

## **Protocol for Phase II Dose-finding Study of ASP4070**

**—A Randomized, Double-blind, Placebo-controlled, Dose-finding Study in Patients  
With Cedar Pollinosis Using an Environmental Exposure Chamber—**

**ISN/Protocol 4070-CL-0020**

Sponsor:

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## I. SIGNATURES

### 1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, ICH Guidelines and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the Sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement.

This clinical study will be conducted in accordance with GCP for trials on gene, cellular, and tissue-based products. Of GCP-related terms presented in the protocol, those that are related to ASP4070 shall be read as though replaced by their corresponding terms related to GCP for trials on gene, cellular, and tissue-based products as shown below.

GCP for trials on pharmaceutical products	GCP for trials on gene, cellular, and tissue-based products
Drug	Product
Adverse drug reaction	Defect
Toxicity	Safety
Pharmacological action	Indication and performance
Pharmacokinetics and drug metabolism	Disposition
Dosage and dose regimen	Dosage, dose regimen, and usage



## II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor

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Corporate name: [REDACTED]

Location: [REDACTED]

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### III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

#### List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANCOVA	Analysis of covariance
API	Astellas Pharma Inc.
AST	Aspartate aminotransferase (GOT)
BAT	Basophil activation test
BUN	Blood urea nitrogen
CK	Creatine kinase
Cl	Chlorine
Cre	Creatinine
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCTP	Good Gene, Cellular, and Tissue-based Products Manufacturing Practice
GMP	Good Manufacturing Practice
$\gamma$ -GTP	$\gamma$ -glutamyltranspeptidase
HBs antigen	Hepatitis B surface antigen
HCV	Hepatitis C virus
IAS	Immunological analysis set
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IFN- $\gamma$	Interferon gamma
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IRB	Institutional Review Board
ISN	International study number
ITI	Immunomic Therapeutics, Inc.
IUD	Intrauterine device
IUS	Intrauterine system
JRC	Japanese red cedar
JRQLQ	Japanese Rhinoconjunctivitis Quality of Life Questionnaire
K	Potassium

<b>Abbreviations</b>	<b>Description of abbreviations</b>
LAMP	Lysosomal associated membrane protein
LDH	Lactate dehydrogenase
MC	Mountain cedar
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
Na	Sodium
PGx	Pharmacogenomics
PPS	Per protocol set
PSAS	Pollinosis symptom analysis set
QOL	Quality of life
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCIT	Subcutaneous immunotherapy
SDA	Secondary data analysis
SFL	Screen Failure Log
SLIT	Sublingual immunotherapy
SOP	Standard Operating Procedure
T-Bil	Total bilirubin
T-Cho	Total cholesterol
TG	Triglyceride
Th	T helper cell
TNF	Tumor necrosis factor
TNNSMS	Total non-nasal symptom medication score
TNNS	Total non-nasal symptom score
TNSMS	Total nasal symptom medication score
TNSS	Total nasal symptom score
TP	Total protein
TSMS	Total symptom medication score
TSS	Total symptom score
UA	Uric acid
WHODDE	WHO Drug Dictionary Enhanced

## Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

## IV. SYNOPSIS

<b>Date and Version # of Protocol Synopsis:</b> Version 2.0, 09 Mar 2018	
<b>Sponsor:</b> Astellas Pharma Inc. (API),	<b>Protocol Number:</b> 4070-CL-0020
<b>Name of Study Drug:</b> ASP4070	<b>Phase of Development:</b> Phase II
<b>Title of Study:</b> Phase II Dose-finding Study of ASP4070 —A randomized, double-blind, placebo-controlled, dose-finding study in patients with cedar pollinosis using an environmental exposure chamber—	
<b>Planned Study Period:</b> Primary study period: From Apr 2017 to Jan 2018 Pollinosis symptoms survey period: From 01 Feb 2018 to 31 Mar 2018 Additional study period: From Apr 2018 to May 2018 Long-term safety follow-up period: From Jan 2018 to Oct 2018	
<b>Study Objective(s):</b> To evaluate the efficacy, safety, and dose response for ASP4070 vaccinated in patients with cedar pollinosis.	
<b>Planned Total Number of Study Centers and Location(s):</b> 1 study center, Japan	
<b>Study Population:</b> Patients with cedar pollinosis aged from 20 to 64 years	
<b>Number of Subjects to be Enrolled / Randomized:</b> Total number: 150 subjects ASP4070 4 mg group (4 mg × 8 times): 50 subjects ASP4070 1 mg group (1 mg × 8 times): 50 subjects Placebo group: 50 subjects	
<b>Study Design Overview:</b> A randomized, double-blind, placebo-controlled, dose-finding study The efficacy, safety, and dose response when ASP4070 (mixture containing equivalent amount of Cry j 1-LAMP plasmid and Cry j 2-LAMP plasmid, 4 mg/0.4 mL or 1 mg/0.4 mL) will be intradermally vaccinated 8 times at 14-day intervals will be evaluated with placebo (physiological saline) as the control. The study will conduct cedar pollen exposure using an environmental exposure chamber (OHIO Chamber; hereinafter, “chamber”), and the efficacy and dose response will be evaluated using clinical symptoms (nasal and eye symptoms) as indicators. Two factors, “Class from results of Japanese red cedar (JRC) pollen-specific immunoglobulin E (IgE) antibody test performed at Screening visit 1” and “Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2,” will be used as stratification factors to randomly allocate subjects into three groups—ASP4070 4 mg group, ASP4070 1 mg group, or placebo group—in a ratio of 1:1:1, and the subjects will be vaccinated with the study drug. After a set period after the final vaccination of the study drug, re-exposure to cedar pollen in the	

chamber will be conducted and the efficacy will be evaluated using clinical symptoms as indicators. Efficacy evaluation will be conducted 4, 8, and 12 weeks after the final vaccination to confirm the timing of effectiveness. The primary study period of the study will be until the end of the one week of post-observational period after the final evaluation in the chamber on Day 183 (12 weeks after the final vaccination).

The treatment code will be broken when the primary study period is completed and all data entered in case report forms are fixed. Even after code breaking, the study will be continued with the investigator, sub-investigator, study coordinator, and subjects remaining blinded.

Subjects who have completed the primary study period will be the target of a survey on cedar pollinosis symptoms during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018). Subjects will make entries in the Pollinosis Symptoms Survey Diary every day on information regarding nasal and eye symptoms. If a subject experiences intolerable nasal and eye symptoms during this period, then the use of rescue drugs will be allowed.

An additional test of immune responses will be performed during the long-term safety follow-up period on subjects who have completed the pollinosis symptoms survey period and have provided additional consent to the additional test. The additional test will determine the parameters (specific IgE antibody [anti-JRC] and basophil activation test [BAT]) after the end of the cedar pollen dispersal season (May 2018).

After the end of the primary study period, safety information (serious adverse event [SAE]) will be collected for approximately 9 months (1 year from the final vaccination of the study drug) as the long-term safety follow-up period. Safety information (SAE) will be collected for 1 year after the final vaccination of the study drug even from subjects who discontinue their participation in the study during the primary study period if they have received at least one vaccination of the study drug.

Among subjects in the placebo group or optimal dose group (ASP4070 4 mg group or 1 mg group) who complete the primary study period, those who provide written consent again will be the target of a Phase II Second-Year Follow-up Study [4070-CL-0021] that is planned to be implemented.

#### **Inclusion/Exclusion Criteria:**

##### **Inclusion:**

Subject is eligible for the study if all of the following 1 to 11 apply:

1. Subject who has provided written consent using the informed consent form approved by the Institutional Review Board of the study site before starting any study-related procedure
2. Subject of either sex who is aged from 20 to 64 years at the time of informed consent
3. Subject who has nasal symptoms (sneezing, nasal discharge, or nasal congestion) and eye symptoms (itchy eyes or watery eyes) of pollinosis during the cedar pollen dispersal seasons in 2016 and 2017
4. Subject who has the Japanese red cedar (JRC) pollen-specific IgE antibody test result of Class 3 or higher in the allergy test at Screening visit 1
5. Subject who satisfies the following criteria for change in the mean of the nasal symptom score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2
  - Total 3 nasal symptom score (3TNSS) worsens by 2 or more, 2 or more individual nasal symptom score (sneezing, nasal discharge, and nasal congestion) worsens by 1 or more
6. Female subject must satisfy the following criteria
  - Subject of non-childbearing potential must satisfy either of the following criteria:
    - Subject who is post-menopausal (defined as at least 1 year without any menses) prior to Screening visit 1

- Subject who is surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

Or, subject of childbearing potential (subject who does not meet the above definition of “female subject of non-childbearing potential”) must meet all of the following criteria:

- Subject must agree not to try to become pregnant during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
- Subject must have a negative urine pregnancy test at Screening visit 1 and on Day 1 (prior to vaccination)
- Subject must consistently use two forms of highly effective birth control\* (at least one of which must be a barrier method) during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer) if heterosexually active

\*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method)

7. Female subject must agree not to breastfeed during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
8. Female subject must not donate ova during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
9. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control\* (at least one of which must be a barrier method) from the initial study drug vaccination until 28 days after the final vaccination of the study drug
10. Male subject must not donate sperm from the initial study drug vaccination until 28 days after the final vaccination of the study drug
11. Subject agrees not to participate in another intervention study while on treatment

Subject is eligible for the additional test of the study if the following 12 and 13 both apply:

12. Subject has completed the pollinosis symptoms survey period
13. Subject has provided written consent using the informed consent form approved by the Institutional Review Board of the study site before starting any procedure related to the additional test of the study

Waivers to the inclusion criteria will **NOT** be allowed.

**Exclusion:**

Subject will be excluded from participation if any of the following apply:

1. Subject whose allergy test result to other antigens than JRC pollen (test result of IgE antibody specific to alnus, Japanese white birch, ragweed, artemisia, cocksfoot, dermatophagoides farinae, dermatophagoides pteronyssinus, *Aspergillus*, *Candida*, *Alternaria*, house dust 1, house dust 2, cat dander, and dog dander) is Class 4 or higher at Screening visit 1
2. Subject who has received specific immunotherapy (including desensitization therapy) for cedar pollinosis in the past
3. Subject who has received specific or non-specific immunotherapy within 5 years prior to Screening visit 1
4. Subject who has received laser therapy/surgery for treating nasal symptoms within 3 years

- prior to Screening visit 1
5. Subject who has used the following drugs within 14 days prior to entering the chamber at Screening visit 2.  
Topical steroid, histamine H1-receptor antagonist, chemical mediator-isolation inhibitor, T helper cell 2 (Th2) cytokine inhibitor, thromboxane A2 synthesis inhibitor, thromboxane A2 receptor antagonist, leukotriene receptor antagonist  
(Among the above drugs, use of medications for external use on the skin is allowed. However, use at the study drug vaccination site on the day before Day 1 is not allowed.)
  6. Subject who has used the following drugs within 84 days prior to entering the chamber at Screening visit 2  
Biological agents, such as antibiotics (anti-tumor necrosis factor alpha [TNF $\alpha$ ] antibody, anti-IgE monoclonal antibody, etc.)
  7. Subject who has used the following drugs within 84 days prior to the first vaccination of the study drug  
Systemic steroids and immunosuppressants (Use of medications for external use on the skin are allowed. However, use at the study drug vaccination site on the day before Day 1 is not allowed.)
  8. Subject who has received or is planning to receive vaccination of a live vaccine within 28 days prior to the first vaccination of the study drug, and/or subject who has received or is planning to receive vaccination of an inactivated vaccine/toxoid within 7 days prior to the first vaccination of the study drug
  9. Subject who has a history of serious allergic reactions, such as anaphylactic shock and generalized exanthema, caused by food and/or medical products (including vaccine) in the past
  10. Subject who has a positive immunological test result for hepatitis B surface antigen (HBs antigen) or hepatitis C virus (HCV) antibody at Screening visit 1
  11. Subject who has a complication of nasal disorder (nasal polyp, nasal septum deviation, chronic sinusitis, etc.) that may affect efficacy evaluation
  12. Subject who has autoimmune disease or other serious primary disease
  13. Subject who has been diagnosed with immunodeficiency in the past
  14. Subject who has a complication of seasonal allergic rhinitis, perennial allergic rhinitis, rhinitis medicamentosa, or non-allergic rhinitis against antigens other than cedar and cypress that require medical treatment
  15. Subject who has a complication of cardiovascular disease (including congestive cardiac failure, angina pectoris, and cardiac arrhythmias that require medical treatment)
  16. Subject who has a complication of hepatic disease (including viral hepatitis and drug-induced liver injury)
  17. Subject who has a complication of renal disease (including acute kidney injury, glomerulonephritis, and interstitial nephritis)
  18. Subject who has a complication of respiratory disease (including bronchial asthma and chronic bronchitis that require medical treatment)
  19. Subject who has a complication of malignant tumor or has been diagnosed with or has received treatment for malignant tumor within 5 years prior to the first vaccination of the study drug
  20. Subject who has been diagnosed with mental conditions, such as schizophrenia, bipolar disorder, and major depressive disorder, or dementia
  21. Subject who has a complication that may have an impact on the evaluation of local and systemic reactions
  22. Subject who has received vaccination of Cry j 2-LAMP vaccine
  23. Subject who has participated in a study of ASP4070 and received vaccination of the study drug



<p>24. Subject who has participated in any clinical study or post-marketing clinical study of any other medical drug or device within 12 weeks (84 days) prior to Screening visit 1, or subject who is participating in such a study at present</p> <p>25. Subject who is an employee of the Sponsor or CRO or medical institution involved in the study</p> <p>26. Subject who is considered by the investigator or sub-investigator as unsuitable for study participation</p> <p>Waivers to the exclusion criteria will <b>NOT</b> be allowed.</p>
<p><b>Investigational Product(s):</b> ASP4070</p> <p><b>Dose(s) and Mode of Administration:</b> 4 mg/0.4 mL or 1 mg/0.4 mL, 8 times by intradermal vaccination at 14-day intervals.</p> <p>Interdermal injection device manufactured by Terumo will be used for vaccination.</p>
<p><b>Comparative Drug(s):</b> Placebo (physiological saline)</p> <p><b>Dose(s) and Mode of Administration:</b> 0.4 mL placebo, 8 times by intradermal vaccination at 14-day intervals.</p> <p>Interdermal injection device manufactured by Terumo will be used for vaccination.</p>
<p><b>Concomitant Medication Restrictions or Requirements:</b></p> <p>The use of the following medications will be prohibited:</p> <ol style="list-style-type: none"> <li>1. Until the end of the pollinosis symptoms survey period Immunotherapy specific to cedar pollinosis (including desensitization therapy)</li> <li>2. From 5 years prior to Screening visit 1 until the end of the pollinosis symptoms survey period Specific or non-specific immunotherapy</li> <li>3. From 14 days prior to entering the chamber at Screening visit 2 until the end of the pollinosis symptoms survey period Topical steroid, histamine H1-receptor antagonist, chemical mediator-isolation inhibitor, Th2 cytokine inhibitor, thromboxane A2 synthesis inhibitor, thromboxane A2 receptor antagonist, leukotriene receptor antagonist (Among the above drugs, use of medications for external use on the skin will be allowed. However, use at the study drug vaccination site from the day before Day 1 until 28 days after the final vaccination of the study drug will not be allowed.) If a subject experiences intolerable nasal and eye symptoms during the pollinosis symptoms survey period, then the use of the following rescue drugs will be allowed. <ul style="list-style-type: none"> <li>• Tramazoline hydrochloride nasal drops</li> <li>• Ketotifen fumarate eye drops</li> <li>• Fexofenadine hydrochloride tablets</li> </ul> </li> <li>4. From 84 days prior to entering the chamber at Screening visit 2 until the end of the pollinosis symptoms survey period Biological agents, such as antibiotics (anti-TNF<math>\alpha</math> antibody, anti-IgE monoclonal antibody, etc.)</li> <li>5. From 84 days prior to the first vaccination of the study drug until the end of the pollinosis symptoms survey period and from the informed consent for the additional test until the completion of the additional test Systemic steroid/immunosuppressants (Use of medications for external use on the skin will be allowed. However, use at the study drug vaccination site from the day before Day 1 until 28 days after the final vaccination of the study drug will not be allowed.)</li> <li>6. From 28 days prior to the first vaccination of the study drug until 28 days after the final vaccination of the study drug</li> </ol>

<p>Live vaccine</p> <p>7. From 7 days prior to the first vaccination of the study drug until 28 days after the final vaccination of the study</p> <p>Inactivated vaccine/toxoid</p> <p>The following therapies will be prohibited:</p> <ol style="list-style-type: none"> <li>From 3 years prior to Screening visit 1 until the end of the pollinosis symptoms survey period <ul style="list-style-type: none"> <li>Laser therapy/surgery for treating nasal symptoms</li> </ul> </li> <li>From leaving the chamber at 4, 8, and 12 weeks after the final vaccination until the completion of the Symptoms Survey After Chamber <ul style="list-style-type: none"> <li>Acts that physically remove pollen, such as nasal wash (including nebulizer use) and eye wash</li> </ul> </li> <li>During the pollinosis symptoms survey period <ul style="list-style-type: none"> <li>The use of objects that physically shield the body from pollen, such as masks/goggles This restriction does not apply to cases in which the investigator or sub-investigator deems the use to be unavoidable (such as medical personnel and factory workers), but the usage should be kept to the minimum.</li> <li>Acts that physically remove pollen, such as nasal wash (including nebulizer use) and eye wash</li> </ul> </li> </ol>
<p><b>Duration of Treatment:</b></p> <p>Vaccination of 8 times at 14-day intervals (Day 1, Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and Day 99)</p>
<p><b>Formal Stopping Rules:</b></p> <p>Discontinuation Criteria for Individual Subjects</p> <ol style="list-style-type: none"> <li>Adverse events <ul style="list-style-type: none"> <li>It is considered difficult for the subject to continue to participate in the study due to an AE.</li> </ul> </li> <li>Consent withdrawal <ul style="list-style-type: none"> <li>Subject withdraws consent for further treatment.</li> </ul> </li> <li>Lost to follow-up <ul style="list-style-type: none"> <li>Subject is lost to follow-up due to the subject's personal reasons, such as moving away from the study site and busyness.</li> <li>Subject is lost to follow-up due to discontinuation of visits (or due to being unable to reach by any means).</li> </ul> </li> <li>Protocol deviation <ul style="list-style-type: none"> <li>Subject is found after vaccination to have been deviated from the inclusion/exclusion criteria and is judged unsuitable for further participation in the study.</li> <li>Another serious deviation from the protocol is found.</li> </ul> </li> <li>Death <ul style="list-style-type: none"> <li>Subject died.</li> </ul> </li> <li>Other <ul style="list-style-type: none"> <li>Subject is judged by the investigator or sub-investigator to be unsuitable for further participation in the study or a request is made by the Sponsor to discontinue study treatment due to safety reasons.</li> </ul> </li> </ol>
<p><b>Endpoints for Evaluation:</b></p> <p><u>Primary efficacy endpoint:</u></p> <p>Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion)</p>

score (3TNSS) during 120 to 180 minutes (every 15 minutes, total of 5 time points) after start of cedar pollen exposure as compared to the score before cedar pollen exposure

Secondary efficacy endpoints:

- Total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS)
- Total 4 nasal symptom (sneezing, nasal discharge, nasal congestion, and itchy nose) score (4TNSS)
- Individual nasal symptom (sneezing, nasal discharge, nasal congestion, and itchy nose) score
- Total non-nasal symptom (itchy eyes and watery eyes) score (TNNSS)
- Individual eye symptom (itchy eyes and watery eyes) score
- Total symptom score (TSS)
- Time to occurrence of nasal or eye symptoms from start of cedar pollen exposure in the chamber
- Nasal discharge amount and sneezing count per 30 minutes during chamber exposure

With regard to symptoms after leaving the chamber, a survey will be conducted on nasal and eye symptoms until 3 days after leaving the chamber.

Other Efficacy Endpoints (For Pollinosis Symptoms Survey during the pollinosis symptoms survey period)

Endpoints during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018):

- Total 3 nasal symptom score (3TNSS)
- Individual nasal symptom (sneezing, nasal discharge, and nasal congestion) score
- Total non-nasal symptom score (TNNSS)
- Individual eye symptom (itchy eyes and watery eyes) score
- Total symptom score (TSS)
- Total nasal symptom medication score (TNSMS)
- Total non-nasal symptom medication score (TNNMS)
- Total symptom medication score (TSMS)
- Troubles with daily life
- Japanese Rhinoconjunctivitis Quality of Life Questionnaire: JRQLQ No 1
- Overall evaluation by the subject

Immune response endpoints (primary study period)

Immunoglobulin G (IgG) antibody, specific IgG antibody (anti-JRC, anti-Cry j 1, and anti-Cry j 2), specific IgG4 antibody (anti-JRC), IgE antibody, specific IgE antibody (anti-JRC), anti-LAMP antibody, basophil activation test (BAT)

Immune response endpoints (additional test)

Specific IgE antibody (anti-JRC), basophil activation test (BAT)

Safety endpoints

- Adverse events that occur during the primary study period.  
(Nasal and eye symptoms induced by cedar pollen exposure in the chamber will be separately collected as efficacy endpoints and will not be considered as AEs)

- 12-lead electrocardiogram, vital signs, laboratory assessments
- Local reactions and systemic reactions accompanying study drug vaccination that occur from each day of study drug vaccination until 14 days after vaccination
- SAEs that occur within approximately 9 months after the end of the primary study period (until 12 months after the final vaccination of the study drug) (long-term safety follow-up period)

**Statistical Methods:**

**Sample size justification:**

The number of subjects required for 80% probability of detecting superiority of the ASP4070 group over the placebo group was calculated. Among the study results of other drugs targeting patients with cedar pollinosis using a chamber, studies with published data that allow the effect size to be calculated were confirmed and the effect size was 0.668, 0.903, and 0.962 for bilastine, montelukast, and levocetirizine, respectively. Based on these effect sizes, with regard to the effect on the primary endpoint, the change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS) during 120 to 180 minutes after entering the chamber to the score before cedar pollen exposure, the effect size of ASP4070 was assumed to be 0.650. Using the significance level of the test to be 5% two-sided, when a hierarchical procedure is used for comparison with the placebo group in the order of high-dose group to low-dose group, if the effect size 0.650 is the same for the low-dose group as for the high-dose group, then the probability of detecting superiority of the low-dose group against the placebo group was calculated by simulation. Assuming the standard deviation to be 1, as a result of 10,000 simulations, the number of subjects required to ensure a detection power of over 80% was 48 subjects. Considering dropout cases, the number of subjects in each group was set to 50 subjects and 150 subjects in total.

**Efficacy:**

The FAS will be used for primary analysis. With regard to the change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS) during 120 to 180 minutes after start of cedar pollen exposure as compared to the score before cedar pollen exposure, the difference in the adjusted mean between each active drug group and the placebo group on Day 183, two-sided 95% confidence interval and two-sided P value will be calculated using a mixed model for repeated measures assuming an unstructured covariance structure within subjects with explanatory variables being the vaccination group (ASP4070 4 mg, ASP4070 1 mg, and placebo), evaluation time (Day 127, Day 155, and Day 183), "Class from results of Japanese red cedar (JRC) pollen-specific IgE antibody test performed at Screening visit 1," "Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2," and interaction of the vaccination group and evaluation time.

With the significance level of the test to be 5% two-sided, the test will be conducted using hierarchical procedures in the following order:

1. Comparison between the ASP4070 4 mg group and placebo group
2. Comparison between the ASP4070 1 mg group and placebo group

**Pharmacokinetics:**

Not applicable

**Pharmacodynamics:**

Not applicable

**Immune response:**

With regard to Immune Response Endpoints, calculation of descriptive statistics or frequency tabulation by vaccination group and time point according to the scale and characteristics of the variables will be conducted.

**Safety:**

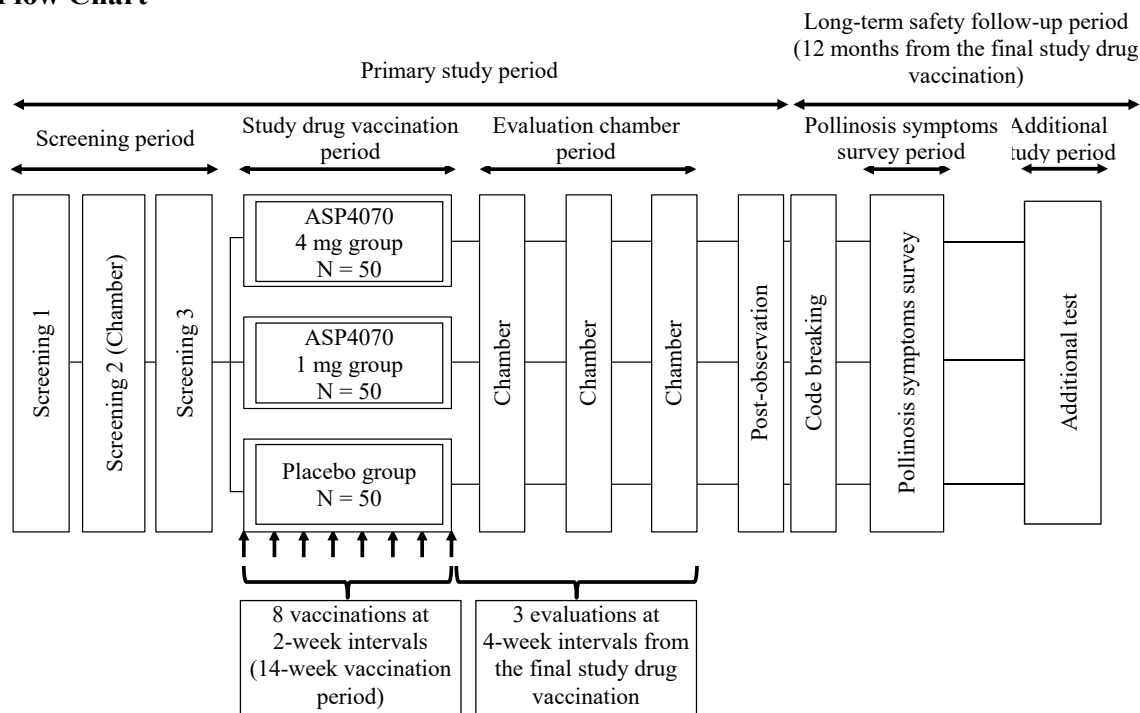
With regard to adverse events and those whose relationship to the study drug cannot be ruled out, frequency tabulation by vaccination group will be conducted. With regard to laboratory test values, vital signs, etc., calculation of descriptive statistics or frequency tabulation by vaccination group and time point according to the scale and characteristics of the variables will be conducted.

**Interim analyses:**

Not applicable.

## V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

### Flow Chart



- After code breaking, the Sponsor will be unblinded, but the study will be continued with the investigator, sub-investigator, study coordinator, and subjects remaining blinded.
- Cedar pollinosis symptoms will be surveyed during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018).
- The additional test of immune responses will be performed during the long-term safety follow-up period on subjects who have completed the pollinosis symptoms survey period and have provided additional consent to the additional test.
- Subjects will report whenever SAEs occur during the long-term safety follow-up period. Even if there is no contact from a subject, in principle, the subject will be asked about the occurrence of SAEs at 6 months and 12 months after the final vaccination. With regard to subjects who have discontinued the study during the primary study period, if the study drug had been vaccinated even once, then safety information (SAEs) will be collected for 1 year after the final vaccination.

**Table 1: Schedule of Assessments**

Item \ Visit day	Primary study period																After Pollinosis Symptoms Survey	Additional test
	Screening period			Study drug vaccination period								Evaluation chamber period			Post-observation	Discontinuation <sup>3)</sup>		
	Screening visit 1	Screening visit 2 <sup>1)</sup>	Screening visit 3 <sup>2)</sup>	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 127	Day 155	Day 183				
Period (Day)			28 ± 7 from Screening visit 2 <sup>4)</sup>	1	15 ± 3	29 ± 3	43 ± 3	57 ± 3	71 ± 3	85 ± 3	99 ± 3	127 ± 7	155 ± 7	183 ± 7	7 ± 3 from Day 183	—	Apr 2018	May 2018 <sup>21)</sup>
Informed consent	○																○ <sup>20)</sup>	
Inclusion/exclusion criteria	○	○	○	○														
Randomization				○														
Target disease	○	○	○															
Subject demographics	○																	
Physical examination <sup>5)</sup>	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Vaccination				○	○	○	○	○	○	○	○							
Chamber evaluation		○										○	○	○				
Vital signs <sup>6),7)</sup>	○	○	○	○	○	○	○	○	○	○	○	○	○	○		○		
12-lead electrocardiogram <sup>6)</sup>	○			○								○		○		○		
Immunological test <sup>8)</sup>	○																	
JRC allergy test <sup>9)</sup>	○		○															
Allergy test other than JRC <sup>8)</sup>	○																	
Pregnancy test (urine) <sup>6),10)</sup>	○			○		○		○		○		○	○	○		○		
Hematology test, blood biochemistry test, and urinalysis <sup>6),11)</sup>	○		○	○				○				○		○		○		
Consent for PGx <sup>12)</sup>				←										→				
PGx blood sampling <sup>6),13)</sup>				←										→				
Consent for SDA				○														
SDA blood sampling <sup>6),14)</sup>				○								○		○				
Parameters <sup>6),15),16)</sup>				○				○				○	○	○		○		○ <sup>22)</sup>
Adverse events	←													→		○		
Local/Systemic Reaction Survey Diary <sup>17)</sup>				←							→							
Symptoms Survey After Chamber Period Diary <sup>18)</sup>												←		→				
Pollinosis Symptoms Survey Diary <sup>19)</sup>																	↔	

○: To be performed

- 1) Based on the results of tests and observations conducted at Screening visit 1, only those subjects who satisfy the Inclusion Criteria and do not fall under the Exclusion Criteria will be the target of Screening visit 2 onward.
- 2) Based on the symptom score at the chamber evaluation at Screening visit 2, only those subjects who satisfy the inclusion criterion 5 will be the target of Screening visit 3 onward.
- 3) Only those subjects who discontinue the study before Day 183 will be the target. In principle, discontinuation tests are conducted upon the decision to discontinue.
- 4) Conducted no later than 7 days prior to Day 1.
- 5) For visits with study drug vaccination, conduct physical examination (subjective symptoms, objective findings) 1 hour after study drug vaccination before allowing the patient to leave the clinic.
- 6) For visits with study drug vaccination and chamber evaluation, conduct all other tests before vaccination and chamber evaluation.
- 7) Refer to “5.4.3 Vital Signs” for test items.
- 8) Refer to “5.2.2 Medical History” for test items.
- 9) Refer to “5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease” for test items.
- 10) For female subjects only. Not required for subjects who are post-menopausal (defined as at least 1 year without any menses) at Screening visit 1 or subjects who are surgically sterile or have had hysterectomy or oophorectomy, and the possibility of pregnancy can be negated.
- 11) Refer to “5.4.4 Laboratory Assessments” for test items.
- 12) Obtain before conducting PGx blood sampling.
- 13) To be conducted once during the period from Day 1 to Day 183.
- 14) To be conducted only if blood is sampled when sample processing is possible.
- 15) Refer to “5.7.1 Immune Response Assessment (Parameters)” for test items.
- 16) BAT is to be conducted only if blood is sampled when sample processing is possible. If blood is not sampled on Day 1, then further blood sampling will be unnecessary.
- 17) To be entered every day from each day of study drug vaccination to 14 days after vaccination.
- 18) To be entered every day until 3 days after leaving the chamber (day of chamber evaluation, and 1, 2, and 3 days after leaving).
- 19) Survey will be conducted with the target as subjects who have completed the primary study period. To be entered every day from 01 Feb 2018 to 31 Mar 2018.
- 20) Informed consent for the additional test.
- 21) If a systemic steroid or an immunosuppressant (excluding external use on the skin) is used after the end of the pollinosis symptoms survey period up to informed consent for the additional test, the additional test will be performed 28 days after the last dose of the drug or later.
- 22) The additional test will determine BAT and specific IgE antibody (anti-JRC) only.



## VI. ACCEPTABLE RANGE OF SCHEDULE OF ASSESSMENTS

The acceptable time ranges of tests and observations specified in the schedule of the primary study period are as follows. Pharmacogenomics (PGx) blood sampling will be conducted only once during the period from Day 1 to Day 183, and the acceptable range is the same as any other visit with blood sampling. The acceptable range is not specified for the discontinuation test; however, in principle, it will be conducted on the day when discontinuation is decided.

[Vital signs (Axillary body temperature, sitting blood pressure, and sitting pulse rate)]

Screening visit 1	After consent is obtained
Screening visit 2	After Screening visit 1 + 1 day
Screening visit 3	28 days $\pm$ 7 days from Screening visit 2 and also until Day 1 – 7 days
Day 1	Until before study drug vaccination on Day 1
Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99	Within $\pm$ 3 days of the scheduled day
Day 127, Day 155, Day 183	Within $\pm$ 7 days of the scheduled day

[Hematology test, blood biochemistry test, and urinalysis]

Screening visit 1	After consent is obtained
Screening visit 3	28 days $\pm$ 7 days from Screening visit 2 and also until Day 1 – 7 days
Day 1	Until before study drug vaccination on Day 1
Day 57	Within $\pm$ 3 days of the scheduled day
Day 127, Day 183	Within $\pm$ 7 days of the scheduled day

[12-lead electrocardiogram]

Screening visit 1	After consent is obtained
Day 1	Until before study drug vaccination on Day 1
Day 127, Day 183	Within $\pm$ 7 days of the scheduled day

[Pregnancy test (urine)]

Screening visit 1	After consent is obtained
Day 1	Until before study drug vaccination on Day 1
Day 29, Day 57, Day 85	Within $\pm$ 3 days of the scheduled day
Day 127, Day 155, Day 183	Within $\pm$ 7 days of the scheduled day

[JRC allergy test]

Screening visit 1	After consent is obtained
Screening visit 3	28 days $\pm$ 7 days from Screening visit 2 and also until Day 1 – 7 days

[Allergy test other than JRC, immunological test]

Screening visit 1	After consent is obtained
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[Parameters]

Day 1	Until before study drug vaccination on Day 1
Day 57	Within $\pm 3$ days of the scheduled day
Day 127, Day 155, Day 183	Within $\pm 7$ days of the scheduled day

[Evaluation in chamber]

Screening visit 2	After Screening visit 1 + 1 day
Day 127, Day 155, Day 183	Within $\pm 7$ days of the scheduled day

[SDA blood sampling]

Day 1	Until before study drug vaccination on Day 1
Day 127, Day 183	Within $\pm 7$ days of the scheduled day

The acceptable time range for the additional test is as follows.

[Parameters]

Additional test	May 2018
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If a systemic steroid or an immunosuppressant (excluding external use on the skin) is used after the end of the pollinosis symptoms survey period up to informed consent for the additional test, the additional test will be performed 28 days after the last dose of the drug or later.

## **1 INTRODUCTION**

### **1.1 Background**

#### **1.1.1 Target Disease and Other Treatment Methods and Their Problems**

Japanese red cedar (JRC) is the main cause of pollinosis in Japan and its pollen may trigger cedar pollinosis. JRC pollen dispersal starts early in February and reaches its peak in March. The pollen grains of JRC are spherical and approximately 30 µm in diameter, and their major allergens include Cry j 1 and Cry j 2.

JRC pollinosis exhibits typical type-1 allergic symptoms, such as nasal symptoms, including sneezing, nasal discharge, and nasal congestion, and eye symptoms, including itchy eyes and watery eyes, during the JRC pollen dispersal season. Therefore, it is known to significantly affect the QOL and work productivity of patients, and the prevalence of pollinosis in Japan is estimated to be over 20% [Environmental Health and Safety Division, Environmental Health Department, Ministry of the Environment, 2014]. Currently available treatment methods for cedar pollinosis include antigen removal/avoidance, drug therapy, surgical therapy, and allergen immunotherapy. It is possible to use cedar pollen masks to eliminate/avoid the antigen and thereby reduce exposure to cedar pollen. However, it is impossible to completely eliminate/avoid pollen. Although drugs with various different mechanisms of action have been available in the market to treat pollinosis at various levels of severity, drug therapy is not more than a symptomatic treatment that requires drugs to be continuously taken every year during the season while they have symptoms. Surgical therapy has the possibility of recurrence of allergic symptoms and has not yet reached the level of leading to a permanent cure or long-term remission of cedar pollinosis. Allergen immunotherapy includes subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), which were developed with the aim that patients may be able to achieve a permanent cure or long-term remission. However, this therapy may cause serious adverse reactions, such as anaphylaxis, and is inconvenient since long-term/frequent administration is required. Hence, the dropout rate of patients during treatment is high and it has not been widely adopted in clinical practice.

For the reasons mentioned above, there is a growing need to develop a treatment method that is safer than any existing therapy and which provides a permanent cure or long-lasting symptom relief. The Allergy Measures Promotion Board of the Ministry of Health, Labour and Welfare (MHLW) has considered the development of a permanent cure through treatment, such as allergen immunotherapy, and therefore, developing new methods are necessary actions in the future.

#### **1.1.2 Characteristics of ASP4070**

ASP4070 is a DNA vaccine against JRC pollinosis (pITI-JRC2\*LAMP-vax) developed by Immunomic Therapeutics, Inc. (ITI), which may provide a new treatment option to patients who suffer from JRC pollinosis. It is a bivalent vaccine made up of two plasmids mixed in a

ratio of 1:1, each encoding one of the two major cedar allergens—Cry j 1 and Cry j 2—as a fusion protein with lysosome-associated membrane protein (LAMP).

ASP4070 efficiently induces CD4<sup>+</sup> T-cell response by co-localizing antigen protein with major histocompatibility complex (MHC) class II molecules [Geuze, 1998] localized in lysosomes [Marques et al., 2003]. Furthermore, the nucleic acid components of DNA vaccines are known to induce Type I interferon production [Ishii et al., 2008], and hence, it is predicted that T helper cell 1 (Th1) cell-dominated immune response is induced. Induction of Immunoglobulin E (IgE) production by an increase in allergen-specific Th2 cell response is considered to be the cause of the onset of allergies [Woodfolk and Platts-Mills, 2002], and it is anticipated that ASP4070 shifts the Th1/Th2 balance toward Th1 predominance and may suppress allergic symptoms. In addition, allergen expressed as a fusion protein with LAMP-1 is known to be expressed only within lysosomes in the cytosol. In theory, it is unlikely to leak outside the cell and cause serious adverse reactions, such as anaphylaxis. Thus, ASP4070 is expected to resolve the safety problem, which is one of the concerns related to the existing allergen immunotherapies. Furthermore, patients are expected to receive therapeutic benefits with short-term treatment, and this vaccine has a high possibility of being convenient as well.

ITI has previously conducted three phase I studies (Phase IA, Phase IB, and Phase IC) on the Cry j 2-LAMP vaccine (single component vaccine with only Cry j 2-LAMP plasmid) with Japanese or people of Japanese descent in the US, and all studies confirmed no problem with tolerability.

API has previously conducted a Japanese phase I study [4070-CL-0010] with the aim of investigating the safety and immune response when ASP4070 is vaccinated in patients with JRC allergy. As a result of intramuscular (4 mg × 4 times, 4 mg × 1 time) and intradermal (4 mg × 4 times, 1 mg × 4 times, 4 mg × 1 time, 1 mg × 1 time) vaccination of ASP4070, this phase I study confirmed that there were no problems in tolerability among any of the groups.

This study is a phase II dose-finding study [4070-CL-0020] to evaluate the efficacy and safety of ASP4070 in patients with JRC allergy using an environmental exposure chamber.

## **1.2 Non-clinical and Clinical Data**

### **1.2.1 Non-clinical Data**

#### **1.2.1.1 Pharmacological Actions**

The expression of Cry j 1-LAMP-1 fusion protein and Cry j 2-LAMP-1 fusion protein in the cell was observed after introducing Cry j 1-LAMP plasmid and Cry j 2-LAMP plasmid into human embryonic kidney-derived 293T cell lines. Following the administration of ASP4070 to mice, Cry j 1-specific IgG2a production and Cry j 2-specific IgG2a production were induced. However, Cry j 1- or Cry j 2-specific IgE production was not apparently induced. Furthermore, cultivation of spleen cells from ASP4070-administered mice in the presence of JRC pollen extract showed the production of interferon gamma (IFN-γ), but no clear

Interleukin-4 (IL-4) production was evident. The above results suggest that administration of ASP4070 to mice induces Th1 cell-dominated immune response to JRC pollen antigen.

The effect of difference between the administration route and number of administration of ASP4070 on immunogenicity was investigated in mice. The production level of Cry j 1- and Cry j 2-specific IgG2a antibody by ASP4070 administration was the highest for intradermal administration as compared to intra muscular and subcutaneous administration. In addition, a total of 9 times of ASP4070 intradermal administration each week showed an increased production of Cry j 1- and Cry j 2-specific IgG2a antibody with increased number of administration.

### **1.2.1.2 Toxicity**

With regard to toxicity studies, an 8-week intramuscular administration and a 4-week withholding study of Cry j 2-LAMP plasmid in rabbits (dose, 4.128 mg/body; administration, once every two weeks); a 4-week intramuscular administration study of Cry j 1-LAMP plasmid, Cry j 2-LAMP plasmid, and ASP4070 (bivalent vaccine containing both plasmids) in rabbits (dose, 2 mg/body for each plasmid and 4 mg/body for ASP4070; administration, once weekly); and a 13-week intramuscular administration study of ASP4070 in rabbits (dose, 10 mg/body; administration, once weekly) were conducted. Neither of the studies showed toxic changes that may have been related to administration. Injection sites showed inflammatory reactions and although their incidence and severity were slightly higher than those in the vehicle control group, all inflammatory reactions detected were minimal or mild and reversible. Based on the degree of change at injection sites, it was considered that ASP4070 is unlikely to cause a clinically significant tissue injury. In the tissue distribution study of plasmid DNA in rabbits, the plasmid DNA copy number on Day 60 post-dose in any tissue was less than a threshold level at which chromosomal DNA integration needed to be examined, thereby suggesting an extremely low risk of chromosomal DNA integration.

### **1.2.1.3 Pharmacokinetics**

A tissue distribution study of plasmid DNA was conducted in accordance with the FDA Guidelines (Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications) to evaluate residual plasmid DNA. Following a single intramuscular dose of Cry j 2-LAMP plasmid to rabbits, a high level of plasmid DNA was observed at the injection site (muscle and subcutaneous tissue) and lymph nodes. Plasmid DNA level in the tissue decreased over time and was less than the quantification limit on Day 60 post-dose in most rabbits.

## **1.2.2 Clinical Study Data**

### **1.2.2.1 Japanese Phase I Study (4070-CL-0010)**

API has previously conducted a Japanese phase I study with the aim of investigating the safety and immune response when ASP4070 was vaccinated in 66 patients with JRC allergy. Refer to the Investigator's Brochure for details.

This phase I study consisted of two parts: Part 1 and Part 2. Part 1 was an open-label, uncontrolled study to investigate the safety of intramuscular and intradermal vaccination of ASP4070 (4 mg  $\times$  4 times), and Part 2 was a placebo-controlled, double-blind, randomized parallel group comparative study to investigate the safety and immune response of intramuscular (4 mg  $\times$  4 times or 4 mg  $\times$  1 time) and intradermal (4 mg  $\times$  4 times, 1 mg  $\times$  4 times, 4 mg  $\times$  1 time, or 1 mg  $\times$  1 time) vaccination of ASP4070.

With regard to the safety, although AEs, such as local reaction and systemic reaction, occurred during Part 1 and Part 2 of the primary study, none was considered as major problems. There were no significant changes in laboratory assessments, vital signs, and 12-lead electrocardiogram during Part 1 and Part 2. There were no significant problems with regard to the safety during the primary evaluation period and the long-term safety follow-up period.

With regard to the immunological response, negative conversion in the skin prick test at the last observation in the primary study (Day 127) was reported in 4 patients, including 1 patient each in the intramuscular ASP4070 4 mg  $\times$  1 time, intradermal ASP4070 4 mg  $\times$  4 times, intradermal ASP4070 4 mg  $\times$  1 time, and intradermal ASP4070 1 mg  $\times$  1 time groups. No negative conversion in the skin prick test was found among patients receiving placebo in the intramuscular vaccination group or intradermal vaccination group. Various antibody levels, cytokines, and histamine release were measured but no differences in changes of these items were found among the treatment groups. All patients were negative to the anti-LAMP antibody at all time points in Part 1 and Part 2.

In the additional investigation, pollinosis symptoms during JRC pollen dispersal season were investigated but no differences were found among the treatment groups in any of the endpoints.

#### **1.2.2.2 Overseas Phase I Studies**

ITI has previously conducted three phase I studies (Phase IA, Phase IB, and Phase IC) in the US using Cry j 2-LAMP vaccine (single component vaccine that includes only Cry j 2-LAMP plasmid) targeting Japanese/people of Japanese descent. Refer to the Investigator's Brochure for details.

##### **1.2.2.2.1 Phase IA Study (US)**

Cry j 2-LAMP vaccine (4 doses of either 2 mg or 4 mg) was administered to 24 subjects in order to evaluate the safety and changes in immunologic biomarkers (skin prick test, etc.). Of the 24 subjects who lived in Japan, 18 subjects were positive to JRC pollen or mountain cedar (MC) pollen in the skin prick test, and 6 subjects were negative to both JRC pollen and MC pollen in the skin prick test. The skin prick test was performed before the start of the study and after vaccination of Cry j 2-LAMP vaccine 4 times (Day 132), and the results showed a conversion from positive to negative skin test in 14 of 17 subjects who had been positive to JRC pollen, MC pollen, or Cry j 2 at the start of the study. Among these subjects, a conversion to negative skin test was reported in 7 of 8 subjects who received 2-mg doses of

Cry j 2-LAMP vaccine and in 7 of 9 subjects who received 4-mg doses of Cry j 2-LAMP vaccine. All of the 6 subjects who had been skin test negative to all of JRC, MC, and Cry j 2 at the start of the study did not experience a conversion to positive skin test but remained negative. With regard to the safety, 88 AEs were reported in 20 subjects. Most of these AEs occurred from Day 0 to Day 72, and only 2 AEs were reported from Day 73 to Day 132. The most frequent AE was injection site erythema (24 events in 11 subjects), followed by fatigue (14 events in 7 subjects), and headache (14 events in 7 subjects). The majority of AEs were mild in severity and none required treatment. No anti-LAMP antibodies were detected. There were no relevant changes in laboratory tests, vital signs, or physical examination. Thus, no significant concerns regarding the tolerability of Cry j 2-LAMP vaccine were identified.

#### **1.2.2.2.2 Phase IB Study (US)**

The long-term safety of Cry j 2-LAMP vaccine and the safety of a booster injection of Cry j 2-LAMP vaccine (2 mg) were evaluated in 17 subjects who had received Cry j 2-LAMP vaccine in the Phase IA study, and long-term changes in immunologic biomarkers were also evaluated. The skin prick test was performed before the start of this study and after a booster vaccination (Day 50 and Day 80). The results of the skin prick test indicated that 13 subjects who were positive to JRC pollen or MC pollen at the start of the Phase IA study and subsequently participated in the Phase IB study were all negative at the start of this study. Among these subjects, the negative skin tests were maintained in 11 of 12 subjects who completed the study until Day 80. Among these 11 subjects, 2 of these subjects did not receive a booster injection of Cry j 2-LAMP vaccine but remained negative. A total of 4 subjects who had a negative prick test result for JRC and MC before the start of the Phase IA study remained to have a negative result without converting to positive. With regard to the safety, 9 AEs were reported in 3 subjects. Furthermore, 6 of these events occurred in 2 subjects after the booster vaccination of Cry j 2-LAMP vaccine. The reported AEs were mild or moderate in severity and eventually resolved. There were no clinically significant changes in laboratory assessments, vital signs, and physical examination, and there was no concern about the long-term safety and safety of booster vaccinations.

#### **1.2.2.2.3 Phase IC Study (US)**

Cry j 2-LAMP vaccine (Group 2, 2.16 mg; Group 3, 1.08 mg) or physiological saline (Group 1) was intradermally administered 4 times using the Biojector® 2000 device to 22 subjects, of whom 17 subjects were positive to any of JRC pollen, MC pollen, or Cry j 2 in the skin prick test and 5 subjects were negative to all JRC pollen, MC pollen, and Cry j 2 in the skin prick test, and the safety and changes in immune response biomarkers (skin prick test, etc.) were evaluated. The results of the skin prick test obtained from 10 subjects in Group 1 showed a conversion to negative skin test on Day 132 in 3 of 4 subjects who were positive to any one of JRC, MC, or Cry j 2 at screening. Among 9 subjects who completed the study until Day 132, a conversion from negative to positive skin test on Day 132 was found in 4 subjects who were negative to any one of JRC, MC, or Cry j 2 at screening. Among 6 subjects in Group 2, a conversion to negative skin test on Day 132 was found in 3 of 5 subjects (60%)

who were positive to JRC at screening. A conversion to negative skin test on Day 132 was also found in 1 of 4 subjects (25%) who were positive to MC at screening and 3 of 5 subjects (60%) who were positive to Cry j 2 at screening. Among 6 subjects in Group 3, a conversion to negative skin test on Day 132 was found in 1 of 2 subjects (50%) who were positive to JRC at screening. Among 3 subjects who were positive to MC at screening, 1 subject was still positive on Day 132 and 1 of the remaining 2 subjects (33%) was confirmed to be converted to negative skin test at discontinuation (Day 14), and the other subject remained positive at discontinuation (Day 102). Among 4 subjects who completed the study until Day 132, a conversion from negative to positive skin test on Day 132 was found in 2 subjects who were negative to any one of JRC, MC, or Cry j 2 at screening. A conversion to negative skin test on Day 132 was also found in 1 of 3 subjects (33%) who were positive to Cry j 2 at screening. With regard to the safety, 321 AEs were reported across the three groups after the start of vaccination. No serious adverse events (SAEs) occurred. The most frequently reported AEs across the three groups included injection site-related AEs (257 events), most of which had already been reported in the Phase IA and Phase IB studies. No anti-LAMP antibodies were detected. There were no relevant changes in laboratory tests, vital signs, and physical examination. Thus, no significant concerns regarding the tolerability of Cry j 2-LAMP vaccine were identified.

### 1.3 Summary of Key Safety Information for Study Drugs

Summary of the safety information for the study drug as provided below. Refer to the Investigator's Brochure for details.

Although AEs, such as local reaction and systemic reaction, occurred during Japanese phase I study upon intramuscular or intradermal vaccination of ASP4070 2 mg or 4 mg, it was confirmed that there is no problem in the tolerability of up to 4 mg ASP4070. There were no problematic changes in laboratory assessments, vital signs, and 12-lead electrocardiogram during Part 1 and Part 2. In addition, during the long-term safety follow-up period, although an SAE (event name: benign parotid tumour) occurred in 1 subject in the ASP4070 4 mg  $\times$  1 time (intramuscular vaccination) group, this was an event that occurred approximately 5 months after the final vaccination and a relationship to the study drug was negated. Otherwise, there were no SAE and local reactions reported during the long-term safety follow-up period.

In the US, signs of systemic symptoms, such as anaphylaxis, against the vaccine were not found in the Phase IA, Phase IB, and Phase IC studies using only Cry J 2-LAMP plasmid and there were no occurrences of other SAEs. In addition, the majority of AEs were transient injection site reactions and all were confirmed to have recovered without treatment.

### 1.4 Risk-Benefit Assessment

ASP4070 is a DNA vaccine designed to express the antigen as a fusion protein with LAMP-1. ASP4070 can effectively induce CD4<sup>+</sup> T-cell response by co-localization of the expressed



fusion protein with MHC Class II molecules localized in the lysosome [Geuze, 1998; Marques et al., 2003]. The nucleotide component of DNA vaccine is also known to induce Type I interferon production [Ishii et al., 2008], which may induce a Th1-dominant immune response. In reality, experiments with ASP4070 have shown that administration to mice leads to an increase in mice IgG2a antibody production that is induced and produced by Th1 cells, whereas IgE antibody that is induced and produced by Th2 cells was not induced. IgE production induced by the enhanced allergen-specific Th2 cell response is considered to be responsible for the onset of allergy [Woodfolk and Platts-Mills, 2002] and ASP4070 is expected to suppress allergic symptoms by rendering the Th1/Th2 balance to Th1-dominant.

LAMP-1 fusion protein is known only to be expressed in lysosomes in cytoplasm [Marques et al., 2003], and in a study where antigen-LAMP-1 fusion protein expressing plasmid was administered to mice, antigen-LAMP-1 fusion protein was not detected in circulatory blood [Tan et al., 2006]. Therefore, the risk of anaphylaxis, which has been one of the concerns for conventional allergen immunotherapy, is considered to be low.

Common AEs in previous clinical studies with Cry j 2-LAMP vaccine or ASP4070 included local reactions and systemic reactions that are normally observed with vaccination (refer to the Investigator's Brochure for details). After study drug vaccination, the investigator or sub-investigator should be watchful of these symptoms associated with vaccination and treat any symptoms as necessary to ensure the safety of subjects.

In the environmental exposure chamber, JRC pollen that exists in the natural environment will be used and subjects will be exposed to JRC pollen levels approximately in the same level as observed within Tokyo Prefecture [Hashiguchi et al., 2009], and it is assumed that symptoms similar to those under the natural environment will occur with the pollen exposure. In addition, these symptoms may continue for 2 or 3 days after leaving the chamber. In case of unanticipated events, subjects will be continuously monitored during the assessment in the chamber and the investigator or sub-investigator will treat any symptoms as necessary to ensure the safety of subjects.

## **2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS**

### **2.1 Study Objectives**

To evaluate the efficacy, safety, and dose response for ASP4070 vaccinated in patients with cedar pollinosis.

### **2.2 Study Design and Dose Rationale**

#### **2.2.1 Study Design**

This study is a randomized, double-blind, placebo-controlled, dose-finding study.

The efficacy, safety, and dose response when ASP4070 (mixture containing equivalent amount of Cry j 1-LAMP plasmid and Cry j 2-LAMP plasmid, 4 mg/0.4 mL or 1 mg/0.4 mL) will be intradermally vaccinated 8 times at 14-day intervals will be evaluated with placebo (physiological saline) as the control. The study will conduct cedar pollen exposure using an environmental exposure chamber (OHIO Chamber; hereinafter, “chamber”), and the efficacy and dose response will be evaluated using clinical symptoms (nasal and eye symptoms) as indicators.

Two factors, “Class from results of Japanese red cedar (JRC) pollen-specific IgE antibody test performed at Screening visit 1” and “Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2,” will be used as stratification factors to randomly allocate subjects into three groups—ASP4070 4 mg group, ASP4070 1 mg group, or placebo group—in a ratio of 1:1:1, and the subjects will be vaccinated with the study drug.

After a set period after the final vaccination of the study drug, re-exposure to cedar pollen in the chamber will be conducted and the efficacy will be evaluated using clinical symptoms as indicators. Efficacy evaluation will be conducted 4, 8, and 12 weeks after the final vaccination to confirm the timing of effectiveness. The primary study period of the study will be until the end of the one week of post-observational period after the final evaluation in the chamber on Day 183 (12 weeks after the final vaccination).

The treatment code will be broken when the primary study period is completed and all data entered in case report forms are fixed. Even after code breaking, the study will be continued with the investigator, sub-investigator, study coordinator, and subjects remaining blinded.

Subjects who have completed the primary study period will be the target of a survey on cedar pollinosis symptoms during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018). Subjects will make entries in the Pollinosis Symptoms Survey Diary every day on information regarding nasal and eye symptoms. If a subject experiences intolerable nasal and eye symptoms during this period, then the use of rescue drugs will be allowed.

An additional test of immune responses will be performed during the long-term safety follow-up period on subjects who have completed the pollinosis symptoms survey period and have provided additional consent to the additional test. The additional test will determine the parameters (specific IgE antibody [anti-JRC] and basophil activation test [BAT]) after the end of the cedar pollen dispersal season (May 2018).

After the end of the primary study period, safety information (SAE) will be collected for approximately 9 months (1 year from the final vaccination of the study drug) as the long-term safety follow-up period. Safety information (SAE) will be collected for 1 year after the final vaccination of the study drug even from subjects who discontinue their participation in the study during the primary study period if they have received at least one vaccination of the study drug.

Among subjects in the placebo group or optimal dose group (ASP4070 4 mg group or 1 mg group) who complete the primary study period, those who provide written consent again will be the target of a Phase II Second-Year Follow-up Study [4070-CL-0021] that is planned to be implemented.

## **2.2.2 Dose Rationale**

This study will intradermally vaccinate ASP4070 4 mg or ASP4070 1 mg 8 times at two-week intervals (vaccination period of 14 weeks).

With regard to the study drug vaccination amount, 4 mg, the maximum dose confirmed to have no problems regarding the tolerability in Japanese phase I study was designated as the high dose group, and additionally, to investigate dose-response relationship, 1 mg was to be investigated as the low dose group. Vaccination interval was the same as that in phase I studies and set at 2-week intervals. The number of vaccination was set to 8 times (vaccination period of 14 weeks) because an increase in immune response was confirmed upon an increase in the number of vaccinations from 7 to 9 times of vaccination, efficacy against seasonal allergies has been confirmed for up to 8 times of peptide immunotherapy developed in recent years, and patient burden is high for long-term treatment.

During the phase I studies with vaccination up to 4 times, there was no trend suggesting an increase in AE incidence or aggravation of severity accompanying an increase in the number of vaccinations, and pre-clinical toxicity studies did not show any findings of changes related to toxicity with administration up to 13 times.

Both intradermal and intramuscular vaccination have been confirmed in clinical studies conducted in the US and Japan as vaccination routes without any problems from the viewpoint of safety. In addition, many immune response-related cells, such as dendritic cells, exist in the epidermis, and intradermal vaccination has been reported to efficiently reinforce antigen recognition by the immune system and showed a higher immunogenicity than intramuscular vaccination [Hickling et al., 2011; Kenney et al., 2004]. Therefore, intradermal vaccination was selected for this study.

## **2.3 Endpoints**

### **2.3.1 Primary Efficacy Endpoints**

Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS) during 120 to 180 minutes (every 15 minutes, total of 5 time points) after start of cedar pollen exposure as compared to the score before cedar pollen exposure

Subjects will assess for each symptom (sneezing, nasal discharge, and nasal congestion) using the following score every 15 minutes from before cedar pollen exposure until 180 minutes after cedar pollen exposure.

0: None (no symptoms)

- 1: Mild (symptoms present but easily tolerated)
- 2: Moderate (awareness of symptoms; bothersome, but tolerable)
- 3: Severe (definite awareness of symptoms; difficult to tolerate, but does not interfere with the activities of daily living)
- 4: Very severe (difficult to tolerate and interferes with the activities of daily living)

[Rationale]

The three main symptoms of sneezing, nasal discharge, and nasal congestion are the main pollinosis symptoms and the indicator of severity of these nasal symptoms is the total 3 nasal symptom score (3TNSS). In addition, results from other studies using a chamber have confirmed that clinical symptoms induced by cedar pollen exposure in the chamber reaches a plateau at 90 to 120 minutes after start of JRC pollen exposure. [Hashiguchi et al., 2009].

Based on the above, it was considered that clinical symptoms might be more accurately evaluated by cedar pollen exposure in the chamber. The primary endpoint was designated as the mean of total 3 nasal symptom score (3TNSS) at 120 to 180 minutes, which is after symptoms have stabilized.

### 2.3.2 Secondary Efficacy Endpoints

- Total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS)
- Total 4 nasal symptom (sneezing, nasal discharge, nasal congestion, and itchy nose) score (4TNSS)
- Individual nasal symptom (sneezing, nasal discharge, nasal congestion, and itchy nose) score
- Total non-nasal symptom (itchy eyes and watery eyes) score (TNNSS)
- Individual eye symptom (itchy eyes and watery eyes) score
- Total symptom score (TSS)

Subjects will score each symptom (sneezing, nasal discharge, nasal congestion, itchy nose, itchy eyes, and watery eyes) used for tabulation of the above items, using the indicators in “2.3.1 Primary Efficacy Endpoints.”

The following items are also assessed.

- Time to occurrence of nasal or eye symptoms (time point when the score of nasal or eye symptom worsens by one or more as compared to before JRC pollen exposure) from start of cedar pollen exposure in the chamber
- Nasal discharge amount and sneezing count per 30 minutes during chamber exposure  
Nasal discharge amount is the difference in the weight of the tissue paper before and after use by subjects who are instructed to use pre-allocated tissues for blowing their nose.

With regard to symptoms after leaving the chamber, a survey will be conducted on nasal and eye symptoms until 3 days after leaving the chamber.

### 2.3.3 Other Efficacy Endpoints

Endpoints during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018):

- Total 3 nasal symptom score (3TNSS)
- Individual nasal symptom (sneezing, nasal discharge, and nasal congestion) score
- Total non-nasal symptom score (TNNSS)
- Individual eye symptom (itchy eyes and watery eyes) score
- Total symptom score (TSS)
- Total nasal symptom medication score (TNSMS)
- Total non-nasal symptom medication score (TNNSMS)
- Total symptom medication score (TSMS)
- Troubles with daily life
- Japanese Rhinoconjunctivitis Quality of Life Questionnaire: JRQLQ No 1
- Overall evaluation by the subject

For each symptom score, subjects will record the following items in their Pollinosis Symptoms Survey Diary every day. Section “12.3 Classification of Severity of Pollinosis Symptoms” will be referred to with regard to nasal and eye symptoms and troubles with daily life.

- Nasal symptoms: Sneezing, nasal discharge, and nasal congestion, each graded with a 5-level score of 0, 1, 2, 3, and 4.
- Eye symptoms: Itchy eyes and watery eyes, each graded with a 4-level score of 0, 1, 2, and 3.
- Troubles with daily life: 5-level score of 0, 1, 2, 3, and 4.

Total nasal symptom medication score, total eye symptom medication score, and total nasal and eye symptom medication score will be used for scoring rescue drug use status and for calculating endpoints.

JRQLQ No 1 will be entered every 2 weeks during the pollinosis symptoms survey period for a total of 5 times.

Overall evaluation by the subject is conducted by subjects after the end of the pollinosis symptoms survey period.

- Overall evaluation by the subject: 5-level evaluation on overall evaluation of symptoms during the pollinosis symptoms survey period.

### 2.3.4 Immune Response Endpoints

Immune response endpoints (primary study period)

Immunoglobulin G (IgG) antibody, specific IgG antibody (anti-JRC, anti-Cry j 1, anti-Cry j 2), specific IgG4 antibody (anti-JRC), IgE antibody, specific IgE antibody (anti-JRC), anti-LAMP antibody, basophil activation test (BAT)

Immune response endpoints (additional test)

Specific IgE antibody (anti-JRC), basophil activation test (BAT)

### **2.3.5 Safety Endpoints**

- AEs that occur during the primary study period  
(Nasal and eye symptoms induced by cedar pollen exposure in the chamber will be separately collected as efficacy endpoints and will not be considered as AEs)
- 12-lead electrocardiogram, vital signs, laboratory assessments
- Local reactions and systemic reactions accompanying study drug vaccination that occur from each day of study drug vaccination until 14 days after vaccination
- SAEs that occur within approximately 9 months after the end of the primary study period (until 12 months after the final vaccination of the study drug) (long-term safety follow-up period)

## **3 STUDY POPULATION**

### **3.1 Selection of Study Population**

Patients with cedar pollinosis aged from 20 to 64 years

### **3.2 Inclusion Criteria**

Subject is eligible for the study if all of the following 1 to 11 apply:

1. Subject who has provided written consent using the informed consent form approved by the Institutional Review Board (IRB) of the study site before starting any study-related procedure
2. Subject of either sex who is aged from 20 to 64 years at the time of informed consent
3. Subject who has nasal symptoms (sneezing, nasal discharge, or nasal congestion) and eye symptoms (itchy eyes or watery eyes) of pollinosis during the cedar pollen dispersal seasons in 2016 and 2017
4. Subject who has the JRC pollen-specific IgE antibody test result of Class 3 or higher in the allergy test at Screening visit 1
5. Subject who satisfies the following criteria for change in the mean of the nasal symptom score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2
  - Total 3 nasal symptom score (3TNSS) worsens by 2 or more, 2 or more individual nasal symptom score (sneezing, nasal discharge, and nasal congestion) worsens by 1 or more

6. Female subject must satisfy the following criteria

Subject of non-childbearing potential must satisfy either of the following criteria:

- Subject who is post-menopausal (defined as at least 1 year without any menses) prior to Screening visit 1
- Subject who is surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

Or, subject of childbearing potential (subject who does not meet the above definition of “female subject of non-childbearing potential”) must meet all of the following criteria:

- Subject must agree not to try to become pregnant during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
- Subject must have a negative urine pregnancy test at Screening visit 1 and on Day 1 (prior to vaccination)
- Subject must consistently use two forms of highly effective birth control\* (at least one of which must be a barrier method) during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer) if heterosexually active

\*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception
- Established intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method)

7. Female subject must agree not to breastfeed during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
8. Female subject must not donate ova during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer)
9. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control\* (at least one of which must be a barrier method) from the initial study drug vaccination until 28 days after the final vaccination of the study drug
10. Male subject must not donate sperm from the initial study drug vaccination until 28 days after the final vaccination of the study drug
11. Subject agrees not to participate in another intervention study while on treatment

Subject is eligible for the additional test of the study if the following 12 and 13 both apply:

12. Subject has completed the pollinosis symptoms survey period
13. Subject has provided written consent using the informed consent form approved by the Institutional Review Board of the study site before starting any procedure related to the additional test of the study

Waivers to the inclusion criteria will **NOT** be allowed.

[Rationale]

- 1 and 13: Designated in consideration of ethics in accordance with the “Ordinance on Good Clinical Practice (GCP) for trials on gene, cellular, and tissue-based products” (MHLW ordinance No. 89, 30 Jul 2014)
- 2: The age was set to 20 years or older, when subjects themselves have the ability to determine whether or not to participate in a clinical study. The upper limit was set to 64 years because the study is targeting non-elderly patients.
- 3 to 5: Designated to select JRC pollinosis patients who are the target of this study.
- 6 to 10: Designated as general exclusion items to ensure the safety of subjects.
- 11: Designated to appropriately conduct evaluation of this study.
- 12: Designated to target subjects who have been investigated for cedar pollinosis symptoms during the pollinosis symptoms survey period.

### 3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject whose allergy test result to other antigens than JRC pollen (test result of IgE antibody specific to alnus, Japanese white birch, ragweed, artemisia, cocksfoot, dermatophagoides farinae, dermatophagoides pteronyssinus, *Aspergillus*, *Candida*, *Alternaria*, house dust 1, house dust 2, cat dander, and dog dander) is Class 4 or higher at Screening visit 1
2. Subject who has received specific immunotherapy (including desensitization therapy) for cedar pollinosis in the past
3. Subject who has received specific or non-specific immunotherapy within 5 years prior to Screening visit 1
4. Subject who has received laser therapy/surgery for treating nasal symptoms within 3 years prior to Screening visit 1
5. Subject who has used the following drugs within 14 days prior to entering the chamber at Screening visit 2  
Topical steroid, histamine H1-receptor antagonist, chemical mediator-isolation inhibitor, T helper cell 2 (Th2) cytokine inhibitor, thromboxane A2 synthesis inhibitor, thromboxane A2 receptor antagonist, leukotriene receptor antagonist  
(Among the above drugs, use of medications for external use on the skin is allowed. However, use at the study drug vaccination site on the day before Day 1 is not allowed.)
6. Subject who has used the following drugs within 84 days prior to entering the chamber at Screening visit 2



Biological agents, such as antibiotics (anti-tumor necrosis factor alpha [TNF $\alpha$ ] antibody, anti-IgE monoclonal antibody, etc.)

7. Subject who has used the following drugs within 84 days prior to the first vaccination of the study drug  
Systemic steroids and immunosuppressants (Use of medications for external use on the skin are allowed. However, use at the study drug vaccination site on the day before Day 1 is not allowed.)
8. Subject who has received or is planning to receive vaccination of a live vaccine within 28 days prior to the first vaccination of the study drug, and/or subject who has received or is planning to receive vaccination of an inactivated vaccine/toxoid within 7 days prior to the first vaccination of the study drug
9. Subject who has a history of serious allergic reactions, such as anaphylactic shock and generalized exanthema, caused by food and/or medical products (including vaccine) in the past
10. Subject who has a positive immunological test result for hepatitis B surface antigen (HBs antigen) or hepatitis C virus (HCV) antibody at Screening visit 1
11. Subject who has a complication of nasal disorder (nasal polyp, nasal septum deviation, chronic sinusitis, etc.) that may affect efficacy evaluation
12. Subject who has autoimmune disease or other serious primary disease
13. Subject who has been diagnosed with immunodeficiency in the past
14. Subject who has a complication of seasonal allergic rhinitis, perennial allergic rhinitis, rhinitis medicamentosa, or non-allergic rhinitis against antigens other than cedar and cypress that require medical treatment
15. Subject who has a complication of cardiovascular disease (including congestive cardiac failure, angina pectoris, and cardiac arrhythmias that require medical treatment)
16. Subject who has a complication of hepatic disease (including viral hepatitis and drug-induced liver injury)
17. Subject who has a complication of renal disease (including acute kidney injury, glomerulonephritis, and interstitial nephritis)
18. Subject who has a complication of respiratory disease (including bronchial asthma and chronic bronchitis that require medical treatment)
19. Subject who has a complication of malignant tumor or has been diagnosed with or has received treatment for malignant tumor within 5 years prior to the first vaccination of the study drug
20. Subject who has been diagnosed with mental conditions, such as schizophrenia, bipolar disorder, and major depressive disorder, or dementia

21. Subject who has a complication that may have an impact on the evaluation of local and systemic reactions
22. Subject who has received vaccination of Cry j 2-LAMP vaccine
23. Subject who has participated in a study of ASP4070 and received vaccination of the study drug
24. Subject who has participated in any clinical study or post-marketing clinical study of any other medical drug or device within 12 weeks (84 days) prior to Screening visit 1, or subject who is participating in such a study at present
25. Subject who is an employee of the Sponsor or CRO or medical institution involved in the study
26. Subject who is considered by the investigator or sub-investigator as unsuitable for study participation

Waivers to the exclusion criteria will **NOT** be allowed.

[Rationale]

- 1 to 7, 11, 13, and 14: Designated because of the possibility of an effect on efficacy evaluation of the study drug.
- 8 to 10, 12, and 15 to 20: Designated to ensure the safety of subjects.
- 21: Designated because of the possibility of an effect on safety evaluation of the study drug.
- 22 and 23: Designated because of the possibility of an effect on safety and efficacy evaluation of the study drug.
- 24: Designated from ethical considerations and safety considerations for subjects.
- 25: This criterion was set not to select anyone who would be disadvantaged by not participating in the study.
- 26: This criterion was set in consideration of situations other than the above 1 to 25, where the investigator or sub-investigator judges a subject to be ineligible for participating in the study from a scientific and/or ethical perspective.

Among subjects who satisfy all of the inclusion criteria 1 to 11 and do not fall under any of the exclusion criteria, subjects who were determined as reserve subjects will not proceed to procedures after Day 1 and are considered as completing their participation in the study when the number of subjects vaccinated with the drug reaches 150, the target number of subjects.

## 4 TREATMENT

### 4.1 Identification of Investigational Product

#### 4.1.1 Test Drug

Code name	ASP4070
Non-proprietary name	To be determined
Dosage form and strength	Clear and colorless injectable solution: 4 mg/0.4 mL (containing 2 mg each of Cry j 1-LAMP plasmid and Cry j 2-LAMP plasmid)
Lot No.	See the procedures for handling the study products
Storage condition	Stored frozen ( $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ ) and protected from light
Expiration date	See the procedures for handling the study products

#### 4.1.2 Comparative Drug

Code name	Placebo
Non-proprietary name	Physiological saline
Dosage form and strength	0.9% sodium chloride
Lot No.	See the procedures for handling the study products
Storage condition	Stored at room temperature
Expiration date	See the procedures for handling the study products

### 4.2 Packaging and Labeling

All medications used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at API in accordance with API's Standard Operating Procedures (SOPs), Good Gene, Cellular, and Tissue-based Products Manufacturing Practice (GCTP) guidelines (Good Manufacturing Practice [GMP] guidelines for the comparative drug), ICH GCP guidelines, and applicable local laws and regulations.

(Package Form)

ASP4070: 4 mg/0.4 mL vial

Placebo: 5 mL ampule

### 4.3 Study Drug Handling

The head of the study site or the study drug storage manager should take accountability of the study drugs as following issues.

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study products written by the Sponsor.
- The study drug storage manager should prepare and retain records of the study drugs' receipt, the inventory at the study site, the use by each subject, and the return to the Sponsor or alternative disposal of unused study drugs. These records should include

dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study drugs and subjects.

- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol, and reconcile all the study drugs supplied from the Sponsor.

## **4.4 Blinding**

### **4.4.1 Blinding Method**

[Primary study period]

The primary study period of this study is double blinded. Double blinding is conducted to hide which group subjects belong to —ASP4070 4 mg group, ASP4070 1 mg group, or placebo group. ASP4070 4 mg, ASP4070 1 mg, and placebo are all externally indistinguishable when filling the syringe.

The study will not be blinded to the person in charge of randomization list management and study drug adjustment within the study site (hereinafter, “randomization list manager”), ancillary staff of the study site (ancillary randomization list manager), and sub-investigators who are in charge of study drug vaccination. Sub-investigators who are in charge of study drug vaccination will not be involved in this study other than vaccination to subjects, and other investigators will observe and evaluate subjects. However, sub-investigators who are in charge of study drug vaccination may conduct observation and evaluation at Screening visits until the sub-investigator starts to vaccinate subjects with the study drug. Details are provided in the “procedures for blinding compliance.”

[Long-term safety follow-up study period (including pollinosis symptoms survey period and additional study period)]

The treatment code will be broken when the primary study period is completed and all data entered in case report forms are fixed. Even after code breaking, the study will be continued with the investigator, sub-investigator, study coordinator, and subjects remaining blinded.

### **4.4.2 Confirmation of the Indistinguishability of the Study Drugs**

The randomization list manager will confirm the indistinguishability of the study drugs filled in the syringe at each study drug vaccination.

### **4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking**

The treatment allocation manager (CRO) will prepare the randomization list. The treatment allocation manager will prepare and seal one original and two copies, and retain the original. The Sponsor will keep one copy in the sealed condition even after opening the original copy for code breaking. The randomization list manager will use one copy when adjusting study

drug dose and return the sealed copy to the treatment allocation manager after study drug vaccination to the final subject has been completed. The treatment allocation manager will also prepare and seal the treatment code for emergency when responding to a request from the study site. The sealed treatment code for emergency will be retained by the treatment allocation manager.

In principle, code breaking will occur after the completion of vaccination of the study drug, all protocol-specified observation/assessments for the primary study period in all subjects, finalization of the Statistical Analysis Plan (SAP), and all data locked. The treatment allocation manager will unseal the randomization list (original), and the treatment allocation manager will submit the randomization list (original) and randomization list for study sites (copy) to the Sponsor.

#### **4.4.4 Breaking the Treatment Code for Emergency**

In case of an emergency, such as the occurrence of an SAE, the investigator or sub-investigator will be allowed to request the Sponsor to break the treatment code for an emergency. If the sub-investigator is requesting to break the treatment code for emergency, then in principle, prior approval of the investigator will be required. However, if it is difficult to obtain prior approval of the investigator, then the sub-investigator will report after the event. Upon request, the Sponsor will determine whether or not the treatment code for an emergency should be broken. If the code is to be broken, then the Sponsor will instruct the treatment allocation manager to break it. The sponsor will receive contact from the treatment allocation manager regarding the result of the emergency treatment code breaking, and the sponsor will inform the investigator or sub investigator of the result. Breaking of the treatment code for an emergency will be conducted in accordance with the procedure for breaking the emergency treatment code.

#### **4.5 Assignment and Allocation**

The treatment allocation manager will prepare the randomization list prior to the initial vaccination of the study drug to the first subject, which randomly allocates randomization numbers to three groups in a ratio of 1:1:1 to ASP4070 4 mg group, ASP4070 1 mg group, or placebo group, with two factors as stratification factors, “Class of Japanese red cedar (JRC) pollen-specific IgE antibody test results at Screening visit 1” and “Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2.”

Subject allocation to randomization number will be conducted several times by the investigator or sub investigator (excluding sub-investigators who are in charge of study drug vaccination) and completed before the initial study drug vaccination of subjects.

Specific procedures are provided in the “procedures for blinding compliance.”

## 5 TREATMENTS AND EVALUATION

### 5.1 Dosing and Administration of Study Drug and Other Medications

#### 5.1.1 Dose/Dose Regimen and Administration Period

ASP4070 4 mg group: 0.4 mL of ASP4070 4 mg/0.4 mL will be intradermally vaccinated.

ASP4070 1 mg group: 0.1 mL of ASP4070 4 mg/0.4 mL and 0.3 mL of physiological saline will be mixed and a total of 0.4 mL will be intradermally vaccinated.

Placebo group: 0.4 mL of physiological saline will be intradermally vaccinated.

Intradermal injection device manufactured by Terumo (Immucise® intradermal injection needle: Medical device approval No. 22700BZX00264000 and intradermal disposable syringe) will be used for study drug vaccination. For each vaccination, 0.2 mL each of the study drug will be vaccinated into two sites on each arm in principle. Vaccination sites will be in principle the upper arm deltoid.

#### 5.1.2 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

During the primary study period, the following items in the table below for all concomitant medications and treatments used after the start of the first vaccination of the study drug will be entered in the eCRF.

Concomitant treatment		Survey period	Items to be entered in eCRF
Medication	All drugs	From first vaccination of the study drug to completion of the primary study period	Drug name, route of administration, reason for administration, and administration period
Non-medication therapy	All therapies	From first vaccination of the study drug to completion of the primary study period	Therapy name, reason for treatment, and treatment period

The following items in the table below for rescue drugs and items that physically shield the body from JRC pollen, such as masks and goggles, used during the pollinosis symptoms survey period will be entered in the eCRF. From the end of the primary study period until the completion of the pollinosis symptoms survey period, if prohibited concomitant drugs are used, then the same items as for rescue drugs will be entered in the eCRF, and if prohibited concomitant therapies are used, then the therapy name and treatment period will be entered in the eCRF.

Concomitant treatment		Survey period	Items to be entered in eCRF
Medication	Rescue drugs	Pollinosis symptoms survey period	Drug name, daily dose, route of administration, and administration period
Non-medication therapy	Mask, goggles, etc.	Pollinosis symptoms survey period	Therapy name, use status (outdoor/indoor), and period of use

If prohibited concomitant drugs are used from the informed consent for the additional test until the completion of the additional test, the items listed on the table below will be entered in the eCRF. For systemic steroids and immunosuppressants (excluding external use on the skin) used after the end of the pollinosis symptoms survey period up to informed consent for the additional test, entry in the eCRF is not necessary, but the drug name and administration period need to be confirmed.

Concomitant treatment		Survey period	Items to be entered in eCRF
Medication	Prohibited concomitant drugs	From informed consent for the additional test to the completion of the additional test	Drug name, daily dose, route of administration, and administration period

### 5.1.2.1 Prohibited Medications/Therapies

The use of the following medications will be prohibited:

1. Until the end of the pollinosis symptoms survey period  
Immunotherapy specific to cedar pollinosis (including desensitization therapy)
2. From 5 years prior to Screening visit 1 until the end of the pollinosis symptoms survey period  
Specific or non-specific immunotherapy
3. From 14 days prior to entering the chamber at Screening visit 2 until the end of the pollinosis symptoms survey period  
Topical steroid, histamine H1-receptor antagonist, chemical mediator-isolation inhibitor, Th2 cytokine inhibitor, thromboxane A2 synthesis inhibitor, thromboxane A2 receptor antagonist, leukotriene receptor antagonist  
(Among the above drugs, use of medications for external use on the skin will be allowed. However, use at the study drug vaccination site from the day before Day 1 until 28 days after the final vaccination of the study drug will not be allowed.)  
If a subject experiences intolerable nasal and eye symptoms during the pollinosis symptoms survey period, then the use of rescue drugs will be allowed. (Refer to “5.1.2.2 Rescue Drugs”).
4. From 84 days prior to entering the chamber at Screening visit 2 until the end of the pollinosis symptoms survey period

- Biological agents, such as antibiotics (anti-TNF $\alpha$  antibody, anti-IgE monoclonal antibody, etc.)
5. From 84 days prior to the first vaccination of the study drug until the end of the pollinosis symptoms survey period and from the informed consent for the additional test until the completion of the additional test  
Systemic steroid/immunosuppressants  
(Use of medications for external use on the skin will be allowed. However, use at the study drug vaccination site from the day before Day 1 until 28 days after the final vaccination of the study drug will not be allowed.)
  6. From 28 days prior to the first vaccination of the study drug until 28 days after the final vaccination of the study drug  
Live vaccine
  7. From 7 days prior to the first vaccination of the study drug until 28 days after the final vaccination of the study drug  
Inactivated vaccine/toxoid

#### 5.1.2.2 Rescue Drugs

A daily dose of the following rescue drugs may be used for intolerable nasal and eye symptoms (in principle, a score of 4 for any of the nasal symptom score or a score of 3 for any of the eye symptom score) only on the day of occurrence during the pollinosis symptoms survey period. Prophylactic use of rescue drugs will be prohibited. Use status will be entered in the Pollinosis Symptoms Survey Diary.

Drug name	Use condition (to be used only if satisfying the conditions provided below)
Tramazoline hydrochloride nasal drops	Nasal congestion score 4
Ketotifen fumarate eye drops	Eye symptom (itchy eyes or watery eyes) score 3
Fexofenadine hydrochloride tablets	If fulfilling any of the following cases: <ul style="list-style-type: none"> <li>Nasal congestion or eye symptoms are intolerable even with the use of the above nasal/eye drops</li> <li>Sneezing score 4</li> <li>Nasal discharge score 4</li> </ul>

#### 5.1.2.3 Prohibited Non-Medication Therapies

The following therapies will be prohibited.

1. From 3 years prior to Screening visit 1 until the end of the pollinosis symptoms survey period
  - Laser therapy/surgery for treating nasal symptoms
2. From leaving the chamber at 4, 8, and 12 weeks after the final vaccination until the completion of the Symptoms Survey After Chamber
  - Acts that physically remove pollen, such as nasal wash (including nebulizer use) and eye wash



3. During the pollinosis symptoms survey period
  - The use of objects that physically shield the body from pollen, such as masks/goggles  
This restriction does not apply to cases in which the investigator or sub-investigator deems the use to be unavoidable (such as medical personnel and factory workers), but the usage should be kept to the minimum.
  - Acts that physically remove pollen, such as nasal wash (including nebulizer use) and eye wash

### 5.1.3 Treatment Compliance

The sub-investigator who is in charge of study drug vaccination will adequately vaccinate the subject with the study drug. The date of vaccination will be recorded and entered in the eCRF.

### 5.1.4 Restrictions During the Study

The investigator, sub-investigator, or study coordinator will instruct individual subjects to follow the “Requirements for Subjects” provided below during the study period.

1. Visit control  
The subject will visit the study site at a specified schedule in the protocol.
2. Contact regarding concomitant treatment (medication other than the study drug and non-medication therapy)  
If the use of any concomitant treatment (medication [drugs other than the study drug and rescue drug during the pollinosis symptoms survey period] and non-medication therapy) is needed during the period from signing the informed consent form to completion of the pollinosis symptoms survey period, then the subject will contact the study site before using it, if possible, and follow instructions of the investigator or sub-investigator.
3. Exercise  
The subject will not engage in strenuous exercise on the day of study drug vaccination.
4. Alcohol intake  
The subject will not consume an excessive amount of alcohol on the day of study drug vaccination.
5. Bathing  
The subject can take a bath or shower. The subject should be careful not to excessively stimulate the vaccination site on the day of vaccination.
6. Contraception  
The potential effects of the study drug on pregnancy or on the health of the fetus/newborn child are unknown. Therefore, female subjects must consistently use two forms of highly effective birth control (at least one of which must be a barrier method) (refer to “3.2 Inclusion Criteria 6”) during the period from signing the informed consent form to completion of the primary study period or 28 days after the final study drug vaccination (whichever is longer), and male subjects and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting

- of two forms of birth control (at least one of which must be a barrier method) during the period from the initial study drug vaccination until 28 days after the final study drug vaccination.
7. Breastfeeding  
Female subjects must not breastfeed during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer).
  8. Donation of ova/sperm  
Female subjects must not donate ova during the primary study period or for 28 days after the final vaccination of the study drug (whichever period is longer).  
Male subjects must not donate sperm from the initial study drug vaccination until 28 days after the final vaccination of the study drug.
  9. Local/Systemic Reaction Survey Diary  
Subjects will make entries in the Local/Systemic Reaction Survey Diary every day from Day 1 until 14 days after the final vaccination of the study drug and bring it to the study site on each visit day.
  10. Symptoms Survey After Chamber Period Diary  
Subjects will make entries in the Symptoms Survey After Chamber Period Diary every day until 3 days after leaving the chamber and bring it to the study site on each visit day.
  11. Pollinosis Symptoms Survey Diary  
Subjects will make entries in the Pollinosis Symptoms Survey Diary every day from 01 Feb 2018 to 31 Mar 2018. After the survey of pollinosis symptoms is completed, the overall evaluation will be immediately conducted. Subjects will bring the diary with entries to the study site on each visit day.
  12. Contact of safety information to medical institutions  
If any SAEs occur during study participation (including long-term safety follow-up period), then subjects will contact the medical institution.
  13. Other  
Subjects will not engage in anything that may fall under any of the exclusion criteria.

## **5.2 Demographics and Baseline Characteristics**

### **5.2.1 Demographics**

The investigator or sub-investigator will investigate by a test and an interview regarding date of consent, age (at the time of consent), sex, height, and body weight at Screening visit 1 and enter in the eCRF.

### **5.2.2 Medical History**

Previous disease is defined as a disease that has been resolved by the time vaccination of the study drug starts, and concurrent disease is defined as a disease that persists at the time of the start of study drug vaccination. All concurrent diseases will be investigated and the diagnosis name will be recorded in the medical record or other source document and also entered in the

eCRF. Previous diseases will be confirmed based on the Inclusion Criteria and Exclusion Criteria but entry into eCRF will not be necessary.

The following items should be examined at Screening visit 1 and confirmed that they do not fall under the Exclusion Criteria.

- Immunological tests (HBs antigen, HCV antibody)
- Allergy test other than JRC (specific IgE antibody to alnus, Japanese white birch, ragweed, artemisia, cocksfoot, dermatophagoides farinae, dermatophagoides pteronyssinus, *Aspergillus*, *Candida*, *Alternaria*, house dust 1, house dust 2, cat dander, and dog dander)

### 5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

Information of the following will be obtained and recorded in the eCRF.

- Target disease, target disease period, overall evaluation of cedar pollinosis in 2017 (good [almost no symptoms], fairly good [mild], normal [moderate], slightly bad [severe], extremely bad [most severe])
- Symptoms score upon chamber evaluation at Screening visit 2 and evaluation date  
Chamber evaluation at Screening visit 2 will be conducted using the same exposure conditions as that in chamber evaluation for efficacy evaluation and evaluated using the same scoring (refer to “5.3.1 Nasal and Eye Symptoms During Chamber Period”).

JRC allergy test (specific IgE antibody against JRC) will be conducted at Screening visit 1 and Screening visit 3 and the test result will be obtained directly by an electronic file from the centralized testing company.

## 5.3 Efficacy Assessment

### 5.3.1 Nasal and Eye Symptoms During Chamber Period

With regard to nasal symptoms (sneezing, nasal discharge, nasal congestion, and itchy nose) and eye symptoms (itchy eyes and watery eyes) upon chamber evaluation at 4, 8, and 12 weeks after the final vaccination of the study drug (exposure to JRC pollens, 8,000/m<sup>3</sup>; exposure duration, 180 minutes). Subjects will use the following score for assessment every 15 minutes from before cedar pollen exposure until 180 minutes after cedar pollen exposure. Each symptom score at each time point and evaluation date will be entered in the eCRF.

- 0: None (no symptoms)
- 1: Mild (symptoms present but easily tolerated)
- 2: Moderate (awareness of symptoms; bothersome, but tolerable)
- 3: Severe (definite awareness of symptoms; difficult to tolerate, but does not interfere with the activities of daily living)
- 4: Very severe (difficult to tolerate and interferes with the activities of daily living)

In addition, nasal discharge amount (measured by weight of the tissue paper before and after use by subjects who are instructed to use pre-allocated tissues for blowing their nose) and sneezing count per 30 minutes will be measured during chamber exposure and the results and evaluation date will be entered in the eCRF.

### 5.3.2 Symptoms Survey After Chamber Period

A survey on nasal and eye symptoms until 3 days after leaving the chamber (day of chamber evaluation, 1, 2, and 3 days after leaving the chamber) will be conducted using the Symptoms Survey After Chamber Period Diary. Subjects will make a diary entry once every day using the symptoms score described in “5.3.1 Nasal and Eye Symptoms During Chamber Period” for evaluation. Each symptom score and evaluation date will be entered in the eCRF.

### 5.3.3 Pollinosis Symptoms Survey During 2018 JRC Pollen Dispersal Season

Targeting subjects who have completed the primary study period, the following items will be evaluated regarding pollinosis symptoms during the pollinosis symptoms survey period (01 Feb 2018–31 Mar 2018) using the Pollinosis Symptoms Survey Diary. Nasal and eye symptoms and troubles with daily life will be determined based on “12.3 Classification of Severity of Pollinosis Symptoms.” JRQLQ No 1 will be entered every 2 weeks during the pollinosis symptoms survey period (at the start of survey, 2, 4, and 6 weeks after the start of survey, and at the end of survey) for a total of 5 times. With regard to the following items, entries will be made into the eCRF. With regard to the use status of drugs other than rescue drugs, only information on prohibited medication will be entered into the eCRF.

- Nasal symptoms: Sneezing, nasal discharge, and nasal congestion, each graded with a 5-level score of 0, 1, 2, 3, and 4.
- Eye symptoms: Itchy eyes and watery eyes, each graded with a 4-level score of 0, 1, 2, and 3.
- Troubles with daily life: 5-level score of 0, 1, 2, 3, and 4.
- Rescue drug use status: Use/no use, drug name, administration route, use amount
- Use status of drugs other than rescue drugs: Use/no use, drug name, administration route, use amount
- Use status of items to physically shield from JRC pollen: Use/no use, therapy name, use status (outdoor/indoor)
- Movement status to areas outside the Kanto region: Movement/no movement, area of movement
- JRQLQ No 1
- Overall evaluation by the subject: With regard to the overall evaluation of symptoms during the pollinosis symptoms survey period, evaluation will be conducted in 5 levels (good [almost no symptoms], fairly good [mild], normal [moderate], slightly bad [severe], and extremely bad [most severe]) after the end of the pollinosis symptoms survey period.

Furthermore, data on the JRC pollen dispersal amount that is publicized after the end of the JRC pollen dispersal season in 2018 will be obtained and used for analysis of efficacy evaluation of the pollinosis symptoms survey period.

## **5.4 Safety Assessment**

### **5.4.1 Adverse Events**

#### **5.4.1.1 Adverse Events (Primary Study Period)**

The survey period for AEs will be from obtaining informed consent until the end of the final observation of the primary study period. Nasal and eye symptoms induced by cedar pollen exposure in the chamber will be separately collected as efficacy endpoints and not considered as AEs.

Refer to “5.5 Adverse Events and Other Safety Aspects” regarding information on collection of AEs and data handling.

#### **5.4.1.2 Adverse Events (Long-term Safety Follow-up Period)**

Long-term safety of ASP4070 will be investigated for 9 months from the last observation in the primary study period (for 12 months from the final vaccination of the study drug). If SAEs occur, then the subject will contact the study site. With regard to subjects who have discontinued the study during the primary study period, if the study drug had been vaccinated even once, then safety information (SAEs) will be collected for 1 year after the final vaccination. SAEs will be assessed in accordance with Section “5.5.2 Definition of Serious Adverse Events (SAEs).” Even if there is no contact from the subject, in principle, the subject will be asked about the occurrence of SAEs at 6 months and 12 months after the final vaccination of the study drug either when the subject visits the study site or by phone.

### **5.4.2 Local/Systemic Reaction Survey Diary**

The Local/Systemic Reaction Survey Diary will be used to survey the following designated items occurring from the date of study drug vaccination until 14 days after vaccination. Subjects will make an entry into the diary every day.

- Local reactions: Pain, tenderness, erythema/redness, and induration/swelling
- Systemic reactions: Nausea/vomiting, diarrhea, headache, fatigue, and myalgia

### **5.4.3 Vital Signs**

Axillary body temperature, sitting blood pressure, and sitting pulse rate at rest will be measured on each assessment day. See “Table 1: Schedule of Assessments” for the day of conducting the assessments. The measurement results and measurement date will be recorded in the eCRF.

#### 5.4.4 Laboratory Assessments

Laboratory Assessments items to be conducted during the study are as follows. See “Table 1: Schedule of Assessments” for the day of conducting the assessments. Measurements will be conducted at the study site.

1. Hematology test, blood biochemistry test, and urinalysis  
Test results will be obtained by an electronic file. The clinical significance of any laboratory assessments results that are outside the reference range will be determined and recorded by the investigator or sub-investigator.
  - Hematology  
Hb, Ht, RBC, WBC, differential leukocyte count (neutrophil, lymphocyte, monocyte, eosinophil, and basophil), PLT
  - Blood biochemistry  
TP, ALB, AST, ALT,  $\gamma$ -GTP, ALP, LDH, UA, T-Bil, BUN, Cre, CK, CRP (quantitative), Na, K, Cl, T-Cho, TG
  - Urinalysis  
Protein, glucose, occult blood, urobilinogen
2. Pregnancy test (urine, only female subjects)  
The pregnancy test is not necessary for subjects who are post-menopausal (defined as at least 1 year without any menses) prior to Screening visit 1 or subjects who are surgically sterile or have had hysterectomy or oophorectomy, and the possibility of pregnancy can be negated. The test results and testing date will be entered in the eCRF.

#### 5.4.5 Physical Examination

The following will be assessed or examined. See “Table 1: Schedule of Assessments” for the day of conducting the assessments.

1. Subjective symptoms  
The investigator, sub-investigator, or study coordinator will confirm subjective symptoms of the subject. The subject will report any “subjective symptom” that occurs during the primary study period to the investigator, sub-investigator, or study coordinator.
2. Objective findings  
The investigator or sub-investigator will interview and/or examine the subject as much as possible at visit or when a subjective symptom is reported by the subject.

Upon entry into the chamber, the investigator or sub-investigator will comprehensively determine whether there are any problems related to safety or whether there are any clinical symptoms that may affect pollinosis symptom evaluation from the subject’s subjective symptoms and objective findings.

#### 5.4.6 Electrocardiogram (ECG)

The investigator or sub-investigator will analyze the 12-lead ECG data and determine which of the following should be categorized: “Normal,” “clinically insignificantly abnormal,” or

“clinically significantly abnormal.” See “Table 1: Schedule of Assessments” for the day of conducting the assessments. The dates and results of measurements will be entered in the eCRF. If ECG data are assessed as “clinically insignificantly abnormal” or “clinically significantly abnormal,” then details of the abnormality will be entered in the eCRF.

## **5.5 Adverse Events and Other Safety Aspects**

### **5.5.1 Definition of Adverse Events (AEs)**

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

To identify all events that may be related to the procedures of the study and therefore require a change in study conduct, even if the subject has not received the drug, API will collect information on AEs. The collection of AEs will start when written consent is obtained and will be conducted until the completion of the last observation of the primary study period.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

Based on the entries in the Local/Systemic Reaction Survey Diary, if the investigator or sub-investigator examines the subject and determines that the following items occurred from the date of study drug vaccination until 14 days after vaccination and a relationship with the study drug cannot be negated, then it will be evaluated as a local/systemic reaction at the vaccination site.

- Local reactions: Pain, tenderness, erythema/redness, and induration/swelling
- Systemic reactions: Nausea/vomiting, diarrhoea, headache, fatigue, and myalgia

With regard to AEs observed after obtaining informed consent until starting the first vaccination of the study drug, the event name, date of onset, timing, seriousness, severity, date of resolution, and outcome will be recorded in the eCRF.

With regard to AEs observed after starting the first vaccination of the study drug, the event name, presence/absence of local/systemic reaction, category of local/systemic reaction (if present), date of onset, timing, seriousness, severity, action(s) taken, date of resolution, outcome, causality with study drug/intradermal injection device, and reason for causality

assessment will be investigated and recorded in the eCRF. With regard to local reactions, the number of sites and timing of study drug vaccination that triggered the onset will be recorded in the eCRF.

Seriousness (serious or non-serious), causal relationship to the study drug (not related, possible, probable), and severity (mild, moderate, severe, life-threatening) will be assessed in accordance with Sections “5.5.2 Definition of Serious Adverse Events (SAEs),” “5.5.3 Criteria for Causal Relationship to the Study Drug/Intradermal Injection Device,” and “5.5.4 Criteria for Defining the Severity of an Adverse Event,” respectively.

If a diagnosis is made from the signs and/or symptoms, then the diagnosis should be recorded in preference to the listing of individual signs and symptoms. If a diagnosis is not made from the signs and/or symptoms, then the investigator or sub-investigator should record each sign and symptom as an individual AE. An AE that recurs after resolution or an AE that worsens in severity will be handled as a new AE.

Nasal and eye symptoms induced by cedar pollen exposure in the chamber will be separately collected as efficacy endpoints and will be not considered as AEs.

### **5.5.2 Definition of Serious Adverse Events (SAEs)**

An adverse event is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.



Any AE that falls under the criteria presented in Section “12.4 Events That Should Be Handled as Serious Adverse Events” should be handled as an SAE and reported in accordance with Section “5.5.5 Reporting of Serious Adverse Events (SAEs).” Additional information may be required.

### 5.5.3 Criteria for Causal Relationship to the Study Drug/Intradermal Injection Device

Adverse events that fall under either “Possible” or “Probable” should be defined as “adverse events whose relationship to the study drugs could not be ruled out” or “adverse events whose relationship with the intradermal injection device could not be ruled out.”

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

### 5.5.4 Criteria for Defining the Severity of an Adverse Event

Local reactions (pain, tenderness, erythema/redness, and induration/swelling) and systemic reactions (nausea/vomiting, diarrhoea, headache, fatigue, and myalgia) will be graded by reference to Sections “12.1 Classification of Severity of Local Reactions at Vaccination Site” and “12.2 Classification of Severity of Systemic Reactions.”

Severity of other AEs will be assessed according to the following four levels:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities
- Life-threatening: Necessity for urgent intervention

### 5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator or sub-investigator must report to the head of the study site and must contact the Sponsor/delegated CRO by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the Sponsor/delegated CRO by fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the Sponsor/delegated CRO should be informed by phone.

Contact information for the Sponsor:

[REDACTED], Astellas Pharma Inc.

Fax: [REDACTED]

Phone No.: [REDACTED]

Contact information for the delegated CRO:

[REDACTED]

Fax: [REDACTED]

### 5.5.6 Follow-up of Adverse Events

All AEs occurring after the initial study drug vaccination and all SAEs occurring during the long-term safety follow-up period are to be followed up by the investigator or sub-investigator until resolved or judged to be no longer clinically significant, or until they are clearly determined as chronic.

Even if the subject does not return to normal or level before study drug administration, the follow-up can be considered unnecessary or completed when the investigator or sub-investigator deems the follow-up as unnecessary or completed and the reason is appropriately entered in the source reference material.

### 5.5.7 Procedure in Case of Pregnancy

If a female subject becomes pregnant during the primary study period after the completion of the initial study drug vaccination or for 28 days after the final study drug vaccination (whichever is later), or the partner of a male subject becomes pregnant during the period from the completion of the final vaccination to 28 days after the final study drug vaccination, the investigator should report the information to the Sponsor/delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- “Spontaneous abortion” includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as “possible” by the investigator
- In the case of a delivery of a living newborn, the “normality” of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

#### **5.5.8 Emergency Procedures and Management of Overdose**

If any symptom occurs due to ASP4070 overdose, then the investigator or sub-investigator will provide the subject with emergency care or general maintenance therapy depending on the symptom severity and perform appropriate examinations, such as vital signs, 12-lead ECG, and laboratory tests, to ensure the safety of the subject. These are only supportive measures, because there are no established ASP4070 overdose management methods.

#### **5.5.9 Supply of New Information Affecting the Conduct of the Study**

1. When information is obtained regarding serious and unexpected adverse drug reactions that are specified in Article 273 of the Enforcement Regulations of the Pharmaceutical Affairs Law, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the Sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with “8.2.3.4 Supply of New and Important Information Influencing the Subject’s Consent and Revision of the Written Information.”
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator’s Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

### **5.5.10 Deviations From the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects**

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

## **5.6 Test Drug Concentration**

Not applicable

## **5.7 Other Measurements, Assessments or Methods**

### **5.7.1 Immune Response Assessment (Parameters)**

The following parameters will be measured to confirm the immune response to ASP4070. Appropriate markers will be evaluated in an exploratory manner. See “Table 1: Schedule of Assessments” for the day of conducting the assessments. Measurement will be conducted at the centralized testing company and the date of blood sampling will be entered in the eCRF. The test result will be obtained directly by an electronic file from the centralized testing company after code breaking.

BAT will be performed only if blood is sampled at a time/day when sample processing is possible. If blood sampling for BAT is not conducted on Day 1, then sampling for BAT will not be subsequently required.

See “Table 1: Schedule of Assessments” for the time point of the additional test. The test result will be obtained directly by an electronic file from the centralized testing company.

[Primary study period]

- IgG antibody, specific IgG antibody(anti-JRC, anti-Cry j 1, anti-Cry j 2), specific IgG4 antibody (anti-JRC), IgE antibody , specific IgE antibody (anti-JRC), anti-LAMP antibody, basophil activation test (BAT)

[Additional test]

- Specific IgE antibody (anti-JRC), basophil activation test (BAT)

### **5.7.2 Objective of Secondary Data Analysis**

- Blood sampling for Secondary Data Analysis (SDA) will be conducted only if the content of analysis has been approved by the study site. The procedures described in Sections “5.7.2.1 Sampling and Storage of Secondary Data Analysis Samples,” “5.7.2.2 Disposal of Secondary Data Analysis Samples,” “5.7.2.3 Disclosure of Secondary Data Analysis Results,” “8.2 Ethics and Protection of Subject Confidentiality,” and “8.3 Administrative Matters” will be followed.
- To conduct research on the action mechanism of the study drug against cedar pollinosis and measurement/analysis of exploratory biomarkers related to efficacy/safety evaluation, biological samples will be stored for a maximum of 2 years.

#### **5.7.2.1 Sampling and Storage of Secondary Data Analysis Samples**

Blood will be sampled at a time/day when sample processing is possible from those among subjects participating in the study who have provided written consent to collect and store blood samples for SDA. The date of consent and that of blood sampling for each subject will be fully recorded and entered in the eCRF. The investigator, sub-investigator, or study coordinator will take 19 mL of peripheral blood from the brachial vein three times during the study period (Day 1, Day 127, and Day 183) using a storage tube and a portion will be stored frozen at  $-80^{\circ}\text{C}$  and the remainder stored at room temperature until the sample is collected from the study site. The sample collection/delivery institution will collect blood samples for SDA, temporarily store the samples frozen, and later deliver to the [REDACTED], which is the Secondary Data Analysis sample storage institution. The Secondary Data Analysis sample storage institution will receive the sampled blood and keep the samples frozen until analysis. However, the storage period of blood samples will be a maximum of 2 years after data are locked.

Anonymization of the sample: SDA in this study will anonymize the samples by a single code. The study site will allocate subject identification codes.

#### **5.7.2.2 Disposal of Secondary Data Analysis Samples**

When the storage period of the sample has ended, the investigator, sub-investigator, or study coordinator has received contact from the subject to withdraw consent to SDA, or the Sponsor has decided to dispose of the stored samples, the label on the sample tube from the relevant subjects will be immediately taken off and the Secondary Data Analysis sample storage institution will appropriately dispose of the sample. If SDA is conducted before the end of the storage period or withdrawal of consent, then data obtained from analysis will not be disposed.

#### **5.7.2.3 Disclosure of Secondary Data Analysis Results**

This study is exploratory and the results obtained from a biomarker research are considered as lacking in precision and reliability. Therefore, the results of this study will not be disclosed by the Sponsor to subjects and study sites.

### **5.7.3 Objective of Pharmacogenomics Research**

- Blood sampling for pharmacogenomics research will be conducted only if the content of analysis has been approved by the study site. Follow the procedures in Sections “5.7.3.1 Sampling and Storage of Pharmacogenomics Sample,” “5.7.3.2 Disposal of Pharmacogenomics Sample,” “5.7.3.3 Disclosure of Genetic Information,” “8.2 Ethics and Protection of Subject Confidentiality,” and “8.3 Administrative Matters.”
- With regard to preparation for future studies on the efficacy or safety and the relationship with genomes/genes related to this test drug, the biological samples will be stored for a maximum of 15 years.
- Biological samples will be collected and stored to enable exploratory research markers that predict drug response (efficacy and toxicity [adverse reactions]) by comprehensive analysis of genetic information from this clinical study and other clinical studies using this test drug in the future.
- Genomic/gene analysis samples may be sampled to explore markers related to the occurrence of an adverse reaction if any serious adverse reactions are observed.

#### **5.7.3.1 Sampling and Storage of Pharmacogenomics Sample**

Blood will be sampled from those among subjects participating in the study who have provided written consent to collect and store blood samples for pharmacogenomics research. The investigator, sub-investigator, or study coordinator will take 5 mL of peripheral blood from the brachial vein one time between Day 1 and Day 183 using a storage tube and it will be stored at 4°C until the sample is collected from the study site. The date of consent and that of blood sampling for each subject will be fully recorded and entered in the eCRF. The sample collection/delivery institution will collect blood samples for pharmacogenomics research, temporarily store the samples frozen (approximately –20°C or lower), and deliver to the pharmacogenomics sample storage institution. The pharmacogenomics sample storage institution will receive the sampled blood and keep the samples frozen (approximately –80°C) until analysis in the future. However, the storage period of blood samples will be a maximum of 15 years after data are locked.

Anonymization of the sample: Pharmacogenomics research in this study will anonymize the samples by a single code. The study site will allocate subject identification codes.

#### **5.7.3.2 Disposal of Pharmacogenomics Sample**

When the storage period of the sample has ended, the investigator, sub-investigator, or study coordinator has received contact from the subject to withdraw consent to pharmacogenomics research, or the Sponsor has decided to dispose of the stored samples, the label on the sample tube from the relevant subjects will be immediately taken off and the pharmacogenomics sample storage institution will appropriately dispose of the sample. If genomic/gene analysis is conducted before the end of the storage period or withdrawal of consent, data obtained from analysis will not be disposed.

### 5.7.3.3 Disclosure of Genetic Information

Even if pharmacogenomics research is conducted in the future, this study is exploratory and gene analysis results (gene measurement results, relationship between genes and drug response) are considered as lacking in precision and reliability. Therefore, in principle, the results of gene analysis will not be disclosed by the Sponsor to subjects and study sites.

## 5.8 Total Amount of Blood

The amount of blood to be collected in the study is as follows. Blood will be collected as needed if a follow-up of clinical laboratory values becomes necessary.

[Primary study period]

Test item	Amount of blood per draw (mL)	Frequency	Total amount of blood (mL)
Hematology	2	6	12
Blood biochemistry	6	6	36
Immunological tests	3	1	3
JRC allergy test	2	1	2
JRC allergy test Allergy test other than JRC	6	1	6
Parameters <sup>1)</sup>	14	5	70
Total			129

- If consent for pharmacogenomics research is obtained, then a further 5 mL will be sampled one time between Day 1 and Day 183.
- If consent for SDA is obtained, then a further 19 mL each will be sampled on Day 1, Day 127, and Day 183.
- If blood sampling for BAT is not conducted during the primary study period, blood sampling for the parameters will be 12 mL each time.
- Reserve subjects will participate up to Screening visit 3, and the total amount of blood will be 27 mL.

1) IgG antibody, specific IgG antibody (anti-JRC, anti-Cry j 1, anti-Cry j 2), specific IgG4 antibody (anti-JRC), IgE antibody, specific IgE antibody (anti-JRC), anti-LAMP antibody, basophil activation test (BAT)

[Additional study period]

Test item	Amount of blood per draw (mL)	Frequency	Total amount of blood (mL)
Parameters <sup>2)</sup>	4	1	4
Total			4

- 2) Specific IgE antibody (anti-JRC), basophil activation test (BAT)

## **5.9 Phase II Second-Year Follow-up Study (4070-CL-0021)**

To preliminarily collect information regarding the continued effect until the subsequent year and necessity for additional vaccinations in the subsequent year, and to collect safety data on subjects who are vaccinated for multiple years, a second-year, follow-up study is scheduled.

In the second-year, follow-up study, subjects who have been allocated to the optimal dose group (ASP4070 4 mg group or 1 mg group) or placebo group in the study, completed the primary study period and also provided consent to participate in the second-year, follow-up study will be the target for one additional vaccination approximately one year after the final vaccination of this study. After obtaining consent for the second-year, follow-up study, chamber evaluation once before and after the study drug vaccination is scheduled to be conducted.

## **6 DISCONTINUATION**

### **6.1 Discontinuation of Individual Subject(s)**

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

#### **Discontinuation Criteria for Individual Subjects**

1. Adverse events
  - It is considered difficult for the subject to continue to participate in the study due to an AE.
2. Consent withdrawal
  - Subject withdraws consent for further treatment.
3. Lost to follow-up
  - Subject is lost to follow-up due to the subject's personal reasons, such as moving away from the study site and busyness.
  - Subject is lost to follow-up due to discontinuation of visits (or due to being unable to reach by any means).



4. Protocol deviation
  - Subject is found after vaccination to have been deviated from the inclusion/exclusion criteria and is judged unsuitable for further participation in the study.
  - Another serious deviation from the protocol is found.
5. Death
  - Subject died.
6. Other
  - Subject is judged by the investigator or sub-investigator to be unsuitable for further participation in the study or a request is made by the Sponsor to discontinue study treatment due to safety reasons.

## **6.2 Discontinuation of the Site**

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor and the head of the study site.

## **6.3 Discontinuation of the Study**

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

# **7 STATISTICAL METHODOLOGY**

The statistical analysis will be coordinated by the responsible biostatistician of the Sponsor. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings, and figures to be produced. The SAP for the primary study period will be finalized before code breaking at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR). A separate SAP will be written for the pollinosis symptoms survey period during the pollen dispersal season and additional study period.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

## **7.1 Sample Size**

A total of 150 subjects, with 50 study drug vaccination subjects in each group

[Rationale]

The number of subjects required for 80% probability of detecting superiority of the ASP4070 group over the placebo group was calculated. Among the study results of other drugs targeting patients with cedar pollinosis using a chamber, studies with published data that allow the effect size to be calculated were confirmed and the effect size was 0.668<sup>a)</sup>, 0.903<sup>b)</sup>, and 0.962<sup>c)</sup> for bilastine [Hashiguchi et al., 2017], montelukast [Hashiguchi et al., 2012], and levocetirizine [Hashiguchi et al., 2013], respectively. Based on these effect sizes, with regard to the effect on the primary endpoint, the change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS) during 120 to 180 minutes after entering the chamber to the score before cedar pollen exposure, the effect size of ASP4070 was assumed to be 0.650. Using the significance level of the test to be 5% two-sided, when a hierarchical procedure is used for comparison with the placebo group in the order of high-dose group to low-dose group, if the effect size 0.650 is the same for the low-dose group as for the high-dose group, then the probability of detecting superiority of the low-dose group against the placebo group was calculated by simulation. Assuming the standard deviation to be 1, as a result of 10,000 simulations, the number of subjects required to ensure a detection power of over 80% was 48 subjects. Considering dropout cases, the number of subjects in each group was set to 50 subjects and 150 subjects in total.

- a) With regard to the total 4 nasal symptom score (sneezing, nasal discharge, nasal congestion, and itchy nose) from 0 to 240 minutes after entering the environmental exposure chamber on Day 2 of administration, the mean for the bilastine 20 mg group and placebo group was 84.4 and 109.5, respectively, the standard deviation was 33.0 and 41.6, respectively, and the effect size was 0.668.
- b) With regard to the mean of the total 3 nasal symptom score (sneezing, nasal discharge, and nasal congestion) from 120 to 180 minutes after entering the environmental exposure chamber, the mean of the montelukast 7 days group and placebo group was 2.31 and 3.17, respectively, the standard deviation was 0.17 and 0.20, respectively, and the effect size was 0.903.
- c) With regard to the AUC of the total 4 nasal symptom score (sneezing, nasal discharge, nasal congestion, itchy nose) from 0 to 180 minutes after entering the environmental exposure chamber, the mean of the levocetirizine single agent group and placebo group was 16.78 and 31.35, respectively, the standard deviation was 14.01 and 16.21, respectively, and the effect size was 0.962.

## 7.2 Analysis Set

The following policies will apply to analysis sets in principle, but allocation of subjects to analysis sets will be determined in the Classification Meeting by reference to opinions or advice of medical experts as needed.

### 7.2.1 Full Analysis Set (FAS)

The full analysis set will consist of all subjects who are randomized, are vaccinated with the study drug at least once, and have at least one measurement for efficacy evaluation obtained after vaccination of the study drug. This is the primary analysis set for efficacy analyses.

### **7.2.2 Per Protocol Set (PPS)**

The per protocol set will consist of the subset of the FAS who do not meet criteria for the following PPS exclusion.

- Violates Inclusion Criteria
- Falls under Exclusion Criteria
- Has not completed all the specified vaccinations
- Has not been evaluated for efficacy on Day 183
- Use of prohibited concomitant drug or non-medication therapy during the primary study period, which may affect efficacy evaluation
- Other significant protocol deviation

### **7.2.3 Safety Analysis Set (SAF)**

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who are vaccinated with the study drug at least once.

### **7.2.4 Immunological Analysis Set (IAS)**

#### **7.2.4.1 IAS**

The immunological analysis set will consist of all subjects who are randomized, are vaccinated with the study drug at least once, and have at least one measurement for immunological response endpoint after vaccination of the study drug.

#### **7.2.4.2 IAS-2**

The immunological analysis set 2 (IAS-2) will consist of subjects who have provided additional consent for the additional test and have at least one measurement for immunological response endpoint during the additional study period.

### **7.2.5 Pollinosis Symptom Analysis Set (PSAS)**

The Pollinosis Symptom Analysis Set will consist of all subjects who are randomized, are vaccinated with the study drug at least once, and have at least one measurement for an endpoint on pollinosis symptoms during the pollen dispersal season after vaccination of the study drug.

## **7.3 Demographics and Other Baseline Characteristics**

Demographics and other baseline characteristics will be summarized by treatment group for the FAS, PPS, SAF, IAS, and PSAS. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

## 7.4 Analysis of Efficacy

The primary efficacy endpoint and secondary endpoints will be analyzed for the FAS and PPS. The results of statistical tests will be interpreted based on the FAS. The PPS will be used to assess the robustness of statistical test results based on the FAS.

Analysis of Other Efficacy Endpoints will be conducted for the PSAS.

### 7.4.1 Analysis of Primary Endpoint

#### 7.4.1.1 Primary Analysis

The FAS will be used for primary analysis. With regard to the change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score (3TNSS) during 120 to 180 minutes after start of cedar pollen exposure as compared to the score before cedar pollen exposure, the difference in the adjusted mean between each active drug group and the placebo group on Day 183, two-sided 95% confidence interval and two-sided P value will be calculated using a mixed model for repeated measures assuming an unstructured covariance structure within subjects with explanatory variables being the vaccination group (ASP4070 4 mg, ASP4070 1 mg, and placebo), evaluation time (Day 127, Day 155, and Day 183), “Class from results of Japanese red cedar (JRC) pollen-specific IgE antibody test performed at Screening visit 1,” “Change in the mean of total 3 nasal symptom (sneezing, nasal discharge, and nasal congestion) score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2,” and interaction of the vaccination group and evaluation time.

With the significance level of the test to be 5% two-sided, the test will be conducted using hierarchical procedures in the following order:

1. Comparison between the ASP4070 4 mg group and placebo group
2. Comparison between the ASP4070 1 mg group and placebo group

#### 7.4.1.2 Secondary Analysis

- Analysis that is the same as the analysis of primary endpoints described in “7.4.1.1 Primary Analysis” will be conducted for the PPS.
- Using the FAS and PPS, the summary statistics on the actual measured value and change from baseline for each evaluation time by vaccination group will be calculated.
- Using the FAS and PPS, based on the mixed model for repeated measures described in “7.4.1.1 Primary Analysis,” the difference in the adjusted mean between each active drug group and the placebo group and two-sided 95% confidence interval will be calculated on Day 127 and Day 155.
- Using the FAS and PPS, line plots for the mean for each evaluation time will be created.
- Using the FAS and PPS, individual line plots for the actual measured value and change from baseline will be created.

#### 7.4.1.3 Subgroup Analysis

Exploratory subgroup analysis on baseline values, such as demographics and nasal and eye symptoms, will be conducted.

#### 7.4.2 Analysis of Secondary Endpoints

Analysis of secondary endpoints will be conducted for the FAS and PPS.

1. Total 3 nasal symptom score (3TNSS), total 4 nasal symptom score (4TNSS), individual nasal symptom score, total non-nasal symptom score (TNNSS), individual eye symptom score, and total symptom score (TSS) for every 15 minutes
  - Summary statistics by vaccination group will be calculated for the actual measured value every 15 minutes and change from the score prior to cedar pollen exposure will be calculated.
  - Line plots for the mean will be created.
  - Individual line plots will be created.
2. Change in the mean of the following scores during 120 to 180 minutes after start of cedar pollen exposure as compared to the score before cedar pollen exposure: total 4 nasal symptom score (4TNSS), individual nasal symptom score, total non-nasal symptom score (TNNSS), individual eye symptom score, and total symptom score (TSS)
  - Summary statistics by vaccination group will be calculated for the actual measured value and change from baseline for each evaluation period.
  - The difference in the adjusted mean between each active drug group and the placebo group and two-sided 95% confidence interval will be calculated for each evaluation time using a mixed model for repeated measures assuming an unstructured covariance structure within subjects with explanatory variables being the vaccination group, evaluation time, “Class from results of Japanese red cedar (JRC) pollen-specific IgE antibody test conducted at Screening visit 1,” “Change in the mean score during 120 to 180 minutes after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure at Screening visit 2,” and interaction of the vaccination group and evaluation time.
  - Line plots for the mean will be created for each evaluation time.
  - Individual line plots for the actual measured value and change from baseline will be created.
3. Change in the mean of the following scores during 15 to 180 minutes after start of cedar pollen exposure as compared to the score before cedar pollen exposure: total 3 nasal symptom score (3TNSS), total 4 nasal symptom score (4TNSS), individual nasal symptom score, total non-nasal symptom score (TNNSS), individual eye symptom score, and total symptom score (TSS)
  - Summary statistics by vaccination group will be calculated for the actual measured value and change from baseline for each evaluation time.
  - Line plots for the mean will be created for each evaluation period.

- Individual line plots for the actual measured value and change from baseline will be created.
- 4. Time to the occurrence of nasal or eye symptoms from start of cedar pollen exposure in the chamber
  - 25, 50, 75 percentile of the predicted value and their 95% confidence interval will be calculated by the Kaplan–Meier method. If no symptoms occur, then the evaluation will be censored at 180 minutes.
  - A Kaplan–Meier plot value will be created.
- 5. Nasal discharge amount and sneezing count per 30 minutes during chamber exposure
  - Summary statistics of the actual measurement value at every 30 minutes will be calculated for each evaluation time.
  - Number of subjects and percentage by severity at every 30 minutes will be calculated for each evaluation time.
  - Line plots for the mean will be created.
  - Individual line plots will be created.

#### **7.4.3 Other Efficacy Endpoints Analysis**

Analysis of pollinosis symptoms during the JRC pollen dispersal season in 2018 will be conducted for the PSAS.

- Summary statistics of the mean of individual symptom score and daily activity interference score will be calculated for each evaluation time.
- Line plots of the mean of individual symptom score and daily activity interference score will be calculated.
- Individual line plots of individual symptom score and daily activity interference score will be calculated.
- A frequency table of JRQLQ No 1 will be prepared.
- A frequency table of overall evaluation will be prepared.

The transition of JRC pollen dispersal amount will be displayed together in line plots.

#### **7.5 Analysis of Immunological Response**

Analysis of immunological response will be conducted for the IAS or IAS-2.

- Summary statistics of the actual measured value and change from the baseline for continuous variables will be calculated for each evaluation time.
- Frequency tables of continuous variables will be prepared for each evaluation time.
- Individual line plots of the actual measured value and change from the baseline for continuous variables will be calculated.

#### **7.6 Analysis of Safety**

Analysis of safety will be conducted for the SAF.

### **7.6.1 Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and vaccination group. The number and percentage of AEs by severity will also be calculated. All AEs will be listed.

### **7.6.2 Local Reaction and Systemic Reaction**

The number of occurrences of, and number and percentage of subjects with designated local reactions and systemic reactions will be summarized by symptom and vaccination group. The number of occurrences of, and number and percentage with subjects of designated local reactions and systemic reactions by severity will be calculated.

### **7.6.3 Laboratory Assessments**

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by vaccination group and evaluation time. Shifts relative to normal ranges from baseline to each evaluation time during treatment period in lab tests will also be tabulated.

### **7.6.4 Vital Signs**

Descriptive statistics will be used to summarize vital sign results and changes from baseline by vaccination group and evaluation time.

### **7.6.5 ECGs**

The 12-lead ECG results will be summarized by vaccination group and evaluation time.

## **7.7 Analysis of Pharmacokinetics**

Not applicable

## **7.8 Other Analyses**

### **7.8.1 Secondary Data Analysis**

SDA related to the action mechanism of the test drug against cedar pollinosis and efficacy/safety evaluation is scheduled to be conducted, but the content of analysis is not yet determined. The Sponsor will start the research when a specific content is determined. At that time, prior to the implementation of the research, the Sponsor will prepare a research plan for review by the Sponsor's ethical review board for whether it is appropriate or not for research implementation from the ethical and scientific viewpoint and obtain approval.

### **7.8.2 Analysis of Pharmacogenomics Data**

At present, the content of analysis for pharmacogenomics investigation is not yet determined. In the future, there is a possibility of exploratory investigation to determine whether there is a relationship between genetic analysis results and results of the study (clinical information: e.g., pharmacological activity, toxicity). The Sponsor will start the research when a specific content is determined. At that time, prior to the implementation of the research, the Sponsor will prepare a research plan (disposal method of reference material and timing) for review by the Sponsor's ethical review board for whether it is appropriate or not for research implementation from the ethical and scientific viewpoint and obtain approval.

### **7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)**

No formal interim analysis is planned.

### **7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information**

Final analytical handling of missing data, outliers, and analysis time points will be determined before database hard lock, considering the opinions and advice of medical experts as needed. Subjects or values excluded from analyses will be presented in the listing of individual values but will be excluded in the summarization, such as summary statistics.

#### **7.10.1 Time Points for Primary Study Period**

The acceptable time ranges for the time points for analysis are as follows. The day of the first vaccination of the study drug is defined as Day 1 and the day before the first vaccination is defined as Day -1. If multiple data are obtained at the same time point, then data obtained on the closest day to the scheduled day will be used for analysis. If data are present before and after the scheduled day with the same day difference, then data obtained after the scheduled day will be used for analysis.



[Vital Signs (Axillary body temperature, sitting blood pressure, and sitting pulse rate)]

Timing	Scheduled day	Acceptable range
Screening visit 1	Date of informed consent	After date of informed consent until the day before Screening visit 2
Screening visit 2	Visit date of Screening visit 2	After Screening visit 2 until –21 day of Screening visit 3
Screening visit 3	28 days from Screening visit 2	28 days $\pm$ 7 days from Screening visit 2 and also until Day 1 – 7 days
Day 1	Day 1	Until before study drug vaccination on Day 1
Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99	Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, Day 99	Within $\pm$ 3 days of the scheduled day*
Day 127, Day 155, Day 183	Day 127, Day 155, Day 183	Within $\pm$ 7 days of the scheduled day

\*: If the study drug is vaccinated, then data before study drug vaccination will be used.

[Hematology test, blood biochemistry test, and urinalysis]

Timing	Scheduled day	Acceptable range
Screening visit 1	Date of informed consent	After date of informed consent until the day before Screening visit 2
Screening visit 3	28 days from Screening visit 2	28 days $\pm$ 7 days from Screening visit 2 and also until Day 1 – 7 days
Day 1	Day 1	Until before study drug vaccination on Day 1
Day 57	Day 57	Within $\pm$ 3 days of the scheduled day*
Day 127, Day 183	Day 127, Day 183	Within $\pm$ 7 days of the scheduled day

\*: If the study drug is vaccinated, then data before study drug vaccination will be used.

[12-lead electrocardiogram]

Timing	Scheduled day	Acceptable range
Screening visit 1	Date of informed consent	After date of informed consent until the day before Screening visit 2
Day 1	Day 1	Until before study drug vaccination on Day 1
Day 127, Day 183	Day 127, Day 183	Within $\pm$ 7 days of the scheduled day

[Parameters]

Timing	Scheduled day	Acceptable range
Day 1	Day 1	Until before study drug vaccination on Day 1
Day 57	Day 57	Within $\pm$ 3 days of the scheduled day*
Day 127, Day 155, Day 183	Day 127, Day 155, Day 183	Within $\pm$ 7 days of the scheduled day

\*: If the study drug is vaccinated, then data before study drug vaccination will be used.

[Evaluation in chamber]

Timing	Scheduled day	Acceptable range
Screening visit 2	Visit date for Screening visit 2	After Screening visit 2 until –21 day of Screening visit 3
Day 127, Day 155, Day 183	Day 127, Day 155, Day 183	Within $\pm 7$ days of the scheduled day

### 7.10.2 Time Points for Pollinosis Symptoms Survey Period and Additional Study Period

[Pollinosis symptoms during the JRC pollen dispersal season]

Time points to evaluate pollinosis symptoms during the JRC pollen dispersal season in 2018 will be determined before database hard lock, based on data, such as the collected symptom scores and data of JRC pollen dispersal amount.

[Parameters]

The acceptable time ranges for the time points for analysis are as follows.

Timing	Scheduled day	Acceptable range
Additional test	16 May 2018	From 01 May 2018 until 31 May 2018

## 8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

### 8.1 Procedure for Clinical Study Quality Control

#### 8.1.1 Data Collection

##### 8.1.1.1 Case Report Form

The investigator, sub-investigator, or study coordinator will use the Electronic Data Capture (EDC) system for data entry.

The investigator, sub-investigator, or study coordinator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. The source documents should be appropriately maintained at the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Hematology test, blood biochemistry test and urinalysis, pregnancy test, and immunological tests will be performed at the study site, and JRC allergy test, allergy tests other than JRC, and parameter measurements will be performed at the centralized testing company. [REDACTED] of API will electronically obtain the results of the hematology test, blood biochemistry test, and urinalysis from the study site and JRC allergy test and parameter measurements from the centralized testing company at a pre-determined time. The test result is obtained by an electronic file from the centralized testing company at the pre-determined time.

With regard to subjects who drop out before the initial study drug vaccination, the minimum demographics (sex, age, and informed consent date), AEs, reason for dropping out, and date of dropout will be entered in the Screen Failure Log (SFL).

#### **8.1.1.2 Survey Diary**

The investigator, sub-investigator, or study coordinator will confirm the Survey Diary (Local/Systemic Reaction Survey Diary, Symptoms Survey After Chamber Period Diary, and Pollinosis Symptoms Survey Diary) with entries by the subjects and the required items will be entered in the eCRF.

Subjects will confirm the entered content at each hospital visit with the study coordinator and if there are any unclear entries, then additions or modifications will be made as necessary and the revision date will be written at the addition/modification and signed or sealed.

#### **8.1.2 Specification of Source Documents**

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (e.g., age, sex, height, body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- Adverse events and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation
- Randomization number
- Local/Systemic Reaction Survey Diary
- Symptoms Survey After Chamber Period Diary
- Pollinosis Symptoms Survey Diary

With regard to the following data, information entered in the eCRF will be considered as source data; however, if relevant information is recorded in the medical records, then information in the medical records will be handled as source data.

- Details of AEs (time of onset, outcome, severity, seriousness, actions taken, other actions, and causal relationship to the study drug)
- Day of last observation, day of discontinuation, reason for discontinuation

- Other comments entered in the eCRF (including comments in reports for follow-up observations, if follow-up observations for AEs are performed)

### **8.1.3 Clinical Study Monitoring**

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

### **8.1.4 Direct Access to Source Data/Documents**

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the Sponsor monitors and auditors, the IRB, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

### **8.1.5 Data Management**

Data management will be coordinated by [REDACTED] of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. eCRF retrieval and correction process will be referenced in the CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary Enhanced (WHODDE) respectively.

## **8.2 Ethics and Protection of Subject Confidentiality**

### **8.2.1 Institutional Review Board (IRB)**

Prior to the study contract, the protocol and various documents used for obtaining informed consent of subjects will be discussed and approved by the IRB of the study site to guarantee the protection of the rights, safety, and well-being of subjects. The contract with the study site will be concluded after the approval by the IRB.

## **8.2.2 Ethical Conduct of the Study**

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

Pharmacogenomics research will be conducted in accordance with the “Ethical Guidelines for Human Genome and Gene Analysis Research” (Notification No. 1 from the Ministry of Education, Culture, Sports, Science and Technology [MEXT], MHLW, and Ministry of Economy, Trade and Industry, 2004) and “Regarding Clinical Studies Using Pharmacogenomics” (Notification from Head of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health and Labour, 30 Sep 2008) in addition to the above.

SDA related to efficacy and safety evaluation using samples taken during the clinical study period will be conducted in accordance with the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” (Notification No. 3 from MEXT and MHLW, 2014) in addition to items that must be adhered to during study implementation.

## **8.2.3 Informed Consent of Subjects**

### **8.2.3.1 Subject Information and Consent**

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed (or a personal seal will be placed) and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed or sealed informed consent form will be given to the subject and the original will be placed in the subject’s medical record. An entry must also be made in the subject’s dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor, regulatory authorities, and other applicable individuals upon request.

### **8.2.3.2 Subject Information and Consent on Secondary Data Analysis**

If SDA is approved at the study site, then other than consent to participating in the clinical study, consent will be required regarding SDA. Prior to the study implementation, the investigator will prepare the informed consent documents for subjects on SDA with the cooperation of the Sponsor and will revise this as needed. The prepared or revised informed consent document and other explanation documents will be submitted to the Sponsor and prior approval of the IRB/Independent Ethics Committee of the study site will be obtained.

Informed consent regarding SDA can only be obtained from subjects who have already consented to the clinical study. Separate from withdrawing consent to the clinical study, it is possible to withdraw consent to SDA only. With regard to consent to SDA, it is necessary to follow the instructions in “8.2.3.1 Subject Information and Consent.”

If consent to SDA is withdrawn, then any samples for SDA that are remaining at the time of withdrawal of consent will be disposed.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor of the regulatory authorities, and other applicable individuals upon request.

### **8.2.3.3 Subject Information and Consent on Pharmacogenomics Research**

If the pharmacogenomics research is approved at the study site, then other than consent to participating in the clinical study, consent will be required regarding the pharmacogenomics research. Prior to the study implementation, the investigator will prepare the informed consent documents for subjects on the pharmacogenomics research with the cooperation of the Sponsor and will revise this as needed. The prepared or revised informed consent document and other explanation documents will be submitted to the Sponsor and prior approval of the IRB/Independent Ethics Committee of the study site will be obtained.

Informed consent regarding the pharmacogenomics research can only be obtained from subjects who have already consented to the clinical study. Separate from withdrawing consent to the clinical study, it is possible to withdraw consent to the pharmacogenomics research only. With regard to consent to the pharmacogenomics research, it is necessary to follow the instructions in “8.2.3.1 Subject Information and Consent.”

If consent to the pharmacogenomics research is withdrawn, then any samples for the pharmacogenomics research that are remaining at the time of withdrawal of consent will be disposed.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor of the regulatory authorities, and other applicable individuals upon request.

### **8.2.3.4 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information**

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
2. The investigator must update their ICF and submit it for approval to the IRB. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout the primary study period. The investigator or

his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign or place a personal seal on and date the informed consent form. A copy of the signed or sealed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

#### **8.2.4 Subject Confidentiality**

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

All individuals and organizations involved in the study must pay very careful attention to protect subjects' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable local and regional laws.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

### **8.3 Administrative Matters**

#### **8.3.1 Arrangement for Use of Information and Publication of the Clinical Study**

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

After agreement between investigator(s) and sponsor, the manuscript can be submitted for publication.

### 8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- Investigator's Brochure (and amendments, where applicable)
- eCRFs and JUTOKUNA YUUGAIJISHOU HOUKOKUSHO
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the Sponsor:

- Agreement in the study protocol that is signed or sealed by the investigator
- Current Curricula Vitae of the investigator
- List of sub-investigators and study coordinators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

At the end of the study, the Sponsor is responsible for the collection of:

- Study-related documentation

The investigator will archive all study data (e.g., Subject Identification Code List, source data, electronic media containing eCRF data, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation.

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in 1. or 2. below, whichever comes later:

1. Approval date of marketing of the test drug (if development of the drug is stopped, until three years after the decision to discontinue development is notified)
2. Until three years after discontinuation or termination of the study

The following are the main documents to be retained at the study site.

1. Source documents (clinical data, documents, and records for preparing the eCRF), hospital records, medical records, test records, memoranda, subject diary or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, subject files and study-related



- records kept at either a pharmacy, a laboratory, or medical technical office, as well as laboratory test slips, worksheets specified by the Sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written informed consent forms, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CVs of investigators, list of sub-investigators, list of signatures and print of seals (copy), electronic media containing eCRF data, etc.
  3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 51-1, MHLW Ordinance No. 89), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds one year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), the review result report of the IRB (including continuous deliberation), etc.
  4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications.
  5. Records related to sample for SDA.  
To be able to handle withdrawal of consent of the subject regarding SDA and storage of samples for SDA, the study sites where SDA has been approved will store the list of subject identification code and informed consent document for SDA (including revised editions).
  6. Records related to sample for pharmacogenomics research.  
To be able to handle withdrawal of consent of the subject regarding pharmacogenomics research and storage of samples for pharmacogenomics research, the study sites where pharmacogenomics research has been approved will store the list of subject identification code and informed consent document for pharmacogenomics research (including revised editions) for a maximum of 15 years after data lock.

### **8.3.3 Protocol Amendment and/or Revision**

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments and/or revisions. Depending on the nature of the amendment, either approval of the IRB and regulatory authority or notification to the IRB and regulatory authority may be required. The changes will become effective only after the approval of the Sponsor, the investigator, and the IRB followed by the approval of the head of the study site.

### **8.3.4 Insurance of Subjects and Others**

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. Both parties should work together towards compensation settlement.
3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

### **8.3.5 Signatory Investigator for Clinical Study Report**

The signatories for the clinical study report are the Sponsor and medical expert.

## **9 QUALITY ASSURANCE**

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP for trials on gene, cellular, and tissue-based products, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, eCRFs, and source documents. Direct access to these documents will be required by the auditors.

## **10 STUDY ORGANIZATION**

### **10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Other Evaluation Committee(s)**

Not applicable

### **10.2 Other Study Organization**

See attachments

### **10.3 Registration of Subjects**

Not applicable

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## 12 APPENDICES

### 12.1 Classification of Severity of Local Reactions at Vaccination Site

Local reaction to injectable product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort when touched	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Does not interfere with activity: No trouble with daily activities despite the presence of symptoms

Interferes with activity: Troubles with some of the daily activities

Prevents daily activity: Troubles with any daily activities

#### **Reference**

FDA: Guidance for industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007.

## 12.2 Classification of Severity of Systemic Reactions

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhoea	2 – 3 loose stools/24 hours	4 – 5 stools/24 hours	6 or more watery stools/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

No interference with activity: No trouble with daily activities despite the presence of symptoms

Some interference with activity: Troubles with some of the daily activities

Prevents daily activity: Troubles with any daily activities

### Reference

FDA: Guidance for industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007.

### 12.3 Classification of Severity of Pollinosis Symptoms

	++++ (4)	+++ (3)	++ (2)	+ (1)	– (0)
Sneezing attack	≥21 times	20–11 times	10–6 times	5–1 times	Below +
Nasal discharge	≥21 times	20–11 times	10–6 times	5–1 times	Below +
Nasal congestion	Completely obstructed all day	Severe nasal congestion causing prolonged oral breathing in a day	Severe nasal congestion causing occasional oral breathing in a day	Nasal congestion without oral breathing	Below +
Itchy eyes		Unbearably itchy	Significantly itchy	Slightly itchy	Does not bother the patient
Watery eyes		Troubles with activities due to tears	Substantial amount of tears	Has tears but not much troubles with activities	No trouble
Troubles with daily life	Impossible	Painful and complicating daily life	Intermediate between (+++) and (+)	Few troubles	Below +

#### Reference

Practical Guideline for the Management of Allergic Rhinitis in Japan 2016 (revised 8th edition).  
Japanese.

## 12.4 Events That Should Be Handled as Serious Adverse Events

If any of the following events occurs during the study, then the event should be considered as an SAE and should be reported in accordance with the requirements detailed in Section “5.5.5 Reporting of Serious Adverse Events (SAE).”

- Acute hepatic failure
- Acute renal failure
- Acute respiratory failure
- Agranulocytosis
- Anaphylaxis
- Any malignancy
- Aplastic anaemia
- Transmission of an infectious agent via product
- Congenital anomalies
- Hepatic necrosis
- Malignant hypertension
- Pulmonary hypertension
- Convulsion
- Torsades de pointes
- Toxic epidermal necrolysis
- Ventricular fibrillation
- Haemolytic anaemia
- Bone marrow failure
- Myocardial infarction
- Cardiac arrest
- Deafness
- Blindness
- Pancreatitis acute
- Acute graft versus host disease
- Septic shock
- Sepsis
- Rhabdomyolysis
- Respiratory failure
- Stevens-Johnson syndrome

## 12.5 Common Serious Adverse Events

Not applicable

(GPF 4.1)