



Clinical trial results:

The LOGIC 2 Trial A Phase II, Multi-Center, Open-Label Study Of Sequential LGX818/MEK162 Combination Followed By A Rational Combination With Targeted Agents After Progression, To Overcome Resistance In Adult Patients With Locally Advanced Or Metastatic BRAF V600 Melanoma

Summary

EudraCT number	2013-004552-38
Trial protocol	NL GB ES IT
Global end of trial date	13 January 2023

Results information

Result version number	v1 (current)
This version publication date	19 January 2024
First version publication date	19 January 2024

Trial information

Trial identification

Sponsor protocol code	CLGX818X2109 (C4221013)
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02159066
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 East 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	12 July 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-tumor activity of LGX818/MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2014
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	Australia: 11
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 38
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	158
EEA total number of subjects	59

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)	118
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study had 2 parts. In Part I, 158 subjects were enrolled and treated with encorafenib/ binimetinib (LGX818/MEK162) combination. In Part II, 58 subjects received tailored combination treatment.

Pre-assignment

Screening details:

In Part I, subjects were treated until disease progression (PD). Based on the genetic assessment of a tumor biopsy obtained at PD, subjects from Part I entered Part II. Part II combination treatment were: encorafenib/ binimetinib + buparlisib (BKM120), infigratinib (BGJ398), capmatinib (INC280) or ribociclib (LEE011).

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part I: Encorafenib + Binimetinib (naive)

Arm description:

Subjects naive to selective V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, received encorafenib 450 milligram (mg) once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for encorafenib and binimetinib was defined as 21 days of daily continuous treatment.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

450 mg once a day. No dose reduction below 150 mg.

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

Dosage and administration details:

45 mg twice a day. No dose reduction below 15 mg.

Arm title	Part I: Encorafenib + Binimetinib (non-naive)
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Arm description:

Subjects non-naive to selective BRAF and MEK inhibitors, received encorafenib 450 mg once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for both drugs was defined as 21 days of daily continuous treatment.

Arm type	Experimental
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Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 45 mg twice a day. No dose reduction below 15 mg.	
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 450 mg once a day. No dose reduction below 150 mg.	
Arm title	Part II: Encorafenib + Binimetinib + Ribociclib
Arm description: Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and ribociclib 100 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For ribociclib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Ribociclib was taken for 21 consecutive days followed by a 7-day planned break.	
Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200 mg (starting dose) once a day. No dose reduction below 50 mg.	
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 100 mg (starting dose) once a day. Dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg.	
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	MEK162
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 45 mg twice a day. No dose reduction below 15 mg.	
Arm title	Part II: Encorafenib + Binimetinib + Infigratinib
Arm description: Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and infigratinib 75 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For infigratinib dose escalation was allowed till 125 mg and dose reduction was permitted till 25 mg. Infigratinib was taken for 21 consecutive days followed by a 7-day planned break.	
Arm type	Experimental

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

450 mg once a day. No dose reduction below 150 mg.

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

Dosage and administration details:

45 mg twice a day. No dose reduction below 15 mg.

Investigational medicinal product name	Infigratinib
Investigational medicinal product code	BGJ398
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (starting dose) once a day. Dose escalation was allowed till 125 mg and dose reduction was permitted till 25 mg.

Arm title	Part II: Encorafenib + Binimetinib + Capmatinib
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Arm description:

Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and capmatinib 200 mg (starting dose) capsule or 400 mg (starting dose) tablet twice a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For capmatinib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Treatment cycle for encorafenib, binimetinib and capmatinib was defined as 21 days of daily continuous treatment.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg (starting dose) once a day. No dose reduction below 50 mg.

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg (starting dose) capsule or 400 mg (starting dose) tablet twice a day. Dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg.

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

Dosage and administration details:

45 mg twice a day. No dose reduction below 15 mg.

Arm title	Part II: Encorafenib + Binimetinib + Buparlisib
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Arm description:

Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and buparlisib 60 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For buparlisib dose escalation was allowed till 100 mg and dose reduction was permitted till 30 mg. Treatment cycle for encorafenib, binimetinib and buparlisib was defined as 21 days of daily continuous treatment.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

450 mg once a day. No dose reduction below 150 mg.

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

Dosage and administration details:

45 mg twice a day. No dose reduction below 15 mg.

Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg (starting dose) once a day. Dose escalation was allowed till 100 mg and dose reduction was permitted till 30 mg.

Number of subjects in period 1	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)	Part II: Encorafenib + Binimetinib + Ribociclib
Started	75	83	38
Completed	0	4	0
Not completed	75	79	38
Adverse event, serious fatal	11	9	1
Physician decision	2	9	1
Subjects/Guardian Decision	9	3	-
Adverse event, non-fatal	7	5	1
Progressive Disease	37	46	35
Missing Data	1	-	-
Study Terminated by Sponsor	3	3	-
New Therapy for Study Indication	5	4	-

Number of subjects in period 1	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Started	1	13	6
Completed	0	0	0
Not completed	1	13	6
Adverse event, serious fatal	-	2	1
Physician decision	-	-	-
Subjects/Guardian Decision	-	2	-
Adverse event, non-fatal	-	1	1
Progressive Disease	1	7	4
Missing Data	-	-	-
Study Terminated by Sponsor	-	-	-
New Therapy for Study Indication	-	1	-

Baseline characteristics

Reporting groups^[1]

Reporting group title	Part I: Encorafenib + Binimetinib (naive)
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Reporting group description:

Subjects naive to selective V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, received encorafenib 450 milligram (mg) once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for encorafenib and binimetinib was defined as 21 days of daily continuous treatment.

Reporting group title	Part I: Encorafenib + Binimetinib (non-naive)
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Reporting group description:

Subjects non-naive to selective BRAF and MEK inhibitors, received encorafenib 450 mg once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for both drugs was defined as 21 days of daily continuous treatment.

Reporting group title	Part II: Encorafenib + Binimetinib + Ribociclib
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Reporting group description:

Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and ribociclib 100 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For ribociclib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Ribociclib was taken for 21 consecutive days followed by a 7-day planned break.

Reporting group title	Part II: Encorafenib + Binimetinib + Infigratinib
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Reporting group description:

Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and infigratinib 75 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For infigratinib dose escalation was allowed till 125 mg and dose reduction was permitted till 25 mg. Infigratinib was taken for 21 consecutive days followed by a 7-day planned break.

Reporting group title	Part II: Encorafenib + Binimetinib + Capmatinib
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Reporting group description:

Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and capmatinib 200 mg (starting dose) capsule or 400 mg (starting dose) tablet twice a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For capmatinib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Treatment cycle for encorafenib, binimetinib and capmatinib was defined as 21 days of daily continuous treatment.

Reporting group title	Part II: Encorafenib + Binimetinib + Buparlisib
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Reporting group description:

Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and buparlisib 60 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For buparlisib dose escalation was allowed till 100 mg and dose reduction was permitted till 30 mg. Treatment cycle for encorafenib, binimetinib and buparlisib was defined as 21 days of daily continuous treatment.

Notes:

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

Justification: In Part I, 158 subjects were enrolled and out of these, 58 subjects entered Part II of the study.

Reporting group values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)	Part II: Encorafenib + Binimetinib + Ribociclib
Number of subjects	75	83	38
Age categorical			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			

18-44 years	14	24	9
45-64 years	43	37	19
65 years and over	18	22	10
Not disclosed	0	0	0
Age Continuous			
"0" suggests that age of subject has been masked in Infigratinib arm to avoid risk of identification of the subject. "99999" suggests no standard deviation estimated as there was only 1 evaluable subject.			
Units: years			
arithmetic mean	55.3	53.9	54.6
standard deviation	± 12.91	± 13.81	± 13.85
Sex: Female, Male			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Female	28	39	22
Male	47	44	16
Not disclosed	0	0	0
Ethnicity (NIH/OMB)			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Hispanic or Latino	3	7	1
Not Hispanic or Latino	72	76	37
Not disclosed	0	0	0
Race, Customized			
Race is reported. Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Caucasian	74	82	37
Asian	1	1	1
Not disclosed	0	0	0

Reporting group values	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Number of subjects	1	13	6
Age categorical			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
18-44 years	0	0	1
45-64 years	0	7	4
65 years and over	0	6	1
Not disclosed	1	0	0
Age Continuous			
"0" suggests that age of subject has been masked in Infigratinib arm to avoid risk of identification of the subject. "99999" suggests no standard deviation estimated as there was only 1 evaluable subject.			
Units: years			
arithmetic mean	0	63.5	50.5
standard deviation	± 99999	± 8.84	± 10.50
Sex: Female, Male			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			

Female	0	5	1
Male	0	8	5
Not disclosed	1	0	0
Ethnicity (NIH/OMB)			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	13	6
Not disclosed	1	0	0
Race, Customized			
Race is reported. Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Caucasian	0	13	6
Asian	0	0	0
Not disclosed	1	0	0

Reporting group values	Total		
Number of subjects	216		
Age categorial			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
18-44 years	48		
45-64 years	110		
65 years and over	57		
Not disclosed	1		
Age Continuous			
"0" suggests that age of subject has been masked in Infigratinib arm to avoid risk of identification of the subject. "99999" suggests no standard deviation estimated as there was only 1 evaluable subject.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Female	95		
Male	120		
Not disclosed	1		
Ethnicity (NIH/OMB)			
Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Hispanic or Latino	11		
Not Hispanic or Latino	204		
Not disclosed	1		
Race, Customized			
Race is reported. Subject in Infigratinib arm has been reported under "Not disclosed" category to avoid risk of identification of the subject.			
Units: Subjects			
Caucasian	212		

Asian	3		
Not disclosed	1		

End points

End points reporting groups

Reporting group title	Part I: Encorafenib + Binimetinib (naive)
Reporting group description: Subjects naive to selective V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, received encorafenib 450 milligram (mg) once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for encorafenib and binimetinib was defined as 21 days of daily continuous treatment.	
Reporting group title	Part I: Encorafenib + Binimetinib (non-naive)
Reporting group description: Subjects non-naive to selective BRAF and MEK inhibitors, received encorafenib 450 mg once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for both drugs was defined as 21 days of daily continuous treatment.	
Reporting group title	Part II: Encorafenib + Binimetinib + Ribociclib
Reporting group description: Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and ribociclib 100 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For ribociclib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Ribociclib was taken for 21 consecutive days followed by a 7-day planned break.	
Reporting group title	Part II: Encorafenib + Binimetinib + Infigratinib
Reporting group description: Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and infigratinib 75 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For infigratinib dose escalation was allowed till 125 mg and dose reduction was permitted till 25 mg. Infigratinib was taken for 21 consecutive days followed by a 7-day planned break.	
Reporting group title	Part II: Encorafenib + Binimetinib + Capmatinib
Reporting group description: Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and capmatinib 200 mg (starting dose) capsule or 400 mg (starting dose) tablet twice a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For capmatinib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Treatment cycle for encorafenib, binimetinib and capmatinib was defined as 21 days of daily continuous treatment.	
Reporting group title	Part II: Encorafenib + Binimetinib + Buparlisib
Reporting group description: Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and buparlisib 60 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For buparlisib dose escalation was allowed till 100 mg and dose reduction was permitted till 30 mg. Treatment cycle for encorafenib, binimetinib and buparlisib was defined as 21 days of daily continuous treatment.	
Subject analysis set title	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 450 mg/ binimetinib 45 mg + buparlisib 60 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 450 mg/ binimetinib 45 mg + buparlisib 90 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II: Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg

Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 450 mg/ binimetinib 45 mg + infigratinib 75 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 200 mg/ binimetinib 45 mg + capmatinib 200 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 200 mg/ binimetinib 45 mg + capmatinib 300 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 200 mg/ binimetinib 45 mg + capmatinib 400 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects in received encorafenib 100 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject analysis set type	Per protocol
Subject analysis set description: Subejcts in received encorafenib 200 mg/ binimetinib 30 mg + ribociclib 400 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects in received encorafenib 200 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects in received encorafenib 200 mg/ binimetinib 45 mg + ribociclib 400 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 200 mg/ binimetinib 45 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 450 mg/ binimetinib 45 mg + buparlisib 60 mg. This subject analysis set is for PK related endpoint.	
Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg
Subject analysis set type	Per protocol
Subject analysis set description: Subjects received encorafenib 450 mg/ binimetinib 45 mg + buparlisib 90 mg. This subject analysis set	

is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 450 mg/ binimetinib 45 mg + infigratinib 75 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 100 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 200 mg/ binimetinib 30 mg + ribociclib 400 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 200 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 200 mg/ binimetinib 45 mg + ribociclib 400 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 300 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 450 mg/ binimetinib 45 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 300 mg/ binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Ribociclib 600mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 450 mg/ binimetinib 45 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 450 mg/ binimetinib 45 mg + capmatinib 300 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects received encorafenib 200 mg/ binimetinib 45 mg + capmatinib 400 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects received encorafenib 450 mg/ binimetinib 45 mg + buparlisib 90 mg. This subject analysis set is for PK related endpoint.

Subject analysis set title	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects received encorafenib 300 mg/binimetinib 30 mg + ribociclib 600 mg. This subject analysis set is for PK related endpoint.

Primary: Overall Response Rate (ORR): Part II

End point title	Overall Response Rate (ORR): Part II ^{[1][2]}
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End point description:

ORR: percentage of subjects with confirmed complete response (CR) and partial response (PR). Response evaluation criteria in solid tumors (RECIST) v1.1: a) CR: disappearance of all non-nodal target lesions. Any pathological lymph nodes assigned as target lesions that had a reduction in short axis to <10 mm. Disappearance of all non-target lesions. All lymph nodes assigned a non-target lesion must be non-pathological in size (<10 mm short axis); b) PR: at least a 30 percent (%) decrease in sum of diameter of all target lesions, taking as reference baseline sum of diameters. Any radiological assessments taken >30 days after last dose of study therapy or after antineoplastic agents other than study treatments taken by subjects was excluded from the best overall response derivation. Confirmation of CR or PR was to be at least 4 weeks apart from previous radiological assessment. Full analysis set (FAS) for Part II evaluated.

End point type	Primary
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End point timeframe:

From the start of the treatment until disease/clinical progression or death or early study discontinuation, whichever happened earlier (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

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

Justification: Only descriptive data was planned to be evaluated.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Percentage of subjects				
number (confidence interval 95%)	2.6 (0.1 to 13.8)	0 (0 to 0)	0 (0.0 to 24.7)	0 (0.0 to 45.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) and Serious AEs (SAEs): Part I

End point title	Number of Subjects With Adverse Events (AEs) and Serious AEs (SAEs): Part I ^[3]
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End point description:

An AE was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occurred after subjects signed informed consent has been obtained. An SAE was an AE resulting in any of the following outcomes: was fatal or life-threatening; resulted in persistent or significant disability/incapacity; constituted a congenital anomaly/birth defect; was medically significant; required inpatient hospitalization or prolongation of existing hospitalization. Safety set included all subjects who received at least 1 dose of encorafenib or binimetinib for Part I and had at least 1 valid post-baseline safety assessment.

End point type	Secondary
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End point timeframe:

Day 1 up to 30 days after last dose (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
AEs	75	78		
SAEs	47	37		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Dose Limiting Toxicities (DLTs) in Cycle 1: Part II

End point title	Number of Subjects With Dose Limiting Toxicities (DLTs) in Cycle 1: Part II ^[4]
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End point description:

DLT was defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first cycle (first 21 days for infigratinib and capmatinib; 28 days for ribociclib and buparlisib) of treatment initiation and met the defined criteria for study. Dose-determining analysis set (DDS) consisted of all subjects from the safety set for Part II who met the minimum requirements for safety evaluation and minimum exposure or experienced DLT during the first cycle of the assigned triple combination treatment. No subjects were included in the dose-determining analysis set in the encorafenib/binimetinib+ infigratinib or buparlisib arm, hence no subjects analyzed for these reporting arms for this endpoint.

End point type	Secondary
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End point timeframe:

Cycle 1 (21 days following the first dose of the combination treatment with infigratinib and capmatinib; 28 days for the combination with ribociclib and buparlisib)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	0 ^[5]	12	0 ^[6]
Units: Subjects	1		0	

Notes:

[5] - No subjects were included in the dose-determining analysis set.

[6] - No subjects were included in the dose-determining analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With AEs and SAEs: Part II

End point title	Number of Subjects With AEs and SAEs: Part II ^[7]
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End point description:

An AE was defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occurred after subjects signed informed consent has been obtained. An SAE was an AE resulting in any of the following outcomes: was fatal or life-threatening; resulted in persistent or significant disability/incapacity; constituted a congenital anomaly/birth defect; was medically significant; required inpatient hospitalization or prolongation of existing hospitalization. Safety set included all subjects who received at least 1 dose of 3rd combination agent for Part II and had at least 1 valid post-baseline safety assessment.

End point type	Secondary
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End point timeframe:

Day 1 up to 30 days after last dose (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
AEs	37	1	12	6
SAEs	19	0	6	4

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Post-baseline Hematology Results Based on Common Terminology Criteria for Adverse Events (CTCAE) Grade: Part I

End point title	Number of Subjects With Worst Post-baseline Hematology Results Based on Common Terminology Criteria for Adverse Events (CTCAE) Grade: Part I ^[8]
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End point description:

Parameters evaluated were: Activated partial thromboplastin time (APTT) (seconds [sec]) - CTCAE

graded high, fibrinogen (gram per liter [g/L]) - CTCAE graded low, hemoglobin (g/L) - CTCAE graded low, hemoglobin (g/L) - CTCAE graded high, prothrombin international normalized ratio (PINR) - CTCAE graded high, lymphocytes (10⁹/L) - CTCAE graded low, lymphocytes (10⁹/L) - CTCAE graded high, neutrophils (10⁹/L) - CTCAE graded low, platelets (10⁹/L) - CTCAE graded low, leukocytes (10⁹/L) - CTCAE graded low, leukocytes (10⁹/L) - CTCAE graded high. CTCAE version 4.03 was used: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening consequences; grade 0 = values not meeting any of the criteria for grade 1 or higher. Safety set for Part I evaluated. In results reported below: post-baseline has been abbreviated as PB, graded high as GH and graded low as GL.

End point type	Secondary
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End point timeframe:

Baseline up to last dose (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
APTT-CTCAE GH Worst PB value Grade 0	46	54		
Fibrinogen-CTCAE GL Worst PB value Grade 0	28	36		
Hemoglobin-CTCAE GL Worst PB value Grade 0	21	17		
Hemoglobin-CTCAE GH Worst PB value Grade 0	70	80		
PINR -CTCAE GH Worst PB value Grade 0	44	34		
Lymphocytes-CTCAE GL Worst PB value Grade 0	23	27		
Lymphocytes-CTCAE GH Worst PB value Grade 0	61	68		
Neutrophils-CTCAE GL Worst PB value Grade 0	52	62		
Platelets-CTCAE GL Worst PB value Grade 0	59	71		
Leukocytes-CTCAE GL Worst PB value Grade 0	52	61		
Leukocytes-CTCAE GH Worst PB value Grade 0	66	78		
APTT-CTCAE GH Worst PB value Grade 1	1	4		
Fibrinogen-CTCAE GL Worst PB value Grade 1	8	9		
Hemoglobin-CTCAE GL Worst PB value Grade 1	28	39		
Hemoglobin-CTCAE GH Worst PB value Grade 1	4	2		
PINR -CTCAE GH Worst PB value Grade 1	0	2		
Lymphocytes-CTCAE GL Worst PB value Grade 1	22	24		
Lymphocytes-CTCAE GH Worst PB value Grade 1	0	0		
Neutrophils-CTCAE GL Worst PB value Grade 1	4	6		
Platelets-CTCAE GL Worst PB value Grade 1	14	11		

Leukocytes-CTCAE GL Worst PB value Grade 1	11	14		
Leukocytes-CTCAE GH Worst PB value Grade 1	0	0		
APTT -CTCAE GH Worst PB value Grade 2	0	0		
Fibrinogen-CTCAE GL Worst PB value Grade 2	5	7		
Hemoglobin-CTCAE GL Worst PB value Grade 2	18	20		
Hemoglobin-CTCAE GH Worst PB value Grade 2	0	0		
PINR-CTCAE GH Worst PB value Grade 2	0	0		
Lymphocytes-CTCAE GL Worst PB value Grade 2	13	12		
Lymphocytes-CTCAE GH Worst PB value Grade 2	2	6		
Neutrophils-CTCAE GL Worst PB value Grade 2	5	4		
Platelets-CTCAE GL Worst PB value Grade 2	2	0		
Leukocytes-CTCAE GL Worst PB value Grade 2	3	3		
Leukocytes-CTCAE GH Worst PB value Grade 2	0	0		
APTT-CTCAE GH Worst PB value Grade 3	0	0		
Fibrinogen-CTCAE GL Worst PB value Grade 3	4	1		
Hemoglobin-CTCAE GL Worst PB value Grade 3	8	6		
Hemoglobin-CTCAE GH Worst PB value Grade 3	1	0		
PINR -CTCAE GH Worst PB value Grade 3	0	0		
Lymphocytes-CTCAE GL Worst PB value Grade 3	6	10		
Lymphocytes-CTCAE GH Worst PB value Grade 3	1	0		
Neutrophils-CTCAE GL Worst PB value Grade 3	3	1		
Platelets-CTCAE GL Worst PB value Grade 3	0	0		
Leukocytes-CTCAE GL Worst PB value Grade 3	0	0		
Leukocytes-CTCAE GH Worst PB value Grade 3	0	0		
APTT -CTCAE GH Worst PB value Grade 4	0	0		
Fibrinogen-CTCAE GL Worst PB value Grade 4	0	0		
Hemoglobin-CTCAE GL Worst PB value Grade 4	0	0		
Hemoglobin-CTCAE GH Worst PB value Grade 4	0	0		
PINR-CTCAE GH Worst PB value Grade 4	0	0		
Lymphocytes-CTCAE GL Worst PB value Grade 4	0	1		
Lymphocytes-CTCAE GH Worst PB value Grade 4	0	0		
Neutrophils-CTCAE GL Worst PB value Grade 4	0	0		

Platelets-CTCAE GL Worst PB value Grade 4	0	0		
Leukocytes-CTCAE GL Worst PB value Grade 4	0	0		
Leukocytes-CTCAE GH Worst PB value Grade 4	0	0		
APTT -CTCAE GH Worst PB value Missing	28	25		
Fibrinogen-CTCAE GL Worst PB value Missing	30	30		
Hemoglobin-CTCAE GL Worst PB value Missing	0	1		
Hemoglobin-CTCAE GH Worst PB value Missing	0	1		
PINR -CTCAE GH Worst PB value Missing	31	47		
Lymphocytes-CTCAE GL Worst PB value Missing	11	9		
Lymphocytes-CTCAE GH Worst PB value Missing	11	9		
Neutrophils-CTCAE GL Worst PB value Missing	11	10		
Platelets-CTCAE GL Worst PB value Missing	0	1		
Leukocytes-CTCAE GL Worst PB value Missing	9	5		
Leukocytes-CTCAE GH Worst PB value Missing	9	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Post-baseline Hematology Results Based on CTCAE Grade: Part II

End point title	Number of Subjects With Worst Post-baseline Hematology Results Based on CTCAE Grade: Part II ^[9]
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End point description:

Parameters evaluated were: APTT (sec) - CTCAE graded high, fibrinogen (g/L) - CTCAE graded low, hemoglobin (g/L) - CTCAE graded low, hemoglobin (g/L) - CTCAE graded high, PINR - CTCAE graded high, lymphocytes (10⁹/L) - CTCAE graded low, lymphocytes (10⁹/L) - CTCAE graded high, neutrophils (10⁹/L) - CTCAE graded low, platelets (10⁹/L) - CTCAE graded low, leukocytes (10⁹/L) - CTCAE graded low, leukocytes (10⁹/L) - CTCAE graded high. CTCAE version 4.03 was used: grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening consequences; grade 0 = values not meeting any of the criteria for grade 1 or higher. Safety set included all subjects who received at least 1 dose of 3rd combination agent for Part II and had at least 1 valid post-baseline safety assessment. In results reported below: post-baseline has been abbreviated as PB, graded high as GH and graded low as GL

End point type	Secondary
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End point timeframe:

Baseline up to last dose (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
APTT-CTCAE GH Worst PB value Grade 0	27	1	9	4
Fibrinogen-CTCAE GL Worst PB value Grade 0	13	0	6	3
Hemoglobin-CTCAE GL Worst PB value Grade 0	4	0	4	2
Hemoglobin-CTCAE GH Worst PB value Grade 0	37	1	11	6
PINR-CTCAE GH Worst PB value Grade 0	14	1	8	1
Lymphocytes -CTCAE GL Worst PB value Grade 0	5	0	4	2
Lymphocytes-CTCAE GH Worst PB value Grade 0	29	0	11	6
Neutrophils-CTCAE GL Worst PB value Grade 0	10	0	11	6
Platelets-CTCAE GL Worst PB value Grade 0	33	1	11	6
Leukocytes-CTCAE GL Worst PB value Grade 0	8	0	11	6
Leukocytes-CTCAE GH Worst PB value Grade 0	31	0	11	6
APTT-CTCAE GH Worst PB value Grade 1	0	0	0	0
Fibrinogen-CTCAE GL Worst PB value Grade 1	3	1	1	0
Hemoglobin-CTCAE GL Worst PB value Grade 1	15	1	5	1
Hemoglobin-CTCAE GH Worst PB value Grade 1	0	0	1	0
PINR-CTCAE GH Worst PB value Grade 1	0	0	0	0
Lymphocytes -CTCAE GL Worst PB value Grade 1	7	0	4	3
Lymphocytes-CTCAE GH Worst PB value Grade 1	0	0	0	0
Neutrophils-CTCAE GL Worst PB value Grade 1	9	0	0	0
Platelets-CTCAE GL Worst PB value Grade 1	4	0	1	0
Leukocytes-CTCAE GL Worst PB value Grade 1	8	0	0	0
Leukocytes-CTCAE GH Worst PB value Grade 1	0	0	0	0
APTT-CTCAE GH Worst PB value Grade 2	0	0	0	0
Fibrinogen-CTCAE GL Worst PB value Grade 2	2	0	1	0
Hemoglobin-CTCAE GL Worst PB value Grade 2	14	0	2	1
Hemoglobin-CTCAE GH Worst PB value Grade 2	0	0	0	0
PINR-CTCAE GH Worst PB value Grade 2	0	0	0	0
Lymphocytes-CTCAE GL Worst PB value Grade 2	9	0	3	1
Lymphocytes-CTCAE GH Worst PB value Grade 2	0	0	0	0

Neutrophils-CTCAE GL Worst PB value Grade 2	6	0	0	0
Platelets-CTCAE GL Worst PB value Grade 2	0	0	0	0
Leukocytes-CTCAE GL Worst PB value Grade 2	12	0	0	0
Leukocytes-CTCAE GH Worst PB value Grade 2	0	0	0	0
APTT-CTCAE GH Worst PB value Grade 3	0	0	0	0
Fibrinogen-CTCAE GL Worst PB value Grade 3	1	0	0	0
Hemoglobin-CTCAE GL Worst PB value Grade 3	4	0	1	2
Hemoglobin-CTCAE GH Worst PB value Grade 3	0	0	0	0
PINR-CTCAE GH Worst PB value Grade 3	0	0	0	0
Lymphocytes-CTCAE GL Worst PB value Grade 3	7	0	0	0
Lymphocytes-CTCAE GH Worst PB value Grade 3	0	0	0	0
Neutrophils-CTCAE GL Worst PB value Grade 3	1	0	0	0
Platelets-CTCAE GL Worst PB value Grade 3	0	0	0	0
Leukocytes-CTCAE GL Worst PB value Grade 3	3	0	0	0
Leukocytes-CTCAE GH Worst PB value Grade 3	0	0	0	0
APTT-CTCAE GH Worst PB value Grade 4	0	0	0	0
Fibrinogen-CTCAE GL Worst PB value Grade 4	0	0	0	0
Hemoglobin-CTCAE GL Worst PB value Grade 4	0	0	0	0
Hemoglobin-CTCAE GH Worst PB value Grade 4	0	0	0	0
PINR-CTCAE GH Worst PB value Grade 4	0	0	0	0
Lymphocytes-CTCAE GL Worst PB value Grade 4	1	0	0	0
Lymphocytes-CTCAE GH Worst PB value Grade 4	0	0	0	0
Neutrophils-CTCAE GL Worst PB value Grade 4	1	0	0	0
Platelets-CTCAE GL Worst PB value Grade 4	0	0	0	0
Leukocytes-CTCAE GL Worst PB value Grade 4	0	0	0	0
Leukocytes-CTCAE GH Worst PB value Grade 4	0	0	0	0
APTT-CTCAE GH Worst PB value Missing	11	0	4	2
Fibrinogen-CTCAE GL Worst PB value Missing	19	0	5	3
Hemoglobin-CTCAE GL Worst PB value Missing	1	0	1	0
Hemoglobin-CTCAE GH Worst PB value Missing	1	0	1	0
PINR-CTCAE GH Worst PB value Missing	24	0	5	5
Lymphocytes-CTCAE GL Worst PB value Missing	9	1	2	0
Lymphocytes-CTCAE GH Worst PB value Missing	9	1	2	0

Neutrophils-CTCAE GL Worst PB value Missing	11	1	2	0
Platelets-CTCAE GL Worst PB value Missing	1	0	1	0
Leukocytes-CTCAE GL Worst PB value Missing	7	1	2	0
Leukocytes-CTCAE GH Worst PB value Missing	7	1	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Post-baseline Serum Chemistry Results Based on CTCAE Grade: Part I

End point title	Number of Subjects With Worst Post-baseline Serum Chemistry Results Based on CTCAE Grade: Part I ^[10]
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End point description:

Albumin (g/L)-CTCAE graded low, alkaline phosphatase (units per liter [U/L])-CTCAE graded high, alanine aminotransferase (AT) (U/L)-CTCAE graded high, amylase (U/L)-CTCAE graded high, aspartate AT (U/L)-CTCAE graded high, bilirubin (micromole per liter [umol/L])-CTCAE graded high, creatinine (umol/L)-CTCAE graded high, creatine kinase (U/L)-CTCAE graded high, gamma glutamyl transferase (GT) (U/L)-CTCAE graded high, glucose (millimole per liter [mmol/L])-CTCAE graded low, high, potassium (mmol/L)-CTCAE graded low, potassium (mmol/L)-CTCAE graded high, magnesium (mmol/L)-CTCAE graded low, high, phosphate (mmol/L)-CTCAE graded low, sodium (mmol/L)-CTCAE graded low, sodium (mmol/L)-CTCAE graded high, urate (umol/L)-CTCAE graded high. Grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life-threatening consequences; grade 0=values not meeting any of the criteria for >=grade 1. Safety set for Part I evaluated. In rows below, graded low=GL, graded high=GH, post-baseline value=PBV

End point type	Secondary
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End point timeframe:

Baseline up to last dose (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
Albumin-CTCAE GL Worst PBV Grade 0	32	40		
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 0	39	43		
Alanine AT-CTCAE GH Worst PBV Grade 0	38	51		
Amylase-CTCAE GH Worst PBV Grade 0	53	52		
Aspartate AT-CTCAE GH Worst PBV Grade 0	38	50		
Bilirubin-CTCAE GH Worst PBV Grade 0	73	81		
Creatine Kinase-CTCAE GH Worst PBV Grade 0	22	56		

Creatinine-CTCAE GH Worst PBV Grade 0	2	4		
Gamma GT-CTCAE GH Worst PBV Grade 0	20	33		
Glucose-CTCAE GL Worst PBV Grade 0	55	67		
Glucose-CTCAE GH Worst PBV Grade 0	56	60		
Potassium-CTCAE GL Worst PBV Grade 0	65	74		
Potassium-CTCAE GH Worst PBV Grade 0	54	66		
Magnesium-CTCAE GL Worst PBV Grade 0	66	68		
Magnesium-CTCAE GH Worst PBV Grade 0	74	79		
Phosphate-CTCAE GL Worst PBV Grade 0	40	62		
Sodium-CTCAE GL Worst PBV Grade 0	54	53		
Sodium-CTCAE GH Worst PBV Grade 0	66	75		
Urate-CTCAE GH Worst PBV Grade 0	75	82		
Albumin-CTCAE GL Worst PBV Grade 1	35	29		
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 1	28	31		
Alanine AT-CTCAE GH Worst PBV Grade 1	27	28		
Amylase-CTCAE GH Worst PBV Grade 1	14	6		
Aspartate AT-CTCAE GH Worst PBV Grade 1	30	29		
Bilirubin-CTCAE GH Worst PBV Grade 1	1	0		
Creatine Kinase-CTCAE GH Worst PBV Grade 1	30	15		
Creatinine-CTCAE GH Worst PBV Grade 1	57	56		
Gamma GT-CTCAE GH Worst PBV Grade 1	19	18		
Glucose-CTCAE GL Worst PBV Grade 1	15	7		
Glucose-CTCAE GH Worst PBV Grade 1	4	10		
Potassium-CTCAE GL Worst PBV Grade 1	7	5		
Potassium-CTCAE GH Worst PBV Grade 1	18	15		
Magnesium-CTCAE GL Worst PBV Grade 1	8	14		
Magnesium-CTCAE GH Worst PBV Grade 1	1	3		
Phosphate-CTCAE GL Worst PBV Grade 1	3	3		
Sodium-CTCAE GL Worst PBV Grade 1	21	24		
Sodium-CTCAE GH Worst PBV Grade 1	9	6		
Urate-CTCAE GH Worst PBV Grade 1	0	0		
Albumin-CTCAE GL Worst PBV Grade 2	8	12		
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 2	5	5		
Alanine AT-CTCAE GH Worst PBV Grade 2	5	2		
Amylase-CTCAE GH Worst PBV Grade 2	5	2		
Aspartate AT-CTCAE GH Worst PBV Grade 2	4	2		
Bilirubin-CTCAE GH Worst PBV Grade 2	1	0		

Creatine Kinase-CTCAE GH Worst PBV Grade 2	18	8		
Creatinine-CTCAE GH Worst PBV Grade 2	14	22		
Gamma GT-CTCAE GH Worst PBV Grade 2	14	13		
Glucose-CTCAE GL Worst PBV Grade 2	1	1		
Glucose-CTCAE GH Worst PBV Grade 2	3	0		
Potassium-CTCAE GL Worst PBV Grade 2	0	0		
Potassium-CTCAE GH Worst PBV Grade 2	2	0		
Magnesium-CTCAE GL Worst PBV Grade 2	0	0		
Magnesium-CTCAE GH Worst PBV Grade 2	0	0		
Phosphate-CTCAE GL Worst PBV Grade 2	24	12		
Sodium-CTCAE GL Worst PBV Grade 2	0	0		
Sodium-CTCAE GH Worst PBV Grade 2	0	1		
Urate-CTCAE GH Worst PBV Grade 2	0	0		
Albumin-CTCAE GL Worst PBV Grade 3	0	1		
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 3	3	3		
Alanine AT-CTCAE GH Worst PBV Grade 3	5	0		
Amylase-CTCAE GH Worst PBV Grade 3	2	2		
Aspartate AT-CTCAE GH Worst PBV Grade 3	3	1		
Bilirubin-CTCAE GH Worst PBV Grade 3	0	1		
Creatine Kinase-CTCAE GH Worst PBV Grade 3	4	2		
Creatinine-CTCAE GH Worst PBV Grade 3	2	0		
Gamma GT-CTCAE GH Worst PBV Grade 3	20	15		
Glucose-CTCAE GL Worst PBV Grade 3	0	0		
Glucose-CTCAE GH Worst PBV Grade 3	7	5		
Potassium-CTCAE GL Worst PBV Grade 3	3	3		
Potassium-CTCAE GH Worst PBV Grade 3	1	0		
Magnesium-CTCAE GL Worst PBV Grade 3	1	0		
Magnesium-CTCAE GH Worst PBV Grade 3	0	0		
Phosphate-CTCAE GL Worst PBV Grade 3	8	4		
Sodium-CTCAE GL Worst PBV Grade 3	0	5		
Sodium-CTCAE GH Worst PBV Grade 3	0	0		
Urate-CTCAE GH Worst PBV Grade 3	0	0		
Albumin-CTCAE GL Worst PBV Grade 4	0	0		
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 4	0	0		
Alanine AT-CTCAE GH Worst PBV Grade 4	0	0		
Amylase-CTCAE GH Worst PBV Grade 4	0	1		
Aspartate AT-CTCAE GH Worst PBV Grade 4	0	0		

Bilirubin-CTCAE GH Worst PBV Grade 4	0	0		
Creatine Kinase-CTCAE GH Worst PBV Grade 4	1	1		
Creatinine-CTCAE GH Worst PBV Grade 4	0	0		
Gamma GT-CTCAE GH Worst PBV Grade 4	2	3		
Glucose-CTCAE GL Worst PBV Grade 4	0	0		
Glucose-CTCAE GH Worst PBV Grade 4	1	0		
Potassium-CTCAE GL Worst PBV Grade 4	0	0		
Potassium-CTCAE GH Worst PBV Grade 4	0	1		
Magnesium-CTCAE GL Worst PBV Grade 4	0	0		
Magnesium-CTCAE GH Worst PBV Grade 4	0	0		
Phosphate-CTCAE GL Worst PBV Grade 4	0	1		
Sodium-CTCAE GL Worst PBV Grade 4	0	0		
Sodium-CTCAE GH Worst PBV Grade 4	0	0		
Urate-CTCAE GH Worst PBV Grade 4	0	0		
Albumin-CTCAE GL Worst PBV Missing	0	1		
Alkaline Phosphatase-CTCAE GH Worst PBV Missing	0	1		
Alanine AT-CTCAE GH Worst PBV Missing	0	2		
Amylase-CTCAE GH Worst PBV Missing	1	20		
Aspartate AT-CTCAE GH Worst PBV Missing	0	1		
Bilirubin-CTCAE GH Worst PBV Missing	0	1		
Creatine Kinase-CTCAE GH Worst PBV Missing	0	1		
Creatinine-CTCAE GH Worst PBV Missing	0	1		
Gamma GT-CTCAE GH Worst PBV Missing	0	1		
Glucose-CTCAE GL Worst PBV Missing	4	8		
Glucose-CTCAE GH Worst PBV Missing	4	8		
Potassium-CTCAE GL Worst PBV Missing	0	1		
Potassium-CTCAE GH Worst PBV Missing	0	1		
Magnesium-CTCAE GL Worst PBV Missing	0	1		
Magnesium-CTCAE GH Worst PBV Missing	0	1		
Phosphate-CTCAE GL Worst PBV Missing	0	1		
Sodium-CTCAE GL Worst PBV Missing	0	1		
Sodium-CTCAE GH Worst PBV Missing	0	1		
Urate-CTCAE GH Worst PBV Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Worst Post-baseline Serum Chemistry Results

Based on CTCAE Grade: Part II

End point title	Number of Subjects With Worst Post-baseline Serum Chemistry Results Based on CTCAE Grade: Part II ^[11]
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End point description:

Albumin (g/L)- CTCAE graded low, alkaline phosphatase (U/L)- CTCAE graded high, alanine AT (U/L)- CTCAE graded high, amylase (U/L) - CTCAE graded high, aspartate AT (U/L)- CTCAE graded high, bilirubin (umol/L)- CTCAE graded high, creatinine (umol/L) - CTCAE graded high, creatine kinase (U/L)- CTCAE graded high, gamma GT (U/L)- CTCAE graded high, glucose (mmol/L)- CTCAE graded low, high, potassium (mmol/L)- CTCAE graded low, potassium (mmol/L)- CTCAE graded high, magnesium (mmol/L)- CTCAE graded low, high, phosphate (mmol/L)- CTCAE graded low, sodium (mmol/L)- CTCAE graded low, sodium (mmol/L)- CTCAE graded high, urate (umol/L)- CTCAE graded high. Grade 1= mild, Grade 2= moderate, Grade 3= severe, Grade 4= life-threatening consequences; Grade 0= values not meeting any of the criteria for >=grade 1. Safet set for Part II evaluated. In rows below, graded low=GL, graded high=GH, post-baseline value=PBV.

End point type	Secondary
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End point timeframe:

Baseline up to last dose (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
Albumin-CTCAE GL Worst PBV Grade 0	16	1	1	3
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 0	22	1	7	1
Alanine AT-CTCAE GH Worst PBV Grade 0	27	1	9	4
Amylase-CTCAE GH Worst PBV Grade 0	27	1	9	1
Aspartate AT-CTCAE GH Worst PBV Grade 0	27	1	8	3
Bilirubin-CTCAE GH Worst PBV Grade 0	37	1	12	6
Creatine Kinase-CTCAE GH Worst PBV Grade 0	20	0	6	3
Creatinine-CTCAE GH Worst PBV Grade 0	1	0	0	1
Gamma GT-CTCAE GH Worst PBV Grade 0	20	1	5	0
Glucose -CTCAE GL Worst PBV Grade 0	24	0	11	5
Glucose-CTCAE GH Worst PBV Grade 0	26	1	10	4
Potassium -CTCAE GL Worst PBV Grade 0	34	1	11	5
Potassium-CTCAE GH Worst PBV Grade 0	32	1	9	3
Magnesium -CTCAE GL Worst PBV Grade 0	35	1	10	4
Magnesium-CTCAE GH Worst PBV Grade 0	36	1	12	5
Phosphate -CTCAE GL Worst PBV Grade 0	25	1	7	4
Sodium-CTCAE GL Worst PBV Grade 0	28	1	10	3
Sodium-CTCAE GH Worst PBV Grade 0	35	1	12	4

Urate-CTCAE GH Worst PBV Grade 0	37	1	12	5
Albumin-CTCAE GL Worst PBV Grade 1	13	0	6	0
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 1	10	0	3	4
Alanine AT-CTCAE GH Worst PBV Grade 1	6	0	2	1
Amylase-CTCAE GH Worst PBV Grade 1	1	0	2	0
Aspartate AT-CTCAE GH Worst PBV Grade 1	6	0	4	2
Bilirubin-CTCAE GH Worst PBV Grade 1	0	0	0	0
Creatine Kinase-CTCAE GH Worst PBV Grade 1	14	1	4	2
Creatinine-CTCAE GH Worst PBV Grade 1	25	1	4	3
Gamma GT-CTCAE GH Worst PBV Grade 1	9	0	2	1
Glucose -CTCAE GL Worst PBV Grade 1	6	1	1	0
Glucose-CTCAE GH Worst PBV Grade 1	2	0	1	1
Potassium-CTCAE GL Worst PBV Grade 1	3	0	1	0
Potassium-CTCAE GH Worst PBV Grade 1	4	0	3	2
Magnesium -CTCAE GL Worst PBV Grade 1	2	0	2	1
Magnesium-CTCAE GH Worst PBV Grade 1 1	1	0	0	0
Phosphate -CTCAE GL Worst PBV Grade 1	2	0	1	1
Sodium-CTCAE GL Worst PBV Grade 1	7	0	2	2
Sodium-CTCAE GH Worst PBV Grade 1	2	0	0	1
Urate-CTCAE GH Worst PBV Grade 1	0	0	0	0
Albumin-CTCAE GL Worst PBV Grade 2	7	0	3	1
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 2	3	0	2	1
Alanine AT-CTCAE GH Worst PBV Grade 2	2	0	0	0
Amylase-CTCAE GH Worst PBV Grade 2	0	0	0	1
Aspartate AT-CTCAE GH Worst PBV Grade 2	3	0	0	0
Bilirubin-CTCAE GH Worst PBV Grade 2	0	0	0	0
Creatine Kinase-CTCAE GH Worst PBV Grade 2	3	0	0	0
Creatinine-CTCAE GH Worst PBV Grade 2	11	0	8	1
Gamma GT-CTCAE GH Worst PBV Grade 2	1	0	2	2
Glucose -CTCAE GL Worst PBV Grade 2	0	0	0	0
Glucose-CTCAE GH Worst PBV Grade 2	0	0	0	0
Potassium -CTCAE GL Worst PBV Grade 2	0	0	0	0
Potassium-CTCAE GH Worst PBV Grade 2	1	0	0	0
Magnesium -CTCAE GL Worst PBV Grade 2	0	0	0	0
Magnesium-CTCAE GH Worst PBV Grade 2	0	0	0	0
Phosphate -CTCAE GL Worst PBV Grade 2	7	0	3	0
Sodium-CTCAE GL Worst PBV Grade 2	0	0	0	0

Sodium-CTCAE GH Worst PBV Grade 2	0	0	0	0
Urate-CTCAE GH Worst PBV Grade 2	0	0	0	0
Albumin-CTCAE GL Worst PBV Grade 3	1	0	2	1
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 3	2	0	0	0
Alanine AT-CTCAE GH Worst PBV Grade 3	1	0	1	0
Amylase-CTCAE GH Worst PBV Grade 3	0	0	0	0
Aspartate AT-CTCAE GH Worst PBV Grade 3	1	0	0	1
Bilirubin-CTCAE GH Worst PBV Grade 3	0	0	0	0
Creatine Kinase-CTCAE GH Worst PBV Grade 3	0	0	2	0
Creatinine-CTCAE GH Worst PBV Grade 3	0	0	0	0
Gamma GT-CTCAE GH Worst PBV Grade 3	7	0	3	3
Glucose -CTCAE GL Worst PBV Grade 3	0	0	0	0
Glucose-CTCAE GH Worst PBV Grade 3	1	0	1	0
Potassium -CTCAE GL Worst PBV Grade 3	0	0	0	0
Potassium-CTCAE GH Worst PBV Grade 3	0	0	0	0
Magnesium -CTCAE GL Worst PBV Grade 3	0	0	0	0
Magnesium-CTCAE GH Worst PBV Grade 3	0	0	0	0
Phosphate -CTCAE GL Worst PBV Grade 3	1	0	1	0
Sodium-CTCAE GL Worst PBV Grade 3	2	0	0	0
Sodium-CTCAE GH Worst PBV Grade 3	0	0	0	0
Urate-CTCAE GH Worst PBV Grade 3	0	0	0	0
Albumin-CTCAE GL Worst PBV Grade 4	0	0	0	0
Alkaline Phosphatase-CTCAE GH Worst PBV Grade 4	0	0	0	0
Alanine AT-CTCAE GH Worst PBV Grade 4	1	0	0	1
Amylase-CTCAE GH Worst PBV Grade 4	2	0	0	0
Aspartate AT-CTCAE GH Worst PBV Grade 4	0	0	0	0
Bilirubin-CTCAE GH Worst PBV Grade 4	0	0	0	0
Creatine Kinase-CTCAE GH Worst PBV Grade 4	0	0	0	0
Creatinine-CTCAE GH Worst PBV Grade 4	0	0	0	0
Gamma GT-CTCAE GH Worst PBV Grade 4	0	0	0	0
Glucose-CTCAE GL Worst PBV Grade 4	0	0	0	0
Glucose-CTCAE GH Worst PBV Grade 4	1	0	0	0
Potassium-CTCAE GL Worst PBV Grade 4	0	0	0	0
Potassium-CTCAE GH Worst PBV Grade 4	0	0	0	0
Magnesium-CTCAE GL Worst PBV Grade 4	0	0	0	0
Magnesium-CTCAE GH Worst PBV Grade 4	0	0	0	0
Phosphate-CTCAE GL Worst PBV Grade 4	2	0	0	0

Sodium-CTCAE GL Worst PBV Grade 4	0	0	0	0
Sodium-CTCAE GH Worst PBV Grade 4	0	0	0	0
Urate-CTCAE GH Worst PBV Grade 4	0	0	0	0
Albumin-CTCAE GL Worst PBV Missing	1	0	1	1
Alkaline Phosphatase-CTCAE GH Worst PBV Missing	1	0	1	0
Alanine AT-CTCAE GH Worst PBV Missing	1	0	1	0
Amylase-CTCAE GH Worst PBV Missing	8	0	2	4
Aspartate AT-CTCAE GH Worst PBV Missing	1	0	1	0
Bilirubin-CTCAE GH Worst PBV Missing	1	0	1	0
Creatine Kinase-CTCAE GH Worst PBV Missing	1	0	1	1
Creatinine-CTCAE GH Worst PBV Missing	1	0	1	1
Gamma GT-CTCAE GH Worst PBV Missing	1	0	1	0
Glucose-CTCAE GL Worst PBV Missing	8	0	1	1
Glucose-CTCAE GH Worst PBV Missing	8	0	1	1
Potassium-CTCAE GL Worst PBV Missing	1	0	1	1
Potassium-CTCAE GH Worst PBV Missing	1	0	1	1
Magnesium-CTCAE GL Worst PBV Missing	1	0	1	1
Magnesium-CTCAE GH Worst PBV Missing	1	0	1	1
Phosphate-CTCAE GL Worst PBV Missing	1	0	1	1
Sodium-CTCAE GL Worst PBV Missing	1	0	1	1
Sodium-CTCAE GH Worst PBV Missing	1	0	1	1
Urate-CTCAE GH Worst PBV Missing	1	0	1	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Newly Occurring Notably Abnormal Vital Signs: Part I

End point title	Number of Subjects With Newly Occurring Notably Abnormal Vital Signs: Part I ^[12]
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End point description:

Vital signs evaluated were: Low/high systolic blood pressure (BP) (millimeter of Mercury [mmHg]): less than or equal to (\leq) 90 mmHg with decrease from baseline of ≥ 20 mmHg / ≥ 160 mmHg with increase from baseline of ≥ 20 mmHg; low/high diastolic BP [mmHg]: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg / ≥ 100 mmHg with increase from baseline of ≥ 15 mmHg; low/high pulse rate (beats per minute [bpm]): ≤ 50 bpm with decrease from baseline of ≥ 15 bpm / ≥ 120 bpm with increase from baseline of ≥ 15 bpm; low/high weight (kilogram [kg]): $\geq 20\%$ decrease/increase from baseline; and low/high body temperature (degree Celsius [C]): ≤ 36 C / ≥ 37.5 C. Safety set for Part I evaluated. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified rows.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
Sitting Pulse Rate: High (n= 75, 79)	2	8		
Sitting Pulse Rate: Low (n= 75, 80)	5	4		
Sitting Systolic BP: High (n= 74, 80)	18	5		
Sitting Systolic BP: Low (n= 75, 78)	3	2		
Sitting Diastolic BP: High (n= 75, 79)	11	4		
Sitting Diastolic BP: Low (n= 74, 80)	5	3		
Weight: High (n= 74, 71)	0	2		
Weight: Low (n= 74, 71)	0	0		
Body temperature: High (n= 74, 79)	14	14		
Body temperature: Low (n= 60, 71)	44	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Newly Occurring Notably Abnormal Vital Signs: Part II

End point title	Number of Subjects With Newly Occurring Notably Abnormal Vital Signs: Part II ^[13]
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End point description:

Vital signs evaluated were: Low/high systolic BP (mmHg): ≤ 90 mmHg with decrease from baseline of ≥ 20 mmHg / ≥ 160 mmHg with increase from baseline of ≥ 20 mmHg; low/high diastolic BP [mmHg]: ≤ 50 mmHg with decrease from baseline of ≥ 15 mmHg / ≥ 100 mmHg with increase from baseline of ≥ 15 mmHg; low/high pulse rate (bpm): ≤ 50 bpm with decrease from baseline of ≥ 15 bpm / ≥ 120 bpm with increase from baseline of ≥ 15 bpm; low/high weight (kg): $\geq 20\%$ decrease/increase from baseline; and low/high body temperature (C): ≤ 36 C / ≥ 37.5 C. Safety set for Part II evaluated. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified rows.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
Sitting Pulse Rate: High (n= 37, 1, 13, 6)	2	0	0	1
Sitting Pulse Rate: Low (n= 37, 1, 13, 6)	1	0	0	0
Sitting Systolic BP: High (n= 37, 1, 11, 6)	2	0	4	0
Sitting Systolic BP: Low (n= 37, 1, 13, 6)	0	0	0	0
Sitting Diastolic BP: High (n= 37, 1, 13, 6)	2	0	1	0
Sitting Diastolic BP: Low (n= 37, 1, 13, 6)	1	0	0	0
Weight: High (n= 36, 1, 13, 5)	0	0	0	0
Weight: Low (n= 36, 1, 13, 5)	1	0	0	0
Body temperature: High (n= 36, 1, 13, 6)	3	0	1	1
Body temperature: Low (n= 30, 1, 11, 5)	14	1	6	3

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Notable Electrocardiograms (ECG) Values: Part I

End point title	Number of Subjects With Notable Electrocardiograms (ECG) Values: Part I ^[14]
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End point description:

Abnormality categories were: Heart rate (HR): increase from baseline >25% and to a value >100 bpm, decrease from baseline >25% and to a value <60 bpm; PR: increase from baseline >25% and to a value >200 millisecond (ms); QRS: increase from baseline >25% and to a value >110 ms; QT: increase from baseline >30 ms, increase from baseline >60 ms, new interval >450 ms, new interval >480 ms, new interval >500 ms; and Corrected QT interval by Fridericia (QTcF): increase from baseline >30 ms, increase from baseline >60 ms, new interval >450 ms, new interval >480 ms, new interval >500 ms. New = newly occurred post-baseline value. Safety set for Part I evaluated. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified rows. In results reported below, increase from baseline has been abbreviated as IFB, and decrease from baseline as DFB.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
HR: IFB >25% & to a value >100 bpm (n = 74, 80)	10	5		
HR: DFB>25% & to a value <60 bpm (n = 74, 80)	37	23		
PR: IFB >25% & to a value >200 ms (n = 72, 80)	5	1		
QRS: IFB >25% & to a value >110 ms (n = 75, 80)	3	0		
QT: IFB >30 ms (n = 75, 80)	61	48		
QT: IFB >60 ms (n = 75, 80)	29	15		
QT: New Interval >450 ms (n = 75, 78)	24	4		
QT: New Interval >480 ms (n = 75, 80)	5	3		
QT: New Interval >500 ms (n = 75, 80)	3	0		
QTcF: IFB >30 ms (n = 75, 80)	46	31		
QTcF: IFB >60 ms (n = 75, 80)	4	2		
QTcF: New Interval >450 ms (n = 74, 77)	28	15		
QTcF: New Interval >480 ms (n = 75, 80)	4	0		
QTcF: New Interval >500 ms (n = 75, 80)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Notable ECG Values: Part II

End point title	Number of Subjects With Notable ECG Values: Part II ^[15]
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End point description:

Abnormality categories were: HR: increase from baseline >25% and to a value >100 bpm, decrease from baseline >25% and to a value <60 bpm; PR: increase from baseline >25% and to a value >200 ms; QRS: increase from baseline >25% and to a value >110 ms; QT: increase from baseline >30 ms, increase from baseline >60 ms, new interval >450 ms, new interval >480 ms, new interval >500 ms; and QTcF: increase from baseline >30 ms, increase from baseline >60 ms, new interval >450 ms, new interval >480 ms, new interval >500 ms. New = newly occurred post-baseline value. Safety set for Part II evaluated. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified rows. In results reported below, increase from baseline has been abbreviated as IFB, and decrease from baseline as DFB. Here "99999" = data not available as there was no subject evaluable.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
HR: IFB>25% & to a value >100 bpm (n=38, 1, 13, 6)	3	0	2	1
HR: DFB>25% & to a value <60 bpm (n=38, 1, 13, 6)	14	0	7	0
PR: IFB>25% & to a value >200 ms (n=37, 1, 13, 6)	1	0	2	0
QRS: IFB>25% & to a value >110 ms (n=38, 1, 13, 6)	0	0	0	0
QT: IFB>30 ms (n=38, 1, 13, 6)	24	0	9	0
QT: IFB>60 ms (n=38, 1, 13, 6)	2	0	0	0
QT: New Interval >450 ms (n=37, 0, 13, 6)	3	99999	3	0
QT: New Interval >480 ms (n=38, 1, 13, 6)	1	0	0	0
QT: New Interval >500 ms (n=38, 1, 13, 6)	0	0	0	0
QTcF: IFB>30 ms (n=38, 1, 13, 6)	11	0	2	1
QTcF: IFB>60 ms (n=38, 1, 13, 6)	0	0	0	0
QTcF: New Interval >450 ms (n=37, 1, 13, 5)	14	0	3	0
QTcF: New Interval >480 ms (n=38, 1, 13, 6)	0	0	0	0
QTcF: New Interval >500 ms (n=38, 1, 13, 6)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At least One Dose Interruption: Part I

End point title	Number of Subjects With At least One Dose Interruption: Part
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End point description:

In this endpoint, number of subjects with at least 1 dose interruption for encorafenib and binimetinib, respectively were reported. Safety set included all subjects who received at least 1 dose of encorafenib or binimetinib for Part I and had at least 1 valid post-baseline safety assessment.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
Encorafenib	46	40		
Binimetinib	44	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At least One Dose Interruption: Part II

End point title	Number of Subjects With At least One Dose Interruption: Part II ^[17]
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End point description:

In this endpoint, number of subjects with at least 1 dose interruption for encorafenib, binimetinib, and each third combination agent were reported. Safety set included all subjects who received at least 1 dose of 3rd combination agent for Part II and had at least 1 valid post-baseline safety assessment. Here, "n" signifies number of subjects evaluable for specified drug. Here "99999" signifies that data not available as there was no subject evaluable.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
Encorafenib (n =38, 1, 13, 6)	14	0	4	2
Binimetinib (n =38, 1, 13, 6)	13	0	5	3
Ribociclib (n =38, 0, 0, 0)	11	99999	99999	99999
Infigratinib (n =0, 1, 0, 0)	99999	0	99999	99999
Capmatinib (n =0, 0, 13, 0)	99999	99999	5	99999
Buparlisib (n =0, 0, 0, 6)	99999	99999	99999	2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At least One Dose Reduction: Part I

End point title	Number of Subjects With At least One Dose Reduction: Part
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End point description:

In this endpoint, number of subjects with at least 1 dose reduction for encorafenib and binimetinib, respectively were reported. Safety set included all subjects who received at least 1 dose of encorafenib or binimetinib for Part I and had at least 1 valid post-baseline safety assessment.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
Encorafenib	9	14		
Binimetinib	32	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At least One Dose Reduction: Part II

End point title	Number of Subjects With At least One Dose Reduction: Part
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End point description:

In this endpoint, number of subjects with at least 1 dose reduction for encorafenib, binimetinib, and each third combination agent were reported. Safety set included all subjects who received at least 1 dose of 3rd combination agent for Part II and had at least 1 valid post-baseline safety assessment. Here, "n" signifies number of subjects evaluable for specified drug. Here "99999" signifies that data not available as there was no subject evaluable.

End point type	Secondary
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End point timeframe:

During study treatment (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Subjects				
Encorafenib (n = 38, 1, 13, 6)	1	0	0	1
Binimetinib (n = 38, 1, 13, 6)	11	0	5	3
Ribociclib (n = 38, 0, 0, 0)	1	99999	99999	99999
Infigratinib (n = 0, 1, 0, 0)	99999	0	99999	99999
Capmatinib (n = 0, 0, 13, 0)	99999	99999	7	99999
Buparlisib (n = 0, 0, 0, 6)	99999	99999	99999	1

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Dose Intensity: Part I

End point title	Actual Dose Intensity: Part I ^[20]
End point description:	Dose intensity across all cycles = cumulative dose/duration of exposure. Safety set included all subjects who received at least 1 dose of encorafenib or binimetinib for Part I and had at least 1 valid post-baseline safety assessment.
End point type	Secondary
End point timeframe:	During study treatment (maximum treatment exposure for Part I was 403.7 weeks)
Notes:	[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Milligram per day				
arithmetic mean (standard deviation)				
Encorafenib	425.311 (± 53.5392)	408.711 (± 65.5297)		
Binimetinib	81.920 (± 13.0994)	82.083 (± 10.9117)		

Statistical analyses

No statistical analyses for this end point

Secondary: Actual Dose Intensity: Part II

End point title | Actual Dose Intensity: Part II^[21]

End point description:

Dose intensity across all cycles = cumulative dose/duration of exposure. Safety set included all subjects who received at least 1 dose of 3rd combination agent for Part II and had at least 1 valid post-baseline safety assessment. Here, "n" signifies number of subjects evaluable for specified drug. Here "99999" signifies: 1) that data (both mean and standard deviation) is not available as there was no subject evaluable or 2) standard deviation not available as only 1 subject was evaluable.

End point type | Secondary

End point timeframe:

During study treatment (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Milligram per day				
arithmetic mean (standard deviation)				
Encorafenib (n =38, 1, 13, 6)	197.856 (± 42.6637)	450.000 (± 99999)	195.945 (± 8.4015)	405.014 (± 102.5218)
Binimetinib (n =38, 1, 13, 6)	79.749 (± 14.7267)	90.000 (± 99999)	87.373 (± 3.6593)	78.791 (± 20.1538)
Ribociclib (n =38, 0, 0, 0)	486.628 (± 79.4485)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Infigratinib (n =0, 1, 0, 0)	99999 (± 99999)	60.227 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0, 0, 13, 0)	99999 (± 99999)	99999 (± 99999)	579.519 (± 259.1157)	99999 (± 99999)
Buparlisib (n =0, 0, 0, 6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	72.206 (± 15.7019)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS: Part II

End point title | PFS: Part II^[22]

End point description:

PFS : time from the start date of study drug in Part II until documented PD or death due to any cause. All subjects who had not progressed or died at the time of the data cut-off were censored at the date of last tumor assessment (other than those who were unknown or missing) prior to cut-off date or start date of new anti-neoplastic therapy, whichever is earlier. Per RECIST 1.1, PD= At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. FAS for Part II evaluated. Here "99999" signifies: 1) 95% CI not available as only 1 subject was evaluable and 2) Upper limit of 95% CI could not be estimated as there were insufficient number of subjects with events.

End point type | Secondary

End point timeframe:

From start of study drug until documented PD or death due to any cause (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Months				
median (confidence interval 95%)	2.1 (1.7 to 2.1)	2.1 (-99999 to 99999)	2.1 (1.0 to 3.7)	1.4 (0.4 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR): Part I

End point title | Duration of Response (DOR): Part I^[23]

End point description:

DOR: time between date of first documented response (CR or PR) and date of first documented progression or death due to underlying cancer. If there was no progression or death due to underlying cancer, then the subject was censored at the date of last tumor assessment other than unknown. CR: disappearance of all non-nodal target lesions (TLs). Any pathological lymph nodes assigned as TLs must have had a reduction in short axis to <10 mm. Disappearance of all non-TLs. All lymph nodes assigned a non-TL must be non-pathological in size (<10 mm short axis). PR: at least a 30% decrease in sum of diameter of all TLs, taking as reference baseline sum of diameters. PD: at least a 20% increase in sum of diameter of all measured TLs, taking as the reference the smallest sum of diameter of all TLs recorded at or after baseline. Sum must also demonstrate an absolute increase of at least 5 mm. FAS for Part I was evaluated. Here, "Number of Subjects Analyzed" signifies confirmed responders.

End point type | Secondary

End point timeframe:

From date of first documented response (CR or PR) till the date of first documented progression or death due to underlying cancer or censoring date (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	21		
Units: Months				
median (confidence interval 95%)	10.9 (8.1 to 14.1)	5.6 (3.9 to 13.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS): Part I

End point title | Progression-Free Survival (PFS): Part I^[24]

End point description:

PFS was defined as the time from the start date of study drug in Part I until documented PD or death due to any cause. All subjects who had not progressed or died at the time of the data cut-off were censored at the date of last tumor assessment (other than those who were unknown or missing) prior to cut-off date or start date of new anti-neoplastic therapy, whichever is earlier. Per RECIST 1.1, PD= At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For Part I, FAS consisted of all subjects who received at least 1 dose (partial or full) of encorafenib or binimetinib.

End point type | Secondary

End point timeframe:

From start of study drug until documented PD or death due to any cause (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Months				
median (confidence interval 95%)	11.1 (8.1 to 15.0)	3.3 (2.1 to 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTR: Part II

End point title | TTR: Part II^[25]

End point description:

TTR was defined as the time between the start date of study drug in Part II and first documented response (CR or PR). RECIST v1.1: a) CR = disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions had a reduction in short axis to <10 mm. Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesion must be non-pathological in size (<10 mm short axis) and b) PR = at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameter. For Part II, FAS

consisted of all subjects who received at least 1 dose of encorafenib or binimetinib or the assigned third agent following the assignment of the triple combination treatment. Here, "Number of Subjects Analyzed" signifies subjects evaluable for this endpoint who were responders. Here "99999" signifies: 95% CI not available as only 1 subject was evaluable.

End point type	Secondary
End point timeframe:	
From start date of study drug till first documented response (CR or PR) (maximum treatment exposure for Part II was 97.0 weeks)	

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0 ^[26]	0 ^[27]	0 ^[28]
Units: Months				
median (confidence interval 95%)	4.1 (-99999 to 99999)	(to)	(to)	(to)

Notes:

[26] - Subject was not a responder.

[27] - None of the subjects were responders.

[28] - None of the subjects were responders.

Statistical analyses

No statistical analyses for this end point

Secondary: DOR: Part II

End point title	DOR: Part II ^[29]
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End point description:

DOR: time between date of first documented response (CR or PR) & date of first documented progression or death due to underlying cancer. If there was no progression or death due to underlying cancer, then the subject was censored at the date of last tumor assessment other than unknown. CR: disappearance of all non-nodal TLs. Any pathological lymph nodes assigned as TLs must have had a reduction in short axis to <10mm. Disappearance of all non-TLs. All lymph nodes assigned a non-TL must be non-pathological in size (<10mm short axis). PR: at least 30% decrease in sum of diameter of all TLs, taking as reference baseline sum of diameters. PD: at least 20% increase in sum of diameter of all measured TLs, taking as reference the smallest sum of diameter of all TLs recorded at or after baseline. Sum must also demonstrate an absolute increase of at least 5mm. FAS Part II was evaluated. "Number of Subjects Analyzed"=confirmed responders; "99999"=95%CI unavailable as only 1 subject evaluable.

End point type	Secondary
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End point timeframe:

From date of first documented response (CR or PR) till the date of first documented progression or death due to underlying cancer or censoring date (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	0 ^[30]	0 ^[31]	0 ^[32]
Units: Months				
median (confidence interval 95%)	2.1 (-99999 to 99999)	(to)	(to)	(to)

Notes:

[30] - Subject was not a confirmed responder.

[31] - None of the subjects were confirmed responders.

[32] - None of the subjects were confirmed responders.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR): Part I

End point title	Time to Response (TTR): Part I ^[33]
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End point description:

TTR was defined as the time between the start date of study drug in Part I and first documented response (CR or PR). RECIST v1.1: a) CR = disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions had a reduction in short axis to <10 mm. Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesion must be non-pathological in size (<10 mm short axis) and b) PR = at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. For Part I, FAS consisted of all subjects who received at least 1 dose (partial or full) of encorafenib or binimetinib. Here, 'Number of Subjects Analyzed' signifies subjects evaluable for this endpoint who were responders.

End point type	Secondary
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End point timeframe:

From start date of study drug till first documented response (CR or PR) (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	16		
Units: Months				
median (confidence interval 95%)	1.4 (1.38 to 1.41)	0.72 (0.72 to 0.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Part II

End point title	Overall Survival (OS): Part II ^[34]
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End point description:

OS was defined as the time from date of randomization/start of treatment to date of death due to any cause. If a subject was not known to have died, survival was censored at the date of last known date subject alive. For Part II, FAS consisted of all subjects who received at least 1 dose of encorafenib or binimetinib or the assigned third agent following the assignment of the triple combination treatment. Here "99999" signifies: 1) Upper limit was not estimable due to insufficient number of subjects with events, and 2) 95% CI not available as only 1 subject was evaluable.

End point type | Secondary

End point timeframe:

From date of randomization/start of treatment to date of death due to any cause or censoring date (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Months				
median (confidence interval 95%)	10.4 (6.0 to 16.7)	20.8 (-99999 to 99999)	5.6 (1.7 to 99999)	2.5 (0.4 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: DCR: Part II

End point title | DCR: Part II^[35]

End point description:

DCR = percentage of subjects with a best overall response of CR or PR or SD. CR = disappearance of all non-nodal TLs. Any pathological lymph nodes assigned as TLs had a reduction in short axis to <10 mm. Disappearance of all non-TLs. All lymph nodes assigned a non-TL must be non-pathological in size (<10 mm short axis). PR = at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD = neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD. PD= At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all TLs recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. FAS for Part II evaluated. Here "99999" signifies: 95% CI not available as only 1 subject was evaluable.

End point type | Secondary

End point timeframe:

From start date of study drug till first documented response (CR or PR or SD) (maximum treatment exposure for Part II was 97.0 weeks)

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part II: Encorafenib + Binimetinib + Ribociclib	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Buparlisib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	1	13	6
Units: Percentage of subjects				
number (confidence interval 95%)	26.3 (13.4 to 43.1)	0 (-99999 to 99999)	15.4 (1.9 to 45.4)	16.7 (0.4 to 64.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR): Part I

End point title	Disease Control Rate (DCR): Part I ^[36]
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End point description:

DCR = percentage of subjects with a best overall response of CR or PR or SD. CR = disappearance of all non-nodal TLs. Any pathological lymph nodes assigned as TLs had a reduction in short axis to <10 mm. Disappearance of all non-TLs. All lymph nodes assigned a non-TL must be non-pathological in size (<10 mm short axis). PR = at least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters. SD = neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD. PD= At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all TLs recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For Part I, FAS consisted of all subjects who received at least 1 dose (partial or full) of encorafenib or binimetinib.

End point type	Secondary
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End point timeframe:

From start date of study drug till first documented response (CR or PR or SD) (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Percentage of subjects				
number (confidence interval 95%)	92.0 (83.4 to 97.0)	42.2 (31.4 to 53.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Genomic Biomarkers From Tumor Samples: Part I

End point title	Summary of Genomic Biomarkers From Tumor Samples: Part
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End point description:

Number of subjects with multiple alterations in genomic biomarkers like biomarker BRAF, CCND1, CDK4, EGFR, FGFR1, FGFR4, KRAS, MET, NRAS, PIK3CA, and PTEN were reported and alterations included copy number variant/copy number ratio (CNV/CNR), rearrangement, short variant. It was not necessary that all biomarkers had all alterations. For Part I, FAS consisted of all subjects who received at least 1 dose (partial or full) of encorafenib or binimetinib. In results reported below, Rearrangement/Genomic Position has been abbreviated as R/GP and baseline as B.

End point type	Secondary
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End point timeframe:

Baseline up to end of treatment (EOT) (maximum treatment exposure for Part I was 403.7 weeks)

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	83		
Units: Subjects				
BRAF: CNV/CNR at B	4	9		
BRAF: CNV/CNR at EOT	2	3		
BRAF: R/GP at B chr7:140482508-140482692	0	1		
BRAF: R/GP at B chr7:140487121-140487285	0	1		
BRAF: R/GP at B chr7:140487916-140488167	0	1		
BRAF: R/GP at B chr7:140488878-140489055	0	1		
BRAF: R/GP at B cchr7:140489413-140489576	0	1		
BRAF: R/GP at B chr7:140490446-140490656	0	1		
BRAF: R/GP at B chr7:140491528-140491878	0	1		
BRAF: R/GP at B chr7:140491580-140491878	0	1		
BRAF: R/GP at B chr7:140492969-140493301	0	1		
BRAF: R/GP at EOT chr7:140481691-140482150	1	0		
BRAF: R/GP at EOT chr7:140482057-140482467	0	1		
BRAF: R/GP at EOT chr7:140482081-140482482	1	0		
BRAF: R/GP at EOT chr7:140482088-140482296	0	1		
BRAF: R/GP at EOT chr7:140482167-140482382	1	0		
BRAF: R/GP at EOT chr7:140482495-140482731	0	1		
BRAF: R/GP at EOT chr7:140482644-140482867	0	1		
BRAF: R/GP at EOT chr7:140483058-140483257	1	0		

BRAF: R/GP at EOT chr7:140486136-140486408	1	0		
BRAF: R/GP at EOT chr7:140486274-140486561	0	1		
BRAF: R/GP at EOT chr7:140489019-140489575	0	1		
BRAF: R/GP at EOT chr7:140489219-140489431	1	0		
BRAF: R/GP at EOT chr7:140489830-140490002	0	1		
BRAF: R/GP at EOT chr7:140491411-140491879	0	1		
BRAF: R/GP at EOT chr7:140492091-140492240	1	0		
BRAF: R/GP at EOT chr7:140492379-140492708	0	1		
BRAF: R/GP at EOT chr7:140492714-140492997	0	1		
BRAF: R/GP at EOT chr7:140493601-140493951	0	1		
BRAF: R/GP at EOT chr7:140493858-140494232	1	0		
BRAF: Short variant/amino acid change at B V600E	46	53		
BRAF: Short variant/amino acid change at B V600G	1	0		
BRAF: Short variant/amino acid change at B V600K	4	7		
BRAF: Short variant/amino acid change at B V600R	1	0		
BRAF: Short variant/amino acid change at EOT V600E	18	19		
BRAF: Short variant/amino acid change at EOT V600K	0	4		
BRAF: Short variant/amino acid change at EOT V600R	1	0		
CCND1: CNV/CNR at B	1	0		
CDK4: CNV/CNR at B	3	2		
EGFR: CNV/CNR at B	1	3		
EGFR: CNV/CNR at EOT	1	1		
FGFR1: CNV/CNR at B	1	0		
FGFR1: CNV/CNR at EOT	1	0		
FGFR4: CNV/CNR at B	1	0		
KRAS: CNV/CNR at B	2	0		
MET: CNV/CNR at B	4	6		
MET: CNV/CNR at EOT	3	5		
MET: R/GP at EOT chr7:116321020-116321260	1	0		
NRAS: CNV/CNR at B	0	1		
PIK3CA: CNV/CNR at B	1	0		
PTEN: CNV/CNR at B	4	13		
PTEN: CNV/CNR at EOT	5	10		
PTEN: R/GP at EOT chr10:89720538-89720776	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Encorafenib (LGX): Part I

End point title Plasma Concentration for Encorafenib (LGX): Part I^[38]

End point description:

In results reported below, following abbreviations have been used: Cycle 1 (C1), Day 1 (D1), Day 8 (D8), Day 15 (D15), Day 21 (D21), Cycle 2 (C2), Cycle 3 (C3), Cycle 4 (C4), Cycle 5 (C5) and end of treatment (EOT). Maximum treatment exposure for Part I was of 403.7 weeks. Pharmacokinetic analysis set (PAS) consisted of all subjects who had at least one blood sample providing evaluable pharmacokinetic (PK) data. Here, "n" signifies number of subjects evaluable for specified time points.

End point type Secondary

End point timeframe:

C1 (1.5 hrs post-dose on D1; pre-dose, 1.5 hrs post-dose on D15); C2 (pre-dose on D8 and D21); C3 pre-dose on D15; C4 pre-dose on D15; C5 pre-dose on D15; EOT

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1, 1.5 hr (n = 59, 55)	4820 (± 114.2)	4480 (± 124.4)		
C1 D15, Pre-dose (n= 68, 59)	10.0 (± 81.6)	13.8 (± 104.4)		
C1 D15, 1.5 hr (n = 52, 54)	2470 (± 116.7)	2910 (± 91.6)		
C2 D8, Pre-dose (n =69, 48)	9.96 (± 81.7)	14.7 (± 117.5)		
C2 D21, Pre-dose (n =62, 41)	9.04 (± 84.2)	15.6 (± 156.3)		
C3 D15, Pre-dose (n =68, 41)	8.43 (± 82.3)	11.2 (± 114.3)		
C4 D15, Pre-dose (n =63, 30)	9.21 (± 100.3)	12.3 (± 108.9)		
C5 D15, Pre-dose (n = 56, 30)	8.84 (± 59.4)	11.9 (± 72.7)		
EOT (n = 35, 47)	19.6 (± 399.9)	34.5 (± 890.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Encorafenib (LGX): Part II

End point title Plasma Concentration for Encorafenib (LGX): Part II

End point description:

In results reported below, following abbreviations have been used: Cycle 1 (C1), Day 1 (D1), Day 8 (D8), Day 15 (D15), Day 16 (D16), Day 21 (D21), Cycle 2 (C2), Cycle 3 (C3), Cycle 4 (C4), Cycle 5 (C5). Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. Here, "n" signifies number of subjects evaluable for specified time points. In results reported below, "99999" suggests that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable

and where subjects evaluable were 2: dispersion not available as out of 2 subjects, 1 subject had BLQ value; b) no geometric mean and geometric coefficient of variation: below limit of the quantitation (BLQ) value.

End point type	Secondary
End point timeframe:	
C1 (1.5, 4 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6, 8 hrs post-dose on D15; 24 hrs post-dose on D16; pre-dose on D21); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; C4 pre-dose on D1; C5 pre-dose on D1; EOT	

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1: 1.5 hrs (n=0,2,1,2,1,3,1,1,2,0,22)	99999 (± 99999)	3430 (± 17.6)	1860 (± 99999)	1130 (± 3.8)
C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,24)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
C1 D8: Pre-dose (n=3,2,1,3,1,4,1,1,2,1,23)	8.97 (± 89.0)	21.3 (± 150.6)	12.4 (± 99999)	10.3 (± 54.4)
C1 D15: Pre-dose (n=3,2,1,4,1,4,1,1,2,0,22)	11.2 (± 106.3)	18.6 (± 159.4)	7.74 (± 99999)	9.95 (± 40.1)
C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22)	437 (± 228.2)	625 (± 19.5)	1690 (± 99999)	262 (± 345.5)
C1 D15: 1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22)	3050 (± 59.6)	2150 (± 54.6)	2100 (± 99999)	1550 (± 62.4)
C1 D15: 2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22)	1420 (± 39.6)	1320 (± 30.0)	1020 (± 99999)	808 (± 55.0)
C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23)	649 (± 37.5)	770 (± 6.2)	397 (± 99999)	453 (± 24.3)
C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,19)	246 (± 94.6)	433 (± 45.0)	211 (± 99999)	165 (± 68.8)
C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20)	180 (± 94.5)	276 (± 103.8)	99999 (± 99999)	115 (± 55.4)
C1 D16: 24 hrs (n=3,2,1,4,1,4,1,1,2,0,24)	11.3 (± 45.3)	25.1 (± 2066.8)	6.76 (± 99999)	8.10 (± 43.1)
C1 D21: Pre-dose (n=0,0,1,0,0,0,1,1,2,1,20)	99999 (± 99999)	99999 (± 99999)	10.4 (± 99999)	99999 (± 99999)
C2 D1: Pre-dose (n=3,2,1,5,1,3,1,1,2,1,18)	13.5 (± 193.0)	32.6 (± 202.9)	12.7 (± 99999)	19.9 (± 210.5)
C2 D15: Pre-dose (n=1,1,1,4,0,4,1,1,2,1,14)	41.3 (± 99999)	15.6 (± 99999)	13.9 (± 99999)	9.68 (± 36.5)
C3 D1: Pre-dose (n=1,0,1,2,0,4,0,1,0,0,15)	13.9 (± 99999)	99999 (± 99999)	20.5 (± 99999)	23.2 (± 33.1)
C4 D1: Pre-dose (n=1,0,0,0,0,2,1,1,0,0,6)	30.2 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
C5 D1: Pre-dose (n=1,0,0,0,0,0,1,1,0,0,5)	749 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
EOT (n =2,1,1,3,1,4,1,1,2,1,22)	1.77 (± 99999)	99999 (± 99999)	14.3 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1: 1.5 hrs (n=0,2,1,2,1,3,1,1,2,0,22)	3750 (± 99999)	1770 (± 62.9)	878 (± 99999)	2030 (± 99999)
C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,24)	99999 (± 99999)	99999 (± 99999)	238 (± 99999)	297 (± 99999)
C1 D8: Pre-dose (n=3,2,1,3,1,4,1,1,2,1,23)	6.21 (± 99999)	11.7 (± 56.4)	12.5 (± 99999)	15.2 (± 99999)
C1 D15: Pre-dose (n=3,2,1,4,1,4,1,1,2,0,22)	7.95 (± 99999)	13.5 (± 35.0)	9.28 (± 99999)	10.3 (± 99999)
C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22)	139 (± 99999)	127 (± 216.1)	8.55 (± 99999)	601 (± 99999)
C1 D15: 1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22)	2890 (± 99999)	2500 (± 27.9)	366 (± 99999)	1960 (± 99999)
C1 D15: 2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22)	99999 (± 99999)	1550 (± 34.4)	622 (± 99999)	981 (± 99999)
C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23)	1160 (± 99999)	667 (± 20.4)	389 (± 99999)	99999 (± 99999)
C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,19)	266 (± 99999)	317 (± 26.8)	209 (± 99999)	199 (± 99999)
C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20)	257 (± 99999)	217 (± 34.5)	142 (± 99999)	132 (± 99999)
C1 D16: 24 hrs (n=3,2,1,4,1,4,1,1,2,0,24)	5.20 (± 99999)	15.0 (± 20.9)	10.7 (± 99999)	7.85 (± 99999)
C1 D21: Pre-dose (n=0,0,1,0,0,0,1,1,2,1,20)	99999 (± 99999)	99999 (± 99999)	13.6 (± 99999)	13.9 (± 99999)
C2 D1: Pre-dose (n=3,2,1,5,1,3,1,1,2,1,18)	2.91 (± 99999)	14.0 (± 30.3)	8.50 (± 99999)	82.5 (± 99999)
C2 D15: Pre-dose (n=1,1,1,4,0,4,1,1,2,1,14)	99999 (± 99999)	8.49 (± 70.5)	11.1 (± 99999)	16.5 (± 99999)
C3 D1: Pre-dose (n=1,0,1,2,0,4,0,1,0,0,15)	99999 (± 99999)	10.1 (± 72.1)	99999 (± 99999)	99999 (± 99999)
C4 D1: Pre-dose (n=1,0,0,0,0,2,1,1,0,0,6)	99999 (± 99999)	12.5 (± 11.4)	5.95 (± 99999)	7.28 (± 99999)
C5 D1: Pre-dose (n=1,0,0,0,0,0,1,1,0,0,5)	99999 (± 99999)	99999 (± 99999)	10.7 (± 99999)	9.84 (± 99999)
EOT (n =2,1,1,3,1,4,1,1,2,1,22)	99999 (± 99999)	13.9 (± 66.6)	8.24 (± 99999)	6.81 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	29	
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1: 1.5 hrs (n=0,2,1,2,1,3,1,1,2,0,22)	847 (± 28.1)	99999 (± 99999)	1600 (± 85.6)	
C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,24)	626 (± 65.7)	99999 (± 99999)	596 (± 51.1)	
C1 D8: Pre-dose (n=3,2,1,3,1,4,1,1,2,1,23)	9.39 (± 15.9)	7.15 (± 99999)	16.2 (± 116.1)	
C1 D15: Pre-dose (n=3,2,1,4,1,4,1,1,2,0,22)	7.75 (± 37.3)	99999 (± 99999)	20.9 (± 188.5)	
C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22)	473 (± 1248.5)	99999 (± 99999)	175 (± 252.7)	
C1 D15: 1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22)	1450 (± 3.9)	99999 (± 99999)	1850 (± 69.7)	
C1 D15: 2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22)	686 (± 99999)	99999 (± 99999)	1510 (± 48.2)	
C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23)	478 (± 39.6)	99999 (± 99999)	1020 (± 34.3)	
C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,19)	203 (± 11.1)	99999 (± 99999)	567 (± 51.5)	
C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20)	109 (± 2.6)	99999 (± 99999)	412 (± 62.3)	
C1 D16: 24 hrs (n=3,2,1,4,1,4,1,1,2,0,24)	10.8 (± 106.1)	99999 (± 99999)	22.8 (± 199.0)	
C1 D21: Pre-dose (n=0,0,1,0,0,0,1,1,2,1,20)	12.4 (± 60.4)	20.3 (± 99999)	17.5 (± 106.4)	
C2 D1: Pre-dose (n=3,2,1,5,1,3,1,1,2,1,18)	8.19 (± 42.2)	19.2 (± 99999)	11.9 (± 100.9)	
C2 D15: Pre-dose (n=1,1,1,4,0,4,1,1,2,1,14)	12.3 (± 24.3)	8.95 (± 99999)	21.3 (± 115.3)	
C3 D1: Pre-dose (n=1,0,1,2,0,4,0,1,0,0,15)	99999 (± 99999)	99999 (± 99999)	9.34 (± 125.7)	
C4 D1: Pre-dose (n=1,0,0,0,0,2,1,1,0,0,6)	99999 (± 99999)	99999 (± 99999)	13.1 (± 21.8)	
C5 D1: Pre-dose (n=1,0,0,0,0,0,1,1,0,0,5)	99999 (± 99999)	99999 (± 99999)	9.15 (± 44.0)	
EOT (n =2,1,1,3,1,4,1,1,2,1,22)	24.5 (± 259.8)	99999 (± 99999)	16.6 (± 265.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Binimetinib (MEK) and its Metabolite: Part I

End point title	Plasma Concentration for Binimetinib (MEK) and its Metabolite: Part I ^[39]
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End point description:

AR00426032 is metabolite of binimetinib. Maximum treatment exposure for Part I was of 403.7 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified time points.

End point type	Secondary
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End point timeframe:

C1 (1.5 hrs post-dose on D1; pre-dose, 1.5 hrs post-dose on D15); C2 (pre-dose on D8 and D21); C3

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was not evaluated for all arms.

End point values	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Binimetinib: C1 D1, 1.5 hr (n =58, 60)	551 (± 88.8)	482 (± 73.4)		
Binimetinib: C1 D15, Pre-dose (n =66, 56)	40.3 (± 63.5)	43.3 (± 72.9)		
Binimetinib: C1 D15, 1.5 hr (n =53, 54)	461 (± 70.2)	451 (± 50.2)		
Binimetinib: C2 D8, Pre-dose (n =69, 46)	39.9 (± 58.8)	44.8 (± 73.0)		
Binimetinib: C2 D21, Pre-dose (n =62, 39)	38.9 (± 54.9)	53.1 (± 78.2)		
Binimetinib: C3 D15, Pre-dose (n =65, 41)	41.9 (± 60.4)	38.7 (± 94.6)		
Binimetinib: C4 D15, Pre-dose (n =61, 30)	36.2 (± 68.6)	38.8 (± 57.4)		
Binimetinib: C5 D15, Pre-dose (n =56, 30)	41.3 (± 55.7)	39.2 (± 76.1)		
Binimetinib: EOT (n =35, 47)	33.2 (± 179.4)	52.8 (± 180.4)		
AR00426032: C1 D1, 1.5 hr (n =58, 60)	57.6 (± 93.5)	47.5 (± 101.6)		
AR00426032: C1 D15, Pre-dose (n =66, 56)	4.13 (± 70.8)	4.50 (± 64.0)		
AR00426032: C1 D15, 1.5 hr (n =52, 54)	30.6 (± 110.9)	31.9 (± 84.0)		
AR00426032: C2 D8, Pre-dose (n =69, 46)	3.63 (± 60.2)	4.17 (± 88.1)		
AR00426032: C2 D21, Pre-dose (n =62, 39)	4.11 (± 61.0)	4.39 (± 80.2)		
AR00426032: C3 D15, Pre-dose (n =64, 41)	3.71 (± 59.5)	3.90 (± 60.6)		
AR00426032: C4 D15, Pre-dose (n =61, 30)	3.48 (± 65.8)	3.81 (± 56.9)		
AR00426032: C5 D15, Pre-dose (n =56, 30)	3.77 (± 66.9)	3.36 (± 67.3)		
AR00426032: EOT (n =33, 47)	4.09 (± 90.8)	5.88 (± 118.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Binimetinib (MEK) and its Metabolite: Part II

End point title	Plasma Concentration for Binimetinib (MEK) and its Metabolite: Part II
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End point description:

AR00426032 is metabolite of binimetinib. Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table but may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified time points. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable and where subjects evaluable were 2: dispersion not available as out of 2 subjects, 1 subject had BLQ value; b) no geometric mean and geometric coefficient of variation: no subject evaluable, or if subjects were evaluable then all BLQ values. In results reported below, binimetinib is abbreviated as BI, AR00426032 is abbreviated as AR and pre-dose as PD.

End point type	Secondary
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End point timeframe:

C1 (1.5, 4 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6, 8 hrs post-dose on D15; 24 hrs post-dose on D16; pre-dose on D21); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; C4 pre-dose on D1; C5 pre-dose on D1; EOT

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
BI,C1 D1: 1.5 hrs(n=0,2,1,2,1,3,1,1,2,0,21,1,1)	99999 (± 99999)	410 (± 48.8)	416 (± 99999)	313 (± 25.6)
BI, C1 D1: 4 hrs(n=0,0,0,0,0,0,1,1,3,0,24,1,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BI, C1 D8: PD (n=3,2,1,3,1,4,1,1,2,1,21,1,0)	41.6 (± 21.7)	51.1 (± 9.7)	46.0 (± 99999)	74.6 (± 34.5)
BI, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	32.0 (± 17.1)	39.1 (± 57.4)	33.9 (± 99999)	85.6 (± 53.7)
BI, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	150 (± 36.1)	143 (± 496.2)	315 (± 99999)	430 (± 26.8)
BI, C1 D15:1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	386 (± 41.1)	187 (± 351.0)	413 (± 99999)	489 (± 27.1)
BI, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	250 (± 17.1)	143 (± 172.4)	235 (± 99999)	295 (± 29.7)
BI, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	147 (± 21.4)	125 (± 62.1)	98.0 (± 99999)	166 (± 48.9)
BI, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	79.0 (± 36.1)	97.3 (± 32.8)	55.8 (± 99999)	106 (± 53.3)
BI, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	74.9 (± 34.7)	59.7 (± 12.6)	99999 (± 99999)	107 (± 40.9)
BI, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,23,1,0)	44.1 (± 19.1)	30.2 (± 59.2)	42.1 (± 99999)	63.2 (± 64.0)
BI, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,19,1,1)	99999 (± 99999)	99999 (± 99999)	34.0 (± 99999)	99999 (± 99999)
BI, C2 D1: PD (n=3,2,1,5,1,3,1,1,2,1,16,1,1)	38.8 (± 62.5)	42.7 (± 27.8)	40.5 (± 99999)	118 (± 120.1)
BI, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	63.7 (± 99999)	73.0 (± 99999)	63.9 (± 99999)	40.9 (± 50.8)
BI, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,16,1,0)	50.0 (± 99999)	99999 (± 99999)	47.2 (± 99999)	37.8 (± 189.6)

BI, C4D1: PD (n=1,0,0,0,3,1,1,0,0,4,0,0)	46.1 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BI, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	60.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BI, EOT (n=2,1,1,3,1,4,1,1,2,1,21,0,0)	99999 (± 99999)	99999 (± 99999)	36.3 (± 99999)	99999 (± 99999)
AR,C1 D1: 1.5 hrs(n=0,2,1,2,0,3,0,1,2,0,21,1,1)	99999 (± 99999)	22.4 (± 200.6)	12.9 (± 99999)	11.4 (± 85.7)
AR, C1 D1: 4 hrs(n=0,0,0,0,0,0,1,1,3,0,23,1,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
AR, C1 D8: PD (n=3,2,1,3,0,4,1,1,2,1,21,1,0)	3.98 (± 31.9)	2.95 (± 165.3)	1.21 (± 99999)	7.10 (± 122.1)
AR, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	3.14 (± 74.5)	3.80 (± 111.9)	1.21 (± 99999)	11.5 (± 39.5)
AR, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	6.66 (± 43.2)	7.43 (± 455.1)	8.21 (± 99999)	13.1 (± 97.8)
AR, C1 D15:1.5 hrs (n=3,2,1,5,0,4,1,1,2,0,22,0,0)	24.9 (± 92.2)	13.2 (± 1550.1)	15.8 (± 99999)	27.9 (± 85.6)
AR, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	18.5 (± 77.0)	11.3 (± 447.2)	7.75 (± 99999)	18.5 (± 88.4)
AR, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	11.8 (± 40.3)	9.98 (± 142.4)	3.15 (± 99999)	9.46 (± 142.7)
AR, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	6.86 (± 61.8)	7.66 (± 117.7)	1.82 (± 99999)	6.90 (± 142.3)
AR, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	5.94 (± 76.7)	5.24 (± 70.7)	99999 (± 99999)	6.49 (± 124.9)
AR, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,22,1,0)	3.99 (± 61.8)	2.92 (± 159.3)	1.27 (± 99999)	7.79 (± 87.5)
AR, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,17,1,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
AR, C2 D1: PD (n=3,2,1,5,0,3,1,1,2,1,15,1,1)	6.23 (± 82.0)	3.51 (± 36.8)	99999 (± 99999)	13.5 (± 116.8)
AR, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	9.97 (± 99999)	7.52 (± 99999)	1.07 (± 99999)	3.27 (± 65.1)
AR, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,15,1,0)	9.74 (± 99999)	99999 (± 99999)	99999 (± 99999)	6.15 (± 99999)
AR, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	7.10 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
AR, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	6.05 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
AR, EOT (n=2,1,1,3,1,4,1,1,2,1,20,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
	Subject group type	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
BI,C1 D1: 1.5 hrs(n=0,2,1,2,1,3,1,1,2,0,21,1,1)	1100 (± 99999)	508 (± 130.2)	396 (± 99999)	649 (± 99999)
BI, C1 D1: 4 hrs(n=0,0,0,0,0,0,1,1,3,0,24,1,0)	99999 (± 99999)	99999 (± 99999)	152 (± 99999)	106 (± 99999)

BI, C1 D8: PD (n=3,2,1,3,1,4,1,1,2,1,21,1,0)	27.2 (± 99999)	67.4 (± 63.1)	63.0 (± 99999)	31.5 (± 99999)
BI, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	47.3 (± 99999)	50.9 (± 34.4)	54.3 (± 99999)	28.3 (± 99999)
BI, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	401 (± 99999)	180 (± 91.5)	229 (± 99999)	389 (± 99999)
BI, C1 D15:1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	797 (± 99999)	734 (± 45.6)	261 (± 99999)	520 (± 99999)
BI, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	99999 (± 99999)	491 (± 38.0)	207 (± 99999)	331 (± 99999)
BI, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	264 (± 99999)	266 (± 32.5)	130 (± 99999)	99999 (± 99999)
BI, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	112 (± 99999)	141 (± 15.1)	167 (± 99999)	77.4 (± 99999)
BI, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	132 (± 99999)	102 (± 12.4)	116 (± 99999)	65.5 (± 99999)
BI, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,23,1,0)	17.6 (± 99999)	55.9 (± 54.0)	78.3 (± 99999)	29.8 (± 99999)
BI, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,19,1,1)	99999 (± 99999)	99999 (± 99999)	40.4 (± 99999)	38.8 (± 99999)
BI, C2 D1: PD (n=3,2,1,5,1,3,1,1,2,1,16,1,1)	24.6 (± 99999)	54.2 (± 32.4)	58.3 (± 99999)	174 (± 99999)
BI, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	18.9 (± 99999)	49.8 (± 21.2)	63.1 (± 99999)	19.4 (± 99999)
BI, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,16,1,0)	99999 (± 99999)	41.9 (± 49.0)	53.4 (± 99999)	4.82 (± 99999)
BI, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)	53.8 (± 10.6)	63.6 (± 99999)	40.9 (± 99999)
BI, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)	99999 (± 99999)	42.3 (± 99999)	28.5 (± 99999)
BI, EOT (n=2,1,1,3,1,4,1,1,2,1,21,0,0)	99999 (± 99999)	52.1 (± 18.3)	41.0 (± 99999)	32.3 (± 99999)
AR,C1 D1: 1.5 hrs(n=0,2,1,2,0,3,0,1,2,0,21,1,1)	99999 (± 99999)	35.9 (± 274.1)	99999 (± 99999)	22.1 (± 99999)
AR, C1 D1: 4 hrs(n=0,0,0,0,0,0,1,1,3,0,23,1,0)	99999 (± 99999)	99999 (± 99999)	9.40 (± 99999)	4.09 (± 99999)
AR, C1 D8: PD (n=3,2,1,3,0,4,1,1,2,1,21,1,0)	99999 (± 99999)	6.34 (± 54.5)	6.15 (± 99999)	1.10 (± 99999)
AR, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	4.36 (± 99999)	5.45 (± 42.2)	4.16 (± 99999)	99999 (± 99999)
AR, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	11.4 (± 99999)	9.80 (± 75.7)	7.31 (± 99999)	4.35 (± 99999)
AR, C1 D15:1.5 hrs (n=3,2,1,5,0,4,1,1,2,0,22,0,0)	99999 (± 99999)	41.1 (± 25.7)	12.9 (± 99999)	12.6 (± 99999)
AR, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	99999 (± 99999)	34.3 (± 51.3)	9.71 (± 99999)	8.51 (± 99999)
AR, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	22.6 (± 99999)	19.3 (± 76.9)	6.76 (± 99999)	99999 (± 99999)
AR, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	8.89 (± 99999)	9.66 (± 71.5)	5.82 (± 99999)	2.52 (± 99999)
AR, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	8.06 (± 99999)	8.87 (± 76.5)	5.12 (± 99999)	1.95 (± 99999)
AR, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,22,1,0)	1.44 (± 99999)	4.75 (± 25.4)	6.53 (± 99999)	1.08 (± 99999)
AR, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,17,1,1)	99999 (± 99999)	99999 (± 99999)	3.66 (± 99999)	1.47 (± 99999)
AR, C2 D1: PD (n=3,2,1,5,0,3,1,1,2,1,15,1,1)	99999 (± 99999)	5.71 (± 44.2)	4.32 (± 99999)	2.06 (± 99999)
AR, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	1.74 (± 99999)	4.23 (± 62.5)	8.54 (± 99999)	1.63 (± 99999)
AR, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,15,1,0)	99999 (± 99999)	4.35 (± 42.3)	4.50 (± 99999)	1.09 (± 99999)

AR, C4D1: PD (n=1,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)	5.70 (± 11.8)	5.43 (± 99999)	2.78 (± 99999)
AR, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)	99999 (± 99999)	8.89 (± 99999)	1.36 (± 99999)
AR, EOT (n=2,1,1,3,1,4,1,1,2,1,20,0,0)	99999 (± 99999)	6.68 (± 80.1)	3.77 (± 99999)	1.48 (± 99999)

End point values	Part II: Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
BI, C1 D1: 1.5 hrs (n=0,2,1,2,1,3,1,1,2,0,21,1,1)	273 (± 24.6)	99999 (± 99999)	446 (± 59.8)	522 (± 99999)
BI, C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,24,1,0)	129 (± 25.8)	99999 (± 99999)	215 (± 44.5)	99.5 (± 99999)
BI, C1 D8: PD (n=3,2,1,3,1,4,1,1,2,1,21,1,0)	25.1 (± 1.7)	27.2 (± 99999)	51.0 (± 67.8)	37.3 (± 99999)
BI, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	21.1 (± 23.7)	99999 (± 99999)	48.2 (± 70.0)	36.2 (± 99999)
BI, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	161 (± 54.7)	99999 (± 99999)	158 (± 90.1)	99999 (± 99999)
BI, C1 D15: 1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	313 (± 15.9)	99999 (± 99999)	437 (± 46.5)	99999 (± 99999)
BI, C1 D15: 2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	154 (± 99999)	99999 (± 99999)	380 (± 31.2)	178 (± 99999)
BI, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	98.0 (± 60.0)	99999 (± 99999)	241 (± 28.6)	99999 (± 99999)
BI, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	53.3 (± 36.2)	99999 (± 99999)	134 (± 46.5)	99999 (± 99999)
BI, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	42.2 (± 39.2)	99999 (± 99999)	109 (± 54.8)	99999 (± 99999)
BI, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,23,1,0)	23.1 (± 5.2)	99999 (± 99999)	55.2 (± 66.0)	40.5 (± 99999)
BI, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,19,1,1)	13.6 (± 80.7)	19.6 (± 99999)	63.2 (± 51.0)	35.3 (± 99999)
BI, C2 D1: PD (n=3,2,1,5,1,3,1,1,2,1,16,1,1)	23.3 (± 20.2)	58.3 (± 99999)	46.0 (± 71.2)	22.4 (± 99999)
BI, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	15.2 (± 18.2)	14.1 (± 99999)	58.4 (± 68.3)	27.3 (± 99999)
BI, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,16,1,0)	99999 (± 99999)	99999 (± 99999)	45.0 (± 91.8)	42.0 (± 99999)
BI, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)	99999 (± 99999)	77.5 (± 32.1)	99999 (± 99999)
BI, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)	99999 (± 99999)	73.8 (± 25.7)	99999 (± 99999)
BI, EOT (n=2,1,1,3,1,4,1,1,2,1,21,0,0)	13.8 (± 205.5)	99999 (± 99999)	29.0 (± 179.7)	99999 (± 99999)
AR, C1 D1: 1.5 hrs (n=0,2,1,2,0,3,0,1,2,0,21,1,1)	8.05 (± 68.9)	99999 (± 99999)	19.4 (± 99.3)	16.3 (± 99999)
AR, C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,23,1,0)	6.71 (± 145.3)	99999 (± 99999)	12.3 (± 75.3)	4.61 (± 99999)

AR, C1 D8: PD (n=3,2,1,3,0,4,1,1,2,1,21,1,0)	1.73 (± 48.7)	2.09 (± 99999)	5.50 (± 62.6)	2.14 (± 99999)
AR, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	3.81 (± 99999)	99999 (± 99999)	4.19 (± 79.2)	1.09 (± 99999)
AR, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	6.16 (± 490.6)	99999 (± 99999)	7.81 (± 119.0)	99999 (± 99999)
AR, C1 D15:1.5 hrs (n=3,2,1,5,0,4,1,1,2,0,22,0,0)	16.1 (± 151.9)	99999 (± 99999)	18.3 (± 135.9)	99999 (± 99999)
AR, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	16.2 (± 99999)	99999 (± 99999)	18.5 (± 81.2)	4.73 (± 99999)
AR, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	5.21 (± 81.9)	99999 (± 99999)	12.2 (± 78.7)	99999 (± 99999)
AR, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	3.07 (± 95.0)	99999 (± 99999)	7.41 (± 80.2)	99999 (± 99999)
AR, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	2.67 (± 72.9)	99999 (± 99999)	6.73 (± 75.0)	99999 (± 99999)
AR, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,22,1,0)	3.19 (± 99999)	99999 (± 99999)	4.70 (± 80.2)	1.56 (± 99999)
AR, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,17,1,1)	3.18 (± 99999)	1.13 (± 99999)	6.64 (± 56.1)	1.65 (± 99999)
AR, C2 D1: PD (n=3,2,1,5,0,3,1,1,2,1,15,1,1)	4.09 (± 99999)	3.99 (± 99999)	4.03 (± 58.1)	99999 (± 99999)
AR, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	1.99 (± 99999)	1.19 (± 99999)	5.69 (± 57.0)	1.33 (± 99999)
AR, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,15,1,0)	99999 (± 99999)	99999 (± 99999)	4.46 (± 70.2)	1.73 (± 99999)
AR, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)	99999 (± 99999)	5.78 (± 83.0)	99999 (± 99999)
AR, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)	99999 (± 99999)	6.11 (± 67.8)	99999 (± 99999)
AR, EOT (n=2,1,1,3,1,4,1,1,2,1,20,0,0)	3.65 (± 99999)	99999 (± 99999)	4.24 (± 85.5)	99999 (± 99999)

End point values	Part II: Encorafenib 450mg/Binimetinib 45mg+Ribociclib 600mg			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
BI, C1 D1: 1.5 hrs (n=0,2,1,2,1,3,1,1,2,0,21,1,1)	1230 (± 99999)			
BI, C1 D1: 4 hrs (n=0,0,0,0,0,0,1,1,3,0,24,1,0)	99999 (± 99999)			
BI, C1 D8: PD (n=3,2,1,3,1,4,1,1,2,1,21,1,0)	99999 (± 99999)			
BI, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	99999 (± 99999)			
BI, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	99999 (± 99999)			
BI, C1 D15:1.5 hrs (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	99999 (± 99999)			
BI, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	99999 (± 99999)			

BI, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,0,2,0,23,0,0)	99999 (± 99999)		
BI, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	99999 (± 99999)		
BI, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	99999 (± 99999)		
BI, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,23,1,0)	99999 (± 99999)		
BI, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,19,1,1)	8.91 (± 99999)		
BI, C2 D1: PD (n=3,2,1,5,1,3,1,1,2,1,16,1,1)	54.1 (± 99999)		
BI, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	34.9 (± 99999)		
BI, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,16,1,0)	99999 (± 99999)		
BI, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)		
BI, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)		
BI, EOT (n=2,1,1,3,1,4,1,1,2,1,21,0,0)	99999 (± 99999)		
AR,C1 D1: 1.5 hrs(n=0,2,1,2,0,3,0,1,2,0,21,1,1)	64.6 (± 99999)		
AR, C1 D1: 4 hrs(n=0,0,0,0,0,0,1,1,3,0,23,1,0)	99999 (± 99999)		
AR, C1 D8: PD (n=3,2,1,3,0,4,1,1,2,1,21,1,0)	99999 (± 99999)		
AR, C1 D15: PD (n=3,2,1,4,1,4,1,1,2,0,22,1,0)	99999 (± 99999)		
AR, C1 D15: 0.5 hr (n=3,2,1,5,1,4,1,1,2,0,22,0,0)	99999 (± 99999)		
AR, C1 D15:1.5 hrs (n=3,2,1,5,0,4,1,1,2,0,22,0,0)	99999 (± 99999)		
AR, C1 D15:2.5 hrs (n=3,2,1,5,0,4,1,1,1,0,22,1,0)	99999 (± 99999)		
AR, C1 D15: 4 hrs (n=3,2,1,4,1,4,1,1,0,2,0,23,0,0)	99999 (± 99999)		
AR, C1 D15: 6 hrs (n=3,2,1,5,1,4,1,1,2,0,20,0,0)	99999 (± 99999)		
AR, C1 D15: 8 hrs (n=3,2,0,5,1,3,1,1,2,0,20,0,0)	99999 (± 99999)		
AR, C1 D16: 24 hrs (n=3,2,1,5,1,4,1,1,2,0,22,1,0)	99999 (± 99999)		
AR, C1 D21: PD (n=0,0,1,0,0,0,1,1,2,1,17,1,1)	3.11 (± 99999)		
AR, C2 D1: PD (n=3,2,1,5,0,3,1,1,2,1,15,1,1)	17.8 (± 99999)		
AR, C2 D15: PD (n=1,1,1,4,1,4,1,1,2,1,14,1,1)	3.74 (± 99999)		
AR, C3 D1: PD (n=1,0,1,2,0,4,1,1,0,0,15,1,0)	99999 (± 99999)		
AR, C4D1: PD (n=1,0,0,0,0,3,1,1,0,0,4,0,0)	99999 (± 99999)		
AR, C5D1: PD (n=1,0,0,0,0,0,1,1,0,0,5,0,0)	99999 (± 99999)		
AR, EOT (n=2,1,1,3,1,4,1,1,2,1,20,0,0)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Ribociclib (LEE) and its Metabolite: Part II

End point title	Plasma Concentration for Ribociclib (LEE) and its Metabolite: Part II
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End point description:

LEQ803 is metabolite of ribociclib. Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified time points. "99999" suggested that a) geometric mean available but no geometric coefficient of variation; dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 (1.5, 4 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6, 8 hrs post-dose on D15; 24 hrs post-dose on D16; pre-dose on D21); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; C4 pre-dose on D1; C5 pre-dose on D1; EOT

End point values	Part II: Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II: Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg	Part II: Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	3	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Ribociclib, C1 D1: 1.5 hrs(n=1,1,2,0,21,1,1)	220 (± 99999)	117 (± 99999)	107 (± 40.6)	99999 (± 99999)
Ribociclib, C1 D1: 4 hrs(n=1,1,3,0,24,1,0)	213 (± 99999)	84.5 (± 99999)	205 (± 96.0)	99999 (± 99999)
Ribociclib, C1 D8: Pre-dose(n=1,1,2,0,22,1,1)	77.4 (± 99999)	32.3 (± 99999)	30.7 (± 33.5)	99999 (± 99999)
Ribociclib, C1 D15: Pre-dose(n=1,1,2,0,25,1,0)	98.4 (± 99999)	28.2 (± 99999)	30.7 (± 24.9)	99999 (± 99999)
Ribociclib, C1 D15: 0.5 hr(n=1,1,2,0,24,0,0)	86.1 (± 99999)	59.7 (± 99999)	35.4 (± 66.6)	99999 (± 99999)
Ribociclib, C1 D15: 1.5 hrs(n=1,1,2,0,24,0,0)	204 (± 99999)	95.9 (± 99999)	200 (± 240.3)	99999 (± 99999)
Ribociclib, C1 D15: 2.5 hrs(n=1,1,1,0,24,1,0)	321 (± 99999)	126 (± 99999)	718 (± 99999)	99999 (± 99999)
Ribociclib, C1 D15: 4 hrs(n=1,0,2,0,25,0,0)	368 (± 99999)	99999 (± 99999)	341 (± 42.9)	99999 (± 99999)
Ribociclib, C1 D15: 6 hrs(n=1,1,2,0,23,0,0)	434 (± 99999)	109 (± 99999)	239 (± 37.2)	99999 (± 99999)
Ribociclib, C1 D15: 8 hrs(n=1,1,2,0,21,0,0)	311 (± 99999)	83.6 (± 99999)	182 (± 27.1)	99999 (± 99999)
Ribociclib, C1 D16: 24 hrs(n=1,1,2,0,24,1,0)	94.0 (± 99999)	25.6 (± 99999)	52.7 (± 90.4)	99999 (± 99999)
Ribociclib, C1 D21: Pre-dose(n=1,0,1,0,10,1,1)	105 (± 99999)	99999 (± 99999)	102 (± 99999)	99999 (± 99999)
Ribociclib, C2 D1: Pre-dose(n=1,1,1,1,16,0,1)	99999 (± 99999)	19.5 (± 99999)	1.59 (± 99999)	1.07 (± 99999)

Ribociclib, C2 D15: Pre-dose(n=1,1,2,1,15,1,1)	103 (± 99999)	41.5 (± 99999)	53.7 (± 51.2)	36.0 (± 99999)
Ribociclib, C3 D1: Pre-dose(n=1,1,0,0,11,0,0)	1.16 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C4 D1: Pre-dose(n=1,0,0,0,2,0,0)	1.22 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C5 D1: Pre-dose(n=0,0,0,0,2,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Ribociclib, EOT(n=1,1,2,1,21,0,1)	1.94 (± 99999)	60.3 (± 99999)	1.49 (± 99999)	45.8 (± 99999)
LEQ803, C1 D1: 1.5 hrs(n=1,1,2,0,21,1,1)	57.1 (± 99999)	70.2 (± 99999)	68.2 (± 2.4)	99999 (± 99999)
LEQ803, C1 D1: 4 hrs(n=1,1,3,0,24,1,0)	65.2 (± 99999)	50.8 (± 99999)	73.5 (± 20.4)	99999 (± 99999)
LEQ803, C1 D8: Pre-dose(n=1,1,2,0,22,1,1)	64.3 (± 99999)	49.3 (± 99999)	38.1 (± 9.1)	99999 (± 99999)
LEQ803, C1 D15: Pre-dose(n=1,1,2,0,25,1,0)	76.0 (± 99999)	37.1 (± 99999)	32.9 (± 25.7)	99999 (± 99999)
LEQ803, C1 D15: 0.5 hr(n=1,1,2,0,24,0,0)	75.5 (± 99999)	39.5 (± 99999)	32.1 (± 0.7)	99999 (± 99999)
LEQ803, C1 D15: 1.5 hrs(n=1,1,2,0,24,0,0)	92.3 (± 99999)	72.6 (± 99999)	82.7 (± 0.7)	99999 (± 99999)
LEQ803, C1 D15: 2.5 hrs(n=1,1,1,0,24,1,0)	130 (± 99999)	92.5 (± 99999)	126 (± 99999)	99999 (± 99999)
LEQ803, C1 D15: 4 hrs(n=1,0,2,0,25,0,0)	138 (± 99999)	99999 (± 99999)	140 (± 23.4)	99999 (± 99999)
LEQ803, C1 D15: 6 hrs(n=1,1,2,0,23,0,0)	175 (± 99999)	90.2 (± 99999)	111 (± 27.6)	99999 (± 99999)
LEQ803, C1 D15: 8 hrs(n=1,1,2,0,21,0,0)	135 (± 99999)	79.8 (± 99999)	95.2 (± 50.1)	99999 (± 99999)
LEQ803, C1 D16: 24 hrs(n=1,1,2,0,24,1,0)	84.5 (± 99999)	46.8 (± 99999)	42.5 (± 13.8)	99999 (± 99999)
LEQ803, C1 D21: Pre-dose(n=1,0,1,0,10,1,1)	73.8 (± 99999)	99999 (± 99999)	43.7 (± 99999)	99999 (± 99999)
LEQ803, C2 D1: Pre-dose(n=1,1,1,1,16,0,1)	6.68 (± 99999)	14.5 (± 99999)	4.10 (± 99999)	2.70 (± 99999)
LEQ803, C2 D15: Pre-dose(n=1,1,2,1,15,1,1)	90.0 (± 99999)	45.6 (± 99999)	45.7 (± 6.8)	28.0 (± 99999)
LEQ803, C3 D1: Pre-dose(n=1,1,0,0,11,0,0)	7.88 (± 99999)	2.75 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803, C4 D1: Pre-dose(n=1,0,0,0,2,0,0)	7.19 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803, C5 D1: Pre-dose(n=0,0,0,0,2,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803, EOT(n=1,1,2,1,21,0,1)	10.4 (± 99999)	69.3 (± 99999)	5.06 (± 4.6)	23.5 (± 99999)

End point values	Part II: Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Ribociclib 600mg	Part II: Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg	
	Subject group type	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	1	1	
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Ribociclib, C1 D1: 1.5 hrs(n=1,1,2,0,21,1,1)	230 (± 119.7)	784 (± 99999)	185 (± 99999)	

Ribociclib, C1 D1: 4 hrs(n=1,1,3,0,24,1,0)	354 (± 58.5)	99999 (± 99999)	268 (± 99999)
Ribociclib, C1 D8: Pre-dose(n=1,1,2,0,22,1,1)	100 (± 49.9)	127 (± 99999)	80.5 (± 99999)
Ribociclib, C1 D15: Pre-dose(n=1,1,2,0,25,1,0)	104 (± 54.2)	99999 (± 99999)	64.7 (± 99999)
Ribociclib, C1 D15: 0.5 hr(n=1,1,2,0,24,0,0)	179 (± 65.0)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C1 D15: 1.5 hrs(n=1,1,2,0,24,0,0)	508 (± 95.2)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C1 D15: 2.5 hrs(n=1,1,1,0,24,1,0)	627 (± 68.3)	99999 (± 99999)	393 (± 99999)
Ribociclib, C1 D15: 4 hrs(n=1,0,2,0,25,0,0)	707 (± 62.2)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C1 D15: 6 hrs(n=1,1,2,0,23,0,0)	578 (± 55.9)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C1 D15: 8 hrs(n=1,1,2,0,21,0,0)	477 (± 55.2)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C1 D16: 24 hrs(n=1,1,2,0,24,1,0)	120 (± 64.9)	99999 (± 99999)	91.8 (± 99999)
Ribociclib, C1 D21: Pre-dose(n=1,0,1,0,10,1,1)	112 (± 75.8)	115 (± 99999)	69.9 (± 99999)
Ribociclib, C2 D1: Pre-dose(n=1,1,1,1,16,0,1)	7.00 (± 377.8)	132 (± 99999)	99999 (± 99999)
Ribociclib, C2 D15: Pre-dose(n=1,1,2,1,15,1,1)	107 (± 59.4)	102 (± 99999)	113 (± 99999)
Ribociclib, C3 D1: Pre-dose(n=1,1,0,0,11,0,0)	4.06 (± 172.4)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C4 D1: Pre-dose(n=1,0,0,0,2,0,0)	1.59 (± 31.6)	99999 (± 99999)	99999 (± 99999)
Ribociclib, C5 D1: Pre-dose(n=0,0,0,0,2,0,0)	2.16 (± 35.5)	99999 (± 99999)	99999 (± 99999)
Ribociclib, EOT(n=1,1,2,1,21,0,1)	29.0 (± 292.1)	22.8 (± 99999)	99999 (± 99999)
LEQ803, C1 D1: 1.5 hrs(n=1,1,2,0,21,1,1)	47.5 (± 97.4)	63.6 (± 99999)	59.0 (± 99999)
LEQ803, C1 D1: 4 hrs(n=1,1,3,0,24,1,0)	81.1 (± 55.6)	99999 (± 99999)	63.2 (± 99999)
LEQ803, C1 D8: Pre-dose(n=1,1,2,0,22,1,1)	53.7 (± 36.5)	71.2 (± 99999)	47.2 (± 99999)
LEQ803, C1 D15: Pre-dose(n=1,1,2,0,25,1,0)	55.1 (± 33.9)	99999 (± 99999)	49.2 (± 99999)
LEQ803, C1 D15: 0.5 hr(n=1,1,2,0,24,0,0)	60.8 (± 36.9)	99999 (± 99999)	99999 (± 99999)
LEQ803, C1 D15: 1.5 hrs(n=1,1,2,0,24,0,0)	112 (± 46.9)	99999 (± 99999)	99999 (± 99999)
LEQ803, C1 D15: 2.5 hrs(n=1,1,1,0,24,1,0)	133 (± 45.4)	99999 (± 99999)	137 (± 99999)
LEQ803, C1 D15: 4 hrs(n=1,0,2,0,25,0,0)	152 (± 31.2)	99999 (± 99999)	99999 (± 99999)
LEQ803, C1 D15: 6 hrs(n=1,1,2,0,23,0,0)	145 (± 27.2)	99999 (± 99999)	99999 (± 99999)
LEQ803, C1 D15: 8 hrs(n=1,1,2,0,21,0,0)	128 (± 27.6)	99999 (± 99999)	99999 (± 99999)
LEQ803, C1 D16: 24 hrs(n=1,1,2,0,24,1,0)	63.1 (± 36.1)	99999 (± 99999)	59.6 (± 99999)
LEQ803, C1 D21: Pre-dose(n=1,0,1,0,10,1,1)	58.1 (± 39.1)	80.2 (± 99999)	52.9 (± 99999)
LEQ803, C2 D1: Pre-dose(n=1,1,1,1,16,0,1)	8.48 (± 154.5)	80.8 (± 99999)	99999 (± 99999)
LEQ803, C2 D15: Pre-dose(n=1,1,2,1,15,1,1)	58.3 (± 42.7)	61.1 (± 99999)	66.8 (± 99999)

LEQ803, C3 D1: Pre-dose(n=1,1,0,0,11,0,0)	7.57 (± 61.4)	99999 (± 99999)	99999 (± 99999)	
LEQ803, C4 D1: Pre-dose(n=1,0,0,0,2,0,0)	5.72 (± 6.9)	99999 (± 99999)	99999 (± 99999)	
LEQ803, C5 D1: Pre-dose(n=0,0,0,0,2,0,0)	6.07 (± 28.9)	99999 (± 99999)	99999 (± 99999)	
LEQ803, EOT(n=1,1,2,1,21,0,1)	20.6 (± 152.2)	31.2 (± 99999)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Infigratinib (BGJ) and its Metabolites: Part II

End point title	Plasma Concentration for Infigratinib (BGJ) and its Metabolites: Part II
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End point description:

BHS697 and CQM157 are metabolites of infigratinib. Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. Here, "n" signifies number of subjects evaluable for specified time points. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable and where subjects were evaluable: BLQ value.

End point type	Secondary
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End point timeframe:

C1 (1.5 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6 hrs post-dose on D15; 24 hrs post-dose on D16; pre-dose on D21); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; EOT

End point values	Part II: Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Infigratinib, C1 D1: 1.5 hrs (n =1)	15.0 (± 99999)			
Infigratinib, C1 D8: Pre-dose (n =1)	2.67 (± 99999)			
Infigratinib, C1 D15: Pre-dose (n =1)	2.49 (± 99999)			
Infigratinib, C1 D15: 0.5 hr (n =1)	3.39 (± 99999)			
Infigratinib, C1 D15: 1.5 hrs (n =1)	15.2 (± 99999)			
Infigratinib, C1 D15: 2.5 hrs (n =1)	27.5 (± 99999)			
Infigratinib, C1 D15: 4 hrs (n =1)	24.7 (± 99999)			
Infigratinib, C1 D15: 6 hrs (n =1)	20.5 (± 99999)			
Infigratinib, C1 D16: 24 hrs (n =0)	99999 (± 99999)			
Infigratinib, C1 D21: Pre-dose (n =1)	2.05 (± 99999)			
Infigratinib, C2 D1: Pre-dose (n =1)	99999 (± 99999)			

Infigratinib, C2 D15: Pre-dose (n =1)	4.65 (± 99999)			
Infigratinib, C3 D1: Pre-dose (n =1)	99999 (± 99999)			
Infigratinib, EOT (n =1)	2.42 (± 99999)			
BHS697, C1 D1: 1.5 hrs (n =1)	4.83 (± 99999)			
BHS697, C1 D8: Pre-dose (n =1)	2.17 (± 99999)			
BHS697, C1 D15: Pre-dose (n =1)	1.64 (± 99999)			
BHS697, C1 D15: 0.5 hr (n =1)	2.14 (± 99999)			
BHS697, C1 D15: 1.5 hrs (n =1)	6.83 (± 99999)			
BHS697, C1 D15: 2.5 hrs (n =1)	8.53 (± 99999)			
BHS697, C1 D15: 4 hrs (n =1)	6.89 (± 99999)			
BHS697, C1 D15: 6 hrs (n =1)	5.57 (± 99999)			
BHS697, C1 D16: 24 hrs (n =0)	99999 (± 99999)			
BHS697, C1 D21: Pre-dose (n =1)	1.37 (± 99999)			
BHS697, C2 D1: Pre-dose (n =1)	99999 (± 99999)			
BHS697, C2 D15: Pre-dose (n =1)	2.83 (± 99999)			
BHS697, C3 D1: Pre-dose (n =1)	99999 (± 99999)			
BHS697, EOT (n =1)	1.69 (± 99999)			
CQM157, C1 D1: 1.5 hrs (n =1)	13.0 (± 99999)			
CQM157, C1 D8: Pre-dose (n =1)	14.1 (± 99999)			
CQM157, C1 D15: Pre-dose (n =1)	11.1 (± 99999)			
CQM157, C1 D15: 0.5 hr (n =1)	12.0 (± 99999)			
CQM157, C1 D15: 1.5 hrs (n =1)	21.3 (± 99999)			
CQM157, C1 D15: 2.5 hrs (n =1)	28.3 (± 99999)			
CQM157, C1 D15: 4 hrs (n =1)	25.0 (± 99999)			
CQM157, C1 D15: 6 hrs (n =1)	32.2 (± 99999)			
CQM157, C1 D16: 24 hrs (n =0)	99999 (± 99999)			
CQM157, C1 D21: Pre-dose (n =1)	9.65 (± 99999)			
CQM157, C2 D1: Pre-dose (n =1)	99999 (± 99999)			
CQM157, C2 D15: Pre-dose (n =1)	15.5 (± 99999)			
CQM157, C3 D1: Pre-dose (n =1)	99999 (± 99999)			
CQM157, EOT (n =1)	11.9 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Capmatinib (INC): Part II

End point title	Plasma Concentration for Capmatinib (INC): Part II
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End point description:

Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified time points. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable and where subjects were evaluable: BLQ value.

End point type	Secondary
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End point timeframe:

C1 (1.5 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6, 8 hrs post-dose on D15; 24 hrs post-dose on D16); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; C4 pre-dose on D1; C5 pre-dose on D1; EOT

End point values	Part II: Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5	5	1	
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1: 1.5 hrs (n =3, 1, 2)	362 (± 268.6)	715 (± 133.2)	3600 (± 99999)	
C1 D8: Pre-dose (n =3, 1, 4)	74.3 (± 97.2)	129 (± 49.4)	44.4 (± 99999)	
C1 D15: Pre-dose (n =4, 1, 4)	89.3 (± 35.7)	173 (± 41.2)	71.4 (± 99999)	
C1 D15: 0.5 hr (n =5, 1, 4)	196 (± 103.8)	314 (± 49.0)	1880 (± 99999)	
C1 D15: 1.5 hrs (n =5, 1, 4)	636 (± 78.2)	1830 (± 38.3)	3670 (± 99999)	
C1 D15: 2.5 hrs (n =5, 0, 4)	545 (± 81.2)	1530 (± 18.4)	99999 (± 99999)	
C1 D15: 4 hrs (n =4, 1, 4)	401 (± 17.3)	950 (± 39.1)	1230 (± 99999)	
C1 D15: 6 hrs (n =5, 1, 4)	157 (± 63.2)	487 (± 23.3)	264 (± 99999)	
C1 D15: 8 hrs (n =5, 1, 3)	120 (± 50.0)	390 (± 10.5)	268 (± 99999)	
C1 D16: 24 hrs (n =5, 1, 4)	79.6 (± 103.1)	269 (± 68.7)	58.1 (± 99999)	
C2 D1: Pre-dose (n =5, 1, 3)	151 (± 107.6)	227 (± 42.0)	38.7 (± 99999)	
C2 D15: Pre-dose (n =3, 1, 3)	65.2 (± 31.0)	166 (± 80.9)	50.5 (± 99999)	
C3 D1: Pre-dose (n =2, 0, 3)	114 (± 113.4)	96.5 (± 17.9)	99999 (± 99999)	
C4 D1: Pre-dose (n =0, 0, 3)	99999 (± 99999)	175 (± 44.8)	99999 (± 99999)	
C5 D1: Pre-dose (n =0, 1, 0)	99999 (± 99999)	99999 (± 99999)	41.8 (± 99999)	
EOT (n =3, 1, 4)	99999 (± 99999)	65.4 (± 155.0)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for Buparlisib (BKM): Part II

End point title	Plasma Concentration for Buparlisib (BKM): Part II
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End point description:

Maximum treatment exposure for Part II was of 97.0 weeks. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects

Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified time points. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable and where subjects were evaluable: BLQ value.

End point type	Secondary
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End point timeframe:

C1 (1.5 hrs post-dose on D1; pre-dose on D8; pre-dose, 0.5, 1.5, 2.5, 4, 6, 8 hrs post-dose on D15; 24 hrs post-dose on D16); C2 (pre-dose on D1 and D15); C3 pre-dose on D1; C4 pre-dose on D1; C5 pre-dose on D1; EOT

End point values	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
C1 D1: 1.5 hrs (n =1, 1)	213 (± 99999)	213 (± 99999)		
C1 D8: Pre-dose (n =3, 2)	45.0 (± 75.2)	119 (± 3.6)		
C1 D15: Pre-dose (n =3, 2)	49.7 (± 115.9)	97.3 (± 16.2)		
C1 D15: 0.5 hr (n =3, 2)	139 (± 13.4)	229 (± 21.5)		
C1 D15: 1.5 hrs (n =3, 2)	266 (± 51.5)	312 (± 10.9)		
C1 D15: 2.5 hrs (n =3, 2)	176 (± 42.2)	268 (± 11.9)		
C1 D15: 4 hrs (n =3, 2)	115 (± 44.0)	235 (± 39.4)		
C1 D15: 6 hrs (n =3, 2)	94.2 (± 40.0)	171 (± 26.4)		
C1 D15: 8 hrs (n =3, 2)	87.4 (± 63.9)	111 (± 25.5)		
C1 D16: 24 hrs (n =3, 2)	41.8 (± 82.9)	101 (± 1.4)		
C2 D1: Pre-dose (n =3, 2)	54.7 (± 134.9)	110 (± 51.2)		
C2 D15: Pre-dose (n =1, 1)	99.3 (± 99999)	138 (± 99999)		
C3 D1: Pre-dose (n =1, 0)	81.2 (± 99999)	99999 (± 99999)		
C4 D1: Pre-dose (n =1, 0)	73.2 (± 99999)	99999 (± 99999)		
C5 D1: Pre-dose (n =1, 0)	122 (± 99999)	99999 (± 99999)		
EOT (n =2, 1)	1.84 (± 53.4)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration at Steady State (C_{max,ss}) for Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II

End point title	Maximum Observed Plasma Concentration at Steady State (C _{max,ss}) for Encorafenib, Binimetinib, Binimetinib Metabolite,
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite, BHS697 and CQM157 = infigratinib metabolites. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 (minutes) min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	3060 (± 58.8)	2150 (± 54.6)	2100 (± 99999)	1600 (± 62.0)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	386 (± 41.1)	221 (± 237.6)	413 (± 99999)	515 (± 17.0)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	24.9 (± 92.2)	18.1 (± 591.2)	15.8 (± 99999)	27.9 (± 85.6)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	27.5 (± 99999)	99999 (± 99999)
BHS697 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	8.53 (± 99999)	99999 (± 99999)
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	32.2 (± 99999)	99999 (± 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	722 (± 85.3)
Buparlisib (n=3,2,0,5,1,4,0,0,0,0,0,0)	266 (± 51.5)	312 (± 10.9)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1

Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	2890 (± 99999)	2570 (± 23.0)	622 (± 99999)	1960 (± 99999)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	797 (± 99999)	858 (± 13.0)	261 (± 99999)	520 (± 99999)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	22.6 (± 99999)	47.1 (± 29.2)	12.9 (± 99999)	12.6 (± 99999)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	434 (± 99999)	126 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	175 (± 99999)	93.2 (± 99999)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	3670 (± 99999)	1920 (± 31.8)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n=3,2,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
	Subject group type	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	1860 (± 32.1)	2010 (± 99999)	2030 (± 40.6)	99999 (± 99999)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	313 (± 15.9)	584 (± 99999)	489 (± 31.3)	291 (± 99999)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	16.1 (± 151.9)	19.4 (± 99999)	23.7 (± 94.1)	9.04 (± 99999)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	428 (± 84.2)	282 (± 99999)	753 (± 70.6)	597 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	144 (± 19.2)	67.5 (± 99999)	156 (± 36.2)	138 (± 99999)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n=3,2,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax at Steady State (Tmax, ss) for Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II

End point title	Time to Reach Cmax at Steady State (Tmax, ss) for Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite, BHS697 and CQM157 = infigratinib metabolites. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Hour				
median (full range (min-max))				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	1.33 (0.58 to 1.50)	1.54 (1.50 to 1.58)	1.50 (1.50 to 1.50)	1.50 (0.50 to 1.53)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	1.50 (1.33 to 1.67)	2.75 (1.50 to 4.00)	1.50 (1.50 to 1.50)	1.50 (0.50 to 1.58)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	1.50 (1.33 to 1.67)	2.75 (1.50 to 4.00)	1.50 (1.50 to 1.50)	1.50 (1.50 to 1.58)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	2.50 (2.50 to 2.50)	99999 (-99999 to 99999)
BHS697 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	2.50 (2.50 to 2.50)	99999 (-99999 to 99999)
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	5.75 (5.75 to 5.75)	99999 (-99999 to 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	1.53 (1.50 to 2.58)
Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0,0)	1.50 (1.33 to 1.67)	1.50 (1.50 to 1.50)	99999 (-99999 to 99999)	99999 (-99999 to 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Hour				
median (full range (min-max))				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	1.50 (1.50 to 1.50)	1.50 (1.50 to 2.50)	2.37 (2.37 to 2.37)	1.47 (1.47 to 1.47)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	1.50 (1.50 to 1.50)	1.50 (1.50 to 2.50)	1.38 (1.38 to 1.38)	1.47 (1.47 to 1.47)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	4.00 (4.00 to 4.00)	1.92 (1.50 to 2.50)	1.38 (1.38 to 1.38)	1.47 (1.47 to 1.47)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	5.92 (5.92 to 5.92)	2.45 (2.45 to 2.45)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	5.92 (5.92 to 5.92)	4.98 (4.98 to 4.98)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			
BHS697 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	1.50 (1.50 to 1.50)	1.50 (1.50 to 2.50)	99999 (-99999 to 99999)	99999 (-99999 to 99999)
Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Hour				
median (full range (min-max))				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,25,0)	1.00 (0.50 to 1.50)	1.50 (1.50 to 1.50)	1.58 (0.63 to 6.17)	99999 (-99999 to 99999)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,24,1)	1.50 (1.50 to 1.50)	1.50 (1.50 to 1.50)	1.58 (0.50 to 4.08)	1.08 (1.08 to 1.08)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,24,1)	1.50 (1.50 to 1.50)	1.50 (1.50 to 1.50)	1.65 (0.67 to 4.08)	1.08 (1.08 to 1.08)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,26,1)	3.18 (2.33 to 4.03)	1.50 (1.50 to 1.50)	3.65 (1.50 to 6.00)	0.50 (0.50 to 0.50)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,26,1)	3.18 (2.33 to 4.03)	1.50 (1.50 to 1.50)	4.12 (1.55 to 7.00)	1.08 (1.08 to 1.08)
Infigratinib (n=0,0,1,0,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			

BHS697 (n=0,0,1,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			
CQM157 (n=0,0,1,0,0,0,0,0,0,0,0)	99999 (-99999 to 99999)			
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0)	99999 (-99999 to 99999)			
Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0)	99999 (99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)	99999 (-99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Time Zero to Time tau at Steady-State (AUC_{tau,ss}) for Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Capmatinib, and Buparlisib: Part II

End point title	Area Under the Concentration-time Curve From Time Zero to Time tau at Steady-State (AUC _{tau,ss}) for Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Capmatinib, and Buparlisib: Part II
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Hour*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,23,0)	9080 (± 42.2)	10100 (± 18.4)	7420 (± 99999)	4990 (± 42.6)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,23,1)	1580 (± 17.0)	1220 (± 105.7)	1260 (± 99999)	2180 (± 29.4)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,22,1)	116 (± 66.8)	94.4 (± 222.2)	42.0 (± 99999)	124 (± 113.9)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,22,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,22,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3070 (± 52.6)
Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0)	2130 (± 54.6)	3400 (± 18.5)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Hour*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,23,0)	10800 (± 99999)	8570 (± 10.6)	3490 (± 99999)	6000 (± 99999)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,23,1)	3040 (± 99999)	2760 (± 4.8)	1700 (± 99999)	1900 (± 99999)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,22,1)	135 (± 99999)	182 (± 43.1)	81.5 (± 99999)	47.0 (± 99999)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,22,1)	99999 (± 99999)	99999 (± 99999)	5630 (± 99999)	1650 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,22,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	1640 (± 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	12200 (± 99999)	8420 (± 22.0)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Hour*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,23,0)	5740 (± 7.1)	6200 (± 99999)	11300 (± 41.1)	99999 (± 99999)
Binimetinib (n=3,2,1,5,1,4,1,1,2,1,23,1)	1140 (± 21.1)	1740 (± 99999)	2270 (± 29.5)	99999 (± 99999)
AR00426032 (n=3,2,1,5,1,4,1,1,2,1,22,1)	57.9 (± 128.5)	66.9 (± 99999)	115 (± 92.6)	41.1 (± 99999)
Ribociclib (n=0,0,0,0,0,0,1,1,2,1,22,1)	3730 (± 62.5)	2320 (± 99999)	9230 (± 60.9)	5960 (± 99999)
LEQ803 (n=0,0,0,0,0,0,1,1,2,1,22,1)	1900 (± 24.9)	930 (± 99999)	2540 (± 31.3)	2300 (± 99999)
Capmatinib (n=0,0,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Buparlisib (n=3,2,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
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Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life at Steady State (t_{1/2}, ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Capmatinib, and Buparlisib: Part II

End point title	Elimination Half-life at Steady State (t _{1/2} , ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Capmatinib, and Buparlisib: Part II
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite. Elimination half-life means the time required for the plasma concentration to decline by 50% during the elimination phase. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II: Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II: Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,20,0)	3.75 (± 0.302)	5.89 (± 4.32)	3.57 (± 99999)	4.18 (± 1.85)
Binimetinib (n=3,2,1,4,0,4,1,1,2,1,22,1)	8.35 (± 3.52)	3.48 (± 0.484)	1.60 (± 99999)	10.3 (± 6.29)
AR00426032 (n=3,2,1,2,1,3,0,1,2,1,17,0)	6.35 (± 1.21)	4.14 (± 0.683)	1.59 (± 99999)	7.95 (± 4.03)
Ribociclib (n=0,0,0,0,0,0,0,0,1,2,1,18,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803 (n=0,0,0,0,0,0,0,0,1,2,1,11,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n=0,0,0,2,1,1,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	2.18 (± 0.0599)
Buparlisib (n=3,0,0,0,0,0,0,0,0,0,0,0,0)	15.4 (± 4.62)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,20,0)	3.41 (± 99999)	3.96 (± 0.233)	4.27 (± 99999)	3.75 (± 99999)
Binimetinib (n=3,2,1,4,0,4,1,1,2,1,22,1)	99999 (± 99999)	5.88 (± 2.77)	5.84 (± 99999)	3.82 (± 99999)
AR00426032 (n=3,2,1,2,1,3,0,1,2,1,17,0)	2.86 (± 99999)	5.64 (± 2.49)	99999 (± 99999)	4.34 (± 99999)
Ribociclib (n=0,0,0,0,0,0,0,1,2,1,18,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	9.01 (± 99999)
LEQ803 (n=0,0,0,0,0,0,0,1,2,1,11,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	19.9 (± 99999)
Capmatinib (n=0,0,0,2,1,1,0,0,0,0,0,0)	2.50 (± 99999)	2.82 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n=3,0,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Hour				
arithmetic mean (standard deviation)				
Encorafenib (n=3,2,1,5,1,4,1,1,2,1,20,0)	4.32 (± 1.62)	3.83 (± 99999)	3.60 (± 0.711)	99999 (± 99999)
Binimetinib (n=3,2,1,4,0,4,1,1,2,1,22,1)	5.38 (± 3.39)	10.9 (± 99999)	4.13 (± 1.42)	99999 (± 99999)
AR00426032 (n=3,2,1,2,1,3,0,1,2,1,17,0)	6.24 (± 4.43)	99999 (± 99999)	5.91 (± 3.00)	99999 (± 99999)
Ribociclib (n=0,0,0,0,0,0,0,1,2,1,18,1)	8.44 (± 2.21)	10.7 (± 99999)	7.77 (± 1.95)	10.1 (± 99999)
LEQ803 (n=0,0,0,0,0,0,0,1,2,1,11,0)	14.1 (± 4.04)	19.2 (± 99999)	16.0 (± 4.50)	99999 (± 99999)
Capmatinib (n=0,0,0,2,1,1,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n=3,0,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

Secondary: Apparent Total Plasma Clearance at Steady State (Cl, ss/F) of Encorafenib, Binimetinib, Ribociclib, Capmatinib, and Buparlisib: Part II

End point title	Apparent Total Plasma Clearance at Steady State (Cl, ss/F) of Encorafenib, Binimetinib, Ribociclib, Capmatinib, and Buparlisib: Part II
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End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Liter per hour				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	49.6 (± 42.1)	44.7 (± 18.4)	60.7 (± 99999)	40.1 (± 42.6)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,0)	28.5 (± 14.8)	36.9 (± 105.7)	35.6 (± 99999)	20.8 (± 28.1)
Ribociclib (n =0,0,0,0,0,0,0,1,2,1,19,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,3,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	65.9 (± 52.2)
Buparlisib (n =3,1,0,0,0,0,0,0,0,0,0,0)	28.2 (± 53.6)	23.2 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Liter per hour				
geometric mean (geometric coefficient of variation)				

Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	18.6 (± 99999)	23.4 (± 10.7)	28.7 (± 99999)	33.3 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,0)	15.1 (± 99999)	16.3 (± 5.0)	17.4 (± 99999)	15.8 (± 99999)
Ribociclib (n =0,0,0,0,0,0,0,1,2,1,19,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	243 (± 99999)
Capmatinib (n =0,0,0,5,1,3,0,0,0,0,0,0)	24.8 (± 99999)	45.7 (± 24.4)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,1,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Liter per hour				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	34.9 (± 6.9)	32.2 (± 99999)	19.5 (± 44.3)	99999 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,0)	26.5 (± 22.6)	25.9 (± 99999)	19.9 (± 29.2)	99999 (± 99999)
Ribociclib (n =0,0,0,0,0,0,0,1,2,1,19,1)	161 (± 61.1)	173 (± 99999)	62.4 (± 58.5)	99.3 (± 99999)
Capmatinib (n =0,0,0,5,1,3,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,1,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution at Steady State (V_{z, ss}/F) of Encorafenib, Binimetinib, Ribociclib, Capmatinib, and Buparlisib: Part II

End point title	Apparent Volume of Distribution at Steady State (V _{z, ss} /F) of Encorafenib, Binimetinib, Ribociclib, Capmatinib, and Buparlisib: Part II
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End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution is the apparent volume of distribution at steady-state. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min;

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Liter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	268 (± 45.4)	324 (± 69.8)	313 (± 99999)	226 (± 92.9)
Binimetinib (n =3,2,1,4,0,4,1,1,2,1,22,0)	324 (± 58.3)	185 (± 83.4)	82.5 (± 99999)	244 (± 75.9)
Ribociclib (n =0,0,0,0,0,0,0,0,1,2,1,18,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,2,1,1,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	190 (± 30.3)
Buparlisib (n =3,0,0,0,0,0,0,0,0,0,0,0)	604 (± 17.4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Liter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	91.7 (± 99999)	133 (± 13.5)	177 (± 99999)	180 (± 99999)
Binimetinib (n =3,2,1,4,0,4,1,1,2,1,22,0)	99999 (± 99999)	125 (± 56.1)	147 (± 99999)	86.8 (± 99999)
Ribociclib (n =0,0,0,0,0,0,0,0,1,2,1,18,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3160 (± 99999)
Capmatinib (n =0,0,0,2,1,1,0,0,0,0,0,0)	89.5 (± 99999)	233 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,0,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Liter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	91.7 (± 99999)	133 (± 13.5)	177 (± 99999)	180 (± 99999)
Binimetinib (n =3,2,1,4,0,4,1,1,2,1,22,0)	99999 (± 99999)	125 (± 56.1)	147 (± 99999)	86.8 (± 99999)
Ribociclib (n =0,0,0,0,0,0,0,0,1,2,1,18,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3160 (± 99999)
Capmatinib (n =0,0,0,2,1,1,0,0,0,0,0,0)	89.5 (± 99999)	233 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,0,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Liter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,20,0)	210 (± 32.3)	178 (± 99999)	99.3 (± 46.0)	99999 (± 99999)
Binimetinib (n =3,2,1,4,0,4,1,1,2,1,22,0)	184 (± 111.8)	406 (± 99999)	113 (± 48.5)	99999 (± 99999)
Ribociclib (n =0,0,0,0,0,0,0,1,2,1,18,1)	1930 (± 30.5)	2660 (± 99999)	677 (± 65.0)	1440 (± 99999)
Capmatinib (n =0,0,0,2,1,1,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,0,0,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Plasma Concentration at Steady State (Clast, ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II

End point title	Last Measurable Plasma Concentration at Steady State (Clast, ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite, BHS697 and CQM157 = infigratinib metabolites. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: 0.5 hour ± 10 min; 1 hour ± 10 min; 1.5 hour ± 15 min; 2 hour ± 15 min; 2.5 hour ± 15 min; 4 hour ± 30 min; 6 hour ± 30 min; 8 hour ± 60 min; 24 hour ± 2 hour

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,25,0)	11.3 (± 45.3)	25.1 (± 2066.8)	6.76 (± 99999)	15.9 (± 315.9)

Binimetinib (n =3,2,1,5,1,4,1,1,2,1,24,1)	44.1 (± 19.1)	30.2 (± 59.2)	55.8 (± 99999)	63.2 (± 64.0)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,24,1)	3.99 (± 61.8)	2.92 (± 159.3)	1.82 (± 99999)	5.57 (± 130.2)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	20.5 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	5.57 (± 99999)	99999 (± 99999)
CQM157 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	32.2 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	79.6 (± 103.1)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0)	41.8 (± 82.9)	101 (± 1.4)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,25,0)	5.20 (± 99999)	15.0 (± 20.9)	10.7 (± 99999)	7.85 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,24,1)	17.6 (± 99999)	55.9 (± 54.0)	78.3 (± 99999)	29.8 (± 99999)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,24,1)	1.44 (± 99999)	4.75 (± 25.4)	6.53 (± 99999)	1.08 (± 99999)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	94.0 (± 99999)	25.6 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,26,1)	99999 (± 99999)	99999 (± 99999)	84.5 (± 99999)	46.8 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
CQM157 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0)	58.1 (± 99999)	269 (± 68.7)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 45mg+Ribociclib 45mg+Ribociclib 30mg+Ribociclib	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 45mg+Ribociclib 45mg+Ribociclib 30mg+Ribociclib	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 45mg+Ribociclib 45mg+Ribociclib 30mg+Ribociclib	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 45mg+Ribociclib 45mg+Ribociclib 30mg+Ribociclib

	b 600mg	b 400mg	b 600mg	b 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,25,0)	10.8 (± 106.1)	10.5 (± 99999)	33.7 (± 254.3)	99999 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,24,1)	23.1 (± 5.2)	47.9 (± 99999)	58.7 (± 60.2)	40.5 (± 99999)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,24,1)	2.31 (± 47.8)	3.54 (± 99999)	4.68 (± 92.3)	1.56 (± 99999)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,26,1)	52.7 (± 90.4)	34.9 (± 99999)	147 (± 71.8)	91.8 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,26,1)	42.5 (± 13.8)	22.8 (± 99999)	73.2 (± 49.6)	59.6 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
CQM157 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Measured Concentration at the end of a Dosing Interval at Steady State (Ctrough, ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II

End point title	Measured Concentration at the end of a Dosing Interval at Steady State (Ctrough, ss) of Encorafenib, Binimetinib, Binimetinib Metabolite, Ribociclib, Ribociclib Metabolite, Infigratinib, Infigratinib Metabolites, Capmatinib, and Buparlisib: Part II
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End point description:

AR00426032 = binimetinib metabolite, LEQ803 = ribociclib metabolite, BHS697 and CQM157 = infigratinib metabolites. PAS consisted of all subjects who had at least one blood sample providing evaluable PK data. All subjects reported under 'Number of Subjects Analyzed' contributed data to the table; however, may not have evaluable data for every row. Here, "n" signifies number of subjects evaluable for specified drugs. In results reported below, "99999" suggested that a) geometric mean available but no geometric coefficient of variation: dispersion not available as there was only 1 subject evaluable; b) no geometric mean and geometric coefficient of variation: no subjects evaluable.

End point type	Secondary
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End point timeframe:

C1 D15: at the end of a dosing interval at steady-state (24 hour ± 2 hour), taken directly before next administration

End point values	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 60mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Buparlisib 90mg	Part II:Encorafenib 450mg/Binimetinib 45mg+Infigratinib 75mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 200mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	1	5
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,24,0)	11.2 (± 106.3)	18.6 (± 159.4)	7.74 (± 99999)	11.6 (± 51.3)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,1)	32.0 (± 17.1)	39.1 (± 57.4)	33.9 (± 99999)	81.2 (± 47.5)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,23,1)	3.14 (± 74.5)	3.80 (± 111.9)	1.21 (± 99999)	8.22 (± 84.6)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,25,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,25,1)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	2.49 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	1.64 (± 99999)	99999 (± 99999)
CQM157 (n =0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	11.1 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	83.9 (± 34.0)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0,0)	49.7 (± 115.9)	97.3 (± 16.2)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 300mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Capmatinib 400mg	Part II:Encorafenib 100mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 400mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	5	1	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,24,0)	7.95 (± 99999)	13.5 (± 35.0)	9.28 (± 99999)	10.3 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,1)	47.3 (± 99999)	50.9 (± 34.4)	54.3 (± 99999)	28.3 (± 99999)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,23,1)	4.36 (± 99999)	5.45 (± 42.2)	4.16 (± 99999)	99999 (± 99999)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,25,1)	99999 (± 99999)	99999 (± 99999)	98.4 (± 99999)	28.2 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,25,1)	99999 (± 99999)	99999 (± 99999)	76.0 (± 99999)	37.1 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

CQM157 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0)	71.4 (± 99999)	173 (± 41.2)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

End point values	Part II:Encorafenib 200mg/Binimetinib 30mg+Ribociclib 600mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 400mg	Part II:Encorafenib 200mg/Binimetinib 45mg+Ribociclib 600mg	Part II:Encorafenib 300mg/Binimetinib 30mg+Ribociclib 600mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	1	29	1
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Encorafenib (n =3,2,1,5,1,4,1,1,2,1,24,0)	7.75 (± 37.3)	10.4 (± 99999)	21.7 (± 185.4)	99999 (± 99999)
Binimetinib (n =3,2,1,5,1,4,1,1,2,1,23,1)	21.1 (± 23.7)	31.5 (± 99999)	51.0 (± 76.1)	36.2 (± 99999)
AR00426032 (n =3,2,1,5,1,4,1,1,2,1,23,1)	3.81 (± 99999)	1.72 (± 99999)	4.34 (± 79.9)	1.09 (± 99999)
Ribociclib (n =0,0,0,0,0,0,1,1,2,1,25,1)	30.7 (± 24.9)	36.4 (± 99999)	104 (± 54.2)	64.7 (± 99999)
LEQ803 (n =0,0,0,0,0,0,1,1,2,1,25,1)	32.9 (± 25.7)	22.8 (± 99999)	55.1 (± 33.9)	49.2 (± 99999)
Infigratinib (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
BHS697 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
CQM157 (n =0,0,1,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Capmatinib (n =0,0,0,5,1,4,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Buparlisib (n =3,2,0,0,0,0,0,0,0,0,0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 30 days after last dose (maximum treatment exposure for Part I was 403.7 weeks and for Part II was 97.0 weeks)

Adverse event reporting additional description:

Same event may appear as both non-SAE and SAE, but what is presented are distinct events. An event may be categorized as serious in 1 subject and non-serious in other subject, or a subject may have experienced both SAE and non-SAE. Safety set evaluated.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Part I: Encorafenib + Binimetinib (naive)
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Reporting group description:

Subjects naive to selective V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase (MEK) inhibitors, received encorafenib 450 milligram (mg) once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for encorafenib and binimetinib was defined as 21 days of daily continuous treatment.

Reporting group title	Part I: Encorafenib + Binimetinib (non-naive)
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Reporting group description:

Subjects non-naive to selective BRAF and MEK inhibitors, received encorafenib 450 mg once a day and binimetinib 45 mg twice a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. Treatment cycle for both drugs was defined as 21 days of daily continuous treatment.

Reporting group title	Part II: Encorafenib + Binimetinib + Buparlisib
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Reporting group description:

Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and buparlisib 60 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For buparlisib dose escalation was allowed till 100 mg and dose reduction was permitted till 30 mg. Treatment cycle for encorafenib, binimetinib and buparlisib was defined as 21 days of daily continuous treatment.

Reporting group title	Part II: Encorafenib + Binimetinib + Infigratinib
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Reporting group description:

Subjects received encorafenib 450 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and infigratinib 75 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 150 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For infigratinib dose escalation was allowed till 125 mg and dose reduction was permitted till 25 mg. Infigratinib was taken for 21 consecutive days followed by a 7-day planned break

Reporting group title	Part II: Encorafenib + Binimetinib + Capmatinib
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Reporting group description:

Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and capmatinib 200 mg (starting dose) capsule or 400 mg (starting dose) tablet twice a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For capmatinib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Treatment cycle for encorafenib, binimetinib and capmatinib was defined as 21 days of daily continuous treatment.

Reporting group title	Part II: Encorafenib + Binimetinib + Ribociclib
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Reporting group description:

Subjects received encorafenib 200 mg (starting dose) once a day, binimetinib 45 mg (starting dose) twice a day and ribociclib 100 mg (starting dose) once a day until disease progression or no clinical benefit. No dose reduction below 50 mg for encorafenib and 15 mg for binimetinib was permitted for this study. For ribociclib dose escalation was allowed till 600 mg and dose reduction was permitted till 50 mg. Ribociclib was taken for 21 consecutive days followed by a 7-day planned break.

Serious adverse events	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)	Part II: Encorafenib + Binimetinib + Buparlisib
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 75 (62.67%)	37 / 83 (44.58%)	4 / 6 (66.67%)
number of deaths (all causes)	20	29	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	0 / 6 (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
Breast cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Metastases to spine			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Tumour pain			

subjects affected / exposed	0 / 75 (0.00%)	2 / 83 (2.41%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	0 / 6 (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
Prostate cancer			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Metastatic malignant melanoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Tumour ulceration			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Shock			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Vasculitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Pyrexia			
subjects affected / exposed	0 / 75 (0.00%)	4 / 83 (4.82%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
General physical health deterioration			
subjects affected / exposed	1 / 75 (1.33%)	4 / 83 (4.82%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Chills			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Pelvic pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Dyspnoea			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Epistaxis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Hiccups			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Pneumothorax			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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

Pleural effusion			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Pulmonary embolism			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Intraocular pressure increased			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Lipase increased			
subjects affected / exposed	0 / 75 (0.00%)	2 / 83 (2.41%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Procedural pneumothorax			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Post procedural haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Facial bones fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Fall			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Osteoradionecrosis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Periprosthetic fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Wrist fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Femur fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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			
Acute myocardial infarction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Cardiac failure			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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 arrest			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Myocardial infarction			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Nervous system disorders			
Embolic cerebral infarction			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Epilepsy			
subjects affected / exposed	3 / 75 (4.00%)	2 / 83 (2.41%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Brain oedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Aphasia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Headache			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Hemiparesis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Partial seizures			
subjects affected / exposed	2 / 75 (2.67%)	0 / 83 (0.00%)	0 / 6 (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
Paresis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Paraparesis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Paraesthesia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Hypoaesthesia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Hemiplegia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Seizure			

subjects affected / exposed	2 / 75 (2.67%)	0 / 83 (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
Spinal cord compression			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Syncope			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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	3 / 75 (4.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Vertigo positional			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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

Diplopia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Exophthalmos			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Gastric ulcer			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Diarrhoea			

subjects affected / exposed	4 / 75 (5.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Terminal ileitis			
subjects affected / exposed	2 / 75 (2.67%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Rectal haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	4 / 75 (5.33%)	3 / 83 (3.61%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Intussusception			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Intestinal mass			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 75 (2.67%)	6 / 83 (7.23%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	5 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Drug eruption			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Urticaria			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Haematuria			
subjects affected / exposed	2 / 75 (2.67%)	0 / 83 (0.00%)	0 / 6 (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
Acute kidney injury			

subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenomegaly			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Costochondritis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Arthritis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Fibromyalgia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	0 / 6 (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

Groin pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Myopathy toxic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Myalgia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Pain in extremity			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chorioretinitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Arthritis bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Device related infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Diverticulitis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 83 (0.00%)	0 / 6 (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
Erysipelas			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Febrile infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Sepsis			
subjects affected / exposed	1 / 75 (1.33%)	3 / 83 (3.61%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	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
Pneumonia			

subjects affected / exposed	4 / 75 (5.33%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Wound infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (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
Vestibular neuronitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 83 (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
Urosepsis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 83 (0.00%)	0 / 6 (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
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 75 (0.00%)	2 / 83 (2.41%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 75 (0.00%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part II: Encorafenib	Part II: Encorafenib	Part II: Encorafenib
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	+ Binimetinib + Infigratinib	+ Binimetinib + Capmatinib	+ Binimetinib + Ribociclib
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	6 / 13 (46.15%)	19 / 38 (50.00%)
number of deaths (all causes)	1	8	28
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Breast cancer			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Cancer pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Metastases to spine			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Tumour pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 cell carcinoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Prostate cancer			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Tumour ulceration			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Shock			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Vasculitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 / 1 (0.00%)	1 / 13 (7.69%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Disease progression			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Chills			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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

Pelvic pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Hiccups			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 alveolar haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Intraocular pressure increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Injury, poisoning and procedural complications			
Seroma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Procedural pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Facial bones fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Fall			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Osteoradionecrosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Periprosthetic fracture			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Wrist fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Femur fracture			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 failure			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Cardiac arrest			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Sinus tachycardia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Myocardial infarction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Embolic cerebral infarction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Brain oedema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Aphasia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Hemiparesis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Partial seizures			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Paresis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Paraparesis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Hypoaesthesia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Spinal cord compression			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Syncope			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	2 / 38 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo positional			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Diplopia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Exophthalmos			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
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 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Inguinal hernia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Dysphagia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Constipation			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Terminal ileitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Subileus			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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	0 / 1 (0.00%)	1 / 13 (7.69%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Intussusception			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal mass			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Drug eruption			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Urticaria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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			
Nephrolithiasis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Haematuria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Acute kidney injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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			

Adrenomegaly			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Costochondritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Arthritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Fibromyalgia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Groin pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myopathy toxic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Pain in extremity			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chorioretinitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Arthritis bacterial			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Appendicitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Device related infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Diverticulitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Erysipelas			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Febrile infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			

subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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
Wound infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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 / 1 (0.00%)	1 / 13 (7.69%)	0 / 38 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (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	Part I: Encorafenib + Binimetinib (naive)	Part I: Encorafenib + Binimetinib (non-naive)	Part II: Encorafenib + Binimetinib + Buparlisib
Total subjects affected by non-serious adverse events subjects affected / exposed	75 / 75 (100.00%)	73 / 83 (87.95%)	5 / 6 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour haemorrhage subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	0 / 6 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 19	4 / 83 (4.82%) 5	1 / 6 (16.67%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all)	31 / 75 (41.33%) 44 5 / 75 (6.67%) 9 3 / 75 (4.00%) 3 13 / 75 (17.33%) 19 15 / 75 (20.00%) 15 6 / 75 (8.00%) 9	27 / 83 (32.53%) 32 7 / 83 (8.43%) 8 6 / 83 (7.23%) 6 16 / 83 (19.28%) 21 10 / 83 (12.05%) 12 5 / 83 (6.02%) 5	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea	9 / 75 (12.00%) 12	9 / 83 (10.84%) 10	0 / 6 (0.00%) 0

subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	8 / 83 (9.64%) 12	0 / 6 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	0 / 6 (0.00%) 0
Investigations Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 10	5 / 83 (6.02%) 5	0 / 6 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 25	6 / 83 (7.23%) 7	2 / 6 (33.33%) 7
Amylase increased subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 10	6 / 83 (7.23%) 11	0 / 6 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 75 (17.33%) 46	8 / 83 (9.64%) 9	1 / 6 (16.67%) 7
Blood creatine increased subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	4 / 83 (4.82%) 6	0 / 6 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	38 / 75 (50.67%) 138	10 / 83 (12.05%) 29	0 / 6 (0.00%) 0
Ejection fraction decreased subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 7	6 / 83 (7.23%) 10	0 / 6 (0.00%) 0
Blood creatinine increased subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 18	10 / 83 (12.05%) 15	0 / 6 (0.00%) 0
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 9	2 / 83 (2.41%) 2	0 / 6 (0.00%) 0
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	12 / 75 (16.00%) 21	8 / 83 (9.64%) 14	1 / 6 (16.67%) 2
Lipase increased subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 27	7 / 83 (8.43%) 18	0 / 6 (0.00%) 0
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	0 / 6 (0.00%) 0
Weight increased subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 9	5 / 83 (6.02%) 5	0 / 6 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 8	5 / 83 (6.02%) 5	0 / 6 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	14 / 75 (18.67%) 22	8 / 83 (9.64%) 11	0 / 6 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	28 / 75 (37.33%) 44	16 / 83 (19.28%) 27	3 / 6 (50.00%) 5
Leukopenia subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	0 / 6 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 13	2 / 83 (2.41%) 2	0 / 6 (0.00%) 0
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	5 / 83 (6.02%) 6	0 / 6 (0.00%) 0
Retinopathy subjects affected / exposed occurrences (all)	22 / 75 (29.33%) 29	10 / 83 (12.05%) 16	0 / 6 (0.00%) 0
Subretinal fluid			

subjects affected / exposed occurrences (all)	9 / 75 (12.00%) 13	8 / 83 (9.64%) 13	0 / 6 (0.00%) 0
Visual field defect subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	1 / 6 (16.67%) 1
Cataract subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	4 / 83 (4.82%) 5	0 / 6 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 16	8 / 83 (9.64%) 8	0 / 6 (0.00%) 0
Gastrointestinal disorders			
Flatulence subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	3 / 83 (3.61%) 3	0 / 6 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	15 / 75 (20.00%) 28	22 / 83 (26.51%) 39	1 / 6 (16.67%) 1
Nausea subjects affected / exposed occurrences (all)	30 / 75 (40.00%) 50	33 / 83 (39.76%) 52	2 / 6 (33.33%) 3
Diarrhoea subjects affected / exposed occurrences (all)	33 / 75 (44.00%) 60	25 / 83 (30.12%) 37	1 / 6 (16.67%) 1
Constipation subjects affected / exposed occurrences (all)	22 / 75 (29.33%) 29	13 / 83 (15.66%) 13	1 / 6 (16.67%) 1
Abdominal pain subjects affected / exposed occurrences (all)	14 / 75 (18.67%) 19	11 / 83 (13.25%) 16	1 / 6 (16.67%) 1
Skin and subcutaneous tissue disorders			
Hyperkeratosis subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 9	2 / 83 (2.41%) 2	0 / 6 (0.00%) 0
Rash maculo-papular			

subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	5 / 83 (6.02%) 6	0 / 6 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	1 / 6 (16.67%) 1
Alopecia subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 12	4 / 83 (4.82%) 4	0 / 6 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 7	10 / 83 (12.05%) 10	0 / 6 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 9	11 / 83 (13.25%) 28	0 / 6 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 9	6 / 83 (7.23%) 6	0 / 6 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Muscle spasms subjects affected / exposed occurrences (all)	16 / 75 (21.33%) 18	7 / 83 (8.43%) 8	0 / 6 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	26 / 75 (34.67%) 40	15 / 83 (18.07%) 34	1 / 6 (16.67%) 1
Back pain subjects affected / exposed occurrences (all)	16 / 75 (21.33%) 24	6 / 83 (7.23%) 7	1 / 6 (16.67%) 1
Pain in extremity subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 12	9 / 83 (10.84%) 14	1 / 6 (16.67%) 1
Myalgia subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 12	6 / 83 (7.23%) 11	0 / 6 (0.00%) 0
Groin pain			

subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 83 (0.00%) 0	1 / 6 (16.67%) 1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 75 (9.33%)	3 / 83 (3.61%)	0 / 6 (0.00%)
occurrences (all)	11	3	0
Upper respiratory tract infection			
subjects affected / exposed	11 / 75 (14.67%)	3 / 83 (3.61%)	0 / 6 (0.00%)
occurrences (all)	16	3	0
Nasopharyngitis			
subjects affected / exposed	12 / 75 (16.00%)	6 / 83 (7.23%)	0 / 6 (0.00%)
occurrences (all)	28	7	0
Conjunctivitis			
subjects affected / exposed	7 / 75 (9.33%)	1 / 83 (1.20%)	0 / 6 (0.00%)
occurrences (all)	7	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 75 (6.67%)	14 / 83 (16.87%)	0 / 6 (0.00%)
occurrences (all)	6	14	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 83 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part II: Encorafenib + Binimetinib + Infigratinib	Part II: Encorafenib + Binimetinib + Capmatinib	Part II: Encorafenib + Binimetinib + Ribociclib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	11 / 13 (84.62%)	33 / 38 (86.84%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	3 / 38 (7.89%)
occurrences (all)	0	0	4
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	1 / 38 (2.63%)
occurrences (all)	0	1	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	6 / 38 (15.79%)
occurrences (all)	0	1	7
Chills			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	7 / 38 (18.42%)
occurrences (all)	0	0	10
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	3 / 13 (23.08%)	4 / 38 (10.53%)
occurrences (all)	0	7	5
Influenza like illness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	3 / 38 (7.89%)
occurrences (all)	0	0	3
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	3 / 38 (7.89%)
occurrences (all)	0	1	4
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	4 / 38 (10.53%)
occurrences (all)	0	0	5

Amylase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	5 / 38 (13.16%)
occurrences (all)	0	2	8
Blood creatine increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	5 / 38 (13.16%)
occurrences (all)	0	3	6
Ejection fraction decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	4 / 38 (10.53%)
occurrences (all)	0	5	5
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	2 / 38 (5.26%)
occurrences (all)	0	3	3
Lipase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	4 / 38 (10.53%)
occurrences (all)	0	0	8
Weight increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	4 / 38 (10.53%)
occurrences (all)	0	0	4
Headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 13 (23.08%)	10 / 38 (26.32%)
occurrences (all)	0	6	16
Leukopenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	5 / 38 (13.16%)
occurrences (all)	0	0	17
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Subretinal fluid			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	0 / 38 (0.00%)
occurrences (all)	0	3	0
Cataract			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Flatulence			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	10 / 38 (26.32%)
occurrences (all)	0	2	15
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	15 / 38 (39.47%)
occurrences (all)	0	2	19
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	2 / 13 (15.38%)	9 / 38 (23.68%)
occurrences (all)	0	2	15
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	5 / 38 (13.16%)
occurrences (all)	0	1	7
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Hyperkeratosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 1 (0.00%)	1 / 13 (7.69%)	3 / 38 (7.89%)
occurrences (all)	0	1	4
Night sweats			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 1 (0.00%)	0 / 13 (0.00%)	0 / 38 (0.00%)
occurrences (all)	0	0	0
Rash			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Muscle spasms subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	3 / 38 (7.89%) 4
Arthralgia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	2 / 38 (5.26%) 2
Back pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	4 / 38 (10.53%) 4
Pain in extremity subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 13 (7.69%) 1	1 / 38 (2.63%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Groin pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	4 / 38 (10.53%) 5
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 13 (15.38%) 2	3 / 38 (7.89%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Conjunctivitis			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 13 (0.00%) 0	0 / 38 (0.00%) 0
Hypoalbuminaemia			
subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	3 / 13 (23.08%) 5	1 / 38 (2.63%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2014	<p>The reason for the current amendment is to comply with health authority request to better define some DLT criteria by excluding only Grade ≥ 3 cutaneous squamous cell carcinoma, rather than SCC (squamous cell carcinoma), from the DLT definition. Moreover, Grade ≥ 3 laboratory abnormalities, which are clearly drug related, will also be considered DLT.</p> <p>In addition, minor changes for consistency and clarification were implemented.</p>
25 November 2014	<p>This amendment will allow patients who have received treatment with any BRAF and/or MEK inhibitor to begin the trial with the LGX818 and MEK162 prior to disease progression and will allow patients who received LGX818 and/or MEK162 in other trials to enter LOGIC 2 prior to progression. This amendment will allow patients who have received other BRAF and/or MEK inhibitors, and have not progressed, but are not tolerating their treatment, to receive LGX818/MEK162 combination in this trial.</p> <p>Patients who develop brain metastasis during Part I of the study can continue treatment on Part II of the study at the discretion of the Investigator and the Sponsor Medical Monitor.</p> <p>DDI risk assessments as well as the list of concomitant medications for some study treatments have been updated due to emerging data.</p> <p>Changes and clarifications have been made following health authority requests: Patient minimum age must be 18 years at time of informed consent signature. The end of study definition has been expanded to clarify the End of study will be upon completion of the safety follow-up, disease progression follow-up and survival follow-up (only for Part II), whichever comes later, or if the study is terminated early. The followings clarification have been provided; the exclusion criterion for Enrollment in Part 2, patients who become pregnant must discontinue the study, exclusion criterion 10 to explain that total abstinence should be considered only "when this is in line with the preferred and usual lifestyle of the subject", the word "non-malignant" was deleted because it is incorrectly associated to Squamous cell carcinoma/keratoacanthoma lesions. Molecular pre-screening was modified to clarify that for patients in the US, for whom BRAF status is assessed during molecular pre-screening, an FDA-approved BRAF assay must be used.</p>

04 September 2015	<p>This amendment provides guidance to investigators on management of toxicities for BKM120, INC280 and LEE011, provides additional guidance to investigators around management of liver toxicities for BKM12, and documents a change in study sponsorship from Novartis to Array BioPharma.</p> <p>A decision was taken on 10 July 2015 to halt further recruitment to the BKM120 arm, which was communicated to Health Authorities and sites. Pharmacokinetic analysis of the patients already treated with triple combination LGX818 (encorafenib), MEK162 (binimetinib) and BKM120 has shown a significant drug-drug interaction (DDI) between LGX818 and BKM120. The BKM120 exposure in triple combination was found to be substantially reduced, by up to 80% compared to single agent BKM120 based on the preliminary PK analysis. Based on this observed DDI between LGX818 and BKM120, reaching efficacious exposures of BKM120 is unlikely with the current doses of LGX818 and MEK162.</p> <p>Guidance to investigators for the management of liver toxicities when taking INC280 has also been provided. Based on the preclinical data which suggest photosensitization potential for INC280, precautionary measures against ultraviolet exposure are being included in this amendment.</p> <p>The dose modification guidelines for QTcF prolongation specificity for monitoring and dose adjustment to better manage patient safety in patients taking LEE011 has been updated. The protocol has been amended to update the guidelines for the management of hepatic toxicity for patients treated with LEE011.</p> <p>Patients who do not tolerate triple therapy will be allowed to be rechallenged with dual therapy after discussion with Sponsor Medical Monitor and provides clarification regarding antineoplastic therapy. Concomitant medications to be used with caution, Non-clinical, and clinical PK data have been updated.</p>
02 February 2016	<p>This amendment is to provide additional information and guidance to investigators for management of liver toxicities for the INC280 combination. Clarifications in the dose modification guidelines in case of liver toxicity, updated rules with regards to study treatment discontinuation for events that meet the Hy's Law criteria and specific work-up guidelines for potential drug-induced liver injury (DILI) cases are added in the protocol. Patients with increased AST/ALT and total bilirubin (TBIL) values that may be indicative of potential DILI, should be considered as clinically important events; therefore, specific guidance for actions to be taken on study treatment (e.g. discontinuation) and for monitoring of liver function tests (LFTs) have been implemented and clarified. In addition, this protocol is amended to include the following serious adverse event (SAE): a female patient experienced a serious, unexpected, possibly related adverse event (AE) of abnormal LFTs during treatment with a combination of INC280 and gefitinib while enrolled in the [CINC280X2202] study (Initial Investigator Notification Letter issued 12 March 2015). The investigator assessed the AE as suspected to be related to the combination of INC280 and gefitinib. This AE met the criteria of Hy's Law and the hepatotoxicity could not be attributed solely to either drug alone or to the combination. This amendment also introduces the use of INC280 tablets with different dosage strengths (100 mg and 200 mg, instead of 50 mg and 200 mg) in order to improve the convenience of study drug administration for patients. Related to this, the protocol also allows for intra-patient crossover from the capsule formulation to the tablet formulation once the capsule formulation is no longer available. The eligibility criteria for amylase and lipase have been updated to be consistent across the different INC280 studies. The list of prohibited and concomitant medications to be used with caution has been updated.</p>

19 October 2017	<p>As of 12 September 2017, 27 patients in the CLGX818X2109 study (25 in Part I and 2 in Part II [both on LGX818/ MEK162/LEE011 combination]), were continuing to derive benefit from study treatment. In order to minimize the burden on the patients and to reduce their radiation exposure, this amendment allows the frequency of tumor assessments in all Part I continuing patients to be reduced to every 6-12 weeks based on Investigator discretion. Patients may be transitioned to this less frequent imaging schedule once they have completed ≥ 24 months of study treatment in Part I and the Run-in phase.</p> <p>In addition, this protocol is also being amended to change the frequency and type of ophthalmologic examinations. In a separate Phase 3 study (CMEK162B2301; ClinicalTrials.gov identifier NCT01909453) in patients with BRAF V600-mutant melanoma treated with the combination of LGX818 (450 mg once daily [QD]) plus MEK162 (45 mg twice daily [BID]), the median time to onset of retinopathy excluding retinal vein occlusion (in patients with at least one event) was 0.2 months (95% confidence interval [CI] 0.1, 0.9) and there were no patients with a new onset event after 24 months. Based on these findings, and in order to minimize the burden on patients who continue to derive benefit from study treatment, this amendment allows patients who have been receiving study treatment ≥ 24 months in Part I and the Run-in phase and who have not had a retinal adverse event (AE) to be evaluated only for visual acuity at each scheduled patient visit (Day 15 of all cycles) with a full ophthalmic examination required every 12 weeks (i.e., every 4 cycles) or more frequently if clinically indicated, and at End of Study Treatment visit.</p> <p>Additional revisions have been to sections of the protocol that are specific to the Part II triple combination arm with LEE011 in order to reflect recent clinical development changes pertaining to patient selection and dose modification.</p>
26 March 2019	<p>As of the release date of this amendment, 17 patients in the CLGX818X2109 study (16 in Part I and 1 in Part II [LGX818/MEK162/LEE011]) were receiving study treatment. There are no patients ongoing in the Part II triple combination arms with INC280, BGJ398, or BKM120.</p> <p>The protocol is being amended to discontinue enrollment to the triple combination arms containing INC280 and BGJ398 due to the lack of efficacy in these arms and because there is no interest in further clinical development of these combinations. The BKM120 combination was closed on 10 July 2015 due to a significant drug-drug interaction (DDI) between LGX818 and BKM120 (Amendment 3). There have been no responses observed in 13 patients treated in the INC280 arm or in the single patient treated in the BGJ398 arm.</p>
16 December 2019	<p>In June 2018, encorafenib (LGX818) 450 mg orally QD, in combination with binimetinib (MEK162) 45 mg orally BID, received marketing approval in the United States and several jurisdictions for the treatment of patients with unresectable or metastatic BRAF V600-mutant melanoma with subsequent regulatory approvals in the European Union and Japan. This approval was based on the randomized Phase 3 COLUMBUS Study (CMEK162B2301).</p> <p>At this stage of development, the toxicity profile of encorafenib in combination with binimetinib has been well established. As all patients who continue to receive encorafenib and binimetinib under this study protocol have been treated for a minimum of 3 years, this protocol has been amended to reduce the frequency of safety assessments to align with study centers' institutional standards for patients with BRAF V600-mutant locally advanced unresectable or metastatic melanoma.</p> <p>As of the release date of this amendment, 13 patients in the Part I of Study CLGX818X2109 were receiving study treatment with encorafenib and binimetinib. There are no patients receiving treatment in the Part II triple combination arm with LEE011.</p> <p>The protocol has also been amended to discontinue enrollment to the triple combination arm containing LEE011 due to the limited efficacy and minimal interest in further clinical development of this combination. The BKM120 combination was closed on 10 July 2015 due to a significant drug-drug interaction (DDI) between LGX818 and BKM120 (Amendment 03) and the INC280 and BGJ398 arms were closed in Amendment 06 due to the lack of responses observed in the 13 patients treated in the INC280 arm or in the single patient treated in the BGJ398 arm.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported