



Clinical trial results:

A phase Ib/II open-label, multi-center study of the combination of MEK162 plus AMG 479 (ganitumab) in adult patients with selected advanced solid tumors

Summary

EudraCT number	2012-000305-76
Trial protocol	ES GB BE FR DE IT
Global end of trial date	01 April 2015

Results information

Result version number	v1 (current)
This version publication date	17 April 2016
First version publication date	17 April 2016

Trial information

Trial identification

Sponsor protocol code	CMEK162X2111
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01562899
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Array BioPharma, Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, United States, 80301
Public contact	Clinical Operations, Array BioPharma, Inc., +1 303-381-6604, info@arraybiopharma.com
Scientific contact	Clinical Operations, Array BioPharma, Inc., +1 303-381-6604, info@arraybiopharma.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	01 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2015
Global end of trial reached?	Yes
Global end of trial date	01 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Phase Ib was to estimate the maximum tolerated dose (MTD(s)) and/or recommended Phase II dose (RP2D(s)) of binimetinib in combination with ganitumab in patients with advanced KRAS - or BRAF-mutant solid tumors.

The primary objective of Phase II was to estimate the antitumor activity of the binimetinib and ganitumab combination in patients with KRAS-mutant colorectal cancer (CRC, arm 1), with pancreatic adenocarcinoma (arm 2), and in patients with BRAF-mutant melanoma (arm 3).

The study was terminated early due to the current landscape for anti-melanoma therapies and the limited clinical activity observed with the study treatment.

Protection of trial subjects:

The study was conducted according to the ethical principles of the Declaration of Helsinki.

Eligible patients were only included in the study after providing written (witnessed, where required by law or regulation), IEC/IRB-approved informed consent or, if incapable of doing so, after such consent had been provided by a legally acceptable representative of the patient. In cases where the patient's representative gave consent, the patient was to be informed about the study to the extent possible given his/her understanding.

Background therapy:

Not Applicable.

Evidence for comparator:

Not Applicable.

Actual start date of recruitment	27 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 9

Worldwide total number of subjects	77
EEA total number of subjects	53

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)	59
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began on 27-Aug-2012 to the CMEK162X2111 trial. A total of 77 subjects were enrolled. The last subject's last visit occurred on 01-Apr-2015.

Not completed subjects represent those subjects that stopped treatment early, due to a specific reason.

Pre-assignment

Screening details:

Based on the limited clinical activity of the binimetinib combination treatment and the changed landscape for anti-melanoma therapies, the sponsor decided to halt recruitment on 7-Jan-2014.

This halt was not a consequence of any safety concerns, and the treatment of patients in the study continued according to the protocol.

Period 1

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

Blinding implementation details:

Blinding implementation details are not applicable, as this was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)

Arm description:

30 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 30 mg / AMG 12 mg/kg)

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was supplied as tablets with a dosage strengths of 15 mg.

Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.

Arm title	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)
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Arm description:

45 mg binimetinib bid + 9 mg/kg ganitumab q2w (MEK 45 mg / AMG 9 mg/kg)

Arm type	Experimental
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Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Binimetinib was supplied as tablets with a dosage strengths of 15 mg.	
Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.	
Arm title	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Arm description:	
45 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 45 mg / AMG 12 mg/kg)	
Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Binimetinib was supplied as tablets with a dosage strengths of 15 mg.	
Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.	
Arm title	Phase II: CRC (KRAS)
Arm description:	
Patients with KRAS mutant colorectal cancer.	
Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Binimetinib was supplied as tablets with a dosage strengths of 15 mg.	
Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.

Arm title	Phase II: Pancreatic
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Arm description:

Patients with metastatic pancreatic cancer.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was supplied as tablets with a dosage strengths of 15 mg.

Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.

Arm title	Phase II: Melanoma
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Arm description:

Patients with mutant BRAF V600 melanoma.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was supplied as tablets with a dosage strengths of 15 mg.

Investigational medicinal product name	Ganitumab
Investigational medicinal product code	AMG 479
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganitumab was supplied as a sterile liquid for intravenous infusion every second week. Until April 2013, a frozen formulation with a concentration of 30 mg/mL was used; from May 2013 onwards a refrigerated formulation with a concentration of 70 mg/mL was used.

Number of subjects in period 1	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Started	7	6	6
Completed	0	0	0
Not completed	7	6	6
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	3	1	2
Death	-	1	-
Disease Progression	4	3	4

Number of subjects in period 1	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma
Started	26	20	12
Completed	0	0	0
Not completed	26	20	12
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	5	5	1
Death	-	-	-
Disease Progression	21	15	10

Baseline characteristics

Reporting groups

Reporting group title	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)
Reporting group description: 30 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 30 mg / AMG 12 mg/kg)	
Reporting group title	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)
Reporting group description: 45 mg binimetinib bid + 9 mg/kg ganitumab q2w (MEK 45 mg / AMG 9 mg/kg)	
Reporting group title	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Reporting group description: 45 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 45 mg / AMG 12 mg/kg)	
Reporting group title	Phase II: CRC (KRAS)
Reporting group description: Patients with KRAS mutant colorectal cancer.	
Reporting group title	Phase II: Pancreatic
Reporting group description: Patients with metastatic pancreatic cancer.	
Reporting group title	Phase II: Melanoma
Reporting group description: Patients with mutant BRAF V600 melanoma.	

Reporting group values	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Number of subjects	7	6	6
Age categorical			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	5	5	4
>=65 years	2	1	2
Age continuous			
Units: years			
arithmetic mean	52.3	49.3	57.3
standard deviation	± 12.8	± 17.41	± 12.56
Gender categorical			
Units: Subjects			
Female	2	3	4
Male	5	3	2
WHO performance status			
Categories:			
<ul style="list-style-type: none"> • 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 • 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours • 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair 			
Units: Subjects			
0:	1	0	2
1:	6	6	4
Missing:	0	0	0

Height			
Units: centimeters			
arithmetic mean	172.3	167.4	166.7
standard deviation	± 10.96	± 7.59	± 11.91
Weight			
Units: kilograms			
arithmetic mean	89.76	63.1	74.95
standard deviation	± 15.458	± 12.046	± 12.674

Reporting group values	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma
Number of subjects	26	20	12
Age categorical			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	19	14	12
>=65 years	7	6	0
Age continuous			
Units: years			
arithmetic mean	58.2	56.7	47.8
standard deviation	± 10.53	± 10.57	± 11.34
Gender categorical			
Units: Subjects			
Female	14	9	5
Male	12	11	7
WHO performance status			

Categories:

- 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
- 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Units: Subjects			
0:	7	6	6
1:	19	13	6
Missing:	0	1	0
Height			
Units: centimeters			
arithmetic mean	166.7	169.6	167.3
standard deviation	± 10.53	± 8.74	± 7.4
Weight			
Units: kilograms			
arithmetic mean	74.17	60.18	73.5
standard deviation	± 17.554	± 9.058	± 11.269

Reporting group values	Total		
Number of subjects	77		
Age categorical			
Units: Subjects			
<=18 years	0		
Between 18 and 65 years	59		
>=65 years	18		

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	37		
Male	40		
WHO performance status			
Categories: • 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 • 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours • 4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair			
Units: Subjects			
0:	22		
1:	54		
Missing:	1		
Height Units: centimeters arithmetic mean standard deviation	-		
Weight Units: kilograms arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)
Reporting group description: 30 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 30 mg / AMG 12 mg/kg)	
Reporting group title	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)
Reporting group description: 45 mg binimetinib bid + 9 mg/kg ganitumab q2w (MEK 45 mg / AMG 9 mg/kg)	
Reporting group title	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Reporting group description: 45 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 45 mg / AMG 12 mg/kg)	
Reporting group title	Phase II: CRC (KRAS)
Reporting group description: Patients with KRAS mutant colorectal cancer.	
Reporting group title	Phase II: Pancreatic
Reporting group description: Patients with metastatic pancreatic cancer.	
Reporting group title	Phase II: Melanoma
Reporting group description: Patients with mutant BRAF V600 melanoma.	
Subject analysis set title	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic analysis set includes all patients who had at least one blood sample providing evaluable PK data. Patients were analyzed as treated.	
Subject analysis set title	Phase Ib/II: MEK 45 mg + 9 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic analysis set includes all patients who had at least one blood sample providing evaluable PK data. Patients were analyzed as treated.	
Subject analysis set title	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: The pharmacokinetic analysis set includes all patients who had at least one blood sample providing evaluable PK data. Patients were analyzed as treated.	

Primary: Phase Ib: Estimation of Maximum Tolerated Doses (MTDs) and/or recommended Phase II doses (RP2Ds) by measuring incidence of Dose Limiting Toxicities (DLTs)

End point title	Phase Ib: Estimation of Maximum Tolerated Doses (MTDs) and/or recommended Phase II doses (RP2Ds) by measuring incidence of Dose Limiting Toxicities (DLTs) ^{[1][2]}
End point description: MTDs and/or RP2Ds of MEK162 in combination with AMG479 were estimated by measuring incidence of DLTs in Cycle 1.	
End point type	Primary
End point timeframe: Cycle 1 (approximately 28 days)	

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: Statistical analysis not applicable.

[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: Statistical analysis not applicable.

End point values	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: DLTs				
arithmetic mean (standard deviation)	0.117 (± 0.067)	0.127 (± 0.077)	0.159 (± 0.108)	

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Antitumor activity of MEK162 in combination with AMG 479 by evaluating Objective Response Rate (ORR) in colorectal carcinoma and melanoma and at week 10 in pancreatic carcinoma: Objective Response Rate (ORR)

End point title	Phase II: Antitumor activity of MEK162 in combination with AMG 479 by evaluating Objective Response Rate (ORR) in colorectal carcinoma and melanoma and at week 10 in pancreatic carcinoma: Objective Response Rate (ORR) ^{[3][4]}
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End point description:

Estimation of the antitumor activity of MEK162 in combination with AMG479 by evaluating Objective Response Rate (ORR) according to RECIST 1.1 in colorectal carcinoma and melanoma and by evaluating the Disease Control Rate (DCR) per RECIST 1.1 at week 10 in pancreatic carcinoma.

Given the lack of responses in study arms 1 and 3, and the limited clinical anti-tumor activity observed in study arm 2, the Bayesian analysis of DCR at 10 weeks and ORR was not performed.

A summary of the best overall response based on investigator radiology assessment by study arm is below.

End point type	Primary
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End point timeframe:

Week 10 (approximately 24 months)

Notes:

[3] - 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: Statistical analysis not applicable.

[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: Given the lack of responses in study arms 1 and 3, and the limited clinical anti-tumor activity observed in study arm 2, the Bayesian analysis of DCR at 10 weeks and ORR was not performed.

End point values	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	20	12	
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 13.2)	5 (0.1 to 24.9)	0 (0 to 26.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Antitumor activity of MEK162 in combination with AMG 479 by evaluating Disease Control Rate (DCR) in colorectal carcinoma and melanoma and at week 10 in pancreatic carcinoma: Observed Disease Control Rate (DCR)

End point title	Phase II: Antitumor activity of MEK162 in combination with AMG 479 by evaluating Disease Control Rate (DCR) in colorectal carcinoma and melanoma and at week 10 in pancreatic carcinoma: Observed Disease Control Rate (DCR) ^{[5][6]}
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End point description:

Estimation of the antitumor activity of MEK162 in combination with AMG479 by evaluating Objective Response Rate (ORR) according to RECIST 1.1 in colorectal carcinoma and melanoma and by evaluating the Disease Control Rate (DCR) per RECIST 1.1 at week 10 in pancreatic carcinoma.

A summary of the observed BOR and ORR and 95% confidence intervals up to the time of cut-off is described below.

End point type	Primary
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End point timeframe:

Week 10 (approximately 24 months)

Notes:

[5] - 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: Statistical analysis not applicable.

[6] - 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: Statistical analysis not applicable.

End point values	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	20	12	
Units: percentage of subjects				
number (confidence interval 95%)	38.5 (20.2 to 59.4)	35 (15.4 to 59.2)	0 (0 to 26.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of single and multiple dose pharmacokinetics (PK) profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentrations and basic PK parameters of MEK162: Area Under the Curve 0-8 hrs (AUC-8hr)

End point title	(Phase Ib/II) Determination of single and multiple dose pharmacokinetics (PK) profile of MEK162 in combination with
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AMG 479 (ganitumab) by measuring time vs. plasma concentrations and basic PK parameters of MEK162: Area Under the Curve 0-8 hrs (AUC-8hr)

End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	60	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	933 (\pm 52.6)	1439.7 (\pm 33.1)	1576.8 (\pm 47.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Area Under the Curve 0-24 Hrs (AUC-24hr)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Area Under the Curve 0-24 Hrs (AUC-24hr)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	60	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1450.5 (± 28.4)	1923.4 (± 34.9)	2401.2 (± 46.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Area Under the Curve 0-inf (AUC0-inf)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Area Under the Curve 0-inf (AUC0-inf)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
End point timeframe:	
Cycle 1 (Day 1)	

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	42	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1692.9 (± 40.6)	1980 (± 34.9)	2536.7 (± 37.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK

Parameters of MEK162: Maximum Serum Concentration (Cmax)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Maximum Serum Concentration (Cmax)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	60	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	301.6 (± 90.6)	460.5 (± 56)	429.5 (± 59.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Time at which Cmax is Observed (Tmax)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Time at which Cmax is Observed (Tmax)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	60	
Units: hr				
geometric mean (geometric coefficient of variation)	1.6 (± 75)	1.5 (± 76.7)	1.9 (± 90.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Half life (T1/2)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Half life (T1/2)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
End point timeframe:	
Cycle 1 (Day 1)	

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	6	45	
Units: hr				
geometric mean (geometric coefficient of variation)	6.6 (± 25.4)	3.9 (± 43.3)	6.7 (± 50.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK

Parameters of MEK162: Area Under the Curve 0-8 Hrs (AUC-8hr)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Area Under the Curve 0-8 Hrs (AUC-8hr)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	32	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	1428.6 (\pm 22.7)	1421.7 (\pm 26.9)	1745.6 (\pm 72.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Maximum Serum Concentration (Cmax)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Maximum Serum Concentration (Cmax)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 and are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	32	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	338.9 (± 10)	358.1 (± 43.7)	495.8 (± 79)	

Statistical analyses

No statistical analyses for this end point

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Time at which Cmax is observed (Tmax)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Time at which Cmax is observed (Tmax)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 and are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
End point timeframe:	
Cycle 1 (Day 15)	

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	32	
Units: hr				
geometric mean (geometric coefficient of variation)	1 (± 79.1)	1.9 (± 46.8)	1.5 (± 77.8)	

Statistical analyses

Secondary: (Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Accumulation Ratio (Racc)

End point title	(Phase Ib/II) Determination of Single and Multiple Dose Pharmacokinetics (PK) Profile of MEK162 in Combination With AMG 479 (Ganitumab) by Measuring Time vs. Plasma Concentrations and Basic PK Parameters of MEK162: Accumulation Ratio (Racc)
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End point description:

Determination of single and multiple dose PK profile of MEK162 in combination with AMG 479 (ganitumab) by measuring time vs. plasma concentration as well as basic PK parameters of MEK162 at different time points prior and post study drug combination dosing.

Given that the enrollment to the study was prematurely stopped, PK results up to the data cut-off date 23-Sep-2014 are being reported. No additional PK data analysis was performed after this data cut-off.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	6	32	
Units: (hr*ng/mL) / (hr*ng/mL)				
geometric mean (geometric coefficient of variation)	1.7 (± 27.7)	1 (± 28.6)	1.2 (± 53.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: AMG 479 (ganitumab) Pharmacokinetic (PK) concentrations during the first cycle by dose cohort: Concentration at time point 0 (C0)

End point title	AMG 479 (ganitumab) Pharmacokinetic (PK) concentrations during the first cycle by dose cohort: Concentration at time point 0 (C0)
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End point description:

The PK of AMG 479 (ganitumab) was assessed in this study by collecting the concentration at the end of infusion and the concentration 24 hours (CEOI) after the start of the infusion (C24) of AMG 479 (ganitumab) during Day 1 of Cycle 1.

End point type	Secondary
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End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	64	
Units: ug/mL				
median (full range (min-max))	0 (0 to 0)	0 (0 to 0)	0 (0 to 175)	

Statistical analyses

No statistical analyses for this end point

Secondary: AMG 479 (Ganitumab) Pharmacokinetic (PK) Concentrations During the First Cycle by Dose Cohort: Concentration at the End Of the Infusion (CEOI)

End point title	AMG 479 (Ganitumab) Pharmacokinetic (PK) Concentrations During the First Cycle by Dose Cohort: Concentration at the End Of the Infusion (CEOI)
End point description: The PK of AMG 479 (ganitumab) was assessed in this study by collecting the concentration at the end of infusion and the concentration 24 hours (CEOI) after the start of the infusion (C24) of AMG 479 (ganitumab) during Day 1 of Cycle 1.	
End point type	Secondary
End point timeframe: Cycle 1 (Day 1)	

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	61	
Units: ug/mL				
median (full range (min-max))	237 (176 to 341)	125 (105 to 212)	193 (0 to 382)	

Statistical analyses

No statistical analyses for this end point

Secondary: AMG 479 (Ganitumab) Pharmacokinetic (PK) Concentrations During the First Cycle by Dose Cohort: Concentration 24 hours (C24)

End point title	AMG 479 (Ganitumab) Pharmacokinetic (PK) Concentrations During the First Cycle by Dose Cohort: Concentration 24 hours (C24)
End point description: The PK of AMG 479 (ganitumab) was assessed in this study by collecting the concentration at the end of infusion and the concentration 24 hours (CEOI) after the start of the infusion (C24) of AMG 479 (ganitumab) during Day 1 of Cycle 1.	
End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib/II: MEK 30 mg + AMG 12 mg/kg	Phase Ib/II: MEK 45 mg + 9 mg/kg	Phase Ib/II: MEK 45 mg + AMG 12 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	6	60	
Units: ug/mL				
median (full range (min-max))	140 (95 to 191)	77.7 (59 to 143)	128 (0 to 271)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Preliminary anti-tumor activity of MEK162 and AMG 479 (ganitumab) in combination by evaluating the Overall Response Rate (ORR), Duration of Response (DOR) and Progression Free Survival (PFS)

End point title	Phase Ib: Preliminary anti-tumor activity of MEK162 and AMG 479 (ganitumab) in combination by evaluating the Overall Response Rate (ORR), Duration of Response (DOR) and Progression Free Survival (PFS) ^[7]
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End point description:

The assessment the preliminary anti-tumor activity of MEK162 and AMG 479 (ganitumab) in combination by evaluating Overall Response Rate (ORR), Duration of Response (DOR), Progression Free Survival (PFS) as assessed by the investigator according to RECIST 1.1.

No formal efficacy analyses of patients in Phase Ib of the study were performed.

As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was collected for this end point.

End point type	Secondary
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End point timeframe:

Cycle 1 (approximately 6 months)

Notes:

[7] - 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: Statistical analysis not applicable.

End point values	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: Not Applicable				
number (not applicable)	999	999	999	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Further anti-tumor activity of MEK162 & AMG 479 (ganitumab) in combination by evaluating the DOR, PFS and OS by evaluating Disease Control Rate for colorectal carcinoma and melanoma: Progression-free Survival (PFS)

End point title	Phase II: Further anti-tumor activity of MEK162 & AMG 479 (ganitumab) in combination by evaluating the DOR, PFS and OS by evaluating Disease Control Rate for colorectal carcinoma and melanoma: Progression-free Survival (PFS) ^[8]
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End point description:

To further assess the anti-tumor activity of MEK162 and AMG 479 (ganitumab) in combination by evaluating the Duration of Response (DOR) and Progression Free Survival (PFS) per RECIST 1.1 and Overall Survival in all phase II patients and by evaluating the Disease Control Rate (DCR) per RECIST 1.1 for colorectal carcinoma and melanoma.

Given the lack of responses in study arms 1 and 3, and the limited clinical anti-tumor activity observed in study arm 2, the Bayesian analysis of DCR at 10 weeks and ORR was not performed.

Median time of Progression-free Survival (PFS) was estimated for the 3 arms of patients in Phase II.

End point type	Secondary
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End point timeframe:

Approximately 24 months

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: Given the lack of responses in study arms 1 and 3, and the limited clinical anti-tumor activity observed in study arm 2, the Bayesian analysis of DCR at 10 weeks and ORR was not performed.

End point values	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	20	12	
Units: months				
number (confidence interval 95%)	2.2 (1.4 to 2.4)	1.5 (1.4 to 4)	1.6 (1.5 to 2.3)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were collected during the study, which began in August 2012 and concluded in April 2015.

Adverse event reporting additional description:

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)
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Reporting group description:

30 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 30 mg / AMG 12 mg/kg)

Reporting group title	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)
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Reporting group description:

45 mg binimetinib bid + 9 mg/kg ganitumab q2w (MEK 45 mg / AMG 9 mg/kg)

Reporting group title	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
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Reporting group description:

45 mg binimetinib bid + 12 mg/kg ganitumab q2w (MEK 45 mg / AMG 12 mg/kg)

Reporting group title	Phase II: CRC (KRAS)
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Reporting group description:

Patients with KRAS mutant colorectal cancer.

Reporting group title	Phase II: Pancreatic
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Reporting group description:

Patients with metastatic pancreatic cancer.

Reporting group title	Phase II: Melanoma
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Reporting group description:

Patients with mutant BRAF V600 melanoma.

Serious adverse events	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	3 / 6 (50.00%)	4 / 6 (66.67%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Generalised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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

Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Disorientation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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			
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Bilirubin conjugated increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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

Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Troponin I increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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 ischaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Hemianopia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Convulsion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
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			
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (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
Colitis ischaemic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Melaena			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (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
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Ileus			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Pneumatosis intestinalis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
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 and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Escherichia infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (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
Biliary sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Biliary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Lung infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Pyelonephritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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
Urosepsis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (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
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (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

Serious adverse events	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 26 (50.00%)	14 / 20 (70.00%)	3 / 12 (25.00%)
number of deaths (all causes)	1	5	1
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			

subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
General physical health deterioration			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Influenza like illness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Hypoxia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Bilirubin conjugated increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Blood creatinine increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Lipase increased			

subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Hemianopia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Convulsion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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

Heparin-induced thrombocytopenia subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Abdominal pain upper			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Colitis ischaemic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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

Haematemesis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (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
Stomatitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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	3 / 26 (11.54%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (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
Ascites			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Pneumatosis intestinalis			

subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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
Escherichia infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Biliary sepsis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Biliary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Cellulitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Lung infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Pyelonephritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Sepsis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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
Urosepsis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (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
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (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	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 26 (0.00%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (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

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

Non-serious adverse events	Phase Ib: MEK 30 mg + AMG 12 mg/kg (Cohort)	Phase Ib: MEK 45 mg + 9 mg/kg (Cohort)	Phase Ib: MEK 45 mg + AMG 12 mg/kg (Cohort)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pallor			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 7 (42.86%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	3	3	2
Fatigue			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	3	1	3
Asthenia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Chills			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mucosal dryness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Axillary pain			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Generalised oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Localised oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Medical device complication subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Mucosal discolouration subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Reproductive system and breast disorders Dyspareunia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Vulvovaginal dryness subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Dyspnoea			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Laryngospasm			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleuritic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nightmare			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
Blood albumin decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Amylase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Blood glucose increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Lipase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood calcium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood calcium increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood magnesium decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood chloride increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Protein total decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stoma site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Waist circumference increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Wound			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Wound secretion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sunburn			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Cardiac disorders			
Left ventricular dysfunction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nervous system disorders			
Dysgeusia subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Visual field defect subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Dizziness			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ageusia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nerve compression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peroneal nerve palsy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Lymphopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ear discomfort			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Retinal detachment			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Periorbital oedema			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Chorioretinopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Maculopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Retinal pigment epitheliopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye colour change			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abnormal sensation in eye			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Corneal thickening			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Lenticular opacities			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metamorphopsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ocular hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Optic disc disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retinal artery embolism			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Retinal disorder subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Vitreous detachment subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3	3 / 6 (50.00%) 3	4 / 6 (66.67%) 4
Vomiting subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 4	3 / 6 (50.00%) 3	2 / 6 (33.33%) 2
Nausea subjects affected / exposed occurrences (all)	4 / 7 (57.14%) 4	3 / 6 (50.00%) 3	1 / 6 (16.67%) 1
Stomatitis subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	3 / 6 (50.00%) 3	2 / 6 (33.33%) 2
Constipation subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Abdominal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0

Abdominal distension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Duodenal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastric ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Glossitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rectal tenesmus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Tongue oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	1	3	3
Dermatitis acneiform			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
Rash maculo-papular			

subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	3	1	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Rash erythematous			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Circumoral oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Erythema nodosum			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin toxicity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Acne			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Decubitus ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus generalised			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Calculus bladder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Renal impairment subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Groin pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Myositis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Musculoskeletal chest pain			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Biliary sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Fungal skin infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Localised infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Nail infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Oral herpes subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	2 / 6 (33.33%) 2	4 / 6 (66.67%) 4
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	2 / 6 (33.33%) 2
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Dehydration			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase II: CRC (KRAS)	Phase II: Pancreatic	Phase II: Melanoma
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	20 / 20 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 26 (15.38%)	5 / 20 (25.00%)	1 / 12 (8.33%)
occurrences (all)	4	5	1
Hypotension			

subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Deep vein thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pallor			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Haematoma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 26 (26.92%)	6 / 20 (30.00%)	2 / 12 (16.67%)
occurrences (all)	7	6	2
Fatigue			
subjects affected / exposed	6 / 26 (23.08%)	14 / 20 (70.00%)	1 / 12 (8.33%)
occurrences (all)	6	14	1
Asthenia			
subjects affected / exposed	5 / 26 (19.23%)	1 / 20 (5.00%)	4 / 12 (33.33%)
occurrences (all)	5	1	4
Oedema peripheral			
subjects affected / exposed	7 / 26 (26.92%)	7 / 20 (35.00%)	1 / 12 (8.33%)
occurrences (all)	7	7	1
Chills			
subjects affected / exposed	5 / 26 (19.23%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	5	2	0
Face oedema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Non-cardiac chest pain			

subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Mucosal dryness			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Axillary pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Generalised oedema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Localised oedema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Medical device complication			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mucosal discolouration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dyspareunia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vaginal haemorrhage			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 26 (23.08%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	6	0	0
Dyspnoea			
subjects affected / exposed	4 / 26 (15.38%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	4	1	1
Productive cough			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Haemoptysis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 26 (0.00%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Pneumonitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Bronchitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Laryngospasm			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Pleural effusion subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Pleuritic pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 20 (10.00%) 2	0 / 12 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	1 / 12 (8.33%) 1
Depression subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 20 (10.00%) 2	0 / 12 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	14 / 26 (53.85%) 14	4 / 20 (20.00%) 4	1 / 12 (8.33%) 1
Blood albumin decreased subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 20 (5.00%) 1	1 / 12 (8.33%) 1
Amylase increased subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Blood glucose increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Lipase increased			

subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Alanine aminotransferase increased			
subjects affected / exposed	5 / 26 (19.23%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	5	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 26 (26.92%)	5 / 20 (25.00%)	2 / 12 (16.67%)
occurrences (all)	7	5	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood calcium decreased			
subjects affected / exposed	3 / 26 (11.54%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Blood calcium increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 26 (15.38%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences (all)	4	3	0
Blood magnesium decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 26 (3.85%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			

subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 26 (0.00%)	4 / 20 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Blood bilirubin increased			
subjects affected / exposed	3 / 26 (11.54%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	3 / 26 (11.54%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Troponin I increased			
subjects affected / exposed	3 / 26 (11.54%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0
Blood cholesterol increased			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood chloride increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood urea increased			

subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood urine present			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Stoma site pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Waist circumference increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Wound secretion			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Fall			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Joint injury subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Limb injury subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Sunburn subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Atrioventricular block first degree subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Bradycardia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Sinus bradycardia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 20 (15.00%) 3	0 / 12 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Paraesthesia			

subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Ageusia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nerve compression			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Peroneal nerve palsy			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 26 (34.62%)	8 / 20 (40.00%)	2 / 12 (16.67%)
occurrences (all)	9	8	2
Thrombocytopenia			
subjects affected / exposed	9 / 26 (34.62%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	9	2	0
Lymphopenia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Leukocytosis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Ear discomfort subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	1 / 12 (8.33%) 1
Retinal detachment subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	3 / 12 (25.00%) 3
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 20 (5.00%) 1	0 / 12 (0.00%) 0
Chorioretinopathy subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Detachment of retinal pigment epithelium subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 20 (0.00%) 0	3 / 12 (25.00%) 3
Eyelid oedema subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Maculopathy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Retinal pigment epitheliopathy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 20 (0.00%) 0	0 / 12 (0.00%) 0
Eye disorder			

subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	4 / 12 (33.33%)
occurrences (all)	0	2	4
Retinopathy			
subjects affected / exposed	3 / 26 (11.54%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Subretinal fluid			
subjects affected / exposed	0 / 26 (0.00%)	4 / 20 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Visual impairment			
subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Eye colour change			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Abnormal sensation in eye			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Corneal thickening			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye inflammation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Inflammation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lenticular opacities			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metamorphopsia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Ocular hypertension			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema			

subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Optic disc disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Retinal artery embolism			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Retinal disorder			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vitreous detachment			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 26 (50.00%)	7 / 20 (35.00%)	2 / 12 (16.67%)
occurrences (all)	13	7	2
Vomiting			
subjects affected / exposed	11 / 26 (42.31%)	11 / 20 (55.00%)	2 / 12 (16.67%)
occurrences (all)	11	11	2
Nausea			
subjects affected / exposed	10 / 26 (38.46%)	11 / 20 (55.00%)	1 / 12 (8.33%)
occurrences (all)	10	11	1
Stomatitis			
subjects affected / exposed	5 / 26 (19.23%)	7 / 20 (35.00%)	0 / 12 (0.00%)
occurrences (all)	5	7	0
Constipation			
subjects affected / exposed	8 / 26 (30.77%)	7 / 20 (35.00%)	1 / 12 (8.33%)
occurrences (all)	8	7	1
Abdominal pain			
subjects affected / exposed	4 / 26 (15.38%)	5 / 20 (25.00%)	1 / 12 (8.33%)
occurrences (all)	4	5	1

Abdominal pain upper			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	3 / 26 (11.54%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Abdominal distension			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Ascites			
subjects affected / exposed	2 / 26 (7.69%)	2 / 20 (10.00%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Dry mouth			
subjects affected / exposed	2 / 26 (7.69%)	6 / 20 (30.00%)	0 / 12 (0.00%)
occurrences (all)	2	6	0
Duodenal ulcer			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastric ulcer			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)	3 / 20 (15.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Oesophagitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Chapped lips			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Gastrointestinal disorder			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Glossitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rectal tenesmus			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tongue oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 26 (0.00%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	4 / 26 (15.38%)	4 / 20 (20.00%)	1 / 12 (8.33%)
occurrences (all)	4	4	1
Dermatitis acneiform			
subjects affected / exposed	7 / 26 (26.92%)	8 / 20 (40.00%)	1 / 12 (8.33%)
occurrences (all)	7	8	1
Rash maculo-papular			
subjects affected / exposed	5 / 26 (19.23%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	5	1	0
Rash			
subjects affected / exposed	10 / 26 (38.46%)	4 / 20 (20.00%)	5 / 12 (41.67%)
occurrences (all)	10	4	5
Rash erythematous			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Skin fissures			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Circumoral oedema			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Skin toxicity			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Decubitus ulcer			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Eczema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin discolouration			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Skin reaction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			

subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Calculus bladder			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Renal impairment			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Urinary tract pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Myalgia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Myositis			

subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Muscle spasms			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Bacteraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Device related infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Paronychia			
subjects affected / exposed	1 / 26 (3.85%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0

Biliary sepsis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fungal skin infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nail infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 26 (26.92%)	8 / 20 (40.00%)	1 / 12 (8.33%)
occurrences (all)	7	8	1
Hyperglycaemia			

subjects affected / exposed	2 / 26 (7.69%)	7 / 20 (35.00%)	2 / 12 (16.67%)
occurrences (all)	2	7	2
Hyponatraemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Hypokalaemia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Dehydration			
subjects affected / exposed	1 / 26 (3.85%)	2 / 20 (10.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Hyperphosphataemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	5 / 26 (19.23%)	4 / 20 (20.00%)	0 / 12 (0.00%)
occurrences (all)	5	4	0
Hypomagnesaemia			
subjects affected / exposed	0 / 26 (0.00%)	5 / 20 (25.00%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Hypocalcaemia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Hypernatraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 20 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 20 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 26 (0.00%)	1 / 20 (5.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2012	Protocol amendment 1 was issued before the start of enrollment to modify contraception requirements, to add clarifications on the dose-escalation procedures, and to revise DLT definitions. Furthermore, enhanced safety measures were implemented (more frequent monitoring of ocular events, measurements of liver transaminases, liver function tests and cardiac monitoring).
23 September 2013	Protocol amendment 2 was issued after the dose-escalation part was completed. In this amendment, the DLT criteria were updated according to the knowledge and the clinical experience with binimetinib at the time of the amendment, and the dose modification recommendations were adapted accordingly. The number of patients who experienced DLTs during the dose-escalation part was not affected.
27 January 2014	Protocol amendment 3 was issued following the enrollment halt. The protocol was amended to remove follow-up for progression and survival. Of note, there were no changes to the safety follow-up (including 30-day safety follow-up and follow-up for neutralizing antibodies).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 January 2014	Based on the limited clinical activity of the binimetinib combination treatment and the changed landscape for anti-melanoma therapies, Novartis decided to halt recruitment on 7-Jan-2014. The recruitment halt was not a consequence of any safety concerns, and the treatment of patients participating in the study continued according to the protocol.	-

Notes:

Limitations and caveats

None reported