Clinical trial results:
A phase IIa, double-blind, randomised, placebo-controlled, dose-finding study on the efficacy and tolerability of a 6-week treatment with ZED1227 capsules vs. placebo in subjects with well-controlled celiac disease undergoing gluten challenge

Summary

EudraCT number	2017-002241-30
Trial protocol	LT FI DE AT IE
Global end of trial date	27 February 2020

Results information

Result version number	v1 (current)
This version publication date	17 July 2021
First version publication date	17 July 2021

Trial information

Trial identification

Sponsor protocol code	CEC-3/CEL

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstrasse 5, Freiburg, Germany, D-79108
Public contact	Department of Clinical Research, Dr. Falk Pharma GmbH, +49 761 1514 -0, zentrale@drfalkpharma.de
Scientific contact	Department of Clinical Research, Dr. Falk Pharma GmbH, +49 761 1514 -0, zentrale@drfalkpharma.de

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	21 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2020
Global end of trial reached?	Yes
Global end of trial date	27 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to assess the efficacy of 3 different doses of ZED1227 capsules for prevention of gluten-induced mucosal changes in subjects with well-controlled celiac disease undergoing gluten challenge.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days up to week 6 and one follow up vist at week 10 to guarantee their safety and wellbeing.
Prior to recruitment of patients, all relevant documents of the clinical study were submitted and approved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

None.

Evidence for comparator:

As there is no standard therapy, placebo was used as comparator.

Actual start date of recruitment	16 May 2018
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: 29
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 39
Country: Number of subjects enrolled	Germany: 77
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Lithuania: 8
Country: Number of subjects enrolled	Switzerland: 5

Worldwide total number of subjects	163
EEA total number of subjects	158

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	163
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 163 patients were included in Estonia, Finland, Germany, Ireland, Lithuania, Norway and Switzerland from May 2018 to February 2020.

Pre-assignment

Screening details:

Screening Criteria: 1. Signed Informed Consent 2. Aged 18 to 64 years 3. Active Celiac Disease.
In total, 249 patients were screened. Thereof 163 patients were randomised, 159 patients were treated and included in the intention-to-treat analysis set. n=3 no study medication dispensed. n=1 medication administration uncertain.

Period 1

Period 1 title	Treatment Phase (overall trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

One 10 mg ZED1227 capsule in the morning.

Arm type	Experimental
Investigational medicinal product name	10 mg ZED1227
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 10 mg ZED1227 capsule in the morning in fasted state.

Arm title	Arm B

Arm description:

One 50 mg ZED1227 capsule in the morning.

Arm type	Experimental
Investigational medicinal product name	50 mg ZED1227
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 50 mg ZED1227 capsule in the morning in a fasted state.

Arm title	Arm C

Arm description:

One 100 mg ZED1227 capsule in the morning.

Arm type	Experimental

Investigational medicinal product name	100 mg ZED1227
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 100 mg ZED1227 capsule in the morning in fasted state.

Arm title	Arm D

Arm description:

One placebo ZED1227 capsule in the morning.

Arm type	Placebo
Investigational medicinal product name	ZED1227 placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One placebo ZED1227 capsule in the morning in fasted state.

Number of subjects in period 1[1]	Arm A	Arm B	Arm C
Started	41	41	39
Completed	33	39	37
Not completed	8	2	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	8	2	2

Number of subjects in period 1[1]	Arm D
Started	38
Completed	30
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: n=3 no study medication dispensed because of the development of other clinical condition. n=1 lost to follow-up, medication administration uncertain, safety data incompletely available (included in safety analysis set only)

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Phase (overall trial)
Reporting group description:	
163 patients were finally randomised in one of the four treatment groups. 3 patients have been randomised but not treated. 1 patient was lost to follow-up, treatment uncertain (included in safety set only).	

Reporting group values	Treatment Phase (overall trial)	Total	
Number of subjects	159	159	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	159	159	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	41.6		
standard deviation	± 13.4	-	
Gender categorical			
Subjects of both sex were recruited in this trial.			
Units: Subjects			
Female	118	118	
Male	41	41	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
One 10 mg ZED1227 capsule in the morning.	
Reporting group title	Arm B
Reporting group description:	
One 50 mg ZED1227 capsule in the morning.	
Reporting group title	Arm C
Reporting group description:	
One 100 mg ZED1227 capsule in the morning.	
Reporting group title	Arm D
Reporting group description:	
One placebo ZED1227 capsule in the morning.	

Primary: Attenuation of gluten-induced mucosal damage

End point title	Attenuation of gluten-induced mucosal damage
End point description:	
As stipulated in the trial protocol, the primary end-point analysis included all the patients who underwent randomization and had villus height and crypt depth measurements from at least three separate villus–crypt units of sufficient quality in total from the duodenum biopsies available at both the baseline (screening) visit and the final or withdrawal visit (142 patients).	
End point type	Primary
End point timeframe:	
Within 6 weeks starting with baselines/ randomisation to Final Visit (week 6).	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	39	38	30
Units: Ratio of Villus Height to Crypt Depth				
least squares mean (confidence interval 95%)	-0.17 (-0.33 to -0.01)	-0.12 (-0.27 to 0.03)	-0.13 (-0.28 to 0.03)	-0.61 (-0.78 to -0.44)

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Arm A v Arm D

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Generalized linear model (GLM)
Parameter estimate	Mean difference (final values)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.73

Statistical analysis title	Primary analysis
Comparison groups	Arm B v Arm D
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Mean difference (final values)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.77

Statistical analysis title	Primary analysis
Comparison groups	Arm C v Arm D
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Generalized linear model
Parameter estimate	Mean difference (final values)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.77

Secondary: Intraepithelial lymphocyte density

End point title	Intraepithelial lymphocyte density

End point description:

End point type	Secondary

End point timeframe:

Within 6 weeks starting with baselines/ randomisation to Final Visit (week 6).

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	35	39	38	31
Units: No. of cells per 100 epithelial cells				
least squares mean (confidence interval 95%)	8.3 (5.0 to 11.7)	6.9 (3.7 to 10.1)	1.5 (-1.8 to 4.7)	11.0 (7.4 to 14.6)

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Arm A v Arm D
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	2.2

Statistical analysis title	Secondary analysis
Comparison groups	Arm B v Arm D
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	0.6

Statistical analysis title	Secondary analysis
Comparison groups	Arm C v Arm D
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.4
upper limit	-4.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were assessed at all interim visits (week 2, week 4 and week 6 and at the Follow up visit week 10).

Adverse event reporting additional description:

Treatment-Emergent Adverse Events

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Arm A

Reporting group description:

One 10 mg ZED1227 capsule in the morning in fasted state.

Reporting group title	Arm B

Reporting group description:

One 50 mg ZED1227 capsule in the morning in fasted state.

Reporting group title	Arm C

Reporting group description:

One 100 mg ZED1227 capsule in the morning in fasted state.

Reporting group title	Arm D

Reporting group description:

One Placebo ZED1227 capsule in the morning in fasted state.

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Ventricular extrasystoles	Additional description: SAE considered to be related to study treatment, patient discontinued trial.		
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	0 / 40 (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			
Migraine with aura	Additional description: SAE considered to be study related, patient discontinued the trial.		
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Ventricular extrasystoles	Additional description: SAE considered to be related to study treatment, patient discontinued trial.		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine with aura	Additional description: SAE considered to be study related, patient discontinued the trial.		
subjects affected / exposed	0 / 38 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 41 (80.49%)	30 / 41 (73.17%)	32 / 40 (80.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 41 (4.88%)	6 / 41 (14.63%)	2 / 40 (5.00%)
occurrences (all)	2	6	2
Influenza			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			

subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Investigations			
Blood folate decreased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Blood zinc decreased			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	1 / 40 (2.50%)
occurrences (all)	1	2	1
Lipase increased			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Transferrin saturation decreased			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	3	1	2
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 41 (21.95%)	13 / 41 (31.71%)	10 / 40 (25.00%)
occurrences (all)	10	14	14
Migraine			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Migraine with aura			

subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	4 / 40 (10.00%)
occurrences (all)	2	4	4
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)	5 / 41 (12.20%)	5 / 40 (12.50%)
occurrences (all)	3	7	5
Abdominal pain lower			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	3 / 40 (7.50%)
occurrences (all)	2	2	3
Aphthous ulcer			
subjects affected / exposed	2 / 41 (4.88%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	1 / 40 (2.50%)
occurrences (all)	2	3	1
Diarrhoea			
subjects affected / exposed	4 / 41 (9.76%)	5 / 41 (12.20%)	6 / 40 (15.00%)
occurrences (all)	4	6	9
Dyspepsia			

subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	2 / 40 (5.00%)
occurrences (all)	1	2	2
Eructation			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Flatulence			
subjects affected / exposed	3 / 41 (7.32%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	3	4	1
Nausea			
subjects affected / exposed	6 / 41 (14.63%)	7 / 41 (17.07%)	4 / 40 (10.00%)
occurrences (all)	6	8	4
Regurgitation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	4 / 41 (9.76%)	3 / 41 (7.32%)	1 / 40 (2.50%)
occurrences (all)	4	3	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Myalgia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Cystitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	2	1	3
Nasopharyngitis			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	4 / 40 (10.00%)
occurrences (all)	2	4	4
Rhinitis			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	1 / 40 (2.50%)
occurrences (all)	1	2	1
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Arm D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 38 (78.95%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Influenza			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Investigations			
Blood folate decreased			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Blood zinc decreased			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Transferrin saturation decreased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	17		
Migraine			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		

Migraine with aura			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Abdominal distension			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	4		
Abdominal pain lower			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Aphthous ulcer			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Dyspepsia			

subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Eructation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	7		
Regurgitation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	0 / 38 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Infections and infestations			

Cystitis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 5		
Rhinitis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0		
Metabolism and nutrition disorders Folate deficiency subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2018	Amendment 01 (globally amendment dated 08.03.2018) forming Integrated Protocol Version 2.0/08.03.2018
20 December 2018	Amendment 02 (global amendment dated 20.12.2018) forming Integrated Protocol Version 3.0/20.12.2018

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34192430

http://www.ncbi.nlm.nih.gov/pubmed/34192435