Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: To be determined		
Name of Active Ingredient: ASP4070		

SYNOPSIS

Title of Study: A Phase 1 Study of ASP4070 to Confirm the Safety and Immunological Response in Patients With Cedar Pollinosis When Administered as Intramuscular Vaccination and as Intradermal Vaccination (Protocol No. 4070-CL-0010)

Investigators/Coordinating Investigator: [redacted]

Study Center(s): 1 site in Japan

Publication Based on the Study: No publications based on the results of this study were available at the time this report was approved.

Study Period:

Study Initiation Date (Date of First Enrollment): 18 June 2015

Study Completion Date (Date of Last Evaluation): 26 July 2016

Phase of Development: Phase 1

Objectives:

The objectives of this study were to evaluate the safety of ASP4070 and the immunological response to ASP4070 in patients with Japanese red cedar (JRC) pollinosis.

Methodology:

This study consisted of 2 parts, part 1 and part 2.

Part 1

An open-label, uncontrolled study

Safety was evaluated in the ASP4070 intramuscular (IM) vaccination group (4 mg 4 times) and the ASP4070 intradermal (ID) vaccination group (4 mg 4 times).

Part 2

A placebo-controlled, double-blind, randomized, parallel-group, comparative study

Immunological response and safety in the ASP4070 IM vaccination group (4 mg 1 time, 4 mg 4 times) and ASP4070 ID vaccination group (1 mg 1 time, 1 mg 4 times, 4 mg 1 time, 4 mg 4 times) were evaluated as compared to those in the placebo group. The study was double-blinded for the same route of vaccination and open-labelled for the route of vaccination (the IM vaccination group and the ID vaccination group).

In part 1, the first vaccination was given to 1 patient (IM vaccination group) at first, and the first vaccination to the remaining 5 patients (IM vaccination group: 2 patients, ID vaccination group: 3 patients) started at least 7 days after the first vaccination to the first patient.

The first vaccination to the remaining patients in part 2 started at least 14 days after the first vaccination to the 6 patients in part 1.

In both part 1 and part 2, the primary study period was from screening to 3 months after the last vaccination with the study drug (day 127). After the primary study period, safety information was collected for 9 months (for 1 year from the last vaccination with the study drug) as the long-term safety follow-up period. Safety information was collected for 1 year after the last vaccination with the study drug even from patients who discontinued participation in the study during the primary study period, if the patients agreed. The study was unblinded when the primary study period was completed and all entered data were fixed. After unblinding, the investigator, subinvestigator, study coordinator and patients remained blinded. However, the treatment allocation manager, ancillary staff of the study site and subinvestigators in charge of study drug vaccination were unblinded.

An additional investigation on immunological response during long-term safety follow-up period was conducted for the patients in part 2 who had given a new consent to the additional investigation. Variables in the additional investigation were prick test and parameter measurement after the peak JRC pollen dispersal season (Apr-May 2016) and 12 months after first vaccination (day 1). Pollinosis symptoms were also assessed during JRC pollen dispersal season, using data recorded in “pollinosis symptoms survey diary”.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: 66 patients

[Part 1] 6 patients in total (4 mg 4 times IM group, 3 patients; 4 mg 4 times ID group, 3 patients)

[Part 2] 60 patients in total

- IM vaccination (4 mg 1 time IM group, 9 patients; 4 mg 4 times IM group, 9 patients; and Placebo IM group, 3 patients)
- ID vaccination (1 mg 1 time ID group, 9 patients; 1 mg 4 times ID group, 9 patients; 4 mg 1 time ID group, 9 patients; 4 mg 4 times ID group, 9 patients; and Placebo ID group, 3 patients)

Enrolled: 66 patients

Analyzed: 66 patients (part 1, 6 patients; part 2, 60 patients)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

A patient was eligible for enrollment in the study if all of the following criteria 1 to 9 were met:

1. Patient of either sex, 20 to 64 years of age at the time of informed consent
2. Patient with a medical history of nasal symptoms (sneezing, itching, rhinorrhea, and congestion) and/or eye symptoms (itching, redness, and lacrimation) in at least 2 cedar pollen dispersion seasons prior to screening

3. Patient with a JRC pollen-specific immunoglobulin (Ig) E antibody test result of class 3 or higher in the allergy test at screening

4. Patient with a positive prick test result for JRC pollen at screening

5. Patient in whom any past and present medical conditions were considered medically stable

6. Patient who had 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

7. A female patient had to be either:

   Of non-child bearing potential:

   - Postmenopausal (defined as at least 1 year without any menstrual cycle) prior to screening, or
   - Documented surgically sterile or status post-hysterectomy or post-ovariectomy

   Or, if of child bearing potential (defined as female patient who did not meet either of the above definitions of "female patient of nonchildbearing potential"),

   - Had to agree not to become pregnant during the primary study period and until 28 days after the last vaccination with the study drug;
   - Had to have a negative urine pregnancy test at screening and on day 1 (before vaccination); and
   - Had to use 2 (at least 1 of which had to be a barrier method) of the following established contraceptive methods† during the primary study period and until 28 days after the last vaccination with the study drug when engaging in sexual intercourse.

   † The established contraceptive methods were as follows:

   - Contraception by the proper use of an approved oral contraceptive
   - Contraception by hormone infusion or implantation
   - Contraception by the use of an intrauterine device (IUD) or intrauterine system (IUS)
   - Contraception by a barrier method using a male or female condom
   - Male partner had surgical sterilization; and
   - Contraception by the rhythm (Ogino) method

8. A female patient was not allowed to be breastfeeding during the primary study period and until 28 days after the last vaccination with the study drug; and

9. A female patient was not allowed to donate ova during the primary study period and until 28 days after the last vaccination with the study drug.

A patient was eligible for the part 2 additional investigation if both of the following criteria 10 and 11 were met:

10. Patient who participated in part 2 of the study and received vaccinations with the study drug

11. Patient who had provided written consent using the informed consent form approved by the IRB of the study site before starting any procedure for additional investigation

Exclusion Criteria

A patient was excluded from the study if any of the following criteria 1 to 24 were met:

1. Patient with a test result of IgE antibody specific to another antigen than JRC pollen (e.g., 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) of class 3 or higher at screening
2. Patient who was scheduled to receive another vaccination during the primary study period
3. Patient who had received or was planning to receive vaccination with live vaccine within 28 days prior to the first vaccination with the study drug, and/or patient who had received or was planning to receive vaccination with inactivated vaccine/toxoid within 7 days prior to the first vaccination with the study drug
4. Patient who had received specific immunotherapy (including desensitization therapy) for JRC pollinosis in the past
5. Patient who had received specific or non-specific immunotherapy within 5 years prior to screening
6. Patient who had used the following drug(s) prior to the first vaccination with the study drug
    1. Within 56 days prior to the first vaccination with the study drug:

       Topical steroids, histamine H1-receptor antagonists, chemical mediator-isolation inhibitors, T helper cell (Th) 2 cytokine inhibitors, thromboxane A2 synthesis inhibitors, thromboxane A2 receptor antagonists, leukotriene receptor antagonists
    2. Within 84 days prior to the first vaccination with the study drug:

       Systemic steroids, antibody drugs (including anti-tumor necrosis factor [TNF]-alpha antibody and anti-IgE monoclonal antibody)
7. Patient with a past history of allergic reactions such as anaphylactic shock or exanthema generalized caused by food and/or medical products (including vaccines), and/or patient who had a fever of 39.0°C or higher within 2 days after a previous vaccination
8. Patient with an evidently high fever (37.5°C or higher) on the day of vaccination, or patient with a severe acute disease
9. Patient who met any of the following criteria for laboratory and other tests at screening

   The reference range for each test was the range used at the study site.

    1. Biochemistry:

    - Patient with an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value of over 100 IU/L
    - Patient with a creatinine value of over 1.5 mg/dL

    2. Urinary drug test:

- Patient with a positive drug test result for benzodiazepines, cocaine and similar narcotics, stimulant drugs, cannabis, barbituric acids, morphine and similar narcotics, phencyclidines or tricyclic antidepressants

3. Immunological test:

- Patient with a positive test result for hepatitis B surface antigen (HBs antigen), hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) antigen/antibody

10. Patient with an autoimmune disease or other serious primary disease
11. Patient who had been diagnosed with immunodeficiency in the past
12. Patient with a complication of perennial allergic rhinitis, rhinitis medicamentosa, or nonallergic rhinitis requiring medical treatment
13. Patient with a complication of cardiovascular disease (including cardiac failure congestive, angina pectoris, or cardiac arrhythmias that required medical treatment)
14. Patient with a complication of hepatic disease (including hepatitis viral and drug-induced liver injury)
15. Patient with a complication of renal disease (including acute kidney injury, glomerulonephritis and nephritis interstitial, but not including a medical history of calculus)
16. Patient with a complication of respiratory disease (including asthma bronchial that required medical treatment or bronchitis chronic, but not including a medical history of childhood asthma)
17. Patient with a complication of malignant tumor or had been diagnosed or had received treatment for malignant tumor within 5 years prior to the first vaccination with the study drug
18. Patient who was diagnosed with schizophrenia, other mental conditions including bipolar disorder, major depressive disorder, or dementia, or patient who had received drug(s) for the treatment of dementia
19. Patient with a complication of dermatitis atopic
20. Patient with a complication that might have an impact on the results of the local and systemic reaction or prick test assessment
21. Patient who had received vaccination with the *Cryptomeria japonica* (Cry j) 2- lysosomal associated membrane protein (LAMP) vaccine
22. Patient who had participated in any clinical study or postmarketing clinical study of any other medical drugs or devices within 12 weeks (84 days) prior to the first vaccination with the study drug, or patient who was participating in such study at the time
23. Patient who was an employee of the sponsor or contract research organization (CRO) or medical institution involved in the study; and
24. Patient who had any other condition, which in the opinion of the investigator, precluded the patient's participation in the study

A patient was excluded from the part 2 additional investigation if the following criteria were met:

25. Patient who had participated in any clinical study or postmarketing clinical study of any other medical drugs or devices within 12 weeks (84 days) prior to the first written consent for the additional investigation, or patient who was participating in a such study at the time

Test Product, Dose and Mode of Administration, Batch Numbers:

Treatments Administered and Selection and Timing of Doses

ASP4070 4 mg group: 0.4 mL of ASP4070 4 mg/0.4 mL was vaccinated.

ASP4070 1 mg group: A total of 0.4 mL of the study drug consisting of 0.1 mL of ASP4070 4 mg/0.4 mL and 0.3 mL of physiological saline was vaccinated.

Placebo group: 0.4 mL of physiological saline was vaccinated.

IM vaccination group: 0.4 mL of ASP4070 or placebo was intramuscularly vaccinated to the patients in the ASP4070 4 mg or placebo groups, respectively. In principle, the study drug was vaccinated into a single site on the extensor side of the upper arm.

ID vaccination group: A total of 0.4 mL of the study drug was intradermally vaccinated to the patients in the ASP4070 4 mg, ASP4070 1 mg, and placebo groups. In principle, 0.2 mL each of the study drug was vaccinated at 2 sites on the inside of the forearm.

Four-time vaccination group: The study drug was vaccinated to the patients in the ASP4070 4 mg, ASP4070 1 mg, and placebo groups 4 times at 14-day intervals.

One-time vaccination group: The study drug was vaccinated to the patients in the ASP4070 4 mg and ASP4070 1 mg groups once. Patients in these groups were vaccinated 4 times at 14-day intervals, using placebo for the first 3 times and ASP4070 4 mg or 1 mg as the fourth vaccination.

Identity of Investigational Products

The test drug for this study was an ASP4070 4 mg/0.4 mL vial.

Code name	ASP4070
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) The drug product contains phosphate-buffered saline as an ingredient besides the plasmid DNA drug substance
Lot No.	[redacted]
Storage condition	Stored frozen at –20°C ± 5°C and protected from light

Duration of Treatment (or Duration of Study, if applicable): For the total of 4 vaccinations at 14-day intervals (day 1, day 15, day 29 and day 43)

Reference Product, Dose and Mode of Administration, Batch Numbers:

The comparative drug was ASP4070 placebo in a 5-mL ampule.

Code name	Placebo
Dosage form and strength	0.9% sodium chloride
Lot No.	[redacted]
Storage condition	Stored at room temperature

Criteria for Evaluation:

Safety

- Adverse events (AEs) reported during the primary study period after the first vaccination with the study drug
- Local reactions and systemic reactions to vaccination reported by 14 days after vaccination with the study drug
- Vital signs (axillary body temperature, sitting blood pressure, and sitting pulse rate)
- 12-lead electrocardiogram (ECG); and
- Laboratory tests (hematology, biochemistry and urinalysis)

Immunological Response

- Prick test for Japanese cedar pollen

  Qualitative result (negative, positive)

  Wheal size (mm) = wheal size of JRC – wheal size of negative control

  Erythema size (mm) = erythema size of JRC – erythema size of negative control

- Parameters

  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), cytokine (interferon gamma [IFN-γ], interleukin [IL]-4, IL-5, IL-10, IL-12, and IL-13), anti-LAMP antibody (except for part 2 additional investigation) and histamine release test

- Pollinosis Symptom (only for part 2 additional investigation)

  Nasal symptoms, eye symptoms, troubles with daily life and overall response by participants

Statistical Methods:

Safety

For a statistical summary of the safety data, the safety analysis set (SAF) was used. The SAF consisted of all patients who received at least 1 dose of the study drug, and was used for safety analyses.

Treatment-emergent AEs (TEAEs) were defined as any AEs that started or worsened in severity after the initial dose of the study drug through the follow-up period. TEAEs were summarized using Medical Dictionary for Regulatory Activities (MedDRA) (Version 18.0), for primary system organ classes and preferred terms.

The number and percentage of patients with TEAEs, serious AEs (SAEs), TEAEs leading to discontinuation, TEAEs related to the study drug, and TEAEs excluding SAEs were summarized by system organ class, preferred term, part and vaccination group. The number and percentage of patients with TEAEs by severity were also summarized. All TEAEs were listed.

The number and percentage of patients with TEAEs were summarized for each treatment group by time interval for vaccination timing, time interval from the latest vaccination and time interval for duration.

The number and percentage of specified local reactions and systemic reactions were summarized by symptom, part, and vaccination group. The number and percentage of patients with specified local reactions and systemic reactions by severity were also summarized.

The same analyses were applied to local and systemic reactions, as well as TEAEs other than local or systemic reactions.

The number and percentage of patients with potentially clinically significant values in liver enzymes and total bilirubin tests during the investigational period were presented by treatment group.

For quantitative laboratory measurements, descriptive statistics were used to summarize results and change from baseline by part, vaccination group and time point for continuous endpoints, and frequency and percentage for categorical endpoints. Shifts relative to normal ranges from baseline to each time point after vaccination with the study drug in lab tests were also tabulated. Laboratory data were displayed in listings.

Vital signs were summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-patient change was calculated per visit as the postbaseline measurement minus the baseline measurement and summarized by treatment group and visit.

Number and percent of patients with normal, not clinically significant abnormal and clinically significant abnormal results as assessed by the investigator for the 12-lead ECG were tabulated by treatment group at each treatment visit.

Immunological Response

The immunological response analysis set (IAS) for primary study consisted of all patients who received at least 1 dose of the study drug and for whom the immunological response endpoint was evaluated or the data for of the immunological response endpoint were collected at at least 1 time point after vaccination with the study drug. IAS for part 2 additional investigation consisted of patients who had given new consent to the additional investigation among those who had been selected for IAS for part 2 during the primary study period.

All analysis of the immunological response was presented by treatment group for the IAS. The results of analyses were also presented for patients who completed all planned vaccinations in the IAS.

Prick test results were presented using frequency tabulations by treatment group and visit. Descriptive statistics for wheal size and erythema size and those changes from baseline (screening) were presented by treatment group and visit.

Pollinosis symptom results for part 2 additional investigation were presented using descriptive statistics of various scores by treatment group and analysis period.

Summary of Results/Conclusions:

Population:

A total of 164 patients gave informed consent, and 98 patients discontinued before the first vaccination. Of the 98 patients who discontinued before the first vaccination, 6 patients withdrew by the patient's request; and of the remaining 92 patients, 64 patients did not fulfill the inclusion or exclusion criteria and 28 patients discontinued because a sufficient number of patients was reached. A total of 66 patients were treated with the study drug, of whom 6 in part 1 and 60 in part 2.

Part 1

A total of 6 patients (3 patients each in the ASP4070 4 mg 4 times [IM] and ASP4070 4 mg 4 times [ID] groups) were randomized and treated with the study drug [Table 1], and all 6 patients completed the study.

All 6 patients were included in the SAF and the IAS.

Part 2 (Primary Study)

A total of 60 patients (9, 9 and 3 patients in the ASP4070 4 mg 4 times, ASP4070 4 mg 1 time and placebo [IM] groups, and 9, 9, 9, 9 and 3 patients in the ASP4070 4 mg 4 times, ASP4070 1 mg 4 times, ASP4070 4 mg 1 time, ASP4070 1 mg 1 time and placebo [ID] groups, respectively) were randomized and treated with the study drug [Table 2], and 59 (98.3%) patients completed the study. One patient in the ASP4070 4 mg 1 time (IM) group discontinued the study due to a protocol violation (prohibited drug use), and received the last dose on day 43 and discontinued on day 105.

All 60 patients were included in the SAF and the IAS.

Part 2 (Additional Investigation)

Of the 60 patients who were treated with the study drug in part 2, 55 patients (9 and 8 patients in the ASP4070 4 mg 4 times and ASP4070 4 mg 1 time [IM] groups, 9, 8, 8 and 8 patients in the ASP4070 4 mg 4 times, ASP4070 1 mg 4 times, ASP4070 4 mg 1 time and ASP4070 1 mg 1 time [ID] groups, and 5 patients in the pooled placebo group [IM+ID], respectively) participated in the additional investigation [Table 3], and all 55 patients completed the additional investigation. The remaining 5 patients (1 patient in the ASP4070 4 mg 1 time [IM] group, 1 patient each in the ASP4070 1 mg 4 times, ASP4070 4 mg 1 time and ASP4070 1 mg 1 time [ID] groups and 1 patient in the pooled placebo group [IM+ID], respectively) did not participate in the additional investigation, because they did not give new consent to the additional investigation.

All 55 patients were included in the IAS for analysis of the part 2 additional investigation.

Demographics and Other Baseline Characteristics:

Part 1

In part 1, equal numbers of males and females were included (3 patients each) [Table 4]. The mean age ranged from 32.3 to 44.0 years, the mean body weight ranged from 53.30 to 58.30 kg and the mean body mass index (BMI) ranged from 20.40 to 21.63 kg/m^2 across the treatment groups. All patients were positive to the prick test and the mean wheal size ranged from 4.783 to 5.427 mm and the mean erythema size ranged from 11.527 to 19.430 mm. The mean anti-JRC IgE antibody test ranged from 10.887 to 12.717 UA/mL. Demographics and

baseline characteristics were similar between the treatment groups. In the anti-JRC IgE antibody test (class), 5 (83.3%) patients and 1 (16.7%) patient had class 3 and 4, respectively. No notable medical history was reported.

Part 2 (Primary Study)

Of the 60 patients in part 2, 32 (53.3%) patients were females and 28 (46.7%) patients were males Table 5. The mean age ranged from 38.0 to 47.0 years, the mean body weight ranged from 52.33 to 69.23 kg and the mean BMI ranged from 20.13 to 24.73 kg/m^2 across the treatment groups. All patients were positive to the prick test and the mean wheal size ranged from 4.127 to 5.863 mm and the mean erythema size ranged from 7.800 to 21.640 mm across the treatment groups. The mean anti-JRC IgE antibody test ranged from 10.033 to 23.507 UA/mL across the treatment groups. Demographics and baseline characteristics were similar in the different treatment groups. In the anti-JRC IgE antibody test (class), 46 (76.7%), 12 (20.0%) and 2 (3.3%) patients had class 3, 4 and 5, respectively. No notable medical history was reported.

Part 2 (Additional Investigation)

For the 55 patients in part 2 additional investigation, the demographics and baseline characteristics were almost identical to those of 60 patients in part 2 primary study. Of the 55 patients in part 2 additional investigation, 30 (54.5%) patients were females and 25 (45.5%) patients were males. The mean age ranged from 40.6 to 46.8 years, the mean body weight ranged from 56.79 to 67.00 kg and the mean BMI ranged from 21.41 to 23.48 kg/m^2 across the treatment groups. All patients were positive to the prick test and the mean wheal size ranged from 4.973 to 5.623 mm and the mean erythema size ranged from 15.420 to 21.496 mm across the treatment groups. The mean anti-JRC IgE antibody test ranged from 10.579 to 24.150 UA/mL across the treatment groups. Demographics and baseline characteristics were similar in the different treatment groups. In the anti-JRC IgE antibody test (class), 42 (76.4%), 11 (20.0%) and 2 (3.6%) patients had class 3, 4 and 5, respectively.

Immunological Response Results:

Primary Study

Prick Test for Japanese Cedar Pollen

Negative conversion on day 127 was reported in 4 patients: 1 patient each in the ASP4070 4 mg 1 time (IM) group (12.5%), ASP4070 4 mg 4 times (ID) group (11.1%), ASP4070 4 mg 1 time (ID) group (11.1%) and ASP4070 1 mg 1 time (ID) group (11.1%) Table 6. Negative conversion at earlier time points was reported in 1 patient in the ASP4070 4 mg 1 time (IM) group (11.1%) on day 43; in 1 patient each in the ASP4070 4 mg 4 times (IM) group (11.1%), ASP4070 4 mg 4 times (ID) group (11.1%, the same patient in whom negative conversion was reported on day 127) and ASP4070 1 mg 4 times (ID) group (11.1%) on day 71; and in 1 patient in the ASP4070 1 mg 4 times (ID) group (11.1%) on day 99. No negative conversion was observed in the placebo groups.

No notable trends were observed in the mean changes from baseline in the wheal size or in the erythema size in the prick test among the treatment groups both in the IM and ID groups.

Parameters

Total Antibody

No notable trends were observed in the mean changes from baseline in the total antibody (IgG antibody and IgE antibody) among the treatment groups both in the IM and ID groups.

Specific Antibody

[redacted]

No notable trends were observed in the specific IgE class (anti-JRC) change among the treatment groups.

Histamine Release Test

No notable trends were observed in the histamine release test class change among the treatment groups.

Cytokines

No notable trends were observed in the mean changes from baseline in the cytokines (IFN-γ– IL-4+, IFN-γ+ IL-4–, IFN-γ, IL-4, IL-5, IL-10, IL-12, IL-13, IFN-γ+ IL-4+ and IFN-γ– IL-4–) among the treatment groups both in the IM and ID groups.

Anti-LAMP Antibody

All patients were negative to the anti-LAMP antibody throughout the study.

Additional Investigation

Prick Test for Japanese Cedar Pollen

For the patients who did not take anti-allergic drugs prior to prick test, negative conversion during JRC pollen dispersal season was reported in 1 patient in the ASP4070 4 mg 1 time (ID) group (16.7%), and negative conversion after JRC pollen dispersal season was reported in 2 patients: 1 patient each in the ASP4070 4 mg 4 times (ID) group (11.1%, the patient in whom negative conversion was reported on days 71 and 127) and ASP4070 4 mg 1 time (ID) group (12.5%) Table 7. No notable trends were observed in the mean changes from baseline during JRC pollen dispersal season and after the dispersal season in the wheal size or in the erythema size in the prick test among the treatment groups.

Parameters

No notable trends were observed in the mean changes from baseline during JRC pollen dispersal season and after the dispersal season in the parameters of the total antibody, specific antibody, histamine release and cytokines among the treatment groups.

Pollinosis Symptoms

No notable trends were observed in the mean changes from baseline during JRC pollen dispersal season in the symptom scores of TNSS, TNNSS, TSS and others among the treatment groups. No notable trends were observed in the mean changes from baseline during JRC pollen dispersal season in the score of troubles with daily life among the treatment groups. No notable trends were observed among the treatment groups in severity

of pollinosis symptoms in this season, severity of pollinosis symptoms compared to last season and usage condition of medications compared to last season.

Safety Results:

IM and ID vaccination with ASP4070 at 1 and 4 mg was generally safe and well tolerated when 1 or 4 vaccinations were given at 14-day intervals.

Both in part 1 and part 2, no deaths, serious TEAEs or TEAEs leading to permanent discontinuation of the study drug were reported. Most TEAEs were drug-related TEAEs, and many of the drug-related TEAEs were local or systemic reactions. Excluding the erythema reported in part 2, all of the other TEAEs were mild or moderate in severity. In part 2, severe TEAE erythema was reported in 3 (33.3%) and 1 (11.1%) patients in the ASP4070 4 mg 4 times (ID) and ASP4070 4 mg 1 time (ID) groups, respectively. For most local and systemic reactions, the onset by time interval from each vaccination were within 3 days after vaccination. For most TEAEs, the duration by time interval was within 14 days. There were no local reactions that required treatment.

No notable trends were observed in clinical laboratory findings, vital signs or ECG findings.

During long-term safety follow-up period, an SAE of benign salivary gland neoplasm was reported from the patient in ASP4070 4 mg 1 time (IM) group in part 2. The tumour was removed surgically, and considered not related to the study drug.

Part 1

TEAEs were reported in 2 (66.7%) and 3 (100%) patients in the ASP4070 4 mg 4 times (IM) and ASP4070 4 mg 4 times (ID) groups, respectively [Table 8]. All TEAEs were mild or moderate in severity.

Local reactions were reported in 1 (33.3%) and 3 (100%) patients in the ASP4070 4 mg 4 times (IM) and ASP4070 4 mg 4 times (ID) groups, respectively. Excluding the erythema that was moderate, all of the other local reactions were mild in severity.

Systemic reactions were reported in 1 (33.3%) and 0 patients in the ASP4070 4 mg 4 times (IM) and ASP4070 4 mg 4 times (ID) groups, respectively. Of the systemic reactions, conjunctivitis allergic was moderate and headache was mild in severity.

Part 2

TEAEs were reported in 4 (44.4%), 4 (44.4%) and 2 (66.7%) patients in the ASP4070 4 mg 4 times, 4 mg 1 time and placebo (IM) groups, and 9 (100%), 9 (100%), 9 (100%), 3 (33.3%) and 2 (66.7%) patients in the ASP4070 4 mg 4 times, ASP4070 1 mg 4 times, ASP4070 4 mg 1 time, ASP4070 1 mg 1 time and placebo (ID) groups, respectively [Table 9]. Excluding the erythema, all of the other TEAEs were mild or moderate in severity.

Local reactions were reported in 2 (22.2%), 1 (11.1%) and 1 (33.3%) patients in the ASP4070 4 mg 4 times, ASP4070 4 mg 1 time and placebo (IM) groups, and 9 (100%), 8 (88.9%), 9 (100%), 3 (33.3%) and 2 (66.7%) patients in the ASP4070 4 mg 4 times, ASP4070 1 mg 4 times, ASP4070 4 mg 1 time, ASP4070 1 mg 1 time and placebo (ID) groups, respectively. Excluding the erythema, all of the other local reactions were mild or moderate in severity. Severe erythema was reported in 3 (33.3%) and 1 (11.1%) patients in the ASP4070 4 mg 4 times (ID) and ASP4070 4 mg 1 time (ID) groups, respectively.

Systemic reactions were reported in 3 (33.3%), 2 (22.2%) and 2 (66.7%) patients in the ASP4070 4 mg 4 times, ASP4070 4 mg 1 time and placebo (IM) groups, and 4 (44.4%), 5 (55.6%), 1 (11.1%), 0 and 0 patients in the ASP4070 4 mg 4 times, ASP4070 1 mg 4 times, ASP4070 4 mg 1 time, ASP4070 1 mg 1 time and placebo (ID) groups. All systemic reactions were mild or moderate in severity.

In the analysis of vaccination route in part 2, local reactions were reported in 4 (19.0%) and 31 (79.5%) patients in the pooled IM and ID groups, respectively. Local reactions occurring more frequently (≥ 15% higher) in the pooled ID group compared with the IM group included erythema (9.5% in the pooled IM group versus 79.5% in the pooled ID group), swelling (0 versus 43.6%) and induration (0 versus 23.1%).

CONCLUSIONS:

ASP4070 was safe and well tolerated, and no new safety-associated concerns were raised in patients with JRC pollinosis. The incidences of local reactions tended to be higher in the ID groups compared with the IM groups. In primary study, negative conversion in the prick test for Japanese Cedar Pollen was reported at some time points in 1 or 2 patients in each of the ASP4070 groups, compared with none in the placebo groups. No notable trends were observed among the treatment groups in the wheal size or the erythema size in the prick test, or in the parameters of total antibody, specific antibody, histamine release test and cytokines. All patients were negative to the anti-LAMP. During JRC pollen dispersal season and after the dispersal season, no notable trends were observed among the treatment groups in the immunological response to ASP4070 and pollinosis symptoms.

Date of Report: 26 December 2016

Table 1 Analysis Sets in Part 1

	ASP4070 4 mg × 4 times (IM) (n=3)	ASP4070 4 mg × 4 times (ID) (n=3)	Total (n=6)
Randomized and dosed†	3 (100.0%)	3 (100.0%)	6 (100.0%)
Safety analysis set‡	3 (100.0%)	3 (100.0%)	6 (100.0%)
Immunological response analysis set§	3 (100.0%)	3 (100.0%)	6 (100.0%)

†The first patient enrolled in part 1 was not randomized and was allocated to the ASP4070 4 mg × 4 times intramuscular vaccination group.

‡ All patients who received at least 1 dose of the study drug.

§ All patients who received at least 1 dose of the study drug and for whom the immunological response endpoint was evaluated or the data of the immunological response endpoint were collected at at least 1 time point after vaccination with the study drug.

ID: intradermal; IM: intramuscular.

Source: Table 12.1.1.2.1

Table 2 Analysis Sets in Part 2 (Primary Study)

Analysis Set	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=9)	Placebo (IM) (n=3)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=9)	ASP4070 4 mg × 1 time (ID) (n=9)	ASP4070 1 mg × 1 time (ID) (n=9)	Placebo (ID) (n=3)	Total (n=60)
Randomized and dosed	9 (100.0%)	9 (100.0%)	3 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	3 (100.0%)	60 (100.0%)
Safety analysis set†	9 (100.0%)	9 (100.0%)	3 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	3 (100.0%)	60 (100.0%)
Immunological response analysis set‡	9 (100.0%)	9 (100.0%)	3 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	3 (100.0%)	60 (100.0%)

† All patients who received at least 1 dose of the study drug.

‡ All patients who received at least 1 dose of the study drug and for whom the immunological response endpoint was evaluated or the data of the immunological response endpoint were collected at at least 1 time point after vaccination with the study drug.

ID: intradermal; IM: intramuscular.

Source: Table 12.1.1.2.2

Table 3 Analysis Sets in Part 2 (Additional Investigation)

Analysis Set	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=9)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=9)	ASP4070 4 mg × 1 time (ID) (n=9)	ASP4070 1 mg × 1 time (ID) (n=9)	Pooled Placebo (IM+ID) (n=6)	Total (n=60)
Immunological response analysis set†	9 (100.0%)	8 (88.9%)	9 (100.0%)	8 (88.9%)	8 (88.9%)	8 (88.9%)	5 (83.3%)	55 (91.7%)

† Patients who had given new consent to the additional investigation among those who have been selected for the immunological response analysis set for part 2 during the primary study period.

ID: intradermal; IM: intramuscular.

Source: Table 12.1.1.2.3

Table 4 Demographics and Baseline Characteristics in Part 1

	ASP4070 4 mg × 4 times (IM) (n=3)	**ASP4070 4 mg × 4 times (ID) (n=3)**	**Total (n=6)**
Sex, n (%)			
Male	1 (33.3%)	2 (66.7%)	3 (50.0%)
Female	2 (66.7%)	1 (33.3%)	3 (50.0%)
Age (years)			
Mean	32.3	44.0	38.2
SD	4.0	5.3	7.7
Min	28	38	28
Median	33.0	46.0	37.0
Max	36	48	48
Height (cm)			
Mean	161.53	163.57	162.55
SD	5.97	7.84	6.33
Min	156.7	156.2	156.2
Median	159.70	162.70	161.20
Max	168.2	171.8	171.8
Body weight (kg)			
Mean	53.30	58.30	55.80
SD	9.21	11.89	9.90
Min	43.1	44.9	43.1
Median	55.80	62.40	58.40
Max	61.0	67.6	67.6
Body mass index (kg/m^2)			
Mean	20.40	21.63	21.02
SD	3.08	2.82	2.73
Min	16.9	18.4	16.9
Median	21.60	22.90	22.15
Max	22.7	23.6	23.6
Complication			
No	1 (33.3%)	2 (66.7%)	3 (50.0%)
Yes	2 (66.7%)	1 (33.3%)	3 (50.0%)
Prick test			
Negative	0	0	0
Positive	3 (100.0%)	3 (100.0%)	6 (100.0%)
Prick test: wheal size (mm)†			
Mean	5.427	4.783	5.105
SD	0.928	0.847	0.869
Min	4.39	4.25	4.25
Median	5.710	4.340	5.050
Max	6.18	5.76	6.18
Prick test: erythema size (mm)‡			
Mean	19.430	11.527	15.478
SD	3.078	6.246	6.175
Min	16.53	4.36	4.36
Median	19.100	14.410	16.170
Max	22.66	15.81	22.66

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	ASP4070 4 mg × 4 times (IM) (n=3)	**ASP4070 4 mg × 4 times (ID) (n=3)**	**Total (n=6)**
Anti-JRC IgE antibody test (UA/mL)			
Mean	12.717	10.887	11.802
SD	8.262	5.297	6.287
Min	5.65	6.14	5.65
Median	10.700	9.920	10.310
Max	21.80	16.60	21.80
Anti-JRC IgE antibody test (class)			
3	2 (66.7%)	3 (100.0%)	5 (83.3%)
4	1 (33.3%)	0	1 (16.7%)
5	0	0	0
6	0	0	0

All patients who received at least 1 dose of the study drug (Safety Analysis Set). Weight at screening; height at screening; body mass index at screening, calculated as weight / (height^2).

† Wheal size of Japanese Red Cedar – wheal size of negative control in the prick test

‡ Erythema size of Japanese Red Cedar – erythema size of negative control in the prick test

ID: intradermal; IgE: Immunoglobulin E; IM: intramuscular; JRC: Japanese Red Cedar.

Source: Table 12.1.2.1.1

Table 5 Demographics and Baselines Characteristics in Part 2 (Primary Study)

	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=9)	Placebo (IM) (n=3)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=9)	ASP4070 4 mg × 1 time (ID) (n=9)	ASP4070 1 mg × 1 time (ID) (n=9)	Placebo (ID) (n=3)	Total (n=60)
Sex, n (%)									
Male	2 (22.2%)	6 (66.7%)	2 (66.7%)	4 (44.4%)	4 (44.4%)	4 (44.4%)	6 (66.7%)	0	28 (46.7%)
Female	7 (77.8%)	3 (33.3%)	1 (33.3%)	5 (55.6%)	5 (55.6%)	5 (55.6%)	3 (33.3%)	3 (100.0%)	32 (53.3%)
Age (years)									
Mean	41.0	42.7	38.0	40.6	46.1	45.0	43.3	47.0	43.1
SD	8.2	10.2	15.7	8.0	10.6	6.4	9.1	5.3	8.9
Min	29	21	21	29	25	31	24	43	21
Median	41.0	47.0	41.0	39.0	51.0	46.0	47.0	45.0	45.0
Max	53	54	52	52	54	52	51	53	54
Height (cm)									
Mean	161.34	169.83	166.77	166.89	161.94	163.23	165.91	161.37	164.78
SD	7.42	8.28	7.65	6.89	10.09	6.23	9.08	1.92	8.03
Min	150.3	158.5	158.2	156.4	151.7	155.6	151.2	159.3	150.3
Median	160.40	167.70	169.20	166.60	156.60	165.70	166.30	161.70	165.15
Max	172.2	182.1	172.9	176.7	179.0	171.1	176.5	163.1	182.1
Body weight (kg)									
Mean	57.10	66.41	69.23	60.62	56.64	57.42	62.47	52.33	60.18
SD	10.55	13.34	12.55	12.96	10.03	13.86	14.10	7.10	12.42
Min	44.3	45.0	57.7	46.2	44.4	43.3	42.9	45.2	42.9
Median	53.40	67.10	67.40	52.90	52.10	51.20	66.20	52.40	57.40
Max	73.8	82.9	82.6	80.6	73.6	84.3	78.3	59.4	84.3
Body mass index (kg/m^2)									
Mean	21.80	22.99	24.73	21.58	21.44	21.42	22.40	20.13	21.99
SD	2.75	4.49	2.49	3.17	1.90	4.41	2.99	3.20	3.30
Min	18.5	17.9	23.1	18.9	19.3	16.8	18.8	17.0	16.8
Median	21.80	21.50	23.50	19.60	21.20	19.70	22.80	20.00	21.20
Max	26.2	30.6	27.6	26.8	25.2	30.7	26.6	23.4	30.7
Complication									
No	6 (66.7%)	9 (100.0%)	2 (66.7%)	9 (100.0%)	7 (77.8%)	8 (88.9%)	9 (100.0%)	2 (66.7%)	52 (86.7%)
Yes	3 (33.3%)	0	1 (33.3%)	0	2 (22.2%)	1 (11.1%)	0	1 (33.3%)	8 (13.3%)
Prick test result									
Negative	0	0	0	0	0	0	0	0	0
Positive	9 (100.0%)	9 (100.0%)	3 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	9 (100.0%)	3 (100.0%)	60 (100.0%)
Prick test: wheal size (mm)†									
Mean	5.366	5.026	4.127	5.623	4.916	5.074	5.269	5.863	5.191
SD	1.552	1.223	0.824	2.262	1.280	1.340	1.954	1.394	1.558
Min	3.20	3.74	3.38	3.53	3.66	3.91	3.85	4.98	3.20
Median	5.340	4.730	3.990	4.810	4.460	4.350	4.890	5.140	4.810
Max	7.76	7.83	5.01	10.41	7.12	7.59	10.11	7.47	10.41
Prick test: erythema size (mm)‡									
Mean	19.353	18.043	7.800	19.060	20.411	18.400	21.640	20.407	18.947
SD	8.594	6.920	3.678	11.092	6.605	11.023	10.664	5.817	8.981
Min	2.43	4.95	4.27	2.25	11.51	3.74	4.38	15.76	2.25
Median	18.700	19.600	7.520	20.330	21.630	20.910	22.790	18.530	19.150
Max	31.09	29.32	11.61	30.62	32.80	36.01	38.70	26.93	38.70
Anti-JRC IgE antibody test (UA/mL)									
Mean	19.008	10.033	18.283	19.056	11.511	11.723	21.873	23.507	16.070
SD	21.958	6.396	11.904	22.676	7.425	7.199	14.360	16.960	14.837
Min	7.94	5.47	9.85	5.53	4.19	4.01	3.66	4.32	3.66
Median	12.100	8.340	13.100	12.900	9.200	9.840	15.000	29.700	11.650
Max	77.20	25.50	31.90	78.20	23.60	28.90	43.40	36.50	78.20

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	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=9)	Placebo (IM) (n=3)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=9)	ASP4070 4 mg × 1 time (ID) (n=9)	ASP4070 1 mg × 1 time (ID) (n=9)	Placebo (ID) (n=3)	Total (n=60)
Anti-JRC IgE antibody test (class)									
3	8 (88.9%)	8 (88.9%)	2 (66.7%)	7 (77.8%)	7 (77.8%)	8 (88.9%)	5 (55.6%)	1 (33.3%)	46 (76.7%)
4	0	1 (11.1%)	1 (33.3%)	1 (11.1%)	2 (22.2%)	1 (11.1%)	4 (44.4%)	2 (66.7%)	12 (20.0%)
5	1 (11.1%)	0	0	1 (11.1%)	0	0	0	0	2 (3.3%)
6	0	0	0	0	0	0	0	0	0

All patients who received at least 1 dose of the study drug (Safety Analysis Set). Weight at screening; height at screening; body mass index at screening, calculated as weight / (height^2).

Baseline was the last nonmissing measurement prior to initial dosing of the study drug.

† Wheal size of Japanese Red Cedar – wheal size of negative control in the prick test

‡ Erythema size of Japanese Red Cedar – erythema size of negative control in the prick test

ID: intradermal; IgE: Immunoglobulin E; IM: intramuscular; JRC: Japanese Red Cedar.

Source: Table 12.1.2.2.1

Table 6 Qualitative Prick Test Results in Part 2 (Primary Study)

Visit	Result	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=9)	Placebo (IM) (n=3)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=9)	ASP4070 4 mg × 1 time (ID) (n=9)	ASP4070 1 mg × 1 time (ID) (n=9)	Placebo (ID) (n=3)
Screening	Negative	0	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 15	Negative	0	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 29	Negative	0	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 43	Negative	0	1/9 (11.1%)	0	0	0	0	0	0
	Positive	9/9 (100.0%)	8/9 (88.9%)	2/2 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 71	Negative	1/9 (11.1%)	0	0	1/9 (11.1%)	1/9 (11.1%)	0	0	0
	Positive	8/9 (88.9%)	9/9 (100.0%)	3/3 (100.0%)	8/9 (88.9%)	8/9 (88.9%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 99	Negative	0	0	0	0	1/9 (11.1%)	0	0	0
	Positive	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)	9/9 (100.0%)	8/9 (88.9%)	9/9 (100.0%)	9/9 (100.0%)	3/3 (100.0%)
Day 127	Negative	0	1/8 (12.5%)	0	1/9 (11.1%)	0	1/9 (11.1%)	1/9 (11.1%)	0
	Positive	9/9 (100.0%)	7/8 (87.5%)	3/3 (100.0%)	8/9 (88.9%)	9/9 (100.0%)	8/9 (88.9%)	8/9 (88.9%)	3/3 (100.0%)

All patients who received at least 1 dose of the study drug and for whom the immunological response endpoint was evaluated or the data of the immunological response endpoint were collected at at least 1 time point after vaccination with the study drug (Immunological Response Analysis Set).

ID: intradermal; IM: intramuscular.

Source: Table 12.7.1.1.1

Table 7 Qualitative Prick Test Results in Part 2 Including Additional Investigational Period

Visit	Result	ASP4070 4 mg × 4 times (IM) (n=9)	ASP4070 4 mg × 1 time (IM) (n=8)	ASP4070 4 mg × 4 times (ID) (n=9)	ASP4070 1 mg × 4 times (ID) (n=8)	ASP4070 4 mg × 1 time (ID) (n=8)	ASP4070 1 mg × 1 time (ID) (n=8)	Pooled Placebo (IM+ID) (n=5)
Screening	Negative	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	9/9 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	5/5 (100.0%)
Day 15	Negative	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	9/9 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	5/5 (100.0%)
Day 29	Negative	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	9/9 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	5/5 (100.0%)
Day 43	Negative	0	0	0	0	0	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	9/9 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	8/8 (100.0%)	4/4 (100.0%)
Day 71	Negative	1/9 (11.1%)	0	1/9 (11.1%)	1/8 (12.5%)	0	0	0
	Positive	8/9 (88.9%)	8/8 (100.0%)	8/9 (88.9%)	7/8 (87.5%)	8/8 (100.0%)	8/8 (100.0%)	5/5 (100.0%)
Day 99	Negative	0	0	0	1/8 (12.5%)	0	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	9/9 (100.0%)	7/8 (87.5%)	8/8 (100.0%)	8/8 (100.0%)	5/5 (100.0%)
Day 127	Negative	0	1/7 (14.3%)	1/9 (11.1%)	0	1/8 (12.5%)	0	0
	Positive	9/9 (100.0%)	6/7 (85.7%)	8/9 (88.9%)	8/8 (100.0%)	7/8 (87.5%)	8/8 (100.0%)	5/5 (100.0%)
Follow-up Visit 2 †	Negative	0	0	0	0	1/6 (16.7%)	0	0
	Positive	4/4 (100.0%)	6/6 (100.0%)	3/3 (100.0%)	7/7 (100.0%)	5/6 (83.3%)	5/5 (100.0%)	3/3 (100.0%)
Follow-up Visit 3 †	Negative	0	0	1/9 (11.1%)	0	1/8 (12.5%)	0	0
	Positive	9/9 (100.0%)	8/8 (100.0%)	8/9 (88.9%)	8/8 (100.0%)	7/8 (87.5%)	8/8 (100.0%)	4/4 (100.0%)

All patients who received at least 1 dose of the study drug and for whom the immunological response endpoint was evaluated or the data of the immunological response endpoint were collected at at least 1 time point after vaccination with the study drug (Immunological Response Analysis Set).

† Prick test results in patients who took the following drugs prior to prick test were excluded from the analysis.

- Systemic steroid-containing medications within –7 days of prick test
- Anti-allergic drugs within –3 days of prick test

ID: intradermal; IM: intramuscular.

Source: Table 12.7.1.1.4

Table 8 Treatment-emergent Adverse Events in Part 1

MedDRA Version 18.0 System Organ Class Preferred Term	ASP4070 4 mg × 4 times (IM) (n=3) n (%)	ASP4070 4 mg × 4 times (ID) (n=3) n (%)
Overall	**2 (66.7%)**	**3 (100.0%)**
Ear and Labyrinth Disorders	**1 (33.3%)**	**0**
Vertigo	1 (33.3%)	0
Eye Disorders	**2 (66.7%)**	**0**
Conjunctivitis allergic	1 (33.3%)	0
Eye pruritus	1 (33.3%)	0
Gastrointestinal Disorders	**1 (33.3%)**	**0**
Diarrhoea	1 (33.3%)	0
General Disorders and Administration Site Conditions	**1 (33.3%)**	**2 (66.7%)**
Fatigue	0	1 (33.3%)
Induration	0	1 (33.3%)
Pain	1 (33.3%)	1 (33.3%)
Vaccination site pruritus	0	1 (33.3%)
Musculoskeletal and Connective Tissue Disorders	**2 (66.7%)**	**0**
Myalgia	2 (66.7%)	0
Nervous System Disorders	**1 (33.3%)**	**1 (33.3%)**
Headache	1 (33.3%)	1 (33.3%)
Respiratory, Thoracic and Mediastinal Disorders	**2 (66.7%)**	**0**
Nasal obstruction	1 (33.3%)	0
Oropharyngeal pain	1 (33.3%)	0
Rhinorrhoea	1 (33.3%)	0
Sneezing	1 (33.3%)	0
Skin and Subcutaneous Tissue Disorders	**0**	**3 (100.0%)**
Erythema	0	3 (100.0%)

All patients who received at least 1 dose of the study drug (Safety Analysis Set).

The number (n) and percentage (%) of patients are shown.

Sorting order: alphabetical by system organ class and preferred term.

ID: intradermal; IM: intramuscular.

Source: Table 12.6.1.1.1.2

Table 9 Treatment-emergent Adverse Events in Part 2

MedDRA Version 18.0 System Organ Class Preferred Term	ASP4070 4 mg × 4 times (IM) (n=9) n (%)	ASP4070 4 mg × 1 time (IM) (n=9) n (%)	Placebo (IM) (n=3) n (%)	ASP4070 4 mg × 4 times (ID) (n=9) n (%)	ASP4070 1 mg × 4 times (ID) (n=9) n (%)	ASP4070 4 mg × 1 time (ID) (n=9) n (%)	ASP4070 1 mg × 1 time (ID) (n=9) n (%)	Placebo (ID) (n=3) n (%)
Overall	**4 (44.4%)**	**4 (44.4%)**	**2 (66.7%)**	**9 (100.0%)**	**9 (100.0%)**	**9 (100.0%)**	**3 (33.3%)**	**2 (66.7%)**
Eye Disorders	**0**	**0**	**0**	**0**	**1 (11.1%)**	**0**	**0**	**0**
Conjunctivitis allergic	0	0	0	0	1 (11.1%)	0	0	0
Gastrointestinal Disorders	**2 (22.2%)**	**1 (11.1%)**	**0**	**0**	**1 (11.1%)**	**1 (11.1%)**	**0**	**0**
Diarrhoea	1 (11.1%)	0	0	0	0	1 (11.1%)	0	0
Faeces soft	1 (11.1%)	0	0	0	0	0	0	0
Nausea	0	1 (11.1%)	0	0	1 (11.1%)	0	0	0
General Disorders and Administration Site Conditions	**3 (33.3%)**	**2 (22.2%)**	**1 (33.3%)**	**6 (66.7%)**	**8 (88.9%)**	**8 (88.9%)**	**1 (11.1%)**	**1 (33.3%)**
Discomfort	0	0	0	1 (11.1%)	0	0	0	1 (33.3%)
Fatigue	2 (22.2%)	1 (11.1%)	0	2 (22.2%)	2 (22.2%)	2 (22.2%)	0	0
Induration	0	0	0	2 (22.2%)	3 (33.3%)	3 (33.3%)	1 (11.1%)	0
Injection site discolouration	0	0	0	1 (11.1%)	0	2 (22.2%)	0	0
Pain	2 (22.2%)	1 (11.1%)	0	0	1 (11.1%)	1 (11.1%)	0	0
Pyrexia	0	0	1 (33.3%)	0	1 (11.1%)	0	0	0
Swelling	0	0	0	5 (55.6%)	5 (55.6%)	7 (77.8%)	0	0
Vaccination site pruritus	0	0	0	5 (55.6%)	5 (55.6%)	1 (11.1%)	0	0
Infections and Infestations	**1 (11.1%)**	**2 (22.2%)**	**0**	**1 (11.1%)**	**0**	**1 (11.1%)**	**0**	**0**
Nasopharyngitis	1 (11.1%)	2 (22.2%)	0	1 (11.1%)	0	1 (11.1%)	0	0
Investigations	**0**	**1 (11.1%)**	**0**	**1 (11.1%)**	**1 (11.1%)**	**0**	**0**	**0**
Blood creatine phosphokinase increased	0	1 (11.1%)	0	1 (11.1%)	0	0	0	0
C-reactive protein increased	0	0	0	0	1 (11.1%)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**1 (33.3%)**	**0**	**0**	**1 (11.1%)**	**1 (11.1%)**	**0**
Myalgia	0	0	1 (33.3%)	0	0	1 (11.1%)	1 (11.1%)	0
Nervous system disorders	2 (22.2%)	2 (22.2%)	1 (33.3%)	0	3 (33.3%)	0	0	1 (33.3%)
Headache	2 (22.2%)	2 (22.2%)	1 (33.3%)	0	3 (33.3%)	0	0	1 (33.3%)
Hypoaesthesia	0	0	0	0	1 (11.1%)	0	0	0

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MedDRA Version 18.0 System Organ Class Preferred Term	ASP4070 4 mg × 4 times (IM) (n=9) n (%)	ASP4070 4 mg × 1 time (IM) (n=9) n (%)	Placebo (IM) (n=3) n (%)	ASP4070 4 mg × 4 times (ID) (n=9) n (%)	ASP4070 1 mg × 4 times (ID) (n=9) n (%)	ASP4070 4 mg × 1 time (ID) (n=9) n (%)	ASP4070 1 mg × 1 time (ID) (n=9) n (%)	Placebo (ID) (n=3) n (%)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**0**	**0**	**0**	**1 (11.1%)**	**0**	**0**	**0**
Rhinorrhoea	0	0	0	0	1 (11.1%)	0	0	0
Skin and Subcutaneous Tissue Disorders	**1 (11.1%)**	**0**	**1 (33.3%)**	**9 (100.0%)**	**8 (88.9%)**	**9 (100.0%)**	**3 (33.3%)**	**2 (66.7%)**
Erythema	1 (11.1%)	0	1 (33.3%)	9 (100.0%)	8 (88.9%)	9 (100.0%)	3 (33.3%)	2 (66.7%)
Pruritus	0	0	0	0	0	0	0	1 (33.3%)
Rash	0	0	0	1 (11.1%)	0	0	0	0
Urticaria	0	0	0	1 (11.1%)	1 (11.1%)	0	0	0

All patients who received at least 1 dose of the study drug (Safety Analysis Set).

The number (n) and percentage (%) of patients are shown.

Sorting order: alphabetical by system organ class and preferred term.

ID: intradermal; IM: intramuscular.

Source: Table 12.6.1.1.2.2.1