Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Peficitinib (USAN)		
Name of Active Ingredient: ASP015K		

SYNOPSIS

Title of Study: A Phase 2b, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-finding, Multi-center Study to Evaluate the Safety and Efficacy of ASP015K in Moderate to Severe Rheumatoid Arthritis Patients (015K-CL-RA22)

Investigators/Coordinating Investigator: [redacted], MD

Study Center(s): This multi-center study was conducted at 41 sites, 19 sites in the United States, 3 sites in Bulgaria, 4 sites in the Czech Republic, 5 sites in Hungary, 6 sites in Poland and 4 sites in Mexico.

Publication Based on the Study: None

Study Period: 1.5 years

Study Initiation Date (Date of First Visit of First Patient): 19 June 2012

Study Completion Date (Date of Last Visit of Last Patient): 02 December 2013

Phase of Development: Phase 2b

Objectives: The objective of this study was to evaluate the safety and efficacy of ASP015K in moderate to severe rheumatoid arthritis (RA) patients.

Methodology: This was a phase 2b, randomized, double-blind, parallel-group, placebo-controlled, dose-finding, multi-center study with once daily oral ASP015K or matching placebo in patients with moderate to severe RA to evaluate the safety and efficacy of ASP015K monotherapy. After a screening period of up to 4 weeks, patients were equally assigned to an ASP015K 25 mg, ASP015K 50 mg, ASP015K 100 mg, ASP015K 150 mg or placebo group. Study drug was administered with food daily for 12 weeks. At the end of treatment, a follow-up period of 30 days was conducted for patients not rolling over into the optional extension study prior to week 16. Patients who completed the 12-week dosing period in this study may have been offered an opportunity to participate in a long-term, open-label extension study, 015K-CL-RA25. The follow-up visit was conducted only for patients not rolling over into open-label extension Study 015K-CL-RA25 (i.e., patients who rolled over into Study 015K-CL-RA25 were not assessed at follow-up).

Number of Patients (Planned, Enrolled and Analyzed): The total planned enrollment for the study was 275 patients. A total of 289 patients were enrolled Figure 1. All 289 randomized patients were included in the Full Analysis Set (FAS), Safety Analysis Set (SAF) and Pharmacodynamic Analysis Set (PDAS). Eleven patients treated with ASP015K were excluded from the Per Protocol Set due to treatment compliance of less than 75% or a protocol deviation. The Pharmacokinetic Analysis Set population included all of the patients treated with ASP015K that were also included in the FAS, SAF and PDAS populations.

Diagnosis and Main Criteria for Inclusion: Male or female patients aged ≥ 18 years diagnosed with RA according to the 1987 revised criteria of the American College of Rheumatology (ACR) and have had an inadequate response or had intolerance to a previous disease-modifying antirheumatic drug (DMARD) therapy

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were able to participate in this study. Patients were also required to have met the ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II or III and had active RA as evidenced by the following:

- ≥ 6 tender/painful joints (using tender joint count based on 68 joints [TJC68]),
- ≥ 6 swollen joints (using swollen joint count based on 66 joints [SJC66]) and
- C-reactive protein (CRP) of ≥ 0.8 mg/dL or erythrocyte sedimentation rate (ESR) of ≥ 28 mm/hr.

Patients were to be excluded from the study if they had a previous history of clinically significant infections or illness, a history of any malignancy, a history of heart failure, a history of long QT syndrome or prolonged QT interval, received plasma exchange therapy within 60 days prior to first dose, received live or live attenuated virus vaccination within 30 days prior to first dose, received corticosteroid within 28 days prior to first dose or received medications that are cytochrome P450 3A substrates with narrow therapeutic range within 14 days prior to first dose.

Test Product, Dose and Mode of Administration, Batch Numbers: Patients randomly assigned to an ASP015K group received either 25, 50, 100 or 150 mg ASP015K as 5, 10 or 30 mg oral tablets once daily with food. In this study, 3 different lots and 21 different batches of ASP015K tablets were used.

Duration of Treatment (or Duration of Study, if applicable): 12 weeks

Reference Product, Dose and Mode of Administration, Batch Numbers: Patients randomly assigned to the placebo group received matching oral placebo tablets once daily with food. In this study, 1 lot and 10 different batches of placebo tablets were used.

Criteria for Evaluation: The primary efficacy variable was the percentage of patients achieving a response in ACR criteria for 20% improvement in disease severity using the CRP level (ACR20-CRP) at week 12. Safety was assessed through adverse event (AE) reporting, vital signs, clinical laboratory evaluations (hematology, chemistry, urinalysis and fasting lipids profile), 12-lead electrocardiograms (ECGs) and physical examinations. The primary pharmacokinetic parameter measured was the trough plasma concentration (C_{trough}) of ASP015K, and metabolite(s) as appropriate. The pharmacodynamic variables included change from baseline in the lymphocyte subset assays CD3, CD4, CD8, CD19 and CD56/16 and in biomarkers interleukin 6 (IL-6) and matrix metalloproteinase 3 (MMP-3).

Statistical Methods:

The primary efficacy variable of ACR20-CRP at week 12 was summarized by proportion of responders, proportion of non-responders, difference in proportion of responders, odds ratio and 95% CI. A patient was defined as an ACR20-CRP responder at week 12 if the patient met all of the following ACR response criteria:

- At least 20% reduction from baseline at week 12 in TJC68 and
- At least 20% reduction from baseline at week 12 in SJC66 and
- At least 20% reduction from baseline at week 12 in ANY 3 of the 5 following ACR components:

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Name of Finished Product: Peficitinib (USAN)		
Name of Active Ingredient: ASP015K		

- Subject's global assessment of arthritis pain (SGAP) (assessed using a 100 mm visual analog scale [VAS])
- Subject's global assessment of arthritis (SGA) (assessed using a 100 mm VAS)
- Physician's global assessment of arthritis (PGA) (assessed using a 100 mm VAS)
- Health Assessment Questionnaire - Disability Index
- CRP

The primary analysis of the primary efficacy variable was based on a logistic regression model with effects for treatment group and geographic region (North America, Europe, Latin America). Additional analyses using normal approximation were also conducted.

Pharmacokinetic and pharmacodynamic variables were summarized with descriptive statistics.

Only treatment-emergent AEs (TEAEs) in the study period were summarized by TEAE occurrence and TEAE per 100 patient-years. TEAEs were summarized using the number and percentage of patients by MedDRA (v14.0) primary system organ class and preferred term for each treatment group. No statistical hypothesis testing was performed.

Changes from planned analyses included the addition of a summary table of severe infection TEAEs, the inclusion of the placebo treatment group in the PDAS and the updating of the phrase referring to patients who used DMARD medication after day 1 from RA therapy violators to patients who used rescue therapy.

Summary of Results/Conclusions:

Population: The majority of patients in the SAF were female (82%), less than 65 years of age (86.5%) with a mean age of 53.9 years (range: 26 - 82 years), white (81.7%) and not Hispanic or Latino (79.9%) Table 1. Approximately, half of the patients were from the North American region, while 41.2% of patients were from Europe and 11.1% of patients were from Latin America. The demographic characteristics were similar between the treatment groups.

The mean age at onset of RA was 43.48 years and the mean duration of the disease was 10.43 years. The majority of the patients (86.2%) had previously used DMARDs. The baseline disease activity and RA history were similar between the treatment groups.

Efficacy Results: Analysis of the primary efficacy variable by logistic regression adjusted for treatment group and geographic region showed the ASP015K 150 mg group had a statistically significantly higher rate of ACR20-CRP response than did the placebo group (56.3% vs 29.4%, respectively; P = 0.001) Table 2. The proportion of ACR20-CRP responders in the ASP015K 100 mg group was numerically greater than placebo (48.3% vs 29.4%; P = 0.054). The ASP015K 25 mg group had a statistically significantly lower rate of ACR-20-CRP response than did the placebo group (22.0% vs 29.4%, respectively; P = 0.005). The dose-response P value was < 0.001. Analyses done based on normal approximation to the binomial distribution for difference in proportions showed statistical differences between the ASP015K 100 mg and 150 mg groups versus placebo (18.9 % difference [P = 0.039] and 26.8% difference [P = 0.003], respectively).

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Name of Finished Product: Peficitinib (USAN)		
Name of Active Ingredient: ASP015K		

All of the sensitivity analyses performed found statistically significant differences using the logistic regression model between the same treatment groups as the primary analysis (placebo vs the ASP015K 25 mg and ASP015K 150 mg) with the exception of the analysis using the Cochran-Mantel-Haenszel method, which did not find a statistically significant difference between the placebo and ASP015K 25 mg group. The Cochran-Mantel-Haenszel method as well as the last observation carried forward (LOCF) then calculate response method and the response then LOCF method did find a statistically significant increase of responders in the ASP015K 100 mg group over the placebo group, which was not detected in the primary analysis.

None of the subgroup analyses had a statistically significant subgroup/treatment interaction.

Analyses of the secondary efficacy endpoints of time to ACR20-CRP response, ACR50-CRP and change in DAS28-CRP support the efficacy of ASP015K 100 mg and 150 mg in the treatment of RA. Improvements in disease activity were seen early, as demonstrated by a shorter median time to first ACR20-CRP response and statistically significant differences in DAS28-CRP seen in both the ASP015K 100 mg and 150 mg groups as early as week 4.

Pharmacokinetic Results: By week 1, at least two thirds of the maximum median plasma trough concentration was reached for each ASP015K dose group. At each week, the median plasma trough concentrations increased with increasing dose.

Pharmacodynamic Results: There were no consistent changes in matrix metalloproteinase 3 and CD3 (CD45+CD3+) and CD4 (CD45+CD3+CD4+) lymphocytes in any of the ASP015K groups. There was a trend of increasing CD19 (CD45+CD3-CD19+) lymphocytes with increasing ASP015K dose versus placebo as well as a trend of decreasing CD16/56 (CD45+CD3-CD16;56+) lymphocytes.

Safety Results: Overall, 41.6% (99/238 patients) of ASP015K patients and 43.1% (22/51 patients) of placebo patients reported at least 1 TEAE Table 3. The most common TEAEs occurring in the ASP015K groups were upper respiratory tract infection (5.5% [13/238] patients), nausea (5.0% [12/238 patients]), diarrhoea (3.8% [9/238 patients]) and urinary tract infection (3.4% [8/238 patients]). The most common SOC within which both ASP015K and placebo patients experienced the most TEAEs was Infections and Infestations (13.4% [32/238] and 13.7% [7/51], respectively). More patients in the ASP015K groups (11.3% [27/238] patients) experienced TEAEs in the SOC of Gastrointestinal Disorders than the placebo group (5.9% [3/51] patients). Most of the TEAEs were NCI-CTCAE Grade 1 or 2 in severity. There were no life-threatening TEAEs or TEAEs leading to death (NCI-CTCAE Grade 4 or 5) in this study. There were 64 patients who experienced 89 drug-related TEAEs. The most common drug-related TEAEs were upper respiratory tract infection (4.6% [11/238 patients]), nausea (4.2% [10/238 patients]), diarrhoea (2.5% [6/238 patients]), dyspepsia (2.1% [5/238 patients]) and hypercholesterolaemia (1.7% [4/238 patients]).

No deaths occurred during this study. There were 12 patients who experienced 15 serious AEs (SAEs) Table 4. All of the SAEs were considered not related to study drug with the exception of 1 instance of transient ischaemic attack, the only SAE occurring in more than 1 patient (2 patients total). There were 9 patients who experienced 13 TEAEs leading to permanent discontinuation. The only TEAE leading to

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Peficitinib (USAN)		
Name of Active Ingredient: ASP015K		

permanent discontinuation occurring in more than 1 patient was dyspepsia (2 patients total). Only 1 patient experienced a severe infection (any infection SAE or any infection TEAE ≥ Grade 3 in severity), a Grade 3 abscess limb considered not related to study drug in the ASP015K 25 mg group.

Most hematology, chemistry, urinalysis or fasting lipid profile parameters were Grade 1 or 2, and none of these parameters were Grade 4. There were no consistent changes from baseline in vital signs in the ASP015K dose groups compared to placebo. Clinically significant ECG abnormalities were reported in 4 patients at week 12/end of treatment. The ECG abnormalities included a long QT interval, a sinus rhythm, sinus bradycardia and electrical axis deviation.

CONCLUSIONS: In this study of 12-weeks treatment with study drug in a population of RA patients with long-standing disease that had significant exposure to previous biologic therapy (approximately 50%), ASP015K showed a significant dose response on the primary endpoint of ACR20, with the doses of 100 mg once daily and 150 mg once daily showing statistically significant differences as compared to placebo. These higher doses of ASP015K also showed significant differences from placebo on the secondary endpoints of ACR50 and change in DAS28-CRP. Supportive efficacy endpoints showed that treatment with higher doses of ASP015K led to early effects on inflammatory markers (CRP and ESR by week 1) as well as DAS28 (by week 4). Additionally, ASP015K 150 mg had a statistically significant shorter time to ACR20 as compared to placebo. Individual ACR response component analysis showed statistically significant improvements versus placebo in tender and swollen joint counts, and physician and subject's global assessment scores showed greatest improvement at the higher ASP015K doses. Statistically significant differences in change in HAQ-DI were not seen, although there was a greater reduction in the ASP015K 150 mg dose group that approached statistical significance (P = 0.07).

The ASP015K 100 and 150 mg groups also demonstrated a greater response in the "higher bar" endpoints. A greater proportion of patients in these groups achieved DAS28-ESR remission, and both groups were numerically greater in DAS28-CRP remission versus placebo, with the ASP015K 100 mg group achieving statistical significance.

Pharmacokinetic analysis supported the dose response relationship as well as the early clinical effects seen in the active treatment groups. Mean and median plasma trough concentrations increased in a dose-dependent manner. By week 1, at least two thirds of the maximum median plasma trough concentration was reached for each ASP015K dose group. At each week, the median plasma trough concentrations increased with increasing dose.

Safety evaluation revealed no new safety signals with ASP015K and showed that treatment with active drug was well-tolerated. Less than half of all the patients experienced a TEAE. The most common TEAEs were upper respiratory tract infection, nausea, diarrhoea and urinary tract infection. The most common SOC within which both ASP015K and placebo patients experienced the most TEAEs was Infections and Infestations, with upper respiratory tract infection and urinary tract infection being the most common. Patients in the ASP015K groups also commonly experienced TEAEs in the SOC of Gastrointestinal Disorders, such as nausea and

Name of Sponsor/Company: Astellas Pharma Inc.		
Name of Finished Product: Peficitinib (USAN)		
Name of Active Ingredient: ASP015K		

diarrhoea, at a greater incidence than the patients in the placebo group. Most of the TEAEs were mild or moderate in severity. Approximately 5% of all patients experienced TEAEs of Grade 3 severity. There were no TEAEs above Grade 3. Drug-related TEAEs occurring in ≥ 1% more patients in the ASP015K groups versus the placebo group are nausea, upper respiratory tract infection, blood CPK increased (2 of which were of Grade 3 severity) and hypertriglyceridaemia.

No deaths occurred during this study. Less than 5% of all patients experienced an SAE or a TEAE leading to permanent discontinuation. Transient ischaemic attack was the only SAE occurring in more than 1 patient (2 patients in the ASP015K 100 mg group), 1 of which was considered possibly related to ASP015K. Dyspepsia was the only TEAE leading to permanent discontinuation occurring in more than 1 patient (1 patient each in the ASP015K 100 mg and 150 mg groups) and both events were considered probably related to ASP015K. TEAEs of vomiting and skin lesion also led to permanent discontinuation and were considered possibly related to ASP015K.

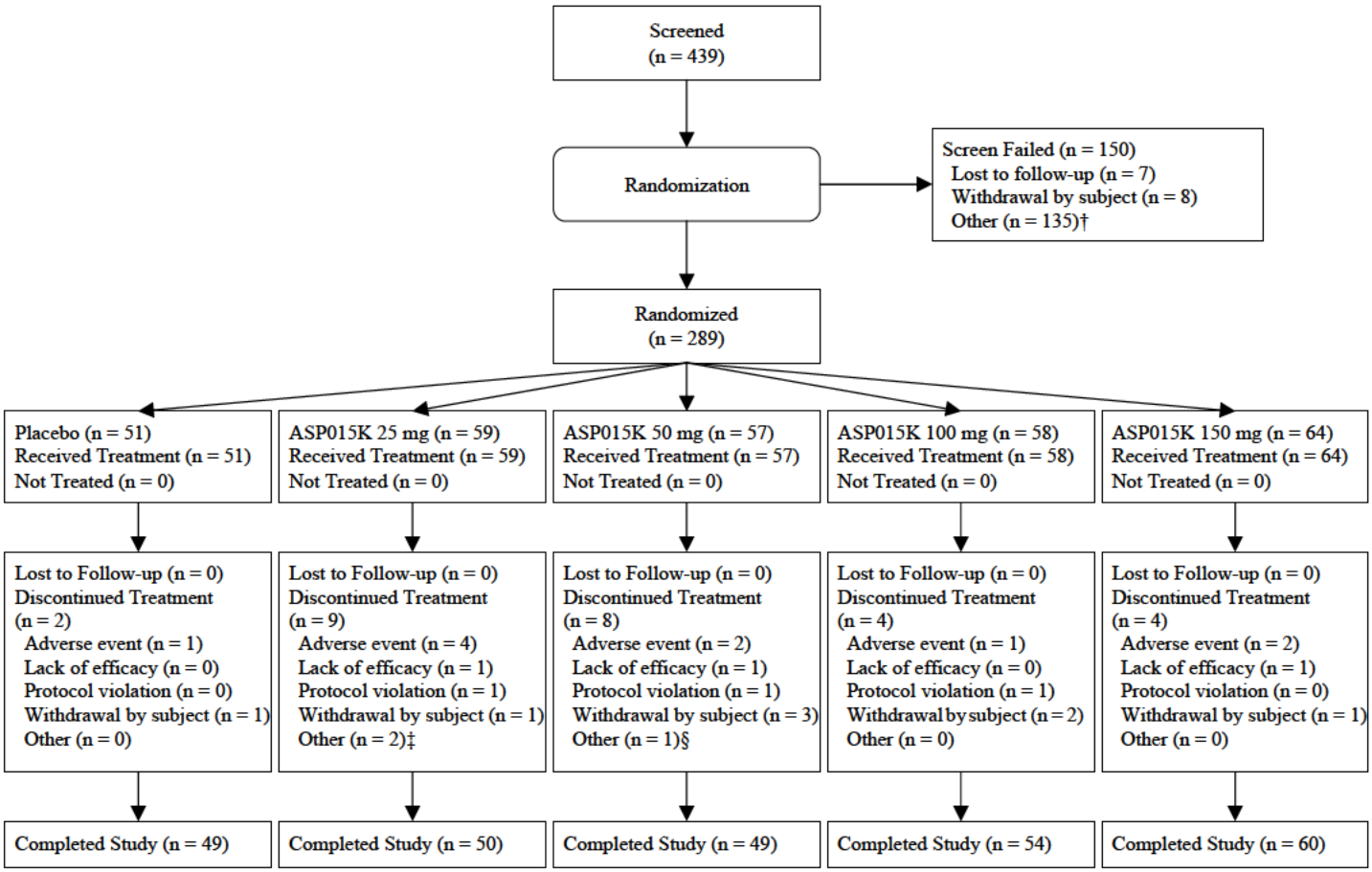
In this study, only 1 patient, who was in the ASP015K 25 mg group, experienced a severe infection of a Grade 3 SAE of abscess limb that was considered not related to study drug; however, the patient was permanently discontinued from study drug.

Dose-dependent decreases in ANC and platelet counts and an increase in creatinine kinase were seen, although these changes were not considered clinically meaningful. No patients experienced confirmed ANC < 1500 cells/ml. Consistent with other agents in this class, dose-dependent increases in serum creatinine and HDL cholesterol were seen.

In conclusion, in this 12 week randomized, double-blind, placebo controlled study evaluating multiple doses of ASP015K in RA patients, treatment with ASP015K was shown to be well-tolerated and efficacious after 12 weeks of treatment. These results support further evaluation of ASP015K in patients with moderate to severe RA, especially at the higher doses of ASP015K.

Date of Report: 01 July 2014

Figure 1 Disposition of Subjects



† A listing specifying "Other" screen failures is provided in [Appendix 13.2.1.1].

‡ Both patients' treatment were interrupted, 1 patient due to adverse event [redacted] and 1 patient due to [redacted]

§ Patient was non-compliant with study drug, [redacted]

Source: Tables 12.1.1.1, 12.1.1.2 and 12.1.1.3 and Appendix 13.2.1.2

Table 1 Demographics

Parameter	Placebo (n = 51)	ASP015K 25 mg (n = 59)	ASP015K 50 mg (n = 57)	ASP015K 100 mg (n = 58)	ASP015K 150 mg (n = 64)	ASP015K Total (n = 238)	Total (n = 289)
Sex, n (%)							
Male	9 (17.6%)	13 (22.0%)	9 (15.8%)	7 (12.1%)	14 (21.9%)	43 (18.1%)	52 (18.0%)
Female	42 (82.4%)	46 (78.0%)	48 (84.2%)	51 (87.9%)	50 (78.1%)	195 (81.9%)	237 (82.0%)
Age Group (Years), n (%)							
< 65	44 (86.3%)	52 (88.1%)	52 (91.2%)	49 (84.5%)	53 (82.8%)	206 (86.6%)	250 (86.5%)
≥ 65	7 (13.7%)	7 (11.9%)	5 (8.8%)	9 (15.5%)	11 (17.2%)	32 (13.4%)	39 (13.5%)
Age (Years)							
Mean	52.7	52.6	54.8	54.9	54.4	54.2	53.9
(SD)	(12.2)	(10.2)	(10.0)	(11.3)	(12.5)	(11.1)	(11.3)
Median	55.5	51.7	54.8	56.2	54.9	54.8	55.0
Min - Max	26 - 75	28 - 70	27 - 77	30 - 80	28 - 82	27 - 82	26 - 82
Race, n (%)							
White	41 (80.4%)	47 (79.7%)	45 (78.9%)	52 (89.7%)	51 (79.7%)	195 (81.9%)	236 (81.7%)
Black or African-American	3 (5.9%)	4 (6.8%)	1 (1.8%)	1 (1.7%)	5 (7.8%)	11 (4.6%)	14 (4.8%)
Asian	1 (2.0%)	0	0	0	0	0	1 (0.3%)
American Indian or Alaska Native	0	1 (1.7%)	0	0	1 (1.6%)	2 (0.8%)	2 (0.7%)
Native Hawaiian or Other Pacific Islanders	0	0	1 (1.8%)	0	1 (1.6%)	2 (0.8%)	2 (0.7%)
Other	6 (11.8%)	7 (11.9%)	10 (17.5%)	5 (8.6%)	6 (9.4%)	28 (11.8%)	34 (11.8%)
Ethnicity, n (%)							
Hispanic or Latino	10 (19.6%)	15 (25.4%)	13 (22.8%)	9 (15.5%)	11 (17.2%)	48 (20.2%)	58 (20.1%)
Not Hispanic or Latino	41 (80.4%)	44 (74.6%)	44 (77.2%)	49 (84.5%)	53 (82.8%)	190 (79.8%)	231 (79.9%)
Geographic Region, n (%)							
North America	24 (47.1%)	30 (50.8%)	28 (49.1%)	27 (46.6%)	29 (45.3%)	114 (47.9%)	138 (47.8%)
Europe	21 (41.2%)	22 (37.3%)	21 (36.8%)	27 (46.6%)	28 (43.8%)	98 (41.2%)	119 (41.2%)
Latin America	6 (11.8%)	7 (11.9%)	8 (14.0%)	4 (6.9%)	7 (10.9%)	26 (10.9%)	32 (11.1%)
Weight (kg)							
Mean	75.7	79.5	76.1	78.4	76.5	77.6	77.3
(SD)	(15.2)	(16.9)	(18.9)	(24.3)	(20.9)	(20.4)	(19.5)
Median	75.00	79.38	73.00	72.00	73.33	73.46	73.89
Min - Max	45.6 - 112.8	52.0 - 118.3	47.0 - 132.0	43.0 - 144.7	47.0 - 143.3	43.0 - 144.7	43.0 - 144.7
Height (cm)							
Mean	162.8	165.3	162.1	163.8	165.9	164.4	164.1
(SD)	(8.3)	(8.0)	(8.8)	(9.1)	(9.6)	(9.0)	(8.9)
Median	162.4	163.8	161.3	162.9	165.8	163.0	163.0
Min - Max	143 - 176	153 - 185	142 - 190	149 - 192	147 - 185	142 - 192	142 - 192
BMI (kg/m^2)							
Mean	28.6	29.1	29.0	29.0	27.5	28.6	28.6
(SD)	(5.6)	(6.1)	(6.8)	(7.9)	(6.0)	(6.7)	(6.5)
Median	27.79	28.76	27.44	27.37	26.70	27.59	27.62
Min - Max	18.4 - 50.0	19.1 - 45.0	17.6 - 45.7	17.9 - 48.5	17.2 - 41.7	17.2 - 48.5	17.2 - 50.0

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

BMI: body mass index; Max: maximum; Min: minimum

Source: Table 12.1.2.1.1

Table 2 ACR20-CRP Response at Week 12 (LOCF and NRI)

Parameter	Placebo (n = 51)	ASP015K 25 mg (n = 59)	ASP015K 50 mg (n = 57)	ASP015K 100 mg (n = 58)	ASP015K 150 mg (n = 64)
Responder (n [%])	15 (29.4%)	13 (22.0%)	21 (36.8%)	28 (48.3%)	36 (56.3%)
Non-responder (n [%])	36 (70.6%)	46 (78.0%)	36 (63.2%)	30 (51.7%)	28 (43.8%)
Difference (95% CI)†	--	-7.4 (-23.8, 9.0)	7.4 (-10.3, 25.1)	18.9 (0.9, 36.8)	26.8 (9.4, 44.3)
P value†	--	0.377	0.411	0.039#	0.003##
Odds Ratio (95% CI)‡	--	0.68 (0.28, 1.61)	1.38 (0.61, 3.13)	2.35 (1.06, 5.23)	3.15 (1.44, 6.92)
P value‡	--	0.005**	0.805	0.054	0.001**

All patients who were randomized and received at least 1 dose of study drug (Full Analysis Set). ACR components were LOCF first and then the ACR20-CRP response was calculated. In addition, all patients with RA rescue therapy prior to or at week 12 were classified as non-responders.

--: not applicable; ACR: American College of Rheumatology; ACR20-CRP: American College of Rheumatology criteria for 20% improvement in disease severity using the c-reactive protein level; LOCF: last observation carried forward; NRI: non-responder imputation; RA: rheumatoid arthritis

**P < 0.01 based on a logistic regression model; #P < 0.05, ##P < 0.01 based on normal approximation

† The difference is in proportion of responders (each ASP015K dose group minus placebo); and the 95% CI and P value are based on a normal approximation to the binomial distribution for difference in proportions.

‡ The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group and geographic region (North America, Europe, Latin America).

Source: Table 12.3.1.1.1

Table 3 Incidence of Common TEAEs Occurring in ≥ 3 Patients

MedDRA (v14.0) System Organ Class Preferred Term	Placebo (n = 51)	ASP015K 25 mg (n = 59)	ASP015K 50 mg (n = 57)	ASP015K 100 mg (n = 58)	ASP015K 150 mg (n = 64)	ASP015K Total (n = 238)
Any TEAE	**22 (43.1%)**	**22 (37.3%)**	**19 (33.3%)**	**30 (51.7%)**	**28 (43.8%)**	**99 (41.6%)**
Infections and Infestations						
Upper respiratory tract infection	2 (3.9%)	4 (6.8%)	0	4 (6.9%)	5 (7.8%)	13 (5.5%)
Urinary tract infection	2 (3.9%)	1 (1.7%)	0	2 (3.4%)	5 (7.8%)	8 (3.4%)
Nasopharyngitis	0	0	2 (3.5%)	1 (1.7%)	0	3 (1.3%)
Gastrointestinal Disorders						
Nausea	0	2 (3.4%)	1 (1.8%)	3 (5.2%)	6 (9.4%)	12 (5.0%)
Diarrhoea	1 (2.0%)	4 (6.8%)	1 (1.8%)	4 (6.9%)	0	9 (3.8%)
Dyspepsia	1 (2.0%)	0	1 (1.8%)	2 (3.4%)	3 (4.7%)	6 (2.5%)
Vomiting	1 (2.0%)	1 (1.7%)	0	1 (1.7%)	0	2 (0.8%)
Investigations						
Blood CPK increased	0	0	0	2 (3.4%)	2 (3.1%)	4 (1.7%)
Musculoskeletal and Connective Tissue Disorders						
Rheumatoid arthritis	1 (2.0%)	1 (1.7%)	3 (5.3%)	0	2 (3.1%)	6 (2.5%)
Synovial cyst	0	1 (1.7%)	0	2 (3.4%)	0	3 (1.3%)
Nervous System Disorders						
Headache	1 (2.0%)	1 (1.7%)	0	4 (6.9%)	1 (1.6%)	6 (2.5%)
Dizziness	0	1 (1.7%)	1 (1.8%)	1 (1.7%)	0	3 (1.3%)
Metabolism and Nutrition Disorders						
Hypertriglyceridaemia	0	0	1 (1.8%)	3 (5.2%)	1 (1.6%)	5 (2.1%)
Hypercholesterolaemia	1 (2.0%)	0	2 (3.5%)	1 (1.7%)	1 (1.6%)	4 (1.7%)
Hyperlipidaemia	1 (2.0%)	0	0	0	2 (3.1%)	2 (0.8%)
Vascular Disorders						
Hypertension	0	1 (1.7%)	0	2 (3.4%)	1 (1.6%)	4 (1.7%)

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

A TEAE was defined as any AE that started or worsened in severity after initial dose of study drug through the follow-up period.

AE: adverse event; CPK: creatine phosphokinase; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.2.1

Table 4 Incidence of Serious TEAEs

MedDRA (v14.0) System Organ Class† Preferred Term	Placebo (n = 51)	ASP015K 25 mg (n = 59)	ASP015K 50 mg (n = 57)	ASP015K 100 mg (n = 58)	ASP015K 150 mg (n = 64)	ASP015K Total (n = 238)
Any Serious TEAE	**3 (3.9%)**	**2 (3.4%)**	**2 (3.5%)**	**4 (6.9%)**	**2 (3.1%)**	**10 (4.2%)**
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal chest pain	0	0	0	0	1 (1.6%)	1 (0.4%)
Rheumatoid arthritis	0	1 (1.7%)	0	0	0	1 (0.4%)
Synovial cyst	0	0	0	1 (1.7%)	0	1 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders						
Asthma	0	0	1 (1.8%)	0	0	1 (0.4%)
Haemoptysis	0	0	1 (1.8%)	0	0	1 (0.4%)
Pleuritic pain	0	0	0	0	1 (1.6%)	1 (0.4%)
Cardiac Disorders						
Atrial fibrillation	0	0	1 (1.8%)	0	0	1 (0.4%)
Myocardial infarction	0	0	0	0	1 (1.6%)	1 (0.4%)
Myocardial ischaemia	1 (2.0%)	0	0	0	0	0
Nervous System Disorders						
Transient ischaemic attack	0	0	0	2 (3.4%)	0	2 (0.8%)
Infections and Infestations						
Abscess limb	0	1 (1.7%)	0	0	0	1 (0.4%)
Injury, Poisoning and Procedural Complications						
Humerus fracture	0	0	0	1 (1.7%)	0	1 (0.4%)
Joint dislocation	1 (2.0%)	0	0	0	0	0
Investigations						
Electrocardiogram abnormal	0	0	0	1 (1.7%)	0	1 (0.4%)

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

A TEAE was defined as any AE that started or worsened in severity after initial dose of study drug through the follow-up period.

[redacted]

AE: adverse event; TEAE: treatment-emergent adverse event

† Sorted in descending frequency for ASP015K total column by System Organ Class, and within that descending frequency by preferred term.

Source: Table 12.6.1.8