



Clinical trial results:

A Phase 2a, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of AMG 714 in Adult Patients with Type II Refractory Celiac Disease, an In Situ Small Bowel T Cell Lymphoma.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004063-36 |
| Trial protocol | FI NL ES |
| Global end of trial date | 02 May 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 May 2018 |
| First version publication date | 10 May 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CELIM-RCD-002 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02633020 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen, Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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 May 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 May 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of AMG 714 in treating refractory celiac disease Type II (RCD-II), an in situ small bowel T-cell lymphoma, in adult patients.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline, and in accordance with the Declaration of Helsinki.

The study protocol, informed consent form (ICF), any recruitment materials, and relevant supporting information were submitted to the human research ethics committee, independent ethics committee (IEC), or institutional review board (IRB) by the Investigator or sponsor-appointed designee.

Investigator or designee had to have obtained the written approval of the ethics committee (EC) or IRB before initiating any subject-related study activity at a study site.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 13 April 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 12 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Finland: 1 |
| Country: Number of subjects enrolled | France: 11 |
| Country: Number of subjects enrolled | United States: 2 |
| Worldwide total number of subjects | 28 |
| EEA total number of subjects | 26 |

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) | 14 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 6 sites in 5 countries, France, Netherlands, Finland, Spain, and the United States.

Pre-assignment

Screening details:

After signing informed consent, subjects were screened for the study. Subjects who met the study entry criteria were randomized at a 2:1 ratio to receive either 8 mg/kg AMG 714 or placebo. Randomization and initial dosing of the first 10 subjects were staggered to allow observation for any possible unanticipated side effects.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | AMG 714 |

Arm description:

Subjects were administered 8 mg/kg AMG 714 via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | AMG 714 |
| Investigational medicinal product code | AMG 714 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered via a 120-minute IV infusion for a total of 7 times over 10 weeks.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects were administered placebo via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| | |
|--|-----------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered via a 120-minute IV infusion for a total of 7 times over 10 weeks.

| Number of subjects in period 1 | AMG 714 | Placebo |
|---------------------------------------|---------|---------|
| Started | 19 | 9 |
| Completed | 18 | 9 |
| Not completed | 1 | 0 |
| Adverse event, non-fatal | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | AMG 714 |
|-----------------------|---------|

Reporting group description:

Subjects were administered 8 mg/kg AMG 714 via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects were administered placebo via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| Reporting group values | AMG 714 | Placebo | Total |
|------------------------|---------|---------|-------|
| Number of subjects | 19 | 9 | 28 |
| Age categorical | | | |
| Units: Subjects | | | |
| 18 - 64 years | 12 | 2 | 14 |
| 65 - 84 years | 7 | 7 | 14 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.0 | 68.4 | |
| standard deviation | ± 10.2 | ± 10.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 8 | 6 | 14 |
| Male | 11 | 3 | 14 |
| Race | | | |
| Units: Subjects | | | |
| White | 19 | 9 | 28 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic/Latino | 0 | 2 | 2 |
| Not Hispanic/Latino | 19 | 7 | 26 |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | AMG 714 |
| Reporting group description: Subjects were administered 8 mg/kg AMG 714 via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects were administered placebo via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10. | |

Primary: Percent Change from Baseline in the Percentage of Aberrant Intestinal Intraepithelial Lymphocytes Versus Total IELs

| | |
|---|---|
| End point title | Percent Change from Baseline in the Percentage of Aberrant Intestinal Intraepithelial Lymphocytes Versus Total IELs |
| End point description: The primary endpoint in this study was the reduction in the percentage of aberrant intestinal intraepithelial lymphocytes (IELs) with respect to total IELs, as assessed by flow cytometry (Immunological Response 1). Aberrant IELs were defined by flow cytometry as surface CD3-negative, intra-cellular CD3-positive IELs (sCD3-, icCD3+). The analysis was conducted using the per protocol (PP) population which included subjects who received study treatment and provided evaluable data for efficacy analysis, excluded non-evaluable subjects and subjects with major protocol deviations. Subjects with atypical RCD-II (a different phenotype of the aberrant IELs compared to the classic phenotype) were further excluded from the PP population for the analyses of Immunological Response 1. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 12 | |

| End point values | AMG 714 | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 8 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 2.45 (± 8.83) | 7.30 (± 11.70) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Primary Analysis |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7451 ^[1] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -4.85 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -30.26 |
| upper limit | 20.56 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 14.7 |

Notes:

[1] - The primary endpoint was analyzed using analysis of covariance (ANCOVA), where the baseline % aberrant IELs vs total IELs was included as a covariate and treatment group as a fixed effect in the statistical model.

Secondary: Percent Change from Baseline in the Percentage of Aberrant Intestinal Intraepithelial Lymphocytes Versus Intestinal Epithelial Cells

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in the Percentage of Aberrant Intestinal Intraepithelial Lymphocytes Versus Intestinal Epithelial Cells |
|-----------------|--|

End point description:

Reduction in the percentage of aberrant intestinal IELs with respect to intestinal epithelial cells (Immunological Response 2) is a composite endpoint calculated by multiplying the percent of aberrant IEL versus total IELs (per flow cytometry) by the percent of total IEL versus intestinal epithelial cells as assessed by IHC.

The analysis was conducted using the per protocol (PP) population which included subjects who received study treatment and provided evaluable data for efficacy analysis, excluded non-evaluable subjects and subjects with major protocol deviations. Subjects with atypical RCD-II (a different phenotype of the aberrant IELs compared to the classic phenotype) were further excluded from the PP population for the analyses of Immunological Response 2.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and Week 12

| End point values | AMG 714 | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 8 | | |
| Units: Percent change | | | | |
| least squares mean (standard error) | 11.66 (± 15.79) | 49.88 (± 21.33) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Primary Analysis |
| Comparison groups | Placebo v AMG 714 |
| Number of subjects included in analysis | 22 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1803 ^[2] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -38.22 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -95.73 |
| upper limit | 19.29 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 27.48 |

Notes:

[2] - Analyzed using analysis of covariance (ANCOVA), where the baseline % aberrant IELs vs intestinal epithelial cells was included as a covariate and treatment group as a fixed effect in the statistical model.

Secondary: Percent Change From Baseline in Villous Height to Crypt Depth Ratio

| | |
|-----------------|---|
| End point title | Percent Change From Baseline in Villous Height to Crypt Depth Ratio |
|-----------------|---|

End point description:

Small bowel biopsies were performed at baseline and week 12; histological assessments were performed by a blinded central pathologist.

The analysis was conducted in the per protocol population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| | | | | |
|-------------------------------------|-----------------|-----------------|--|--|
| End point values | AMG 714 | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 9 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 26.44 (± 14.06) | 15.77 (± 19.36) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Analysis of Change from Baseline in VH:CD Ratio |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6607 ^[3] |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | 10.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -38.97 |
| upper limit | 60.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 24 |

Notes:

[3] - Analysed using analysis of covariance (ANCOVA), where the baseline VH:CD ratio was included as a covariate and treatment group as a fixed effect in the statistical model.

Secondary: Percentage of Participants with Improvement in Marsh Score at Week 12

| | |
|-----------------|---|
| End point title | Percentage of Participants with Improvement in Marsh Score at Week 12 |
|-----------------|---|

End point description:

The Marsh classification system describes the stages of damage in the small intestine as seen under a microscope, with possible values of 0, 1, 2, 3a, 3b, or 3c. A score of 0 (best score) indicates that the intestinal lining is normal and celiac disease highly unlikely, a score of 3c (worst score) indicates increased intra-epithelial lymphocytes, increased crypt hyperplasia and complete villi atrophy.

Improvement is defined as a decrease in score from baseline.

The analysis was conducted in the PP population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 9 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 35.3 | 33.3 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Improvement in Marsh Score |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9204 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 6.01 |

Secondary: Percent Change from Baseline in Total Intraepithelial Lymphocyte Count at Week 12

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Total Intraepithelial Lymphocyte Count at Week 12 |
|-----------------|---|

End point description:

Small bowel biopsies were performed at baseline and week 12; histological assessments were performed by a blinded central pathologist. The total IEL count is the density of IELs vs intestinal epithelial cells measured by immunochemistry.

The analysis was conducted in the PP population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 9 | | |
| Units: percent change | | | | |
| least squares mean (standard error) | 26.84 (± 17.90) | 39.57 (± 24.95) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change from Baseline in Total IELs |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.6885 |
| Method | ANCOVA |
| Parameter estimate | LS Mean Difference |
| Point estimate | -12.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -77.57 |
| upper limit | 52.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 31.34 |

Notes:

[4] - Analysis of covariance (ANCOVA), where the baseline total IEL counts was included as a covariate and treatment group as a fixed effect in the statistical model.

Secondary: Number of Weekly Bowel Movements at Baseline and Week 12

| | |
|-----------------|--|
| End point title | Number of Weekly Bowel Movements at Baseline and Week 12 |
|-----------------|--|

End point description:

Subjects were asked to record every bowel movement during the study using an electronic diary. If no bowel movements were experienced by the subject on any given day, the subject was required to document this in the diary.

The analysis was conducted in the intent-to-treat population which consisted of all randomized subjects who had received at least one dose of the study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 9 | | |
| Units: bowel movements | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n = 19, 8) | 10.3 (± 5.21) | 7.4 (± 4.03) | | |
| Week 12 (n = 18, 9) | 11.3 (± 5.72) | 8.3 (± 3.39) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Total Weekly Bowel Movements |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4469 ^[5] |
| Method | Generalized Linear Mixed Model |
| Parameter estimate | LS Mean Ratio |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[5] - Generalized linear mixed models with subject as a random effect and treatment group, time (week) and their interaction as fixed effects.

Secondary: Percentage of Participants with Diarrhoea at Baseline and Week 12

| | |
|-----------------|---|
| End point title | Percentage of Participants with Diarrhoea at Baseline and Week 12 |
|-----------------|---|

End point description:

The Bristol Stool Form Scale (BSFS) is a pictorial aid to help subjects identify the shape and consistency of their bowel movements. Subjects were asked to complete this form daily using an electronic diary at the time of each bowel movement. The BSFS categorizes bowel movements into 7 types, from Type 1 (separate hard lumps, like nuts; hard to pass) to Type 7 (watery, no solid pieces, entirely liquid). Diarrhoea was defined as at least one BSFS score ≥ 6 for the given week.

The analysis was conducted in the intent-to-treat population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 9 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Baseline | 52.6 | 22.2 | | |
| Week 12 | 36.8 | 44.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Weekly Gastrointestinal Symptom

| | |
|-----------------|---|
| End point title | Change from Baseline in Total Weekly Gastrointestinal Symptom |
|-----------------|---|

End point description:

The GSRS is a 15-question 7-scale questionnaire used to assess 5 dimensions of gastrointestinal syndromes: diarrhea, indigestion, constipation, abdominal pain and reflux. Questions are scored between 1 (no discomfort at all) and 7 (very severe discomfort).

The total GSRS score is calculated as the sum of the scores of all 15 questions, and ranges from 15 (no discomfort at all) to 105 (very severe discomfort in all 5 dimensions of gastrointestinal syndromes).

The analysis was conducted in the intent-to-treat population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 8 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.14 (± 0.13) | 0.20 (± 0.19) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Analysis of Change From Baseline in Weekly GSRS |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4832 ^[6] |
| Method | Linear mixed effects repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.14 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.26 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.19 |

Notes:

[6] - Linear mixed effects repeated measures model (MMRM) with the baseline value, treatment group, time point and a time point-by-treatment group interaction term as fixed effects

Secondary: Change from Baseline in Total Celiac Disease GSRS (CeD-GSRS) Score at

| | |
|-----------------|---|
| End point title | Change from Baseline in Total Celiac Disease GSRS (CeD-GSRS) Score at |
|-----------------|---|

End point description:

The CeD-GSRS score is derived from a subset of questions from GSRS questionnaire (questions 1, 4-9, 11, 12 and 14), which are each assessed on a scale of 1 (no discomfort at all) to 7 (very severe discomfort).

The total CeD-GSRS score ranges from 10 (no discomfort at all) to 70 (very severe discomfort in all celiac syndromes).

The analysis was conducted in the intent-to-treat population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and week 12

| End point values | AMG 714 | Placebo | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 8 | | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | -0.14 (± 0.16) | 0.17 (± 0.24) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Change From Baseline in CeD-GSRS |
| Comparison groups | AMG 714 v Placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5561 ^[7] |
| Method | Linear mixed effects repeated measures |
| Parameter estimate | LS Mean Difference |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.64 |
| upper limit | 0.35 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.24 |

Notes:

[7] - Linear mixed effects repeated measures model (MMRM) with the baseline value, treatment group, time point and a time point-by-treatment group interaction term as fixed effects

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until week 16

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | AMG 714 |
|-----------------------|---------|

Reporting group description:

Subjects were administered 8 mg/kg AMG 714 via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects were administered placebo via intravenous infusion on day 0, day 7 and every 2 weeks thereafter through week 10.

| Serious adverse events | AMG 714 | Placebo | |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 19 (26.32%) | 1 / 9 (11.11%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |

| | | | |
|---|----------------|---------------|--|
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumococcal infection | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tuberculosis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (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: 0 %

| Non-serious adverse events | AMG 714 | Placebo | |
|--|------------------|----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 16 / 19 (84.21%) | 8 / 9 (88.89%) | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 1 / 9 (11.11%) | |
| occurrences (all) | 5 | 3 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cough | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine aminotransferase abnormal | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bacterial test | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood lactate dehydrogenase increased | | | |

| | | | |
|---|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Blood urine present subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Eosinophil count abnormal subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Eosinophil count increased subjects affected / exposed occurrences (all) | 3 / 19 (15.79%) 3 | 0 / 9 (0.00%) 0 | |
| Helicobacter test positive subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Prostatic specific antigen increased subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Protein total decreased subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 3 / 9 (33.33%) 4 | |
| Dizziness postural subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Headache | | | |

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 19 (15.79%) 5 | 0 / 9 (0.00%) 0 | |
| Tremor subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | 0 / 9 (0.00%) 0 | |
| Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 0 / 9 (0.00%) 0 | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 0 / 9 (0.00%) 0 | |
| Eye disorders Erythema of eyelid subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Eye swelling subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 9 (0.00%) 0 | |
| Visual impairment subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 3 | 0 / 9 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 9 (11.11%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 19 (15.79%) 3 | 1 / 9 (11.11%) 1 | |
| Duodenal ulcer subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 9 (11.11%) 1 | |
| Dyspepsia | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Lip dry | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip exfoliation | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 9 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rosacea | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin plaque | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|------------------------------------|-----------------|----------------|--|
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 8 / 19 (42.11%) | 1 / 9 (11.11%) | |
| occurrences (all) | 10 | 1 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 9 (11.11%) | |
| occurrences (all) | 0 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 1 / 9 (11.11%) | |
| occurrences (all) | 2 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 9 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 06 November 2015 | <p>The following major changes and clarifications were made in the sections specified:</p> <ol style="list-style-type: none">1. Addition of contact information for protocol vendors and responsible staff.2. Clarification for selected inclusion/exclusion criteria of 6 months of GFD and IEL cut-off.3. Addition of subject visits with a dietitian at Visits 1, 4, 6, and 8. Addition of the sample questions related to this consultation.4. Addition of PK assessment at Visit 6.5. Revision to Inclusion Criterion #4 to include the following clarification "and after exclusion of other potential causes of symptomatic non-response (eg, microscopic colitis, bacterial overgrowth, lactose intolerance, exocrine pancreatic insufficiency, hyperthyroidism, etc.) and intestinal histological abnormality (autoimmune enteropathy, giardiasis, immunodeficiency, collagenous sprue, Whipple's disease, etc.)."6. Revision to Exclusion Criterion #5 to provide additional examples of exclusionary history of immune suppression.7. Revision of the Physician Global Assessment to include a Rating of Change assessment. The rating of change assessment was to be administered at Visits 1, 2, 3, 4, 6, 8, and 9.8. Addition of a Patient Global Assessment and Rating of Change. The PtGA alone was to be administered at Visit 1. The PtGA and Patient Rating of Change were to be administered at Visits 2, 3, 4, 6, 8, and 9.9. Addition of SAE telephone contact numbers.10. Revision of SAE email contact number.11. Addition of sample Investigational Product labels.12. Addition of IHC assessments (exploratory endpoint).13. Clarification that AEs and SAEs occurring in possible subjects traveling to study sites from countries other than study countries were to be assessed and managed in the same fashion as those appearing in subjects from study countries. |
| 01 February 2016 | <p>The following changes and clarifications were made in the sections specified:</p> <ol style="list-style-type: none">1. Addition of Investigational New Drug Application (IND) number.2. Update of contact information for protocol vendors and responsible staff.3. Minor corrections to Schedule of Study Procedures:<ol style="list-style-type: none">a. Addition of superscript to PK sample collection at Visit 6 (Week 8) to indicate that the sample for PK analysis at this visit should be collected before dosing starts.b. Clarification that the Visit 8 endoscopy and biopsy could be collected 7 days before or after Visit 8.4. Addition of rules to stagger the randomization and initial dosing of the first ten subjects.5. Correct provision of iVYLISA GIP test kit and instructions for home collection from Visit 1 to Visit 2.6. Removal of mandatory hood use for preparation of clinical supplies, as long as preparation was performed using aseptic techniques, under sterile conditions.7. Corrections to the list of Laboratory Parameters to match Schedule of Events:<ol style="list-style-type: none">a. Clarification that "mRNA/DNA" at Screening and Visit 8 (Week 12) means "Biopsy mRNA" and "Biopsy DNA for TcR clonality."b. Addition of "PK" at Visit 7 (Week 10).c. Addition of "Biopsy flow-cytometry" at Visit 8 (Week 12/Day 84) or Early Termination Visit. |

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| 11 July 2016 | <p>The following changes and clarifications were made in the sections specified:</p> <ol style="list-style-type: none"> 1. To reduce burden on patients: <ol style="list-style-type: none"> a. The rules for collection of stool samples were revised to allow a more flexible window of ± 3 days and to allow any place of collection, not only the patient's home. b. The time of collection of the blood cell pellet was changed to allow collection at any time during study. 2. It was clarified throughout the protocol that the DSMB would review unblinded data, including during the interim analysis. 3. Clarification that simultaneous concomitant therapy with topical and systemic steroids was permissible at or below the maximum doses indicated in the protocol. 4. Clarification that, after thawing, the product could be stored for up to 72 hours at $5 \pm 3^{\circ}\text{C}$, and no longer than 12 hours at room temperature. After preparation (once injected in the IV bag), the study drug had to be used immediately and could only be kept at room temperature for a maximum of 12 hours including the 2 hours of the IV administration. These instructions were in line with the study manual and were correctly followed by the sites. 5. Clarification of the instructions to prepare the IV bag by withdrawing the volume of the thawed investigational product needed for the weight of the patient (8 mg per kg, calculating the volume needed given the concentration of investigational product of 100 mg/ml) and injecting this volume directly into a 100 mL 5% dextrose IV bag using the injection port at the base of the bag. These instructions were in line with the study manual and have been correctly followed by the sites. 6. Clarification of the patient populations for analysis and the statistical analysis method for the Marsh score. The definitions and method were consistent with the SAP and were used at completion of the study. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported