Clinical trial results:
A Phase 1b/2, Open-Label, Multi-Center, Dose Escalation Study of Binimetinib In Combination with Panitumumab in Adult Patients with Mutant RAS or Wild-Type RAS Metastatic Colorectal Cancer

Summary

EudraCT number	2013-001986-18
Trial protocol	ES BE IT NL DE FR
Global end of trial date	25 January 2016

Results information

Result version number	v1 (current)
This version publication date	25 November 2017
First version publication date	25 November 2017

Trial information

Trial identification

Sponsor protocol code	CMEK162X2116

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Array BioPharma Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, United States, 80301 Colorado
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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	11 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2016
Global end of trial reached?	Yes
Global end of trial date	25 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase Ib: To estimate the MTD and/or RP2D of MEK162 in combination with panitumumab
Phase II: To assess clinical efficacy of the MEK162 and panitumumab combination

Protection of trial subjects:

In both study phases, doses of study drug were adjusted or interrupted as appropriate based on protocol-defined treatment modifications. If an infusion reaction occurred while panitumumab was being administered, the infusion was stopped immediately, and the patient was closely monitored and treated according to institutional standards.

Background therapy:

Patients who took concomitant medication chronically were advised to maintain the same dose and dose schedule throughout the study period, as medically feasible

Evidence for comparator: -

Actual start date of recruitment	19 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	53
EEA total number of subjects	29

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)	40
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at a total of 8 sites: 2 sites in the United States, and 1 site each in Belgium, Canada, France, Italy, The Netherlands, and Spain. The patient population consisted of adult patients with mutant RAS or WT RAS mCRC. A total of 10 patients were enrolled in Phase 1b and 43 patients were enrolled in Phase 2.

Pre-assignment

Screening details:

Four patients were screened but not enrolled in Phase 1b and 35 patients were screened but not enrolled in Phase 2. Patients were male or female, at least 18 years of age with a histological or cytological confirmation of mCRC, with evidence of measurable disease as determined by RECIST v1.1.

Period 1

Period 1 title	Dose-escalation Phase (Phase 1b)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable, this clinical trial was open-label.

Arms

Arm title	Binimetinib (MEK162) plus Panitumumab

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for Panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

Number of subjects in period 1	Binimetinib (MEK162) plus Panitumumab
Started	10
Completed	53

Joined	43
Late recruitment	43
Late recruitment reason	based on Mutant / WT RAS and anti-EGFRi/- Naive

Period 2

Period 2 title	Efficacy Phase (Phase 2)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable, this study was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for

subsequent doses per institutional guidelines.

Arm title	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

Arm title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

Arm title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Arm description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The tablets were yellow to dark yellow and supplied in dosage strengths of 15 mg. Binimetinib tablets were to be taken orally BID, 12 ± 2 hours apart at approximately the same time each day, 2 hours before and 1 hour after food intake.

Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Panitumumab was dosed based on patient body weight and the starting dose selected for panitumumab was 6 mg/kg Q2W. Each dose of panitumumab dose was administered intravenously at the study site Q2W on Days 1 and 15 of every 28-day cycle according to institutional standards. The panitumumab dose was calculated based on the patient's actual body weight at baseline and was recalculated for subsequent doses per institutional guidelines.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is dose escalation part only (10 patients enrolled) to estimate the maximum tolerated dose (MTD) and/or RP2D of binimetinib in combination with panitumumab. Phase 2 began after the declaration of the MTD/RP2D. For this phase of the study, additional patients were enrolled, based on previous anti-EGFR monoclonal antibody therapy and RAS mutational status, into 1 of 4 different Phase 2 patient groups.

Number of subjects in period 2[2][3]	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve
Started	15	5	15
Completed	15	5	15

Number of subjects in period 2[2][3]	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve
Started	8
Completed	8

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: This study was a multi-center, open-label, dose-finding escalation study comprising 2 parts: Phase 1b was the dose escalation part, and it was followed by a Phase 2 clinical efficacy evaluation. In the first part 10 patients have been enrolled and subsequently 43 patients in the second part have been enrolled to a total of 53 patients globally included.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: This study was a multi-center, open-label, dose-finding escalation study comprising 2 parts: Phase 1b was the dose escalation part, and it was followed by a Phase 2 clinical efficacy evaluation. In the first part 10 patients have been enrolled and subsequently 43 patients in the second part have been enrolled to a total of 53 patients globally included.

Baseline characteristics

Reporting groups	
Reporting group title	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group values	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve
Number of subjects	15	5	15
Age categorical Units: Subjects			
Adults (18-64 years)	13	3	10
From 65-84 years	2	2	5
Age continuous Units: years			
median	56	55	58
full range (min-max)	36 to 71	49 to 75	30 to 79
Gender categorical Units: Subjects			
Female	9	4	9

Male	6	1	6

Reporting group values	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve	Total	
Number of subjects	8	43	
Age categorical Units: Subjects			
Adults (18-64 years)	6	32	
From 65-84 years	2	11	
Age continuous Units: years			
median	55		
full range (min-max)	30 to 79	-	
Gender categorical Units: Subjects			
Female	5	27	
Male	3	16	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All 53 patients were included in the full analysis set (FAS). The FAS included all patients who received at least 1 full or partial dose of binimetinib or panitumumab.

Reporting group values	Full analysis set (FAS)		
Number of subjects	53		
Age categorical Units: Subjects			
Adults (18-64 years)	40		
From 65-84 years	13		
Age continuous Units: years			
median	55		
full range (min-max)	30 to 79		
Gender categorical Units: Subjects			
Female	31		
Male	22		

End points

End points reporting groups

Reporting group title	Binimetinib (MEK162) plus Panitumumab

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Reporting group title	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve

Reporting group description:

Phase 1b was conducted in 10 adult patients with mutant RAS or WT RAS mCRC who had progressed while on standard therapy or following standard therapy, or for whom there was no standard therapy available. During the Phase 1b, the starting dose for the study drug combination was 45 mg twice daily (BID) for binimetinib and 6 mg/kg once every second week (Q2W) of panitumumab based on available data from Array's first-in-human study [ARRAY-162-111] and the recommended panitumumab dose for mCRC in combination with other anticancer agents according to the panitumumab label, respectively.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All 53 patients were included in the full analysis set (FAS). The FAS included all patients who received at least 1 full or partial dose of binimetinib or panitumumab.

Primary: Overall Response Rate (ORR) as per RECIST version 1.1

End point title	Overall Response Rate (ORR) as per RECIST version 1.1

End point description:

Overall response rate is the sum of patients with complete response and partial response.
The best overall response (BOR) was recorded from the start of the treatment until disease progression.

End point type	Primary

End point timeframe:

All patients considered for enrollment in Phase 2. Patients continued treatment with the combination therapy of binimetinib and panitumumab until progression of disease, development of unacceptable toxicity.

End point values	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	5	15	8
Units: number of patiens				
complete response (confirmed)	0	0	0	0
partial response (confirmed)	0	0	1	0

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: number of patiens				
complete response (confirmed)	0			
partial response (confirmed)	1			

Statistical analyses

Statistical analysis title	Statistical Analysis version 9.2

Statistical analysis description:

The clinical study data were analyzed by Array BioPharma Inc. and/or a designated contract research organization. For Bayesian modeling, programs were compiled using R (version 2.13.2) and WinBUGS (version 1.4.3) available in the production environment from MODESIM.

Comparison groups	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi v Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve v Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve v Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	12.3
Variability estimate	Standard deviation

Notes:

[1] - Clopper-Pearson method

Primary: Incidence of dose-limiting toxicities (DLTs) in Cycle 1

End point title	Incidence of dose-limiting toxicities (DLTs) in Cycle 1[2]

End point description:

At least 21 out of the 28 planned daily doses of binimetinib [BID] and both doses of panitumumab [Q2W] in the first 28 days of dosing. A DLT was defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first 28 days of treatment with binimetinib and panitumumab and met the specified criteria for the type of toxicity.

End point type	Primary

End point timeframe:

Patients had been observed for ≥ 28 days following the first dose.

Notes:

[2] - 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: An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle was used to guide the dose escalation of the combination treatment to its maximum tolerated dose/recommended Phase 2 dose.

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: number of patients with DLT				
Dose Limiting Toxicity (all)	5			
DLTs leading to discontinuation	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Kaplan-Meier Estimates of Overall Survival Rate – % [95% CI]. Analysis of OS was performed if at least 50% of the patients died.

End point type	Secondary

End point timeframe:

Overall survival is defined as the time from the start of treatment to the date of death due to any cause. If it was not known whether a patient had died, survival was censored at the date of last contact.

End point values	Binimetinib (MEK162) plus Panitumumab Mutant RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS Anti-EGFRi	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve	Binimetinib (MEK162) plus Panitumumab WT RAS EGFRi-Naïve
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	5	15	8
Units: months				
median (confidence interval 95%)				
50th Percentile Events	3.5 (2.1 to 8)	5.5 (3.9 to 9.6)	5.8 (3.1 to 8)	11.2 (2.1 to 13.3)

End point values	Full analysis set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: months				
median (confidence interval 95%)				
50th Percentile Events	5.5 (3.9 to 8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing antineoplastic treatments was to be collected for 30 days after the last dose of study treatment.

Adverse event reporting additional description:

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (RECIST version 1.1 criteria), were not to be reported as a SAE. Adverse events separate from the progression of malignancy were reported as per the usual guidelines used for such events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	All Phase 2 Patients

Reporting group description:

All Phase 2 Patients (N=43) inlcuded

Reporting group title	Phase 1b

Reporting group description:

Phase 1b (N=10) patients

Reporting group title	All Patients (Phase 1b and Phase 2)

Reporting group description:

All Patients (N=53) included in both Phase 1b and 2 phases

Serious adverse events	All Phase 2 Patients	Phase 1b	All Patients (Phase 1b and Phase 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 43 (51.16%)	3 / 10 (30.00%)	25 / 53 (47.17%)
number of deaths (all causes)	5	2	7
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood CPK increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Hypoxia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sinus tachycardia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Transient ischaemic attack			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Abdominal distension			

subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Septic shock			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	4 / 53 (7.55%)
occurrences causally related to treatment / all	4 / 4	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Small intestinal obstruction			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)	1 / 10 (10.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 10 (10.00%)	2 / 53 (3.77%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumomediastinum			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 43 (0.00%)	1 / 10 (10.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 10 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	All Phase 2 Patients	Phase 1b	All Patients (Phase 1b and Phase 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)	10 / 10 (100.00%)	53 / 53 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 43 (6.98%)	2 / 10 (20.00%)	5 / 53 (9.43%)
occurrences (all)	3	2	5
Hypotension			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences (all)	2	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 43 (37.21%)	9 / 10 (90.00%)	25 / 53 (47.17%)
occurrences (all)	16	9	25
Chills			
subjects affected / exposed	7 / 43 (16.28%)	3 / 10 (30.00%)	10 / 53 (18.87%)
occurrences (all)	7	3	10
Oedema Peripheral			
subjects affected / exposed	8 / 43 (18.60%)	2 / 10 (20.00%)	10 / 53 (18.87%)
occurrences (all)	8	2	10
Pyrexia			
subjects affected / exposed	8 / 43 (18.60%)	2 / 10 (20.00%)	10 / 53 (18.87%)
occurrences (all)	8	2	10
Asthenia			
subjects affected / exposed	8 / 43 (18.60%)	0 / 10 (0.00%)	8 / 53 (15.09%)
occurrences (all)	8	0	8
Feeling Cold			
subjects affected / exposed	0 / 43 (0.00%)	3 / 10 (30.00%)	3 / 53 (5.66%)
occurrences (all)	0	3	3
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 43 (6.98%)	1 / 10 (10.00%)	4 / 53 (7.55%)
occurrences (all)	3	1	4
Cough			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences (all)	2	1	3

Dysphonia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 10 (20.00%)	3 / 53 (5.66%)
occurrences (all)	1	2	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 43 (2.33%)	3 / 10 (30.00%)	4 / 53 (7.55%)
occurrences (all)	1	3	4
Anxiety			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	12 / 43 (27.91%)	5 / 10 (50.00%)	17 / 53 (32.08%)
occurrences (all)	12	5	17
Aspartate Aminotransferase Increased			
subjects affected / exposed	8 / 43 (18.60%)	0 / 10 (0.00%)	8 / 53 (15.09%)
occurrences (all)	8	0	8
Ejection Fraction Decreased			
subjects affected / exposed	6 / 43 (13.95%)	1 / 10 (10.00%)	7 / 53 (13.21%)
occurrences (all)	6	1	7
Blood Creatinine Increased			
subjects affected / exposed	6 / 43 (13.95%)	0 / 10 (0.00%)	6 / 53 (11.32%)
occurrences (all)	6	0	6
Lipase Increased			
subjects affected / exposed	5 / 43 (11.63%)	1 / 10 (10.00%)	6 / 53 (11.32%)
occurrences (all)	5	1	6
Alanine Aminotransferase Increased			
subjects affected / exposed	5 / 43 (11.63%)	0 / 10 (0.00%)	5 / 53 (9.43%)
occurrences (all)	5	0	5
Blood Bilirubin Increased			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	4 / 53 (7.55%)
occurrences (all)	4	0	4
Weight Decreased			
subjects affected / exposed	1 / 43 (2.33%)	3 / 10 (30.00%)	4 / 53 (7.55%)
occurrences (all)	1	3	4
Blood Alkaline Phosphatase			

Increased			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	3 / 43 (6.98%)	3 / 10 (30.00%)	6 / 53 (11.32%)
occurrences (all)	3	3	6
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 43 (20.93%)	0 / 10 (0.00%)	9 / 53 (16.98%)
occurrences (all)	9	0	9
Leukocytosis			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	4 / 53 (7.55%)
occurrences (all)	4	0	4
Eye disorders			
Vision Blurred			
subjects affected / exposed	5 / 43 (11.63%)	2 / 10 (20.00%)	7 / 53 (13.21%)
occurrences (all)	5	2	7
Chorioretinopathy			
subjects affected / exposed	4 / 43 (9.30%)	2 / 10 (20.00%)	6 / 53 (11.32%)
occurrences (all)	4	2	6
Retinal Detachment			
subjects affected / exposed	4 / 43 (9.30%)	1 / 10 (10.00%)	5 / 53 (9.43%)
occurrences (all)	4	1	5
Retinopathy			
subjects affected / exposed	3 / 43 (6.98%)	2 / 10 (20.00%)	5 / 53 (9.43%)
occurrences (all)	3	2	5
Periorbital Oedema			
subjects affected / exposed	1 / 43 (2.33%)	2 / 10 (20.00%)	3 / 53 (5.66%)
occurrences (all)	1	2	3
Vitreous Floaters			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences (all)	2	1	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 43 (72.09%)	7 / 10 (70.00%)	38 / 53 (71.70%)
occurrences (all)	31	7	38

Vomiting			
subjects affected / exposed	24 / 43 (55.81%)	4 / 10 (40.00%)	28 / 53 (52.83%)
occurrences (all)	24	4	28
Nausea			
subjects affected / exposed	22 / 43 (51.16%)	5 / 10 (50.00%)	27 / 53 (50.94%)
occurrences (all)	22	5	27
Abdominal Pain			
subjects affected / exposed	13 / 43 (30.23%)	1 / 10 (10.00%)	14 / 53 (26.42%)
occurrences (all)	13	1	14
Stomatitis			
subjects affected / exposed	10 / 43 (23.26%)	3 / 10 (30.00%)	13 / 53 (24.53%)
occurrences (all)	10	3	13
Constipation			
subjects affected / exposed	10 / 43 (23.26%)	2 / 10 (20.00%)	12 / 53 (22.64%)
occurrences (all)	10	2	12
Dry Mouth			
subjects affected / exposed	5 / 43 (11.63%)	1 / 10 (10.00%)	6 / 53 (11.32%)
occurrences (all)	5	1	6
Dyspepsia			
subjects affected / exposed	4 / 43 (9.30%)	2 / 10 (20.00%)	6 / 53 (11.32%)
occurrences (all)	4	2	6
Abdominal Pain Upper			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	4 / 53 (7.55%)
occurrences (all)	4	0	4
Oral Pain			
subjects affected / exposed	4 / 43 (9.30%)	0 / 10 (0.00%)	4 / 53 (7.55%)
occurrences (all)	4	0	4
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 43 (2.33%)	2 / 10 (20.00%)	3 / 53 (5.66%)
occurrences (all)	1	2	3
Glossodynia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3
Skin and subcutaneous tissue disorders			
Dermatitis Acneiform			

subjects affected / exposed	15 / 43 (34.88%)	8 / 10 (80.00%)	23 / 53 (43.40%)
occurrences (all)	15	8	23
Rash			
subjects affected / exposed	20 / 43 (46.51%)	2 / 10 (20.00%)	22 / 53 (41.51%)
occurrences (all)	20	2	22
Dry Skin			
subjects affected / exposed	11 / 43 (25.58%)	6 / 10 (60.00%)	17 / 53 (32.08%)
occurrences (all)	11	6	17
Rash Maculo-Papular			
subjects affected / exposed	7 / 43 (16.28%)	5 / 10 (50.00%)	12 / 53 (22.64%)
occurrences (all)	7	5	12
Skin Fissures			
subjects affected / exposed	5 / 43 (11.63%)	3 / 10 (30.00%)	8 / 53 (15.09%)
occurrences (all)	5	3	8
Pruritus			
subjects affected / exposed	3 / 43 (6.98%)	1 / 10 (10.00%)	4 / 53 (7.55%)
occurrences (all)	3	1	4
Erythema			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences (all)	2	1	3
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	5 / 43 (11.63%)	3 / 10 (30.00%)	8 / 53 (15.09%)
occurrences (all)	5	3	8
Arthralgia			
subjects affected / exposed	2 / 43 (4.65%)	3 / 10 (30.00%)	5 / 53 (9.43%)
occurrences (all)	2	3	5
Pain In Extremity			
subjects affected / exposed	1 / 43 (2.33%)	2 / 10 (20.00%)	3 / 53 (5.66%)
occurrences (all)	1	2	3
Infections and infestations			
Paronychia			
subjects affected / exposed	5 / 43 (11.63%)	3 / 10 (30.00%)	8 / 53 (15.09%)
occurrences (all)	5	3	8
Folliculitis			

subjects affected / exposed	5 / 43 (11.63%)	3 / 10 (30.00%)	8 / 53 (15.09%)
occurrences (all)	5	3	8
Conjunctivitis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 10 (10.00%)	4 / 53 (7.55%)
occurrences (all)	3	1	4
Sepsis			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3
Urinary Tract Infection			
subjects affected / exposed	2 / 43 (4.65%)	1 / 10 (10.00%)	3 / 53 (5.66%)
occurrences (all)	2	1	3
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	6 / 43 (13.95%)	6 / 10 (60.00%)	12 / 53 (22.64%)
occurrences (all)	6	6	12
Decreased Appetite			
subjects affected / exposed	6 / 43 (13.95%)	5 / 10 (50.00%)	11 / 53 (20.75%)
occurrences (all)	6	5	11
Hypokalaemia			
subjects affected / exposed	9 / 43 (20.93%)	0 / 10 (0.00%)	9 / 53 (16.98%)
occurrences (all)	9	0	9
Dehydration			
subjects affected / exposed	5 / 43 (11.63%)	2 / 10 (20.00%)	7 / 53 (13.21%)
occurrences (all)	5	2	7
Hyponatraemia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 10 (10.00%)	5 / 53 (9.43%)
occurrences (all)	4	1	5
Hypophosphataemia			
subjects affected / exposed	3 / 43 (6.98%)	2 / 10 (20.00%)	5 / 53 (9.43%)
occurrences (all)	3	2	5
Hypoalbuminaemia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3
Hypocalcaemia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 10 (0.00%)	3 / 53 (5.66%)
occurrences (all)	3	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2014	Protocol Version 01, dated 02 April 2014
18 September 2015	Protocol Version 02, dated 18 September 2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported