



Clinical trial results:

A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia

Summary

EudraCT number	2010-023015-33
Trial protocol	GB BE SE IT DE FR
Global end of trial date	18 January 2018

Results information

Result version number	v1 (current)
This version publication date	03 February 2019
First version publication date	03 February 2019

Trial information

Trial identification

Sponsor protocol code	114375
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01376310
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, 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	18 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide continued treatment with trametinib (GSK1120212) for subjects who had previously participated in a trametinib study and who continued to receive clinical benefit as well as have an acceptable safety profile with trametinib.

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	02 November 2010
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	Canada: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	159
EEA total number of subjects	4

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)	92
From 65 to 84 years	66
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

159 subjects received treatment with GSK1120212 and were included in the safety set.

Pre-assignment

Screening details:

Continued treatment with GSK1120212 was provided for subjects who had previously participated in a GSK1120212 study and who continued to receive clinical benefit as well as have an acceptable safety profile with GSK1120212.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.

Arm type	Experimental
Investigational medicinal product name	GSK1120212
Investigational medicinal product code	GSK1120212
Other name	Trametinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of study treatment administered to subjects were individualized based upon the dose/regimen received during their participation in the parent study at the time of transition to the rollover study.

Arm title	Cohort B
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Arm description:

Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.

Arm type	Experimental
Investigational medicinal product name	GSK1120212
Investigational medicinal product code	GSK1120212
Other name	Trametinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of study treatment administered to subjects were individualized based upon the dose/regimen received during their participation in the parent study at the time of transition to the rollover study.

Number of subjects in period 1	Cohort A	Cohort B
Started	126	33
Completed	90	22
Not completed	36	11
Study closed/terminated	1	2
Consent withdrawn by subject	8	2
Physician decision	26	7
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort A
Reporting group description: Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.	
Reporting group title	Cohort B
Reporting group description: Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	126	33	159
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	74	18	92
From 65-84 years	51	15	66
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	61.0	61.7	-
standard deviation	± 12.34	± 11.30	
Sex: Female, Male Units: Subjects			
Female	66	17	83
Male	60	16	76
Race/Ethnicity, Customized Units: Subjects			
White	116	28	144
Black	6	3	9
Asian	2	2	4
Native American/Pacific Islander	2	0	2

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description: Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.	
Reporting group title	Cohort B
Reporting group description: Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.	

Primary: Number of participants with adverse events

End point title	Number of participants with adverse events ^[1]
End point description: Number of participants with adverse events as a measure of safety and tolerability	
End point type	Primary
End point timeframe: Until 30 days after the last dose of study treatment. Subjects may have continued to receive study treatment until disease progression, death, unacceptable toxicity or until locally commercially available. The maximum duration of exposure was 76 months.	

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 statistical analyses were performed.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	33		
Units: Participants				
Adverse Events	119	30		
Treatment-Related Adverse Events	101	26		
Serious Adverse Events	26	13		
Treatment-Related Serious Adverse Events	8	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Cohort A
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Reporting group description:

Subjects on GSK1120212 Monotherapy and have been treated less than 24 weeks in their parent study.

Reporting group title	Cohort B
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Reporting group description:

Subjects on GSK1120212 monotherapy who have been treated for 24 weeks or greater in their parent study. Also, subjects entering this study from any GSK1120212 combo trial.

Reporting group title	All Patients
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Reporting group description:

All Patients

Serious adverse events	Cohort A	Cohort B	All Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 126 (20.63%)	13 / 33 (39.39%)	39 / 159 (24.53%)
number of deaths (all causes)	13	3	16
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	2 / 126 (1.59%)	0 / 33 (0.00%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 126 (1.59%)	2 / 33 (6.06%)	4 / 159 (2.52%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Psychiatric disorders			
Adjustment disorder with depressed mood			

subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	2 / 126 (1.59%)	1 / 33 (3.03%)	3 / 159 (1.89%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac arrest			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Left ventricular dysfunction			
subjects affected / exposed	1 / 126 (0.79%)	1 / 33 (3.03%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 126 (0.79%)	1 / 33 (3.03%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 126 (1.59%)	0 / 33 (0.00%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 126 (0.79%)	1 / 33 (3.03%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 33 (3.03%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	2 / 126 (1.59%)	0 / 33 (0.00%)	2 / 159 (1.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Moraxella infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 126 (1.59%)	3 / 33 (9.09%)	5 / 159 (3.14%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 33 (3.03%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 126 (0.79%)	0 / 33 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A	Cohort B	All Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 126 (91.27%)	28 / 33 (84.85%)	143 / 159 (89.94%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 126 (1.59%)	2 / 33 (6.06%)	4 / 159 (2.52%)
occurrences (all)	2	2	4
Hypertension			
subjects affected / exposed	7 / 126 (5.56%)	0 / 33 (0.00%)	7 / 159 (4.40%)
occurrences (all)	7	0	7
General disorders and administration site conditions			
Chills			
subjects affected / exposed	10 / 126 (7.94%)	2 / 33 (6.06%)	12 / 159 (7.55%)
occurrences (all)	13	2	15
Fatigue			

subjects affected / exposed	43 / 126 (34.13%)	3 / 33 (9.09%)	46 / 159 (28.93%)
occurrences (all)	47	3	50
Mucosal inflammation			
subjects affected / exposed	7 / 126 (5.56%)	4 / 33 (12.12%)	11 / 159 (6.92%)
occurrences (all)	10	7	17
Non-cardiac chest pain			
subjects affected / exposed	4 / 126 (3.17%)	2 / 33 (6.06%)	6 / 159 (3.77%)
occurrences (all)	4	2	6
Oedema			
subjects affected / exposed	5 / 126 (3.97%)	2 / 33 (6.06%)	7 / 159 (4.40%)
occurrences (all)	5	2	7
Oedema peripheral			
subjects affected / exposed	27 / 126 (21.43%)	6 / 33 (18.18%)	33 / 159 (20.75%)
occurrences (all)	33	7	40
Pyrexia			
subjects affected / exposed	10 / 126 (7.94%)	3 / 33 (9.09%)	13 / 159 (8.18%)
occurrences (all)	12	4	16
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 126 (9.52%)	3 / 33 (9.09%)	15 / 159 (9.43%)
occurrences (all)	13	3	16
Dyspnoea			
subjects affected / exposed	17 / 126 (13.49%)	5 / 33 (15.15%)	22 / 159 (13.84%)
occurrences (all)	18	5	23
Dyspnoea exertional			
subjects affected / exposed	2 / 126 (1.59%)	2 / 33 (6.06%)	4 / 159 (2.52%)
occurrences (all)	2	2	4
Epistaxis			
subjects affected / exposed	5 / 126 (3.97%)	2 / 33 (6.06%)	7 / 159 (4.40%)
occurrences (all)	6	2	8
Nasal congestion			
subjects affected / exposed	8 / 126 (6.35%)	0 / 33 (0.00%)	8 / 159 (5.03%)
occurrences (all)	10	0	10
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 126 (6.35%) 8	1 / 33 (3.03%) 1	9 / 159 (5.66%) 9
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	7 / 126 (5.56%) 8	1 / 33 (3.03%) 1	8 / 159 (5.03%) 9
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	9 / 126 (7.14%) 9	1 / 33 (3.03%) 1	10 / 159 (6.29%) 10
Blood creatinine increased subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	2 / 33 (6.06%) 2	4 / 159 (2.52%) 4
Weight decreased subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	2 / 33 (6.06%) 3	4 / 159 (2.52%) 5
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 126 (1.59%) 2	2 / 33 (6.06%) 2	4 / 159 (2.52%) 4
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	12 / 126 (9.52%) 15	3 / 33 (9.09%) 3	15 / 159 (9.43%) 18
Dysgeusia subjects affected / exposed occurrences (all)	8 / 126 (6.35%) 8	1 / 33 (3.03%) 1	9 / 159 (5.66%) 9
Headache subjects affected / exposed occurrences (all)	9 / 126 (7.14%) 11	3 / 33 (9.09%) 3	12 / 159 (7.55%) 14
Migraine subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	2 / 33 (6.06%) 2	2 / 159 (1.26%) 2
Paraesthesia subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	2 / 33 (6.06%) 2	2 / 159 (1.26%) 2
Sciatica			

subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	2 / 33 (6.06%) 2	2 / 159 (1.26%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	15 / 126 (11.90%) 15	3 / 33 (9.09%) 3	18 / 159 (11.32%) 18
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 126 (0.00%) 0	2 / 33 (6.06%) 2	2 / 159 (1.26%) 2
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	6 / 126 (4.76%) 6	5 / 33 (15.15%) 8	11 / 159 (6.92%) 14
Ascites subjects affected / exposed occurrences (all)	5 / 126 (3.97%) 5	2 / 33 (6.06%) 2	7 / 159 (4.40%) 7
Constipation subjects affected / exposed occurrences (all)	14 / 126 (11.11%) 16	7 / 33 (21.21%) 7	21 / 159 (13.21%) 23
Diarrhoea subjects affected / exposed occurrences (all)	36 / 126 (28.57%) 44	12 / 33 (36.36%) 19	48 / 159 (30.19%) 63
Dry mouth subjects affected / exposed occurrences (all)	13 / 126 (10.32%) 13	1 / 33 (3.03%) 1	14 / 159 (8.81%) 14
Dysphagia subjects affected / exposed occurrences (all)	1 / 126 (0.79%) 1	2 / 33 (6.06%) 2	3 / 159 (1.89%) 3
Nausea subjects affected / exposed occurrences (all)	33 / 126 (26.19%) 38	7 / 33 (21.21%) 11	40 / 159 (25.16%) 49
Stomatitis subjects affected / exposed occurrences (all)	10 / 126 (7.94%) 10	2 / 33 (6.06%) 2	12 / 159 (7.55%) 12
Vomiting			

subjects affected / exposed occurrences (all)	28 / 126 (22.22%) 30	6 / 33 (18.18%) 11	34 / 159 (21.38%) 41
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	35 / 126 (27.78%)	1 / 33 (3.03%)	36 / 159 (22.64%)
occurrences (all)	45	1	46
Dry skin			
subjects affected / exposed	15 / 126 (11.90%)	2 / 33 (6.06%)	17 / 159 (10.69%)
occurrences (all)	20	2	22
Nail disorder			
subjects affected / exposed	1 / 126 (0.79%)	3 / 33 (9.09%)	4 / 159 (2.52%)
occurrences (all)	1	3	4
Pruritus			
subjects affected / exposed	12 / 126 (9.52%)	4 / 33 (12.12%)	16 / 159 (10.06%)
occurrences (all)	12	5	17
Rash			
subjects affected / exposed	28 / 126 (22.22%)	7 / 33 (21.21%)	35 / 159 (22.01%)
occurrences (all)	37	10	47
Rash maculo-papular			
subjects affected / exposed	23 / 126 (18.25%)	5 / 33 (15.15%)	28 / 159 (17.61%)
occurrences (all)	25	6	31
Skin fissures			
subjects affected / exposed	5 / 126 (3.97%)	4 / 33 (12.12%)	9 / 159 (5.66%)
occurrences (all)	7	9	16
Skin ulcer			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences (all)	0	2	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 126 (0.79%)	3 / 33 (9.09%)	4 / 159 (2.52%)
occurrences (all)	1	3	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 126 (3.97%)	2 / 33 (6.06%)	7 / 159 (4.40%)
occurrences (all)	5	2	7
Back pain			

subjects affected / exposed	8 / 126 (6.35%)	1 / 33 (3.03%)	9 / 159 (5.66%)
occurrences (all)	8	2	10
Arthritis			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences (all)	0	2	2
Flank pain			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences (all)	0	2	2
Muscle spasms			
subjects affected / exposed	2 / 126 (1.59%)	3 / 33 (9.09%)	5 / 159 (3.14%)
occurrences (all)	4	3	7
Muscular weakness			
subjects affected / exposed	6 / 126 (4.76%)	2 / 33 (6.06%)	8 / 159 (5.03%)
occurrences (all)	7	4	11
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 126 (2.38%)	2 / 33 (6.06%)	5 / 159 (3.14%)
occurrences (all)	3	2	5
Folliculitis			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences (all)	0	4	4
Conjunctivitis			
subjects affected / exposed	3 / 126 (2.38%)	2 / 33 (6.06%)	5 / 159 (3.14%)
occurrences (all)	4	2	6
Furuncle			
subjects affected / exposed	0 / 126 (0.00%)	2 / 33 (6.06%)	2 / 159 (1.26%)
occurrences (all)	0	2	2
Nail infection			
subjects affected / exposed	2 / 126 (1.59%)	2 / 33 (6.06%)	4 / 159 (2.52%)
occurrences (all)	3	2	5
Paronychia			
subjects affected / exposed	2 / 126 (1.59%)	5 / 33 (15.15%)	7 / 159 (4.40%)
occurrences (all)	3	6	9
Oral herpes			
subjects affected / exposed	1 / 126 (0.79%)	2 / 33 (6.06%)	3 / 159 (1.89%)
occurrences (all)	1	3	4

Pharyngitis			
subjects affected / exposed	2 / 126 (1.59%)	2 / 33 (6.06%)	4 / 159 (2.52%)
occurrences (all)	2	2	4
Upper respiratory tract infection			
subjects affected / exposed	3 / 126 (2.38%)	4 / 33 (12.12%)	7 / 159 (4.40%)
occurrences (all)	3	4	7
Urinary tract infection			
subjects affected / exposed	6 / 126 (4.76%)	2 / 33 (6.06%)	8 / 159 (5.03%)
occurrences (all)	6	2	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 126 (14.29%)	2 / 33 (6.06%)	20 / 159 (12.58%)
occurrences (all)	19	2	21
Hypoalbuminaemia			
subjects affected / exposed	7 / 126 (5.56%)	3 / 33 (9.09%)	10 / 159 (6.29%)
occurrences (all)	7	3	10
Dehydration			
subjects affected / exposed	14 / 126 (11.11%)	2 / 33 (6.06%)	16 / 159 (10.06%)
occurrences (all)	15	2	17
Hypokalaemia			
subjects affected / exposed	6 / 126 (4.76%)	2 / 33 (6.06%)	8 / 159 (5.03%)
occurrences (all)	6	3	9

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