



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	CELIM-RCD-002
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 May 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

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

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

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AMG 714

Arm description:

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

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

Dosage and administration details:

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

Arm title	Placebo
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Arm description:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

Notes:

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

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

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

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

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

End point type	Secondary
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End point timeframe:

Baseline and Week 12

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

Statistical analyses

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

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

Notes:

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

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

End point title	Percent Change From Baseline in Villous Height to Crypt Depth Ratio
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End point description:

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

The analysis was conducted in the per protocol population.

End point type	Secondary
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End point timeframe:

Baseline and week 12

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

Statistical analyses

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

Notes:

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

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

End point title	Percentage of Participants with Improvement in Marsh Score at Week 12
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End point description:

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

Improvement is defined as a decrease in score from baseline.

The analysis was conducted in the PP population.

End point type	Secondary
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End point timeframe:

Baseline and week 12

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

Statistical analyses

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

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

End point title	Percent Change from Baseline in Total Intraepithelial Lymphocyte Count at Week 12
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End point description:

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

The analysis was conducted in the PP population.

End point type Secondary

End point timeframe:

Baseline and week 12

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

Statistical analyses

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

Notes:

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

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

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

End point description:

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

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

End point type Secondary

End point timeframe:

Baseline and week 12

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

Statistical analyses

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

Notes:

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

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

End point title	Percentage of Participants with Diarrhoea at Baseline and Week 12
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End point description:

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

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

End point type	Secondary
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End point timeframe:

Baseline and week 12

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Weekly Gastrointestinal Symptom

End point title	Change from Baseline in Total Weekly Gastrointestinal Symptom
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End point description:

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

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

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

End point type	Secondary
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End point timeframe:

Baseline and week 12

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

Statistical analyses

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

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

Notes:

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

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

End point title	Change from Baseline in Total Celiac Disease GSRs (CeD-GSRs) Score at
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End point description:

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

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

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

End point type	Secondary
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End point timeframe:

Baseline and week 12

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

Statistical analyses

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

Variability estimate	Standard error of the mean
Dispersion value	0.24

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until week 16

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	AMG 714
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Reporting group description:

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

Reporting group title	Placebo
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Reporting group description:

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported