EU Clinical Trials Register

Clinical trial results:

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 Subjects Who Have Had an Inadequate Response to Methotrexate

Summary

EudraCT number	2011-006018-15
Trial protocol	BE CZ PL HU BG
Global end of trial date	11 February 2014

Results information

Result version number	v2 (current)
This version publication date	18 February 2017
First version publication date	02 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	015K-CL-RA21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01554696
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2014
Global end of trial reached?	Yes
Global end of trial date	11 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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-inadequate responders (MTX-IRs).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

At screening, patients were currently taking oral Methotrexate (MTX), taken MTX for at least the past 90 days and at a stable dose (single, unchanging dose) between 15 to 25 mg/week for at least 28 days prior to the first dose of study drug. 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. Previous use of a non-anti-TNF (Tumor necrosis factor) biologic Disease-modifying antirheumatic drug (DMARD) (e.g., anakinra, abacept, rituximab, tocilizumab) was prohibited and concurrent use of biologic DMARDs was prohibited during the study. Up to 25% of the total number of patients randomized were allowed to be antitumor 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 were met. Potential patients who previously used anti-TNF therapy were eligible to participate provided the following washout periods were met and fewer than 25% of the randomized patients had taken anti-TNF therapy:
● Etanercept – 28 days
● Certolizumab, adalimumab, golimumab and infliximab – 60 days
● Cyclophosphamide – 180 days
● Gold, azathioprine, minocycline and penicillamine – 28 days
● Leflunomide – 60 days; if the patient has undergone a cholestyramine washout, then the period is reduced to 30 days prior to day 1 dosing

Evidence for comparator:

Placebo was used as comparative drug. The ASP015K matching placebo tablets contained the same ingredients as the test drug except for active drug substance and hydroxy-propyl cellulose.

Actual start date of recruitment	06 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 92
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 14

Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Colombia: 25
Country: Number of subjects enrolled	Mexico: 43
Country: Number of subjects enrolled	United States: 147
Worldwide total number of subjects	379
EEA total number of subjects	164

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	316
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This multi-center study was conducted at 43 sites in a total of 8 countries and 3 regions. The Principal Investigator at each site was a licensed clinician with experience in the therapeutic area of rheumatoid arthritis (RA).

Pre-assignment

Screening details:

Patients with prior anti-TNF use were eligible if the following washout periods were met: Etanercept-28 days, Certolizumab/adalimumab/golimumab/infliximab-60 days, Cyclophosphamide-180 days, Gold/azathioprine/minocycline/penicillamine-28 days, Leflunomide-60 days; if cholestyramine washout was met this was reduced to 30 days prior to day 1 dosing.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

This was a double-blind study. The investigator, patient, clinical staff and Sponsor's study management team were blinded to treatment assignments. The Data and Safety Monitoring Board (DSMB) was provided access to the dosing assignment for periodic review of the unblinded data as documented in the DSMB Charter.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + weekly oral dose of MTX

Arm description:

This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Arm type	Placebo
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate was not provided by the Sponsor, all patients continued to take MTX orally as concomitant medication on a weekly basis.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

ASP015K matching placebo tablets contained the same ingredients as the test drug except for active drug substance and hydroxy-propyl cellulose. Placebo was to be taken orally with food, daily for 12 weeks (days 1-84) after randomization.

Arm title	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX

Arm description:

This arm consisted of ASP015K 25 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The test drug for this study is ASP015K. ASP015K is a round, yellow, film-coated tablet. ASP015K 25 mg once daily was to be taken orally with food, daily for 12 weeks (days 1-84) after randomization.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate was not provided by the Sponsor, all patients continued to take MTX orally as concomitant medication on a weekly basis.

Arm title	ASP015K 50 mg qd + weekly oral dose of MTX

Arm description:

This arm consisted of ASP015K 50 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The test drug for this study is ASP015K. ASP015K is a round, yellow, film-coated tablet. ASP015K 50 mg once daily was to be taken orally with food, daily for 12 weeks (days 1-84) after randomization.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate was not provided by the Sponsor, all patients continued to take MTX orally as concomitant medication on a weekly basis.

Arm title	ASP015K 100 mg qd + weekly oral dose of MTX

Arm description:

This arm consisted of ASP015K 100 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The test drug for this study is ASP015K. ASP015K is a round, yellow, film-coated tablet. ASP015K 100 mg once daily was to be taken orally with food, daily for 12 weeks (days 1-84) after randomization.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate was not provided by the Sponsor, all patients continued to take MTX orally as concomitant medication on a weekly basis.

Arm title	ASP015K 150 mg qd + weekly oral dose of MTX

Arm description:

This arm consisted of ASP015K 150 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	MTX
Pharmaceutical forms	Powder for oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate was not provided by the Sponsor, all patients continued to take MTX orally as concomitant medication on a weekly basis.

Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The test drug for this study is ASP015K. ASP015K is a round, yellow, film-coated tablet. ASP015K 150 mg once daily was to be taken orally with food, daily for 12 weeks (days 1-84) after randomization.

Number of subjects in period 1	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX
Started	72	67	78
Completed	67	65	77
Not completed	5	2	1
Randomized but never dispensed study drug	-	1	-
Protocol violation	-	-	1
Adverse event	1	-	-
Lost to follow-up	1	-	-
Withdrawal by subject	3	1	-
Lack of efficacy	-	-	-

Number of subjects in period 1	ASP015K 100 mg qd + weekly oral dose of MTX	ASP015K 150 mg qd + weekly oral dose of MTX
Started	84	78

Completed	77	72
Not completed	7	6
Randomized but never dispensed study drug	-	-
Protocol violation	-	-
Adverse event	3	4
Lost to follow-up	1	-
Withdrawal by subject	2	2
Lack of efficacy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo + weekly oral dose of MTX
Reporting group description:	
This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.	
Reporting group title	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX
Reporting group description:	
This arm consisted of ASP015K 25 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.	
Reporting group title	ASP015K 50 mg qd + weekly oral dose of MTX
Reporting group description:	
This arm consisted of ASP015K 50 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.	
Reporting group title	ASP015K 100 mg qd + weekly oral dose of MTX
Reporting group description:	
This arm consisted of ASP015K 100 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.	
Reporting group title	ASP015K 150 mg qd + weekly oral dose of MTX
Reporting group description:	
This arm consisted of ASP015K 150 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.	

Reporting group values	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX
Number of subjects	72	67	78
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age values were based on the Safety Analysis Set (SAF) population. The SAF was defined as all patients who received at least 1 dose of study drug.			
Units: years			
arithmetic mean	52.6	52.8	52.3
standard deviation	± 12.2	± 11.9	± 12.6
Gender categorical			
Gender values are based on the SAF population.			
Units: Subjects			
Female	63	55	65
Male	9	11	13

Subject not included in SAF	0	1	0

Reporting group values	ASP015K 100 mg qd + weekly oral dose of MTX	ASP015K 150 mg qd + weekly oral dose of MTX	Total
Number of subjects	84	78	379
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age values were based on the Safety Analysis Set (SAF) population. The SAF was defined as all patients who received at least 1 dose of study drug.			
Units: years			
arithmetic mean	54.5	54.2	
standard deviation	± 12.8	± 12.5	-
Gender categorical			
Gender values are based on the SAF population.			
Units: Subjects			
Female	68	64	315
Male	16	14	63
Subject not included in SAF	0	0	1

End points

End points reporting groups

Reporting group title	Placebo + weekly oral dose of MTX

Reporting group description:

This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Reporting group title	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX

Reporting group description:

This arm consisted of ASP015K 25 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Reporting group title	ASP015K 50 mg qd + weekly oral dose of MTX

Reporting group description:

This arm consisted of ASP015K 50 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Reporting group title	ASP015K 100 mg qd + weekly oral dose of MTX

Reporting group description:

This arm consisted of ASP015K 100 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Reporting group title	ASP015K 150 mg qd + weekly oral dose of MTX

Reporting group description:

This arm consisted of ASP015K 150 mg qd (once a day) taken orally with food, for 12 weeks (days 1-84) after randomization. All patients continued to take their concomitant oral weekly dose of MTX.

Subject analysis set title	H1 Metabolite - ASP015K 25 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the Pharmacokinetic Analysis Set (PKAS). The PKAS consisted of all patients who received at least
1 dose of study drug and who had values of drug concentration for at least 1 time point. The PKAS population included all of the patients treated with ASP015K that were also included in the Full Analysis Set (FAS - all randomized subjects that received at least one study drug dose) and Safety Analysis Set (SAF-all patients who received at least 1 dose of study drug).

Subject analysis set title	H1 Metabolite - ASP015K 50 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the PKAS.

Subject analysis set title	H1 Metabolite - ASP015K 100 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the PKAS.

Subject analysis set title	H1 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the PKAS.

Subject analysis set title	H2 Metabolite - ASP015K 25 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the PKAS.

Subject analysis set title	H2 Metabolite - ASP015K 50 mg + MTX (PKAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The study analysis population consisted of the PKAS.

Subject analysis set title	H2 Metabolite - ASP015K 100 mg + MTX (PKAS)

Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	
Subject analysis set title	H2 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	
Subject analysis set title	H4 Metabolite - ASP015K 25 mg + MTX (PKAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	
Subject analysis set title	H4 Metabolite - ASP015K 50 mg + MTX (PKAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	
Subject analysis set title	H4 Metabolite - ASP015K 100 mg + MTX (PKAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	
Subject analysis set title	H4 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The study analysis population consisted of the PKAS.	

Primary: Percentage of participants achieving a response in American College of Rheumatology (ACR) criteria for 20% improvement in disease severity (ACR 20) using the C-reactive protein (CRP) level (ACR20-CRP) at week 12

End point title	Percentage of participants achieving a response in American College of Rheumatology (ACR) criteria for 20% improvement in disease severity (ACR 20) using the C-reactive protein (CRP) level (ACR20-CRP) at week 12

End point description:

The study analysis population consisted of the Full Analysis Set (FAS), defined as all randomized subjects that received at least one study drug dose. ACR20-CRP responder determined at week 12 if ACR response criteria was met: At least 20% reduction from baseline at week 12 TJC68 count, At least 20% reduction from baseline at week 12 SJC66 count, At least 20% reduction from baseline at week 12 in any 3 of 5 ACR components: subject's global assessment of arthritis pain SGAP (100mm visual analog scale VAS; score 0=no pain, score 100=very severe pain), subject's global assessment of arthritis SGA (100mm VAS; score 0=no disease activity, score 100mm=very severe disease activity), PGA (100mm VAS; score 0=no disease activity, score 100mm=very severe disease activity), Health Assessment Questionnaire-Disability Index HAQ-DI (score from 0 to 3, higher score=greater disability), CRP (mg/dL, higher values= >inflammation). Patient defined as a non-responder if the patient was not a responder.

End point type	Primary

End point timeframe:

Week 12

End point values	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX	ASP015K 100 mg qd + weekly oral dose of MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[1]	66[2]	78[3]	84[4]
Units: percentage of participants				

number (not applicable)				
Responder (R)	44.4	43.9	61.5	46.4
Non-responder (NR)	55.6	56.1	38.5	53.6

Notes:

[1] - R (N= 32), NR (N= 40)

[2] - R (N= 29), NR (N= 37)

[3] - R (N= 48), NR (N= 30)

[4] - R (N= 39), NR (N= 45)

End point values	ASP015K 150 mg qd + weekly oral dose of MTX			
Subject group type	Reporting group			
Number of subjects analysed	78[5]			
Units: percentage of participants				
number (not applicable)				
Responder (R)	57.7			
Non-responder (NR)	42.3			

Notes:

[5] - R (N= 45), NR (N= 33)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

LOCF: Last Observation Carried Forward for missing ACR20 components. NRI: Non-Responder Imputation for missing ACR response. ACR components were LOCFed first and then ACR20 response was calculated. In addition, all subjects with RA rescue therapy prior to or at Week 12 were classified as non-responders for primary analysis of ACR20-CRP response at time of first rescue and until their primary endpoint assessment.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 25 mg qd (once a day) + weekly oral dose of MTX
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.193 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.9

Notes:

[6] - ACR components were LOCF first and then the response was calculated. In addition, all patients with RA rescue therapy prior to or at week 12 were classified as non-responders (ACR50-CRP and ACR70-CRP). The total number of subjects in the statistical analysis are the responders in the Placebo group (32) and ASP015K 25 mg (29).

[7] - Based on logistic regression model: ACR response (responder, non-responder) = Treatment + Prior Anti-TNF Use + Geographic Region. Odds ratio > 1 favors ASP015K.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

LOCF: Last Observation Carried Forward for missing ACR20 components. NRI: Non-Responder Imputation for missing ACR response. ACR components were LOCFed first and then ACR20 response was calculated. In addition, all subjects with RA rescue therapy prior to or at Week 12 were classified as non-responders for primary analysis of ACR20-CRP response at time of first rescue and until their primary endpoint assessment.

Comparison groups	ASP015K 50 mg qd + weekly oral dose of MTX v Placebo + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.036 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	3.87

Notes:

[8] - The total number of subjects in the statistical analysis are the responders in the Placebo group (32) and ASP015K 50 mg (48).

[9] - Based on logistic regression model: ACR response (responder, non-responder) = Treatment + Prior Anti-TNF Use + Geographic Region. Odds ratio > 1 favors ASP015K.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

LOCF: Last Observation Carried Forward for missing ACR20 components. NRI: Non-Responder Imputation for missing ACR response. ACR components were LOCFed first and then ACR20 response was calculated. In addition, all subjects with RA rescue therapy prior to or at Week 12 were classified as non-responders for primary analysis of ACR20-CRP response at time of first rescue and until their primary endpoint assessment.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 100 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.379 [11]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	2.04

Notes:

[10] - The total number of subjects in the statistical analysis are the responders in the Placebo group (32) and ASP015K 100 mg (39).

[11] - Based on logistic regression model: ACR response (responder, non-responder) = Treatment + Prior Anti-TNF Use + Geographic Region. Odds ratio > 1 favors ASP015K.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

LOCF: Last Observation Carried Forward for missing ACR20 components. NRI: Non-Responder Imputation for missing ACR response. ACR components were LOCFed first and then ACR20 response was

calculated. In addition, all subjects with RA rescue therapy prior to or at Week 12 were classified as non-responders for primary analysis of ACR20-CRP response at time of first rescue and until their primary endpoint assessment.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 150 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.186 [13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	3.26

Notes:

[12] - The total number of subjects in the statistical analysis are the responders in the Placebo group (32) and ASP015K 150 mg (45).

[13] - Based on logistic regression model: ACR response (responder, non-responder) = Treatment + Prior Anti-TNF Use + Geographic Region. Odds ratio > 1 favors ASP015K.

Primary: Trough plasma concentration of ASP015K and metabolites

End point title	Trough plasma concentration of ASP015K and metabolites[14][15]

End point description:

The study analysis population consisted of the Pharmacokinetic Analysis Set (PKAS). The PKAS consisted of all patients who received at least 1 dose of study drug and who had values of drug concentration for at least 1 time point. N= number of participants.

End point type	Primary

End point timeframe:

Up to week 12.

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This pharmacokinetic (PK) endpoint pertained to only those arms/subject analysis sets with ASP015K treatment since it measured the trough plasma concentration of ASP015K and metabolites. This was not applicable to the placebo treatment arm.

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics have been summarized for trough plasma concentrations of ASP015K, and metabolites by active treatment group
and time point for each analyte.

End point values	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX	ASP015K 100 mg qd + weekly oral dose of MTX	ASP015K 150 mg qd + weekly oral dose of MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66[16]	78[17]	84[18]	78[19]
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0.164 (± 1.3235)	0.448 (± 3.8524)	0.045 (± 0.4094)	0 (± 0)
Week 1	1.8 (± 5.0241)	3.618 (± 16.1845)	8.177 (± 37.8132)	6.989 (± 7.3098)

Week 2	2.538 (± 9.4912)	2.233 (± 2.7951)	3.853 (± 3.1801)	12.025 (± 45.1589)
Week 4	0.901 (± 1.0425)	3.144 (± 9.0971)	4.02 (± 7.1763)	7.042 (± 7.0535)
Week 8	1.063 (± 1.6138)	3.351 (± 9.1165)	7.79 (± 25.824)	9.838 (± 17.3091)
Week 12	0.753 (± 0.6513)	5.909 (± 19.295)	5.256 (± 7.1434)	11.7 (± 39.9558)

Notes:

[16] - [N= Baseline/65, Week 1/50, Week 2/56, Week 4/52, Week 8/51, Week 12/49]

[17] - [N= Baseline/74, Week 1/56, Week 2/58, Week 4/59, Week 8/58, Week 12/57]

[18] - [N= Baseline/83, Week 1/67, Week 2/65, Week 4/67, Week 8/64, Week 12/57]

[19] - [N= Baseline/77, Week 1/65, Week 2/66, Week 4/65, Week 8/61, Week 12/62]

End point values	H1 Metabolite - ASP015K 25 mg + MTX (PKAS)	H1 Metabolite - ASP015K 50 mg + MTX (PKAS)	H1 Metabolite - ASP015K 100 mg + MTX (PKAS)	H1 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	66[20]	78[21]	84[22]	78[23]
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	0 (± 0)	0.053 (± 0.3776)	0 (± 0)
Week 1	2.096 (± 3.2356)	3.37 (± 5.8755)	6.469 (± 6.293)	10.665 (± 14.6867)
Week 2	1.981 (± 3.318)	3.575 (± 4.1641)	5.889 (± 5.6506)	9.137 (± 8.6281)
Week 4	1.677 (± 1.9554)	3.676 (± 5.0981)	5.927 (± 7.7267)	7.833 (± 7.616)
Week 8	2.206 (± 3.8035)	4.359 (± 11.4328)	7.94 (± 17.7368)	10.949 (± 17.9865)
Week 12	1.997 (± 3.1006)	3.825 (± 4.6887)	6.924 (± 8.2874)	8.413 (± 10.5487)

Notes:

[20] - [N= Baseline/65, Week 1/50, Week 2/55, Week 4/52, Week 8/52, Week 12/53]

[21] - [N= Baseline/74, Week 1/58, Week 2/58, Week 4/59, Week 8/62, Week 12/58]

[22] - [N= Baseline/83, Week 1/68, Week 2/64, Week 4/67, Week 8/63, Week 12/57]

[23] - [N= Baseline/77, Week 1/68, Week 2/67, Week 4/66, Week 8/61, Week 12/64]

End point values	H2 Metabolite - ASP015K 25 mg + MTX (PKAS)	H2 Metabolite - ASP015K 50 mg + MTX (PKAS)	H2 Metabolite - ASP015K 100 mg + MTX (PKAS)	H2 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	66[24]	78[25]	84[26]	78[27]
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0.049 (± 0.3944)	0.554 (± 4.765)	0.213 (± 1.7174)	0 (± 0)
Week 1	4.48 (± 8.4518)	7.92 (± 29.2576)	21.478 (± 96.7487)	21.15 (± 26.1555)
Week 2	4.694 (± 12.2919)	6.627 (± 9.5277)	10.532 (± 9.3593)	28.032 (± 64.5609)
Week 4	2.747 (± 3.8714)	8.032 (± 18.8903)	10.833 (± 15.9375)	21.29 (± 30.0176)

| | Week 8 | 3.835 (± 9.989) | 8.747 (± 21.557) | 22.766 (± 93.0472) | 29.495 (± 56.2249) |
| | Week 12 | 2.832 (± 5.1774) | 12.311 (± 34.0951) | 13.252 (± 16.8922) | 35.453 (± 114.0364) |

Notes:

[24] - [N= Baseline/65, Week 1/50, Week 2/54, Week 4/51, Week 8/51, Week 12/51]

[25] - [N= Baseline/74, Week 1/57, Week 2/58, Week 4/59, Week 8/57, Week 12/57]

[26] - [N= Baseline/83, Week 1/67, Week 2/66, Week 4/67, Week 8/63, Week 12/55]

[27] - [N= Baseline/77, Week 1/65, Week 2/66, Week 4/65, Week 8/60, Week 12/63]

End point values	H4 Metabolite - ASP015K 25 mg + MTX (PKAS)	H4 Metabolite - ASP015K 50 mg + MTX (PKAS)	H4 Metabolite - ASP015K 100 mg + MTX (PKAS)	H4 Metabolite - ASP015K 150 mg + MTX (PKAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	66[28]	78[29]	84[30]	78[31]
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	0 (± 0)	0.026 (± 0.2393)	0 (± 0)
Week 1	1.425 (± 2.1349)	2.109 (± 3.292)	4.992 (± 6.8523)	6.921 (± 8.6144)
Week 2	1.163 (± 1.4283)	2.266 (± 2.0518)	4.332 (± 3.7518)	6.18 (± 5.207)
Week 4	1.07 (± 0.8048)	2.455 (± 2.9556)	4.309 (± 5.8932)	5.48 (± 3.3805)
Week 8	1.336 (± 2.0418)	2.589 (± 3.5547)	5.263 (± 9.7618)	7.067 (± 8.1225)
Week 12	1.414 (± 2.365)	2.937 (± 4.1479)	5.55 (± 8.8286)	6.483 (± 7.3158)

Notes:

[28] - [N= Baseline/65, Week 1/51, Week 2/56, Week 4/51, Week 8/51, Week 12/53]

[29] - [N= Baseline/74, Week 1/58, Week 2/58, Week 4/59, Week 8/61, Week 12/56]

[30] - [N= Baseline/83, Week 1/69, Week 2/65, Week 4/67, Week 8/63, Week 12/57]

[31] - [N= Baseline/77, Week 1/67, Week 2/67, Week 4/67, Week 8/62, Week 12/62]

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving American College of Rheumatology criteria for 50% improvement in disease severity using the c-reactive protein level (ACR50-CRP) response at Week 12

End point title	Percentage of participants achieving American College of Rheumatology criteria for 50% improvement in disease severity using the c-reactive protein level (ACR50-CRP) response at Week 12

End point description:

The study analysis population consisted of the FAS. ACR components were Last Observation Carried Forwrad (LOCF) first and then the response was calculated. In addition, all patients with RA rescue therapy prior to or at week 12 were classified as non-responders. ACR50-CRP responder is defined as per ACR20 but using 50% instead of 20%.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX	ASP015K 100 mg qd + weekly oral dose of MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[32]	66[33]	78[34]	84[35]
Units: percentage of participants				
number (not applicable)				
Responder (R)	26.4	18.2	33.3	33.3
Non-responder (NR)	73.6	81.8	66.7	66.7

Notes:

[32] - R (N= 19), NR (N= 53)

[33] - R (N= 12), NR (N=54)

[34] - R (N= 26), NR (N=52)

[35] - R (N= 28), NR (N=56)

End point values	ASP015K 150 mg qd + weekly oral dose of MTX			
Subject group type	Reporting group			
Number of subjects analysed	78[36]			
Units: percentage of participants				
number (not applicable)				
Responder (R)	37.2			
Non-responder (NR)	62.8			

Notes:

[36] - R (N= 29), NR (N=49)

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (19) and ASP015K 25 mg (12).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 25 mg qd (once a day) + weekly oral dose of MTX
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023 [37]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.39

Notes:

[37] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF (tumor necrosis factor) use and geographic region (North America, Europe, Latin America).

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (19) and ASP015K 50 mg (26).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 50 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.401 [38]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	2.8

Notes:

[38] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (19) and ASP015K 100 mg (28).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 100 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.318 [39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.86

Notes:

[39] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (19) and ASP015K 150 mg (29).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 150 mg qd +

	weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106 [40]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	3.29

Notes:

[40] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Secondary: Percentage of participants achieving American College of Rheumatology criteria for 70% improvement in disease severity (ACR70) response at Week 12

End point title	Percentage of participants achieving American College of Rheumatology criteria for 70% improvement in disease severity (ACR70) response at Week 12

End point description:

The study analysis population consisted of the FAS. ACR components were LOCF first and then the response was calculated. In addition, all patients with RA rescue therapy prior to or at week 12 were classified as non-responders. ACR70-CRP responder is defined as per ACR20 but using 70% instead of 20%.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX	ASP015K 100 mg qd + weekly oral dose of MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72[41]	66[42]	78[43]	84[44]
Units: percentage of participants				
number (not applicable)				
Responder (R)	11.1	9.1	15.4	16.7
Non-responder (NR)	88.9	90.9	84.6	83.3

Notes:

[41] - R (N= 8), NR (N= 64)

[42] - R (N= 6), NR (N= 60)

[43] - R (N= 12), NR (N= 66)

[44] - R (N= 14), NR (N= 70)

End point values	ASP015K 150 mg qd + weekly oral dose of MTX			

Subject group type	Reporting group				
Number of subjects analysed	78[45]				
Units: percentage of participants					
number (not applicable)					
Responder (R)	19.2				
Non-responder (NR)	80.8				

Notes:

[45] - R (N= 15), NR (N= 63)

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The total number of subjects in the statistical analysis are the responders in the Placebo group (8) and ASP015K 25 mg (6).

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 25 mg qd (once a day) + weekly oral dose of MTX
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.202 [46]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	2.47

Notes:

[46] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The total number of subjects in the statistical analysis are the responders in the Placebo group (8) and ASP015K 50 mg (12).

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 50 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.723 [47]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	3.74

Notes:

[47] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America)..

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (8) and ASP015K 100 mg (14).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 100 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.364 [48]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	4.23

Notes:

[48] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
The total number of subjects in the statistical analysis are the responders in the Placebo group (8) and ASP015K 150 mg (15).	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 150 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.183 [49]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	4.7

Notes:

[49] - The odds ratio (odds ratio > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group, prior anti-TNF use and geographic region (North America, Europe, Latin America).

Secondary: Change from Baseline/Day 1 to Week 12/Early Termination (ET) in Disease Activity Score in 28 Joints score based on the c-reactive protein level (DAS28-CRP) score

End point title	Change from Baseline/Day 1 to Week 12/Early Termination (ET) in Disease Activity Score in 28 Joints score based on the

	c-reactive protein level (DAS28-CRP) score

End point description:

The study analysis population consisted of the FAS. DAS28-CRP was used to assess disease activity for RA. The DAS28-CRP score includes the TJC28 (refers to tender joint count based on 28 joints) and SJC28 (refers to swollen joint count based on 28 joints), the CRP level (measured in mg/dL will be converted to mg/L for analysis purposes) and the subject's general health (SGA, measured on 100 mm Visual Analog Scale [VAS]. Higher DAS28-CRP scores indicate greater disease activity. Missing DAS28 component values were imputed using LOCF.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo + weekly oral dose of MTX	ASP015K 25 mg qd (once a day) + weekly oral dose of MTX	ASP015K 50 mg qd + weekly oral dose of MTX	ASP015K 100 mg qd + weekly oral dose of MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	66	78	84
Units: units on a scale				
least squares mean (standard error)	-1.38 (± 0.163)	-1.35 (± 0.169)	-1.84 (± 0.157)	-1.64 (± 0.151)

End point values	ASP015K 150 mg qd + weekly oral dose of MTX			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: units on a scale				
least squares mean (standard error)	-2.01 (± 0.16)			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Difference between Placebo vs. ASP015K 25 mg.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 25 mg qd (once a day) + weekly oral dose of MTX
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.894 [50]
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean of Difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.223

Notes:

[50] - P value was based on an ANCOVA model: DAS28 Change = Treatment + Baseline DAS28 + Prior Anti-TNF Use + Geographic Region.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Difference between Placebo vs. ASP015K 50 mg.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 50 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033 [51]
Method	Regression, Logistic
Parameter estimate	LS Mean of Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.214

Notes:

[51] - P value was based on an ANCOVA model: DAS28 Change = Treatment + Baseline DAS28 + Prior Anti-TNF Use + Geographic Region.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Difference between Placebo vs. ASP015K 100 mg.

Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 100 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.217 [52]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.211

Notes:

[52] - P value was based on an ANCOVA model: DAS28 Change = Treatment + Baseline DAS28 + Prior Anti-TNF Use + Geographic Region.

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
Difference between Placebo vs. ASP015K 150 mg.	
Comparison groups	Placebo + weekly oral dose of MTX v ASP015K 150 mg qd + weekly oral dose of MTX
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [53]
Method	ANCOVA
Parameter estimate	LS Mean of Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.215

Notes:

[53] - P value was based on an ANCOVA model: DAS28 Change = Treatment + Baseline DAS28 + Prior Anti-TNF Use + Geographic Region.

Statistical analysis title	Statistical analysis 4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

An adverse event was any untoward medical occurrence in a patient administered a study drug and which did not necessarily have a causal relationship with the treatment. Adverse events were based on the Safety Analysis Set (SAF) population. The SAF was defined as all patients who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Placebo + MTX
Reporting group description:	
Reporting group 1 description	
Reporting group title	ASP015K 25 mg + MTX
Reporting group description:	
Reporting group 2 description	
Reporting group title	ASP015K 50 mg + MTX
Reporting group description:	
Reporting group 3 description	
Reporting group title	ASP015K 100 mg + MTX
Reporting group description:	
Reporting group 4 description	
Reporting group title	ASP015K 150 mg + MTX
Reporting group description:	
Reporting group 5 description	

Serious adverse events	Placebo + MTX	ASP015K 25 mg + MTX	ASP015K 50 mg + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 72 (0.00%)	0 / 66 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	0 / 72 (0.00%)	0 / 66 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Erysipelas			
subjects affected / exposed	0 / 72 (0.00%)	0 / 66 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 66 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	ASP015K 100 mg + MTX	ASP015K 150 mg + MTX	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 84 (2.38%)	1 / 78 (1.28%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pulmonary mass			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 84 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo + MTX	ASP015K 25 mg + MTX	ASP015K 50 mg + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 72 (18.06%)	9 / 66 (13.64%)	14 / 78 (17.95%)

Nervous system disorders			
Headache			
subjects affected / exposed	1 / 72 (1.39%)	1 / 66 (1.52%)	4 / 78 (5.13%)
occurrences (all)	1	1	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 72 (5.56%)	4 / 66 (6.06%)	2 / 78 (2.56%)
occurrences (all)	4	4	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 72 (5.56%)	2 / 66 (3.03%)	3 / 78 (3.85%)
occurrences (all)	4	2	3
Urinary tract infection			
subjects affected / exposed	5 / 72 (6.94%)	2 / 66 (3.03%)	5 / 78 (6.41%)
occurrences (all)	5	2	5

Non-serious adverse events	ASP015K 100 mg + MTX	ASP015K 150 mg + MTX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 84 (13.10%)	15 / 78 (19.23%)	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 84 (2.38%)	2 / 78 (2.56%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 84 (1.19%)	5 / 78 (6.41%)	
occurrences (all)	1	6	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 84 (4.76%)	3 / 78 (3.85%)	
occurrences (all)	5	3	
Urinary tract infection			
subjects affected / exposed	4 / 84 (4.76%)	6 / 78 (7.69%)	
occurrences (all)	4	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2012	The changes included in Amendment 1 are summarized below: ● Dosing instructions revised to state "take with food" ● Screening period extended to 4 weeks (28 days) ● The follow-up period for patient not rolling-over into the extension study extended to 30 days ● Clarifications and other administrative changes made. These changes to the protocol were included prior to the randomization of any patients.
12 June 2012	The changes included in Amendment 2 are summarized below: ● "Monotherapy" removed from trial design ● Allowed and prohibited concomitant medications updated ● Required washout periods for previous DMARDs updated ● Stratification by geographic region added ● Supine blood pressure requirement removed ● Estimated glomerular filtration rate (GFR) calculation added ● Use of dosing diary added ● Clarifications and other administrative changes made These changes to the protocol were included prior to the randomization of any patients.
05 December 2012	The changes included in Amendment 3 (Czech Republic-specific amendment) are summarized below: ● Age limitation to only enroll patients under the age of 65 years added ● Language regarding compliance with local practice and guidance for tuberculosis (TB) screening via purified protein derivative skin testing added These changes to the protocol were included prior to the randomization of any patients in this country.
01 April 2013	The changes included in Amendment 4 are summarized below: ● Number of planned sites revised ● Optional messenger RNA (mRNA) expression profiling included ● Allowed and prohibited concomitant medications updated ● Inclusion criteria revised to add contraception requirements for both men and women ● Exclusion criteria revised to include other malabsorption syndromes. ● Significant (absolute lymphocyte count [ALC] < 750/mm3) or severe (ALC < 500/mm3) lymphopenia added as an exclusion and discontinuation criteria, respectively ● Recording of prior rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) testing results added ● Clarifications and other administrative changes made These changes to the protocol were included after the randomization of 117 patients, but did not affect the overall outcome of the study.
05 June 2013	The changes included in Amendment 5 (Czech Republic-specific amendment) are summarized below: ● Inclusion criteria revised to include age cap at < 65 years This change to the protocol was included after the randomization of 11 patients in the Czech Republic, but did not affect the overall outcome of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported