Clinical trial results:
A phase Ib/II, open-label, multicenter study of AEB071 and MEK162 in adult patients with metastatic uveal melanoma

Summary

EudraCT number	2013-000281-11
Trial protocol	DE NL ES GB IT
Global end of trial date	15 May 2015

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	13 July 2016

Trial information

Trial identification

Sponsor protocol code	CMEK162X2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01801358
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	15 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2015
Global end of trial reached?	Yes
Global end of trial date	15 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase Ib
To estimate the MTD and/or RP2D of sotrastaurin in combination with binimetinib in patients with metastatic uveal melanoma.

Phase II
To estimate and compare the antitumor activity of the sotrastaurin and binimetinib combination (Arm 1) and binimetinib alone (Arm 2) in patients with metastatic uveal melanoma.

Protection of trial subjects:

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

Informed consent was obtained from each patient in writing before starting any study-specific procedure. The study was described by the Investigator or delegate, who answered any questions, and written information was also provided.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	26 August 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	United States: 7
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 11
Worldwide total number of subjects	38
EEA total number of subjects	31

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)	27
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The CMEK162X2203 study began recruitment on 26-Aug-2013 and concluded on 15-May-2015. Due to an enrollment halt, the Phase II part of the study was not conducted. The sponsor decided to permanently stop recruitment for the study prior to MTD determination.

Pre-assignment

Screening details:

Participant Flow and Baseline Demographics data represents the Full Analysis Set (FAS), which includes all patients who received at least one full or partial dose of sotrastaurin or binimetinib.

Not completed subjects represents subjects that stopped treatment early, due to the corresponding reason.

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:

The CMEK162X2203 study was open-label, therefore blinding implementation details are not applicable.

Arms

Arm title	Phase Ib (Dose Escalation)

Arm description:

Combination of sotrastaurin and binimetinib administered orally bid.

Arm type	Experimental
Investigational medicinal product name	Sotrastaurin
Investigational medicinal product code	AEB071
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Combination of sotrastaurin and binimetinib administered orally bid.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Combination of sotrastaurin and binimetinib administered orally bid.

Number of subjects in period 1	Phase Ib (Dose Escalation)
Started	38
Completed	0
Not completed	38
Physician decision	1

Consent withdrawn by subject	3
Adverse event, non-fatal	4
Disease Progression	30

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description:

The overall study reporting group is comprised of the Phase Ib part of the study, due to an enrollment halt during the Phase Ib dose-escalation part prior to determination of the MTD as dose escalation of sotrastaurin beyond the starting dose was prevented due to sub-optimal tolerability of the combination of sotrastaurin and binimetinib.

Reporting group values	Overall Study	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
< 65 Years	27	27	
≥ 65 Years	11	11	
Age continuous Units: years			
arithmetic mean	56.4		
standard deviation	± 11.39	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	24	24	
Predominant Race Units: Subjects			
Caucasian	31	31	
Unknown	7	7	
Ethnicity Units: Subjects			
Hispanic or Latino	6	6	
Russian	1	1	
Unknown	10	10	
Other	21	21	
Baseline 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:	32	32	
1:	6	6	

Subject analysis sets	
Subject analysis set title	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid
Subject analysis set type	Sub-group analysis

Subject analysis set description: AEB071 150 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 200 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 300 mg bid + MEK162 30 mg bid	
Subject analysis set title	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 300 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 350 mg bid + MEK162 30 mg bid	
Subject analysis set title	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 400 mg bid + MEK162 30 mg bid	

Reporting group values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid
Number of subjects	6	6	6
Age categorical Units: Subjects			
< 65 Years	5	5	5
≥ 65 Years	1	1	1
Age continuous Units: years			
arithmetic mean	48.7	57	52.8
standard deviation	± 15.21	± 10.43	± 10.82
Gender categorical Units: Subjects			
Female	3	2	3
Male	3	4	3
Predominant Race Units: Subjects			
Caucasian	4	3	5
Unknown	2	3	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	2
Russian	1	0	0
Unknown	2	4	2
Other	2	1	2
Baseline 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:	3	6	5
1:	3	0	1

Reporting group values	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid
Number of subjects	6	6	8
Age categorical Units: Subjects			
< 65 Years	3	4	5
≥ 65 Years	3	2	3
Age continuous Units: years			
arithmetic mean	59.8	56.8	61.5
standard deviation	± 9.11	± 10.87	± 10.65
Gender categorical Units: Subjects			
Female	2	2	2
Male	4	4	6
Predominant Race Units: Subjects			
Caucasian	5	6	8
Unknown	1	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	0
Russian	0	0	0
Unknown	1	1	0
Other	4	4	8
Baseline 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:	5	5	8
1:	1	1	0

End points

End points reporting groups

Reporting group title	Phase Ib (Dose Escalation)
Reporting group description: Combination of sotrastaurin and binimetinib administered orally bid.	
Subject analysis set title	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 150 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 200 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 300 mg bid + MEK162 30 mg bid	
Subject analysis set title	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 300 mg bid + MEK162 45 mg bid	
Subject analysis set title	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 350 mg bid + MEK162 30 mg bid	
Subject analysis set title	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: AEB071 400 mg bid + MEK162 30 mg bid	

Primary: Phase Ib: Incidence of Dose Limiting Toxicities (DLT) During the First Cycle

End point title	Phase Ib: Incidence of Dose Limiting Toxicities (DLT) During the First Cycle[1]
End point description: A DLT is defined as an adverse event or abnormal laboratory value as defined in the protocol that is assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days of treatment with AEB071and MEK162.	
End point type	Primary
End point timeframe: Cycle 1 (up to 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: Not applicable.

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[2]	6[3]	5[4]	6[5]
Units: DLTs				
Anaemia	0	0	0	1
Diarrhoea	0	0	2	1
Vomiting	0	0	0	1
Nausea	0	0	0	1
Fatigue	0	0	1	1
General Physical Health Deterioration	0	0	1	0
Malaise	0	0	0	1
Blood Creatinine Increased	0	0	0	0
Ejection Fraction Decreased	0	0	0	0
Dermatitis Acneiform	0	2	0	0
Rash	0	0	0	1

Notes:

[2] - Dose Determining Set

[3] - Dose Determining Set

[4] - Dose Determining Set

[5] - Dose Determining Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[6]	4[7]		
Units: DLTs				
Anaemia	0	0		
Diarrhoea	0	0		
Vomiting	1	1		
Nausea	0	1		
Fatigue	0	0		
General Physical Health Deterioration	0	0		
Malaise	0	0		
Blood Creatinine Increased	1	0		
Ejection Fraction Decreased	0	1		
Dermatitis Acneiform	0	0		
Rash	0	0		

Notes:

[6] - Dose Determining Set

[7] - Dose Determining Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II: The Number of Subjects Experiencing At Least One Adverse Event (AE)

End point title	Phase Ib/II: The Number of Subjects Experiencing At Least One Adverse Event (AE)

End point description:

An adverse event 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 obtained.

Due to an enrollment halt, the Phase II part of the study was not conducted. As EudraCT only allows numerical data entry, the value of 999 indicates "No Value", as no data was analyzed for this end point.

End point type	Secondary

End point timeframe:

From first dose of Cycle 1, Day 1 (C1D1) to time to progression (up to 18 months from Last Patient First Visit)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[8]	6[9]	6[10]	6[11]
Units: participants	6	6	6	6

Notes:

[8] - Safety Set

[9] - Safety Set

[10] - Safety Set

[11] - Safety Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[12]	8[13]		
Units: participants	6	8		

Notes:

[12] - Safety Set

[13] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib/II: The Number of Subjects Experiencing At Least One Serious Adverse Event (SAE)

End point title	Phase Ib/II: The Number of Subjects Experiencing At Least One Serious Adverse Event (SAE)

End point description:

Serious adverse event (SAE) is defined as one of the following:
- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to metastatic uveal melanoma and has not worsened since signing the informed consent
• Social reasons and respite care in the absence of any deterioration in the patient's general condition

Due to an enrollment halt, the Phase II part of the study was not conducted. As EudraCT only allows numerical data entry, the value of 999 indicates "No Value".

End point type	Secondary

End point timeframe:

From first dose of Cycle 1, Day 1 (C1D1) to time to progression (up to 18 months from Last Patient First Visit)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[14]	6[15]	6[16]	6[17]
Units: participants	3	1	3	4

Notes:

[14] - Safety Set

[15] - Safety Set

[16] - Safety Set

[17] - Safety Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[18]	8[19]		
Units: participants	2	6		

Notes:

[18] - Safety Set

[19] - Safety Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Best Overall Response (BOR)

End point title	Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Best Overall Response (BOR)

End point description:

Assessment of the preliminary anti-tumor activity of AEB071 and MEK162 in combination.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

End point type	Secondary

End point timeframe:

Cycle 1 (up to 28 days)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[20]	6[21]	6[22]	6[23]
Units: participants				
Complete Response	0	0	0	0
Partial Response	0	0	0	0
Stable Disease	5	4	4	2
Progressive disease	1	2	1	2
Unknown	0	0	1	2

Notes:

[20] - Full Analysis Set

[21] - Full Analysis Set

[22] - Full Analysis Set

[23] - Full Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[24]	8[25]		
Units: participants				
Complete Response	0	0		
Partial Response	0	0		
Stable Disease	3	5		
Progressive disease	3	2		
Unknown	0	1		

Notes:

[24] - Full Analysis Set

[25] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Duration of Response (DOR)

End point title	Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Duration of Response (DOR)

End point description:

Assessment of the preliminary anti-tumor activity of AEB071 and MEK162 in combination.

Duration of Response (DOR) is not reported, since there were no responses of Complete Response (CR) or Partial Response (PR) at any time during the study.

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

End point timeframe:

Cycle 1 (up to 28 days)

End point values	Phase Ib (Dose Escalation)			
Subject group type	Reporting group			
Number of subjects analysed	38[26]			
Units: participants	999			

Notes:

[26] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Progression Free Survival (PFS)

End point title	Phase Ib: Assessment of The Preliminary Anti-tumor Activity - Progression Free Survival (PFS)

End point description:

Assessment of the preliminary anti-tumor activity of AEB071 and MEK162 in combination.

PFS is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause.

End point type	Secondary

End point timeframe:

Cycle 1 (up to 28 days)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[27]	6[28]	6[29]	6[30]
Units: weeks				
median (inter-quartile range (Q1-Q3))	3.6 (3.2 to 3.7)	3.4 (1.6 to 3.7)	4 (1.7 to 6.5)	3.7 (1.2 to 5.3)

Notes:

[27] - Full Analysis Set

[28] - Full Analysis Set

[29] - Full Analysis Set

[30] - Full Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg	Phase Ib: AEB071 400 mg bid + MEK162 30 mg		

	bid	bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[31]	8[32]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	3.1 (1.8 to 5.4)	3.8 (1.9 to 11.5)		

Notes:

[31] - Full Analysis Set

[32] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for AEB071 - AUC0-8hr (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for AEB071 - AUC0-8hr (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[33]	5[34]	6[35]	6[36]
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	7448.5 (± 46.34)	7136 (± 25.09)	15090 (± 53.89)	14051.2 (± 45.83)

Notes:

[33] - Pharmacokinetic Analysis Set

[34] - Pharmacokinetic Analysis Set

[35] - Pharmacokinetic Analysis Set

[36] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[37]	8[38]		
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	18840.8 (± 36.24)	15217.1 (± 71.48)		

Notes:

[37] - Pharmacokinetic Analysis Set

[38] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for AEB071 - Cmax (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for AEB071 - Cmax (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[39]	5[40]	6[41]	6[42]
Units: ng/ml				
geometric mean (geometric coefficient of variation)	1837.5 (± 35.9)	1932.5 (± 31.18)	2968.1 (± 58.32)	2813 (± 36.83)

Notes:

[39] - Pharmacokinetic Analysis Set

[40] - Pharmacokinetic Analysis Set

[41] - Pharmacokinetic Analysis Set

[42] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[43]	8[44]		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	4459 (± 26.45)	3768.7 (± 57.12)		

Notes:

[43] - Pharmacokinetic Analysis Set

[44] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for AEB071 - Tmax (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for AEB071 - Tmax (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[45]	5[46]	6[47]	6[48]
Units: hr				
median (full range (min-max))	1.6 (0.4 to 4)	1.1 (1 to 4)	1.5 (0.5 to 2)	1 (0.5 to 1.9)

Notes:

[45] - Pharmacokinetic Analysis Set

[46] - Pharmacokinetic Analysis Set

[47] - Pharmacokinetic Analysis Set

[48] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[49]	8[50]		
Units: hr				
median (full range (min-max))	1 (1 to 2)	2.1 (0.5 to 5.8)		

Notes:

[49] - Pharmacokinetic Analysis Set

[50] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for AEB071 - AUC0-8hr (Cycle 1; Day 15)

End point title	Phase Ib: PK Parameters for AEB071 - AUC0-8hr (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[51]	4[52]	2[53]	5[54]
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	5879.9 (± 32.46)	6330.3 (± 29.28)	16737.1 (± 17.56)	15313.6 (± 105.21)

Notes:

[51] - Pharmacokinetic Analysis Set

[52] - Pharmacokinetic Analysis Set

[53] - Pharmacokinetic Analysis Set

[54] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[55]	5[56]		
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	15055.5 (± 78.89)	20629.7 (± 11.81)		

Notes:

[55] - Pharmacokinetic Analysis Set

[56] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for AEB071 - Cmax (Cycle 1; Day 15)

End point title	Phase Ib: PK Parameters for AEB071 - Cmax (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[57]	4[58]	2[59]	5[60]
Units: ng/ml				
geometric mean (geometric coefficient of variation)	1244.6 (± 27.5)	1347.1 (± 28.56)	3065.6 (± 60.1)	3263.8 (± 96.11)

Notes:
[57] - Pharmacokinetic Analysis Set
[58] - Pharmacokinetic Analysis Set
[59] - Pharmacokinetic Analysis Set
[60] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[61]	5[62]		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	3597.2 (± 62.84)	3716.5 (± 23.72)		

Notes:
[61] - Pharmacokinetic Analysis Set
[62] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase lb: PK Parameters for AEB071 - Tmax (Cycle 1; Day 15)

End point title	Phase lb: PK Parameters for AEB071 - Tmax (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:
Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[63]	4[64]	2[65]	5[66]
Units: hr				
median (full range (min-max))	2 (1.1 to 8.3)	1.5 (0.5 to 2)	2.6 (1 to 4.2)	3.9 (2 to 4.2)

Notes:
[63] - Pharmacokinetic Analysis Set
[64] - Pharmacokinetic Analysis Set
[65] - Pharmacokinetic Analysis Set
[66] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[67]	5[68]		
Units: hr				
median (full range (min-max))	1.9 (0.5 to 2.1)	2.1 (2 to 8)		

Notes:

[67] - Pharmacokinetic Analysis Set

[68] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - AUC0-8hr (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for MEK162 - AUC0-8hr (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[69]	5[70]	6[71]	6[72]
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	1587.7 (± 55.75)	1496.7 (± 30.02)	1088.7 (± 49.45)	1590.5 (± 43.49)

Notes:

[69] - Pharmacokinetic Analysis Set

[70] - Pharmacokinetic Analysis Set

[71] - Pharmacokinetic Analysis Set

[72] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[73]	8[74]		
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	984.4 (± 72.57)	962 (± 50.15)		

Notes:

[73] - Pharmacokinetic Analysis Set

[74] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - Cmax (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for MEK162 - Cmax (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[75]	5[76]	6[77]	6[78]
Units: ng/ml				
geometric mean (geometric coefficient of variation)	362 (± 46.74)	432.6 (± 56.3)	245.4 (± 63.08)	328.4 (± 59.07)

Notes:

[75] - Pharmacokinetic Analysis Set

[76] - Pharmacokinetic Analysis Set

[77] - Pharmacokinetic Analysis Set

[78] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[79]	8[80]		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	243.5 (± 53.27)	222.8 (± 58.13)		

Notes:

[79] - Pharmacokinetic Analysis Set

[80] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - Tmax (Cycle 1; Day 1)

End point title	Phase Ib: PK Parameters for MEK162 - Tmax (Cycle 1; Day 1)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[81]	5[82]	6[83]	6[84]
Units: hr				
median (full range (min-max))	1.1 (1 to 3.8)	1.1 (1 to 4.1)	2 (1 to 2.1)	4 (0.5 to 4.1)

Notes:

[81] - Pharmacokinetic Analysis Set

[82] - Pharmacokinetic Analysis Set

[83] - Pharmacokinetic Analysis Set

[84] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[85]	8[86]		
Units: hr				
median (full range (min-max))	2 (0.6 to 2.3)	1.1 (0.5 to 4)		

Notes:

[85] - Pharmacokinetic Analysis Set

[86] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - AUC0-8hr (Cycle 1; Day 15)

End point title	Phase Ib: PK Parameters for MEK162 - AUC0-8hr (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[87]	4[88]	4[89]	4[90]
Units: hr*ng/ml				

geometric mean (geometric coefficient of variation)	1807.4 (± 43.6)	1927.9 (± 42.48)	1374.2 (± 68.21)	1454.7 (± 41.13)

Notes:

[87] - Pharmacokinetic Analysis Set

[88] - Pharmacokinetic Analysis Set

[89] - Pharmacokinetic Analysis Set

[90] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[91]	4[92]		
Units: hr*ng/ml				
geometric mean (geometric coefficient of variation)	1268.5 (± 70.41)	1275.8 (± 39.04)		

Notes:

[91] - Pharmacokinetic Analysis Set

[92] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - Cmax (Cycle 1; Day 15)

End point title	Phase Ib: PK Parameters for MEK162 - Cmax (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[93]	4[94]	4	4[95]
Units: ng/ml				
geometric mean (geometric coefficient of variation)	454.5 (± 42.42)	418.9 (± 34.62)	307 (± 88.45)	362.7 (± 59.8)

Notes:

[93] - Pharmacokinetic Analysis Set

[94] - Pharmacokinetic Analysis Set

[95] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[96]	4[97]		
Units: ng/ml				
geometric mean (geometric coefficient of variation)	340.7 (± 80.64)	284.1 (± 52.79)		

Notes:

[96] - Pharmacokinetic Analysis Set

[97] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: PK Parameters for MEK162 - Tmax (Cycle 1; Day 15)

End point title	Phase Ib: PK Parameters for MEK162 - Tmax (Cycle 1; Day 15)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 (Day 15)

End point values	Phase Ib: AEB071 150 mg bid + MEK162 45mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[98]	4[99]	4[100]	4[101]
Units: hr				
median (full range (min-max))	2 (1.1 to 8.3)	1.6 (1.1 to 4)	3 (1 to 8.2)	2.9 (2 to 4.1)

Notes:

[98] - Pharmacokinetic Analysis Set

[99] - Pharmacokinetic Analysis Set

[100] - Pharmacokinetic Analysis Set

[101] - Pharmacokinetic Analysis Set

End point values	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	5[102]	4[103]		
Units: hr				
median (full range (min-max))	1.9 (0.5 to 2.1)	1.5 (0.5 to 8)		

Notes:

[102] - Pharmacokinetic Analysis Set

[103] - Pharmacokinetic Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected throughout the duration of the trial, which began in August, 2013 and concluded in May, 2015.

Adverse event reporting additional description:

AE reporting is comprised of the Safety Set (SS), which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Phase Ib: AEB071 150 mg bid + MEK162 45 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Reporting group title	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Reporting group title	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Reporting group title	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Reporting group title	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Reporting group title	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid

Reporting group description:

Analysis group comprised of the Safety Set, which is all patients who received at least one dose of AEB071 and MEK162, and have at least one valid post-baseline safety assessment.

Serious adverse events	Phase Ib: AEB071 150 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
number of deaths (all causes)	4	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
BLOOD CREATININE INCREASED			

subjects affected / exposed	0 / 6 (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			
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 6 (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 / 6 (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
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	0 / 6 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALAISE			
subjects affected / exposed	0 / 6 (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
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 6 (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
PYREXIA			

subjects affected / exposed	0 / 6 (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
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 6 (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 / 6 (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
DIARRHOEA			
subjects affected / exposed	0 / 6 (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
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 6 (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 / 1
NAUSEA			
subjects affected / exposed	0 / 6 (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
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	0 / 6 (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
VOMITING			
subjects affected / exposed	0 / 6 (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
Hepatobiliary disorders			

ACUTE HEPATIC FAILURE			
subjects affected / exposed	0 / 6 (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
HEPATIC FAILURE			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (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
HEPATOMEGALY			
subjects affected / exposed	1 / 6 (16.67%)	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
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 6 (16.67%)	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
PNEUMOTHORAX			
subjects affected / exposed	0 / 6 (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
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 6 (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
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 6 (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
Endocrine disorders			
HYPOTHYROIDISM			

subjects affected / exposed	1 / 6 (16.67%)	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
Infections and infestations			
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	0 / 6 (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
INFECTION			
subjects affected / exposed	0 / 6 (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
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 6 (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 / 6 (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
HYPOCALCAEMIA			
subjects affected / exposed	0 / 6 (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

Serious adverse events	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	6 / 8 (75.00%)
number of deaths (all causes)	3	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
BLOOD CREATININE INCREASED			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (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
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (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 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
MALAISE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (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
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (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
ASCITES			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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	2 / 6 (33.33%)	0 / 6 (0.00%)	4 / 8 (50.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL VARICES HAEMORRHAGE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (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
VOMITING			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

ACUTE HEPATIC FAILURE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
HEPATIC FAILURE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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
HEPATOMEGALY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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			
DYSPNOEA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (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
PNEUMOTHORAX			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (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
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
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			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
HYPOTHYROIDISM			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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			
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (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
HYPOCALCAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (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

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

Non-serious adverse events	Phase Ib: AEB071 150 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 200 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 300 mg bid + MEK162 30 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

TUMOUR PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	4 / 6 (66.67%)
occurrences (all)	3	3	4
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	4 / 6 (66.67%)
occurrences (all)	2	2	4
ASTHENIA			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	2
PYREXIA			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
MALAISE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
CHILLS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
COUGH			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
ANXIETY			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	1 / 6 (16.67%)
occurrences (all)	4	5	1
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	4 / 6 (66.67%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
WEIGHT DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
EJECTION FRACTION DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
WEIGHT INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1

CEREBROVASCULAR DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
PRESYNCOPE			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	3 / 6 (50.00%)
occurrences (all)	1	0	3
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Eye disorders			
CHORIORETINOPATHY			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
RETINAL DETACHMENT			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	2	3	1
VISION BLURRED			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
CATARACT			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
EYE DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
EYELID OEDEMA			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
MACULAR OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
PERIORBITAL OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
RETINAL OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
RETINOPATHY			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	6 / 6 (100.00%)	5 / 6 (83.33%)	6 / 6 (100.00%)
occurrences (all)	6	5	6
NAUSEA			
subjects affected / exposed	6 / 6 (100.00%)	3 / 6 (50.00%)	4 / 6 (66.67%)
occurrences (all)	6	3	4
VOMITING			
subjects affected / exposed	5 / 6 (83.33%)	3 / 6 (50.00%)	5 / 6 (83.33%)
occurrences (all)	5	3	5
CONSTIPATION			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
ABDOMINAL PAIN			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
STOMATITIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
DYSPEPSIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

FLATULENCE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
DRY MOUTH			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
GASTRITIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
IMPAIRED GASTRIC EMPTYING			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	5 / 6 (83.33%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	5	2	2
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 6 (0.00%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	0	3	3
PRURITUS			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	2	2
DRY SKIN			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
ACNE			

subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
RASH MACULO-PAPULAR			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
ALOPECIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
PAIN OF SKIN			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
ERYTHEMA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
HYPERHIDROSIS			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
RASH FOLLICULAR			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
XERODERMA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
RENAL COLIC			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
MYALGIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
BACK PAIN			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
MUSCLE SPASMS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Infections and infestations			
RASH PUSTULAR			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
DEHYDRATION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
HYPERKALAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
HYPOKALAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
CACHEXIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Phase Ib: AEB071 300 mg bid + MEK162 45 mg bid	Phase Ib: AEB071 350 mg bid + MEK162 30 mg bid	Phase Ib: AEB071 400 mg bid + MEK162 30 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

Vascular disorders			
HYPERTENSION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	5 / 8 (62.50%)
occurrences (all)	3	3	5
OEDEMA PERIPHERAL			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	3 / 8 (37.50%)
occurrences (all)	3	2	3
ASTHENIA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	3 / 8 (37.50%)
occurrences (all)	2	0	3
PYREXIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
MALAISE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
CHILLS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
COUGH			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Investigations			

BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	2 / 8 (25.00%)
occurrences (all)	2	3	2
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	0 / 8 (0.00%)
occurrences (all)	3	3	0
WEIGHT DECREASED			
subjects affected / exposed	3 / 6 (50.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	3	1	2
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	2 / 8 (25.00%)
occurrences (all)	1	2	2
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	3	0	0
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
WEIGHT INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
CEREBROVASCULAR DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2

NEUROPATHY PERIPHERAL			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
PRESYNCOPE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 6 (50.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	1
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
CHORIORETINOPATHY			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	5 / 8 (62.50%)
occurrences (all)	0	1	5
RETINAL DETACHMENT			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
VISION BLURRED			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	2	1	2
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	3 / 8 (37.50%)
occurrences (all)	0	0	3
CATARACT			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
EYE DISORDER			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
EYELID OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
MACULAR OEDEMA			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
PERIORBITAL OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
RETINAL OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
RETINOPATHY			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	8 / 8 (100.00%)
occurrences (all)	6	6	8
NAUSEA			
subjects affected / exposed	6 / 6 (100.00%)	4 / 6 (66.67%)	7 / 8 (87.50%)
occurrences (all)	6	4	7
VOMITING			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	7 / 8 (87.50%)
occurrences (all)	5	5	7
CONSTIPATION			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	4 / 8 (50.00%)
occurrences (all)	0	1	4
ABDOMINAL PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
DYSPEPSIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
FLATULENCE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	1

DRY MOUTH			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
GASTRITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
IMPAIRED GASTRIC EMPTYING			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	1 / 8 (12.50%)
occurrences (all)	3	2	1
DERMATITIS ACNEIFORM			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	0 / 8 (0.00%)
occurrences (all)	3	2	0
PRURITUS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
DRY SKIN			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
ACNE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
RASH MACULO-PAPULAR			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
ALOPECIA			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
PAIN OF SKIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
ERYTHEMA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
RASH FOLLICULAR			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
XERODERMA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
CHROMATURIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
RENAL COLIC			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
MYALGIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
BACK PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
MUSCLE SPASMS			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
RASH PUSTULAR			
subjects affected / exposed	0 / 6 (0.00%)	4 / 6 (66.67%)	2 / 8 (25.00%)
occurrences (all)	0	4	2
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	3 / 8 (37.50%)
occurrences (all)	2	1	3
DEHYDRATION			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
HYPERKALAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
HYPOALBUMINAEMIA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
HYPOKALAEMIA			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
CACHEXIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2013	Protocol Amendment 1 introduced the following changes: - In order to further reduce the risk of excess toxicity of this novel combination, the starting dose of binimetinib was reduced to 30 mg bid, 50% of the single-agent MTD. The provisional dose levels were adjusted accordingly. - Due to uncertainties regarding the potential AEs associated with this novel combination, DLT criteria for elevations in total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase, creatine kinase and worsening peripheral edema were modified, and eligibility criteria were modified to exclude patients with a serum creatinine > 1.5 x ULN. - Sotrastaurin is primarily metabolized by CYP3A4/5; therefore, the eligibility criteria were modified to exclude patients using medications and herbal supplements known to be strong inhibitors or inducers of CYP3A4/5.
27 November 2013	Protocol Amendment 2 introduced the following changes: - In phase II, to allow comparison of the preliminary anti-tumor activity of the combination of sotrastaurin and binimetinib with single-agent binimetinib. - To change the primary endpoint of the phase II part of the study from ORR to PFS. - To implement a Novartis Steering Committee to review the results of the formal interim analysis for futility in Phase II and define the scope of decisions that were to be made based on the results. - To clarify and update the inclusion and exclusion criteria: - Revised exclusion criterion #1 regarding active central nervous system lesions to align with binimetinib program standards. - Revised exclusion criterion #4 regarding history or current evident of retinal vein occlusion (RVO) or risk factors for RVO to align with binimetinib program standards. - Removed inclusion criterion regarding history of retinal degenerative disease. - Clarified exclusion criteria pertaining to prior exposure to a MEK inhibitor or a PKC inhibitor regarding patients who fail treatment in Phase Ib. - Revised exclusion criteria to extend period for contraception during dosing and after treatment discontinuation to 30 days to align with binimetinib program standards; also revised requirements for use of oral contraceptives to include use of a barrier method. - To introduce new and modify existing safety monitoring. - To include a blood sample request at baseline (Cycle 1, Day 1) and disease progression for assessment of circulating tumor DNA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

15 May 2015	Due to halted enrollment, the Phase II part of the study was not conducted. The Sponsor decided to permanently stop recruitment for the study prior to MTD determination. Remaining patients on treatment with binimetinib and sotrastaurin who were considered by the Investigator to be benefiting from their treatment could have continued treatment and were to be followed up as per protocol. No patients were ongoing as of the data cut-off date. After the last patient last visit (LPLV) was declared, the study was terminated.	-

Notes:

Limitations and caveats

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

N/A

Notes: