



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

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-006020-20 |
| Trial protocol | HU CZ PL BG |
| Global end of trial date | 02 December 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v3 (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-RA22 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01565655 |
| 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 | 02 December 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 December 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the safety and efficacy of ASP015K in moderate to severe Rheumatoid Arthritis (RA) subjects.

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:

This study was comprised of up to a 4-week screening period, a 12-week treatment period and a 30-day follow-up period. Once informed consent was obtained, the disease-modifying antirheumatic drug (DMARD) washout period (as applicable) could begin prior to screening. During screening (day -28 to day -1), entry criteria were confirmed and screening procedures were performed. Randomization occurred on day 1 and study drug was administered for 12 weeks (day 1 to day 84). At the end of treatment (EOT), end of study (EOS) procedures and a follow-up assessment of adverse events (AEs) were conducted for up to 30 days (day 85 to day 115).

DMARD Washout Period: Period of time during which patients do not receive specific DMARD medications, and the effects of the DMARD medication are eliminated (or assumed to be eliminated). The DMARD washout period in this trial begins 1 to 26 weeks prior to start of study drug (duration is based on the disease-modifying antirheumatic drug used).

Evidence for comparator:

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

| | |
|---|--------------|
| Actual start date of recruitment | 19 June 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: 57 |
| Country: Number of subjects enrolled | Bulgaria: 12 |
| Country: Number of subjects enrolled | Czech Republic: 25 |
| Country: Number of subjects enrolled | Hungary: 25 |
| Country: Number of subjects enrolled | Mexico: 32 |
| Country: Number of subjects enrolled | United States: 138 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 289 |
| EEA total number of subjects | 119 |

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) | 249 |
| From 65 to 84 years | 40 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This multi-center study was conducted at 41 sites, 19 sites in the US, 3 sites in Bulgaria, 4 sites in the Czech Republic, 5 sites in Hungary, 6 sites in Poland and 4 sites in Mexico. The Principal Investigator at each site was a licensed clinician with experience in the therapeutic area of rheumatoid arthritis (RA).

Pre-assignment

Screening details:

The study was comprised of a screening period of up to 4 weeks (28 days), a treatment period of 12 weeks and a follow-up period of 30 days.

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.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization.

| | |
|--|--------------------|
| Arm type | Placebo |
| 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. The first dose was taken on Baseline/Day 1 of the treatment period at the site.

| | |
|------------------|--------------------------|
| Arm title | ASP015K 25 mg once daily |
|------------------|--------------------------|

Arm description:

This arm consisted of ASP015K 25 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization.

| | |
|--|--------------------|
| 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.

| | |
|------------------|--------------------------|
| Arm title | ASP015K 50 mg once daily |
|------------------|--------------------------|

Arm description:

This arm consisted of ASP015K 50 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization.

| | |
|--|--------------------|
| 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.

| | |
|------------------|---------------------------|
| Arm title | ASP015K 100 mg once daily |
|------------------|---------------------------|

Arm description:

This arm consisted of ASP015K 100 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization.

| | |
|--|--------------------|
| 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.

| | |
|------------------|---------------------------|
| Arm title | ASP015K 150 mg once daily |
|------------------|---------------------------|

Arm description:

This arm consisted of ASP015K 150 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization.

| | |
|--|--------------------|
| 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 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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily |
|---------------------------------------|---------|--------------------------|--------------------------|
| Started | 51 | 59 | 57 |
| Completed | 49 | 50 | 49 |
| Not completed | 2 | 9 | 8 |
| Protocol violation | - | 1 | 1 |
| Adverse event | 1 | 4 | 2 |
| Patient non-compliant | - | - | 1 |
| Withdrawal by subject | 1 | 1 | 3 |
| Lack of efficacy | - | 1 | 1 |

| | | | |
|---|---|---|---|
| Treatment interrupted due to adverse event | - | 1 | - |
| Treatment interrupted due to antibiotic use | - | 1 | - |

| Number of subjects in period 1 | ASP015K 100 mg once daily | ASP015K 150 mg once daily |
|---|---------------------------|---------------------------|
| Started | 58 | 64 |
| Completed | 54 | 60 |
| Not completed | 4 | 4 |
| Protocol violation | 1 | - |
| Adverse event | 1 | 2 |
| Patient non-compliant | - | - |
| Withdrawal by subject | 2 | 1 |
| Lack of efficacy | - | 1 |
| Treatment interrupted due to adverse event | - | - |
| Treatment interrupted due to antibiotic use | - | - |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------|
| Reporting group title | Placebo |
| Reporting group description: This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 25 mg once daily |
| Reporting group description: This arm consisted of ASP015K 25 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 50 mg once daily |
| Reporting group description: This arm consisted of ASP015K 50 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 100 mg once daily |
| Reporting group description: This arm consisted of ASP015K 100 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 150 mg once daily |
| Reporting group description: This arm consisted of ASP015K 150 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |

| Reporting group values | Placebo | ASP015K 25 mg once daily | ASP015K 50 mg once daily |
|--|---------|--------------------------|--------------------------|
| Number of subjects | 51 | 59 | 57 |
| 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 | 52.7 | 52.6 | 54.8 |
| standard deviation | ± 12.2 | ± 10.2 | ± 10 |
| Gender categorical | | | |
| Gender values are based on the SAF population. | | | |
| Units: Subjects | | | |
| Female | 42 | 46 | 48 |
| Male | 9 | 13 | 9 |

| Reporting group values | ASP015K 100 mg once daily | ASP015K 150 mg once daily | Total |
|--|------------------------------|------------------------------|-------|
| Number of subjects | 58 | 64 | 289 |
| 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 | 54.9 | 54.4 | |
| standard deviation | ± 11.3 | ± 12.5 | - |
| Gender categorical | | | |
| Gender values are based on the SAF population. | | | |
| Units: Subjects | | | |
| Female | 51 | 50 | 237 |
| Male | 7 | 14 | 52 |

End points

End points reporting groups

| | |
|---|---------------------------------------|
| Reporting group title | Placebo |
| Reporting group description: This arm consisted of matching ASP015K placebo taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 25 mg once daily |
| Reporting group description: This arm consisted of ASP015K 25 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 50 mg once daily |
| Reporting group description: This arm consisted of ASP015K 50 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 100 mg once daily |
| Reporting group description: This arm consisted of ASP015K 100 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Reporting group title | ASP015K 150 mg once daily |
| Reporting group description: This arm consisted of ASP015K 150 mg once a daily taken orally with food, for 12 weeks (days 1-84) after randomization. | |
| Subject analysis set title | H1 Metabolite - ASP015K 25 mg (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 (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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily | ASP015K 100 mg once daily |
|-----------------------------------|-------------------|--------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 ^[1] | 59 ^[2] | 57 ^[3] | 58 ^[4] |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responder (R) | 29.4 | 22 | 36.8 | 48.3 |
| Non-Responder (NR) | 70.6 | 78 | 63.2 | 51.7 |

Notes:

[1] - R (N= 15), NR (N= 36)

[2] - R (N= 13), NR (N= 46)

[3] - R (N= 21), NR (N= 36)

[4] - R (N= 28), NR (N= 30)

| | | | | |
|-----------------------------------|---------------------------|--|--|--|
| End point values | ASP015K 150 mg once daily | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 ^[5] | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responder (R) | 56.3 | | | |
| Non-Responder (NR) | 43.8 | | | |

Notes:

[5] - R (N= 36), NR (N= 28)

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 nonresponders. The total number of subjects in the statistical analysis are the responders in the Placebo group (15) and ASP015K 25 mg (13).

| | |
|---|------------------------------------|
| Comparison groups | Placebo v ASP015K 25 mg once daily |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.005 ^[6] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.28 |
| upper limit | 1.61 |

Notes:

[6] - The odds ratio (OR > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group and geographic region.

| | |
|-----------------------------------|------------------------|
| 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 nonresponders. The total number of subjects in the statistical analysis are the responders in the Placebo group (15) and ASP015K 50 mg (21).

| | |
|-------------------|------------------------------------|
| Comparison groups | Placebo v ASP015K 50 mg once daily |
|-------------------|------------------------------------|

| | |
|---|------------------------|
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.805 ^[7] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 3.13 |

Notes:

[7] - The odds ratio (OR > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group and geographic region.

| | |
|-----------------------------------|------------------------|
| 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 nonresponders. The total number of subjects in the statistical analysis are the responders in the Placebo group (15) and ASP015K 100 mg (28).

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v ASP015K 100 mg once daily |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.054 ^[8] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 5.23 |

Notes:

[8] - The odds ratio (OR > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group and geographic region.

| | |
|-----------------------------------|------------------------|
| 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 nonresponders. The total number of subjects in the statistical analysis are the responders in the Placebo group (15) and ASP015K 150 mg (36).

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v ASP015K 150 mg once daily |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.001 ^[9] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.15 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.44 |
| upper limit | 6.92 |

Notes:

[9] - The odds ratio (OR > 1 favors ASP015K) and P value were based on a logistic regression model with effects for treatment group and geographic region.

Primary: Trough plasma concentration of ASP015K and metabolites

| | |
|-----------------|--|
| End point title | Trough plasma concentration of ASP015K and metabolites ^{[10][11]} |
|-----------------|--|

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.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to week 12.

Notes:

[10] - 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.

[11] - 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 once daily | ASP015K 50 mg once daily | ASP015K 100 mg once daily | ASP015K 150 mg once daily |
|--------------------------------------|--------------------------|--------------------------|---------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 59 ^[12] | 57 ^[13] | 58 ^[14] | 64 ^[15] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.754 (± 5.6392) | 3.004 (± 22.482) | 6.485 (± 48.9613) | 0.781 (± 5.3492) |
| Week 1 | 0.881 (± 1.1244) | 1.472 (± 1.1549) | 3.023 (± 2.4352) | 8.286 (± 26.5097) |
| Week 2 | 1.631 (± 5.9792) | 1.373 (± 0.9128) | 6.184 (± 21.8638) | 14.356 (± 46.1079) |
| Week 4 | 2.215 (± 5.7659) | 1.745 (± 2.1049) | 3.145 (± 4.4099) | 10.174 (± 33.6779) |
| Week 8 | 1.022 (± 2.0704) | 1.842 (± 1.7768) | 5.614 (± 15.026) | 6.477 (± 6.2216) |
| Week 12 | 1.034 (± 1.5076) | 2.172 (± 2.1518) | 3.615 (± 3.8422) | 5.964 (± 5.2095) |

Notes:

[12] - [N= Baseline/57, Week 1/45, Week 2/46, Week 4/42, Week 8/41, Week 12/42]

[13] - [N= Baseline/56, Week 1/45, Week 2/51, Week 4/45, Week 8/43, Week 12/44]

[14] - [N= Baseline/57, Week 1/43, Week 2/47, Week 4/48, Week 8/46, Week 12/45]

[15] - [N= Baseline/63, Week 1/49, Week 2/52, Week 4/48, Week 8/49, Week 12/44]

| | | | | |
|------------------|-----------------|-----------------|-----------------|-----------------|
| End point values | H1 Metabolite - | H1 Metabolite - | H1 Metabolite - | H1 Metabolite - |
|------------------|-----------------|-----------------|-----------------|-----------------|

| | ASP015K 25 mg (PKAS) | ASP015K 50 mg (PKAS) | ASP015K 100 mg (PKAS) | ASP015K 150 mg (PKAS) |
|--------------------------------------|-------------------------|-------------------------|--------------------------|--------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 59 ^[16] | 57 ^[17] | 58 ^[18] | 64 ^[19] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.039 (± 0.298) | 0.036 (± 0.2673) | 0.989 (± 7.4704) | 0.099 (± 0.7862) |
| Week 1 | 2.072 (± 3.2626) | 2.748 (± 1.9102) | 7.471 (± 8.0531) | 14.436 (± 26.3264) |
| Week 2 | 2.156 (± 4.0801) | 2.789 (± 2.1451) | 7.453 (± 10.1198) | 12.642 (± 17.5732) |
| Week 4 | 1.824 (± 2.3861) | 3.069 (± 2.7708) | 6.617 (± 10.5697) | 13.6 (± 22.7147) |
| Week 8 | 1.475 (± 1.0352) | 3.819 (± 4.0106) | 7.738 (± 16.2141) | 10.932 (± 21.8831) |
| Week 12 | 1.369 (± 1.3726) | 4.363 (± 5.3775) | 5.24 (± 5.7651) | 11.484 (± 28.8065) |

Notes:

[16] - [N= Baseline/57, Week 1/45, Week 2/46, Week 4/44, Week 8/42, Week 12/43]

[17] - [N= Baseline/56, Week 1/45, Week 2/52, Week 4/43, Week 8/45, Week 12/43]

[18] - [N= Baseline/57, Week 1/44, Week 2/47, Week 4/49, Week 8/45, Week 12/45]

[19] - [N= Baseline/63, Week 1/48, Week 2/51, Week 4/48, Week 8/50, Week 12/44]

| End point values | H2 Metabolite - ASP015K 25 mg (PKAS) | H2 Metabolite - ASP015K 50 mg (PKAS) | H2 Metabolite - ASP015K 100 mg (PKAS) | H2 Metabolite - ASP015K 150 mg (PKAS) |
|--------------------------------------|--|--|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 59 ^[20] | 57 ^[21] | 58 ^[22] | 64 ^[23] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.861 (± 6.5035) | 5.674 (± 42.4611) | 13.729 (± 103.6539) | 0.309 (± 2.005) |
| Week 1 | 2.408 (± 3.4033) | 5.27 (± 8.5534) | 10.613 (± 9.4295) | 44.534 (± 176.3971) |
| Week 2 | 4.383 (± 15.9018) | 5.436 (± 8.5164) | 11.998 (± 16.0264) | 36.376 (± 113.6776) |
| Week 4 | 5.23 (± 16.3477) | 5.952 (± 6.2121) | 10.688 (± 15.8643) | 43.166 (± 162.0641) |
| Week 8 | 2.448 (± 4.2744) | 9.028 (± 19.397) | 18.554 (± 47.2131) | 35.541 (± 139.4458) |
| Week 12 | 2.464 (± 3.7308) | 8.372 (± 11.7188) | 13.515 (± 22.8604) | 20.289 (± 40.9056) |

Notes:

[20] - [N= Baseline/57, Week 1/44, Week 2/46, Week 4/44, Week 8/41, Week 12/42]

[21] - [N= Baseline/56, Week 1/45, Week 2/52, Week 4/44, Week 8/43, Week 12/41]

[22] - [N= Baseline/57, Week 1/43, Week 2/47, Week 4/49, Week 8/45, Week 12/45]

[23] - [N= Baseline/63, Week 1/48, Week 2/51, Week 4/47, Week 8/49, Week 12/44]

| End point values | H4 Metabolite - ASP015K 25 mg (PKAS) | H4 Metabolite - ASP015K 50 mg (PKAS) | H4 Metabolite - ASP015K 100 mg (PKAS) | H4 Metabolite - ASP015K 150 mg (PKAS) |
|--------------------------------------|--|--|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 59 ^[24] | 57 ^[25] | 58 ^[26] | 64 ^[27] |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 0.116 (± 0.8729) | 0.112 (± 0.8379) | 0.57 (± 4.3061) | 0.077 (± 0.4962) |

| | | | | |
|---------|------------------|------------------|-------------------|-------------------|
| Week 1 | 1.114 (± 0.9671) | 1.903 (± 1.4679) | 3.463 (± 2.402) | 8.409 (± 16.5609) |
| Week 2 | 1.326 (± 2.1325) | 1.783 (± 1.0238) | 3.77 (± 3.5126) | 7.043 (± 7.8633) |
| Week 4 | 1.449 (± 2.0105) | 2.16 (± 2.1099) | 3.347 (± 3.7267) | 9.317 (± 18.2902) |
| Week 8 | 1.078 (± 1.2251) | 2.707 (± 3.0481) | 4.776 (± 10.8524) | 7.027 (± 6.0709) |
| Week 12 | 1.013 (± 1.0075) | 3.318 (± 5.5703) | 3.204 (± 2.689) | 6.603 (± 5.95) |

Notes:

[24] - [N= Baseline/57, Week 1/46, Week 2/46, Week 4/44, Week 8/41, Week 12/44]

[25] - [N= Baseline/56, Week 1/45, Week 2/52, Week 4/44, Week 8/45, Week 12/44]

[26] - [N= Baseline/57, Week 1/44, Week 2/47, Week 4/49, Week 8/46, Week 12/44]

[27] - [N= Baseline/63, Week 1/49, Week 2/51, Week 4/48, Week 8/48, Week 12/44]

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 Forward (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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily | ASP015K 100 mg once daily |
|-----------------------------------|--------------------|--------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 ^[28] | 59 ^[29] | 57 ^[30] | 58 ^[31] |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders (R) | 9.8 | 15.3 | 24.6 | 27.6 |
| Non-Responders (NR) | 90.2 | 84.7 | 75.4 | 72.4 |

Notes:

[28] - R (N= 5), NR (N= 46)

[29] - R (N= 9), NR (N= 50)

[30] - R (N= 14), NR (n= 43)

[31] - R (N= 16), NR (n= 42)

| End point values | ASP015K 150 mg once daily | | | |
|-----------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 ^[32] | | | |

| | | | | |
|-----------------------------------|------|--|--|--|
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders (R) | 28.1 | | | |
| Non-Responders (NR) | 71.9 | | | |

Notes:

[32] - R (N= 18), NR (n= 46)

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 (5) and ASP015K 25 mg (9). | |
| Comparison groups | Placebo v ASP015K 25 mg once daily |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.272 ^[33] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 5.34 |

Notes:

[33] - 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).

| | |
|--|------------------------------------|
| 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 (5) and ASP015K 50 mg (14). | |
| Comparison groups | Placebo v ASP015K 50 mg once daily |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.43 ^[34] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.97 |
| upper limit | 9.03 |

Notes:

[34] - 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).

| | |
|-----------------------------------|------------------------|
| 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 (5) and ASP015K 100 mg (16).

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v ASP015K 100 mg once daily |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.074 ^[35] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.29 |
| upper limit | 11.76 |

Notes:

[35] - 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).

| | |
|-----------------------------------|------------------------|
| 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 (5) and ASP015K 150 mg (18).

| | |
|---|-------------------------------------|
| Comparison groups | Placebo v ASP015K 150 mg once daily |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.076 ^[36] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.28 |
| upper limit | 11.27 |

Notes:

[36] - 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).

Secondary: Percentage of participants achieving American College of Rheumatology criteria for 70% improvement in disease severity using the c-reactive protein level (ACR70-CRP) response at Week 12

| | |
|-----------------|---|
| End point title | Percentage of participants achieving American College of Rheumatology criteria for 70% improvement in disease severity using the c-reactive protein level (ACR70-CRP) response at Week 12 |
|-----------------|---|

End point description:

The study analysis population consisted of the FAS. ACR components were Last Observation Carried Forward (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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily | ASP015K 100 mg once daily |
|-----------------------------------|--------------------|--------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 ^[37] | 59 ^[38] | 57 ^[39] | 58 ^[40] |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders (R) | 7.8 | 6.8 | 15.8 | 19 |
| Non-Responders (NR) | 92.2 | 93.2 | 84.2 | 81 |

Notes:

[37] - R (N= 4), NE (N= 47)

[38] - R (N= 4), NE (N= 55)

[39] - R (N= 9), NE (N= 48)

[40] - R (N= 11), NE (N= 47)

| End point values | ASP015K 150 mg once daily | | | |
|-----------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 ^[41] | | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Responders (R) | 10.9 | | | |
| Non-Responders (NR) | 89.1 | | | |

Notes:

[41] - R (N= 7), NE (N= 57)

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 (4) and ASP015K 25 mg (4). | |
| Comparison groups | Placebo v ASP015K 25 mg once daily |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.171 ^[42] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.19 |
| upper limit | 3.52 |

Notes:

[42] - 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).

| 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 (4) and ASP015K 50 mg (9). | |
| Comparison groups | Placebo v ASP015K 50 mg once daily |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.334 ^[43] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 7.55 |

Notes:

[43] - 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).

| 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 (4) and ASP015K 100 mg (11). | |
| Comparison groups | Placebo v ASP015K 100 mg once daily |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.032 ^[44] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 10.76 |

Notes:

[44] - 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).

| 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 (4) and ASP015K 150 mg (7). | |
| Comparison groups | Placebo v ASP015K 150 mg once daily |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.969 ^[45] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.41 |
| upper limit | 5.54 |

Notes:

[45] - 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).

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

| | |
|-----------------|---|
| End point title | Change from Baseline/Day 1 to Week 12/Early Termination (ET) in Disease Activity Score in 28 Joints (DAS28) score based on the CRP level (DAS28-CRP) at week 12 |
|-----------------|---|

End point description:

The study analysis population consisted of the FAS. DAS28-CRP is 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 was to 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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily | ASP015K 100 mg once daily |
|-------------------------------------|-----------------|--------------------------|--------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 51 | 59 | 57 | 58 |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -1.16 (± 0.182) | -1.24 (± 0.169) | -1.52 (± 0.173) | -2.11 (± 0.176) |

| End point values | ASP015K 150 mg once daily | | | |
|-------------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 64 | | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -2.01 (± 0.165) | | | |

Statistical analyses

| | |
|--|---------------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Statistical analysis description: Difference between Placebo vs. ASP015K 25 mg. | |
| Comparison groups | Placebo v ASP015K 25 mg once daily |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.726 ^[46] |
| Method | ANCOVA |
| Parameter estimate | Least Squares (LS) Mean of Difference |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.55 |
| upper limit | 0.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.237 |

Notes:

[46] - P-value was based on an ANCOVA model with fixed effects for treatment and geographic region, treatment-by-geographic region interaction term (if the interaction term is significant at 0.10 level) and baseline DAS28-CRP score as a covariate.

| | |
|--|------------------------------------|
| Statistical analysis title | Statistical analysis 2 |
| Statistical analysis description: Difference between Placebo vs. ASP015K 50 mg. | |
| Comparison groups | Placebo v ASP015K 50 mg once daily |
| Number of subjects included in analysis | 108 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.131 ^[47] |
| Method | ANCOVA |
| Parameter estimate | LS Mean of Difference |
| Point estimate | -0.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.84 |
| upper limit | 0.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[47] - P-value was based on an ANCOVA model with fixed effects for treatment and geographic region, treatment-by-geographic region interaction term (if the interaction term is significant at 0.10 level) and baseline DAS28-CRP score as a covariate.

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical analysis 3 |
| Statistical analysis description: Difference between Placebo vs. ASP015K 100 mg. | |
| Comparison groups | Placebo v ASP015K 100 mg once daily |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 ^[48] |
| Method | ANCOVA |
| Parameter estimate | LS Mean of Difference |
| Point estimate | -0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.42 |
| upper limit | -0.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.239 |

Notes:

[48] - P-value was based on an ANCOVA model with fixed effects for treatment and geographic region, treatment-by-geographic region interaction term (if the interaction term is significant at 0.10 level) and baseline DAS28-CRP score as a covariate.

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical analysis 4 |
| Statistical analysis description: Difference between Placebo vs. ASP015K 150 mg. | |
| Comparison groups | Placebo v ASP015K 150 mg once daily |
| Number of subjects included in analysis | 115 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 ^[49] |
| Method | ANCOVA |
| Parameter estimate | LS Mean of Difference |
| Point estimate | -0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.31 |
| upper limit | -0.39 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.233 |

Notes:

[49] - P-value was based on an ANCOVA model with fixed effects for treatment and geographic region, treatment-by-geographic region interaction term (if the interaction term is significant at 0.10 level) and baseline DAS28-CRP score as a covariate.

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 |
|-----------------------|---------|

Reporting group description:

Reporting group 1 description

| | |
|-----------------------|--------------------------|
| Reporting group title | ASP015K 25 mg once daily |
|-----------------------|--------------------------|

Reporting group description:

Reporting group 2 description

| | |
|-----------------------|--------------------------|
| Reporting group title | ASP015K 50 mg once daily |
|-----------------------|--------------------------|

Reporting group description:

Reporting group 3 description

| | |
|-----------------------|---------------------------|
| Reporting group title | ASP015K 100 mg once daily |
|-----------------------|---------------------------|

Reporting group description:

Reporting group 4 description

| | |
|-----------------------|---------------------------|
| Reporting group title | ASP015K 150 mg once daily |
|-----------------------|---------------------------|

Reporting group description:

Reporting group 5 description

| Serious adverse events | Placebo | ASP015K 25 mg once daily | ASP015K 50 mg once daily |
|---|----------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 2 / 59 (3.39%) | 2 / 57 (3.51%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|----------------|----------------|----------------|
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Joint dislocation | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 59 (0.00%) | 0 / 57 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 1 / 57 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 59 (0.00%) | 0 / 57 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 1 / 57 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 1 / 57 (1.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 59 (1.69%) | 0 / 57 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Synovial cyst | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 0 / 57 (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 | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 1 / 59 (1.69%) | 0 / 57 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | ASP015K 100 mg once daily | ASP015K 150 mg once daily | |
|---|------------------------------|------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 2 / 64 (3.13%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Electrocardiogram abnormal | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 64 (1.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 64 (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 | | | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 0 / 64 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | ASP015K 25 mg once daily | ASP015K 50 mg once daily |
|---|-----------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 51 (13.73%) | 10 / 59 (16.95%) | 5 / 57 (8.77%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 1 / 59 (1.69%) | 0 / 57 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 4 / 59 (6.78%) | 1 / 57 (1.75%) |
| occurrences (all) | 1 | 4 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 2 / 59 (3.39%) | 1 / 57 (1.75%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 51 (1.96%) | 0 / 59 (0.00%) | 3 / 57 (5.26%) |
| occurrences (all) | 1 | 0 | 4 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 4 / 59 (6.78%) | 0 / 57 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 51 (3.92%) | 1 / 59 (1.69%) | 0 / 57 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 51 (0.00%) | 0 / 59 (0.00%) | 1 / 57 (1.75%) |
| occurrences (all) | 0 | 0 | 1 |

| Non-serious adverse events | ASP015K 100 mg once daily | ASP015K 150 mg once daily | |
|---|------------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 58 (29.31%) | 16 / 64 (25.00%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | 1 / 64 (1.56%) | |
| occurrences (all) | 5 | 2 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---------------------|---------------------|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | 0 / 64 (0.00%) 0 | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 6 / 64 (9.38%) 6 | |
| Musculoskeletal and connective tissue disorders Rheumatoid arthritis subjects affected / exposed occurrences (all) | 0 / 58 (0.00%) 0 | 2 / 64 (3.13%) 2 | |
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | 5 / 64 (7.81%) 5 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 3 | 5 / 64 (7.81%) 5 | |
| Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 1 / 64 (1.56%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 26 January 2012 | <p>The changes included in Amendment 4 are summarized below:</p> <ul style="list-style-type: none">• Dosing instructions revised to state "take with food"• Screening period and safety follow-up period extended to 4 weeks (28 days) and 30 days, respectively• The follow-up period for subject not rolling-over into the extension study extended to 30 days• Clarifications and other administrative changes made <p>These changes to the protocol were included prior to the enrollment of any patients</p> |
| 31 May 2012 | <p>The changes included in Amendment 2 are summarized below:</p> <ul style="list-style-type: none">• "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 (eGFR) calculation added• Use of dosing diary added• Clarifications and other administrative changes made <p>These changes to the protocol were included prior to the enrollment of any patients.</p> |
| 05 December 2012 | <p>The changes included in Amendment 3 (Czech Republic-specific amendment) are summarized below:</p> <ul style="list-style-type: none">• Age limitation to only enroll patients under the age of 65 years added• Language regarding compliance with local practice and guidance for tuberculosis screening via purified protein derivative skin testing added <p>These changes to the protocol were included prior to the enrollment of any patients in the Czech Republic.</p> |
| 18 December 2012 | <p>The changes included in Amendment 4 (Bulgaria-specific amendment) are summarized below:</p> <ul style="list-style-type: none">• Eligible patient population as it relates to required prior RA treatment clarified <p>These changes to the protocol were included prior to the enrollment of any patients in Bulgaria.</p> |
| 01 April 2013 | <p>The changes included in Amendment 5 are summarized below:</p> <ul style="list-style-type: none">• Number of planned sites revised• Optional messenger RNA expression profiling included• Allowed and prohibited concomitant medications updated• Inclusion criteria revised to require a demonstrated inadequate response or intolerance to prior DMARD treatment• 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 <p>These changes to the protocol were included after the enrollment of approximately 97 patients, but did not affect the overall outcome of the study.</p> |

| | |
|--------------|--|
| 05 June 2013 | <p>The changes included in Amendment 6 (Czech Republic-specific amendment) are summarized below:</p> <ul style="list-style-type: none"> • Inclusion criteria revised to include age cap at < 65 years <p>This change to the protocol was included after the enrollment of approximately 181 patients, but did not affect the overall outcome of the study.</p> |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported