Clinical trial results:
Double-blind, randomized, placebo-controlled, phase II dose-finding study comparing different doses of ZED1227 capsules with placebo in the treatment of non-alcoholic fatty liver disease (NAFLD) with significant fibrosis

Summary

EudraCT number	2021-002253-29
Trial protocol	ES PL DE BE
Global end of trial date	05 July 2023

Results information

Result version number	v1 (current)
This version publication date	09 August 2024
First version publication date	09 August 2024

Trial information

Trial identification

Sponsor protocol code	CEC-011/NAS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05305599
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstraße 5, Freiburg im Breisgau, Germany, 79108
Public contact	Dept. of Clinical Research&Developm, Dr. Falk Pharma GmbH, +49 49761 1514 0, zentrale@drfalkpharma.de
Scientific contact	Dept. of Clinical Research&Developm, Dr. Falk Pharma GmbH, +49 0761 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	29 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2023
Global end of trial reached?	Yes
Global end of trial date	05 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the efficacy of three doses of ZED1227 versus (vs.) placebo for the 12-week treatment of patients with NAFLD with significant fibrosis

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 4 weeks during treatment and one follow up vist at weeks after end of treatment 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	05 April 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	France: 49
Country: Number of subjects enrolled	Germany: 25
Worldwide total number of subjects	186
EEA total number of subjects	186

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)	117
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total 186 patients were included in 5 countries (Germany, Poland, Spain, France and Belgium) from April 2022 to July 2023.

Pre-assignment

Screening details:

Screening criteria: Signed informed consent • male or female, 18 and 75 years of age • Diagnosed with NAFLD and significant fibroses (stages 2 or 3). 334 patients were screened. Thereof 186 patients were randomised. Of those 177 received study medication and were included in the safety analysis set (SAF). 174 were included in FAS.

Pre-assignment period milestones

Number of subjects started	186
Number of subjects completed	174

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Randomized by mistake: 1
Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	Other: 2
Reason: Number of subjects	Missing: 1

Period 1

Period 1 title	Overall trial (treatment phase) (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

Blinding implementation details:

Blinding was achieved by the application of the same number of capsule s(ZED1227 or placebo) to each patient. Placebo capsules matched verum capsules in size, taste, and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

ZED1227 (low dose) 10 mg

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

Dosage and administration details:

1 capsule twice a day: 1 capsule in the morning and 1 capsule in the evening

Arm title	Group B

Arm description:

ZED1227 (middle dose) 25 mg

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

Dosage and administration details:

1 capsule twice a day: 1 capsule in the morning and 1 capsule in the evening

Arm title	Group C

Arm description:

ZED1227 (high dose) 50 mg

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

Dosage and administration details:

1 capsule twice a day: 1 capsule in the morning and 1 capsule in the evening

Arm title	Group D

Arm description:

Placebo

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

Dosage and administration details:

1 capsule twice a day: 1 capsule in the morning and 1 capsule in the evening

Number of subjects in period 1[1]	Group A	Group B	Group C
Started	41	43	45
Completed	40	42	43
Not completed	1	1	2
Lack of Compliance	-	1	-
Physician decision	-	-	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-

Number of subjects in period 1[1]	Group D
Started	45
Completed	43
Not completed	2

Lack of Compliance	-
Physician decision	-
Consent withdrawn by subject	1
Adverse event, non-fatal	1

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: To meet the requirements of the system, the number of patients entered in the trial period refects the FAS population. These are the patients, that were randomized, received study medication and at least one ample for analysis of the primary endpoint was available.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (treatment phase)

Reporting group description: -

Reporting group values	Overall trial (treatment phase)	Total	
Number of subjects	174	174	
Age categorical Units: Subjects			
Adults (18-64 years)	111	111	
From 65-75 years	63	63	
Age continuous Units: years			
median	63.0		
full range (min-max)	18 to 74	-	
Gender categorical Units: Subjects			
Female	78	78	
Male	96	96	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who received at least one dose of the IMP and had baseline serum levels of PRO-C3 collected.

Reporting group values	FAS		
Number of subjects	174		
Age categorical Units: Subjects			
Adults (18-64 years)	111		
From 65-75 years	63		
Age continuous Units: years			
median	63		
full range (min-max)	18 to 74		
Gender categorical Units: Subjects			
Female	78		
Male	96		

End points

End points reporting groups

Reporting group title	Group A
Reporting group description: ZED1227 (low dose) 10 mg	
Reporting group title	Group B
Reporting group description: ZED1227 (middle dose) 25 mg	
Reporting group title	Group C
Reporting group description: ZED1227 (high dose) 50 mg	
Reporting group title	Group D
Reporting group description: Placebo	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: All randomized patients who received at least one dose of the IMP and had baseline serum levels of PRO-C3 collected.	

Primary: Primary endpoint: relative change in PRO-C3

End point title	Primary endpoint: relative change in PRO-C3
End point description: The relative change (%) of serum levels of released N-terminal propeptide of type III collagen (PRO-C3)	
End point type	Primary
End point timeframe: Between baseline and the end-of-treatment (EOT)/withdrawal visit	

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	43	45	45
Units: Change of PRO-C3				
least squares mean (standard error)	0.3 (± 3.56)	10.2 (± 3.46)	-1.2 (± 3.48)	6.8 (± 3.37)

Statistical analyses

Statistical analysis title	Primary efficacy endpoint FAS
Comparison groups	Group A v Group D

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0921
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.12
upper limit	3.1

Statistical analysis title	Primary efficacy endpoint FAS
Comparison groups	Group B v Group D
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5863
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.16
upper limit	12.92

Statistical analysis title	Primary efficacy endpoint FAS
Comparison groups	Group C v Group D
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0479
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.57
upper limit	1.43

Secondary: Secondary Endpoint: relative change of ELF Score

End point title	Secondary Endpoint: relative change of ELF Score

End point description:

End point type	Secondary

End point timeframe:

Between baseline and the end-of-treatment (EOT)/withdrawal visit

End point values	Group A	Group B	Group C	Group D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	43	45	45
Units: %				
arithmetic mean (standard deviation)	0.70 (± 6.023)	1.68 (± 5.431)	-0.98 (± 5.562)	0.26 (± 5.514)

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	0[1]			
Units: %				
arithmetic mean (standard deviation)	()			

Notes:

[1] - No determined for whole population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were assessed from BL visit, at interim visits (week 4 and week 8), at the end of treatment visit week 12 and at the Follow up visit week 16 .	
Adverse event reporting additional description:	
Treatment-Emergent and Post-Treatment Adverse Events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Group A
Reporting group description:	
ZED1227 (low dose) 10 mg	
Reporting group title	Group B
Reporting group description:	
ZED1227 (middle dose) 25 mg	
Reporting group title	Group C
Reporting group description:	
ZED1227 (high dose) 50 mg	
Reporting group title	Group D
Reporting group description:	
Placebo	

Serious adverse events	Group A	Group B	Group C
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 42 (4.76%)	3 / 45 (6.67%)	1 / 45 (2.22%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Dilated cardiomyopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (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			
Hemorrhoidal hemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorectal varices			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Diverticulum intestinal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Inguinal hernia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal hemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Sleep apnea syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (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
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group D		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Dilated cardiomyopathy			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Hemorrhoidal hemorrhage			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anorectal varices			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal hemorrhage			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Sleep apnea syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Lumbar spinal stenosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 45 (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: 2 %

Non-serious adverse events	Group A	Group B	Group C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 42 (73.81%)	26 / 45 (57.78%)	27 / 45 (60.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Monoclonal gammopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Hyperhidrosis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 45 (4.44%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Influenza like illness			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Swelling face			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Epistaxis			

subjects affected / exposed	2 / 42 (4.76%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	2	0	0
Asthma			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Catarrh			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Sleep disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Lipase increased			

subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Blood insulin increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Chest X-ray abnormal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Glutamate dehydrogenase increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
High density lipoprotein decreased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Low density lipoprotein increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Prothrombin time shortened			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Smear cervix			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Arthropod bite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Face injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Hydrolcele			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial Fibrllation			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Atrioventricular block first degree			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Dilated cardiomyopathy			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 42 (7.14%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	3	1	1
Paraesthesia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Disturbance in attention			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Restless leg			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Anaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Vertigo positional			

subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Astigmatism			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Blepharitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Eye inflammation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Ocular hypertension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Ulcerative keratitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	5 / 42 (11.90%)	2 / 45 (4.44%)	3 / 45 (6.67%)
occurrences (all)	5	2	3
Constipation			
subjects affected / exposed	2 / 42 (4.76%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	2	1	0
Flatulence			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	3 / 45 (6.67%)
occurrences (all)	1	0	3
Abdominal distension			

subjects affected / exposed	1 / 42 (2.38%)	3 / 45 (6.67%)	0 / 45 (0.00%)
occurrences (all)	1	3	0
Nausea			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Abdominal pain lower			
subjects affected / exposed	0 / 42 (0.00%)	2 / 45 (4.44%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Anorectal varices			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Breath odour			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Chronic gastritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Defaecation urgency			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Diverticulum intestinal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dry mouth			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Duodenogastr			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Eructation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Faeces discoloured			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Inguinal hernia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Oesophageal ulcer			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pancreatitis chronic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Proctalgia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Rectal tenesmus			

subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Regurgitation			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Tongue discomfort			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 42 (7.14%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	3	2	1
Rash			
subjects affected / exposed	2 / 42 (4.76%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	2	1	0
Acne			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Erythema			

subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Psoriasis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Renal colic			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	2
Osteoarthritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			

subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	1	1	0
Bursitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Intervertebral disc disorder			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Synovial cyst			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Torticollis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 42 (11.90%)	1 / 45 (2.22%)	2 / 45 (4.44%)
occurrences (all)	5	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	3 / 45 (6.67%)
occurrences (all)	1	1	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	1	1	1

Bronchitis			
subjects affected / exposed	3 / 42 (7.14%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	3	0	1
Urinary tract infection			
subjects affected / exposed	2 / 42 (4.76%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	3	2	1
Cystitis			
subjects affected / exposed	0 / 42 (0.00%)	2 / 45 (4.44%)	0 / 45 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	2 / 42 (4.76%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	3	0	0
Rhinitis			
subjects affected / exposed	2 / 42 (4.76%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	2	0	0
Tonsillitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 45 (2.22%)	1 / 45 (2.22%)
occurrences (all)	1	1	1
Abscess limb			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Infected bite			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1

Lyme disease			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	2 / 45 (4.44%)
occurrences (all)	0	0	2
Diabetes			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Folate deficiency			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	1 / 45 (2.22%)
occurrences (all)	0	0	1
Gout			

subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 45 (0.00%)	0 / 45 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 42 (0.00%)	1 / 45 (2.22%)	0 / 45 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Group D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 45 (73.33%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroma			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Monoclonal gammopathy			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Surgical and medical procedures			
Hyperhidrosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Skin burning sensation			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Swelling face			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		

Epistaxis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Catarrh			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Sleep disorder			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Lipase increased			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Alanine aminotransferase increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Blood insulin increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Blood triglycerides increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Chest X-ray abnormal				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Glutamate dehydrogenase increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
High density lipoprotein decreased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
International normalised ratio increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Low density lipoprotein increased				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Prothrombin time shortened				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Smear cervix				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Arthropod bite			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hand fracture			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Hydrolcele			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial Fibrllation			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Atrioventricular block first degree			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Dilated cardiomyopathy			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Restless leg			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Vertigo positional			

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Eye disorders			
Astigmatism			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blepharitis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Eye inflammation			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Ocular hypertension			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Ulcerative keratitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	6 / 45 (13.33%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Abdominal distension			

subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Abdominal pain upper				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Abdominal pain lower				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Abdominal pain				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Vomiting				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Anorectal varices				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Breath odour				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Chronic gastritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Defaecation urgency				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Diverticulum intestinal				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Duodenogastr				

subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Faeces discoloured				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Gastritis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Haemorrhoidal haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Inguinal hernia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Oesophageal ulcer				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Pancreatitis chronic				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Proctalgia				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Rectal haemorrhage				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Rectal tenesmus				

subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Regurgitation subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Tongue discomfort subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Toothache subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Acne subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Alopecia subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
Dry skin subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0		
Erythema			

subjects affected / exposed occurrences (all) Psoriasis subjects affected / exposed occurrences (all) Rash erythematous subjects affected / exposed occurrences (all) Rash pruritic subjects affected / exposed occurrences (all) Skin irritation subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1 0 / 45 (0.00%) 0		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Pollakiuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Renal colic subjects affected / exposed occurrences (all)	 1 / 45 (2.22%) 1 0 / 45 (0.00%) 0 1 / 45 (2.22%) 1 0 / 45 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all) Pain in extremity	 2 / 45 (4.44%) 2 0 / 45 (0.00%) 0		

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Bursitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Intervertebral disc disorder			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Synovial cyst			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Torticollis			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		

Bronchitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Urinary tract infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Cystitis				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Pneumonia				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Tonsillitis				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			
Conjunctivitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Abscess limb				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Infected bite				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			

Lyme disease				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Otitis externa				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Periodontitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Respiratory tract infection				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Metabolism and nutrition disorders				
Vitamin D deficiency				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Diabetes				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Diabetes mellitus inadequate control				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Diabetic metabolic decompensation				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Folate deficiency				
subjects affected / exposed	0 / 45 (0.00%)			
occurrences (all)	0			
Gout				

subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 45 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2023	One global amendment dated 11 Jan 2023 was made to the original protocol, dated 11 Oct 2021

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported