Clinical trial results:
A phase II, open-label, multicenter study of Dabrafenib plus Trametinib in subjects with BRAF Mutation- positive melanoma that has metastasized to the brain.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2013-003452-21
Trial protocol	ES DE IT
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	15 February 2019
First version publication date	15 February 2019

Trial information

Trial identification

Sponsor protocol code	117277

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02039947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceutical
Sponsor organisation address	CH-4002, Basel, Swaziland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceutical, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceutical, 41 613241111,

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	14 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E cutaneous melanoma with metastases to the brain confirmed by MRI, asymptomatic, without prior local therapy and ECOG score of 0 or 1 (cohort A).
IR was defined as the proportion of subjects with a confirmed intracranial complete response (CR) or partial response (PR) by investigator assessment using modified RECIST 1.1 guidelines

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	21 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	France: 55
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	125
EEA total number of subjects	97

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)	97
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A subject was considered to have completed the study if the subject died during the study treatment or follow-up period or (for subject in Cohort A) had at least 3 years follow-up from the date of first dose of study treatment at the end of the study.

All subjects achieved that definition and then the study ended.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity.

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

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules
Trametinib- 0.5 mg and 2.0 mg tablets

Investigational medicinal product name	Dabrafenib Trametinib
Investigational medicinal product code	
Other name	Dabrafenib Trametinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules
Trametinib- 0.5 mg and 2.0 mg tablets

Arm title	Cohort B

Arm description:

Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity

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

Dosage and administration details:

Dabrafenib- 50 mg and 75 mg capsules

Arm title	Cohort C
Arm description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Arm type	Experimental
Investigational medicinal product name	Dabrafenib Trametinibets
Investigational medicinal product code	
Other name	Dabrafenib Trametinibets
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Dabrafenib- 50 mg and 75 mg capsules Trametinib- 0.5 mg and 2.0 mg tablets	

Arm title	Cohort D
Arm description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Arm type	Experimental
Investigational medicinal product name	Dabrafenib Trametinib
Investigational medicinal product code	
Other name	Dabrafenib Trametinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Dabrafenib-50 mg and 75 mg capsules Trametinib-0.5 mg and 2.0 mg tablets	

Number of subjects in period 1	Cohort A	Cohort B	Cohort C
Started	76	16	16
Completed	76	16	16

Number of subjects in period 1	Cohort D
Started	17
Completed	17

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity.	
Reporting group title	Cohort B
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Reporting group title	Cohort C
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Reporting group title	Cohort D
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	

Reporting group values	Cohort A	Cohort B	Cohort C
Number of subjects	76	16	16
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)	60	12	9
From 65-84 years	16	4	7
85 years and over	0	0	0
Age Continuous Units: Years			
median	53.2	55.1	65.6
standard deviation	± 14.69	± 11.05	± 10.40
Sex: Female, Male Units: Subjects			
Female	36	6	5
Male	40	10	11
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	76	16	16

More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Cohort D	Total	
Number of subjects	17	125	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	97	
From 65-84 years	1	28	
85 years and over	0	0	
Age Continuous Units: Years			
median	47.5		
standard deviation	± 13.01	-	
Sex: Female, Male Units: Subjects			
Female	6	53	
Male	11	72	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	17	125	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description:	
Subjects will receive dabrafenib 150 milligram (mg) twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity.	
Reporting group title	Cohort B
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Reporting group title	Cohort C
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Reporting group title	Cohort D
Reporting group description:	
Subjects will receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily until evidence of disease progression, death, or unacceptable toxicity	
Subject analysis set title	All treated population
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects who receive at least one dose of study medication are comprised the All Treated subjects (ATS) population.	

Primary: Intracranial response (IR) rate

End point title	Intracranial response (IR) rate[1][2]
End point description:	
The intracranial response rate is defined as the percentage of subjects achieving a confirmed intracranial CR or PR. This is based on investigator-assessed best intracranial response.	
End point type	Primary
End point timeframe:	
From the start of treatment until disease progression or the start of new anti-cancer therapy	

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: "because only Cohort A is considered for primary efficacy analysis"

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No hypothesis testing completed for cohort B,C and D

End point values	Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Number of participants	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial response rate of cohorts B, C and D

End point title	Intracranial response rate of cohorts B, C and D[3]

End point description:

The intracranial response rate is defined as the percentage of subjects achieving a confirmed intracranial CR or PR. This is based on investigator-assessed best intracranial response. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

Approximately 2 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No hypothesis testing completed for cohort B,C and D

End point values	Cohort B	Cohort C	Cohort D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	17	
Units: Number of participants	9	7	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control for intracranial, extracranial and overall response for each cohort

End point title	Disease Control for intracranial, extracranial and overall response for each cohort

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

Approximately 2 years

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Number of participants				
Intracranial Response	59	14	12	15
Extracranial Response	60	11	15	11
Overall Response	60	14	12	15

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial response rate (ER) for each cohort

End point title	Extracranial response rate (ER) for each cohort

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

Approximately 2 years

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Number of participants	42	7	12	7

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response (OR) for each cohort

End point title	Overall response (OR) for each cohort

End point description:

Disease Control rate is defined as the percentage of subjects achieving a confirmed intracranial/extracranial/overall CR or PR or SD or Non-CR/Non-PD. This is based on investigator-assessed response. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

Approximately 2 years

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Number of participants	45	9	7	11

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of intracranial, extracranial and overall response for each cohort

End point title	Duration of intracranial, extracranial and overall response for each cohort

End point description:

Duration of intracranial, extracranial and overall response, are defined as the time from first documented evidence of CR or PR until time of first documented intracranial, extracranial, or overall disease progression. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

From first documented evidence of CR or PR until time of first documented intracranial, extracranial, or overall disease progression

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Month				
median (confidence interval 95%)				
Duration of intracranial	6.5 (4.9 to 8.6)	7.3 (3.6 to 12.6)	8.3 (1.3 to 15.0)	4.5 (2.8 to 5.9)
Duration of extracranial	10.2 (5.8 to 9999)	9999 (9999 to 9999)	4.9 (3.0 to 22.4)	5.9 (1.8 to 9999)
Duration of Overall Response	6.2 (4.9 to 8.3)	12.5 (5.3 to 9999)	6.6 (1.3 to 16.3)	4.5 (2.8 to 11.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) for each cohort Based on investigator assessment

End point title	Progression-free survival (PFS) for each cohort Based on investigator assessment

End point description:

PFS is defined as the interval between first dose and the earliest date of disease progression or death due to any cause. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

From the first dose to the earliest date of disease progression or death

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Month				
median (confidence interval 95%)	5.7 (5.3 to 7.3)	7.2 (4.7 to 14.6)	3.7 (1.7 to 6.5)	5.5 (3.7 to 11.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) for each cohort

End point title	Overall survival (OS) for each cohort

End point description:

Overall survival (OS) is defined as the time from the first dose until death due to any cause. No hypothesis testing completed for cohort B,C and D

End point type	Secondary

End point timeframe:

From the first dose to death

End point values	Cohort A	Cohort B	Cohort C	Cohort D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	16	16	17
Units: Month				
median (confidence interval 95%)	10.8 (8.7 to 17.9)	24.3 (7.9 to 9999)	10.1 (4.6 to 17.6)	11.5 (6.8 to 22.4)

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 reported in this record are from date of 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Cohort A
Reporting group description:	
Cohort A	
Reporting group title	Cohort B
Reporting group description:	
Cohort B	
Reporting group title	Cohort C
Reporting group description:	
Cohort C	
Reporting group title	Cohort D
Reporting group description:	
Cohort D	
Reporting group title	Total
Reporting group description:	
Total	

Serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 76 (34.21%)	5 / 16 (31.25%)	4 / 16 (25.00%)
number of deaths (all causes)	54	10	15
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			

subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 76 (5.26%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences causally related to treatment / all	5 / 5	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			

subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocarditis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (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
Presyncope			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (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
Seizure			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			

subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular detachment			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (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
Intestinal perforation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (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 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (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
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort D	Total	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 17 (52.94%)	44 / 125 (35.20%)	
number of deaths (all causes)	13	92	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 17 (11.76%)	9 / 125 (7.20%)	
occurrences causally related to treatment / all	2 / 2	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	2 / 17 (11.76%)	5 / 125 (4.00%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Troponin T increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial ischaemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular detachment			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 76 (97.37%)	16 / 16 (100.00%)	16 / 16 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Lipoma			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Papilloma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic keratosis			

subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Hot flush			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	6 / 76 (7.89%)	3 / 16 (18.75%)	3 / 16 (18.75%)
occurrences (all)	6	3	4
Hypotension			
subjects affected / exposed	1 / 76 (1.32%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	1	2	0
Lymphoedema			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Peripheral venous disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	28 / 76 (36.84%)	5 / 16 (31.25%)	3 / 16 (18.75%)
occurrences (all)	33	6	5
Chest pain			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Chills			
subjects affected / exposed	18 / 76 (23.68%)	6 / 16 (37.50%)	7 / 16 (43.75%)
occurrences (all)	33	13	8
Face oedema			

subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	7 / 76 (9.21%)	4 / 16 (25.00%)	8 / 16 (50.00%)
occurrences (all)	7	5	9
Gait disturbance			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General physical health deterioration			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Ill-defined disorder			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	5 / 76 (6.58%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	5	3	1
Mucosal inflammation			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	11 / 76 (14.47%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	14	2	4
Pain			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Pyrexia			
subjects affected / exposed	45 / 76 (59.21%)	7 / 16 (43.75%)	8 / 16 (50.00%)
occurrences (all)	133	13	19
Temperature regulation disorder			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Thirst			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Xerosis			

subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Prostatomegaly			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	10 / 76 (13.16%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	12	2	1
Dry throat			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	5 / 76 (6.58%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Epistaxis			
subjects affected / exposed	2 / 76 (2.63%)	3 / 16 (18.75%)	1 / 16 (6.25%)
occurrences (all)	3	3	1
Nasal congestion			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Productive cough			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Wheezing			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rhinitis allergic			

subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Agitation			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Apathy			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Confusional state			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Delirium			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	6 / 76 (7.89%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	6	0	0
Depression			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Sleep disorder			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 76 (11.84%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	9	7	1
Amylase increased			

subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 76 (15.79%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	13	3	2
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 76 (7.89%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	6	1	2
Blood cholesterol increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 76 (9.21%)	3 / 16 (18.75%)	0 / 16 (0.00%)
occurrences (all)	11	4	0
Blood creatinine increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	6 / 76 (7.89%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	6	1	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Blood sodium increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			

subjects affected / exposed	4 / 76 (5.26%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Ejection fraction decreased			
subjects affected / exposed	4 / 76 (5.26%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	6	1	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 76 (9.21%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	7	1	1
Lipase increased			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Neutrophil count decreased			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	6	0	1
Neutrophil count increased			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Weight decreased			
subjects affected / exposed	4 / 76 (5.26%)	2 / 16 (12.50%)	3 / 16 (18.75%)
occurrences (all)	4	2	4
Weight increased			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
White blood cell count decreased			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Injury, poisoning and procedural complications			

Animal bite			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Ligament sprain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Procedural pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Aphasia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Aphonia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Cerebellar syndrome			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dizziness			

subjects affected / exposed	5 / 76 (6.58%)	5 / 16 (31.25%)	0 / 16 (0.00%)
occurrences (all)	7	7	0
Dysarthria			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Haemorrhage intracranial			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	28 / 76 (36.84%)	5 / 16 (31.25%)	6 / 16 (37.50%)
occurrences (all)	47	9	9
Hemianopia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	5 / 76 (6.58%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	5	1	0
Paresis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Partial seizures			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Presyncope			

subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 76 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Seizure			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	3 / 16 (18.75%)
occurrences (all)	4	1	3
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Temporal lobe epilepsy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tongue paralysis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tonic clonic movements			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	2
Visual field defect			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Lymphopenia			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Neutropenia			
subjects affected / exposed	11 / 76 (14.47%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	12	2	1

Thrombocytopenia			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 76 (0.00%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	0	3	0
Hypoacusis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Vertigo			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cataract			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Conjunctival irritation			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Dry eye			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Eye pain			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			

subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Posterior capsule opacification			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Punctate keratitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Visual acuity reduced			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vitreous detachment			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	8 / 76 (10.53%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	11	1	0

Abdominal pain lower			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	5 / 76 (6.58%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	6	1	0
Constipation			
subjects affected / exposed	8 / 76 (10.53%)	1 / 16 (6.25%)	4 / 16 (25.00%)
occurrences (all)	9	1	4
Diarrhoea			
subjects affected / exposed	24 / 76 (31.58%)	8 / 16 (50.00%)	3 / 16 (18.75%)
occurrences (all)	30	15	4
Dry mouth			
subjects affected / exposed	5 / 76 (6.58%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	5	2	1
Dyspepsia			
subjects affected / exposed	5 / 76 (6.58%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	5	2	1
Faecalith			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Faeces soft			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Gingival bleeding			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	24 / 76 (31.58%)	7 / 16 (43.75%)	4 / 16 (25.00%)
occurrences (all)	42	9	5

Rectal haemorrhage			
subjects affected / exposed	2 / 76 (2.63%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	2	4	0
Retching			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	3	1	3
Tongue discolouration			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	24 / 76 (31.58%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	32	3	2
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	2 / 76 (2.63%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	3	2	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 76 (6.58%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Actinic elastosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Actinic keratosis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 16 (12.50%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Alopecia			
subjects affected / exposed	7 / 76 (9.21%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	7	0	1
Aquagenic wrinkling of palms			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			

subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	3 / 16 (18.75%)
occurrences (all)	4	1	3
Dry skin			
subjects affected / exposed	7 / 76 (9.21%)	2 / 16 (12.50%)	3 / 16 (18.75%)
occurrences (all)	9	2	3
Ecchymosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	3
Erythema			
subjects affected / exposed	5 / 76 (6.58%)	0 / 16 (0.00%)	4 / 16 (25.00%)
occurrences (all)	7	0	5
Erythema multiforme			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Generalised erythema			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Hyperkeratosis			
subjects affected / exposed	7 / 76 (9.21%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	7	1	0
Intertrigo			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Nail disorder			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Onycholysis			

subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Pain of skin			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Palmar erythema			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	3 / 16 (18.75%)
occurrences (all)	1	0	3
Palmoplantar keratoderma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Panniculitis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Papule			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	5 / 76 (6.58%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	5	0	2
Pruritus generalised			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	9 / 76 (11.84%)	7 / 16 (43.75%)	3 / 16 (18.75%)
occurrences (all)	10	8	3
Rash erythematous			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Rash generalised			
subjects affected / exposed	5 / 76 (6.58%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0

Rash maculo-papular			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin hyperplasia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Skin mass			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Skin striae			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Nocturia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Pollakiuria			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Urinary incontinence			

subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 76 (19.74%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	22	5	2
Back pain			
subjects affected / exposed	11 / 76 (14.47%)	1 / 16 (6.25%)	3 / 16 (18.75%)
occurrences (all)	11	1	3
Bone pain			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	7 / 76 (9.21%)	0 / 16 (0.00%)	4 / 16 (25.00%)
occurrences (all)	9	0	4
Muscular weakness			
subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	5	1	2
Musculoskeletal chest pain			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Myalgia			

subjects affected / exposed	13 / 76 (17.11%)	5 / 16 (31.25%)	2 / 16 (12.50%)
occurrences (all)	17	10	3
Neck pain			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Osteoarthritis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	8 / 76 (10.53%)	3 / 16 (18.75%)	3 / 16 (18.75%)
occurrences (all)	13	3	5
Rhabdomyolysis			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Synovial cyst			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Tendonitis			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Cellulitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	4 / 76 (5.26%)	2 / 16 (12.50%)	0 / 16 (0.00%)
occurrences (all)	4	2	0
Fungal skin infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Herpes zoster			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	7 / 76 (9.21%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	8	0	0
Laryngitis			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	7 / 76 (9.21%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	7	3	2
Onychomycosis			
subjects affected / exposed	2 / 76 (2.63%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Oral candidiasis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Oral herpes			
subjects affected / exposed	3 / 76 (3.95%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	3	3	0
Paronychia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Pharyngitis streptococcal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	2	0
Pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

Postoperative wound infection			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Pulpitis dental			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	4	0	2
Sialoadenitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Tooth infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 76 (1.32%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	9 / 76 (11.84%)	4 / 16 (25.00%)	7 / 16 (43.75%)
occurrences (all)	10	5	7
Dehydration			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Hypocalcaemia			
subjects affected / exposed	3 / 76 (3.95%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	3	0	0
Hypokalaemia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Hyponatraemia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Hypophosphataemia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort D	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	123 / 125 (98.40%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	1	
Lipoma			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	3	
Papilloma			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	0	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Flushing			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	12 / 125 (9.60%)	
occurrences (all)	0	14	
Hypotension			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	3	4	
Lymphoedema			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Peripheral venous disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	5 / 17 (29.41%)	41 / 125 (32.80%)	
occurrences (all)	7	58	
Chest pain			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Chills			
subjects affected / exposed	6 / 17 (35.29%)	37 / 125 (29.60%)	
occurrences (all)	10	52	
Face oedema			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	3 / 17 (17.65%)	22 / 125 (17.60%)	
occurrences (all)	4	26	
Gait disturbance			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Ill-defined disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 17 (0.00%)	8 / 125 (6.40%)	
occurrences (all)	0	9	
Mucosal inflammation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	3 / 17 (17.65%)	18 / 125 (14.40%)	
occurrences (all)	3	23	
Pain			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	1	4	

Pyrexia			
subjects affected / exposed	8 / 17 (47.06%)	68 / 125 (54.40%)	
occurrences (all)	30	161	
Temperature regulation disorder			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	3	
Thirst			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Xerosis			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	1	5	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	2	2	
Prostatomegaly			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	3 / 17 (17.65%)	16 / 125 (12.80%)	
occurrences (all)	3	18	
Dry throat			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	6 / 125 (4.80%)	
occurrences (all)	1	6	
Epistaxis			
subjects affected / exposed	2 / 17 (11.76%)	8 / 125 (6.40%)	
occurrences (all)	2	7	

Nasal congestion			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Productive cough			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Wheezing			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	1	4	
Apathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	2	4	
Delirium			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	2 / 17 (11.76%)	8 / 125 (6.40%)	
occurrences (all)	2	7	
Depression			

subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Sleep disorder			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 17 (17.65%)	15 / 125 (12.00%)	
occurrences (all)	3	20	
Amylase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 17 (17.65%)	20 / 125 (16.00%)	
occurrences (all)	3	21	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 17 (17.65%)	12 / 125 (9.60%)	
occurrences (all)	3	12	
Blood cholesterol increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	2	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 17 (0.00%)	10 / 125 (8.00%)	
occurrences (all)	0	17	
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 17 (0.00%)	8 / 125 (6.40%)	
occurrences (all)	0	8	
Blood phosphorus decreased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Blood potassium decreased			

subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Blood pressure increased			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	0	
Blood sodium increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
C-reactive protein increased			
subjects affected / exposed	0 / 17 (0.00%)	5 / 125 (4.00%)	
occurrences (all)	0	6	
Ejection fraction decreased			
subjects affected / exposed	1 / 17 (5.88%)	7 / 125 (5.60%)	
occurrences (all)	1	9	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 17 (23.53%)	13 / 125 (10.40%)	
occurrences (all)	4	17	
Lipase increased			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	1	6	
Neutrophil count decreased			
subjects affected / exposed	1 / 17 (5.88%)	6 / 125 (4.80%)	
occurrences (all)	1	8	
Neutrophil count increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Weight decreased			
subjects affected / exposed	3 / 17 (17.65%)	12 / 125 (9.60%)	
occurrences (all)	3	13	

Weight increased			
subjects affected / exposed	2 / 17 (11.76%)	6 / 125 (4.80%)	
occurrences (all)	2	6	
White blood cell count decreased			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	0	
Ligament sprain			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Muscle strain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	0	
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Aphasia			
subjects affected / exposed	3 / 17 (17.65%)	4 / 125 (3.20%)	
occurrences (all)	3	4	

Aphonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Cerebellar syndrome			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	3 / 17 (17.65%)	13 / 125 (10.40%)	
occurrences (all)	3	14	
Dysarthria			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Dysgeusia			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Haemorrhage intracranial			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	8 / 17 (47.06%)	47 / 125 (37.60%)	
occurrences (all)	13	70	
Hemianopia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Motor dysfunction			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	2 / 17 (11.76%)	8 / 125 (6.40%)	
occurrences (all)	2	8	
Paresis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	

Partial seizures			
subjects affected / exposed	2 / 17 (11.76%)	2 / 125 (1.60%)	
occurrences (all)	2	1	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Seizure			
subjects affected / exposed	3 / 17 (17.65%)	9 / 125 (7.20%)	
occurrences (all)	3	6	
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	0	
Temporal lobe epilepsy			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Tongue paralysis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Tonic clonic movements			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Tremor			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	5	
Visual field defect			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 17 (11.76%)	6 / 125 (4.80%)	
occurrences (all)	2	10	
Lymphopenia			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	14 / 125 (11.20%)	
occurrences (all)	0	18	
Thrombocytopenia			
subjects affected / exposed	2 / 17 (11.76%)	7 / 125 (5.60%)	
occurrences (all)	2	7	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	3	
Hypoacusis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	3	
Eye disorders			
Asthenopia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Conjunctival irritation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Diplopia			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Dry eye			

subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)		
occurrences (all)	1	3		
Eye pain				
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)		
occurrences (all)	0	1		
Eye pruritus				
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)		
occurrences (all)	2	2		
Eyelid oedema				
subjects affected / exposed	2 / 17 (11.76%)	3 / 125 (2.40%)		
occurrences (all)	3	4		
Lacrimation increased				
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)		
occurrences (all)	0	2		
Posterior capsule opacification				
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)		
occurrences (all)	0	1		
Punctate keratitis				
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)		
occurrences (all)	1	1		
Retinopathy				
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)		
occurrences (all)	0	1		
Vision blurred				
subjects affected / exposed	1 / 17 (5.88%)	6 / 125 (4.80%)		
occurrences (all)	1	5		
Visual acuity reduced				
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)		
occurrences (all)	1	1		
Visual impairment				
subjects affected / exposed	2 / 17 (11.76%)	3 / 125 (2.40%)		
occurrences (all)	2	2		
Vitreous detachment				
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)		
occurrences (all)	1	1		
Vitreous floaters				

subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	5 / 17 (29.41%)	14 / 125 (11.20%)	
occurrences (all)	8	18	
Abdominal pain lower			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	1 / 17 (5.88%)	7 / 125 (5.60%)	
occurrences (all)	4	10	
Constipation			
subjects affected / exposed	6 / 17 (35.29%)	19 / 125 (15.20%)	
occurrences (all)	9	23	
Diarrhoea			
subjects affected / exposed	7 / 17 (41.18%)	42 / 125 (33.60%)	
occurrences (all)	11	54	
Dry mouth			
subjects affected / exposed	3 / 17 (17.65%)	11 / 125 (8.80%)	
occurrences (all)	3	12	
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)	8 / 125 (6.40%)	
occurrences (all)	0	8	
Faecalith			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Faeces soft			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Gastrointestinal disorder			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Gingival bleeding			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	6 / 17 (35.29%)	41 / 125 (32.80%)	
occurrences (all)	9	49	
Rectal haemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	5	
Retching			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	0 / 17 (0.00%)	6 / 125 (4.80%)	
occurrences (all)	0	7	
Tongue discolouration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	6 / 17 (35.29%)	34 / 125 (27.20%)	
occurrences (all)	10	32	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	6	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 17 (0.00%)	6 / 125 (4.80%)	
occurrences (all)	0	6	
Actinic elastosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Actinic keratosis			

subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	2	
Alopecia			
subjects affected / exposed	2 / 17 (11.76%)	10 / 125 (8.00%)	
occurrences (all)	2	10	
Aquagenic wrinkling of palms			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Dermatitis acneiform			
subjects affected / exposed	1 / 17 (5.88%)	8 / 125 (6.40%)	
occurrences (all)	1	9	
Dry skin			
subjects affected / exposed	3 / 17 (17.65%)	15 / 125 (12.00%)	
occurrences (all)	4	17	
Ecchymosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	5	
Erythema			
subjects affected / exposed	1 / 17 (5.88%)	10 / 125 (8.00%)	
occurrences (all)	2	14	
Erythema multiforme			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Generalised erythema			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	6 / 125 (4.80%)	
occurrences (all)	1	6	
Hyperkeratosis			
subjects affected / exposed	0 / 17 (0.00%)	8 / 125 (6.40%)	
occurrences (all)	0	6	
Intertrigo			

subjects affected / exposed	1 / 17 (5.88%)	5 / 125 (4.00%)	
occurrences (all)	1	5	
Nail disorder			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Night sweats			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	1	
Onycholysis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Pain of skin			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Palmar erythema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Palmoplantar keratoderma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Panniculitis			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	4	
Papule			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	2 / 17 (11.76%)	9 / 125 (7.20%)	
occurrences (all)	2	8	
Pruritus generalised			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	

Rash			
subjects affected / exposed	3 / 17 (17.65%)	22 / 125 (17.60%)	
occurrences (all)	4	26	
Rash erythematous			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Rash generalised			
subjects affected / exposed	0 / 17 (0.00%)	5 / 125 (4.00%)	
occurrences (all)	0	5	
Rash maculo-papular			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Skin exfoliation			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Skin fissures			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Skin hyperplasia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	2	4	
Skin mass			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Skin striae			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	3	
Nocturia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Pollakiuria			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Urinary incontinence			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 17 (35.29%)	26 / 125 (20.80%)	
occurrences (all)	11	39	
Back pain			
subjects affected / exposed	2 / 17 (11.76%)	17 / 125 (13.60%)	
occurrences (all)	3	15	
Bone pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Flank pain			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	1	
Joint range of motion decreased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	1 / 17 (5.88%)	12 / 125 (9.60%)	
occurrences (all)	1	13	
Muscular weakness			
subjects affected / exposed	3 / 17 (17.65%)	9 / 125 (7.20%)	
occurrences (all)	5	12	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Musculoskeletal pain			
subjects affected / exposed	1 / 17 (5.88%)	5 / 125 (4.00%)	
occurrences (all)	1	5	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	6 / 17 (35.29%)	26 / 125 (20.80%)	
occurrences (all)	7	39	
Neck pain			
subjects affected / exposed	1 / 17 (5.88%)	5 / 125 (4.00%)	
occurrences (all)	1	5	
Osteoarthritis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)	16 / 125 (12.80%)	
occurrences (all)	2	23	
Rhabdomyolysis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Synovial cyst			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)	5 / 125 (4.00%)	
occurrences (all)	2	6	

Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	4 / 17 (23.53%)	10 / 125 (8.00%)	
occurrences (all)	4	10	
Fungal skin infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	0 / 17 (0.00%)	7 / 125 (5.60%)	
occurrences (all)	0	8	
Laryngitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	0	
Lung infection			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	11 / 125 (8.80%)	
occurrences (all)	0	11	
Onychomycosis			
subjects affected / exposed	1 / 17 (5.88%)	4 / 125 (3.20%)	
occurrences (all)	1	4	
Oral candidiasis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Oral herpes			
subjects affected / exposed	0 / 17 (0.00%)	4 / 125 (3.20%)	
occurrences (all)	0	6	

Paronychia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	3	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	2	
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Postoperative wound infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Pulpitis dental			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	6 / 125 (4.80%)	
occurrences (all)	0	6	
Sialoadenitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	1 / 17 (5.88%)	1 / 125 (0.80%)	
occurrences (all)	1	1	
Tonsillitis			
subjects affected / exposed	0 / 17 (0.00%)	3 / 125 (2.40%)	
occurrences (all)	0	2	
Tooth infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	

Upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)	6 / 125 (4.80%)	
occurrences (all)	2	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 17 (17.65%)	23 / 125 (18.40%)	
occurrences (all)	3	28	
Dehydration			
subjects affected / exposed	1 / 17 (5.88%)	2 / 125 (1.60%)	
occurrences (all)	1	2	
Diabetes mellitus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	0 / 17 (0.00%)	1 / 125 (0.80%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 125 (1.60%)	
occurrences (all)	0	2	
Hypocalcaemia			
subjects affected / exposed	2 / 17 (11.76%)	5 / 125 (4.00%)	
occurrences (all)	2	5	
Hypokalaemia			
subjects affected / exposed	2 / 17 (11.76%)	3 / 125 (2.40%)	
occurrences (all)	4	5	
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	3 / 125 (2.40%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	1 / 17 (5.88%)	5 / 125 (4.00%)	
occurrences (all)	2	6	
Hypophosphataemia			

subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	2 / 125 (1.60%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2014	• Survival follow-up period has been extended in order to collect additional long-term overall survival data. • Addition of secondary objective of long-term (particularly 5-year) OS. • Additional information available: Dabrafenib, another small molecule BRAF-inhibitor received FDA-approval in May 2013 and EMA approval in August 2013. • Reference to abstaining to any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pomelos was removed. • Additional information available: In Jan-2014 the combination of dabrafenib and trametinib received FDA approval, and in February 2014 the combination received approval in Australia.
20 August 2014	A country-specific amendment as requested by the French regulatory agency
16 March 2015	•Study design revised for clarity around treatment discontinuation and follow up of subjects. • Exclusion HIV removed per March 2014 updates to Inc/Exc (combination). • Permanent discontinuation from study treatment revised for clarity around treatment discontinuation and follow up of subjects. • Dosage and administration section revised based on combination dosage and administration March 2014
06 December 2015	• Study Objectives: 1. Primary endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts) and 2. Secondary endpoint number 9 OS changed from 5 to 3 year. • Cohort A subject population updated to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts). And definition of study closure updated from "where all subjects still in follow up have had at least 5 years follow up…" to "where all subjects still in follow up have had at least 3 years follow up…" • Discussion of Design – primary efficacy objective endpoint amended to allow for locally confirmed BRAF V600E (followed by central confirmation as with all other cohorts)
13 July 2016	•Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. • Make administrative changes to align with Novartis processes and procedures
16 May 2017	Amendment 6 did not incorporate amendment 5, as it was only for submission in countries that had not submitted GSK to Novartis sponsorship change • Study design section amended to define study close as when 70% of Cohort A subjects are lost to follow up or completed or when all Cohort A subjects have been followed up for 3 years, whichever is earlier. • Section 10.5 – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy population (Cohort A) and addition of at least three years follow up for all Cohort A subjects Estimation

21 June 2017	Amendment 7 did incorporate amendment 5, as it was for submission in countries that had already submitted GSK to Novartis sponsorship change ● Study design section amended to define study close as when 70% of Cohort A subjects are lost to follow up or completed or when all Cohort A subjects have been followed up for 3 years, whichever is earlier. ● Section 10.5 – Study closure definition amended from 70% of all enrolled study population to 70% of primary efficacy population (Cohort A) and addition of at least three years follow up for all Cohort A subjects. Estimation of study length amended to approximately 5 years from study start

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: