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 in Patients who have had an Inadequate Response to Methotrexate (015K-CL-RA21)

Investigators/Coordinating Investigator: [redacted], MD, PhD

Study Center(s): This multi-center study was conducted at 43 contracted sites, 16 sites in the United States, 2 sites in Belgium, 3 sites in Bulgaria, 5 sites in Colombia, 3 sites in the Czech Republic, 3 sites in Hungary, 7 sites in Poland and 4 sites in Mexico.

Publication Based on the Study: None

Study Period: 1.7 years

Study Initiation Date (Date of First Patient Randomized): 06 July 2012

Study Completion Date (Date of Last Evaluation): 11 February 2014

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 who were methotrexate (MTX)-inadequate responders (MTX-IR).

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 moderate to severe RA patients who were MTX-IR to evaluate the safety and efficacy of ASP015K. Up to 25% of the total number of patients randomized were allowed to be anti-tumor necrosis factor (TNF) experienced patients, which were defined as patients who have previously been exposed to an approved anti-TNF medication, provided the specified protocol criteria are met. 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. All patients continued to take their concomitant oral weekly dose of MTX in addition to daily ASP015K or matching placebo. 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. 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. The follow-up period was conducted only for patients not rolling over into open-label extension study (i.e., patients who rolled over into the extension study were not assessed at follow-up).

Number of Patients (Planned, Enrolled and Analyzed): The total planned enrollment for the study was 375 patients. A total of 379 patients were randomized [Figure 1]. Of those, 378 randomized patients received treatment and were included in the Full Analysis Set (FAS), Safety Analysis Set (SAF) and Pharmacodynamic Analysis Set (PDAS). Four patients treated with ASP015K were excluded from the Per Protocol Set due to treatment compliance of less than 75% or entering the study without satisfying entry criteria. The

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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) for ≥ 6 months and had been treated with oral MTX for ≥ 90 days at a stable dose of 15 to 25 mg/week for ≥ 28 days prior to first dose were able to participate in this study. Lower doses (≥ 7.5 to < 15 mg/week) were accepted if patients had intolerance to higher doses of MTX, provided the same duration and stability requirements were met. 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 at screening, received a non-anti-TNF disease-modifying antirheumatic drug (DMARD), 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 intra-articular or parenteral 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 25, 50, 100 or 150 mg ASP015K as 5, 10 or 30 mg oral tablets once daily with food plus their concomitant oral weekly dose of MTX. In this study, 3 different lots and 21 different batches of ASP015K tablets were used.

Duration of Treatment: 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 plus their concomitant oral weekly dose of MTX. 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 (ACR20) 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.

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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:
    - Subject's global assessment of arthritis pain (assessed using a 100 mm visual analog scale [VAS])
    - Subject's global assessment of arthritis (assessed using a 100 mm VAS)
    - Physician's global assessment of arthritis (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, prior anti-TNF use (prior anti-TNF treatment, no prior anti-TNF treatment) and geographic region (North America, Europe, Latin America). Additional analyses using normal approximation to the binomial distribution 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 additional efficacy analyses run in a subset of patients by geographic region including all planned comparisons planned for the FAS.

Summary of Results/Conclusions:

Population: The majority of patients in the SAF were female (83.3%), with a mean age of 53 years (range: 23 - 93 years), white (77.2%) and not Hispanic or Latino (70.1%) Table 1. Approximately half of the patients were from Europe (43.1%), while 38.9% of patients were from the North American region, and 18.0% of patients were from Latin America. The demographic characteristics were similar between the treatment groups.

The mean age at onset of RA was 45.71 years and the mean duration of the disease was 7.61 years. All patients have previously used DMARDs. The baseline disease activity and RA history were similar between the treatment groups.

Efficacy Results: The ASP015K 50 mg group had a statistically significantly higher rate of ACR20-CRP responders at week 12 than did the placebo group (61.5% vs. 44.4%, respectively; P value: 0.036) Table 2.

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The other ASP015K dosing groups were not statistically different from placebo in the proportion of ACR20-CRP responders at week 12. Analyses done based on normal approximation to the binomial distribution for difference in proportions showed a statistical difference between the ASP015K 50 mg group versus placebo.

All of the sensitivity analyses performed found statistically significant differences between the same treatment groups as the primary analysis with the exception of the analysis using last observation carried forward (LOCF) then calculate response, response then LOCF and observed data. These 3 analyses did not find statistically significant differences between any of the treatment groups and placebo.

None of the subgroup analyses had a statistically significant subgroup/treatment interaction. The percent of responders in the placebo group was higher in patients from Latin America and North America versus Europe (75.0% and 50.0% vs 28.1%, respectively).

Due to the high placebo response rate together with the significant number of patients enrolled in Latin America and Site [redacted] in North America, a post-hoc analysis was conducted to evaluate efficacy response without the Latin America sites and Site [redacted] in North America. Analysis of the ACR20-CRP response excluding the Latin American regions showed no statistically significant difference at week 12 using logistic regression, but showed a statistically significant difference for the 50 mg and 150 mg dose groups versus placebo using normal approximation to the binomial distribution for difference in proportions. Analyses excluding Site [redacted] were consistent with the primary results. Excluding this site did not meaningfully affect ACR20-CRP differences between the active groups and placebo even though it did lower the overall placebo response rate.

Overall, ASP015K 50 mg and 150 mg used once daily demonstrated clear efficacy across multiple efficacy endpoints, including the primary endpoint (50 mg) and secondary endpoints (50 and 150 mg). These effects occurred early after initiation of treatment with continued improvement until week 12.

Pharmacokinetic Results: By week 1, at least 75% of the maximum median C_{trough} was reached for each ASP015K dose group. At each week, the median C_{trough} increased with increasing dose.

Pharmacodynamic Results: As ASP015K dose increased, CD19 (CD45+CD3-CD19+) lymphocytes increased and CD16/56 (CD45+CD3-CD16;56+) lymphocytes decreased at week 12/end of treatment. In all ASP015K groups, IL-6 decreased at week 12/end of treatment.

Safety Results: Less than half of the patients experienced a TEAE Table 3. The most common TEAEs (urinary tract infection and upper respiratory tract infection) were in the SOC of Infections and Infestations in both the patients in the placebo group and the ASP015K groups. In the SOCs of Gastrointestinal Disorders and Nervous System Disorders, the incidence was similar between the ASP015K groups and placebo, while more patients in the ASP015K groups (5.9%) experienced TEAEs in the SOC of Metabolism and Nutrition Disorders than the placebo group (1.4%). Most of the TEAEs were mild or moderate in severity. Overall, 5 patients reported 10 TEAEs with Grade 3 in 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 urinary tract infection, upper respiratory tract infection, herpes zoster, nasopharyngitis and nausea.

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No deaths occurred during this study. Less than 3% of all patients experienced a serious AE (SAE) Table 4 or a TEAE leading to permanent discontinuation. None of the SAEs or TEAE leading to permanent discontinuation occurred in more than 1 patient. Viral infection was the only SAE that was considered related (possibly) to ASP015K. One TEAE of RA flare leading to discontinuation was considered related (probably) to study drug in the ASP015K 150 mg group. Two TEAEs of leukopenia and neutropenia reported by 1 patient in the ASP015K 150 mg group and 1 TEAE of abdominal pain upper in the placebo group were considered possibly related to the study drug.

In this study, 3 patients experienced a severe infection (any infection SAEs or any infection TEAEs ≥ Grade 3 in severity) of which 1 TEAE of viral infection was study drug related. This patient was permanently discontinued from the study.

A dose-dependent decrease in mean absolute neutrophil count (ANC) and mean platelet count and a dose-dependent increase in mean creatine kinase, mean serum creatinine, lactate dehydrogenase (LDH), cholesterol and high-density lipoprotein (HDL) cholesterol were seen in the ASP015K dose groups at week 12 versus placebo. Seven female patients in the ASP015K groups and 1 female patient in the placebo group had moderate liver abnormalities, which resolved at the next visit. No patient had a marked liver abnormality. There were no consistent changes from baseline in the other hematological, chemical, urinalysis or fasting lipid profile parameters in the ASP015K dose groups compared to placebo.

There were no consistent changes from baseline in vital signs in the ASP015K dose groups compared to placebo. One patient experienced a clinically significant ECG abnormality, which was reported as a TEAE of mild intensity. [redacted]

CONCLUSIONS: In this randomized, double-blind, placebo-controlled study in moderately to severely active RA patients on concomitant MTX, treatment with ASP015K did not demonstrate a dose response on the primary endpoint of ACR20-CRP response, with only the ASP015K 50 mg dose group showing a statistically significant greater response than placebo. While the ASP015K 50 mg, 100 mg and 150 mg groups showed numerically greater responses than the placebo group in ACR50 and ACR70 response, none of them were statistically significantly different from placebo.

While the ASP015K 50 mg dose group unexpectedly showed a greater ACR20-CRP response than the higher ASP015K dose groups, the secondary endpoints evaluating the continuous outcome measures of DAS28-CRP and DAS28-ESR [redacted] suggests that there was a dose-dependent response, with the earliest and greatest changes seen in the highest ASP015K dose of 150 mg once daily.

[redacted]

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Evaluation of the primary endpoint, ACR20-CRP response, may have been confounded by the higher placebo response rate of 44.4% than the assumed placebo response rate of 30% in the sample size calculation. A prespecified analysis of response by region showed that Latin America had a high placebo response rate of 75% and North America, which included only the United States, also had a higher than expected placebo response rate of 50%. Analyses by region showed that only in the EU, where the placebo response rate was in the expected range based on previous RA studies, was there a statistically significant difference between active and placebo groups with the greatest responses shown in the 100 mg and 150 mg dose group as compared to placebo. Post-hoc analyses excluding Latin America did demonstrate a better dose-response on the primary endpoint with both the 50 mg and 150 mg dose groups being statistically significantly different from placebo (56.9% and 58.5%, respectively, vs 38.3%), driven mainly by a decrease in the placebo response rate as opposed to an increase in the active group response rates.

Further analysis of the North America region showed a high placebo response rate at Site [redacted], which enrolled a substantial number of subjects (n = 55). Post-hoc analyses excluding this site, while lowering the placebo response rate, were similar to the primary results. This was due to the fact that response rates in the ASP015K groups were also high (higher than placebo, in fact) and, thus, exclusion of these subjects did not alter the overall interpretation of the results.

Preliminary pharmacokinetic results suggested similar exposure to that previously observed in Study 015K-CL-RA22, which may rule out the possibility that concomitant MTX use had an impact on ASP015K pharmacokinetics.

ASP015K appeared to be well-tolerated at all dose levels, and no new safety signals were identified. The most common TEAEs were urinary tract infection, upper respiratory tract infection, diarrhea, headache and nasopharyngitis. There were 3 patients who experienced an SAE, 1 patient with pulmonary mass and 1 patient with viral infection occurred in the ASP015K 100 mg group; and 1 patient with erysipelas in the ASP015K 150 mg group. There were 8 patients who experienced 9 TEAEs leading to permanent discontinuation in this study (leukopenia, neutropenia, viral infection, RA [exacerbation], tremor, pregnancy, dysuria, pulmonary mass and abdominal pain upper). A total of 3 patients experienced a severe infection (viral infection, erysipelas and urinary tract infection) that was considered as events of special interest. A dose-dependent decrease in mean ANC and mean platelet count were seen, although these changes were not considered clinically meaningful. Dose-dependent increases in mean creatine kinase, mean serum creatinine, LDH and mean total and HDL cholesterol were seen in the ASP015K dose groups at week 12 versus placebo, although these changes were not considered clinically meaningful.

In conclusion, in this 12-week randomized, double-blind, placebo controlled study evaluating multiple doses of ASP015K and MTX in RA patients who have had an inadequate response to MTX, treatment with ASP015K did not demonstrate a dose-response on the primary endpoint of ACR20-CRP, although supportive analyses evaluating other efficacy measures such as DAS28 as well [redacted] did suggest a dose-response in the overall population. Prespecified analyses suggested that region,

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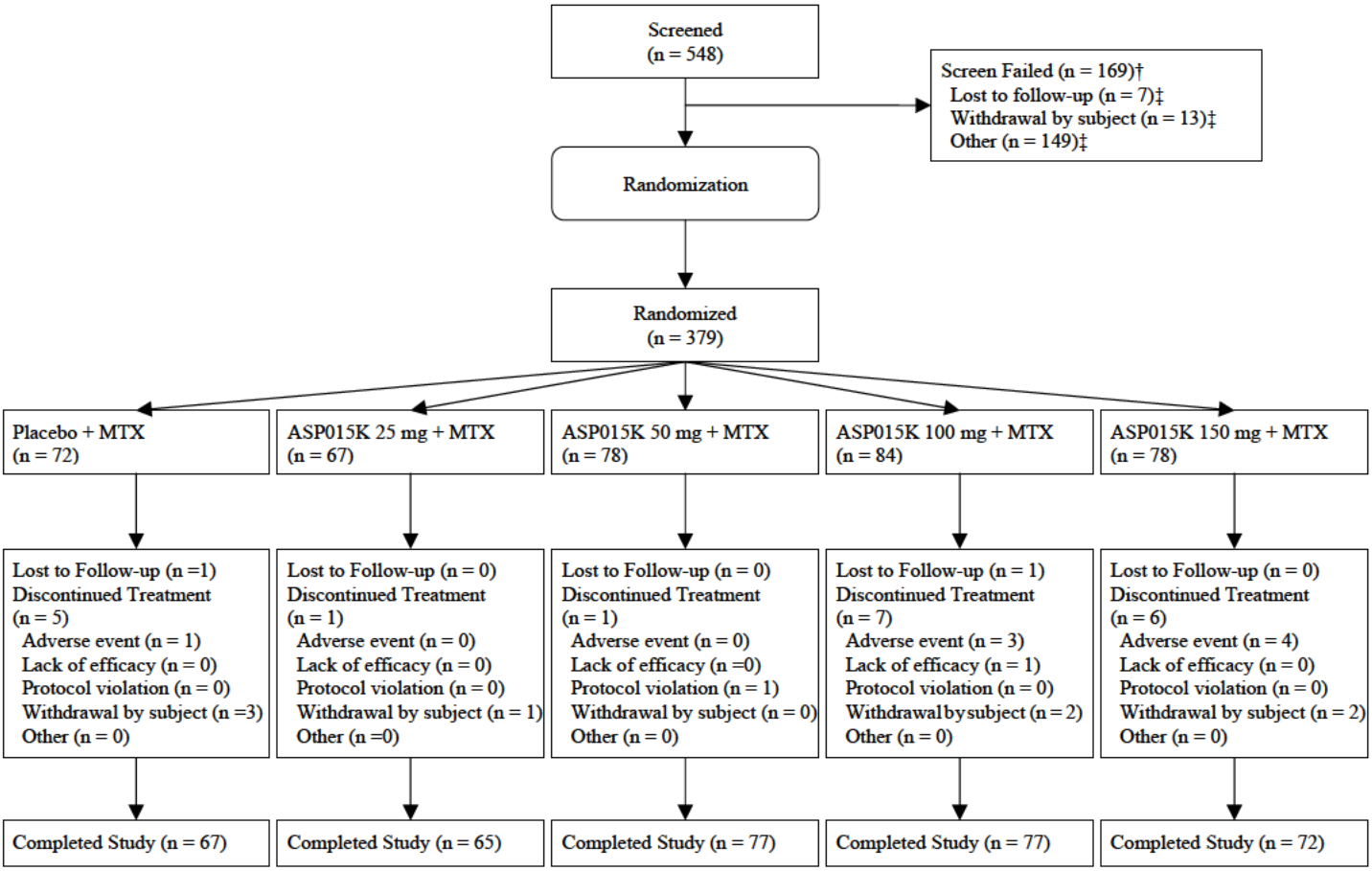
especially Latin America, may have confounded evaluation of the efficacy of ASP015K due to the high placebo response rate, and analyses excluding this region showed a better dose-response on ACR responses as well as DAS28, with the greatest effect seen in the ASP015K dose groups, consistent with previous studies. The overall data from this study, taken together with other studies evaluating ASP015K in moderately to severely active RA, does support the overall safety of this therapy in the treatment of RA as well as supporting further evaluation of the efficacy of this treatment, especially at higher doses of ASP015K.

Date of Report: 17 April 2015 (Reissued CSR).

Figure 1 Disposition of Patients



MTX: methotrexate

† Patients who signed informed consent but discontinued before randomization are considered screen failures.

‡ Only the primary reason was reported. Number of patients in the screened failed row was used as the denominator for calculating percentages for the primary reason categories.

Source: Tables 12.1.1.1, 12.1.1.2 and 12.1.1.3

Table 1 Summary of Demographics and Baseline Characteristics for Patients in the Safety Analysis Set

Parameter Category/ Statistics	Placebo + MTX (n = 72)	ASP015K 25 mg + MTX (n = 66)	ASP015K 50 mg + MTX (n = 78)	ASP015K 100 mg + MTX (n = 84)	ASP015K 150 mg + MTX (n = 78)	ASP015K Total (n = 306)	Total (n = 378)
Sex, n (%)							
Male	9 (12.5%)	11 (16.7%)	13 (16.7%)	16 (19.0%)	14 (17.9%)	54 (17.6%)	63 (16.7%)
Female	63 (87.5%)	55 (83.3%)	65 (83.3%)	68 (81.0%)	64 (82.1%)	252 (82.4%)	315 (83.3%)
Race, n (%)							
White	59 (81.9%)	49 (74.2%)	59 (75.6%)	66 (78.6%)	59 (75.6%)	233 (76.1%)	292 (77.2%)
Black or African American	0	2 (3.0%)	5 (6.4%)	2 (2.4%)	4 (5.1%)	13 (4.2%)	13 (3.4%)
Asian	1 (1.4%)	1 (1.5%)	0	0	3 (3.8%)	4 (1.3%)	5 (1.3%)
American Indian or Alaska Native	1 (1.4%)	0	2 (2.6%)	1 (1.2%)	0	3 (1.0%)	4 (1.1%)
Other	11 (15.3%)	14 (21.2%)	12 (15.4%)	15 (17.9%)	12 (15.4%)	53 (17.3%)	64 (16.9%)
Ethnicity, n (%)							
Not Hispanic or Latino	52 (72.2%)	45 (68.2%)	52 (66.7%)	56 (66.7%)	60 (76.9%)	213 (69.6%)	265 (70.1%)
Hispanic or Latino	20 (27.8%)	21 (31.8%)	26 (33.3%)	28 (33.3%)	18 (23.1%)	93 (30.4%)	113 (29.9%)
Geographic Region							
North America	28 (38.9%)	24 (36.4%)	34 (43.6%)	28 (33.3%)	33 (42.3%)	119 (38.9%)	147 (38.9%)
Europe	32 (44.4%)	29 (43.9%)	31 (39.7%)	39 (46.4%)	32 (41.0%)	131 (42.8%)	163 (43.1%)
Latin America	12 (16.7%)	13 (19.7%)	13 (16.7%)	17 (20.2%)	13 (16.7%)	56 (18.3%)	68 (18.0%)
Age, years							
Mean (SD)	52.6 (12.2)	52.8 (11.9)	52.3 (12.6)	54.5 (12.8)	54.2 (12.5)	53.5 (12.5)	53.3 (12.4)
Median	53.1	53.7	53.8	56.1	54.6	54.5	54.1
Minimum - Maximum	23 - 79	30 -79	24 -79	25 -93	23 - 77	23 - 93	23 - 93
Weight (kg)							
Mean (SD)	75.6 (17.9)†	74.9 (20.1)	76.1 (18.3)	77.2 (19.2)	75.5 (19.2)	76.0 (19.1)	75.9 (18.8)‡
Median	72.6	68.2	74.0	74.5	70.5	71.6	72.0
Minimum - Maximum	33.2 - 119.7	48.4 - 131.1	44.0 - 135.6	48.5 - 131.5	46.7 - 130.0	44.0 - 135.6	33.2 - 135.6
Height (cm)							
Mean (SD)	161.1 (9.9)†	161.4 (9.7)	162.1 (9.3)	163.9 (11.1)	163.2 (8.6)	162.7 (9.7)	162.4 (9.8)‡
Median	160.5	159.5	162.6	161.5	162.5	162.0	162.0
Minimum - Maximum	135 - 189	145 - 190	142 - 191	143 - 193	142 - 184	142 - 193	135 - 193
Body Mass Index (kg/m^2)							
Mean (SD)	29.2 (6.9)†	28.5 (5.8)	28.9 (6.2)	28.6 (5.9)	28.2 (6.0)	28.6 (5.9)	28.7 (6.1)‡
Median	27.8	28.0	27.7	27.3	26.7	27.4	27.6
Minimum - Maximum	18.0 - 47.6	17.8 - 42.8	17.4 - 48.4	19.1 - 45.9	20.4 - 47.1	17.4 - 48.4	17.4 - 48.4

All enrolled patients who received the study drug (Safety Analysis Set)

MTX: methotrexate

† Mean is of 71 patients.

‡ Mean is of 377 patients.

Source: Table 12.1.2.1.1

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

Parameter	Placebo + MTX (n = 72)	ASP015K 25 mg + MTX (n = 66)	ASP015K 50 mg + MTX (n = 78)	ASP015K 100 mg + MTX (n = 84)	ASP015K 150 mg + MTX (n = 78)
Responder (n [%])	32 (44.4%)	29 (43.9%)	48 (61.5%)	39 (46.4%)	45 (57.7%)
Non-responder (n [%])	40 (55.6%)	37 (56.1%)	30 (38.5%)	45 (53.6%)	33 (42.3%)
Difference (95% CI)†	--	-0.5 (-17.1, 16.1)	17.1 (1.3, 32.9)	2.0 (-13.7, 17.7)	13.2 (-2.6, 29.1)
P value†	--	0.952	0.033#	0.804	0.102
Odds Ratio (95% CI)‡	--	0.96 (0.49, 1.90)	2.00 (1.04, 3.87)	1.08 (0.57, 2.04)	1.69 (0.88, 3.26)
P value‡	--	0.193	0.036*	0.379	0.186

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; MTX: methotrexate; NRI: non-responder imputation; RA: rheumatoid arthritis; TNF: tumor necrosis factor

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

† The difference is in proportion of responders (each ASP015K dose group minus placebo); and, the P value and 95% CI 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 are based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region.

Source: Table 12.3.1.1.1

Table 3 Incidence of Common TEAEs Occurring in ≥ 3 Patients in any Treatment Group

MedDRA (v14.0) System Organ Class Preferred Term	Placebo + MTX (n = 72)	ASP015K 25 mg + MTX (n = 66)	ASP015K 50 mg + MTX (n = 78)	ASP015K 100 mg + MTX (n = 84)	ASP015K 150 mg + MTX (n = 78)	ASP015K + MTX Total (n = 306)
Any TEAE	**34 (47.2%)**	**28 (42.4%)**	**39 (50.0%)**	**40 (47.6%)**	**39 (50.0%)**	**146 (47.7%)**
Infections and Infestations						
Urinary tract infection	5 (6.9%)	2 (3.0%)	5 (6.4%)	4 (4.8%)	6 (7.7%)	17 (5.6%)
Upper respiratory tract infection	4 (5.6%)	2 (3.0%)	3 (3.8%)	4 (4.8%)	3 (3.8%)	12 (3.9%)
Nasopharyngitis	2 (2.8%)	2 (3.0%)	3 (3.8%)	1 (1.2%)	2 (2.6%)	8 (2.6%)
Bronchitis	2 (2.8%)	0	2 (2.6%)	1 (1.2%)	0	3 (1.0%)
Herpes zoster	0	0	0	2 (2.4%)	1 (1.3%)	3 (1.0%)
Gastroenteritis viral	1 (1.4%)	1 (1.5%)	1 (1.3%)	0	0	2 (0.7%)
Gastrointestinal Disorders						
Diarrhoea	4 (5.6%)	4 (6.1%)	2 (2.6%)	1 (1.2%)	5 (6.4%)	12 (3.9%)
Abdominal pain upper	2 (2.8%)	2 (3.0%)	0	2 (2.4%)	1 (1.3%)	5 (1.6%)
Nausea	1 (1.4%)	2 (3.0%)	0	2 (2.4%)	1 (1.3%)	5 (1.6%)
Vomiting	0	2 (3.0%)	2 (2.6%)	1 (1.2%)	0	5 (1.6%)
Gastritis	0	0	0	2 (2.4%)	2 (2.6%)	4 (1.3%)
Abdominal pain	1 (1.4%)	0	0	1 (1.2%)	2 (2.6%)	3 (1.0%)
Constipation	1 (1.4%)	0	0	2 (2.4%)	0	2 (0.7%)
Nervous System Disorders						
Headache	1 (1.4%)	1 (1.5%)	4 (5.1%)	2 (2.4%)	2 (2.6%)	9 (2.9%)
Dizziness	1 (1.4%)	2 (3.0%)	1 (1.3%)	1 (1.2%)	1 (1.3%)	5 (1.6%)
Paraesthesia	1 (1.4%)	1 (1.5%)	0	0	1 (1.3%)	2 (0.7%)
Metabolism and Nutrition Disorders						
Hypercholesterolaemia	1 (1.4%)	1 (1.5%)	3 (3.8%)	2 (2.4%)	0	6 (2.0%)
Hypertriglyceridaemia	1 (1.4%)	3 (4.5%)	0	1 (1.2%)	0	4 (1.3%)
Hyperlipidaemia	0	0	2 (2.6%)	1 (1.2%)	0	3 (1.0%)
Impaired fasting glucose	0	0	1 (1.3%)	1 (1.2%)	1 (1.3%)	3 (1.0%)
Investigations						
Bacterial test positive	0	1 (1.5%)	1 (1.3%)	1 (1.2%)	1 (1.3%)	4 (1.3%)
Blood CPK increased	0	1 (1.5%)	0	2 (2.4%)	0	3 (1.0%)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	0	0	2 (2.6%)	1 (1.2%)	1 (1.3%)	4 (1.3%)
Oropharyngeal pain	1 (1.4%)	0	2 (2.6%)	0	1 (1.3%)	3 (1.0%)
General Disorders and Administration Site Conditions						
Fatigue	0	0	2 (2.6%)	0	1 (1.3%)	3 (1.0%)
Oedema peripheral	0	0	0	0	3 (3.8%)	3 (1.0%)
Blood and Lymphatic System Disorders						
Anaemia	0	1 (1.5%)	1 (1.3%)	1 (1.2%)	0	3 (1.0%)
Psychiatric Disorders						
Depression	0	1 (1.5%)	1 (1.3%)	1 (1.2%)	0	3 (1.0%)
Insomnia	0	0	0	3 (3.6%)	0	3 (1.0%)
Renal and Urinary Disorders						
Proteinuria	2 (2.8%)	0	0	0	1 (1.3%)	1 (0.3%)
Vascular Disorders						
Hypertension	0	0	1 (1.3%)	2 (2.4%)	1 (1.3%)	4 (1.3%)

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

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

CPK: creatine phosphokinase; MTX: methotrexate; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.2.1

Table 4 Incidence of Serious TEAEs

MedDRA (v14.0) Preferred Term	**Placebo + MTX (n = 72)**	**ASP015K 25 mg + MTX (n = 66)**	**ASP015K 50 mg + MTX (n = 78)**	**ASP015K 100 mg + MTX (n = 84)**	**ASP015K 150 mg + MTX (n = 78)**	**ASP015K + MTX Total (n = 306)**
Any Serious TEAE	**0**	**0**	**0**	**2 (2.4%)**	**1 (1.3%)**	**3 (1.0%)**
Erysipelas	0	0	0	0	1 (1.3%)	1 (0.3%)
Viral infection	0	0	0	1 (1.2%)	0	1 (0.3%)
Pulmonary mass	0	0	0	1 (1.2%)	0	1 (0.3%)

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

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

MTX: methotrexate; TEAE: treatment-emergent adverse event

Source: Table 12.6.1.8