Clinical trial results:
A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer

Summary

EudraCT number	2011-001161-41
Trial protocol	GB NO DE ES NL IT
Global end of trial date	07 January 2021

Results information

Result version number	v4 (current)
This version publication date	20 April 2022
First version publication date	21 October 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	113928

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01336634
WHO universal trial number (UTN)	-
Other trial identifiers	CDRB436E2201: Novartis

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the overall response rate (ORR) in subjects with stage IV BRAF V600E mutant non-small cell lung cancer administered dabrafenib as a single agent (Cohort A) and in combination with trametinib (Cohorts B and C).

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	05 August 2011
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	France: 59
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Netherlands: 26
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	177
EEA total number of subjects	109

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)	79
From 65 to 84 years	90
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in 50 sites across 11 countries: Netherlands(2), United States(15), Germany(4), Spain(7), France(8), Italy(3), Taiwan(2), South Korea(3), United Kingdom(3), Japan(2),

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 (Dabrafenib Monotherapy)

Arm description:

Participants with or without prior systemic anti-cancer therapy received Dabrafenib 150 mg BID until disease progression, death, or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Arm type	Experimental
Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436, GSK2118436
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib study treatment was provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Each capsule contains 50 mg or 75 mg of free base (present as the mesylate salt)

Arm title	Cohort B - Double Combination (D+T) mBRAF V600E

Arm description:

Participants who had received 1-3 prior lines of systemic anti-cancer therapies for advanced stage/metastatic disease received Dabrafenib 150 mg BID and Trametinib 2 mg once daily (OD). Treatment continued until disease progression, death, or unacceptable AEs or investigator discretion to discontinue.

Arm type	Experimental
Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	TMT212, GSK1120212
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Trametinib study treatment was provided as 0.5 mg and 2 mg tablets. Each tablet contained 0.5 mg or 2 mg of trametinib parent (present as the dimethyl sulfoxide solvate)

Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436, GSK2118436
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib study treatment was provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC)

capsules. Each capsule contains 50 mg or 75 mg of free base (present as the mesylate salt)

Arm title	Cohort C - Double Combination (D+T) naive mBRAF V600E

Arm description:

Participants who had not received any prior systemic anti-cancer for metastatic disease therapies were given Dabrafenib 150 mg BID and Trametinib 2 mg OD. Treatment continued until disease progression, death, or unacceptable AEs or at investigator discretion to discontinue.

Arm type	Experimental
Investigational medicinal product name	Trametinib
Investigational medicinal product code	
Other name	TMT212, GSK1120212
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Trametinib study treatment was provided as 0.5 mg and 2 mg tablets. Each tablet contained 0.5 mg or 2 mg of trametinib parent (present as the dimethyl sulfoxide solvate)

Investigational medicinal product name	Dabrafenib
Investigational medicinal product code	
Other name	DRB436, GSK2118436
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dabrafenib study treatment was provided as 50 mg and 75 mg hydroxypropyl methylcellulose (HPMC) capsules. Each capsule contains 50 mg or 75 mg of free base (present as the mesylate salt)

Number of subjects in period 1	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E
Started	84	57	36
2nd Line Plus All Treated	78	57	0 [1]
1st Line All Treated	6 [2]	2 [3]	34
Crossover	20 [4]	0 [5]	0 [6]
Completed	70	49	27
Not completed	14	8	9
Study closed/terminated	5	6	6
Physician decision	1	1	-
Consent withdrawn by subject	6	-	2
Lost to follow-up	2	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: All Treated Population who had not received any prior anti-cancer therapy for metastatic disease.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (Dabrafenib Monotherapy)
Reporting group description:	
Participants with or without prior systemic anti-cancer therapy received Dabrafenib 150 mg BID until disease progression, death, or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.	
Reporting group title	Cohort B - Double Combination (D+T) mBRAF V600E
Reporting group description:	
Participants who had received 1-3 prior lines of systemic anti-cancer therapies for advanced stage/metastatic disease received Dabrafenib 150 mg BID and Trametinib 2 mg once daily (OD). Treatment continued until disease progression, death, or unacceptable AEs or investigator discretion to discontinue.	
Reporting group title	Cohort C - Double Combination (D+T) naive mBRAF V600E
Reporting group description:	
Participants who had not received any prior systemic anti-cancer for metastatic disease therapies were given Dabrafenib 150 mg BID and Trametinib 2 mg OD. Treatment continued until disease progression, death, or unacceptable AEs or at investigator discretion to discontinue.	

Reporting group values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E
Number of subjects	84	57	36
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)	36	29	14
From 65-84 years	46	26	18
85 years and over	2	2	4
Age Continuous Units: Years			
arithmetic mean	64.8	65.1	67.8
standard deviation	± 10.51	± 10.14	± 11.00
Sex: Female, Male Units: Participants			
Female	44	28	22
Male	40	29	14
Race/Ethnicity, Customized Units: Subjects			
White	64	49	30
Asian	18	4	3
African American Heritage	2	0	0
Native Hawaiian or other Pacific islander	0	0	1
Black or African American	0	2	1

Other	0	2	1
ECOG Performance Status			
The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classifies participants according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). ECOG PS: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
Grade 0	20	17	13
Grade 1	52	35	22
Grade 2	12	5	1

Reporting group values	Total		
Number of subjects	177		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	79		
From 65-84 years	90		
85 years and over	8		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	94		
Male	83		
Race/Ethnicity, Customized			
Units: Subjects			
White	143		
Asian	25		
African American Heritage	2		
Native Hawaiian or other Pacific islander	1		
Black or African American	3		
Other	3		
ECOG Performance Status			
The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classifies participants according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). ECOG PS: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
Grade 0	50		
Grade 1	109		

Grade 2	18		

Subject analysis sets

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Crossover - Double Combination (D+T)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression, death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Crossover - Double Combination (D+T)
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Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression, death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
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Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

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Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression, death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease

progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Reporting group values	Cohort A (Dabrafenib Monotherapy)	Crossover - Double Combination (D+T)	Cohort A (Dabrafenib Monotherapy)
Number of subjects	78	20	65
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	27	4	5.4
standard deviation	±	±	±
Sex: Female, Male			
Units: Participants			
Female			
Male			
Race/Ethnicity, Customized			
Units: Subjects			
White			
Asian			
African American Heritage			
Native Hawaiian or other Pacific islander			
Black or African American			
Other			
ECOG Performance Status			
The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classifies participants according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). ECOG PS: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
Grade 0			
Grade 1			
Grade 2			

Reporting group values	Crossover - Double Combination (D+T)	Cohort A (Dabrafenib Monotherapy)	Crossover - Double Combination (D+T)
Number of subjects	18	27	4

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean standard deviation	11.0 ±	11.8 ±	13.4 ±
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Asian African American Heritage Native Hawaiian or other Pacific islander Black or African American Other			
ECOG Performance Status			
The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classifies participants according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). ECOG PS: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
Grade 0 Grade 1 Grade 2			

Reporting group values	Cohort A (Dabrafenib Monotherapy)	Cohort A (Dabrafenib Monotherapy)	
Number of subjects	67	84	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years arithmetic mean standard deviation	 12.7 ±	 ±	
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Asian African American Heritage Native Hawaiian or other Pacific islander Black or African American Other			
ECOG Performance Status			
The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classifies participants according to their functional impairment, with scores ranging from 0 (fully active) to 5 (dead). ECOG PS: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours			
Units: Subjects			
Grade 0 Grade 1 Grade 2			

End points reporting groups

Reporting group title	Cohort A (Dabrafenib Monotherapy)

Reporting group description:

Participants with or without prior systemic anti-cancer therapy received Dabrafenib 150 mg BID until disease progression, death, or unacceptable adverse event(s) (AEs) or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Reporting group title	Cohort B - Double Combination (D+T) mBRAF V600E

Reporting group description:

Participants who had received 1-3 prior lines of systemic anti-cancer therapies for advanced stage/metastatic disease received Dabrafenib 150 mg BID and Trametinib 2 mg once daily (OD). Treatment continued until disease progression, death, or unacceptable AEs or investigator discretion to discontinue.

Reporting group title	Cohort C - Double Combination (D+T) naive mBRAF V600E

Reporting group description:

Participants who had not received any prior systemic anti-cancer for metastatic disease therapies were given Dabrafenib 150 mg BID and Trametinib 2 mg OD. Treatment continued until disease progression, death, or unacceptable AEs or at investigator discretion to discontinue.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Crossover - Double Combination (D+T)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression, death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Crossover - Double Combination (D+T)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression, death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Crossover - Double Combination (D+T)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Crossover - Double Combination (Dabrafenib+Trametinib): Participants received Dabrafenib 150 mg BID in combination with Trametinib 2 mg once daily and continued treatment until disease progression,

death, or unacceptable adverse event.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Subject analysis set title	Cohort A (Dabrafenib Monotherapy)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants who have relapsed or progressed after receiving at least one line of prior anti-cancer therapy for metastatic disease received dabrafenib 150 mg BID. It was continued until disease progression or death or unacceptable AEs or investigator discretion to discontinue or decision to crossover from monotherapy to combination therapy.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1][2]

End point description:

ORR was defined as the percentage of participants with a confirmed Complete Response (CR) or Partial Response (PR) by investigator assessment as per RECIST v1 .1 criteria. Specifically, ORR = (number of subjects with a confirmed best overall response of CR or PR) divided by the total number of subjects in the corresponding analysis population.

End point type	Primary

End point timeframe:

From study treatment start date until first documented complete response or partial response, assessed up to approximately 50 months

Notes:

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

[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: Endpoint applicable to Cohort A (Dabrafenib Monotherapy), Cohort B - Double Combination (D+T) mBRAF V600E, Cohort C - Double Combination (D+T) naive mBRAF V600E and Crossover Population defined as subset of subjects in the monotherapy cohort All Treated Population who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

End point values	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Cohort A (Dabrafenib Monotherapy)	Crossover - Double Combination (D+T)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	57	36	78	20
Units: Participants	39	23	27	4

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) based on Local Investigator assessment

End point title	Progression Free Survival (PFS) based on Local Investigator assessment[3]

End point description:

Progression Free Survival (PFS) was defined as the time from study treatment start date to the date of first radiologically documented progression or death due to any cause. If a patient did not progress or die at the time of the analysis data cut-off or start of new antineoplastic therapy, PFS was censored at the date of the last adequate tumor assessment before the earliest of the cut-off date or the start date of additional anti-neoplastic therapy. Progression was defined using Response Evaluation Criteria In Solid Tumors Criteria RECIST v1.1, as 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline and/or unequivocal progression of the non-target lesions and/or appearance of a new lesion. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

From study treatment start date until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 113 months

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: Endpoint applicable to Cohort A (Dabrafenib Monotherapy), Cohort B - Double Combination (D+T) mBRAF V600E, Cohort C - Double Combination (D+T) naive mBRAF V600E and Crossover Population defined as subset of subjects in the monotherapy cohort All Treated Population who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

End point values	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Cohort A (Dabrafenib Monotherapy)	Crossover - Double Combination (D+T)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	48	28	65	18
Units: Months				
median (confidence interval 95%)	10.2 (6.9 to 16.7)	10.8 (7.0 to 14.5)	5.4 (2.8 to 6.9)	11.0 (3.0 to 18.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) based on Local Investigator assessment

End point title	Duration of Response (DoR) based on Local Investigator assessment[4]

End point description:

Duration of Response (DoR) was defined as the time from the first documented occurrence of response (PR or CR) until the date of the first documented progression based on RECIST v1.1 or death.

End point type	Secondary

End point timeframe:

From first documented evidence of CR or PR (the response prior to confirmation) until time of documented disease progression or death due to any cause, whichever comes first, assessed up to approximately 113 months

Notes:

[4] - 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: Endpoint applicable to Cohort A (Dabrafenib Monotherapy), Cohort B - Double Combination (D+T) mBRAF V600E, Cohort C - Double Combination (D+T) naive mBRAF V600E and Crossover Population defined as subset of subjects in the monotherapy cohort All Treated Population who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

End point values	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Cohort A (Dabrafenib Monotherapy)	Crossover - Double Combination (D+T)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	39	23	27	4
Units: Months				
median (confidence interval 95%)	9.8 (6.9 to 18.3)	10.2 (8.3 to 15.2)	11.8 (5.4 to 23.5)	13.4 (7.6 to 19.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[5]

End point description:

Overall Survival (OS) was defined as the time from first dose until death due to any cause. If a patient was not known to have died at the time of analysis cut-off, OS was censored at the date of last contact.

End point type	Secondary

End point timeframe:

From study treatment start date until date of of death from any cause, assessed up to approximately 113 months

Notes:

[5] - 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: Endpoint applicable to Cohort A (Dabrafenib Monotherapy), Cohort B - Double Combination (D+T) mBRAF V600E, Cohort C - Double Combination (D+T) naive mBRAF V600E and Crossover Population defined as subset of subjects in the monotherapy cohort All Treated Population who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

End point values	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Cohort A (Dabrafenib Monotherapy)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49	27	67	
Units: Months				
median (confidence interval 95%)	18.2 (14.3 to 28.6)	17.3 (12.3 to 40.2)	12.7 (7.3 to 16.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment Emergent Adverse Events

End point title	Number of participants with Treatment Emergent Adverse Events

End point description:

The distribution of adverse events (AE) was done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Secondary

End point timeframe:

From study treatment start date till 30 days safety follow-up, assessed up to approximately 81 months

End point values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Crossover - Double Combination (D+T)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	84	57	36	20
Units: Participants				
Treatment Emergent Adverse Events (TAEs)	82	54	36	20
Treatment Emergent Serious Adverse Events (TESAEs)	37	38	24	9
Deaths due to AE causally related to treatment	2	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of Dabrafenib

End point title	Apparent clearance (CL/F) of Dabrafenib

End point description:

Blood samples from participants were collected for population pharmacokinetic analysis including the apparent base clearance (CL/F) following oral dosing of dabrafenib. Concentrations of dabrafenib was determined in plasma samples using the currently approved analytical methodology.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	53	30	
Units: Liter/hour (L/hr)				
geometric mean (confidence interval 95%)	30.5 (29.1 to 32.0)	21.4 (19.37 to 23.70)	23.9 (22.02 to 25.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Oral volume of distribution (V/F) of Dabrafenib

End point title	Oral volume of distribution (V/F) of Dabrafenib

End point description:

Blood samples from participants were collected for population pharmacokinetic analysis including the oral volume of distribution (V/F) following oral dosing of dabrafenib. Blood samples from participants were collected for population pharmacokinetic analysis including the apparent base clearance (CL/F) following oral dosing of dabrafenib. Concentrations of dabrafenib was determined in plasma samples using the currently approved analytical methodology.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	53	30	
Units: Liter (L)				
geometric mean (confidence interval 95%)	50.6 (47.4 to 54.0)	38.1 (30.93 to 46.97)	48.1 (42.15 to 54.95)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of Trametinib

End point title	Apparent clearance (CL/F) of Trametinib

End point description:

Blood samples from participants were collected for population pharmacokinetic analysis including the apparent base clearance (CL/F) following oral dosing of trametinib. Blood samples from participants were collected for population pharmacokinetic analysis including the apparent base clearance (CL/F) following oral dosing of dabrafenib. Concentrations of trametinib was determined in plasma samples using the currently approved analytical methodology.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	54	30	
Units: Liter/hour (L/hr)				
geometric mean (confidence interval 95%)	(to)	4.9 (4.62 to 5.19)	5.03 (4.64 to 5.46)	

Notes:

[6] - Only applicable to subjects who received at least one dose of Trametinib

Statistical analyses

No statistical analyses for this end point

Secondary: Oral volume of distribution (V/F) of Trametinib

End point title	Oral volume of distribution (V/F) of Trametinib

End point description:

Blood samples from participants were collected for population pharmacokinetic analysis including the oral volume of distribution (V/F) following oral dosing of trametinib. Concentrations of trametinib was determined in plasma samples using the currently approved analytical methodology.

End point type	Secondary

End point timeframe:

Week 3, Week 6, Week 12 and Week 18

End point values	Cohort A (Dabrafenib Monotherapy)	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	54	30	
Units: Liter (L)				
geometric mean (confidence interval 95%)	(to)	91.98 (78.58 to 107.66)	103.48 (84.58 to 126.59)	

Notes:

[7] - Only applicable to subjects who received at least one dose of Trametinib

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths[8]

End point description:

On treatment deaths were collected from FPFT up to 30 days after study drug discontinuation, for a maximum duration with dabrafenib and trametinib of 81 months (study treatment with dabrafenib and trametinib ranged from 0.3 to 80.0 months).
Deaths post treatment survival follow up were collected after the on- treatment period, up to approximately 9 years. Patients who didn't die during the on-treatment period and had not stopped study participation at the time of data cut-off (end of study) were censored.

End point type	Post-hoc

End point timeframe:

up to 81 months (study treatment with dabrafenib and trametinib), up to approximately 9 years (study duration)

Notes:

[8] - 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: Endpoint applicable to Cohort A (Dabrafenib Monotherapy), Cohort B - Double Combination (D+T) mBRAF V600E, Cohort C - Double Combination (D+T) naive mBRAF V600E and Crossover Population defined as subset of subjects in the monotherapy cohort All Treated Population who were assigned to monotherapy cohort and elected to crossover to combination treatment following disease progression on monotherapy.

End point values	Cohort B - Double Combination (D+T) mBRAF V600E	Cohort C - Double Combination (D+T) naive mBRAF V600E	Crossover - Double Combination (D+T)	Cohort A (Dabrafenib Monotherapy)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	57	36	20	84
Units: Participants				
On-treatment deaths	12	5	4	15
Post-treatment deaths	38	21	13	38
All deaths	50	26	17	53

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from First Patient First Treatment (FPFT) up to 30 days after study drug discontinuation, assessed up to approximately 81 months.

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	23.1

Reporting groups

Reporting group title	Cohort A: DAB 150MG BID

Reporting group description:

Cohort A: DAB 150MG BID

Reporting group title	Crossover DAB+TRA: DAB 150MG BID, TRA 2mG QD

Reporting group description:

Crossover DAB+TRA: DAB 150MG BID, TRA 2mG QD

Reporting group title	Cohort C: DAB 150MG BID, TRA 2mG QD

Reporting group description:

Cohort C: DAB 150MG BID, TRA 2mG QD

Reporting group title	Cohort B: DAB 150MG BID, TRA 2mG QD

Reporting group description:

Cohort B: DAB 150MG BID, TRA 2mG QD

Serious adverse events	Cohort A: DAB 150MG BID	Crossover DAB+TRA: DAB 150MG BID, TRA 2mG QD	Cohort C: DAB 150MG BID, TRA 2mG QD
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 84 (44.05%)	9 / 20 (45.00%)	24 / 36 (66.67%)
number of deaths (all causes)	15	4	5
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	5 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Colon adenoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Keratoacanthoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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 neoplasm malignant			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Neoplasm progression			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Squamous cell carcinoma			

subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	7 / 84 (8.33%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Hypotension			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Chest pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Chills			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fatigue			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
General physical health deterioration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Malaise			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Pyrexia			
subjects affected / exposed	5 / 84 (5.95%)	1 / 20 (5.00%)	4 / 36 (11.11%)
occurrences causally related to treatment / all	3 / 6	0 / 1	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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

Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pleural effusion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pneumothorax spontaneous			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pulmonary embolism			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Respiratory failure			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	5 / 36 (13.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Ejection fraction decreased			
subjects affected / exposed	2 / 84 (2.38%)	1 / 20 (5.00%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	2 / 2	0 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Lymphocyte count decreased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Incisional hernia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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

Multiple injuries			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stoma site haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Atrial fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Cardiac arrest			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiopulmonary failure			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pericardial effusion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Dizziness			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Encephalopathy			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Haemorrhage intracranial			

subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Transient ischaemic attack			

subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Lymphopenia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pancytopenia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Splenic thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Vertigo positional			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (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
Macular oedema			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (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
Retinal dystrophy			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ascites			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Gastric haemorrhage			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal pain			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal mass			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Large intestinal obstruction			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Melaena			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Nausea			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Oesophageal stenosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic duct stenosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pancreatitis acute			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Toothache			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Vomiting			

subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Hepatocellular injury			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Malignant biliary obstruction			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Rash			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient acantholytic dermatosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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			

Haematuria			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Renal artery thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Urinary retention			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myalgia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Bronchitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Cystitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Furuncle			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (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
Gastritis viral			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Legionella infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Respiratory tract infection			
subjects affected / exposed	3 / 84 (3.57%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Sepsis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Septic shock			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Urinary tract infection			

subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Hypercalcaemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Hyperglycaemia			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (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
Hypophosphataemia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B: DAB 150MG BID, TRA 2mG QD		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 57 (66.67%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Keratoacanthoma				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lip squamous cell carcinoma				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neoplasm progression				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Squamous cell carcinoma				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				

subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest discomfort				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inflammation				

subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	10 / 57 (17.54%)			
occurrences causally related to treatment / all	12 / 14			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax spontaneous				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Respiratory failure				

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

C-reactive protein increased				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	4 / 57 (7.02%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphocyte count decreased				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
White blood cell count decreased				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Incisional hernia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stoma site haemorrhage				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Toxicity to various agents				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac disorders				
Arrhythmia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failure				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Transient ischaemic attack				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Splenic thrombosis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Macular hole				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Macular oedema				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Retinal dystrophy				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterovesical fistula				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				

subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal toxicity				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal mass				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic duct stenosis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haemorrhage				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Toothache				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant biliary obstruction			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient acantholytic dermatosis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal artery thrombosis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Tubulointerstitial nephritis				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary bladder haemorrhage				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacterial infection				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bronchitis			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Furuncle			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis viral			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis viral			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Legionella infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection bacterial				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malnutrition				

subjects affected / exposed	0 / 57 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A: DAB 150MG BID	Crossover DAB+TRA: DAB 150MG BID, TRA 2mG QD	Cohort C: DAB 150MG BID, TRA 2mG QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 84 (97.62%)	20 / 20 (100.00%)	36 / 36 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	6 / 84 (7.14%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
Basal cell carcinoma			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	2	0	4
Keratoacanthoma			
subjects affected / exposed	6 / 84 (7.14%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
Melanocytic naevus			
subjects affected / exposed	11 / 84 (13.10%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences (all)	19	1	0
Seborrhoeic keratosis			
subjects affected / exposed	11 / 84 (13.10%)	2 / 20 (10.00%)	2 / 36 (5.56%)
occurrences (all)	14	3	4
Skin papilloma			
subjects affected / exposed	26 / 84 (30.95%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	40	0	1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	1	2	3
Hypertension			

subjects affected / exposed	4 / 84 (4.76%)	4 / 20 (20.00%)	4 / 36 (11.11%)
occurrences (all)	4	4	6
Hypotension			
subjects affected / exposed	6 / 84 (7.14%)	0 / 20 (0.00%)	5 / 36 (13.89%)
occurrences (all)	6	0	5
Orthostatic hypotension			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 84 (29.76%)	3 / 20 (15.00%)	4 / 36 (11.11%)
occurrences (all)	31	7	8
Chest pain			
subjects affected / exposed	4 / 84 (4.76%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences (all)	5	1	0
Chills			
subjects affected / exposed	12 / 84 (14.29%)	3 / 20 (15.00%)	10 / 36 (27.78%)
occurrences (all)	18	3	16
Fatigue			
subjects affected / exposed	24 / 84 (28.57%)	2 / 20 (10.00%)	15 / 36 (41.67%)
occurrences (all)	26	2	16
Feeling cold			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Gait disturbance			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Hyperthermia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	5 / 36 (13.89%)
occurrences (all)	3	0	10
Malaise			

subjects affected / exposed	5 / 84 (5.95%)	1 / 20 (5.00%)	4 / 36 (11.11%)
occurrences (all)	5	1	5
Mucosal inflammation			
subjects affected / exposed	6 / 84 (7.14%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	7	1	2
Non-cardiac chest pain			
subjects affected / exposed	5 / 84 (5.95%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	8	1	1
Oedema peripheral			
subjects affected / exposed	3 / 84 (3.57%)	5 / 20 (25.00%)	13 / 36 (36.11%)
occurrences (all)	9	7	22
Pain			
subjects affected / exposed	2 / 84 (2.38%)	1 / 20 (5.00%)	4 / 36 (11.11%)
occurrences (all)	2	1	4
Pyrexia			
subjects affected / exposed	31 / 84 (36.90%)	9 / 20 (45.00%)	22 / 36 (61.11%)
occurrences (all)	52	21	69
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 84 (32.14%)	5 / 20 (25.00%)	10 / 36 (27.78%)
occurrences (all)	39	7	12
Dysphonia			
subjects affected / exposed	9 / 84 (10.71%)	3 / 20 (15.00%)	5 / 36 (13.89%)
occurrences (all)	9	5	5
Dyspnoea			
subjects affected / exposed	18 / 84 (21.43%)	3 / 20 (15.00%)	9 / 36 (25.00%)
occurrences (all)	22	4	11
Epistaxis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	4
Haemoptysis			
subjects affected / exposed	8 / 84 (9.52%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	9	3	2
Oropharyngeal pain			

subjects affected / exposed	3 / 84 (3.57%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	3	1	2
Pleural effusion			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	6 / 84 (7.14%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	7	1	1
Pulmonary embolism			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
Nasal congestion			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 84 (3.57%)	3 / 20 (15.00%)	1 / 36 (2.78%)
occurrences (all)	4	3	1
Confusional state			
subjects affected / exposed	2 / 84 (2.38%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
Depression			
subjects affected / exposed	3 / 84 (3.57%)	2 / 20 (10.00%)	2 / 36 (5.56%)
occurrences (all)	3	2	2
Insomnia			
subjects affected / exposed	7 / 84 (8.33%)	0 / 20 (0.00%)	5 / 36 (13.89%)
occurrences (all)	8	0	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Amylase increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 84 (3.57%)	2 / 20 (10.00%)	3 / 36 (8.33%)
occurrences (all)	3	2	3
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	5	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Blood creatinine increased			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	2
C-reactive protein increased			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Lipase increased			
subjects affected / exposed	2 / 84 (2.38%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences (all)	3	2	0
Weight decreased			
subjects affected / exposed	15 / 84 (17.86%)	2 / 20 (10.00%)	9 / 36 (25.00%)
occurrences (all)	16	2	9
Weight increased			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	4
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	2	0	4
Fall			
subjects affected / exposed	2 / 84 (2.38%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	9	2	2
Limb injury			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	3 / 36 (8.33%)
occurrences (all)	0	1	3
Thermal burn			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Atrioventricular block			
subjects affected / exposed	1 / 84 (1.19%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Bradycardia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Sinus bradycardia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Tachycardia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 84 (9.52%)	1 / 20 (5.00%)	9 / 36 (25.00%)
occurrences (all)	9	2	11
Dysgeusia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Headache			
subjects affected / exposed	17 / 84 (20.24%)	3 / 20 (15.00%)	8 / 36 (22.22%)
occurrences (all)	20	4	11
Memory impairment			
subjects affected / exposed	2 / 84 (2.38%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	2	2	1
Paraesthesia			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Sciatica			

subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Taste disorder			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	2
Anaemia			
subjects affected / exposed	11 / 84 (13.10%)	1 / 20 (5.00%)	7 / 36 (19.44%)
occurrences (all)	15	1	12
Lymphopenia			
subjects affected / exposed	6 / 84 (7.14%)	2 / 20 (10.00%)	2 / 36 (5.56%)
occurrences (all)	7	2	3
Neutropenia			
subjects affected / exposed	2 / 84 (2.38%)	3 / 20 (15.00%)	1 / 36 (2.78%)
occurrences (all)	2	8	2
Thrombocytopenia			
subjects affected / exposed	5 / 84 (5.95%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	5	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 84 (1.19%)	3 / 20 (15.00%)	1 / 36 (2.78%)
occurrences (all)	1	3	1
Eye disorders			
Cataract			
subjects affected / exposed	2 / 84 (2.38%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	2	2	1
Dry eye			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	5	0	3
Eye pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Periorbital oedema			

subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Vision blurred			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	7	0	3
Visual acuity reduced			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	3	0	0
Visual impairment			
subjects affected / exposed	3 / 84 (3.57%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	3	1	2
Photopsia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 84 (1.19%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Abdominal pain			
subjects affected / exposed	9 / 84 (10.71%)	2 / 20 (10.00%)	6 / 36 (16.67%)
occurrences (all)	13	2	6
Abdominal pain upper			
subjects affected / exposed	4 / 84 (4.76%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences (all)	4	1	0
Anal incontinence			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	10 / 84 (11.90%)	6 / 20 (30.00%)	6 / 36 (16.67%)
occurrences (all)	12	9	6
Diarrhoea			
subjects affected / exposed	17 / 84 (20.24%)	5 / 20 (25.00%)	15 / 36 (41.67%)
occurrences (all)	29	16	22
Dry mouth			
subjects affected / exposed	2 / 84 (2.38%)	2 / 20 (10.00%)	3 / 36 (8.33%)
occurrences (all)	3	2	3

Dyspepsia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	3	0	3
Dysphagia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	2
Gastritis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 84 (4.76%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	4	2	0
Nausea			
subjects affected / exposed	24 / 84 (28.57%)	9 / 20 (45.00%)	21 / 36 (58.33%)
occurrences (all)	37	10	32
Toothache			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Vomiting			
subjects affected / exposed	18 / 84 (21.43%)	6 / 20 (30.00%)	11 / 36 (30.56%)
occurrences (all)	30	8	23
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 84 (1.19%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Actinic keratosis			
subjects affected / exposed	11 / 84 (13.10%)	3 / 20 (15.00%)	3 / 36 (8.33%)
occurrences (all)	19	5	8
Alopecia			
subjects affected / exposed	18 / 84 (21.43%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	18	0	1
Dermal cyst			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	3	0	3
Dry skin			

subjects affected / exposed	26 / 84 (30.95%)	2 / 20 (10.00%)	14 / 36 (38.89%)
occurrences (all)	28	2	19
Eczema			
subjects affected / exposed	2 / 84 (2.38%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Erythema			
subjects affected / exposed	2 / 84 (2.38%)	4 / 20 (20.00%)	5 / 36 (13.89%)
occurrences (all)	2	4	9
Erythema nodosum			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	0	1	4
Hair texture abnormal			
subjects affected / exposed	7 / 84 (8.33%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	7	0	0
Hyperhidrosis			
subjects affected / exposed	3 / 84 (3.57%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	3	2	1
Hyperkeratosis			
subjects affected / exposed	26 / 84 (30.95%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	46	2	1
Madarosis			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 84 (23.81%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	23	0	1
Papule			
subjects affected / exposed	11 / 84 (13.10%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	13	0	1
Pruritus			
subjects affected / exposed	14 / 84 (16.67%)	2 / 20 (10.00%)	6 / 36 (16.67%)
occurrences (all)	14	2	7
Rash			
subjects affected / exposed	15 / 84 (17.86%)	3 / 20 (15.00%)	11 / 36 (30.56%)
occurrences (all)	16	5	12

Rash macular			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Rash maculo-papular			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	0 / 36 (0.00%)
occurrences (all)	7	0	0
Rash papular			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	4	0	4
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Skin lesion			
subjects affected / exposed	4 / 84 (4.76%)	0 / 20 (0.00%)	4 / 36 (11.11%)
occurrences (all)	5	0	5
Urticaria			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	6	0	3
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 84 (25.00%)	8 / 20 (40.00%)	8 / 36 (22.22%)
occurrences (all)	32	15	12
Back pain			
subjects affected / exposed	11 / 84 (13.10%)	3 / 20 (15.00%)	9 / 36 (25.00%)
occurrences (all)	13	3	9
Groin pain			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	1 / 36 (2.78%)
occurrences (all)	0	3	1
Joint stiffness			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Muscle spasms			

subjects affected / exposed	2 / 84 (2.38%)	3 / 20 (15.00%)	5 / 36 (13.89%)
occurrences (all)	2	5	8
Muscular weakness			
subjects affected / exposed	7 / 84 (8.33%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	8	1	3
Musculoskeletal chest pain			
subjects affected / exposed	6 / 84 (7.14%)	2 / 20 (10.00%)	4 / 36 (11.11%)
occurrences (all)	7	2	4
Myalgia			
subjects affected / exposed	10 / 84 (11.90%)	3 / 20 (15.00%)	4 / 36 (11.11%)
occurrences (all)	12	4	7
Neck pain			
subjects affected / exposed	4 / 84 (4.76%)	3 / 20 (15.00%)	2 / 36 (5.56%)
occurrences (all)	4	3	2
Pain in extremity			
subjects affected / exposed	17 / 84 (20.24%)	2 / 20 (10.00%)	4 / 36 (11.11%)
occurrences (all)	20	2	4
Spinal osteoarthritis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 84 (7.14%)	3 / 20 (15.00%)	0 / 36 (0.00%)
occurrences (all)	9	4	0
Conjunctivitis			
subjects affected / exposed	2 / 84 (2.38%)	1 / 20 (5.00%)	1 / 36 (2.78%)
occurrences (all)	2	3	1
Folliculitis			
subjects affected / exposed	4 / 84 (4.76%)	1 / 20 (5.00%)	0 / 36 (0.00%)
occurrences (all)	4	3	0
Gastroenteritis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	3	0	2
Influenza			
subjects affected / exposed	1 / 84 (1.19%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2

Laryngitis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	8 / 84 (9.52%)	3 / 20 (15.00%)	7 / 36 (19.44%)
occurrences (all)	9	3	7
Pneumonia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 20 (0.00%)	5 / 36 (13.89%)
occurrences (all)	2	0	6
Rhinitis			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	6	0	3
Upper respiratory tract infection			
subjects affected / exposed	8 / 84 (9.52%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	8	0	1
Urinary tract infection			
subjects affected / exposed	5 / 84 (5.95%)	2 / 20 (10.00%)	7 / 36 (19.44%)
occurrences (all)	7	4	11
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Decreased appetite			
subjects affected / exposed	25 / 84 (29.76%)	6 / 20 (30.00%)	12 / 36 (33.33%)
occurrences (all)	34	6	15
Dehydration			
subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	5	0	2
Hyperglycaemia			
subjects affected / exposed	7 / 84 (8.33%)	2 / 20 (10.00%)	2 / 36 (5.56%)
occurrences (all)	8	2	2
Hypoalbuminaemia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	1 / 36 (2.78%)
occurrences (all)	6	0	1
Hypokalaemia			

subjects affected / exposed	5 / 84 (5.95%)	0 / 20 (0.00%)	3 / 36 (8.33%)
occurrences (all)	8	0	3
Hypomagnesaemia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	2 / 36 (5.56%)
occurrences (all)	4	0	7
Hyponatraemia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 20 (0.00%)	4 / 36 (11.11%)
occurrences (all)	4	0	5
Hypophosphataemia			
subjects affected / exposed	6 / 84 (7.14%)	1 / 20 (5.00%)	2 / 36 (5.56%)
occurrences (all)	13	1	2
Vitamin D deficiency			
subjects affected / exposed	0 / 84 (0.00%)	2 / 20 (10.00%)	0 / 36 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Cohort B: DAB 150MG BID, TRA 2mG QD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 57 (94.74%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Basal cell carcinoma			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Keratoacanthoma			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Melanocytic naevus			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	3		
Seborrhoeic keratosis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Skin papilloma			

subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Hypotension			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	8		
Orthostatic hypotension			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 57 (36.84%)		
occurrences (all)	30		
Chest pain			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Chills			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	26		
Fatigue			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	15		
Feeling cold			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Hyperthermia			

subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	6		
Malaise			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Mucosal inflammation			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Non-cardiac chest pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	22 / 57 (38.60%)		
occurrences (all)	32		
Pain			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	102		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 57 (31.58%)		
occurrences (all)	23		
Dysphonia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	18		
Epistaxis			

subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	7		
Haemoptysis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	11		
Pulmonary embolism			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	6		
Depression			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	7		
Amylase increased			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	8		
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	12		
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Blood creatinine increased			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	8		
C-reactive protein increased			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Weight decreased			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	12		
Weight increased			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Fall			

subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Limb injury			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Atrioventricular block			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	8		
Dysgeusia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	7		
Headache			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	21		
Memory impairment			

subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Taste disorder			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	7		
Anaemia			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	11		
Lymphopenia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	23		
Thrombocytopenia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	7		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	9		
Eye disorders			
Cataract			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Dry eye			

subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Eye pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Periorbital oedema			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	4		
Visual acuity reduced			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Visual impairment			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Photopsia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	12		
Anal incontinence			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	14		

Diarrhoea			
subjects affected / exposed	18 / 57 (31.58%)		
occurrences (all)	34		
Dry mouth			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Dysphagia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Gastritis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	24 / 57 (42.11%)		
occurrences (all)	39		
Toothache			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	24 / 57 (42.11%)		
occurrences (all)	62		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Actinic keratosis			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	2		
Alopecia			

subjects affected / exposed	6 / 57 (10.53%)			
occurrences (all)	7			
Dermal cyst				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	22 / 57 (38.60%)			
occurrences (all)	28			
Eczema				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences (all)	5			
Erythema				
subjects affected / exposed	7 / 57 (12.28%)			
occurrences (all)	10			
Erythema nodosum				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences (all)	10			
Hair texture abnormal				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences (all)	3			
Hyperhidrosis				
subjects affected / exposed	4 / 57 (7.02%)			
occurrences (all)	4			
Hyperkeratosis				
subjects affected / exposed	7 / 57 (12.28%)			
occurrences (all)	7			
Madarosis				
subjects affected / exposed	0 / 57 (0.00%)			
occurrences (all)	0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences (all)	3			
Papule				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences (all)	1			

Pruritus subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 16		
Rash subjects affected / exposed occurrences (all)	16 / 57 (28.07%) 29		
Rash macular subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0		
Rash papular subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		
Skin lesion subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Urticaria subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	17 / 57 (29.82%) 29		
Back pain subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 9		
Groin pain			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Joint stiffness			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	16		
Muscular weakness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Neck pain			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	6		
Spinal osteoarthritis			
subjects affected / exposed	0 / 57 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	13		
Conjunctivitis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Folliculitis			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		

Gastroenteritis subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		
Laryngitis subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2		
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 9		
Pneumonia subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 6		
Rhinitis subjects affected / exposed occurrences (all)	7 / 57 (12.28%) 15		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6		
Metabolism and nutrition disorders Cell death subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Decreased appetite subjects affected / exposed occurrences (all)	17 / 57 (29.82%) 26		
Dehydration subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 3		
Hyperglycaemia			

subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	11		
Hypophosphataemia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Vitamin D deficiency			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2011	Amendment No. 1: Updated the inclusion/exclusion criteria, updated the QTc withdrawal criteria and the Dose Modification section, added an Independent Data Monitoring Committee. In addition, language specific to French sites was added. Throughout the protocol, minor administrative and typographical changes were made.
13 October 2011	Amendment No. 02: Increased the frequency of cardiac monitoring from every 12 weeks to every 9 weeks. Other clarifications to the PGx sections in the main text and in Appendix 1, description of physical exam and list of laboratory tests were made. Guidelines for management of renal insufficiency were added. A baseline sample for cytokine profiling was added (in the event a subject develops fever, the baseline cytokine values are available).
30 April 2012	Amendment No. 03: was a country specific amendment that changed the QTc stopping criteria to 500 msec for UK subjects and clarified the definition of abstinence.
15 June 2012	Amendment No. 04: Changed Inclusion to clarify that the failed chemotherapy regimen must have been a platinum-based chemotherapy; changed Exclusion Criteria #9 regarding the length of time a subject must be disease free from 5 years to 3 years; allowed for continued treatment with GSK2118436 beyond disease progression; updated the Dose Modification Guidelines for Fever and the Renal Insufficiency Guidelines for consistency with the current asset-specific language; added the UK to Appendix 3 (country-specific QTc stopping criteria of 500 msec); clarified restrictions on certain foods known to affect drug metabolism; clarified when an MRI or CT is required at baseline and on-study; removed the requirement for males who choose abstinence as their contraceptive method to begin abstinence 14 days BEFORE administration of GSK2118436; clarified the definition of abstinence; fixed T&E footnotes, lessened the frequency of efficacy assessments beginning at Week 36 and onwards, and removed the ANC measurement on Day 8; clarified SAE language for consistency with current asset language.
20 August 2012	Amendment No. 05: Updated the Background section (Section 1.1) to include the currently available safety and efficacy data for GSK2118436; changed Inclusion Criterion (#7) to clarify for the reader that additional details on mutation testing and central confirmation of mutation testing are provided in Section 7.1.1; changes to Section 7.1.1 included clarification on BRAF mutation testing and intent that all subject have tissue available for central confirmation (when testing at inclusion is performed at a local laboratory) (also affected T&E footnote); removed the requirement for men to use contraception (Inclusion Criterion #9 and Section 7.4.2); changed the limit for use of anti-cancer treatment prior to dosing with GSK2118436 from 28 days to 14 days (Exclusion Criteria #2 and #3); added defined safety and efficacy criteria that need to be met in order to allow treatment with GSK2118436 beyond disease progression (Section 4.2.1); updated Section 5.7, Guidelines for Dose Modification and Events of Special Interest, in line with current asset language; clarified QTc Stopping Criteria to delineate QTcF v QTcB and QTc uncorrected stopping values; and clarified protocol-specific SAE language for consistency with current asset language (removed LVEF stopping criteria as a protocol-specific SAE).
24 January 2013	Amendment No. 06 was a country specific amendment for France and the UK that specifies QTc stopping criteria in Appendix 3. Footnotes to the Time and Events Table were also renumbered.

16 April 2013	Amendment No. 07: Added the study expansion cohort (n=20) increasing total sample size to 60 subjects, updated the eligibility criteria to remove the requirement of disease progression on a platinum-based chemotherapy prior to study enrollment to allow inclusion of first line metastatic patients in the expansion cohort and allow subjects with HCV clearance, updated QTc stopping criteria, removed herbal remedies as a prohibitive medication (St Johns Wort still prohibited), updated the prohibitive and cautionary medication list, increased the frequency of dermatologic assessments to every 9 weeks, changed blood sample for cfDNA at disease progression from optional to required, replaced "GSK2118436" with "dabrafenib" throughout the document and additional administrative level clarifications and edits. Section 1.2.1 deleted, please refer to the Dabrafenib Investigator's Brochure for all background/clinical trial information on dabrafenib.
25 September 2013	Amendment No. 08: Added the dabrafenib/trametinib combination therapy cohort (n=40) increasing the total sample size to 100 subjects, ophthalmic examination added at screening, Week 6 and as clinically necessary thereafter for combination treatment only, combination cohort specific inclusion/exclusion criteria added, combination cohort specific dose modification and toxicity management guidelines added, option to crossover from monotherapy to combination treatment at time of radiologic disease progression added, ECHO and ECG schedule clarified as baseline, Week 6 and every 9 weeks thereafter
14 October 2014	Amendment No. 09: Updated secondary medical monitor. Added Cohort C to enroll 25 first line subjects. Additional language added to study rationale in Section 1.2.1. Revised required laboratory value for PT/INR and PTT in Section 4.1.2. Removed HIV from Exclusion Criterion #7 and revised Exclusion Criterion #15 in Section 4.1.3. Additional language added to Section 4.2.1 and Section 4.2.3 to clarify requirements for continuing study treatment post-PD and for crossover requirements. Updated dose modification and toxicity management language throughout Section 5.9. Updated general dose modification guidelines in Section 5.9.2. Updated dose modification guidelines and stopping criteria for LVEF in Section 5.10.1. Updated liver chemistry stopping and follow-up criteria in Section 5.10.3. Guidelines for holding study drug following radiation treatment added to Section 6.1. Specified that body fluid sample (e.g., pleural effusion) is not acceptable for BRAF mutation testing sample in Section 7.1.1. Added confirmation of measurable disease by independent review at baseline prior to enrollment in Section 7.1.2. Updated language regarding ophthalmic examination requirements in Section 7.3.2.3. Added language in Section 7.3.2.9.2 allowing investigator to decide if basal cell carcinoma should be reported as SAE or not. Specified in Section 7.4.1 that females should wait at least 4 months after last dose of the combination therapy before nursing. Specified in Section 7.7 that body fluid sample (e.g., pleural effusion) is not preferred for PD biomarker sample. Added Section 9.1.3 to describe hypothesis and study design for Cohort C. Updated Section 9.2 regarding Cohort C. Updated Investigator Brochures citations to current versions. Appendix 4 added regarding additional monitoring requirements for subjects in France only.
08 June 2016	Amendment No. 10: Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Made administrative changes to align with Novartis processes and procedures.
31 May 2018	Amendment No. 11: Section 5.9.3.5.: contraception section for male subjects was revised to align with the most recent Invesigator's Brochures. Sections Protocol Design, 3, and 4.2.2.: inserted additional criterion for study completion. I.e.; progression of all patients in cohorts B and C, and added the dabrafenib/trametinib rollover trial as a treatment option at the time of study completion for patients who are still benefiting from study treatment.
09 December 2019	Amendment No. 12: The objective of this amendment was (1) to add dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) which have been reported during treatment with dabrafenib in combination with trametinib, and (2) to change the duration of male and female contraception following the last dose of dabrafenib from 4 weeks to 2 weeks. The 2 weeks was based on a conservative calculation of the 5 half lives of dabrafenib and metabolites. These changes were made in order to align with updated information available in dabrafenib and trametinib Investigator's Brochure Edition 11.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported