Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: Cry j 1-LAMP plasmid and Cry j 2-LAMP plasmid		

SYNOPSIS

Title of Study: Phase 2 Dose-finding Study of ASP4070 −A Randomized, Double-blind, Placebo-controlled, Dose-finding Study in Patients With Cedar Pollinosis Using an Environmental Exposure Chamber—

Investigator/Coordinating Investigator: [redacted]

Study Center: [redacted]

Publication Based on the Study: Not applicable

Study Period:

Study Initiation Date (Date of First Informed Consent): 13 Apr 2017

Study Completion Date (Date of Last Study Evaluation): 29 May 2018

Phase of Development: Phase 2

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

Methodology: This study was a randomized, double-blind, placebo-controlled, dose-finding study. A total of 150 patients (50 patients in each treatment group) with cedar pollinosis were planned to randomly allocate to 3 groups in a ratio of 1:1:1 to ASP4070 4 mg group, ASP4070 1 mg group or placebo group. 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 (3TNSS) 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," were used as stratification factors to randomization. The patients were received the allocated study drug.

The treatment code was broken when the primary study period had been completed and all data entered in case report forms (CRFs) had been fixed. Even after code breaking, the study was continued the long-term safety follow-up study period (including pollinosis symptoms survey period and additional study period) with the investigator, subinvestigator, study coordinator and patients remaining blinded.

Number of Patients (Planned, Enrolled and Analyzed): The number of patients planned for the study was a total of 150 patients (50 in ASP4070 4 mg group, 50 in ASP4070 1 mg group and 50 in the placebo group). A total of 150 patients were randomized (50 patients for each treatment group) and 142 patients completed the study (47 in ASP4070 4 mg group, 48 in ASP4070 1 mg group and 47 in the placebo group).

Diagnosis and Main Criteria for Inclusion: Patients who had provided written informed consent prior to any study-specific procedures and being candidates for participation in the study were screened for the following

inclusion/exclusion criteria before enrollment into the study. Patients who were candidates for participation in the study were assessed over 3 visits (screening visit 1, 2 and 3) to determine their eligibilities.

Inclusion:

1. 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
2. Patient of either sex who was aged from 20 to 64 years at the time of informed consent
3. Patient who had 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. Patient who had the JRC pollen-specific IgE antibody test result of Class 3 or higher in the allergy test at screening visit 1
5. Patient who satisfied 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
   - 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 patient must satisfy the following criteria

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

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

   Or, patient of childbearing potential (patient who did not meet the above definition of "female patient of non-childbearing potential") must meet all of the following criteria:

   - Patient 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 was longer)
   - Patient must have a negative urine pregnancy test at screening visit 1 and on day 1 (prior to vaccination)
   - Patient must consistently use 2 forms of highly effective birth control (at least 1 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 was longer) if heterosexually active
7. Female patient must agree not to breastfeed during the primary study period or for 28 days after the final vaccination of the study drug (whichever period was longer)
8. Female patient must not donate ova during the primary study period or for 28 days after the final vaccination of the study drug (whichever period was longer)
9. Male patient and their female spouse/partners who were of childbearing potential must be using highly effective contraception consisting of 2 forms of birth control (at least 1 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 patient must not donate sperm from the initial study drug vaccination until 28 days after the final vaccination of the study drug
11. Patient agreed not to participate in another intervention study while on treatment

Patient was eligible for the additional test of the study if the following 12 and 13 both applied:

12. Patient had completed the pollinosis symptoms survey period
13. Patient had provided written consent using the informed consent form approved by the IRB of the study site before starting any procedure related to the additional test of the study

Exclusion:

1. Patient 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) was Class 4 or higher at screening visit 1
2. Patient who had received specific immunotherapy (including desensitization therapy) for cedar pollinosis in the past
3. Patient who had received specific or non-specific immunotherapy within 5 years prior to screening visit 1
4. Patient who had received laser therapy/surgery for treating nasal symptoms within 3 years prior to screening visit 1
5. Patient who had 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 (Th) 2 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 was allowed. However, use at the study drug vaccination site on the day before day 1 was not allowed.)
6. Patient who had 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 [TNFα] antibody, anti-IgE monoclonal antibody, etc.)
7. Patient who had 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 were allowed. However, use at the study drug vaccination site on the day before day 1 was not allowed.)
8. Patient who had received or was planning to receive vaccination of a live vaccine within 28 days prior to the first vaccination of the study drug, and/or patient who had received or was planning to receive vaccination of an inactivated vaccine/toxoid within 7 days prior to the first vaccination of the study drug
9. Patient who had 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. Patient who had a positive immunological test result for hepatitis B surface antigen or hepatitis C virus antibody at screening visit 1
11. Patient who had a complication of nasal disorder (nasal polyp, nasal septum deviation, chronic sinusitis, etc.) that might had affected efficacy evaluation
12. Patient who had autoimmune disease or other serious primary disease
13. Patient who had been diagnosed with immunodeficiency in the past
14. Patient who had 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. Patient who had a complication of cardiovascular disease (including congestive cardiac failure, angina pectoris and cardiac arrhythmias that require medical treatment)
16. Patient who had a complication of hepatic disease (including viral hepatitis and drug-induced liver injury)

17. Patient who had a complication of renal disease (including acute kidney injury, glomerulonephritis and interstitial nephritis)
18. Patient who had a complication of respiratory disease (including bronchial asthma and chronic bronchitis that require medical treatment)
19. Patient who had a complication of malignant tumor or had been diagnosed with or had received treatment for malignant tumor within 5 years prior to the first vaccination of the study drug
20. Patient who had been diagnosed with mental conditions, such as schizophrenia, bipolar disorder and major depressive disorder, or dementia
21. Patient who had a complication that might had had an impact on the evaluation of local and systemic reactions
22. Patient who had received vaccination of Cry j 2-lysosome-associated membrane protein (LAMP) vaccine
23. Patient who had participated in a study of ASP4070 and received vaccination of the study drug
24. Patient who had 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 patient who was participating in such a study at present
25. Patient who was an employee of the sponsor or contract research organization (CRO) or medical institution involved in the study
26. Patient who was considered by the investigator or subinvestigator as unsuitable for study participation

Test Product, Dose and Mode of Administration, Batch Numbers: ASP4070 Injection 4 mg/0.4 mL, intradermally, [redacted]

Duration of Treatment: The number of vaccination was set to 8 times with 14-day intervals (vaccination period of 14 weeks).

Reference Product, Dose and Mode of Administration, Batch Numbers: ASP4070 Placebo Injection (physiological saline), intradermally, [redacted]

Criteria for Evaluation: Primary and secondary efficacy endpoints in this study were as follows:

Primary efficacy endpoints: Change in the mean of 3TNSS during 120 to 180 minutes (every 15 minutes, total of 5 time points) after start of cedar pollen exposure in the chamber as compared to the score before cedar pollen exposure.

Secondary efficacy endpoints:

- 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 (time point when the score of nasal or eye symptom worsens by 1 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

Other Efficacy Endpoints (during the pollinosis symptoms survey period):

- 3TNSS
- Individual nasal symptom (sneezing, nasal discharge and nasal congestion) score
- TNNSS
- Individual eye symptom (itchy eyes and watery eyes) 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): JRQLQ No 1
- Overall evaluation by the patient

Immune response endpoints: 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 and basophil activation test (BAT) for primary study period, and specific IgE antibody (anti-JRC) and BAT for additional test

Safety endpoints: Adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory assessments, local reactions and systemic reactions and SAEs that occur within approximately 9 months after the end of the primary study period

Statistical Methods:

Populations for Analysis:

The full analysis set (FAS) consisted of all patients who were randomized, were vaccinated with the study drug at least once, and had at least 1 measurement for efficacy evaluation obtained after vaccination of the study drug.

The per protocol set (PPS) consisted of the subset of the FAS who did not meet criteria for the PPS exclusion.

The safety analysis set (SAF) consisted of all patients who were vaccinated with the study drug at least once.

The immunological analysis set (IAS) consisted of all patients who were randomized, were vaccinated with the study drug at least once, and had at least 1 measurement for immunological response endpoint after vaccination of the study drug.

The IAS-2 consisted of patients who had provided additional consent for the additional test and had at least 1 measurement for immunological response endpoint during the additional study period.

The pollinosis symptom analysis set (PSAS) consisted of all patients who were randomized, were vaccinated with the study drug at least once, and had at least 1 measurement for an endpoint on pollinosis symptoms during the pollen dispersal season after vaccination of the study drug.

Efficacy:

The FAS was used for primary analysis. With regard to the change in the mean of 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 group and the placebo group on day 183, 2-sided 95% confidence interval (CI) and 2-sided P value were calculated using a mixed model for repeated measures

(MMRM) assuming an unstructured covariance structure within patients with explanatory variables being the treatment group (ASP4070 4 mg, ASP4070 1 mg and placebo), evaluation time (day 127, day 155 and day 183), the stratification factors and interaction of the treatment group and evaluation time.

With the significance level of the test to be 5% 2-sided, the tests were to 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

Secondary endpoints were analyzed based on FAS as follows:

- Descriptive statistics were calculated for actual values.
- For change in the mean of each variable after start of cedar pollen exposure as compared to those before cedar pollen exposure, descriptive statistics were calculated for actual values and change from specified time points.
- For change in the mean of some variables after start of cedar pollen exposure as compared to those before cedar pollen exposure, the adjusted mean difference between each ASP4070 drug group and the placebo group with 2-sided 95% CI and 2-sided P value were calculated using a MMRM.
- For time to event variables, 25, 50, 75 percentile of the predicted value and their 95% CI were calculated by the Kaplan-Meier method.

Other Efficacy Endpoints (during the pollinosis symptoms survey period):

- Descriptive statistics were presented for each symptom score in 4 analysis periods.

<u>Safety:</u>

Adverse events:

The coding dictionary for this study was MedDRA/Japanese version ver.19.0. It was used to summarize AEs by SOC and preferred term (PT). The number of treatment emergent adverse events (TEAEs) and number and percentage of patients with TEAEs, as classified by SOC and PT were summarized for each treatment group. Summaries were provided for:

- TEAEs
- Drug related TEAEs
- Serious TEAEs
- Drug related serious TEAEs
- TEAEs leading to permanent discontinuation of study drug
- Drug related TEAEs leading to permanent discontinuation of study drug

Laboratory parameters, vital signs and 12-lead ECG:

Quantitative variables were summarized using descriptive statistics for each treatment group at each time point. Additionally, a within-patient change was calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Frequency tabulations of qualitative clinical were presented for each treatment group at each time point.

Summary of Results/Conclusions:

Population:

A total of 150 patients were randomized to ASP4070 4 mg group, ASP4070 1 mg group or placebo group for 50 patients each [Table 1]. Of the 150 randomized patients, 142 patients (47 in ASP4070 4 mg group, 48 in ASP4070 1 mg group and 47 in the placebo group) completed the study, and 8 patients (3 in ASP4070 4 mg group, 2 in ASP4070 1 mg group and 3 in the placebo group) discontinued the study. There was no discontinuation due to AEs in primary study period in all treatment groups. After completion of the primary study period, total 142 patients subsequently performed the pollinosis symptoms survey period, and completed this period [Table 2].

For primary study period, all 150 patients were included in the SAF. The FAS, PPS and IAS consisted of 145, 141 and 147 patients, respectively.

In the FAS, the mean (SD) age of patients was 38.4 (8.7) years, and almost half of patients were age ≥ 40 to < 50 years. No apparent difference was found among the ASP4070 4 mg, ASP4070 1 mg and placebo groups for any of the demographics or baseline characteristics except sex. Although the male (33.3% [16/48]) in ASP4070 4 mg was half of the female (66.7% [32/48]) in same group, the male in placebo groups was equal to the female (50.0% [24/48] each) [Table 3].

The patients in the category that was the duration of disease ≥ 20 years were the most frequent with approximately 40%. The most patients (approximately 80%) had slightly bad (severe) or very bad (most severe) in the severity of pollinosis symptoms in 2017. Almost half of the patients were in the class 3 of JRC specific IgE antibody test. In approximately 60% of patients, change in mean of 3TNSS 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 was observed < 5.

No apparent unbalances were found in the baseline values for efficacy variables among ASP4070 4 mg, ASP4070 1 mg and placebo groups.

Efficacy Results:

For the primary and major secondary efficacy endpoints in the primary study period;

- The primary analysis of the primary endpoint was the change from pre-exposure in the mean of 3TNSS during 120 to 180 minutes at day 183. The adjusted mean differences (95% CI) were 0.09 (-0.52, 0.69) for ASP4070 4 mg vs placebo and -0.01 (-0.61, 0.59) for ASP4070 1 mg vs placebo. There was no statistically significant difference between ASP4070 4 mg and placebo in the primary analysis of the primary endpoint (P = 0.777, MMRM) [Table 4 and Figure 1]. The hierarchical testing procedure stopped at the first statistical testing. Therefore, both ASP4070 4 mg and ASP4070 1 mg did not reach a statistical significance as compared to placebo in the primary analysis of the primary endpoint. At day 127 and day 155, the change from pre-exposure in the mean of 3TNSS during 120 to 180 minutes showed similar trends to that at day 183.
- The analysis results of primary endpoint in the PPS were consistent with those in the FAS.
- There were no apparent difference and specific trend among any subgroups.
- The secondary endpoints of the change from pre-exposure in the mean of 4TNSS [Table 5 and Figure 2], TNNSS [Table 6 and Figure 3] and 5TSS [Table 7 and Figure 4] during 120 to 180 minutes at day 183 showed similar trends to primary endpoint. No difference in the nasal discharge amount among groups was observed.

For the other efficacy endpoints in the pollinosis symptoms survey period;

- The higher scores (worse symptoms) were observed in the mean of TNSMS during any period in active groups compared to placebo group. The adjusted mean differences (95% CI) were 2.09 (0.32, 3.86) for ASP4070 4 mg vs placebo during period B, which was statically significant in favor of the placebo group (P = 0.021, ANCOVA). There were no statistically significant difference between ASP4070 1 mg and placebo (P = 0.275, ANCOVA).
- The higher scores (worse symptoms) were observed in the mean of TNNSMS during any period in active groups compared to placebo group. The adjusted mean differences (95% CI) were 1.25 (0.27, 2.23) for ASP4070 4 mg vs placebo during period B, which was statically significant in favor of the placebo group (P = 0.013, ANCOVA). There were no statistically significant difference between ASP4070 1 mg and placebo (P = 0.115, ANCOVA).
- The higher scores (worse symptoms) were observed in the mean of TSMS during any period in active groups compared to placebo group. The adjusted mean differences (95% CI) were 3.34 (0.79, 5.88) for ASP4070 4 mg vs placebo during period B, which was statically significant in favor of the placebo group (P = 0.010, ANCOVA). There were no statistically significant difference between ASP4070 1 mg and placebo (P = 0.171, ANCOVA).
- The changes of symptom scores (TNSS, TNNSS and TSS) in pollinosis symptoms survey period showed higher scores (worse symptom) in active groups compared to placebo group similar to the symptom medication scores (TNSMS, TNNSMS and TSMS).
- The score for each questionnaire in the JRQLQ II and the score for general state in the JRQLQ III showed worse score in ASP4070 4 mg group compared to placebo group.

Key findings in immune response were;

- [redacted]
- [redacted]
- No trend in anti-JRC-specific IgE, anti-JRC-specific IgG, anti-JRC-specific IgG4 and BAT change was observed.
- The positive anti-LAMP antibody was observed after day 57 in 7 patients in the ASP4070 4 mg group and 6 patients in ASP4070 1 mg group, but no safety concerns were accompanied.
- The mean change between before and after pollinosis season at additional test in anti-JRC-IgE in active groups tended to be higher than that in placebo, but no difference in median change was observed. No changes in BAT at additional test in each group were observed.

Safety Results:

Key findings were;

- The incidences of TEAEs were 98.0% (49/50) in the ASP4070 4 mg group, 88.0% (44/50) in the ASP4070 1 mg group and 56.0% (28/50) in the placebo group [Table 10]. The common TEAEs (≥ 20% in any treatment group) by PT were vaccination site pruritus, erythema, tenderness, nasopharyngitis, headache

and pain. The incidences of these common TEAEs were higher in the active groups than those in the placebo group [Table 11]. All TEAEs were mild or moderate in severity, except for 3 severe events reported in the ASP4070 4 mg group.

- The incidences of drug-related TEAEs were 90.0% (45/50) in the ASP4070 4 mg group, 74.0% (37/50) in the ASP4070 1 mg group and 36.0% (18/50) in the placebo group. The common drug-related TEAEs (> 10% in any treatment group) by PT were vaccination site pruritus, erythema, tenderness, pain, induration, headache, fatigue and swelling. The incidences of these common drug-related TEAEs except fatigue were higher in the active groups than those in the placebo group.
- Neither death nor TEAEs leading to withdrawal of treatment were reported in all treatment groups.
- Two SAEs (appendiceal abscess and appendicitis) were observed in different 2 patients in ASP4070 4 mg group after the last vaccination. Both SAEs were resolved/recovered with treatments, and not related to the study drug, and they did not lead to discontinue the study.

CONCLUSIONS:

- For the primary endpoint, both ASP4070 4 mg and ASP4070 1 mg did not demonstrate superiority to placebo. The adjusted mean differences (95% CI) were 0.09 (-0.52, 0.69) for ASP4070 4 mg vs placebo and -0.01 (-0.61, 0.59) for ASP4070 1 mg vs placebo.
- ASP4070 was safe and well tolerated.

Date of Report: 27 Dec 2018

Table 1 Study Disposition in Primary Study Period (All Randomized Patients)

Parameter	Category	ASP4070 4 mg (n = 50)	ASP4070 1 mg (n = 50)	Placebo (n = 50)	Total (n = 150)
Study Discontinuation	No	47 (94.0%)	48 (96.0%)	47 (94.0%)	142 (94.7%)
	Yes	3 (6.0%)	2 (4.0%)	3 (6.0%)	8 (5.3%)
Primary End of Study Reason †	Completed	47 (94.0%)	48 (96.0%)	47 (94.0%)	142 (94.7%)
	Adverse Event	0	0	0	0
	Death	0	0	0	0
	Lost to Follow-up	0	0	0	0
	Protocol Deviation	0	0	0	0
	Withdrawal by Patient	1 (2.0%)	2 (4.0%)	3 (6.0%)	6 (4.0%)
	Study Terminated by Sponsor	0	0	0	0
	Other	2 (4.0%)	0	0	2 (1.3%)

† Only the primary protocol-specified reason for discontinuation was collected.
Source: Table 12.1A.1.3

Table 2 Study Disposition in Pollinosis Symptoms Survey Period (All Patients Who Completed Primary Study Period)

Parameter	Category	ASP4070 4 mg (n = 47)	ASP4070 1 mg (n = 48)	Placebo (n = 47)	Total (n = 142)
Study Discontinuation in Pollinosis Symptoms Survey Period	No	47 (100.0%)	48 (100.0%)	47 (100.0%)	142 (100.0%)
Primary End of Study Reason in Pollinosis Symptoms Survey Period †	Completed	47 (100.0%)	48 (100.0%)	47 (100.0%)	142 (100.0%)
	Adverse Event	0	0	0	0
	Death	0	0	0	0
	Lost to Follow-up	0	0	0	0
	Protocol Deviation	0	0	0	0
	Withdrawal by Patient	0	0	0	0
	Study Terminated by Sponsor	0	0	0	0
	Other	0	0	0	0

† Only the primary protocol-specified reason for discontinuation was collected.

Source: Table 12.1B.1.2

Table 3 Demographic Characteristics (Full Analysis Set)

Parameter	Category/ Statistic	ASP4070 4 mg (n = 48)	ASP4070 1 mg (n = 49)	Placebo (n = 48)	Total (n = 145)
Sex	Male	16 (33.3%)	19 (38.8%)	24 (50.0%)	59 (40.7%)
	Female	32 (66.7%)	30 (61.2%)	24 (50.0%)	86 (59.3%)
Age at Informed Consent (Years)	n	48	49	48	145
	Mean (SD)	38.8 (8.4)	38.3 (8.5)	38.1 (9.3)	38.4 (8.7)
	Median	41.0	41.0	40.0	41.0
	Min, Max	21, 50	21, 51	20, 50	20, 51
Age at Informed Consent (Years) Group	≥ 20 to < 30	8 (16.7%)	9 (18.4%)	12 (25.0%)	29 (20.0%)
	≥ 30 to < 40	14 (29.2%)	13 (26.5%)	12 (25.0%)	39 (26.9%)
	≥ 40 to < 50	25 (52.1%)	24 (49.0%)	21 (43.8%)	70 (48.3%)
	≥ 50	1 (2.1%)	3 (6.1%)	3 (6.3%)	7 (4.8%)
Height at Screening Visit 1 (cm)	Mean (SD)	161.67 (7.31)	164.06 (8.06)	164.94 (10.09)	163.56 (8.62)
	Median	161.70	164.00	163.25	162.50
	Min, Max	145.6, 176.0	151.6, 183.2	148.6, 186.2	145.6, 186.2
Weight at Screening Visit 1 (kg)	Mean (SD)	56.61 (9.68)	59.95 (10.98)	57.68 (9.93)	58.09 (10.24)
	Median	55.50	60.00	56.35	56.60
	Min, Max	43.2, 79.4	41.2, 83.9	41.3, 80.7	41.2, 83.9
Body Mass Index at Screening Visit 1 (kg/m^2)	Mean (SD)	21.56 (2.58)	22.15 (2.89)	21.12 (2.58)	21.61 (2.71)
	Median	21.17	22.14	20.57	21.14
	Min, Max	17.0, 29.6	16.9, 27.6	17.2, 28.6	16.9, 29.6
Duration of Disease (Years)	< 5	3 (6.3%)	4 (8.2%)	3 (6.3%)	10 (6.9%)
	≥ 5 to < 10	6 (12.5%)	8 (16.3%)	11 (22.9%)	25 (17.2%)
	≥ 10 to < 15	9 (18.8%)	12 (24.5%)	7 (14.6%)	28 (19.3%)
	≥ 15 to < 20	11 (22.9%)	4 (8.2%)	10 (20.8%)	25 (17.2%)
	≥ 20	19 (39.6%)	21 (42.9%)	17 (35.4%)	57 (39.3%)
Duration of Disease (Years) Group	< 10	9 (18.8%)	12 (24.5%)	14 (29.2%)	35 (24.1%)
	≥ 10 to < 20	20 (41.7%)	16 (32.7%)	17 (35.4%)	53 (36.6%)
	≥ 20	19 (39.6%)	21 (42.9%)	17 (35.4%)	57 (39.3%)
Severity of Pollinosis Symptoms in 2017	Good (Almost Asymptomatic)	0	0	0	0
	Slightly Good (Mild)	1 (2.1%)	1 (2.0%)	1 (2.1%)	3 (2.1%)
	Not Bad (Moderate)	9 (18.8%)	9 (18.4%)	9 (18.8%)	27 (18.6%)
	Slightly Bad (Severe)	25 (52.1%)	22 (44.9%)	18 (37.5%)	65 (44.8%)
	Very Bad (Most Severe)	13 (27.1%)	17 (34.7%)	20 (41.7%)	50 (34.5%)
Severity of Pollinosis Symptoms in 2017 Group	Good	0	0	0	0
	Slightly Good or Not Bad	10 (20.8%)	10 (20.4%)	10 (20.8%)	30 (20.7%)
	Slightly Bad or Very Bad	38 (79.2%)	39 (79.6%)	38 (79.2%)	115 (79.3%)
Class of JRC Specific IgE Antibody Test at Screening Visit 1	3	26 (54.2%)	26 (53.1%)	26 (54.2%)	78 (53.8%)
	4	16 (33.3%)	15 (30.6%)	17 (35.4%)	48 (33.1%)
	5	3 (6.3%)	6 (12.2%)	4 (8.3%)	13 (9.0%)
	6	3 (6.3%)	2 (4.1%)	1 (2.1%)	6 (4.1%)
Class of JRC Specific IgE Antibody Test at Screening Visit 1	3	26 (54.2%)	26 (53.1%)	26 (54.2%)	78 (53.8%)
	≥ 4	22 (45.8%)	23 (46.9%)	22 (45.8%)	67 (46.2%)

Max: Maximum; Min: Minimum.

Source: Table 12.1A.2.1.1

Table 4 Change From Pre-exposure in Mean Total 3 Nasal Symptom Score During 120 to 180 Minutes at Day 183 – MMRM (Full Analysis Set)

Statistic	ASP4070 4 mg (n = 48)	ASP4070 1 mg (n = 49)	Placebo (n = 48)
Mean (SD)	2.04 (1.30)	1.91 (1.82)	1.98 (1.34)
Adjusted Mean Difference (ASP4070 - Placebo)	0.09	-0.01	NA
95% Confidence Interval of Adjusted Mean Difference (ASP4070-Placebo)	(-0.52, 0.69)	(-0.61, 0.59)	NA
P-value	0.777	0.983 †	NA

For MMRM, restricted maximum likelihood was used, KENWARD-ROGER was used to estimate of degree of freedom of denominator, and "Unstructured" was assumed as structure of variance-covariance matrix.

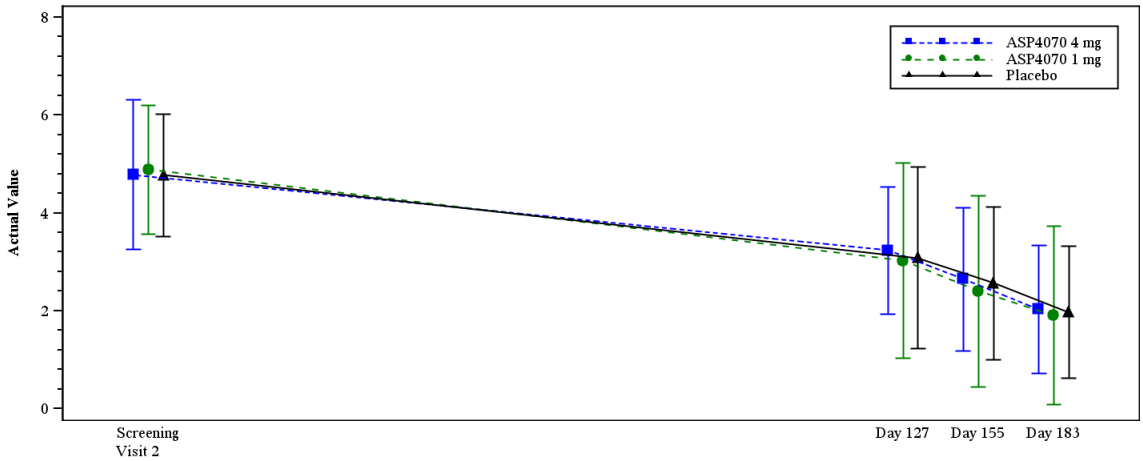
The MMRM model included treatment group, stratification factors, analysis visit and interaction of treatment group and analysis visit.

NA: not applicable.

† The P-value was calculated and shown for reference.

Source: Table 12.3A.1.1

Figure 1 Mean (± SD) Plot of Change From Pre-exposure in Mean Total 3 Nasal Symptom Score During 120 to 180 Minutes (Full Analysis Set)



Number of subjects				
ASP4070 4 mg	48	47	47	47
ASP4070 1 mg	49	49	47	48
Placebo	48	48	46	47

Source: Figure 12.3A.1.1.1

Table 5 Change From Pre-exposure in Mean 4 Nasal Symptom Score During 120 to 180 Minutes at Day 183- MMRM (Full Analysis Set)

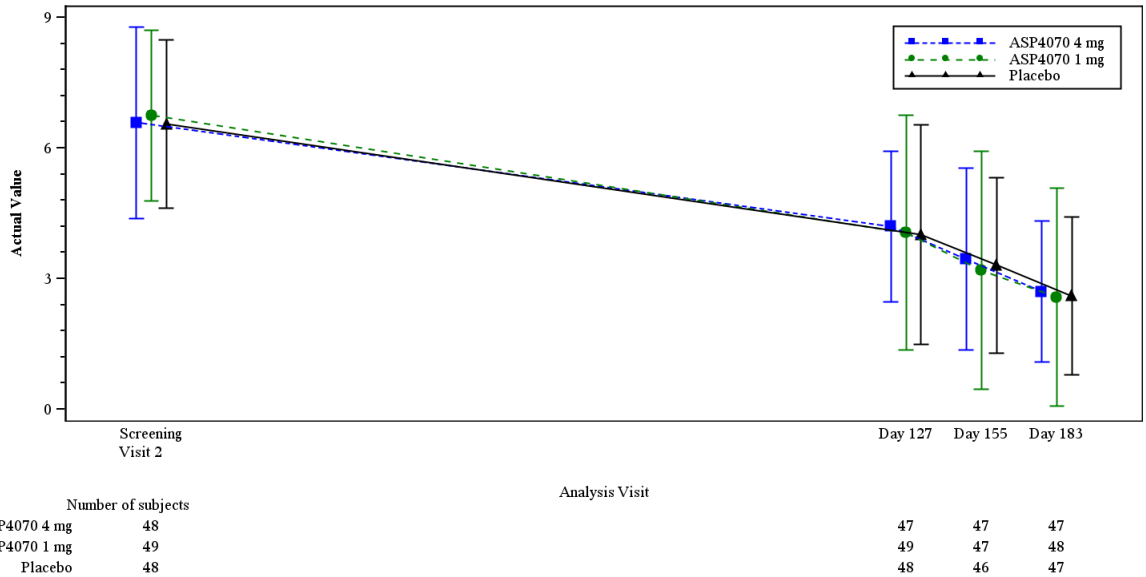
Statistic	ASP4070 4 mg (n = 48)	ASP4070 1 mg (n = 49)	Placebo (n = 48)
Mean (SD)	2.71 (1.61)	2.58 (2.50)	2.62 (1.81)
Adjusted Mean Difference (ASP4070 - Placebo)	0.16	0.07	NA
95% Confidence Interval of Adjusted Mean Difference (ASP4070-Placebo)	(-0.64, 0.97)	(-0.73, 0.87)	NA
P-value	0.690	0.868	NA

For MMRM, restricted maximum likelihood was used, KENWARD-ROGER was used to estimate of degree of freedom of denominator, and "Unstructured" was assumed as structure of variance-covariance matrix.

The MMRM model included treatment group, stratification factors, analysis visit and interaction of treatment group and analysis visit.

Source: Table 12.3A.3.2.1

Figure 2 Mean (± SD) Plot of Change From Pre-exposure in Mean Total 4 Nasal Symptom Score During 120 to 180 Minutes (Full Analysis Set)



Source: Figure 12.3A.3.1.1

Table 6 Change From Pre-exposure in Mean Total Non-nasal Symptom Score During 120 to 180 Minutes at Day 183 - MMRM (Full Analysis Set)

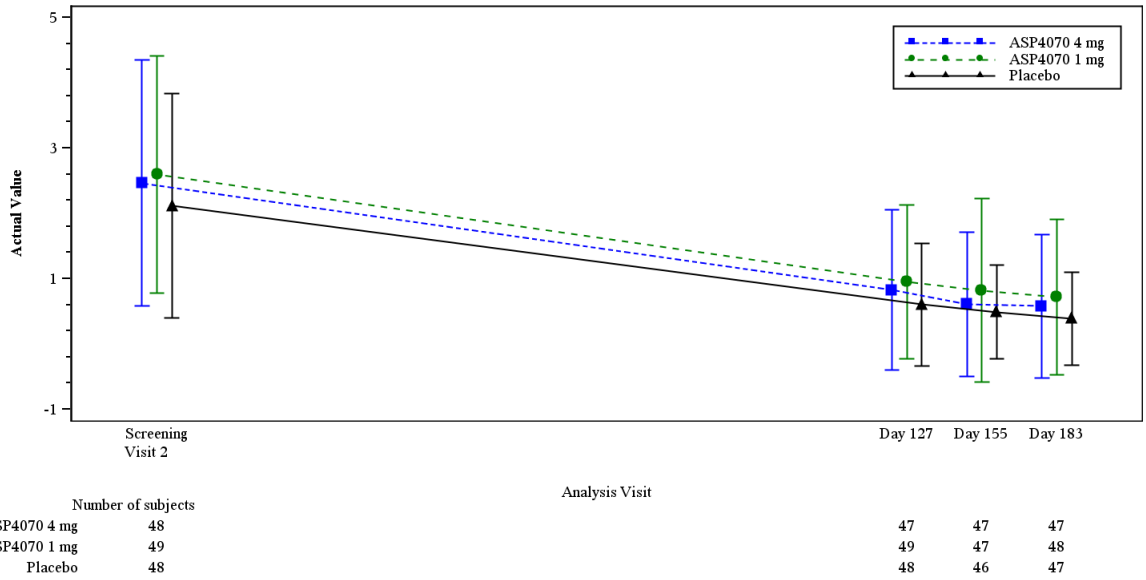
Statistic	ASP4070 4 mg (n = 48)	ASP4070 1 mg (n = 49)	Placebo (n = 48)
Mean (SD)	0.59 (1.09)	0.73 (1.19)	0.40 (0.71)
Adjusted Mean Difference (ASP4070 - Placebo)	0.19	0.35	NA
95% Confidence Interval of Adjusted Mean Difference (ASP4070-Placebo)	(-0.22, 0.59)	(-0.05, 0.76)	NA
P-value	0.364	0.082	NA

For MMRM, restricted maximum likelihood was used, KENWARD-ROGER was used to estimate of degree of freedom of denominator, and "Unstructured" was assumed as structure of variance-covariance matrix.

The MMRM model included treatment group, stratification factors, analysis visit and interaction of treatment group and analysis visit.

Source: Table 12.3A.5.2.1

Figure 3 Mean (± SD) Plot of Change From Pre-exposure in Mean Total Non-nasal Symptom Score During 120 to 180 Minutes (Full Analysis Set)



Source: Figure 12.3A.5.1.1

Table 7 Change From Pre-exposure in Mean Total 5 Symptom Score During 120 to 180 Minutes at Day 183 - MMRM (Full Analysis Set)

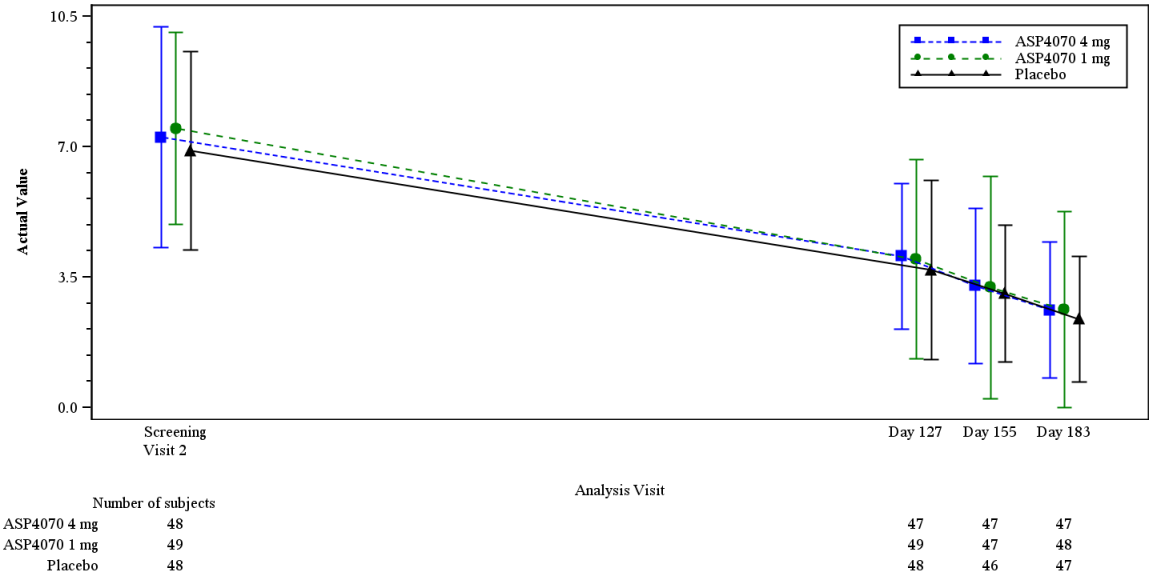
Statistic	ASP4070 4 mg (n = 48)	ASP4070 1 mg (n = 49)	Placebo (n = 48)
Mean (SD)	2.63 (1.82)	2.64 (2.62)	2.38 (1.68)
Adjusted Mean Difference (ASP4070 - Placebo)	0.27	0.35	NA
95% Confidence Interval of Adjusted Mean Difference (ASP4070-Placebo)	(-0.55, 1.09)	(-0.47, 1.17)	NA
P-value	0.514	0.400	NA

For MMRM, restricted maximum likelihood was used, KENWARD-ROGER was used to estimate of degree of freedom of denominator, and "Unstructured" was assumed as structure of variance-covariance matrix.

The MMRM model included treatment group, stratification factors, analysis visit and interaction of treatment group and analysis visit.

Source: Table 12.3A.7.2.1

Figure 4 Mean (± SD) Plot of Change From Pre-exposure in Mean Total 5 Symptom Score During 120 to 180 Minutes (Full Analysis Set)



Source: Figure 12.3A.7.1.1

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[redacted]

Table 10 Overview of Treatment-emergent Adverse Events and Death (Safety Analysis Set)

	ASP4070 4 mg (n = 50) n (%) #E		ASP4070 1 mg (n = 50) n (%) #E		Placebo (n = 50) n (%) #E	
TEAE	49 (98.0%)	552	44 (88.0%)	357	28 (56.0%)	64
Mild	33 (66.0%)	524	33 (66.0%)	342	18 (36.0%)	53
Moderate	13 (26.0%)	25	11 (22.0%)	15	10 (20.0%)	11
Severe	3 (6.0%)	3	0	0	0	0
Life-threatening Possibility	0	0	0	0	0	0
Drug-Related † TEAE	45 (90.0%)	508	37 (74.0%)	316	18 (36.0%)	37
Device-Related † TEAE	0	0	0	0	0	0
Serious TEAE	2 (4.0%)	2	0	0	0	0
Drug-Related † Serious TEAE	0	0	0	0	0	0
TEAE Leading to Withdrawal of Treatment	0	0	0	0	0	0
Drug-Related † TEAE Leading to Withdrawal of Treatment	0	0	0	0	0	0
Death	0	0	0	0	0	0
Local Reaction	34 (68.0%)	287	24 (48.0%)	123	7 (14.0%)	14
Systemic Reaction	13 (26.0%)	34	13 (26.0%)	48	9 (18.0%)	14
TEAEs Other Than Local or Systemic Reactions	48 (96.0%)	231	40 (80.0%)	186	21 (42.0%)	36
Drug-Related † TEAEs Other Than Local or Systemic Reactions	38 (76.0%)	187	31 (62.0%)	145	6 (12.0%)	9

Number of patients (n), percentage of patients (%) and number of events (#E) are shown.

† Possible or probable, as assessed by the investigator, or records where relationship is missing.

Source: Tables 12.6A.1.1.1 and 12.6A.1.1.4

Table 11 Treatment-emergent Adverse Events ≥ 5% in Any Treatment Group (Safety Analysis Set)

MedDRA v19.0 System Organ Class Preferred Term	ASP4070 4 mg (n = 50) n (%) #E		ASP4070 1 mg (n = 50) n (%) #E		Placebo (n = 50) n (%) #E	
Overall	48 (96.0%)	550	44 (88.0%)	357	28 (56.0%)	64
Gastrointestinal Disorders						
Diarrhoea	5 (10.0%)	6	4 (8.0%)	4	1 (2.0%)	1
Nausea	3 (6.0%)	3	1 (2.0%)	1	2 (4.0%)	2
General Disorders and Administration Site Conditions						
Fatigue	5 (10.0%)	13	6 (12.0%)	19	7 (14.0%)	8
Induration	8 (16.0%)	24	2 (4.0%)	6	0	0
Pain	11 (22.0%)	32	5 (10.0%)	10	1 (2.0%)	1
Swelling	8 (16.0%)	14	1 (2.0%)	2	0	0
Tenderness	23 (46.0%)	71	13 (26.0%)	62	5 (10.0%)	6
Vaccination site pruritus	37 (74.0%)	179	29 (58.0%)	134	0	0
Infections and Infestations						
Nasopharyngitis	18 (36.0%)	19	11 (22.0%)	12	9 (18.0%)	13
Musculoskeletal and Connective Tissue Disorders						
Myalgia	3 (6.0%)	3	4 (8.0%)	4	4 (8.0%)	4
Nervous System Disorders						
Headache	8 (16.0%)	13	14 (28.0%)	27	4 (8.0%)	5
Respiratory, Thoracic and Mediastinal Disorders						
Rhinorrhoea	1 (2.0%)	1	5 (10.0%)	5	2 (4.0%)	2
Skin and Subcutaneous Tissue Disorders						
Erythema	31 (62.0%)	146	15 (30.0%)	43	2 (4.0%)	7

Number of patients (n), percentage of patients (%) and number of events (#E) are shown.

Source: Table 12.6A.1.1.10