



Clinical trial results:

A multicenter Phase II, open label, single arm study to evaluate the efficacy and safety of ruxolitinib in the treatment of anemic myelofibrosis subjects

Summary

EudraCT number	2016-003552-75
Trial protocol	HU GR DE ES AT BG BE IT
Global end of trial date	15 February 2019

Results information

Result version number	v1 (current)
This version publication date	29 February 2020
First version publication date	29 February 2020

Trial information

Trial identification

Sponsor protocol code	CINC424A2411
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02966353
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2019
Global end of trial reached?	Yes
Global end of trial date	15 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the spleen length response rate at Week 24

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Turkey: 3
Worldwide total number of subjects	51
EEA total number of subjects	37

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)	20
From 65 to 84 years	28
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening evaluations were performed to determine the eligibility for the study and establish a baseline prior to dosing.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All Subjects
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Arm description:

10 mg BID (2 tablets of 5mg) was self-administered as starting dose for all patients. This dose was maintained for the first 12 weeks and titrated up thereafter unless they had met criteria for dose hold or dose reduction. Dose was to have been increased or decreased per standardized dosing paradigm and not to have exceeded 25 mg bid.

Arm type	Experimental
Investigational medicinal product name	ruxolitinib
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ruxolitinib 10 mg b.i.d. (two 5-mg tablets of ruxolitinib taken orally) was self-administered as the starting dose for treatment. This dose was maintained for the first 12 weeks of the study and up-titrated thereafter unless the subject met criteria for dose hold or dose reduction

Number of subjects in period 1	All Subjects
Started	51
Completed after data cutoff	1 ^[1]
Completed	29
Not completed	22
Adverse event, serious fatal	4
Consent withdrawn by subject	7
Physician decision	3
Adverse event, non-fatal	4
Protocol deviation	2
Progressive disease	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One participant completed one week after 30 days follow up for safety

Baseline characteristics

Reporting groups

Reporting group title	All Subjects
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Reporting group description:

10 mg BID (2 tablets of 5mg) was self-administered as starting dose for all patients. This dose was maintained for the first 12 weeks and titrated up thereafter unless they had met criteria for dose hold or dose reduction. Dose was to have been increased or decreased per standardized dosing paradigm and not to have exceeded 25 mg bid.

Reporting group values	All Subjects	Total	
Number of subjects	51	51	
Age Categorical			
Units:			
<=18 years	0	0	
Between 18 and 65 years	20	20	
>=65 years	31	31	
Sex: Female, Male			
Units:			
Female	21	21	
Male	30	30	
Race/Ethnicity, Customized			
Units: Subjects			
White	48	48	
Asian	3	3	
Type of myelofibrosis-n			
Units: Subjects			
Primary myelofibrosis	34	34	
Post-polycythemia vera myelofibrosis	6	6	
Post-essential thrombocythemia myelofibrosis	11	11	
Bone Marrow Fibrosis Grade at Diagnosis			
Units: Subjects			
Grade 0	0	0	
Grade 1	6	6	
Grade 2	26	26	
Grade 3	18	18	
Missing	1	1	
Constitutional symptoms			
Units: Subjects			
Present	29	29	
Absent	22	22	
Time since initial diagnosis			
Units: months			
arithmetic mean	32.9		
standard deviation	± 44.16	-	
Palpable spleen length (cm) below costal margin			
Units: spleen length - centimeters			

arithmetic mean	11.7		
standard deviation	± 6.20	-	
Hemoglobin level			
Units: g/dL			
arithmetic mean	88.6		
standard deviation	± 9.74	-	
Platelets			
Units: 10E9/L			
arithmetic mean	236.7		
standard deviation	± 176.88	-	

End points

End points reporting groups

Reporting group title	All Subjects
Reporting group description: 10 mg BID (2 tablets of 5mg) was self-administered as starting dose for all patients. This dose was maintained for the first 12 weeks and titrated up thereafter unless they had met criteria for dose hold or dose reduction. Dose was to have been increased or decreased per standardized dosing paradigm and not to have exceeded 25 mg bid.	

Primary: Percentage of participants with at least 50% reduction in spleen length from baseline at Week 24

End point title	Percentage of participants with at least 50% reduction in spleen length from baseline at Week 24 ^[1]
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End point description:

Percentage of participants achieving a 50% reduction in spleen length at week 24. For subjects with palpable spleen at baseline and non-palpable at post-baseline, the post-baseline spleen are imputed as 0. Subjects who had palpable, but missing spleen length at baseline is excluded from the analysis. Subjects with missing spleen length at Week 24 or who withdraw earlier from the study are considered as a non-responder. The 95% CI is computed using exact Clopper-Pearson method.

End point type	Primary
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End point timeframe:

Baseline up to week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal analysis was performed

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (confidence interval 95%)	56.0 (41.3 to 70.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least 50% reduction in spleen length from baseline at Week 48

End point title	Percentage of participants with at least 50% reduction in spleen length from baseline at Week 48
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End point description:

Percentage of participants achieving a 50% reduction in spleen length at week 48. For subjects with palpable spleen at baseline and non-palpable at post-baseline, the post-baseline spleen is imputed as 0. Subjects who had palpable, but missing spleen length at baseline is excluded from the analysis. Subjects with missing spleen length at Week 48 or who withdraw earlier from the study are considered as a non-responder. The 95% CI is computed using exact Clopper-Pearson method.

End point type	Secondary
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End point timeframe:
Baseline up to week 48

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (confidence interval 95%)	36.0 (22.9 to 50.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants by spleen length reduction from baseline category at Week 24 and Week 48

End point title	Percentage of participants by spleen length reduction from baseline category at Week 24 and Week 48
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End point description:

The edge of the spleen shall be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. For subjects with palpable spleen at baseline and non-palpable at post-baseline, the post-baseline spleen is imputed as 0.

End point type	Secondary
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End point timeframe:

baseline, weeks 24 and 48

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: percentage of participants				
number (not applicable)				
Week 24 ≤ -50% n=43	65.1			
Week 24 -50%, -25% n=43	11.6			
Week 24 -25%, -5% n=43	9.3			
Week 24 -5%, 5% n=43	4.7			
Week 24 5%, 25% n=43	9.3			
Week 24 25%, 50% n=43	0			
Week 24 >50% n=43	0			
Week 24 remained non-palpable n=43	0			
Week 24 became palpable n=43	0			
Week 48 ≤ -50% n=36	50.0			
Week 48 -50%, -25% n=36	22.2			
Week 48 -25%, -5% n=36	16.7			
Week 48 -5%, 5% n=36	5.6			

Week 48 5%, 25% n=36	2.8			
Week 48 25%, 50% n=36	2.8			
Week 48 >50% n=36	0			
Week 48 remained non-palpable n=36	0			
Week 48 became palpable n=36	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with at least a 50% reduction in Myelofibrosis 7 Item Symptom Scale (MF-7) and Myelofibrosis Symptom Assessment Form (MFSAF) at Week 24

End point title	Percentage of participants with at least a 50% reduction in Myelofibrosis 7 Item Symptom Scale (MF-7) and Myelofibrosis Symptom Assessment Form (MFSAF) at Week 24
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End point description:

The MF-7 is a disease specific questionnaire comprised of 7 items that measures the severity of seven of the most prevalent associated symptoms including: tiredness, early satiety, abdominal discomfort, night sweats, itching (pruritus), bone pain (diffuse not joint or arthritis) and pain under ribs on left side. Each item was scored on a scale ranging from 0 (absent) to 10 (worst imaginable). The MF-7 score is computed as the sum of the observed scores in the individual items to achieve a 0 to 70 score. There would be one recall period of 24 hours used in this questionnaire. A separate question on Inactivity was to be measured for severity of this symptom on a scale from 0 (absent) to 10 (worst imaginable). This would allow the computation of the MFSAF v2.0 questionnaire results, as 6 out of 7 items in the latter PRO are in overlap with MF7 (they also share same 0-10 range Likert scale and ascending order, absent to worst imaginable).

End point type	Secondary
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End point timeframe:

Baseline and week 24

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of participants				
number (confidence interval 95%)				
MF-7 Total Symptom score	51.1 (35.8 to 66.3)			
Modified MFSAF v2.0 Total symptom score	55.6 (40.0 to 70.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (PGIC) at Week 24 and Week 48

End point title	Patient Global Impression of Change (PGIC) at Week 24 and Week 48
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End point description:

The PGIC is comprised of a single question intended to measure a subject's perspective of improvement or deterioration over time relative to treatment. The PGIC uses a seven-point scale where '1' equals very much improved and '7' equals very much worse.

End point type	Secondary
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End point timeframe:

Baseline up to week 48

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Participants				
Week 24 n=41 Very much improved	5			
Week 24 n=41 Much improved	20			
Week 24 n=41 Minimally improved	9			
Week 24 n=41 No change	6			
Week 24 n=41 Minimally worse	1			
Week 24 n=41 Much worse	0			
Week 24 n=41 Very much worse	0			
Week 48 n=33 Very much improved	5			
Week 48 n=33 Much improved	15			
Week 48 n=33 Minimally improved	9			
Week 48 n=33 No change	4			
Week 48 n=33 Minimally worse	0			
Week 48 n=33 Much worse	0			
Week 48 n=33 Very much worse	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants transfusion independency from baseline up to week 96

End point title	Percentage of participants transfusion independency from baseline up to week 96
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End point description:

Percentage is based on number of subjects who are transfusion dependent at baseline. Transfusion dependence (TD) is defined as subjects receiving 6 or more units of transfusions 12 weeks prior to baseline. Transfusion independence (TI) rate is defined as subjects who are transfusion dependent at baseline and require no unit of transfusion for ≥ 12 weeks at any time during the study. Transfusion response rate is defined as subjects who are TD at baseline and have 5 or less units of transfusion for ≥ 12 weeks at any time during the study.

End point type	Secondary
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End point timeframe:

Baseline up to week 96

End point values	All Subjects			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (not applicable)				
Transfusion dependent participants at baseline	18.0			
Week 24 transfusion independent rate	0.0			
Week 24 transfusion responder rate	44.4			
Week 48 transfusion independent rate	0.0			
Week 48 transfusion responder rate	66.7			
Week 72 transfusion independent rate	0.0			
Week 72 transfusion responder rate	66.7			
Week 96 transfusion independent rate	0.0			
Week 96 transfusion responder rate	66.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 100 weeks

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 51 (33.33%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac failure acute			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Haemolytic anaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			

subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	2 / 51 (3.92%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 1			
Respiratory syncytial virus bronchitis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Staphylococcal bacteraemia				

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 51 (84.31%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Keratoacanthoma			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	6		
Hypertension			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Peripheral venous disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	7		
Fatigue			

subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Chest discomfort			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Early satiety			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Catarrh			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Dyspnoea exertional			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		
Pulmonary mass			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pulmonary oedema			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	8		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	7		
Blood alkaline phosphatase increased			

subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		
Blood creatinine increased			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	6		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 51 (11.76%)		
occurrences (all)	8		
Platelet count decreased			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Amylase increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood phosphorus increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood potassium increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Blood uric acid increased			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		

Weight increased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all) Subcutaneous haematoma subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2 1 / 51 (1.96%) 1 1 / 51 (1.96%) 1		
Cardiac disorders Arrhythmia subjects affected / exposed occurrences (all) Atrial fibrillation subjects affected / exposed occurrences (all) Cardiac disorder subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1 2 / 51 (3.92%) 3 1 / 51 (1.96%) 1		
Nervous system disorders Cerebrovascular accident subjects affected / exposed occurrences (all) Cognitive disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1 1 / 51 (1.96%) 1 1 / 51 (1.96%) 1 1 / 51 (1.96%) 1		

Encephalopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 51 (33.33%)		
occurrences (all)	51		
Thrombocytopenia			
subjects affected / exposed	14 / 51 (27.45%)		
occurrences (all)	18		
Coagulopathy			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Haemorrhagic disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Leukocytosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Eye disorders			
Retinal haemorrhage subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Retinal vascular disorder subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3		
Constipation subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 51 (11.76%) 7		
Abdominal distension subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Inguinal hernia subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1		
Nausea subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2		
Rectal haemorrhage			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	5		
Hyperhidrosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Mucocutaneous haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Chronic kidney disease			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Dysuria			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Nocturia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pollakiuria			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Bursitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Connective tissue disorder			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Myalgia			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	5		
Oral herpes			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 51 (9.80%)		
occurrences (all)	6		
Bacteraemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		
Dysentery			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

Herpes zoster			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Klebsiella bacteraemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Nasal herpes			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Otitis externa			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Gout			

subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	3		
Haemosiderosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		
Hypoglycaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Lactic acidosis			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported