efficacy, and dosage regimen for resumption of treatment

PMDA asked the applicant to explain the applicant's views on the appropriate duration of treatment with the proposed allergen product.

The applicant responded as follows:
Results of a clinical study of SLIT involving 78 patients with allergic rhinitis associated with house dust mites has been reported. In the study, patients were assigned to receive SLIT for 3 years (19 patients), 4 years (21 patients), or 5 years (17 patients) or drug therapy alone as the control (21 patients). All groups were monitored for 15 years. In all the 3 SLIT groups, symptom and medication scores were reduced to <50% of the baseline value following 3 years of treatment, and the clinical effect was maintained following completion of SLIT. However, symptoms tended to recur, and symptom and medication scores exceeded 50% of the baseline value at 7 years after the completion of SLIT in the 3-year SLIT group; at 8 years after the completion of SLIT in the 4-year and 5-year groups (Marogna M et al. *J Allergy Clin Immunol*. 2010;126:969-975). When Grazax (Gramineae pollen SLIT tablets approved in Europe) was administered for 3 years, its clinical effect was sustained for 2 years (Durham SR et al. *J Allergy Clin Immunol*. 2012;129:717-725). Guidelines recommend at least 3 years of SCIT as hyposensitization therapy to maintain the long-lasting effect after treatment discontinuation (WHO Position Paper 1998, Japan Rhinology Society Guideline for Immunotherapy for Allergic Rhinitis 2012, *Japanese Journal of Rhinology*, 2012;51). Based on the above, to maintain the long-term efficacy of the proposed allergen product following the completion of SLIT, as with SCIT, treatment over an extended period of at least 3 years will be necessary.

PMDA asked the applicant to explain the timing and methods for determining whether to continue SLIT with the proposed allergen product in patients unresponsive to the therapy.

The applicant responded as follows:
In the Phase III clinical study, patients whose mean Period-A TNSMS was ≥20% lower than the mean of the placebo group (First season, 6.89; Second season, 4.57) were defined as responders. As a result, the response rate was 55.6% (n = 145) for the first season and 67.2% (n = 162) for the second season, showing that the latter was higher. Patients whose mean Period-A TNSMS was greater than the mean of the placebo group were defined as non-responders. As a result, the non-response rate was 31.0% (n = 81) for the first season, and lower (20.3%, n = 49) for the second season. Among patients who had failed to respond to SLIT in the first season, 32 patients reponded to SLIT in the second season, while 36 patients remained unresponsive to SLIT. Although these results may have been affected by the facts that Japanese cedar pollen dispersal was high during the first season but was low during the second season, the above results also suggest that patients may respond to continued therapy. Therefore, the applicant considers that it is inappropriate to discontinue therapy immediately even if patients do not respond during the first season.

On the other hand, some patients have been documented not to respond or to show minimal response to hyposensitization therapy, and it is not recommendable to continue offering them hyposensitization therapy without due consideration. Physicians are recommended to decide whether to continue therapy at the end of the first season after accounting for all factors, including symptom improvement, patient's perception, and QOL.

PMDA asked the applicant to explain the dosage regimens for two ways of resuming SLIT: the resumption of treatment following short-term discontinuation due to safety or other reasons; and the resumption of treatment for recurrence of symptoms after remission.

The applicant responded as follows:
For the proposed allergen product groups in the Phase III clinical study, treatment was temporarily discontinued due to adverse drug reactions in 5 patients (duration of discontinuation, 1-8 days) and discontinued for ≥2 weeks due to adverse events or other reasons (duration of discontinuation, 14-35

days) in 9 patients. In all these patients, treatment was resumed at the maintenance dose (once daily 1 mL of 2000 JAU/mL). There were no marked differences in scores such as one for the primary endpoint between these patients and the total proposed allergen product group, nor were any adverse drug reactions associated with resumption of treatment reported, suggesting that short-term discontinuation does not affect efficacy or safety. However, no data are currently available for resumption of treatment following long-term discontinuation, nor can the risk of anaphylaxis following resumption of treatment be ruled out. Based on these considerations, physicians are advised to determine the initial dose for resumption of treatment after discontinuation by considering individual factors such as type and severity of symptoms leading to discontinuation and the duration of discontinuation. SLIT should be resumed under the supervision of a physician if deemed appropriate.

No data is available for the resumption of Japanese cedar pollen SLIT in patients with recurrent symptoms after remission. However, a report on house dust mite SLIT in allergic rhinitis patients indicates that the efficacy seen with the initial treatment is achieved more rapidly when the therapy is resumed after recurrence of symptoms (Marogna M et al. *J Allergy Clin Immunol.* 2010;126:969-975), suggesting that the proposed allergen product may also be effective when treatment is resumed. When resuming SLIT with the proposed allergen product in patients with recurrent allergy symptoms after remission, it is best to avoid re-starting treatment during a pollen season and to set a dose escalation period for resumption of treatment, as in the case of the initial treatment.

PMDA concluded as follows:
Information on the appropriate duration of treatment, the timeframe required to determine lack of efficacy, and the dosage regimen for resumption of treatment is important when treating patients with the proposed allergen product in clinical settings. Nevertheless, no established findings are available at this time, and physicians need to make their own judgments based on information such as individual patients' conditions. It is necessary to develop treatment guidelines with the help of related academic societies and to make the above-mentioned information availablein clinical practice. The applicant should, via post-marketing surveillance, gather more information on the efficacy of continued therapy in non-responders during the first season and the safety of SLIT resumed in patients who discontinued treatment due to safety or other reasons. It is desirable to investigate the efficacy and safety of SLIT resumed in patients with recurrent symptoms after remission and the duration of treatment necessary to achieve sustained remission, such as by conducting a post-marketing clinical study.

4.(i).B.(3) Indications
Related academic societies have begun to use the term "allergen immunotherapy" instead of "hyposensitization therapy." At the time the application was submitted, the proposed indication was "Japanese cedar pollinosis (allergen immunotherapy)." PMDA considers that no general consensus has been achieved to date regarding the term "allergen immunotherapy." PMDA has concluded it would be appropriate to align the indications for the proposed allergen product with the existing Japanese cedar pollen extracts by changing the term to "Japanese cedar pollinosis (hyposensitization therapy)."

4.(i).B.(4) Safety and post-marketing safety measures
PMDA asked the applicant to discuss the occurrence of adverse events and adverse drug reactions in the Phase III clinical study by summarizing the data for different treatment periods.

The applicant responded as follows:
In the Phase III clinical study, there were no deaths or anaphylaxis, and the incidence of serious adverse events in the proposed allergen product group was 2.6%, while that in the placebo group was comparable (2.3%). A causal relationship to the investigational product was ruled out in all events. Adverse drug reactions reported relatively frequently in the proposed allergen product groups were those related to Oedema mouth and other intraoral findings. No severe adverse drug reactions emerged; all adverse drug reactions were mild, except for moderate throat irritation, dysphonia, and toxic skin eruption. However, localized allergic symptoms, such as, Oedema mouth, stomatitis, dysphonia, and throat irritation were reported in the Phase III clinical study, and these symptoms can potentially lead to dyspnoea due to airway constriction, including pharyngeal/laryngeal edema and asthma-like symptoms. While not serious, systemic allergic symptoms such as toxic skin eruption and

urticaria have been reported. Healthcare professionals and patients must be cautioned against the onset of localized and systemic allergic symptoms.

Table 10 summarizes the adverse events reported for different administration periods in the Phase III clinical study. A number of adverse events were seen at and after Week 9 of the first season, probably due to wintertime cold-related events, including nasopharyngitis, upper respiratory tract inflammation, and influenza. Of a total of 52 adverse drug reactions in the proposed allergen product group, 21 adverse drug reactions occurred within the first 2 weeks (the dose escalation period), while 36 of the 52 adverse drug reactions (69.2%) occurred within 4 weeks after the initiation of administration. The occurrence of adverse drug reactions decreased thereafter; the number of adverse drug reactions reported in the proposed allergen product group for every 12 weeks after Week 24 was ≤1. The occurrence of major adverse drug reactions at different treatment periods was as follows: Those reported during the dose escalation period were intraoral symptoms such as stomatitis, throat irritation and ear pruritus; of those reported during the early phase of the dose maintenance period (Weeks 3-4), Oedema mouth was common; and after Week 4, the incidence of adverse drug reactions decreased, but moderate adverse drug reactions (throat irritation and dysphonia/toxic skin eruption [1 patient each]) that had not been reported previously occurred in 2 patients. These results indicate the need for close attention, since many intraoral events were noted especially during the first 4 weeks of administration, including the dose escalation period. While incidence and severity during the dose maintenance period (after Week 4) were not higher than during the dose escalation period for any event, close and sustained attention must be paid to the potential onset of localized and systemic allergic symptoms and anaphylaxis during the dose maintenance period as well.

Table 10. Adverse events reported in ≥2% of patients in either group duringdifferent treatment periods (safety analysis population)

Adverse events	Treatment group	Dose escalation period (Weeks 1-2)	Dose maintenance period (Weeks 3-4)	Dose maintenance period (Weeks 5-8)	First season (≥ Week 9)	Second season	Total
Nasopharyngitis	Proposed allergen product	9	6	20	51	133	219
	Placebo	7	4	24	47	106	188
Upper respiratory tract inflammation	Proposed allergen product	4	3	2	18	19	46
	Placebo	1	3	1	12	21	38
Influenza	Proposed allergen product	1	0	0	9	7	17
	Placebo	0	0	0	3	12	15
Headache	Proposed allergen product	3	0	0	4	10	17
	Placebo	2	0	0	14	12	28
Pharyngitis	Proposed allergen product	1	1	0	7	9	18
	Placebo	2	1	5	3	8	19
Dental caries	Proposed allergen product	0	1	0	5	6	12
	Placebo	0	1	0	3	9	13
Oedema mouth	Proposed allergen product	0	9	1	0	0	10
	Placebo	0	0	0	0	0	0
Back pain	Proposed allergen product	0	0	0	2	7	9
	Placebo	0	0	0	3	5	8
Gastroenteritis	Proposed allergen product	0	1	0	1	5	7
	Placebo	0	0	0	3	5	8
Stomatitis	Proposed allergen product	4	0	1	1	1	7
	Placebo	0	0	1	4	0	5
Coughing	Proposed allergen product	0	0	0	2	5	7
	Placebo	1	1	0	1	2	5
Eczema	Proposed allergen product	0	0	0	1	7	8
	Placebo	0	0	0	1	4	5
Rhinorrhoea	Proposed allergen product	2	0	0	0	4	6
	Placebo	2	0	0	0	3	5
Diarrhea	Proposed allergen product	1	0	0	5	3	9
	Placebo	0	0	0	1	2	3
Gingivitis	Proposed allergen product	0	0	0	4	2	6
	Placebo	0	0	0	0	1	1
Rash	Proposed allergen product	1	0	0	2	2	5
	Placebo	1	1	0	3	1	6
Oropharyngeal pain	Proposed allergen product	0	0	0	1	1	2
	Placebo	0	0	0	2	6	8

Number of events

PMDA asked the applicant to explain the risk of treatment-induced anaphylaxis by accounting for literature findings etc. for SLIT and to describe in detail safety measures to prevent or treat anaphylaxis, for the following reasons: (1) While the Phase III clinical study did not document anaphylaxis, only a limited number of patients were evaluated; and (2) since hyposensitization therapy involves the administration of allergens to relevant patients, those patients should be monitored closely for anaphylaxis.

The applicant responded as follows:
In 58 studies of SLIT (a total of 1,019,826 doses in 3984 subjects), no deaths or anaphylaxis events occurred, but 14 serious adverse events were observed (Cox LS et al. *J Allergy Clin Immunol.* 2006;117:1021-1035). Based on the results, the incidence rate of serious adverse events has been estimated at 1.4 events per 100,000 doses, or 1 event per 285 patients (WAO Position Paper 2009). Since 2000, the total number of doses of SLIT products used in foreign post-marketing settings has been estimated to be approximately one billion; 11 cases of anaphylaxis have been reported, suggesting that anaphylaxis would occur at a rate of 1 per 100 million SLIT doses (Calderón MA et al. *Allergy.* 2012;67:302-311). As for SCIT, American Academy of Allergy Asthma and Immunology (AAAAI) studies estimate the incidence rate of death at 1 per 2 to 2.5 million doses (Reid MJ et al. *J Allergy Clin Immunol.* 1993;92:6-15, Lockey RF et al. *J Allergy Clin Immunol.* 1987;79:660-677, Bernstein DI et al. *J Allergy Clin Immunol.* 2004;113:1129-1136) and that of lethal reactions (severe respiratory disorders and/or decreased blood pressure requiring emergency epinephrine) at 4.7 events per year, or 1 event per one million doses (Amin HS et al. *J Allergy Clin Immunol.* 2006;117:169-175). In a meta-analysis of 36 studies of hyposensitization therapy in patients with seasonal allergic rhinitis, the safety of SCIT and SLIT was compared. The reported incidence of anaphylaxis requiring epinephrine was 1.07% (n = 12) for SCIT and 0.05% (n = 1) for SLIT (Bona DD et al. *J Allergy Clin Immunol.* 2012;130:1097-1107). These findings suggest that the incidence of allergic symptoms localized to the administration site is relatively high for SLIT, but that these symptoms are mostly mild and followed by rapid recovery, with lower incidence of anaphylaxis compared to SCIT. However, the onset of anaphylaxis and its progression to shock are likely for SLIT as well. As safety measures, the applicant plans to provide guidance and information to healthcare professionals and patients to alert them to such risks.

The main safety measures planned by the applicant are as follows:

- Periodic safety update reports for SLIT products approved in Europe and other regions revealed that more than half of serious cases of anaphylaxis occurring after dosing (13 of 21 subjects) occurred at 2 to 20 minutes after the initial dose. The resulting recommendation in Europe is to administer the initial dose under the supervision of a physician. Most cases of serious anaphylaxis are likely to occur on the day of the initial dose; the initial dose should be administered at a medical institution under the supervision of a physician. Once the initial dose of the proposed allergen product has been administered, the patient is instructed to rest for at least 30 minutes post-dose and is closely monitored under the supervision of a physician.

- When a patient takes the proposed allergen product outside a medical institution following the initial dose—at home, for example, the patient and/or his or her family are advised that the patient should be carefully monitored for occurrence of any adverse drug reactions or adverse events, or any sudden change in physical condition for at least 30 minutes post-dose, and that the patient should refrain from active exercises, abstain from alcohol, and avoid taking a bath before and after taking the product. If any abnormalities in physical condition are noted, patients are instructed to discontinue the proposed allergen product and contact a medical institution immediately to consult a physician.

- The onset of signs of anaphylaxis is cautioned in the package insert and other informational materials. Information on the diagnosis and treatment of anaphylaxis is provided to physicians by preparing materials based on the Japanese version of WAO Anaphylaxis Guidelines (*Anaphylaxis: Diagnosis and Treatment. Clinical Criteria for Diagnosis*) (Ebisawa M. et al. *Jpn J Allergol.* 2013;62:144-154). Informational materials for patients will be prepared to alert and educate patients regarding precautions to safeguard against anaphylaxis, initial symptoms, signs for early detection, and steps to be taken in the event of initial symptoms (including consulting a physician immediately). Informational materials will recommend that patients take the proposed allergen product during the daytime and/or in the presence of a family member to enable appropriate actions to be taken in the event of any abnormal reactions.

- With respect to risk factors for anaphylaxis, it is indicated that hypersensitivity is mediated by high allergen exposure, increasing the risk of anaphylaxis (Calderón MA et al. *Allergy.* 2012;67:302-311). Thus, no new therapy should be commenced during pollen season. It is highly likely that resumption of treatment may result in the onset of anaphylaxis or shock in patients who have experienced shock following the administration of the proposed allergen product; it should be informed that resumption of treatment must be avoided in these patients.

- If the proposed allergen product is administered to patients after intraoral surgery or those with intraoral injuries or inflammation, the absorption of the product may be affected. An alert will be provided to exercise the utmost care when deciding whether to administer the proposed allergen product in such cases.

- Given the large number of patients with Japanese cedar pollinosis, physicians without prior experience with hyposensitization therapy are also expected to offer the proposed allergen product, and the product is expected to be prescribed to outpatients and generally administered by patients themselves at home. The following management system will be implemented: Internet-based e-learning courses are provided to all physicians wishing to use the proposed allergen product to ensure that physicians prescribing the product have adequate knowledge of hyposensitization therapy and provide appropriate response to adverse drug reactions, including anaphylaxis. This e-learning courses also ensure that physicians are aware of the importance of proper use of the proposed allergen product and give appropriate guidance for patients on actions to be taken in the event of adverse drug reactions. At pharmacies, the proposed allergen product is dispensed after confirmation that the prescribing physician is allowed to prescribe the product.

PMDA considers that the following additional measures are necessary, in addition to the above-mentioned safety measures planned by the applicant:

- In the warning section of the package insert, it is necessary to caution that use of the proposed allergen product should be limited to physicians with adequateknowledge of the product, adequate knowledge of and experience in hyposensitization therapy, and capability of properly instructing patients to use the product.

- The initial dose should be administered at a medical institution where prompt and appropriate actions can be taken in the event of anaphylaxis or shock.

- It is necessary to refrain from providing information suggesting that SLIT is safer than SCIT, and to provide appropriate information on the risk of anaphylaxis associated with the proposed allergen product. The therapy should be commenced only after patients are informed of such risks.

- Appropriate guidance should be provided to patients, including reminders to adhere to the specified dosage regimen, to immediately spit out the proposed allergen product and gargle in the event of an overdose, to refrain from discontinuing or resuming treatment based on the patient's own judgment; and to refrain from providing the product to other persons.

- Guidance should also be provided to patients' family members concerning actions to be taken in the case of abnormal events such as anaphylaxis. The proposed allergen product is basically administered by patients themselves outside medical institutions, and patients may be unable to contact a medical institution when experiencing a serious adverse drug reaction. It is necessary to ensure that each patient carries a portable patient card listing contact information for medical institutions as well as instructing whoever finds the patient to contact a medical institution immediately if abnormal events such as anaphylaxis occur.

- It should be cautioned that when a patient experienced localized or systemic allergic symptoms after the initial dose, it is necessary to consider whether or not the second and subsequent doses are also administered to the patient under the supervision of a physician.

PMDA concludes as follows:
It is generally considered that the allergen exposure for SLIT is lower than that for SCIT, which would result in a low incidence of anaphylaxis. However, only a little clinical evidence on SLIT is accumulated and there are limited data to compare the safety of SCIT and SLIT. Additionally, there is very little information on the risk of anaphylaxis associated with Japanese cedar pollen SLIT, and hyposensitization therapy is a treatment with allergens. From a safety perspective, the risks of anaphylaxis associated with SLIT should be recognized. Thus, it is important to avoid providing information suggesting that SLIT is safer than SCIT and to provide appropriate information on the risks of anaphylaxis associated with the proposed allergen product to ensure safety. Since the proposed allergen product is the first product for SLIT utilized as hyposensitization therapy in Japan, more patients may be interested in the product and physicians without prior experience with hyposensitization therapy are likely to offer the product in clinical settings, out of the expectation that SLIT is a more convenient and safer therapy than SCIT. Therefore, it is necessary to implement an appropriate safety management system for marketing the proposed allergen product. Post-marketing safety measures should be fully discussed at the Expert Discussion.

4.(i).B.(5) Post-marketing surveillance

The applicant is planning to conduct a use-results survey (target sample size of 3000) in order to analyze the safety and efficacy of the proposed allergen product in routine clinical use in a post-marketing setting and to confirm the safety and efficacy of long-term use of the product (1-year follow-up).

PMDA deems it necessary to observe at least 3 years (3 seasons) and gather efficacy data for long-term treatment because ≥3 years of treatment is recommended to maintain the therapeutic effect for an extended period after the completion of therapy (WHO position paper 1998, Japan Rhinology Society Guideline for Immunotherapy for Allergic Rhinitis 2012, *Japanese Journal of Rhinology*, 2012;51) in order to investigate the ratio of patients achieving remission and the duration of remission, and to collect information on the timeframe required to determine lack of efficacy and the efficacy and safety of resumed SLIT with the proposed allergen product.

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 Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that performing a regulatory review based on the submitted application documents would pose no problems.

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 (5.3.5.1.1). The inspection of the data collected by the sponsor revealed that some subject data was impacted by a system failure of the electronic patient diary data collection system, but the sponsor took the appropriate actions, such as by excluding affected data from analyses and implementing preventative measures to avoid similar system failures. The above-mentioned findings were identified as issues to be improved, but the appropriate actions were taken. Therefore, PMDA concluded that the studies overall were conducted in accordance with GCP and that performing a regulatory review based on the submitted application documents would pose no problems.

IV. Overall Evaluation

PMDA has concluded that the submitted data demonstrated the efficacy of theproduct in the treatment of Japanese cedar pollinosis (hyposensitization therapy). As for the safety of the product, appropriate safety measures must be taken against the risk of anaphylaxis. Thus, it is essential to educate and provide guidance to healthcare professionals and patients. Furthermore, a long-term post-marketing

surveillance lasting ≥3 years (3 seasons) should be conducted to examine the achievement and maintenance of remission following long-termtreatment, the timeframe required to determine lack of efficacy, and the safety and efficacy of resumed SLIT with the product. Thereafter, the collected information must be provided to physicians and patients as it becomes available.

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

Review Report (2)

September 24, 2013

I. Product Submitted for Registration

[Brand name]	(a) Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle (b) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle (c) Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack
[Non-proprietary name]	None
[Name of applicant]	Torii Pharmaceutical Co., Ltd.
[Dates of application]	(a) and (b) December 25, 2012 (c) March 22, 2013

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, dosage and administration, and indications

The expert advisors supported PMDA's conclusions regarding the efficacy, dosage and administration, and indications of the proposed allergen product, as described in Review Report (1).

In the Expert Discussion, taking account of several factors such as the conditions under which the Phase III clinical study was conducted, the expert advisors has concluded that it is necessary to caution the following on the package insert. The applicant took appropriate action accordingly.

- Before prescribing the proposed allergen product, physicians should consider whether its use is appropriate, taking account of patient symptoms observed during the previous Japanese cedar pollen season while weighing other therapeutic options.

- The efficacy and safety of the proposed allergen product in patients with high titers for IgE antibodies specific to allergens other than Japanese cedar pollen have not been established.

- There is no experience in the use of the proposed allergen product in elderly patients ≥65 years of age. Since immunological and other physiological functions are typically diminished in the elderly, sufficient therapeutic effects may not be achieved with the proposed allergen product or more serious adverse drug reactions may occur.

Furthermore, the expert advisors supported PMDA's view that the development of the proposed allergen product in Japanese cedar pollinosis patients <12 years of age should be considered, offering the opinion that the development of such a product should be commenced promptly, given the high clinical need for sublingual immunotherapy (SLIT) in patients <12 years of age. The applicant replied that the development of the proposed allergen product used for SLIT in patients <12 years of age would be considered.

(2) Safety and post-marketing safety measures

The expert advisors supported PMDA's conclusions regarding the safety and post-marketing safety measures for the proposed allergen product as described in Review Report (1). The expert advisors offered the opinion that all possible safety measures should be taken against the risk of anaphylaxis

associated with the proposed allergen product and that the following aspects should be additionally investigated to ensure safety:

- It should be ensured that physicians who have completed relevant e-learning coursesbelong to a medical institution capable of providing prompt and appropriate response to anaphylaxis and other adverse reactions, such as by measuring vital signs, injecting adrenaline intramuscularly, and administering oxygen inhalation. Moreover, it should be confirmed that the medical institution has an established system for transporting patients to another medical institution capable of providing the necessary emergency care, even if the patient condition becomes unmanageable.

- Portable patient cards should indicate the primary care facility and the contact information of a medical institution for emergency care.

- Operating procedures for pharmacists should be developed to ensure that pharmacists will supply the proposed allergen product to patients after confirming the following matters: The therapy is not allowed to be initiated during the Japanese cedar pollen season; the proposed allergen product has been prescribed by a physician who has completed relevant e-learning courses; and the patient is carrying the portable patient card in which necessary information is filled appropriately including contact information for emergency care. Pharmacists should be encouraged to take the same e-learning courses taken by physicians.

- The package insert should include the statement that the proposed allergen product is best taken during the daytime and/or in the presence of a family member so that appropriate actions can be taken in the event of anaphylaxis and other adverse reactions.

- Patient information materials explaining the actions to be taken based on the type and severity of allergic symptoms should be provided to patients.

- Physician information materials should be developed to inform physicians that if SLIT with the proposed allergen product is resumed in patients with recurrent symptoms after long-term withdrawal or discontinuation due to remission, the therapy should be restarted with the dosage regimen for the dose escalation period under the supervision of a physician in order to ensure the safety of resumed therapy.

Based on Review Report (1) and the above-mentioned points, PMDA instructed the applicant to reconsider safety measures, and the applicant duly responded.

(3) Post-marketing surveillance

As described in “4.(i).B.(1) Efficacy” and “4.(i).B.(2) Dosage and administration” of Review Report (1), the following points related to clinical use of the proposed allergen product need to be investigated by gathering as much information as possible in the post-marketing setting: the achievement and maintenance of remission after long-term treatment, the duration of treatment required to achieve sustained remission; the timeframe required to determine lack of efficacy; and the efficacy and safety of resumption of SLIT with the proposed allergen product. This PMDA’s opinion was supported by the expert advisors, and PMDA instructed the applicant to plan a long-term post-marketing surveillance suitable for investigating the above-mentioned points.

The applicant explained as follows:

A long-term specified use-results survey will be performed to follow up the patients with Japanese cedar pollinosis (target sample size of 2000 patients) treated with the proposed allergen product in clinical settings for 2 years (2 seasons). The survey is intended to collect efficacy and safety data of the proposed allergen product in routine clinical use, thereby investigating changes in the efficacy in each season and the efficacy and safety of resumption of SLIT following short-term discontinuation due to adverse drug reactions or other reasons, or discontinuation due to remission; and gathering information on adverse events, such as shock, anaphylaxis, or allergic reactions to the proposed allergen product. Furthermore, the applicant plans to conduct a clinical study lasting ≥3 years (3

seasons) in order to investigate the maintenance of the efficacy after discontinuation due to remission and the duration of treatment necessary to maintain remission.

PMDA considers that the applicant should conduct the above-mentioned use-results survey and clinical study swiftly and make the resulting information available in clinical practice in an appropriate manner.

III. Overall Evaluation

Based on the outcome of the above review, PMDA has concluded that the product may be approved for the indications and the dosage and administration as shown below with the following conditions for approval. PMDA has concluded that the re-examination period of the product is 6 years; neither the drug substance nor the drug product is classified as a poisonous drug or powerful drug; and the product is not classified as a biological product or a specified biological product.

[Indication] Japanese cedar pollinosis (hyposensitization therapy)

[Dosage and Administration] 1. Dose escalation period (Weeks 1-2)

The usual dosage of Cedartolen for adults and children ≥12 years of age for the first 2 weeks of administration (dose escalation period) is described in the dosing schedule shown below. The specified dose should be administered as sublingual drops once daily and be held under the tongue for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

Week 1 (dose escalation period)		Week 2 (dose escalation period)	
Cedartolen Sublingual Drop - Japanese Cedar Pollen 200 JAU/mL Bottle		Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Bottle	
Day 1	0.2 mL	Day 1	0.2 mL
Day 2	0.2 mL	Day 2	0.2 mL
Day 3	0.4 mL	Day 3	0.4 mL
Day 4	0.4 mL	Day 4	0.4 mL
Day 5	0.6 mL	Day 5	0.6 mL
Day 6	0.8 mL	Day 6	0.8 mL
Day 7	1 mL	Day 7	1 mL

2. Dose maintenance period (From Week 3 onward)

During the dose maintenance period following the dose escalation period, the entire contents (1 mL) of a Cedartolen Sublingual Drop - Japanese Cedar Pollen 2,000 JAU/mL Pack is placed under the tongue once daily and held in place for 2 minutes before being swallowed. For the next 5 minutes, it is necessary to refrain from gargling, eating, or drinking.

[Conditions for approval] Prior to marketing of the product, the applicant is required to take necessary measures to ensure that the product is prescribed and administered only by physicians with adequate knowledge of and experience with sublingual hyposensitization therapy; that the product is administered only under the supervision of physicians capable of adequately managing and explaining the associated risks at medical institutions that allow such physicians to do so; and that the product is dispensed at pharmacies only after the prescribing physician and medical institution are confirmed to meet such requirements.