



## 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 Celiac Disease

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-003647-19 |
| Trial protocol           | FI             |
| Global end of trial date | 14 March 2017  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 29 March 2018 |
| First version publication date | 29 March 2018 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | CELIM-NRCD-001 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02637141 |
| 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                       | 14 March 2017 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 14 March 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 attenuating the effects of gluten exposure in adults with celiac disease.

Protection of trial subjects:

This trial was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines, as required by Fimea, 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 independent ethics committees (IECs) by the Investigator or Sponsor-appointed designee and written approval must have been received from the IECs before initiating any study activity.

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 2016 |
| 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 | Finland: 64 |
| Worldwide total number of subjects   | 64          |
| EEA total number of subjects         | 64          |

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)      | 49 |
| From 65 to 84 years       | 15 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at three sites in Finland.

### Pre-assignment

Screening details:

All participants who met the study entry criteria were randomized at a 1:1:1 ratio to receive 150 mg or 300 mg AMG 714 or placebo once every 2 weeks for a total of 6 administrations over a period of 10 weeks. Randomization was stratified by study site and sex.

### 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            |
| <b>Arm title</b>             | AMG 714 150 mg |

Arm description:

Participants received 150 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks.

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

Dosage and administration details:

AMG 714 150 mg administered by subcutaneous injection

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | AMG 714 300 mg |
|------------------|----------------|

Arm description:

Participants received 300 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks.

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

Dosage and administration details:

AMG 714 300 mg administered by subcutaneous injection

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants received placebo subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

Matching placebo administered by subcutaneous injection

| <b>Number of subjects in period 1</b> | AMG 714 150 mg | AMG 714 300 mg | Placebo |
|---------------------------------------|----------------|----------------|---------|
| Started                               | 22             | 22             | 20      |
| Received Treatment                    | 22             | 21             | 19      |
| Completed                             | 20             | 20             | 19      |
| Not completed                         | 2              | 2              | 1       |
| Consent withdrawn by subject          | 1              | 1              | 1       |
| Adverse event                         | 1              | 1              | -       |

## Baseline characteristics

### Reporting groups

|  |                |
|--|----------------|
| Reporting group title  | AMG 714 150 mg |
| Reporting group description:<br>Participants received 150 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks. |                |
| Reporting group title  | AMG 714 300 mg |
| Reporting group description:<br>Participants received 300 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks. |                |
| Reporting group title  | Placebo        |
| Reporting group description:<br>Participants received placebo subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks.            |                |

| Reporting group values  | AMG 714 150 mg | AMG 714 300 mg | Placebo        |
|---|----------------|----------------|----------------|
| Number of subjects  | 22             | 22             | 20             |
| Age categorical<br>Units: Subjects                                      |                |                |                |
| 18 - 64 years   | 17             | 20             | 12             |
| 65 - 84 years   | 5              | 2              | 8              |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 51.0<br>± 15.5 | 47.8<br>± 15.1 | 54.7<br>± 14.9 |
| Gender categorical<br>Units: Subjects                                   |                |                |                |
| Female  | 16             | 17             | 14             |
| Male  | 6              | 5              | 6              |
| Race<br>Units: Subjects   |                |                |                |
| White   | 22             | 22             | 20             |
| Ethnicity<br>Units: Subjects  |                |                |                |
| Hispanic/Latino   | 1              | 0              | 0              |
| Not Hispanic/Latino   | 21             | 22             | 20             |

| Reporting group values  | Total |  |  |
|---|-------|--|--|
| Number of subjects  | 64    |  |  |
| Age categorical<br>Units: Subjects                                      |       |  |  |
| 18 - 64 years   | 49    |  |  |
| 65 - 84 years   | 15    |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -     |  |  |

|                     |    |  |  |
|---------------------|----|--|--|
| Gender categorical  |    |  |  |
| Units: Subjects     |    |  |  |
| Female              | 47 |  |  |
| Male                | 17 |  |  |
| Race                |    |  |  |
| Units: Subjects     |    |  |  |
| White               | 64 |  |  |
| Ethnicity           |    |  |  |
| Units: Subjects     |    |  |  |
| Hispanic/Latino     | 1  |  |  |
| Not Hispanic/Latino | 63 |  |  |

## End points

### End points reporting groups

|  |                |
|--|----------------|
| Reporting group title  | AMG 714 150 mg |
| Reporting group description:<br>Participants received 150 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks. |                |
| Reporting group title  | AMG 714 300 mg |
| Reporting group description:<br>Participants received 300 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks. |                |
| Reporting group title  | Placebo        |
| Reporting group description:<br>Participants received placebo subcutaneous injection once every 2 weeks for a total of 6 times over 10 weeks.            |                |

### Primary: Percent Change From Baseline in Villous Height to Crypt Depth Ratio (VH:CD) at Week 12

|   |  |
|---|--|
| End point title   | Percent Change From Baseline in Villous Height to Crypt Depth Ratio (VH:CD) at Week 12 |
| End point description:<br>Attenuation of the effects of gluten exposure was assessed by measuring the percent change from baseline in villous height to crypt depth ratio after 10 weeks of gluten challenge. Villi are the small fingerlike projections that line the small intestine and promote nutrient absorption and are often shortened in patients with Celiac disease. Crypts are grooves between the villi that are often elongated in patients with Celiac disease. A decreased VH:CD ratio indicates worsening disease. Small bowel biopsies were performed at baseline and week 12; histological assessments were performed by a blinded central pathologist.<br>The analysis was conducted in the per protocol 1 (PP1) population which excluded non-evaluable subjects and subjects with major protocol deviations thought to affect the study's ability to assess the effect of treatment, and included subjects who received gluten challenge for at least 1 week. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline and week 12  |  |

| End point values                    | AMG 714 150 mg    | AMG 714 300 mg    | Placebo           |  |
|-------------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type                  | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed         | 15 <sup>[1]</sup> | 19 <sup>[2]</sup> | 15 <sup>[3]</sup> |  |
| Units: percent change               |                   |                   |                   |  |
| least squares mean (standard error) | -62.66 (± 5.39)   | -53.78 (± 4.83)   | -60.17 (± 5.22)   |  |

Notes:

[1] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[2] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[3] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

### Statistical analyses



|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Primary Analysis           |
| Comparison groups                       | AMG 714 150 mg v Placebo   |
| Number of subjects included in analysis | 30                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[4]</sup> |
| P-value                                 | = 0.7271 <sup>[5]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | -2.49                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -16.82                     |
| upper limit                             | 11.83                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 7.1                        |

Notes:

[4] - P-values smaller than 0.05 were considered statistically significant.

[5] - The model included baseline VH:CD ratio, site, and sex as covariates and treatment group as a fixed effect.

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>       | Primary Analysis           |
| Comparison groups                       | AMG 714 300 mg v Placebo   |
| Number of subjects included in analysis | 34                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[6]</sup> |
| P-value                                 | = 0.3438 <sup>[7]</sup>    |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | LS Mean Difference         |
| Point estimate                          | 6.39                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -7.07                      |
| upper limit                             | 19.85                      |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 6.67                       |

Notes:

[6] - P-values smaller than 0.05 were considered statistically significant.

[7] - The model included baseline VH:CD ratio, site, and sex as covariates and treatment group as a fixed effect.

## Secondary: Percent Change from Baseline in Intraepithelial Lymphocyte Density at Week 12

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

End point description:

Intra-epithelial lymphocytes (IELS) are white blood cells found in the epithelial layer of the intestines where they function to preserve the integrity of the mucosal barrier by protecting the epithelium against pathogen or immuneinduced pathology. Increased intraepithelial lymphocytes is associated with celiac disease.

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 PP1 population.

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

End point timeframe:

Baseline and week 12

| End point values                    | AMG 714 150 mg    | AMG 714 300 mg    | Placebo            |  |
|-------------------------------------|-------------------|-------------------|--------------------|--|
| Subject group type                  | Reporting group   | Reporting group   | Reporting group    |  |
| Number of subjects analysed         | 15 <sup>[8]</sup> | 19 <sup>[9]</sup> | 15 <sup>[10]</sup> |  |
| Units: percent change               |                   |                   |                    |  |
| least squares mean (standard error) | 95.14 (± 15.06)   | 68.22 (± 13.64)   | 109.46 (± 14.65)   |  |

Notes:

[8] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[9] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[10] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

### Statistical analyses

| Statistical analysis title              | Analysis of Change From Baseline in IEL Density |
|---|---|
| Comparison groups                       | AMG 714 150 mg v Placebo                        |
| Number of subjects included in analysis | 30  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.4746 <sup>[11]</sup>                        |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -14.32  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -54.39  |
| upper limit                             | 25.74   |
| Variability estimate                    | Standard error of the mean                      |
| Dispersion value                        | 19.85   |

Notes:

[11] - The model included baseline VH:CD ratio, site, and sex as covariates and treatment group as a fixed effect.

| Statistical analysis title              | Analysis of Change From Baseline in IEL Density |
|---|---|
| Comparison groups                       | Placebo v AMG 714 300 mg                        |
| Number of subjects included in analysis | 34  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.0343 <sup>[12]</sup>                        |
| Method                                  | ANCOVA  |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -41.24  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -79.28                     |
| upper limit          | -3.2                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 18.85                      |

Notes:

[12] - The model included baseline VH:CD ratio, site, and sex as covariates and treatment group as a fixed effect.

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

|                 |   |
|-----------------|---|
| End point title | Number 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. The analysis was conducted in the PP1 population.

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

End point timeframe:

Baseline and week 12

| End point values            | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 15 <sup>[13]</sup> | 19 <sup>[14]</sup> | 15 <sup>[15]</sup> |  |
| Units: participants         | 0                  | 0                  | 0                  |  |

Notes:

[13] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[14] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

[15] - Subjects with a post-baseline biopsy after week 6 who received gluten challenge for at least 1 week

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change from Baseline in Anti-Tissue Transglutaminase (tTG) Immunoglobulin A (IgA) Antibodies at Week 12

|                 |   |
|-----------------|---|
| End point title | Percent Change from Baseline in Anti-Tissue Transglutaminase (tTG) Immunoglobulin A (IgA) Antibodies at Week 12 |
|-----------------|---|

End point description:

Levels of anti-tTG IgA antibodies were determined in serum using enzyme-linked immunosorbent assay (ELISA) immunoassay.

The analysis was conducted in the PP1 population.

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

End point timeframe:

Baseline and week 12

| <b>End point values</b>             | AMG 714 150 mg      | AMG 714 300 mg     | Placebo            |  |
|-------------------------------------|---------------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group     | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 15 <sup>[16]</sup>  | 18 <sup>[17]</sup> | 15 <sup>[18]</sup> |  |
| Units: percent change               |                     |                    |                    |  |
| least squares mean (standard error) | 5019.77 (± 1482.59) | 1562.42 (± 784.83) | 617.53 (± 866.44)  |  |

Notes:

[16] - Per protocol 1 population with available data

[17] - Per protocol 1 population with available data

[18] - Per protocol 1 population with available data

## Statistical analyses

| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Anti-tTG IgA |
|---|--|
| Comparison groups                       | AMG 714 150 mg v Placebo                         |
| Number of subjects included in analysis | 30   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.014 <sup>[19]</sup>                          |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | 4402.25  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 936.39   |
| upper limit                             | 7868.1   |
| Variability estimate                    | Standard error of the mean                       |
| Dispersion value                        | 1717.4   |

Notes:

[19] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Anti-tTG IgA |
|---|--|
| Comparison groups                       | Placebo v AMG 714 300 mg                         |
| Number of subjects included in analysis | 33   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.4228 <sup>[20]</sup>                         |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | 944.9  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -1410.65   |
| upper limit                             | 3300.44  |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 1167.22                    |

Notes:

[20] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

## Secondary: Change from Baseline in Anti-deamidated Gliadin Peptide (DGP) Antibodies at Week 12

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Anti-deamidated Gliadin Peptide (DGP) Antibodies at Week 12 |
|-----------------|---|

End point description:

Levels of serum anti-DGP antibodies (IgA and IgG) were determined using ELISA immunoassay. The analysis was conducted in the PP1 population.

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

End point timeframe:

Baseline and week 12

| End point values                    | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 15 <sup>[21]</sup> | 18 <sup>[22]</sup> | 15 <sup>[23]</sup> |  |
| Units: kU/L                         |                    |                    |                    |  |
| least squares mean (standard error) |                    |                    |                    |  |
| Immunoglobulin A                    | 43.19 (± 12.85)    | 18.47 (± 10.70)    | 25.38 (± 11.44)    |  |
| Immunoglobulin G                    | 28.29 (± 21.45)    | 17.98 (± 14.57)    | 15.12 (± 16.02)    |  |

Notes:

[21] - Per protocol 1 population with available data

[22] - Per protocol 1 population with available data

[23] - Per protocol 1 population with available data

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of Change From Baseline in Anti-DGP IgA |
| Comparison groups                       | AMG 714 150 mg v Placebo                         |
| Number of subjects included in analysis | 30   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.3034 <sup>[24]</sup>                         |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | 17.8   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -16.68   |
| upper limit                             | 52.29  |
| Variability estimate                    | Standard error of the mean                       |
| Dispersion value                        | 17.09  |

Notes:

[24] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Anti-DGP-IgA |
| Comparison groups                       | Placebo v AMG 714 300 mg                         |
| Number of subjects included in analysis | 33   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.6569 [25]                                    |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | -6.92  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -38.11   |
| upper limit                             | 24.28  |
| Variability estimate                    | Standard error of the mean                       |
| Dispersion value                        | 15.46  |

Notes:

[25] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Anti-DGP-IgG |
| Comparison groups                       | Placebo v AMG 714 150 mg                         |
| Number of subjects included in analysis | 30   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.6254 [26]                                    |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | 13.17  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -40.46   |
| upper limit                             | 67.2   |
| Variability estimate                    | Standard error of the mean                       |
| Dispersion value                        | 26.77  |

Notes:

[26] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Anti-DGP IgG |
| Comparison groups                       | Placebo v AMG 714 300 mg                         |
| Number of subjects included in analysis | 33   |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | = 0.8955 [27]                                    |
| Method                                  | Mixed-effect Model Repeat Measurement            |
| Parameter estimate                      | LS Mean Difference                               |
| Point estimate                          | 2.86   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -40.84                     |
| upper limit          | 46.57                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 21.66                      |

Notes:

[27] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

## 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 using the electronic diary.

The analysis was conducted in the PP1 population.

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

End point timeframe:

Baseline and week 12

| End point values                     | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
|--------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed          | 15 <sup>[28]</sup> | 19 <sup>[29]</sup> | 14 <sup>[30]</sup> |  |
| Units: bowel movements               |                    |                    |                    |  |
| arithmetic mean (standard deviation) |                    |                    |                    |  |
| Baseline                             | 8.9 (± 3.66)       | 10.2 (± 3.96)      | 9.6 (± 2.92)       |  |
| Week 12                              | 9.3 (± 2.58)       | 11.5 (± 5.25)      | 11.6 (± 3.99)      |  |

Notes:

[28] - Per protocol 1 population with available data

[29] - Per protocol 1 population with available data

[30] - Per protocol 1 population with available data

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of Total Weekly Bowel Movements |
| Comparison groups                       | AMG 714 150 mg v Placebo                 |
| Number of subjects included in analysis | 29                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.1612 <sup>[31]</sup>                 |
| Method                                  | Generalized Linear Mixed Models          |
| Parameter estimate                      | LS Mean Ratio                            |
| Point estimate                          | 0.83                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.63                                     |
| upper limit                             | 1.08                                     |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.11                       |

Notes:

[31] - Generalized linear mixed models with subject as a random effect and treatment group, site, sex, time (week), and time point-by-treatment group interaction as fixed effects.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Total Weekly Bowel Movements |
| Comparison groups                       | Placebo v AMG 714 300 mg                 |
| Number of subjects included in analysis | 33                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.781 <sup>[32]</sup>                  |
| Method                                  | Generalized Linear Mixed Models          |
| Parameter estimate                      | LS Mean Ratio                            |
| Point estimate                          | 1.03                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.81                                     |
| upper limit                             | 1.32                                     |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 0.13                                     |

Notes:

[32] - Generalized linear mixed models with subject as a random effect and treatment group, site, sex, time (week), and time point-by-treatment group interaction as fixed effects.

## Secondary: Number of Participants with Diarrhoea at Baseline and Week 12

|                 |   |
|-----------------|---|
| End point title | Number 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 at least one BSFS score  $\geq 6$  for the given week.

The analysis was conducted in the PP1 population.

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

End point timeframe:

Baseline and Week 12

| End point values            | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
|-----------------------------|--------------------|--------------------|--------------------|--|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed | 15 <sup>[33]</sup> | 19 <sup>[34]</sup> | 15 <sup>[35]</sup> |  |
| Units: participants         |                    |                    |                    |  |
| Baseline                    | 4                  | 9                  | 7                  |  |
| Week 12                     | 1                  | 5                  | 6                  |  |

Notes:

[33] - Per protocol 1 population

[34] - Per protocol 1 population

[35] - Per protocol 1 population



## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change from Baseline in Total Weekly Gastrointestinal Symptom Rating Scale (GSRS) Score at Week 12

|                 |  |
|-----------------|--|
| End point title | Percent Change from Baseline in Total Weekly Gastrointestinal Symptom Rating Scale (GSRS) Score at Week 12 |
|-----------------|--|

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 PP1 population.

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

End point timeframe:

Baseline and week 12

| End point values                    | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type                  | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 15 <sup>[36]</sup> | 19 <sup>[37]</sup> | 14 <sup>[38]</sup> |  |
| Units: percent change               |                    |                    |                    |  |
| least squares mean (standard error) | 4.14 (± 9.01)      | 14.96 (± 8.17)     | 17.58 (± 8.93)     |  |

Notes:

[36] - Per protocol 1 population with available data

[37] - Per protocol 1 population with available data

[38] - Per protocol 1 population with available data

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Weekly GSRS |
| Comparison groups                       | AMG 714 150 mg v Placebo                        |
| Number of subjects included in analysis | 29  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.2761 <sup>[39]</sup>                        |
| Method                                  | Mixed-effect Model Repeat Measurement           |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -13.44  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -37.66  |
| upper limit                             | 10.77   |
| Variability estimate                    | Standard error of the mean                      |
| Dispersion value                        | 12.33   |

Notes:

[39] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in Weekly GSRS |
| Comparison groups                       | Placebo v AMG 714 300 mg                        |
| Number of subjects included in analysis | 33  |
| Analysis specification                  | Pre-specified                                   |
| Analysis type                           | superiority                                     |
| P-value                                 | = 0.8221 <sup>[40]</sup>                        |
| Method                                  | Mixed-effect Model Repeat Measurement           |
| Parameter estimate                      | LS Mean Difference                              |
| Point estimate                          | -2.62   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -25.51  |
| upper limit                             | 20.27   |
| Variability estimate                    | Standard error of the mean                      |
| Dispersion value                        | 11.66   |

Notes:

[40] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

### Secondary: Change from Baseline in Total Celiac Disease GSRS (CeD-GSRS) Score at Week 12

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Total Celiac Disease GSRS (CeD-GSRS) Score at Week 12 |
|-----------------|---|

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 PP1 population.

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

End point timeframe:

Baseline and Week 12

|                                     |                    |                    |                    |  |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| <b>End point values</b>             | AMG 714 150 mg     | AMG 714 300 mg     | Placebo            |  |
| Subject group type                  | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed         | 15 <sup>[41]</sup> | 19 <sup>[42]</sup> | 14 <sup>[43]</sup> |  |
| Units: units on a scale             |                    |                    |                    |  |
| least squares mean (standard error) | 0.65 (± 1.52)      | 1.77 (± 1.37)      | 3.41 (± 1.52)      |  |

Notes:

[41] - Per protocol 1 population with available data

[42] - Per protocol 1 population with available data

[43] - Per protocol 1 population with available data

### Statistical analyses

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Analysis of Change From Baseline in CeD-GSRS |
| Comparison groups                 | AMG 714 150 mg v Placebo                     |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 29                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.1908 <sup>[44]</sup>              |
| Method                                  | Mixed-effect Model Repeat Measurement |
| Parameter estimate                      | LS Mean Difference                    |
| Point estimate                          | -2.76                                 |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | -6.89                                 |
| upper limit                             | 1.38                                  |
| Variability estimate                    | Standard error of the mean            |
| Dispersion value                        | 2.1                                   |

Notes:

[44] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Analysis of Change From Baseline in CeD-GSRS |
| Comparison groups                       | Placebo v AMG 714 300 mg                     |
| Number of subjects included in analysis | 33   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| P-value                                 | = 0.4088 <sup>[45]</sup>                     |
| Method                                  | Mixed-effect Model Repeat Measurement        |
| Parameter estimate                      | LS Mean Difference                           |
| Point estimate                          | -1.64  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -5.53  |
| upper limit                             | 2.25   |
| Variability estimate                    | Standard error of the mean                   |
| Dispersion value                        | 1.98   |

Notes:

[45] - The model included baseline value, treatment group, site, sex, time point, and a time point-by-treatment group interaction term as fixed effects and subject as a random effect.

## 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 | 150 mg AMG 714 |
|-----------------------|----------------|

Reporting group description:

Participants received 150 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6... more times over 10 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | 300 mg AMG 714 |
|-----------------------|----------------|

Reporting group description:

Participants received 300 mg AMG 714 via subcutaneous injection once every 2 weeks for a total of 6... more times over 10 weeks.

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

Reporting group description:

Participants received placebo via subcutaneous injection once every 2 weeks for a total of 6... more times over 10 weeks.

| Serious adverse events                            | 150 mg AMG 714 | 300 mg AMG 714 | Placebo        |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 0 / 19 (0.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    |                |                |                |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | 150 mg AMG 714   | 300 mg AMG 714   | Placebo           |
|---|------------------|------------------|-------------------|
| Total subjects affected by non-serious adverse events |                  |                  |                   |
| subjects affected / exposed                           | 21 / 22 (95.45%) | 20 / 21 (95.24%) | 19 / 19 (100.00%) |
| Vascular disorders                                    |                  |                  |                   |
| Haematoma   |                  |                  |                   |
| subjects affected / exposed                           | 0 / 22 (0.00%)   | 0 / 21 (0.00%)   | 2 / 19 (10.53%)   |
| occurrences (all)                                     | 0                | 0                | 2                 |
| Hypertension  |                  |                  |                   |

|  |                 |                  |                 |
|--|-----------------|------------------|-----------------|
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 0               | 1                | 0               |
| Temporal arteritis                                   |                 |                  |                 |
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 0               | 1                | 0               |
| Surgical and medical procedures                      |                 |                  |                 |
| Lipoma excision                                      |                 |                  |                 |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 1               | 0                | 0               |
| General disorders and administration site conditions |                 |                  |                 |
| Chest pain   |                 |                  |                 |
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 0 / 21 (0.00%)   | 2 / 19 (10.53%) |
| occurrences (all)                                    | 0               | 0                | 2               |
| Chills   |                 |                  |                 |
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 0               | 1                | 0               |
| Fatigue  |                 |                  |                 |
| subjects affected / exposed                          | 2 / 22 (9.09%)  | 5 / 21 (23.81%)  | 5 / 19 (26.32%) |
| occurrences (all)                                    | 2               | 5                | 5               |
| Impaired healing                                     |                 |                  |                 |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 1               | 0                | 0               |
| Injection site reaction                              |                 |                  |                 |
| subjects affected / exposed                          | 8 / 22 (36.36%) | 11 / 21 (52.38%) | 5 / 19 (26.32%) |
| occurrences (all)                                    | 27              | 30               | 27              |
| Mucosal dryness                                      |                 |                  |                 |
| subjects affected / exposed                          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)   | 0 / 19 (0.00%)  |
| occurrences (all)                                    | 1               | 0                | 0               |
| Oedema peripheral                                    |                 |                  |                 |
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 0 / 21 (0.00%)   | 1 / 19 (5.26%)  |
| occurrences (all)                                    | 0               | 0                | 1               |
| Pyrexia  |                 |                  |                 |
| subjects affected / exposed                          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)   | 2 / 19 (10.53%) |
| occurrences (all)                                    | 0               | 1                | 2               |
| Reproductive system and breast disorders             |                 |                  |                 |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Vulvovaginal dryness<br>subjects affected / exposed<br>occurrences (all)               | 1 / 22 (4.55%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0 |
| Vulvovaginal pruritus<br>subjects affected / exposed<br>occurrences (all)              | 1 / 22 (4.55%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders  |                     |                     |                     |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 22 (0.00%)<br>0 | 1 / 21 (4.76%)<br>1 | 0 / 19 (0.00%)<br>0 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 22 (0.00%)<br>0 | 1 / 21 (4.76%)<br>1 | 0 / 19 (0.00%)<br>0 |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 22 (4.55%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 22 (4.55%)<br>1 | 1 / 21 (4.76%)<br>1 | 0 / 19 (0.00%)<br>0 |
| Pharyngeal oedema<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 22 (4.55%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0 |
| Tonsillolith<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 22 (0.00%)<br>0 | 1 / 21 (4.76%)<br>1 | 0 / 19 (0.00%)<br>0 |
| Psychiatric disorders  |                     |                     |                     |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 22 (4.55%)<br>1 | 0 / 21 (0.00%)<br>0 | 0 / 19 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 22 (0.00%)<br>0 | 0 / 21 (0.00%)<br>0 | 1 / 19 (5.26%)<br>1 |
| Investigations   |                     |                     |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 22 (4.55%)<br>1 | 1 / 21 (4.76%)<br>1 | 1 / 19 (5.26%)<br>1 |

|                                      |                |                |                 |
|--------------------------------------|----------------|----------------|-----------------|
| Aspartate aminotransferase increased |                |                |                 |
| subjects affected / exposed          | 1 / 22 (4.55%) | 1 / 21 (4.76%) | 1 / 19 (5.26%)  |
| occurrences (all)                    | 1              | 1              | 1               |
| Blood albumin decreased              |                |                |                 |
| subjects affected / exposed          | 1 / 22 (4.55%) | 0 / 21 (0.00%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 1              | 0              | 0               |
| Blood albumin increased              |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 1 / 21 (4.76%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |
| Blood alkaline phosphatase increased |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 1 / 19 (5.26%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Blood calcium increased              |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 2 / 21 (9.52%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0              | 2              | 0               |
| Blood phosphorus increased           |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 1 / 19 (5.26%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Blood potassium increased            |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 0 / 21 (0.00%) | 1 / 19 (5.26%)  |
| occurrences (all)                    | 0              | 0              | 1               |
| Body temperature decreased           |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 1 / 21 (4.76%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |
| Hepatic enzyme increased             |                |                |                 |
| subjects affected / exposed          | 1 / 22 (4.55%) | 1 / 21 (4.76%) | 2 / 19 (10.53%) |
| occurrences (all)                    | 1              | 1              | 2               |
| Neutrophil count decreased           |                |                |                 |
| subjects affected / exposed          | 0 / 22 (0.00%) | 1 / 21 (4.76%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0              | 1              | 0               |
| Neutrophil count increased           |                |                |                 |
| subjects affected / exposed          | 1 / 22 (4.55%) | 2 / 21 (9.52%) | 0 / 19 (0.00%)  |
| occurrences (all)                    | 1              | 2              | 0               |
| White blood cell count increased     |                |                |                 |

|  |                      |                       |                       |
|--|----------------------|-----------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 22 (4.55%)<br>1  | 3 / 21 (14.29%)<br>3  | 0 / 19 (0.00%)<br>0   |
| White blood cells urine positive<br>subjects affected / exposed<br>occurrences (all) | 0 / 22 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1   | 0 / 19 (0.00%)<br>0   |
| Injury, poisoning and procedural complications                                       |                      |                       |                       |
| Procedural headache<br>subjects affected / exposed<br>occurrences (all)              | 0 / 22 (0.00%)<br>0  | 1 / 21 (4.76%)<br>1   | 0 / 19 (0.00%)<br>0   |
| Thermal burn<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 22 (4.55%)<br>1  | 0 / 21 (0.00%)<br>0   | 0 / 19 (0.00%)<br>0   |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 22 (4.55%)<br>1  | 0 / 21 (0.00%)<br>0   | 0 / 19 (0.00%)<br>0   |
| Wound complication<br>subjects affected / exposed<br>occurrences (all)               | 1 / 22 (4.55%)<br>1  | 0 / 21 (0.00%)<br>0   | 0 / 19 (0.00%)<br>0   |
| Cardiac disorders  |                      |                       |                       |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 22 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0   | 2 / 19 (10.53%)<br>2  |
| Nervous system disorders   |                      |                       |                       |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 22 (4.55%)<br>1  | 0 / 21 (0.00%)<br>0   | 0 / 19 (0.00%)<br>0   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 22 (18.18%)<br>5 | 7 / 21 (33.33%)<br>13 | 8 / 19 (42.11%)<br>14 |
| Migraine<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 22 (4.55%)<br>1  | 1 / 21 (4.76%)<br>1   | 0 / 19 (0.00%)<br>0   |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 22 (0.00%)<br>0  | 0 / 21 (0.00%)<br>0   | 1 / 19 (5.26%)<br>1   |
| Polyneuropathy   |                      |                       |                       |



|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Presyncope                           |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Tremor                               |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Blood and lymphatic system disorders |                 |                 |                 |
| Anaemia                              |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                    | 0               | 0               | 1               |
| Neutropenia                          |                 |                 |                 |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Ear and labyrinth disorders          |                 |                 |                 |
| Ear pain                             |                 |                 |                 |
| subjects affected / exposed          | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 1               | 0               | 0               |
| Eye disorders                        |                 |                 |                 |
| Eye pain                             |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Ocular hyperaemia                    |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0               | 2               | 0               |
| Photopsia                            |                 |                 |                 |
| subjects affected / exposed          | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 0               | 1               | 0               |
| Gastrointestinal disorders           |                 |                 |                 |
| Abdominal discomfort                 |                 |                 |                 |
| subjects affected / exposed          | 2 / 22 (9.09%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                    | 2               | 0               | 0               |
| Abdominal distension                 |                 |                 |                 |
| subjects affected / exposed          | 7 / 22 (31.82%) | 4 / 21 (19.05%) | 6 / 19 (31.58%) |
| occurrences (all)                    | 8               | 6               | 6               |
| Abdominal pain                       |                 |                 |                 |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed      | 1 / 22 (4.55%)  | 3 / 21 (14.29%) | 1 / 19 (5.26%)  |
| occurrences (all)                | 1               | 3               | 1               |
| Abdominal pain upper             |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 5 / 21 (23.81%) | 4 / 19 (21.05%) |
| occurrences (all)                | 1               | 8               | 5               |
| Aphthous ulcer                   |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 1               | 1               | 0               |
| Constipation                     |                 |                 |                 |
| subjects affected / exposed      | 3 / 22 (13.64%) | 0 / 21 (0.00%)  | 2 / 19 (10.53%) |
| occurrences (all)                | 3               | 0               | 2               |
| Diarrhoea                        |                 |                 |                 |
| subjects affected / exposed      | 5 / 22 (22.73%) | 8 / 21 (38.10%) | 6 / 19 (31.58%) |
| occurrences (all)                | 5               | 10              | 7               |
| Dyspepsia                        |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 1 / 21 (4.76%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 1               | 2               | 1               |
| Faeces soft                      |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Flatulence                       |                 |                 |                 |
| subjects affected / exposed      | 3 / 22 (13.64%) | 2 / 21 (9.52%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 3               | 2               | 1               |
| Frequent bowel movements         |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 0               | 0               | 1               |
| Gastrointestinal pain            |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Gastrooesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Haemorrhoidal haemorrhage        |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Lip blister                      |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed            | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0               |
| Nausea                                 |                 |                 |                 |
| subjects affected / exposed            | 7 / 22 (31.82%) | 4 / 21 (19.05%) | 2 / 19 (10.53%) |
| occurrences (all)                      | 9               | 5               | 2               |
| Oesophagitis                           |                 |                 |                 |
| subjects affected / exposed            | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Oral disorder                          |                 |                 |                 |
| subjects affected / exposed            | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Oral pruritus                          |                 |                 |                 |
| subjects affected / exposed            | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 1               | 0               | 0               |
| Regurgitation                          |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 2 / 19 (10.53%) |
| occurrences (all)                      | 0               | 0               | 6               |
| Stomatitis                             |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                      | 0               | 0               | 1               |
| Tongue disorder                        |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0               |
| Tongue eruption                        |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                      | 0               | 0               | 1               |
| Toothache                              |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                      | 0               | 1               | 0               |
| Vomiting                               |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 2 / 21 (9.52%)  | 3 / 19 (15.79%) |
| occurrences (all)                      | 0               | 2               | 4               |
| Skin and subcutaneous tissue disorders |                 |                 |                 |
| Blister                                |                 |                 |                 |
| subjects affected / exposed            | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                      | 0               | 0               | 1               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Dry skin  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Eczema  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 22 (18.18%) | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 7               | 0               | 1               |
| Pain of skin                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Pruritus  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 22 (13.64%) | 1 / 21 (4.76%)  | 2 / 19 (10.53%) |
| occurrences (all)                               | 5               | 1               | 2               |
| Pruritus generalised                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                               | 1               | 0               | 0               |
| Rash  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 22 (18.18%) | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                               | 5               | 1               | 0               |
| Urticaria                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Renal and urinary disorders                     |                 |                 |                 |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 4 / 21 (19.05%) | 3 / 19 (15.79%) |
| occurrences (all)                               | 1               | 5               | 4               |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 22 (4.55%)  | 2 / 21 (9.52%)  | 3 / 19 (15.79%) |
| occurrences (all)                               | 1               | 2               | 3               |
| Joint swelling                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                               | 0               | 0               | 1               |
| Muscle spasms                                   |                 |                 |                 |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Musculoskeletal pain             |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 0               | 1               | 2               |
| Musculoskeletal stiffness        |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 0               | 0               | 1               |
| Pain in extremity                |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 3 / 21 (14.29%) | 3 / 19 (15.79%) |
| occurrences (all)                | 1               | 4               | 3               |
| Temporomandibular joint syndrome |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Infections and infestations      |                 |                 |                 |
| Conjunctivitis                   |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 1               | 0               |
| Gastroenteritis                  |                 |                 |                 |
| subjects affected / exposed      | 1 / 22 (4.55%)  | 0 / 21 (0.00%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 1               | 0               | 0               |
| Gingivitis                       |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 1 / 21 (4.76%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 2               | 0               |
| Herpes simplex                   |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 0 / 21 (0.00%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 0               | 0               | 2               |
| Influenza                        |                 |                 |                 |
| subjects affected / exposed      | 3 / 22 (13.64%) | 2 / 21 (9.52%)  | 1 / 19 (5.26%)  |
| occurrences (all)                | 4               | 3               | 1               |
| Nasopharyngitis                  |                 |                 |                 |
| subjects affected / exposed      | 5 / 22 (22.73%) | 7 / 21 (33.33%) | 7 / 19 (36.84%) |
| occurrences (all)                | 7               | 8               | 7               |
| Oral herpes                      |                 |                 |                 |
| subjects affected / exposed      | 0 / 22 (0.00%)  | 2 / 21 (9.52%)  | 0 / 19 (0.00%)  |
| occurrences (all)                | 0               | 2               | 0               |

|                                    |                |                |                 |
|------------------------------------|----------------|----------------|-----------------|
| Rhinitis                           |                |                |                 |
| subjects affected / exposed        | 1 / 22 (4.55%) | 0 / 21 (0.00%) | 0 / 19 (0.00%)  |
| occurrences (all)                  | 1              | 0              | 0               |
| Sinusitis                          |                |                |                 |
| subjects affected / exposed        | 1 / 22 (4.55%) | 2 / 21 (9.52%) | 1 / 19 (5.26%)  |
| occurrences (all)                  | 1              | 2              | 1               |
| Urinary tract infection            |                |                |                 |
| subjects affected / exposed        | 2 / 22 (9.09%) | 0 / 21 (0.00%) | 0 / 19 (0.00%)  |
| occurrences (all)                  | 3              | 0              | 0               |
| Vulvovaginal mycotic infection     |                |                |                 |
| subjects affected / exposed        | 0 / 22 (0.00%) | 1 / 21 (4.76%) | 0 / 19 (0.00%)  |
| occurrences (all)                  | 0              | 1              | 0               |
| Metabolism and nutrition disorders |                |                |                 |
| Decreased appetite                 |                |                |                 |
| subjects affected / exposed        | 1 / 22 (4.55%) | 1 / 21 (4.76%) | 2 / 19 (10.53%) |
| occurrences (all)                  | 1              | 1              | 2               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date           | Amendment  |
|----------------|--|
| 20 May 2016    | <p>The following changes were made:</p> <ol style="list-style-type: none"><li>1. To reduce burden on patients, gluten stool sample collection was made optional except for the two samples collected at the time of the endoscopy and biopsy collection (Screening and Week 12 / Early Termination, which remain mandatory).</li><li>2. The rules for collection of stool samples were revised to allow a more flexible window of <math>\pm 3</math> days and to allow any place of collection rather than the patient's home only.</li><li>3. The time of collection of the blood cell pellet was changed to allow collection at any time during study.</li><li>4. The cut-off value of mucosal damage, under which subjects were excluded from the gluten challenge, was lowered from 2 to 1.8. Subjects with VH:CD of <math>\leq 1.8</math> were not allowed to receive gluten challenge, while subjects with VH:CD <math>\geq 1.9</math> could receive challenge.</li><li>5. The age limit was increased to 80 years old.</li><li>6. The cut-off criterion of symptoms at baseline was increased from a CeD-GSRS score of 2 to 2.3.</li><li>7. The following discretion was added to Inclusion Criterion 10: "...unless investigator considers the abnormalities to be not clinically significant."</li><li>8. A note was added to indicate that the Sponsor could arrange with the study sites the conduct of some of the intermediate visits at the subject's home, provided that appropriate healthcare personnel conducted the visit with similar standards to visits conducted at the study site.</li><li>9. A duplicated sentence on mini-gut experiments in biopsy fragments was removed and minor inconsistencies were corrected.</li><li>10. The procedure for retaining unused vials was clarified.</li><li>11. It was clarified that the alternation of side of the abdomen for the SC injections was between visits and not between the two injections in the same visit.</li><li>12. It was clarified that the DSMB could, and was expected to, review unblinded data. The safety findings insufficient to trigger the stopping rules could, if judged appropriate by the DSMB, lead to suspension of enrollment during review.</li></ol> |
| 29 August 2016 | <p>The following changes and clarifications were made:</p> <ol style="list-style-type: none"><li>1. Elimination of the stool test as an eligibility criterion, since endoscopy and biopsy already identified patients with gluten contamination, as revealed by mucosal atrophy.</li><li>2. Removal of the exclusion criterion for blood donation 3 months before study entry, initially meant to prevent anemia by avoiding administering gluten challenge to patients who had had a recent blood donation; the precaution was considered unnecessary and preventing otherwise eligible patients from enrolling in the study. Blood donation remained prohibited during the study.</li><li>3. Modest villous atrophy threshold was changed for patients not receiving the gluten challenge to avoid excluding a few candidates, which would otherwise be considered eligible for the study.</li></ol>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported