Clinical trial results:
A Phase 2, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib
Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-Mutant Melanoma Brain Metastasis

Summary

EudraCT number	2018-004555-21
Trial protocol	BE NL IT
Global end of trial date	02 June 2021

Results information

Result version number	v1 (current)
This version publication date	15 January 2023
First version publication date	15 January 2023

Trial information

Trial identification

Sponsor protocol code	C4221006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Alias ID: ARRAY-818-201

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, 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	05 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Safety Lead-in: Evaluate the safety of a high-dose regimen of encorafenib + binimetinib combination therapy in subjects with BRAFV600-mutant melanoma who had asymptomatic brain metastasis. Phase 2: 1) If the high-dose regimen was determined to be safe based on results of the Safety Lead-in phase, then evaluate the antitumor activity in brain metastases of the standard and high dose regimens of encorafenib + binimetinib combination therapy in subjects with BRAFV600-mutant melanoma who had asymptomatic brain metastasis; 2) If the high-dose regimen was determined not to be safe based on the results of the Safety Lead-in phase, then evaluate the antitumor activity in brain metastases of the standard dosing regimen of encorafenib + binimetinib combination in subjects with BRAFV600-mutant melanoma who have asymptomatic brain metastasis.

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 Harmonization (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	30 April 2019
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	Argentina: 2
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	13
EEA total number of subjects	2

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)	8
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study had 2 parts, Safety lead-in (SLI) and Phase 2. In Phase 2, subjects would be randomised either to the standard-dose or high-dose treatment, only if high dose was determined to be safe in safety lead-in.

Pre-assignment

Screening details:

Pfizer and the Steering Committee reviewed safety lead-in data and decided not to evaluate high dose combination of encorafenib + binimetinib in Phase 2 of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID

Arm description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received combination therapy of encorafenib (300 milligram [mg] orally, twice daily [BID]) and binimetinib (45 mg orally, BID) in 28-day cycles and continued until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Arm type	Experimental
Investigational medicinal product name	Encorafenib + Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Encorafenib 300 mg BID and Binimetinib 45 mg BID in 28 days cycle.

Arm title	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID

Arm description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received standard combination therapy of encorafenib (450 mg orally, once daily [QD]) and binimetinib (45 mg orally, BID) in 28-day cycles and subjects who were able to tolerate the encorafenib 450 mg dose further received 600 mg QD after 4 Weeks. Subjects were followed up to 30 days after last dose of study drug.

Arm type	Experimental
Investigational medicinal product name	Encorafenib + Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Encorafenib 450 mg QD and Binimetinib 45 mg BID in 28 days cycle.

Number of subjects in period 1	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID
Started	10	3
Completed	0	0
Not completed	10	3
Death	7	3
Unspecified	1	-
Study termination by sponsor	2	-

Baseline characteristics

Reporting groups

Reporting group title	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received combination therapy of encorafenib (300 milligram [mg] orally, twice daily [BID]) and binimetinib (45 mg orally, BID) in 28-day cycles and continued until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received standard combination therapy of encorafenib (450 mg orally, once daily [QD]) and binimetinib (45 mg orally, BID) in 28-day cycles and subjects who were able to tolerate the encorafenib 450 mg dose further received 600 mg QD after 4 Weeks. Subjects were followed up to 30 days after last dose of study drug.

Reporting group values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID	Total
Number of subjects	10	3	13
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	3	8
From 65-84 years	5	0	5
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	63.2	45.7	
standard deviation	± 12.94	± 5.86	-
Sex: Female, Male Units: Subjects			
Female	2	1	3
Male	8	2	10
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	9	3	12
More than one race	0	0	0
Unknown or Not Reported	1	0	1

Ethnicity Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	8	2	10
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received combination therapy of encorafenib (300 milligram [mg] orally, twice daily [BID]) and binimetinib (45 mg orally, BID) in 28-day cycles and continued until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received standard combination therapy of encorafenib (450 mg orally, once daily [QD]) and binimetinib (45 mg orally, BID) in 28-day cycles and subjects who were able to tolerate the encorafenib 450 mg dose further received 600 mg QD after 4 Weeks. Subjects were followed up to 30 days after last dose of study drug.

Primary: Number of Subjects With Dose Limiting Toxicities (DLTs): Safety Lead-in (SLI) Phase

End point title	Number of Subjects With Dose Limiting Toxicities (DLTs): Safety Lead-in (SLI) Phase[1][2]

End point description:

DLT: any adverse event (AE) or laboratory abnormality not explained by underlying disease/disease progression/intercurrent illness/concomitant therapies/resulting in inability to tolerate 75% of planned dose of binimetinib or encorafenib during Cycle 1. LVEF >10%, Grade (G)>=3 cardiac disorders; G3/4 hypertension vascular disorders; G3/4 rash,hand foot skin reaction, photosensitivity; G3/4 diarrhea, nausea/vomiting; Total bilirubin (TBL) G>=3 (>3.0*upper limit of normal [ULN)]);AST/ALT>5-8*ULN>5 days,>8*ULN,>3*ULN concurrent TBL>2*ULN;G>=3 serum creatinine, CK elevation, ECG QTcF prolonged,G3 troponin, electrolyte>72 hours,G3/4 amylase/lipase.G4 ANC, platelet count>7 days;G3/4 platelet count, other AE except lymphopenia. G>=3 retinopathy, other disorder>21 days; G2 uveitis/eye pain/blurred vision/decreased visual acuity; G4 other disorder; Other hematologic/non hematologic G>=3 AE. This endpoint was planned to be analysed in SLI phase only. Dose-determining set included.

End point type	Primary

End point timeframe:

Cycle 1 of safety lead-in phase (up to 28 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Adverse Events Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI _CTCAE) Version (v) 4.03: SLI Phase

End point title	Number of Subjects With Treatment Emergent Adverse Events Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI _CTCAE) Version (v) 4.03: SLI Phase[3][4]

End point description:

AE:any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship.TEAEs: events between 1st dose of study drug up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state or start of subsequent anticancer drug therapy-1 day, whichever occurred first. Grades by NCI CTCAE v.4.03: G1=asymptomatic or mild ,clinical or diagnostic observations only,intervention not indicated; G2=moderate,minimal,local/noninvasive intervention indicated,limiting age-appropriate instrumental activities of daily life (ADL); G3=severe or medically significant but not immediately life-threatening,hospitalisation or prolongation of existing hospitalisation indicated,disabling,limiting self-care ADL; G4=life-threatening consequence,urgent intervention indicated; G5=death related to AE. Subjects with AEs per maximum grades were reported.Safety set:all subjects who received at least 1 dose of any study drug.

End point type	Primary

End point timeframe:

Day 1 of dosing up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
Grade 1	1			
Grade 2	3			
Grade 3	5			
Grade 4	1			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Hepatology Laboratory Test Abnormalities: SLI Phase

End point title	Number of Subjects With Hepatology Laboratory Test

	Abnormalities: SLI Phase[5][6]

End point description:

Hepatology laboratory abnormalities included following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT or AST greater than or equal to (>=) 3*upper limit normal (ULN), >=5*ULN, >=10*ULN, >=20*ULN; total bilirubin (TBILI): >=2*ULN; ALT >=3*ULN and TBILI >=2*ULN; AST >=3*ULN and TBILI >=2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN and ALP >2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN and ALP <=2*ULN or missing. Only those laboratory test parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in SLI phase only.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be analysed for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
ALT: >=3*ULN	3			
ALT: >=5*ULN	1			
AST: >=3*ULN	3			
ALT or AST: >=3*ULN	3			
ALT or AST: >=5*ULN	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Shift From Baseline for Hematology and Coagulation Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: SLI Phase

End point title	Number of Subjects With Shift From Baseline for Hematology and Coagulation Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: SLI Phase[7][8]

End point description:

Hematology and coagulation laboratory test included: activated partial thromboplastin time prolonged (APTTP), anemia, hemoglobin (Hg) increased (inc), international normalised ratio (INR) increased, leukocytosis (Lkc), lymphocyte count decreased (LCD), lymphocyte count increased (LCI), neutrophil count decreased (NCD), platelet count decreased (PCD), and white blood cell decreased (WBCD). Laboratory results were categorically summarised according to the NCI-CTCAE criteria v4.03. Grade 1= mild; Grade 2= moderate; Grade 3= severe and Grade 4= life-threatening or disabling. Number of subjects with shift from baseline for hematology and coagulation laboratory test were assessed. Only those laboratory test parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. Here, "n" signifies subjects evaluable for specified rows.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[7] - 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 analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
APTTP: G0 (baseline) to G0 (post-baseline), n=6	5			
APTTP: G0 (baseline) to G1 (post-baseline), n=6	1			
Anemia: G0 (baseline) to G0 (post-baseline), n=10	2			
Anemia: G0 (baseline) to G1 (post-baseline), n=10	7			
Anemia: G0 (baseline) to G2 (post-baseline), n=10	1			
Hg inc: G0 (baseline) to G0 (post-baseline), n=10	10			
INR inc: G0 (baseline) to G0 (post-baseline), n=10	10			
Lkc: G0 (baseline) to G0 (post-baseline), n=10	10			
LCD: G0 (baseline) to G0 (post-baseline), n=9	2			
LCD: G0 (baseline) to G1 (post-baseline), n=9	2			
LCD: G0 (baseline) to G2 (post-baseline), n=9	2			
LCD: G0 (baseline) to G3 (post-baseline), n=9	3			
LCI: G0 (baseline) to G0 (post-baseline), n=9	8			
LCI: G0 (baseline) to G2 (post-baseline), n=9	1			
NCD: G0 (baseline) to G0 (post-baseline), n=9	8			
NCD: G0 (baseline) to G2 (post-baseline), n=9	1			
PCD: G0 (baseline) to G0 (post-baseline), n=10	7			
PCD: G0 (baseline) to G1 (post-baseline), n=10	3			
WBCD: G0 (baseline) to G0 (post-baseline), n=10	8			
WBCD: G0 (baseline) to G2 (post-baseline), n=10	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Shift From Baseline for Biochemistry Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: SLI Phase

End point title	Number of Subjects With Shift From Baseline for Biochemistry Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: SLI Phase[9][10]

End point description:

Biochemistry laboratory test included:alanine aminotransferase increased (AAI),alkaline phosphatase increased (API),aspartate aminotransferase increased (AsAI),blood bilirubin increased (BBI),creatine kinase increased (CKI), creatinine increased (CrI),hypercalcemia (hypercal),hyperglycemia (hypergly),hyperkalemia (hyperkal),hypermagnesemia (hypermag),hypernatremia (hypernat),hypoalbuminemia (hypoalb),hypocalcemia (hypocal),hypoglycemia (hypogly),hypokalemia (hypokal),hypomagnesemia (hypomag),hyponatremia (hyponat),hypophosphatemia (hypophos),lipase increased (LI), and serum amylase increased (SMI).Laboratory results were categorically summarised according to the NCI-CTCAE criteria v4.03.G1= mild;G2= moderate;G3= severe,G4= life-threatening or disabling.Number of subjects with shift from baseline for biochemistry lab test were assessed. Only those lab test parameters in which at least 1 subject had data were reported.Safety set included. Here, n=subjects evaluable for specified rows.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[9] - 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 analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
AAI: G0 (baseline) to G0 (post-baseline), n=8	2			
AAI: G0 (baseline) to G1 (post-baseline), n=8	3			
AAI: G0 (baseline) to G2 (post-baseline), n=8	2			
AAI: G0 (baseline) to G3 (post-baseline), n=8	1			
AAI: G1 (baseline) to G1 (post-baseline), n=2	2			

API: G0 (baseline) to G0 (post-baseline), n=8	5			
API: G0 (baseline) to G1 (post-baseline), n=8	3			
API: G1 (baseline) to G0 (post-baseline), n=2	2			
AsAI: G0 (baseline) to G0 (post-baseline), n=8	4			
AsAI: G0 (baseline) to G1 (post-baseline), n=8	2			
AsAI: G0 (baseline) to G2 (post-baseline), n=8	2			
AsAI: G1 (baseline) to G0 (post-baseline), n=2	1			
AsAI: G1 (baseline) to G1 (post-baseline), n=2	1			
BBI: G0 (baseline) to G0 (post-baseline), n=10	10			
CKI: G0 (baseline) to G0 (post-baseline), n=10	6			
CKI: G0 (baseline) to G1 (post-baseline), n=10	3			
CKI: G0 (baseline) to G4 (post-baseline), n=10	1			
CrI: G0 (baseline) to G1 (post-baseline), n=10	9			
CrI: G0 (baseline) to G2 (post-baseline), n=10	1			
Hypercal: G0(baseline) to G0(post-baseline),n=10	10			
Hypergly:G0(baseline) to G0 (post-baseline),n=8	5			
Hypergly: G0(baseline) to G1(post-baseline),n=8	1			
Hypergly: G0(baseline) to G3(post-baseline),n=8	2			
Hypergly:Baseline to post-baseline,n=2	1			
Hypergly:Missing(baseline)toG1 (post-baseline)n=2	1			
Hyperkal:G0(baseline) to G0(post-baseline),n=10	10			
Hypermag:G0(baseline) to G0(post-baseline),n=10	9			
Hypermag:G0(baseline) to G1(post-baseline),n=10	1			
Hypernat:G0(baseline) to G0(post-baseline),n=10	10			
Hypoalb:G0(baseline) to G0(post-baseline),n=9	6			
Hypoalb:G0(baseline) to G1(post-baseline),n=9	3			
Hypoalb:G2(baseline) to G2(post-baseline),n=1	1			
Hypocal:G0(baseline) to G0(post-baseline),n=10	8			
Hypocal:G0(baseline) to G1(post-baseline),n=10	2			
Hypogly:G0(baseline) to G0(post-baseline),n=10	10			
Hypokal:G0(baseline) to G0(post-baseline),n=10	10			

Hypomag:G0(baseline) to G0(post-baseline),n=10	10			
Hyponat:G0(baseline) to G0(post-baseline),n=8	3			
Hyponat:G0(baseline) to G1(post-baseline),n=8	2			
Hyponat:G0(baseline) to G3(post-baseline),n=8	3			
Hyponat:G1(baseline) to G0(post-baseline),n=2	1			
Hyponat:G1(baseline) to G3(post-baseline),n=2	1			
Hypophos:G0(baseline)toG0(post-baseline),n=7	6			
Hypophos:G0(baseline)toG2(post-baseline),n=7	1			
Hypophos:Missing(baseline)toG0(post-baseline),n=2	1			
Hypophos:Missing(baseline)toG2(post-baseline),n=2	1			
LI: G0(baseline) to G0(post-baseline), n=10	7			
LI: G0(baseline) to G1(post-baseline), n=10	3			
SMI: G0(baseline) to G0(post-baseline), n=10	10			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Notable Abnormal Vital Signs: SLI Phase

End point title	Number of Subjects With Notable Abnormal Vital Signs: SLI Phase[11][12]

End point description:

Vital signs:systolic & diastolic blood pressure (BP),pulse rate,weight & temperature.Systolic & diastolic BP was measured in millimeters of mercury (mmHg) based on criteria: High Systolic BP:>=160 mmHg & increase>=20 mmHg from baseline; High Diastolic BP:>=100 mmHg & increase>=15 mmHg from baseline; Low Systolic BP:<=90 mmHg with decrease from baseline of >=20 mmHg; Low Diastolic BP:<=50 mmHg with decrease from baseline of >=15 mmHg; Pulse rate was measured in beats per minute (bpm) based on criteria:High pulse rate>=120 bpm with increase from baseline of >=15 bpm;Low pulse rate <=50 bpm with decrease from baseline of >=15 bpm;Weight was measured in in kilogram (kg) based on criteria:Increase from baseline of >=10%,:>=20% decrease from baseline; Temperature was measured in degree Celsius (C) based on criteria:High body temperature>=37.5 degree C,Low body temperature<=36 degree C.Only those vital signs parameters in which at least 1 subject had data were reported.Safety set included.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[11] - 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 analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
High systolic BP	2			
Low diastolic BP	1			
High pulse rate	1			
Low pulse rate	1			
Increased body weight	2			
High body temperature	1			
Low body temperature	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Notable Abnormal Electrocardiogram (ECG) Values: SLI Phase

End point title	Number of Subjects With Notable Abnormal Electrocardiogram (ECG) Values: SLI Phase[13][14]

End point description:

In this endpoint, number of subjects with notable abnormal ECG values included: Fridericia's Correction Formula (QTcF) values in millisecond (msec) based on following criteria: 1) Increase from baseline >30 msec; 2) Increase from baseline >60 msec; 3) New >450 msec; 4) New >480 msec; and 5) New >500 msec; heart rate (HR) values in bpm based on following criteria: 1) Increase from baseline >25% and to a value >100; 2) Decrease from baseline >25% and to a value <50. Only those ECG parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in phase 2 only.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[13] - 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 analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
QTcF: New >450 msec	6			
QTcF:Increase from baseline >30 msec	5			

HR:Increase from baseline >25% & to a value >100	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to AEs: SLI Phase

End point title	Number of Subjects With Incidence of Dose Interruptions, Dose Modifications and Discontinuations due to AEs: SLI Phase[15][16]

End point description:

An AE is any untoward medical occurrence in clinical investigation subject administered a product or medical device; event need not necessarily to have a causal relationship with treatment or usage. In this endpoint, number of subjects with incidence of dose interruptions, dose modifications and discontinuations due to AEs were reported. The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in SLI phase only.

End point type	Primary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in SLI Phase, maximum duration up to 10.4 months

Notes:

[15] - 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 analysed for this endpoint.

[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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Subjects				
Dose interruptions due to AE	6			
Dose modifications due to AE	4			
Discontinuations due to AE	1			

Statistical analyses

No statistical analyses for this end point

Primary: Brain Metastasis Response Rate (BMRR) Based on Modified Response Evaluation Criteria in Solid Tumors Version 1.1 (mRECIST v1.1): Phase 2

End point title	Brain Metastasis Response Rate (BMRR) Based on Modified Response Evaluation Criteria in Solid Tumors Version 1.1

	(mRECIST v1.1): Phase 2[17][18]

End point description:

BMRR was reported in terms of percentage of subjects who achieved a confirmed best overall response (BOR) of confirmed complete response (CR) or partial response (PR) in brain metastasis per mRECIST v1.1 from date of first dose until disease progression, death due to any cause, or start of subsequent anticancer therapy, whichever occurred first. BOR: best response recorded from date of first dose of study treatment until progression by investigator assessment at each time point. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Primary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in Phase 2 (approximately up to 8.3 months)

Notes:

[17] - 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 analysed for this endpoint.

[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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Percentage of subjects				
number (confidence interval 95%)	66.7 (9.4 to 99.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial Response Rate Based on RECIST v1.1: SLI Phase and Phase 2

End point title	Extracranial Response Rate Based on RECIST v1.1: SLI Phase and Phase 2

End point description:

Extracranial response rate was defined as the percentage of subjects with a BOR of confirmed CR or confirmed PR in extracranial lesions by investigator assessment per RECIST v1.1. BOR: best response recorded from date of first dose of study treatment until progression by investigator assessment at each time point. CR: disappearance of all target lesions. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy

initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Percentage of subjects				
number (confidence interval 95%)	60.0 (26.2 to 87.8)	100 (29.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global Response Rate: SLI Phase and Phase 2

End point title	Global Response Rate: SLI Phase and Phase 2

End point description:

Global response rate was defined as the percentage of subjects with a BOR of confirmed CR or confirmed PR by investigator assessment in brain metastasis and extracranial lesions per combined mRECIST v1.1 and RECIST v1.1, respectively. BOR: best response recorded from date of first dose of study treatment until progression by investigator assessment at each time point. CR: disappearance of all target lesions. Any pathological lymph nodes must be <10 mm on the short axis. PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference the baseline sum of the diameters (e.g., percent change from baseline). PD: at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Percentage of subjects				
number (confidence interval 95%)	50.0 (18.7 to 81.3)	100 (29.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) for Brain Metastasis Response Based on mRECIST v1.1: SLI Phase and Phase 2

End point title	Disease Control Rate (DCR) for Brain Metastasis Response Based on mRECIST v1.1: SLI Phase and Phase 2

End point description:

DCR was defined as the percentage of subjects with a BOR of CR, PR or stable disease (SD) by investigator assessment per mRECIST v1.1. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters recorded since the treatment started. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Percentage of subjects				
number (confidence interval 95%)	100 (69.2 to 100)	100 (29.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR for Extracranial Response Based on RECIST v1.1: SLI Phase and Phase 2

End point title	DCR for Extracranial Response Based on RECIST v1.1: SLI Phase and Phase 2

End point description:

DCR was defined as the percentage of subjects with a BOR of CR, PR or SD by Investigator assessment per RECIST v1.1. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of

diameters of target lesions, taking as reference the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum demonstrates an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Percentage of subjects				
number (confidence interval 95%)	70.0 (34.8 to 93.3)	100 (29.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) for Brain Metastasis Response Based on mRECIST v1.1: SLI Phase and Phase 2

End point title	Duration of Response (DOR) for Brain Metastasis Response Based on mRECIST v1.1: SLI Phase and Phase 2

End point description:

DOR: time from date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause. CR: disappearance of all target lesions. PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. DOR (months)=(date of event or censoring – date of first CR or PR + 1)/30.4375. If subject with CR or PR did not have an event at time of analysis cutoff or with an event more than 16 weeks (for first 11 cycles after treatment start date) or 24 weeks (after Cycle 11) after last adequate tumor assessment, subject was censored on date of last adequate tumor assessment that documented no progression. Safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Months				
median (confidence interval 95%)	3.3 (2.8 to 8.5)	5.6 (5.0 to 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR for Global Response: SLI Phase and Phase 2

End point title	DCR for Global Response: SLI Phase and Phase 2

End point description:

DCR was defined as the percentage of subjects with a BOR of CR, PR or SD by Investigator assessment per RECIST v1.1. CR: disappearance of all target lesions. Any pathological lymph nodes must be <10 mm on the short axis. PR: at least a 30% decrease in the sum of the diameters of target lesions, taking as a reference the baseline sum of the diameters (e.g., percent change from baseline). SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to quality for PD. PD: at least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of at least 5 mm. The safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Percentage of subjects				
number (confidence interval 95%)	90.0 (55.5 to 99.7)	100 (29.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR for Global Response: SLI Phase and Phase 2

End point title	DOR for Global Response: SLI Phase and Phase 2

End point description:

DOR: time from date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause. CR: disappearance of all target lesions. PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. DOR (months) = (date of event or censoring – date of first CR or PR + 1)/30.4375. If a subject with CR or PR did not have an event at time of analysis cutoff or with an event more than 16 weeks (for first 11 cycles after treatment start date) or 24 weeks (after Cycle 11) after last adequate tumor assessment, subject was censored on date of last adequate tumor assessment that documented no progression. Safety set included all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

From date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 8.5)	5.0 (3.9 to 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) for Brain Metastasis Based on mRECIST v1.1: SLI Phase and Phase 2

End point title	Progression Free Survival (PFS) for Brain Metastasis Based on mRECIST v1.1: SLI Phase and Phase 2

End point description:

PFS was defined as the time from date of the first dose of study treatment to the earliest documented disease progression (PD) by Investigator assessment, or death due to any cause, whichever occurs first. PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase of at least 5 mm. If a subject did not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS was censored at the date of last adequate tumor assessment. Data for this endpoint was not evaluated, due to limited number of subjects who had event.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment to the earliest documented disease progression by investigator assessment, or death due to any cause, whichever occurs first in SLI (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[19] - Data was not evaluated, due to limited number of subjects who had event.

[20] - Data was not evaluated, due to limited number of subjects who had event.

Statistical analyses

No statistical analyses for this end point

Secondary: DOR for Extracranial Response Based on RECIST v1.1: SLI Phase and Phase 2

End point title	DOR for Extracranial Response Based on RECIST v1.1: SLI Phase and Phase 2

End point description:

DOR: time from date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause. CR: disappearance of all target lesions. PR: at least 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference smallest sum of diameters recorded since treatment started. In addition, sum must have absolute increase of at least 5 mm. DOR (months) = (date of event or censoring – date of first CR or PR + 1)/30.4375. If a subject with CR or PR did not have an event at time of analysis cutoff or with an event more than 16 weeks (for first 11 cycles after treatment start date) or 24 weeks (after Cycle 11) after last adequate tumor assessment, subject was censored on date of last adequate tumor assessment that documented no progression. Data for this endpoint was not evaluated, due to limited number of subjects who had event.

End point type	Secondary

End point timeframe:

From date of first radiographic response (CR or PR) to earliest documented disease progression or death due to any cause in SLI Phase (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[21] - Data was not evaluated, due to limited number of subjects who had event.

[22] - Data was not evaluated, due to limited number of subjects who had event.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS for Global Tumor Assessment: SLI Phase and Phase 2

End point title	PFS for Global Tumor Assessment: SLI Phase and Phase 2

End point description:

PFS was defined as the time from date of the first dose of study treatment to the earliest documented disease progression (PD) by Investigator assessment, or death due to any cause, whichever occurs first. PD: at least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum of diameters recorded since the treatment started (i.e., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of at least 5 mm. Global tumor assessment consists of brain metastasis and extracranial lesions. If a subject did not had a PFS event at the time of the analysis cutoff or at the start of any new anticancer therapy, PFS was censored at the date of last adequate tumor assessment. Data for this outcome measure was not evaluated, due to limited number of subjects who had event.

End point type	Secondary

End point timeframe:

From date of first dose of study treatment to the earliest documented disease progression by investigator assessment, or death due to any cause, whichever occurs first in SLI (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[23]	0[24]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[23] - Data was not evaluated, due to limited number of subjects who had event.

[24] - Data was not evaluated, due to limited number of subjects who had event.

Statistical analyses

No statistical analyses for this end point

Secondary: BMRR Based on mRECIST v1.1: SLI Phase

End point title	BMRR Based on mRECIST v1.1: SLI Phase[25]

End point description:

BMRR: percentage of subjects who achieved a confirmed best overall response (BOR) of confirmed CR or PR in brain metastasis per mRECIST v1.1 from date of first dose until disease progression, death due to any cause, or start of subsequent anticancer therapy, whichever occurs first. BOR: best response recorded from date of first dose of study treatment until progression by investigator assessment at each time point. CR: Disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters (e.g., percent change from baseline). The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

From date of first dose until disease progression, death due to any cause or subsequent therapy initiation, whichever occurred first in SLI Phase (approximately up to 10.4 months)

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Percentage of subjects				
number (confidence interval 95%)	60.0 (26.2 to 87.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival: Safety Lead-in Phase and Phase 2

End point title	Overall Survival: Safety Lead-in Phase and Phase 2

End point description:

Overall survival (OS) was defined as the time from date of the first dose of study treatment to the date of death due to any cause. If a death was not observed by the date of the analysis cutoff, OS was censored at the date of last contact. OS (months) = (date of death or censoring – date of first dose +1)/30.4375. Data for this endpoint was not evaluated, due to limited number of subjects who had

End point type	Secondary

End point timeframe:

From date of first dose of study treatment to the earliest documented disease progression by investigator assessment, or death due to any cause, whichever occurs first in SLI (approximately up to 10.4 months) and Phase 2 (approximately up to 8.3 months)

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[26]	0[27]		
Units: Months				
arithmetic mean (standard deviation)	()	()		

Notes:

[26] - Data was not evaluated, due to limited number of subjects who had event.

[27] - Data was not evaluated, due to limited number of subjects who had event.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent AEs of Maximum Severity Grades Based on NCI CTCAE v4.03: Phase 2

End point title	Number of Subjects With Treatment Emergent AEs of Maximum Severity Grades Based on NCI CTCAE v4.03: Phase 2[28]

End point description:

AE: any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. TEAEs: event between 1st dose of study drug up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state or start of subsequent anticancer drug therapy 1 day, whichever occurred first. Grades by NCI CTCAE v.4.03: G1=asymptomatic or mild, clinical or diagnostic observations only,intervention not indicated;G2=moderate, minimal,local/noninvasive intervention indicated, limiting age-appropriate instrumental ADL); G3=severe or medically significant but not immediately life-threatening, hospitalisation or prolongation of existing hospitalisation indicated,disabling,limiting self-care ADL; G4=life-threatening consequence,urgent intervention indicated; G5=death related to AE. Only those categories in which at least 1 subject had data were reported. Safety set:all subjects who received at least 1 dose of any study drug.

End point type	Secondary

End point timeframe:

Day 1 of dosing up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

Notes:

[28] - 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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Grade 2	2			
Grade 4	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hepatology Laboratory Test Abnormalities: Phase 2

End point title	Number of Subjects With Hepatology Laboratory Test Abnormalities: Phase 2[29]

End point description:

Hepatology laboratory abnormalities included following parameters: ALT, AST, ALT or AST >=3*ULN, >=5*ULN, >=10*ULN, >=20*ULN; TBILI: >=2*ULN; ALT >=3*ULN and TBILI >=2*ULN; AST >=3*ULN and TBILI >=2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN and ALP >2*ULN; ALT or AST >=3*ULN and TBILI >=2*ULN and ALP <=2*ULN or missing. Only those laboratory test parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in phase 2 only.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
ALT: >=3*ULN	2			
ALT: >=5*ULN	1			
ALT: >=10*ULN	1			
ALT: >=20*ULN	1			
AST: >=3*ULN	1			
AST: >=5*ULN	1			
AST: >=10*ULN	1			
ALT or AST: >=3*ULN	2			
ALT or AST: >=5*ULN	1			
ALT or AST: >=10*ULN	1			
ALT or AST: >=20*ULN	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline for Hematology and Coagulation Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: Phase 2

End point title	Number of Subjects With Shift From Baseline for Hematology and Coagulation Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: Phase 2[30]

End point description:

Hematology and coagulation laboratory test included: activated partial thromboplastin time prolonged (APTTP), anemia, hemoglobin (Hg) increased (inc), international normalised ratio (INR) increased, leukocytosis (Lkc), lymphocyte count decreased (LCD), lymphocyte count increased (LCI), neutrophil count decreased (NCD), platelet count decreased (PCD), and white blood cell decreased (WBCD). Laboratory results were categorically summarised according to the NCI-CTCAE criteria v4.03. Grade 1= mild; Grade 2= moderate; Grade 3= severe and Grade 4= life-threatening or disabling. Number of subjects with shift from baseline for hematology and coagulation laboratory test were assessed. Only those laboratory test parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. Here, "n" signifies subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

Notes:

[30] - 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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
APTTP: G0 (baseline) to G0 (post-baseline), n=1	1			
Anemia: G0 (baseline) to G1 (post-baseline), n=2	1			
Anemia: G0 (baseline) to G2 (post-baseline), n=2	1			
Anemia: G1 (baseline) to G1 (post-baseline), n=1	1			
Hg inc: G0 (baseline) to G0 (post-baseline), n=3	3			
INR inc: G0 (baseline) to G0 (post-baseline), n=1	1			
Lkc: G0 (baseline) to G0 (post-baseline), n=3	3			
LCD: G0 (baseline) to G0 (post-baseline), n=3	2			
LCD: G0 (baseline) to G1 (post-baseline), n=3	1			
LCI: G0 (baseline) to G0 (post-baseline), n=3	3			
NCD: G0 (baseline) to G0 (post-baseline), n=3	2			
NCD: G0 (baseline) to G2 (post-baseline), n=3	1			
PCD: G0 (baseline) to G0 (post-baseline), n=3	2			
PCD: G0 (baseline) to G1 (post-baseline), n=3	1			
WBCD: G0 (baseline) to G0 (post-baseline), n=3	2			
WBCD: G0 (baseline) to G1 (post-baseline), n=3	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From Baseline for Biochemistry Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: Phase 2

End point title	Number of Subjects With Shift From Baseline for Biochemistry Laboratory Test Abnormalities Based on NCI-CTCAE v4.03: Phase 2[31]

End point description:

Biochemistry laboratory test included:alanine aminotransferase increased (AAI),alkaline phosphatase increased (API),aspartate aminotransferase increased (AsAI),blood bilirubin increased (BBI),creatine kinase increased (CKI), creatinine increased (CrI),hypercalcemia (hypercal),hyperglycemia (hypergly),hyperkalemia (hyperkal),hypermagnesemia (hypermag),hypernatremia (hypernat),hypoalbuminemia (hypoalb),hypocalcemia (hypocal),hypoglycemia (hypogly),hypokalemia (hypokal),hypomagnesemia (hypomag),hyponatremia (hyponat),hypophosphatemia (hypophos),lipase increased (LI), and serum amylase increased (SMI).Laboratory results were categorically summarised

criteria v4.03.G1= mild;G2= moderate;G3= severe,G4= life-threatening or disabling.Number of subjects with shift from baseline for biochemistry lab test were assessed. Only those lab test parameters in which at least 1 subject had data were reported.Safety set included. Here, n=subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

Notes:

[31] - 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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
AAI: G0 (baseline) to G2 (post-baseline), n=1	1			
AAI: G1 (baseline) to G0 (post-baseline), n=2	1			
AAI: G1 (baseline) to G4 (post-baseline), n=2	1			
API: G0 (baseline) to G0 (post-baseline), n=2	1			
API: G0 (baseline) to G1 (post-baseline), n=2	1			
API: G2 (baseline) to G2 (post-baseline), n=1	1			
AsAI: G0 (baseline) to G1 (post-baseline), n=2	1			
AsAI: G0 (baseline) to G3 (post-baseline), n=2	1			
AsAI: G1 (baseline) to G0 (post-baseline), n=1	1			
BBI: G0 (baseline) to G0 (post-baseline), n=3	3			
CK inc: G0 (baseline) to G1 (post-baseline), n=3	2			
CK inc: G0 (baseline) to G2 (post-baseline), n=3	1			
CrI: G0 (baseline) to G1 (post-baseline), n=3	1			
CrI: G0 (baseline) to G2 (post-baseline), n=3	2			
Hypercal: G0 (baseline) to G0 (post-baseline), n=3	3			
Hypergly: G0 (baseline) to G0 (post-baseline), n=3	3			
Hyperkal: G0 (baseline) to G0 (post-baseline), n=3	3			
Hypermag: G0 (baseline) to G0 (post-baseline), n=3	3			
Hypernat: G0 (baseline) to G0 (post-baseline), n=3	3			

Hypoalb: G0 (baseline) to G0 (post-baseline), n=2	2			
Hypoalb: G1 (baseline) to G0 (post-baseline), n=1	1			
Hypocal: G0 (baseline) to G0 (post-baseline), n=3	1			
Hypocal: G0 (baseline) to G1 (post-baseline), n=3	2			
Hypogly: G0 (baseline) to G0 (post-baseline), n=3	3			
Hypokal: G0 (baseline) to G0 (post-baseline), n=3	2			
Hypokal: G0 (baseline) to G1 (post-baseline), n=3	1			
Hypomag: G0 (baseline) to G0 (post-baseline), n=3	3			
Hyponat: G0 (baseline) to G0 (post-baseline), n=3	3			
Hypophos: G0 (baseline) to G0 (post-baseline), n=3	3			
LI: G0 (baseline) to G0 (post-baseline), n=3	2			
LI: G0 (baseline) to G1 (post-baseline), n=3	1			
SAI: G0 (baseline) to G0 (post-baseline), n=3	2			
SAI: G0 (baseline) to G1 (post-baseline), n=3	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Change in Notable Abnormal Vital Signs: Phase 2

End point title	Number of Subjects With Clinically Significant Change in Notable Abnormal Vital Signs: Phase 2[32]

End point description:

Vital signs: systolic & diastolic BP, pulse rate, weight & temperature. Systolic & diastolic BP was measured in mmHg based on criteria: High Systolic BP:>=160 mmHg & increase>=20 mmHg from baseline; High Diastolic BP:>=100 mmHg & increase>=15 mmHg from baseline; Low Systolic BP:<=90 mmHg with decrease from baseline of >=20 mmHg; Low Diastolic BP:<=50 mmHg with decrease from baseline of >=15 mmHg; Pulse rate was measured in bpm based on criteria: High pulse rate>=120 bpm with increase from baseline of >=15 bpm; Low pulse rate <=50 bpm with decrease from baseline of >=15 bpm; Weight was measured in in kg based on criteria: Increase from baseline of >=10%,:>=20% decrease from baseline; Temperature was measured in degree C based on criteria: High body temperature>=37.5 degree C, Low body temperature<=36 degree C. Only those vital signs parameters in which at least 1 subject had data were reported. Safety set included.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

Notes:

[32] - 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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
Increased body weight	1			
Low body temperature	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Notable Abnormal Electrocardiogram (ECG) Values: Phase 2

End point title	Number of Subjects With Notable Abnormal Electrocardiogram (ECG) Values: Phase 2[33]

End point description:

In this end point, number of subjects with notable abnormal ECG values included: QTcF values in msec based on following criteria: 1) increase from baseline >30 msec; 2) increase from baseline >60 msec; 3) new >450 msec; 4) new >480 msec; and 5) new >500 msec; heart rate values in bpm based on following criteria: 1) Increase from baseline >25% and to a value >100; 2) Decrease from baseline >25% and to a value <50. Only those vital ECG parameters in which at least 1 subject had data were reported. The safety set included all subjects who received at least 1 dose of any study drug. This endpoint was planned to be analysed in phase 2 only.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to 30 days after last dose of study drug in Phase 2, maximum duration up to 8.3 months

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: Only Phase 2 arm was planned to be analysed for this endpoint.

End point values	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Subjects				
QTcF: Increase from baseline >30	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Encorafenib and its Metabolite LHY746: SLI

Phase

End point title	Plasma Concentrations of Encorafenib and its Metabolite LHY746: SLI Phase[34]

End point description:

In this end point, plasma concentrations (in nanogram per milliliter [ng/mL]) of encorafenib and its metabolite LHY746 at Cycle 1 Day 1 (C1D1), Cycle 1 Day 15 (C1D15), Cycle 2 Day 1 (C2D1), and Cycle 3 Day 1 (C3D1) at different time points were reported. The pharmacokinetic (PK) analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose, Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose, Cycle 2, Cycle 3 Day 1: Pre-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Encorafenib C1D1: 0.5 hrs post dose, n=8	65.5 (± 328.8)			
Encorafenib C1D1: 1.5 hrs post dose, n=8	1830 (± 325.5)			
Encorafenib C1D1: 3 hrs post dose, n=8	2120 (± 36.3)			
Encorafenib C1D1: 6 hrs post dose, n=7	1170 (± 67.7)			
Encorafenib C1D15: pre-dose, n=6	92.3 (± 87.9)			
Encorafenib C1D15: 0.5 hrs post dose, n=6	182 (± 243.5)			
Encorafenib C1D15: 1.5 hrs post dose, n=6	745 (± 132.7)			
Encorafenib C1D15: 3 hrs post dose, n=6	953 (± 50.0)			
Encorafenib C1D15: 6 hrs post dose, n=6	332 (± 61.0)			
Encorafenib C2D1: pre-dose, n=4	59.7 (± 65.7)			
Encorafenib C3D1: pre-dose, n=5	50.1 (± 47.8)			
LHY746 C1D1: 0.5 hrs post dose, n=8	6.46 (± 114.1)			
LHY746 C1D1: 1.5 hrs post dose, n=8	123 (± 345.5)			
LHY746 C1D1: 3 hrs post dose, n=6	296 (± 46.7)			
LHY746 C1D1: 6 hrs post dose, n=7	277 (± 62.7)			
LHY746 C1D15: pre-dose, n=6	892 (± 101.1)			
LHY746 C1D15: 0.5 hrs post dose, n=6	941 (± 88.2)			
LHY746 C1D15: 1.5 hrs post dose, n=6	1040 (± 93.4)			
LHY746 C1D15: 3 hrs post dose, n=8	1690 (± 64.3)			
LHY746 C1D15: 6 hrs post dose, n=6	1520 (± 59.0)			
LHY746 C2D1: pre-dose, n=4	655 (± 91.3)			

LHY746 C3D1: pre-dose, n=5	256 (± 2956.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Plasma Concentrations of Binimetinib and its Metabolite AR00426032: SLI Phase[35]

End point description:

In this end point, plasma concentrations of binimetinib and its metabolite AR00426032 at C1D1, C1D15, C2D1, and C3D1 at different time points were reported. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose: Cycle 2, Cycle 3 Day 1: Pre-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib C1D1: 0.5 hrs post dose, n=8	86.6 (± 567.4)			
Binimetinib C1D1: 1.5 hrs post dose, n=8	297 (± 341.9)			
Binimetinib C1D1: 3 hrs post dose, n=8	233 (± 83.2)			
Binimetinib C1D1: 6 hrs post dose, n=7	151 (± 91.6)			
Binimetinib C1D15: pre-dose, n=6	47.7 (± 71.8)			
Binimetinib C1D15: 0.5 hrs post dose, n=6	151 (± 67.8)			
Binimetinib C1D15: 1.5 hrs post dose, n=6	232 (± 121.1)			
Binimetinib C1D15: 3 hrs post dose, n=6	215 (± 55.2)			
Binimetinib C1D15: 6 hrs post dose, n=6	79.9 (± 56.6)			
Binimetinib C2D1: pre-dose, n=4	42.0 (± 47.8)			

Binimetinib C3D1: pre-dose, n=5	30.0 (± 65.3)			
AR00426032 C1D1: 0.5 hrs post dose, n=8	8.10 (± 132.4)			
AR00426032 C1D1: 1.5 hrs post dose, n=8	30.3 (± 345.7)			
AR00426032 C1D1: 3 hrs post dose, n=8	31.7 (± 60.1)			
AR00426032 C1D1: 6 hrs post dose, n=7	21.9 (± 36.6)			
AR00426032 C1D15: pre-dose, n=6	3.13 (± 53.0)			
AR00426032 C1D15: 0.5 hrs post dose, n=6	5.89 (± 136.9)			
AR00426032 C1D15: 1.5 hrs post dose, n=6	10.6 (± 56.8)			
AR00426032 C1D15: 3 hrs post dose, n=6	12.5 (± 58.0)			
AR00426032 C1D15: 6 hrs post dose, n=6	4.71 (± 62.8)			
AR00426032 C2D1: pre-dose, n=4	2.97 (± 29.6)			
AR00426032 C3D1: pre-dose, n=5	1.57 (± 42.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to 6 Hours (AUC 0-6) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to 6 Hours (AUC 0-6) of Encorafenib and its Metabolite LHY746: SLI Phase[36]

End point description:

In this end point, area under the plasma concentration-time curve from zero to 6 hours (AUC 0-6) after administration of encorafenib and its metabolite LHY746 in nanogram*hour per milliliter (ng*hr/mL) at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng*hr/mL				
geometric mean (geometric coefficient				

of variation)				
Encorafenib: C1D1, n=7	9530 (± 50.6)			
Encorafenib: C1D15, n=6	3930 (± 52.8)			
LHY746: C1D1, n=7	1230 (± 60.1)			
LHY746: C1D15, n=6	8160 (± 67.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-6 of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	AUC0-6 of Binimetinib and its Metabolite AR00426032: SLI Phase[37]

End point description:

In this end point, area under the plasma concentration-time curve from zero to 6 hours (AUC 0-6) after administration of binimetinib and its metabolite AR00426032 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib: C1D1n =7	1410 (± 85.5)			
Binimetinib: C1D15, n=6	1050 (± 39.7)			
AR00426032: C1D1, n=7	159 (± 65.9)			
AR00426032: C1D15, n=6	53.9 (± 48.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to last Time Point (AUClast) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to last Time Point (AUClast) of Encorafenib and its Metabolite LHY746: SLI Phase[38]

End point description:

In this end point, area under the plasma concentration-time curve from zero to the last measurable time point (AUClast) after administration of encorafenib and its metabolite LHY746 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Encorafenib: C1D1, n=8	9190 (± 47.8)			
Encorafenib: C1D15, n=6	7490 (± 52.8)			
LHY746: C1D1, n=8	1180 (± 56.9)			
LHY746: C1D15, n=6	29600 (± 73.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	AUClast of Binimetinib and its Metabolite AR00426032: SLI Phase[39]

End point description:

In this end point, area under the plasma concentration-time curve from zero to the last measurable time point (AUClast) after administration of binimetinib and its metabolite AR00426032 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib: C1D1, n=8	1350 (± 79.1)			
Binimetinib: C1D15, n=6	1440 (± 43.9)			
AR00426032: C1D1, n=8	156 (± 60.6)			
AR00426032: C1D15, n=6	77.9 (± 49.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to Tau (AUCtau) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to Tau (AUCtau) of Encorafenib and its Metabolite LHY746: SLI Phase[40]

End point description:

In this end point, area under the plasma concentration-time curve from time zero to the last measurable time point Tau (AUCtau) of encorafenib and its metabolite LHY746 over a dosing interval (6 hours as appropriate) of C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[40] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng*hr/mL				
geometric mean (geometric coefficient				

of variation)				
Encorafenib, n=6	7490 (± 52.8)			
LHY746, n=6	29600 (± 73.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	AUCtau of Binimetinib and its Metabolite AR00426032: SLI Phase[41]

End point description:

In this end point, area under the plasma concentration-time curve from time zero to the last measurable time point Tau (AUCtau) of encorafenib and its metabolite LHY746 over a dosing interval (6 hours as appropriate) of C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[41] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib, n=6	1440 (± 43.9)			
AR00426032, n=6	77.9 (± 49.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) After Drug Administration of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Maximum Observed Plasma Concentration (Cmax) After Drug Administration of Encorafenib and its Metabolite LHY746: SLI Phase[42]

End point description:

In this end point, maximum observed plasma concentration (Cmax) after administration of encorafenib

and its metabolite LHY746 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[42] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Encorafenib: C1D1, n=8	3210 (± 47.7)			
Encorafenib: C1D15, n=6	1370 (± 79.3)			
LHY746: C1D1, n=8	340 (± 47.2)			
LHY746: C1D15, n=6	1720 (± 65.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Cmax of Binimetinib and its Metabolite AR00426032: SLI

End point description:

In this end point, maximum observed plasma concentration (Cmax) after administration of binimetinib and its metabolite AR00426032 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[43] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib: C1D1, n=8	506 (± 85.5)			
Binimetinib: C1D15, n=6	359 (± 40.5)			
AR00426032: C1D1, n=8	53.9 (± 77.8)			
AR00426032: C1D15, n=6	16.9 (± 54.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Cmin) at the end of a Dosing Interval at Steady State of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Minimum Observed Plasma Concentration (Cmin) at the end of a Dosing Interval at Steady State of Encorafenib and its Metabolite LHY746: SLI Phase[44]

End point description:

In this end point, minimum observed plasma concentration (Cmin) after administration of encorafenib and its metabolite LHY746 at C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[44] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Encorafenib, n=6	91.1 (± 88.3)			
LHY746, n=6	829 (± 99.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmin of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Cmin of Binimetinib and its Metabolite AR00426032: SLI

End point description:

In this end point, minimum observed plasma concentration (Cmin) after administration of binimetinib and its metabolite AR00426032 at C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[45] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Binimetinib, n=6	47.7 (± 71.8)			
AR00426032, n=6	3.04 (± 47.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Ctrough of Encorafenib and its Metabolite LHY746: SLI

End point description:

In this end point, measured concentration at the end of a dosing interval (Ctrough) of encorafenib and its metabolite LHY746 at C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n'

signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[46] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Encorafenib, n=6	332 (± 61.0)			
LHY746, n=6	1520 (± 59.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Ctrough of Binimetinib and its Metabolite AR00426032: SLI Phase[47]

End point description:

In this end point, measured concentration at the end of a dosing interval (Ctrough) of binimetinib and its metabolite AR00426032 at C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[47] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				

geometric mean (geometric coefficient of variation)				
Binimetinib, n=6	79.9 (± 56.6)			
AR00426032, n=6	4.71 (± 62.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Time to Reach Maximum Concentration (Tmax) of Encorafenib and its Metabolite LHY746: SLI Phase[48]

End point description:

In this end point, time to reach maximum concentration (Tmax) of encorafenib and its metabolite LHY746 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[48] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
median (full range (min-max))				
Encorafenib: C1D1, n=8	1.53 (1.47 to 3.00)			
Encorafenib: C1D15, n=6	1.55 (0.43 to 3.00)			
LHY746: C1D1, n=8	4.33 (1.47 to 6.00)			
LHY746: C1D15, n=6	3.00 (2.92 to 5.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Tmax of Binimetinib and its Metabolite AR00426032: SLI

End point description:

In this end point, time to reach maximum concentration (Tmax) of binimetinib and its metabolite AR00426032 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[49] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
median (full range (min-max))				
Binimetinib: C1D1, n=8	1.50 (1.45 to 6.08)			
Binimetinib: C1D15, n=6	1.55 (0.43 to 2.98)			
AR00426032: C1D1, n=8	1.53 (1.47 to 6.08)			
AR00426032: C1D15, n=6	1.58 (0.43 to 3.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Last PK Sample (Tlast) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Time of Last PK Sample (Tlast) of Encorafenib and its Metabolite LHY746: SLI Phase[50]

End point description:

In this end point, time of last PK sample (Tlast) of encorafenib and its metabolite LHY746 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[50] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
median (full range (min-max))				
Encorafenib: C1D1, n=8	5.78 (3.00 to 6.08)			
Encorafenib: C1D15, n=6	24.00 (24.00 to 24.00)			
LHY746: C1D1, n=8	5.78 (3.00 to 6.08)			
LHY746: C1D15, n=6	24.00 (24.00 to 24.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Tlast of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Tlast of Binimetinib and its Metabolite AR00426032: SLI

End point description:

In this end point, time of last PK sample (Tlast) of binimetinib and its metabolite AR00426032 at C1D1, and C1D15 were assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[51] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
median (full range (min-max))				

Binimetinib: C1D1, n=8	5.78 (3.00 to 6.08)			
Binimetinib: C1D15, n=6	12.00 (12.00 to 12.00)			
AR00426032: C1D1, n=8	5.78 (3.00 to 6.08)			
AR00426032: C1D15, n=6	12.00 (12.00 to 12.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Between AUClast,ss and AUClast (RAUC) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Accumulation Ratio Between AUClast,ss and AUClast (RAUC) of Encorafenib and its Metabolite LHY746: SLI Phase[52]

End point description:

In this end point, accumulation ratio of encorafenib and its metabolite LHY746 calculated as: C1D15 AUC0-6 divided by C1D1 AUC0-6 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[52] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
geometric mean (geometric coefficient of variation)				
Encorafenib, n=6	0.468 (± 46.0)			
LHY746, n=6	7.25 (± 46.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: RAUC of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	RAUC of Binimetinib and its Metabolite AR00426032: SLI Phase

	[53]

End point description:

In this end point, accumulation ratio of binimetinib and its metabolite AR00426032 calculated as: C1D15 AUC0-6 divided by C1D1 AUC0-6 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[53] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
geometric mean (geometric coefficient of variation)				
Binimetinib, n=6	0.877 (± 60.4)			
AR00426032, n=6	0.359 (± 93.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Between Cmax,ss and Cmax (RCmax) of Encorafenib and its Metabolite LHY746: SLI Phase

End point title	Accumulation Ratio Between Cmax,ss and Cmax (RCmax) of Encorafenib and its Metabolite LHY746: SLI Phase[54]

End point description:

In this endpoint, accumulation ratio of encorafenib and its metabolite LHY746 calculated as: C1D15 Cmax divided by C1D1 Cmax was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[54] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
geometric mean (geometric coefficient of variation)				
Encorafenib, n=6 LHY746, n=6	0.490 (± 71.8) 5.78 (± 41.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rcmax of Binimetinib and its Metabolite AR00426032: SLI Phase

End point title	Rcmax of Binimetinib and its Metabolite AR00426032: SLI Phase[55]

End point description:

In this end point, accumulation ratio of binimetinib and its metabolite AR00426032 calculated as: C1D15 Cmax divided by C1D1 Cmax was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[55] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ratio				
geometric mean (geometric coefficient of variation)				
Binimetinib, n=6 AR00426032, n=6	0.818 (± 95.9) 0.347 (± 130.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of AUClast Values of the Metabolite Compared to Parent (MRAUClast) of LHY746: SLI Phase

End point title	Ratio of AUClast Values of the Metabolite Compared to Parent (MRAUClast) of LHY746: SLI Phase[56]

End point description:

In this end point, ratio of AUClast values of the metabolite compared to parent, corrected for molecular weight, for LHY746/encorafenib at C1D1, and C1D15 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[56] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ratio				
geometric mean (geometric coefficient of variation)				
C1D1, n=7 C1D15, n=6	0.164 (± 21.7) 2.64 (± 36.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: MRAUClast of AR00426032: SLI Phase

End point title	MRAUClast of AR00426032: SLI Phase[57]

End point description:

In this end point, ratio of AUClast values of the metabolite compared to parent, corrected for molecular weight, for AR00426032/binimetinib at C1D1, and C1D15 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[57] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ratio				
geometric mean (geometric coefficient of variation)				
C1D1, n=7 C1D15, n=6	0.109 (± 54.1) 0.0494 (± 63.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of Cmax Values of the Metabolite Compared to Parent (MRCmax) of LHY746: SLI Phase

End point title	Ratio of Cmax Values of the Metabolite Compared to Parent (MRCmax) of LHY746: SLI Phase[58]

End point description:

In this end point, ratio of Cmax values of the metabolite compared to parent, corrected for molecular weight, for LHY746/encorafenib at C1D1, and C1D15 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[58] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ratio				
geometric mean (geometric coefficient of variation)				
C1D1, n=8	0.135 (± 16.7)			

C1D15, n=6	1.59 (± 47.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: MRCmax of AR00426032: SLI Phase

End point title	MRCmax of AR00426032: SLI Phase[59]

End point description:

In this end point, ratio of Cmax values of the metabolite compared to parent, corrected for molecular weight, for AR00426032/ binimetinib at C1D1, and C1D15 was assessed. PK analysis set included all subjects who received at least 1 dose of any study drug and had at least 1 PK blood collection after the first dose of study drug with associated bioanalytical results. Here 'N' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable for specified rows. This endpoint was planned to be analysed in SLI phase only.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 0.5, 1.5, 3, 6 hours post-dose: Cycle 1 Day 15: Predose, 0.5, 1.5, 3, 6 hours (hrs.) post-dose

Notes:

[59] - 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: Only Safety-Lead in arm was planned to be analysed for this endpoint.

End point values	SLI Phase: Encorafenib 300 mg BID+Binimetinib 45 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: ratio				
geometric mean (geometric coefficient of variation)				
C1D1, n=8 C1D15, n=6	0.103 (± 49.3) 0.0453 (± 53.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 of dosing up to 30 days after last dose of study drug in Safety Lead-in Phase (maximum up to 10.4 months) and Phase 2 (maximum up to 8.3 months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorised as serious in 1 subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received standard combination therapy of encorafenib (450 mg orally, QD) and binimetinib (45 mg orally, BID) in 28-day cycles and subjects who were able to tolerate the encorafenib 450 mg dose further received 600 mg QD after 4 Weeks. Subjects were followed up to 30 days after last dose of study drug.

Reporting group title	SLI Phase: Encorafenib 300 mg BID + Binimetinib 45 mg BID

Reporting group description:

Subjects diagnosed with BRAFV600-mutant melanoma brain metastasis received combination therapy of encorafenib (300 mg orally, BID) and binimetinib (45 mg orally, BID) in 28-day cycles and continued until disease progression, unacceptable toxicity, withdrawal of consent, start of subsequent anticancer therapy, or death, whichever occurred first. Subjects were followed up to 30 days after last dose of study drug.

Serious adverse events	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID	SLI Phase: Encorafenib 300 mg BID + Binimetinib 45 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	
number of deaths (all causes)	3	7	
number of deaths resulting from adverse events			
Vascular disorders			
Air embolism			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase 2: Encorafenib 450 mg QD + Binimetinib 45 mg BID	SLI Phase: Encorafenib 300 mg BID + Binimetinib 45 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	10 / 10 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Neoplasm skin			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	
Facial pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	6 / 10 (60.00%)	
occurrences (all)	1	9	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	4 / 10 (40.00%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Nasal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Wheezing			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory tract congestion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Stress			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)	3 / 10 (30.00%)	
occurrences (all)	3	4	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 3 (66.67%)	5 / 10 (50.00%)	
occurrences (all)	6	8	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	4	
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	5	
Platelet count decreased			

subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Troponin T increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Disturbance in attention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Facial paresis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	1 / 3 (33.33%)	3 / 10 (30.00%)	
occurrences (all)	1	5	
Lethargy			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	4	
Eye disorders			
Macular oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Retinopathy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Abdominal pain upper			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)	5 / 10 (50.00%)	
occurrences (all)	3	7	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	5 / 10 (50.00%)	
occurrences (all)	3	9	
Dysphagia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 3 (66.67%)	5 / 10 (50.00%)	
occurrences (all)	3	8	
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	4 / 10 (40.00%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			

Actinic keratosis				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Hyperkeratosis				
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)		
occurrences (all)	0	2		
Erythema				
subjects affected / exposed	1 / 3 (33.33%)	0 / 10 (0.00%)		
occurrences (all)	1	0		
Dermal cyst				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Melanocytic hyperplasia				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Angioedema				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Pain of skin				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Papule				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Pruritus				
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)		
occurrences (all)	0	2		
Photosensitivity reaction				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Purpura				
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)		
occurrences (all)	0	1		
Rash				
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)		
occurrences (all)	0	2		

Rash macular			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	4 / 10 (40.00%)	
occurrences (all)	0	4	
Rash pruritic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Seborrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vitiligo			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Skin disorder			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Renal impairment			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	4	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Myositis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Folliculitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Onychomycosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rhinitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	5	
Abnormal loss of weight			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2020	To revise subject eligibility criteria based on investigator feedback and changes in standard of care for the treatment of asymptomatic brain metastases. Study design was updated to allow for flexibility regarding if the high-dose regimen was not tolerated and to simplify the overall study design.
07 August 2020	To evaluate the safety, tolerability and efficacy for subjects with intra-patient dose escalation up to 600 mg QD encorafenib in Phase 2. To include update safety/risk data. Adverse events and serious adverse events revised to align with Pfizer standard operating procedures. Per Pfizer TLF reduction initiative, the safety parameters (body weight, ECOG PS, dermatologic, ECHO/MUGA and ophthalmic examination) were not summarised descriptively in the tables.
04 January 2021	1) Clarification of Safety reporting for cardiovascular and death events; 2) Inclusion of Health Canada recommendations for additional ECG criteria that may qualify as serious adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 June 2021	Pfizer and the Steering Committee reviewed safety lead-in data and decided not to evaluate high dose combination of encorafenib + binimetinib in Phase 2 of the study.	-

Notes:

Limitations and caveats

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

Data for pharmacokinetic end points for "Phase 2" was not collected and analysed as sampling was insufficient to support noncompartmental analysis in subjects.

Notes: