



Clinical trial results:

A Phase 2b, Randomized, Double-Blind, PPlacebo-Controlled Dose-Ranging Study of the Efficacy and Safety of ALV003 Treatment in Symptomatic Celiac Disease Patients Maintained on a Gluten-Free Diet Summary

EudraCT number	2013-003660-31
Trial protocol	FI GB IE NO
Global end of trial date	28 May 2015

Results information

Result version number	v1 (current)
This version publication date	01 December 2016
First version publication date	01 December 2016

Trial information

Trial identification

Sponsor protocol code	ALV003-1221
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01917630
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alvine Pharmaceuticals . Inc (former)
Sponsor organisation address	75 Shoreway Road, Suite B, San Carlos, United States, CA 94070
Public contact	Andre Western, Smerud Medical Research International, +47 90526246, andre.western@smerud.com
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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	25 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2015
Global end of trial reached?	Yes
Global end of trial date	28 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the effect of different dose levels of ALV003 administered for 12 weeks on mucosal morphometry as measured by the villus height to crypt depth ratio (Vh:Cd).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to withdraw at any time. All patients were informed about the study both orally and in writing, and signed the informed consent prior to any study related procedure took place. Patients were treated in the clinic with standard care for this population.

Background therapy:

No treatments that were not test or comparator products was used across the two arms in the trial.

Evidence for comparator:

Based on experience in prior clinical studies, the target clinical dose is thought to be 300-600 mg TID. This study will include those doses, and will bracket them with 100 mg TID and 900 mg TID doses, including placebo.

As shown previously, ALV003 has the potential to cause symptoms similar to gluten. The use of a placebo is important measure being taken to control for non-study treatment related symptoms.

Actual start date of recruitment	26 August 2013
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	Norway: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	United States: 444
Worldwide total number of subjects	489
EEA total number of subjects	15

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	416
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 82 sites: USA; 74 sites, Canada; 4 sites, Ireland, UK, Norway and Finland; 1 site each. A total of 1919 subjects were screened, of which 344 were screen failures. 1575 subjects were enrolled of which 1081 were never randomized. Of the 494 subjects randomized, 489 subject are included in analysis of this study.

Pre-assignment

Screening details:

Adults diagnosed with celiac disease, on gluten free diet and at least one self-reported moderate or severe symptom included in the CDSD.

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, Monitor, Carer, Assessor

Blinding implementation details:

The ALV003 is provided as 2 formulated drug substances: ALV001 and ALV002 to be administered in a 1:1 ratio together with a flavor pack. Placebo drug and all different study drug concentrations come in identical packs, and are to be administered three times each day with each gluten-free major meal.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo of ALV003. 30 % of population. 494 patients were randomized, but 489 patients are included in the safety population, as 5 patient never received study drug. They belong to the groups Placebo=1, 30mg=1, 450mg=1 and 900mg=2.

The Modified Intent-to-Treat (MITT) Population included all randomized patients who were on study treatment for at least 6 weeks with study treatment compliance of 80% or greater during the first 12 weeks of study treatment and had a post-treatment observation of the analysis parameter performed ≤ 14 days of the last study treatment during the first 12 weeks. This gave a total of 405 patients: Placebo= 125, 100mg= 47, 300mg= 77, 450mg= 39, 600mg= 80 and 900mg= 37.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). The ALV001 and ALV002 placebos contain the same excipients as the corresponding ALV001 and ALV002 drug substances, except for the removal of monothioglycerol and EDTA. All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).

Arm title	ALV003 100 mg
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Arm description:

ALV003, 100 mg, 10 % of population

Arm type	Experimental
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Investigational medicinal product name	ALV003 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use
Dosage and administration details:	
ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).	
Arm title	ALV003, 300 mg
Arm description:	
ALV003, 300 mg, 20 % of population	
Arm type	Experimental
Investigational medicinal product name	ALV003, 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Ocular use
Dosage and administration details:	
ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).	
Arm title	ALV003, 450 mg
Arm description:	
ALV003, 450 mg, 10 % of population	
Arm type	Experimental
Investigational medicinal product name	ALV003, 450 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use
Dosage and administration details:	
ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).	
Arm title	ALV003, 600 mg
Arm description:	
ALV003, 600 mg, 20% of population	
Arm type	Experimental
Investigational medicinal product name	ALV003, 600 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use
Dosage and administration details:	
ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).	
Arm title	ALV003, 900 mg

Arm description: ALV003, 900 mg, 10 % of population	
Arm type	Experimental
Investigational medicinal product name	ALV003, 900 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

ALV003 will be provided as two formulated drug substances: ALV001 and ALV002 (which, when administered together in a 1:1 (w/w) ratio, are known as ALV003). All are free-flowing white to off-white powders. ALV001, ALV002, and the matching placebos will be provided in separate foil stick-packs along with a flavor pack, and are to be stored at room temperature (15 to 25°C).

Number of subjects in period 1	Placebo	ALV003 100 mg	ALV003, 300 mg
Started	148	50	97
Completed	125	47	78
Not completed	23	3	19
Consent withdrawn by subject	12	1	6
Physician decision	-	-	1
non-compliance with CDSD completion	1	-	2
Adverse event, non-fatal	9	2	9
Lost to follow-up	1	-	1

Number of subjects in period 1	ALV003, 450 mg	ALV003, 600 mg	ALV003, 900 mg
Started	48	99	47
Completed	43	80	39
Not completed	5	19	8
Consent withdrawn by subject	1	8	3
Physician decision	-	-	-
non-compliance with CDSD completion	-	1	-
Adverse event, non-fatal	4	7	5
Lost to follow-up	-	3	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo of ALV003. 30 % of population. 494 patients were randomized, but 489 patients are included in the safety population, as 5 patient never received study drug. They belong to the groups Placebo=1, 30mg=1, 450mg=1 and 900mg=2. The Modified Intent-to-Treat (MITT) Population included all randomized patients who were on study treatment for at least 6 weeks with study treatment compliance of 80% or greater during the first 12 weeks of study treatment and had a post-treatment observation of the analysis parameter performed ≤ 14 days of the last study treatment during the first 12 weeks. This gave a total of 405 patients: Placebo= 125, 100mg= 47, 300mg= 77, 450mg= 39, 600mg= 80 and 900mg= 37.	
Reporting group title	ALV003 100 mg
Reporting group description:	
ALV003, 100 mg, 10 % of population	
Reporting group title	ALV003, 300 mg
Reporting group description:	
ALV003, 300 mg, 20 % of population	
Reporting group title	ALV003, 450 mg
Reporting group description:	
ALV003, 450 mg, 10 % of population	
Reporting group title	ALV003, 600 mg
Reporting group description:	
ALV003, 600 mg, 20% of population	
Reporting group title	ALV003, 900 mg
Reporting group description:	
ALV003, 900 mg, 10 % of populaiton	

Reporting group values	Placebo	ALV003 100 mg	ALV003, 300 mg
Number of subjects	148	50	97
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	125	41	75
From 65-84 years	23	9	22
85 years and over	0	0	0
Gender categorical			
Per group			
Units: Subjects			
Female	123	34	75
Male	25	16	22

Ethnicity			
Units: Subjects			
Non-hispanic	144	47	96
Hispanic	4	3	1
Race			
Units: Subjects			
White	142	47	96
Black or African American	1	0	0
Asian	0	1	0
American Indian	1	1	0
Other	4	1	1

Reporting group values	ALV003, 450 mg	ALV003, 600 mg	ALV003, 900 mg
Number of subjects	48	99	47
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	44	88	43
From 65-84 years	4	11	4
85 years and over	0	0	0
Gender categorical			
Per group			
Units: Subjects			
Female	38	70	41
Male	10	29	6
Ethnicity			
Units: Subjects			
Non-hispanic	48	96	47
Hispanic	0	3	0
Race			
Units: Subjects			
White	47	96	45
Black or African American	0	0	0
Asian	0	0	1
American Indian	1	1	1
Other	0	2	0

Reporting group values	Total		
Number of subjects	489		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	416		
From 65-84 years	73		
85 years and over	0		
Gender categorical			
Per group			
Units: Subjects			
Female	381		
Male	108		
Ethnicity			
Units: Subjects			
Non-hispanic	478		
Hispanic	11		
Race			
Units: Subjects			
White	473		
Black or African American	1		
Asian	2		
American Indian	5		
Other	8		

Subject analysis sets

Subject analysis set title	Placebo, safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

149 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 148 subjects are in the safety analysis and 125 in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean: 0.27 (-0.65 - 1.32), $P < 0.0001$

Subject analysis set title	ALV003, 300 mg, safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

98 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 97 started and are in the safety analysis and 78 subjects are included in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean = 0.15 (-0.80 - 1.28), $P = 0.0018$

Subject analysis set title	ALV003, 450 mg, safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

49 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 48 subjects are included in the safety analysis, and 43 completed the study and are in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean = 0.05 (-1.18 - 0.77), $p = 0.5560$

Subject analysis set title	ALV003, 900 mg, safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

49 subjects were randomized. One patient was non-compliant with CDSD completion and was withdrawn prior to receiving study drug. One patient was withdrawn by the investigator prior to receiving study drug. These two patients are not included in the safety analysis. 47 subjects are included in the safety analysis, while 39 subjects completed the study and are in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean = 0.11 (-0.87 - 1.48), $p = 0.1449$

Subject analysis set title	ALV003, 100 mg, safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
50 patients were randomized, and all are included in the safety analysis. 47 subjects completed the study and are in the Vh:Cd analysis.	
Vh:Cd change from baseline: Mean = 0.12 (-0.88 - 1.85), p=0.0805	
Subject analysis set title	ALV003, 600 mg, safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
99 subjects were randomized and all are included in the safety analysis. 80 subjects completed the study and are in the Vh:Cd analysis.	
Vh:Cd change from baseline: Mean = 0.14 (-0.77 - 1.72), p = 0.0157	
Subject analysis set title	600mg + 900mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
600+900	
Subject analysis set title	600mg + 450mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
600+450	
Subject analysis set title	300mg + 450mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
300+450	
Subject analysis set title	300mg + 100mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
300+100	

Reporting group values	Placebo, safety population	ALV003, 300 mg, safety population	ALV003, 450 mg, safety population
Number of subjects	148	97	48
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	125	75	44
From 65-84 years	23	22	4
85 years and over	0	0	0
Gender categorical			
Per group			
Units: Subjects			
Female	123	75	38
Male	25	22	10
Ethnicity			
Units: Subjects			
Non-hispanic	144	96	48
Hispanic	4	1	0

Race			
Units: Subjects			
White	142	96	47
Black or African American	1	0	0
Asian	0	0	0
American Indian	1	0	1
Other	4	1	0

Reporting group values	ALV003, 900 mg, safety population	ALV003, 100 mg, safety population	ALV003, 600 mg, safety population
Number of subjects	47	50	99
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	41	88
From 65-84 years	4	9	11
85 years and over	0	0	0
Gender categorical			
Per group			
Units: Subjects			
Female	41	34	70
Male	6	16	29
Ethnicity			
Units: Subjects			
Non-hispanic	47	47	96
Hispanic	0	3	3
Race			
Units: Subjects			
White	45	47	96
Black or African American	0	0	0
Asian	1	1	0
American Indian	1	1	1
Other	0	1	2

Reporting group values	600mg + 900mg	600mg + 450mg	300mg + 450mg
Number of subjects	117	119	116
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			

Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical			
Per group			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
Non-hispanic			
Hispanic			
Race			
Units: Subjects			
White			
Black or African American			
Asian			
American Indian			
Other			

Reporting group values	300mg + 100mg		
Number of subjects	124		
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical			
Per group			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
Non-hispanic			
Hispanic			
Race			
Units: Subjects			
White			
Black or African American			
Asian			
American Indian			
Other			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo of ALV003. 30 % of population. 494 patients were randomized, but 489 patients are included in the safety population, as 5 patient never received study drug. They belong to the groups Placebo=1, 30mg=1, 450mg=1 and 900mg=2. The Modified Intent-to-Treat (MITT) Population included all randomized patients who were on study treatment for at least 6 weeks with study treatment compliance of 80% or greater during the first 12 weeks of study treatment and had a post-treatment observation of the analysis parameter performed ≤ 14 days of the last study treatment during the first 12 weeks. This gave a total of 405 patients: Placebo= 125, 100mg= 47, 300mg= 77, 450mg= 39, 600mg= 80 and 900mg= 37.	
Reporting group title	ALV003 100 mg
Reporting group description: ALV003, 100 mg, 10 % of population	
Reporting group title	ALV003, 300 mg
Reporting group description: ALV003, 300 mg, 20 % of population	
Reporting group title	ALV003, 450 mg
Reporting group description: ALV003, 450 mg, 10 % of population	
Reporting group title	ALV003, 600 mg
Reporting group description: ALV003, 600 mg, 20% of population	
Reporting group title	ALV003, 900 mg
Reporting group description: ALV003, 900 mg, 10 % of populaiton	
Subject analysis set title	Placebo, safety population
Subject analysis set type	Safety analysis
Subject analysis set description: 149 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 148 subjects are in the safety analysis and 125 in the Vh:Cd analysis. Vh:Cd change from baseline: Mean: 0.27 (-0.65 - 1.32), $P < 0.0001$	
Subject analysis set title	ALV003, 300 mg, safety population
Subject analysis set type	Safety analysis
Subject analysis set description: 98 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 97 started and are in the safety analysis and 78 subjects are included in the Vh:Cd analysis. Vh:Cd change from baseline: Mean = 0.15 (-0.80 - 1.28), $P = 0.0018$	
Subject analysis set title	ALV003, 450 mg, safety population
Subject analysis set type	Safety analysis
Subject analysis set description: 49 subjects were randomized. One patient withdrew consent prior to receiving study drug, hence the patient is not included in the safety analysis. 48 subjects are included i the safety analysis, and 43 completed the study and are in the Vh:Cd analysis. Vh:Cd change from baseline: Mean = 0.05 (-1.18 - 0.77), $p = 0.5560$	
Subject analysis set title	ALV003, 900 mg, safety population
Subject analysis set type	Safety analysis
Subject analysis set description: 49 subjects were randomized. One patient was non-compliant with CDSD completion and was withdrawn prior to receiving study drug. One patient was withdrawn by the investigator prior to receiving study drug. These two patients are not included in the safety analysis. 47 subjects are included in the safety	

analysis, while 39 subjects completed the study and are in the Vh:Cd analysis.
Vh:Cd change from baseline: Mean = 0.11 (-0.87 - 1.48), p=0.1449

Subject analysis set title	ALV003, 100 mg, safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

50 patients were randomized, and all are included in the safety analysis. 47 subjects completed the study and are in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean = 0.12 (-0.88 - 1.85), p=0.0805

Subject analysis set title	ALV003, 600 mg, safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

99 subjects were randomized and all are included in the safety analysis. 80 subjects completed the study and are in the Vh:Cd analysis.

Vh:Cd change from baseline: Mean = 0.14 (-0.77 - 1.72), p= 0.0157

Subject analysis set title	600mg + 900mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

600+900

Subject analysis set title	600mg + 450mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

600+450

Subject analysis set title	300mg + 450mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

300+450

Subject analysis set title	300mg + 100mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

300+100

Primary: 600mg +900mg vs placebo

End point title	600mg +900mg vs placebo
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End point description:

Week 12 treatment difference: P = 0.0084

End point type	Primary
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End point timeframe:

baseline, 12 weeks

End point values	Placebo, safety population	600mg + 900mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	117		
Units: mean				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	MITT ANCOVA
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was conducted in the MITT population using an ANCOVA model. The dependent variable was the change from baseline at Week 12 in Vh:Cd and the model included effects for treatment group, baseline serology status, and the baseline value of Vh:Cd. The primary comparison was between the 600 mg + 900 mg groups versus the placebo group.	
Comparison groups	Placebo, safety population v 600mg + 900mg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0084 ^[2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.264
upper limit	-0.039

Notes:

[1] - Data for the analysis of the separate group "600+900" is not available

[2] - The analysis of the group "600+900" vs placebo shows that placebo is significant better than the "600+900" group.

Secondary: 300mg + 100mg vs placebo

End point title	300mg + 100mg vs placebo
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo, safety population	300mg + 100mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	124		
Units: mm				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	300+100 vs placebo
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was carried out in the MITT Population using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline at Week 12 in Vh:Cd and the model included effects for treatment group, baseline serology status, and the	

baseline value of Vh:Cd.

Comparison groups	Placebo, safety population v 300mg + 100mg
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.013 ^[4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.249
upper limit	0.032
Variability estimate	Standard deviation

Notes:

[3] - Data for the separate group "300 + 100" is not available. The comparison is the "300+100" group versus placebo.

[4] - The analysis is done for "300+100" vs placebo and the result shows that placebo is significant better than the group "300+100".

Secondary: 300mg vs placebo

End point title	300mg vs placebo
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo, safety population	ALV003, 300 mg, safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	77		
Units: mm				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	0.15 (-0.8 to 1.28)		

Statistical analyses

Statistical analysis title	300 vs placebo
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was carried out in the MITT Population using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline at Week 12 in Vh:Cd and the model included effects for treatment group, baseline serology status, and the baseline value of Vh:Cd.	
Comparison groups	Placebo, safety population v ALV003, 300 mg, safety population

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0425 ^[6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.248
upper limit	-0.004

Notes:

[5] - The analysis is the 300 group versus placebo.

[6] - The analysis of the group "300" vs placebo shows that placebo is significant better than the group.

Secondary: 300mg + 450mg vs placebo

End point title	300mg + 450mg vs placebo
End point description:	
Week 12 treatment difference. P = 0.0020	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo, safety population	300mg + 450mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	116		
Units: mm				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	300+450 vs placebo
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was carried out in the MITT Population using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline at Week 12 in Vh:Cd and the model included effects for treatment group, baseline serology status, and the baseline value of Vh:Cd.	
Comparison groups	Placebo, safety population v 300mg + 450mg

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other ^[7]
P-value	= 0.002 ^[8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.289
upper limit	-0.065

Notes:

[7] - Separate analysis for the group "300+450" is not available. The comparison is the "300+450" group versus placebo.

[8] - The analysis of the group "300+450" vs placebo shows that placebo is significant better than the "300+450" group.

Secondary: 600mg + 450mg vs placebo

End point title	600mg + 450mg vs placebo
End point description:	
Week 12 treatment difference. P = 0-0009	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo, safety population	600mg + 450mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	119		
Units: mm				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	600+450 vs placebo
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was carried out in the MITT Population using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline at Week 12 in Vh:Cd and the model included effects for treatment group, baseline serology status, and the baseline value of Vh:Cd.	
Comparison groups	Placebo, safety population v 600mg + 450mg

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	= 0.0009 ^[10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.301
upper limit	-0.078

Notes:

[9] - Separate analysis of the group "600+450" is not available. The comparison is the "600+450" group versus placebo.

[10] - The analysis of the group "600+450" vs placebo shows that placebo is significant better than the "600+450" group.

Secondary: 600 mg vs placebo

End point title	600 mg vs placebo
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo, safety population	ALV003, 600 mg, safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	125	80		
Units: mm				
arithmetic mean (full range (min-max))	0.27 (-0.65 to 1.32)	1 (1 to 1)		

Statistical analyses

Statistical analysis title	600 vs placebo
Statistical analysis description:	
The primary efficacy endpoint was the change from baseline at Week 12 in intestinal mucosal morphometry (Vh:Cd). The primary efficacy analysis was carried out in the MITT Population using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline at Week 12 in Vh:Cd. Primary comparison was between the 600mg+900mg group versus placebo.	
Comparison groups	Placebo, safety population v ALV003, 600 mg, safety population

Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136 ^[11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.273
upper limit	-0.031

Notes:

[11] - The analysis of the group 600 vs placebo shows that placebo is significant better than the 600 group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline, Week 12

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo of ALV003. 30 % of population.

Reporting group title	ALV003 100 mg
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Reporting group description:

ALV003, 100 mg, 10 % of population

Reporting group title	ALV003, 300 mg
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Reporting group description:

ALV003, 300 mg, 20 % of population

Reporting group title	ALV003, 450 mg
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Reporting group description:

ALV003, 450 mg, 10 % of population

Reporting group title	ALV003, 600 mg
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Reporting group description:

ALV003, 600 mg, 20% of population

Reporting group title	ALV003, 900 mg
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Reporting group description:

ALV003, 900 mg, 10 % of populaiton

Serious adverse events	Placebo	ALV003 100 mg	ALV003, 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 148 (2.03%)	0 / 50 (0.00%)	1 / 97 (1.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation	Additional description: Relevant history includes atrial fibrillation, hypertension, asthma, anemia, celiac disease, and thrombocytosis.		
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Optic neuritis	Additional description: The patient complained of severe blurry vision and was referred to an ophthalmologist who diagnosed left optic neuritis and blindness. Patient stated that she had vision problems in the past.		

subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute	Additional description: Medical history included celiac disease, hiatal hernia, lupus, duodenitis, esophagitis, hypercholesterolemia, and depression. The patient was diagnosed with severe acute pancreatitis that may have been caused by the recent use of lovastatin.		
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Gallstone ileus	Additional description: Cholelithiasis (not in dictionary) (not gallstone ileus). Relevant past medical history included hiatal hernia, celiac disease, and pericardial hemorrhage.		
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	Additional description: Relevant medical history includes celiac disease, COPD, chronic bronchitis, and current tobacco use and medications to control COPD.		
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events			
ALV003, 450 mg	ALV003, 600 mg	ALV003, 900 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation	Additional description: Relevant history includes atrial fibrillation, hypertension, asthma, anemia, celiac disease, and thrombocytosis.		
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Optic neuritis	Additional description: The patient complained of severe blurry vision and was referred to an ophthalmologist who diagnosed left optic neuritis and blindness. Patient stated that she had vision problems in the past.		

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute	Additional description: Medical history included celiac disease, hiatal hernia, lupus, duodenitis, esophagitis, hypercholesterolemia, and depression. The patient was diagnosed with severe acute pancreatitis that may have been caused by the recent use of lovastatin.		
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Gallstone ileus	Additional description: Cholelithiasis (not in dictionary) (not gallstone ileus). Relevant past medical history included hiatal hernia, celiac disease, and pericardial hemorrhage.		
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	Additional description: Relevant medical history includes celiac disease, COPD, chronic bronchitis, and current tobacco use and medications to control COPD.		
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	ALV003 100 mg	ALV003, 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 148 (56.08%)	24 / 50 (48.00%)	55 / 97 (56.70%)
Vascular disorders			
Arterial rupture			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Early satiety			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	2 / 148 (1.35%)	1 / 50 (2.00%)	1 / 97 (1.03%)
occurrences (all)	2	1	1
Feeling abnormal			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Feeling jittery			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Nodule			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	2 / 148 (1.35%)	1 / 50 (2.00%)	2 / 97 (2.06%)
occurrences (all)	2	1	3
Pyrexia			
subjects affected / exposed	2 / 148 (1.35%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	2	1	0

Vessel puncture site pain subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Vessel puncture site swelling subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Otitis media subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Reproductive system and breast disorders Bartholin's cyst subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Menopausal symptoms subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Vulvovaginal dryness subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Menstrual discomfort subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Ovarian cyst subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Asthma subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0

Cough			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Laryngospasm			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Respiratory failure			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
Panic attack			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Blood urine present			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Differential white blood cell count abnormal			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Haematocrit decreased			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Helicobacter test positive			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary scan abnormal			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Serum ferritin decreased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Urine output increased			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	1 / 97 (1.03%)
occurrences (all)	0	1	1
Weight decreased			

subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Weight increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Back injury			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Concussion			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	2 / 97 (2.06%)
occurrences (all)	0	0	2
Fibula fracture			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Muscle contusion			

subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Muscle strain subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Road traffic accident subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 148 (1.35%) 2	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Nervous system disorders Carpal tunnel syndrome subjects affected / exposed occurrences (all)	3 / 148 (2.03%) 3	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Cubital tunnel syndrome subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	2 / 148 (1.35%) 2	1 / 50 (2.00%) 1	2 / 97 (2.06%) 2
Dysaesthesia subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Headache			

subjects affected / exposed occurrences (all)	3 / 148 (2.03%) 3	3 / 50 (6.00%) 4	0 / 97 (0.00%) 0
Migraine			
subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	3 / 50 (6.00%) 3	3 / 97 (3.09%) 3
Optic neuritis			
subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 2	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Sinus headache			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Syncope			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Tremor			
subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Iron deficiency anaemia			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Neutrophilia			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Vertigo			
subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	1 / 97 (1.03%) 1
Eye disorders			

Conjunctival disorder subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Conjunctivitis allergic subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	1 / 50 (2.00%) 1	0 / 97 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	1 / 50 (2.00%) 1	3 / 97 (3.09%) 3
Abdominal distension subjects affected / exposed occurrences (all)	4 / 148 (2.70%) 4	0 / 50 (0.00%) 0	3 / 97 (3.09%) 3
Abdominal pain subjects affected / exposed occurrences (all)	6 / 148 (4.05%) 7	0 / 50 (0.00%) 0	4 / 97 (4.12%) 4
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Abdominal tenderness subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Abnormal faeces			

subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Acquired oesophageal web			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Breath odour			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Colitis microscopic			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	3 / 148 (2.03%)	2 / 50 (4.00%)	1 / 97 (1.03%)
occurrences (all)	3	2	1
Diarrhoea			
subjects affected / exposed	7 / 148 (4.73%)	0 / 50 (0.00%)	6 / 97 (6.19%)
occurrences (all)	8	0	6
Diverticulum intestinal			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	1 / 148 (0.68%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Duodenal ulcer			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Duodenitis			
subjects affected / exposed	1 / 148 (0.68%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Erosive duodenitis			

subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Erosive oesophagitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	7 / 148 (4.73%)	0 / 50 (0.00%)	4 / 97 (4.12%)
occurrences (all)	7	0	6
Food poisoning			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gastric disorder			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gastric polyps			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gastric ulcer			
subjects affected / exposed	2 / 148 (1.35%)	1 / 50 (2.00%)	1 / 97 (1.03%)
occurrences (all)	2	1	1
Gastritis			
subjects affected / exposed	3 / 148 (2.03%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	3	1	0
Gastritis erosive			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 148 (0.68%)	1 / 50 (2.00%)	1 / 97 (1.03%)
occurrences (all)	1	1	1
Glossodynia			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	2 / 97 (2.06%)
occurrences (all)	0	0	2
Hiatus hernia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
Impaired gastric emptying			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Mucous stools			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	12 / 148 (8.11%)	5 / 50 (10.00%)	9 / 97 (9.28%)
occurrences (all)	13	6	9
Oesophageal pain			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Oesophageal stenosis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			

subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pancreatitis acute			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	6 / 148 (4.05%)	2 / 50 (4.00%)	3 / 97 (3.09%)
occurrences (all)	10	2	4
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Gallbladder disorder			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	2 / 97 (2.06%)
occurrences (all)	0	0	2
Dermatitis allergic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			

subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Dermatitis herpetiformis			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Lichen sclerosus			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Pruritus generalised			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Rash pruritic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1

Oliguria			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Polyuria			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Urine odour abnormal			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Arthritis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Bone pain			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Bursitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Fibromyalgia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Joint swelling			

subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Morphoea			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	1 / 148 (0.68%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	1	1	0
Osteopenia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Plantar fasciitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Tendon pain			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	2	0	1
candidiasis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0

Ear infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	1	0	1
Furuncle			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	4 / 97 (4.12%)
occurrences (all)	0	0	5
Gastroenteritis viral			
subjects affected / exposed	5 / 148 (3.38%)	0 / 50 (0.00%)	2 / 97 (2.06%)
occurrences (all)	6	0	2
Herpes zoster			
subjects affected / exposed	3 / 148 (2.03%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	3	0	0
Hordeolum			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	6 / 148 (4.05%)	1 / 50 (2.00%)	0 / 97 (0.00%)
occurrences (all)	7	1	0
Kidney infection			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Mononucleosis syndrom			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1

lyme disease			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	6 / 148 (4.05%)	1 / 50 (2.00%)	2 / 97 (2.06%)
occurrences (all)	8	1	2
Pharyngitis streptococcal			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	4 / 148 (2.70%)	2 / 50 (4.00%)	2 / 97 (2.06%)
occurrences (all)	4	2	2
Tooth abscess			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	2 / 148 (1.35%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 148 (2.03%)	2 / 50 (4.00%)	4 / 97 (4.12%)
occurrences (all)	3	2	4
Urinary tract infection			
subjects affected / exposed	2 / 148 (1.35%)	1 / 50 (2.00%)	2 / 97 (2.06%)
occurrences (all)	2	1	2
Vaginal infection			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Vaginitis bacterial			
subjects affected / exposed	0 / 148 (0.00%)	0 / 50 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	1 / 148 (0.68%)	0 / 50 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0

Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Folate deficiency subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	1 / 50 (2.00%) 1	1 / 97 (1.03%) 1
Food intolerance subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	1 / 97 (1.03%) 1
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 148 (0.68%) 1	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 148 (0.00%) 0	0 / 50 (0.00%) 0	0 / 97 (0.00%) 0

Non-serious adverse events	ALV003, 450 mg	ALV003, 600 mg	ALV003, 900 mg
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 48 (45.83%)	54 / 99 (54.55%)	21 / 47 (44.68%)
Vascular disorders			
Arterial rupture subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Hot flush			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Early satiety			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	2 / 48 (4.17%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	2	1	0
Feeling jittery			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Irritability			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Nodule			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Vessel puncture site pain subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Vessel puncture site swelling subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Otitis media subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Reproductive system and breast disorders Bartholin's cyst subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Menopausal symptoms subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Vulvovaginal dryness subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Menstrual discomfort subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Ovarian cyst			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Asthma			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Laryngospasm			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 48 (0.00%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	0	2	0

Panic attack subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Differential white blood cell count abnormal subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Haematocrit decreased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Helicobacter test positive subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Hepatobiliary scan abnormal subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Serum ferritin decreased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Urine output increased			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Back injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Concussion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Fibula fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Muscle contusion subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Muscle strain subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Road traffic accident subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Congenital, familial and genetic disorders Gilbert's syndrome subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Nervous system disorders Carpal tunnel syndrome subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Cubital tunnel syndrome subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Dysaesthesia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 48 (4.17%)	3 / 99 (3.03%)	0 / 47 (0.00%)
occurrences (all)	2	4	0
Migraine			
subjects affected / exposed	0 / 48 (0.00%)	2 / 99 (2.02%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
Optic neuritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Sinus headache			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Neutrophilia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vertigo			

subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Eye disorders			
Conjunctival disorder subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Conjunctivitis allergic subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Eye swelling subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Abdominal distension subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	4 / 99 (4.04%) 4	0 / 47 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	1 / 99 (1.01%) 2	1 / 47 (2.13%) 2
Abdominal tenderness			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Abnormal faeces			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Acquired oesophageal web			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Breath odour			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Colitis microscopic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 48 (4.17%)	6 / 99 (6.06%)	2 / 47 (4.26%)
occurrences (all)	2	6	2
Diverticulum intestinal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Duodenal ulcer			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Duodenitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
Dysphagia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Erosive duodenitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Erosive oesophagitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Faeces discoloured			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	4 / 48 (8.33%)	5 / 99 (5.05%)	1 / 47 (2.13%)
occurrences (all)	4	6	1
Food poisoning			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastric disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastric polyps			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastric ulcer			
subjects affected / exposed	0 / 48 (0.00%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Gastritis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 99 (2.02%)	1 / 47 (2.13%)
occurrences (all)	1	2	1
Gastritis erosive			
subjects affected / exposed	1 / 48 (2.08%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
Gastrointestinal inflammation			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 48 (2.08%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	1	1	0
Glossodynia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Haematemesis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Hiatus hernia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Impaired gastric emptying			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Mucous stools			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 48 (4.17%)	8 / 99 (8.08%)	8 / 47 (17.02%)
occurrences (all)	2	10	10
Oesophageal pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Oesophageal stenosis			

subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Oesophagitis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Pancreatitis acute			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)	7 / 99 (7.07%)	4 / 47 (8.51%)
occurrences (all)	2	7	5
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gallbladder disorder			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Dermatitis contact			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Dermatitis herpetiformis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Lichen sclerosus			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 48 (2.08%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
Rash macular			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Rash pruritic			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Oliguria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Polyuria			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Urine odour abnormal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
Arthritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Fibromyalgia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Joint swelling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Morphoea			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Osteopenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	0	2	1
Plantar fasciitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Tendon pain			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Tendonitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	1	2	0
candidiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0

Cellulitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 48 (0.00%)	2 / 99 (2.02%)	0 / 47 (0.00%)
occurrences (all)	0	2	0
Furuncle			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	1 / 47 (2.13%)
occurrences (all)	0	1	1
Gastroenteritis viral			
subjects affected / exposed	2 / 48 (4.17%)	6 / 99 (6.06%)	1 / 47 (2.13%)
occurrences (all)	2	7	1
Herpes zoster			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Hordeolum			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	2 / 47 (4.26%)
occurrences (all)	0	1	2
Kidney infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0

Mononucleosis syndrom			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
lyme disease			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 48 (2.08%)	3 / 99 (3.03%)	0 / 47 (0.00%)
occurrences (all)	1	3	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 48 (0.00%)	1 / 99 (1.01%)	0 / 47 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	2 / 48 (4.17%)	5 / 99 (5.05%)	1 / 47 (2.13%)
occurrences (all)	2	5	1
Tooth abscess			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	3 / 99 (3.03%)	0 / 47 (0.00%)
occurrences (all)	0	3	0
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	3 / 99 (3.03%)	2 / 47 (4.26%)
occurrences (all)	1	3	2
Vaginal infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	1	0	0
Vaginitis bacterial			
subjects affected / exposed	0 / 48 (0.00%)	0 / 99 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0

Viral infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Folate deficiency subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Food intolerance subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	0 / 47 (0.00%) 0
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 99 (0.00%) 0	1 / 47 (2.13%) 1
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 99 (1.01%) 1	0 / 47 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2013	<ul style="list-style-type: none">• Modified ALV003 dose levels and randomization ratios of study medication group assignments. The 100 mg and 450 mg dose levels were added and the 1200 mg dose level was removed. The dose levels (100, 300, 450, 600 and 900 mg) evaluated in this study are based on in vitro studies that suggest that the target dose for ALV003 could range from 300 mg to 600 mg up to 3 times daily with each gluten-free major meal. The randomization ratios were modified to 3:1:2:1:2:1 (placebo, 100 mg, 300 mg, 450 mg, 600 mg, and 900 mg, respectively) to allow for appropriate dose exploration. The randomization ratios allowed for adequately powered evaluation of the target dose levels to permit dose selection for future pivotal studies.• Revised statistical methods section to reflect changes to ALV003 dose levels and randomization ratios and exploratory comparisons• Removed celiac disease gene expression profiling• Included a revised CDSD© (version 01March 2013)• Revised exclusion criterion #6 to define refractory celiac disease• Clarified exclusion criterion #9 to allow for the use of mini-dose aspirin (81 mg)• Clarified the collection of TEAEs and protocolrelated AEs• Defined minimum compliance levels for CDSD© ($\geq 75\%$ from day of enrollment to randomization) and for study medication (6 weeks of treatment)
10 September 2013	<ul style="list-style-type: none">• Allowed for the enrollment of approximately 20 patients into Study Period 3, an additional 12 weeks of double-blind treatment. Those patients who completed the 12-week, double-blind treatment and underwent the Week 12 endoscopy/biopsy in Study Period 2 were eligible to receive their originally assigned study medication. Extension of dosing allowed for the evaluation of the safety and tolerability of up to 24 weeks of treatment, as well as exploration of the change in villus morphometric measures over a 24-week period of time.• Revised the first question of CDSD© based on feedback from FDA• Added inclusion criterion #11 to allow for enrollment of non-English speaking patients in Europe• Added exclusion criterion #17 to clarify who would be allowed to participate in the study to minimize potential bias.• Revised the timing for a urine pregnancy test for women of childbearing potential from the time of randomization to immediately prior to administration of first dose of study medication.
14 April 2014	<ul style="list-style-type: none">• Described what constitutes effective methods of contraception for some European countries• Described access to treatment codes should unblinding become necessary• Described the activities of the IDMC and data parameters that the IDMC would use to evaluate interim safety• Included the Study Medication Dosing Diary that illustrates how the patient was to prepare and administer the study medication and provided a place for the patient to record each gluten-free major meal eaten and each dose of study medication taken.
16 July 2014	<ul style="list-style-type: none">• Revised the screening estimates that allowed for the enrollment of up to 1500 patients into the study in order to meet the protocol randomization goal of 500 patients.• Provided clarification on the timing of the followup visit for patients who failed to be randomized, patients who completed either Study Period 2 or Study Period 3, and patients who withdrew early from double-blind treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported