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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	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

Arm title	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

Arm title	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

Number of subjects in period 1	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:	
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:	
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:	
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 Units: Subjects			
18 - 64 years	17	20	12
65 - 84 years	5	2	8
Age continuous Units: years			
arithmetic mean	51.0	47.8	54.7
standard deviation	± 15.5	± 15.1	± 14.9
Gender categorical Units: Subjects			
Female	16	17	14
Male	6	5	6
Race Units: Subjects			
White	22	22	20
Ethnicity Units: Subjects			
Hispanic/Latino	1	0	0
Not Hispanic/Latino	21	22	20

Reporting group values	Total		
Number of subjects	64		
Age categorical Units: Subjects			
18 - 64 years	49		
65 - 84 years	15		
Age continuous Units: years			
arithmetic mean			
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:	
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:	
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:	
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:	
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. 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:	
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[1]	19[2]	15[3]	
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

Statistical analysis title	Primary Analysis
Comparison groups	AMG 714 150 mg v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.7271 [5]
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.

Statistical analysis title	Primary Analysis
Comparison groups	AMG 714 300 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.3438 [7]
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[8]	19[9]	15[10]	
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 [11]
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 [12]
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[13]	19[14]	15[15]	
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

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[16]	18[17]	15[18]	
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

Statistical analysis title	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 [19]
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.

Statistical analysis title	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 [20]
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[21]	18[22]	15[23]	
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 [24]
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.

Statistical analysis title	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.

Statistical analysis title	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.

Statistical analysis title	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[28]	19[29]	14[30]	
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 [31]
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.

Statistical analysis title	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 [32]
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 >= 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[33]	19[34]	15[35]	
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[36]	19[37]	14[38]	
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

Statistical analysis title	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 [39]
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.

Statistical analysis title	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 [40]
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

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[41]	19[42]	14[43]	
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

Statistical analysis title	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 [44]
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.

Statistical analysis title	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 [45]
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			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pruritus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Pharyngeal oedema			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Tonsillolith			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	1 / 19 (5.26%)
occurrences (all)	1	1	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	1 / 22 (4.55%)	3 / 21 (14.29%)	0 / 19 (0.00%)
occurrences (all)	1	3	0
White blood cells urine positive			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Procedural headache			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Wound complication			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	4 / 22 (18.18%)	7 / 21 (33.33%)	8 / 19 (42.11%)
occurrences (all)	5	13	14
Migraine			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	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	The following changes were made: 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). 2. 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 rather than the patient's home only. 3. The time of collection of the blood cell pellet was changed to allow collection at any time during study. 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 ≤ 1.8 were not allowed to receive gluten challenge, while subjects with VH:CD ≥ 1.9 could receive challenge. 5. The age limit was increased to 80 years old. 6. The cut-off criterion of symptoms at baseline was increased from a CeD-GSRS score of 2 to 2.3. 7. The following discretion was added to Inclusion Criterion 10: "…unless investigator considers the abnormalities to be not clinically significant." 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. 9. A duplicated sentence on mini-gut experiments in biopsy fragments was removed and minor inconsistencies were corrected. 10. The procedure for retaining unused vials was clarified. 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. 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.
29 August 2016	The following changes and clarifications were made: 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. 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. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported