Clinical trial results:
A Single Arm, Open Label, Phase II, Multicenter Study to Assess the Detection of the BRAF V600 Mutation on cfDNA from Plasma in Patients with Advanced Melanoma

Summary

EudraCT number	2015-001731-20
Trial protocol	BE PL
Global end of trial date	16 July 2019

Results information

Result version number	v1 (current)
This version publication date	26 July 2020
First version publication date	26 July 2020

Trial information

Trial identification

Sponsor protocol code	ML29741

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02768207
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	16 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main trial objective was to estimate the frequency of the BRAFV600 mutation in a new mutation analysis in response to a mutant plasma cfDNA test result in participants with BRAF wild-type status based on a prior tissue test result.

Protection of trial subjects:

All participants were required to sign an Informed Consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2016
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	Belgium: 78
Country: Number of subjects enrolled	Poland: 94
Worldwide total number of subjects	172
EEA total number of subjects	172

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)	95
From 65 to 84 years	72
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult participants with unresectable or metastatic melanoma. Participants possessing a BRAF V600 mutation were eligible to move to the second study phase (treatment phase).

Period 1

Period 1 title	Pre-Screening Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pre-Screening Phase (mITT population)

Arm description:

Participants in the modified intention to treat (mITT) population were tested for the presence of the BRAFV600 mutation using plasma cfDNA.

Arm type	No Intervention
Investigational medicinal product name	Blood draw for plasma sample
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Unknown use

Dosage and administration details:

No intervention was administered in this arm. Samples were collected to determine the presence of the BRAFV600 mutation using plasma cfDNA. The EudraCT platform will not allow for the proper recording of this arm as "no intervention."

Number of subjects in period 1	Pre-Screening Phase (mITT population)
Started	172
Completed	40
Not completed	132
Consent withdrawn by subject	6
Physician decision	6
Did not meet inclusion criteria	1
Not eligible	1
Unspecified	4
Not eligible for treatment phase	113
Met exclusion criteria	1

Period 2

Period 2 title	Treatment Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment Phase (STITT population)

Arm description:

Participants in the study treatment intention to treat (STITT) population with the BRAF V600 mutation received vemurafenib tablets at the recommended dose of 960 milligrams (mg) orally twice daily (BID) on Days 1-28 of each 28-day treatment cycle. Participants also received cobimetinib tablets at the recommended dose of 60 mg orally once daily (QD) on Days 1-21 of each 28-day cycle until disease progression, withdrawal of consent, or the development of unacceptable toxicity.

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

Dosage and administration details:

Three 20 mg tablets taken orally QD on Days 1-21 of each 28-day cycle.

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

Dosage and administration details:

Four tablets totaling 960 mg BID on Days 1-28 of each 28-day cycle.

Number of subjects in period 2	Treatment Phase (STITT population)
Started	40
Completed	0
Not completed	40
Consent withdrawn by subject	1
End of follow-up after 18 months	5
Disease progression	24
Adverse event, non-fatal	9
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Pre-Screening Phase
Reporting group description:	
Participants were tested for the presence of the BRAFV600 mutation using plasma cfDNA.	

Reporting group values	Pre-Screening Phase	Total	
Number of subjects	172	172	
Age categorical Units: Subjects			
Adults (18-64 years)	95	95	
From 65-84 years	72	72	
85 years and over	5	5	
Age continuous Units: years			
arithmetic mean	60.0		
standard deviation	± 15.5	-	
Gender categorical Units: Subjects			
Female	88	88	
Male	84	84	

End points

End points reporting groups

Reporting group title	Pre-Screening Phase (mITT population)
Reporting group description:	
Participants in the modified intention to treat (mITT) population were tested for the presence of the BRAFV600 mutation using plasma cfDNA.	
Reporting group title	Treatment Phase (STITT population)
Reporting group description:	
Participants in the study treatment intention to treat (STITT) population with the BRAF V600 mutation received vemurafenib tablets at the recommended dose of 960 milligrams (mg) orally twice daily (BID) on Days 1-28 of each 28-day treatment cycle. Participants also received cobimetinib tablets at the recommended dose of 60 mg orally once daily (QD) on Days 1-21 of each 28-day cycle until disease progression, withdrawal of consent, or the development of unacceptable toxicity.	

Primary: Number of Participants with BRAF V600 Mutation as Assessed Using the Idylla^TM Diagnostic Platform

End point title	Number of Participants with BRAF V600 Mutation as Assessed Using the Idylla^TM Diagnostic Platform[1]
End point description:	
End point type	Primary
End point timeframe:	
Days -56 to -1 (Pre-screening period)	

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: No formal statistical analyses were planned for this endpoint.

End point values	Pre-Screening Phase (mITT population)			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Participants	42			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of BRAF V600 Mutation as Determined on Plasma cfDNA

End point title	Concentration of BRAF V600 Mutation as Determined on Plasma cfDNA[2]
End point description:	
End point type	Primary
End point timeframe:	
Days -56 to -1 (Pre-screening period)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analyses were planned for this endpoint.

End point values	Pre-Screening Phase (mITT population)			
Subject group type	Reporting group			
Number of subjects analysed	172			
Units: Cycle quantification (Cq) value				
arithmetic mean (confidence interval 95%)	39.70 (37.96 to 41.43)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants by BRAF Mutation Status

End point title	Number of Participants by BRAF Mutation Status[3]

End point description:

End point type	Primary

End point timeframe:

Days -56 to -1 (Pre-screening period)

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: No formal statistical analyses were planned for this endpoint.

End point values	Pre-Screening Phase (mITT population)			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Participants				
BRAF V600 Mutation Subtype E/D	37			
BRAF V600 Mutation Subtype K/R/M	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with BRAF V600 Mutation as Assessed Using the Idylla^TM Diagnostic Platform in Participants With BRAF Wild-Type Based on a Prior Tissue Test Result

End point title	Number of Participants with BRAF V600 Mutation as Assessed Using the Idylla^TM Diagnostic Platform in Participants With BRAF Wild-Type Based on a Prior Tissue Test Result[4]

End point description:

End point type	Primary

End point timeframe:

Days -56 to -1 (Pre-screening period)

Notes:

[4] - 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: No formal statistical analyses were planned for this endpoint.

End point values	Pre-Screening Phase (mITT population)			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Participants	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response as Assessed by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Percentage of Participants with Objective Response as Assessed by the Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death whichever occurs first (up to 38 months)

End point values	Treatment Phase (STITT population)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage of Participants				
number (confidence interval 95%)	80.6 (64.0 to 91.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death whichever occurs first (up to 38 months)

End point values	Treatment Phase (STITT population)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Months				
median (confidence interval 95%)	13.6 (9.5 to 16.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response as Assessed by Investigator According to RECIST v1.1

End point title	Duration of Response as Assessed by Investigator According to RECIST v1.1

End point description:

End point type	Secondary

End point timeframe:

Baseline up to disease progression or death whichever occurs first (Up to 38 months)

End point values	Treatment Phase (STITT population)			
Subject group type	Reporting group			
Number of subjects analysed	40[5]			
Units: Months				
median (confidence interval 95%)	11.0 (9.2 to 9999)			

Notes:

[5] - 9999 = value not available due to insufficient number of participants with the event

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Baseline up to death (up to 38 months)

End point values	Treatment Phase (STITT population)			
Subject group type	Reporting group			
Number of subjects analysed	40[6]			
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)			

Notes:

[6] - 9999 = value not available due to insufficient number of participants with the event

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

Day 1 Cycle 1 up to 4 weeks after end of treatment or until initiation of another anti-cancer therapy, whichever occurs first (up to 38 months)

End point values	Treatment Phase (STITT population)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
AE	39			
SAE	15			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 3 years

Adverse event reporting additional description:

Adverse events are reported for the study treatment safety analysis population (STSAP), which contains all enrolled participants treated with at least one dose of cobimetinib or vemurafenib.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Treatment Phase

Reporting group description:

Participants with the BRAF V600 mutation received vemurafenib tablets at the recommended dose of 960 milligrams (mg) orally twice daily (BID) on Days 1-28 of each 28-day treatment cycle. Participants also received cobimetinib tablets at the recommended dose of 60 mg orally once daily (QD) on Days 1-21 of each 28-day cycle until disease progression, withdrawal of consent, or the development of unacceptable toxicity.

Serious adverse events	Treatment Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 40 (37.50%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ejection fraction decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Transaminases increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Tumour pain			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Flushing			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	11 / 40 (27.50%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	12		
Oedema peripheral			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	10		
Face oedema			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Mucosal inflammation			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Investigations			
Blood creatinine phosphokinase increased			
subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	17		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
C-reactive protein increased			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Ejection fraction decreased			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood creatinine increased			

subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 4		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 9 3 / 40 (7.50%) 3 2 / 40 (5.00%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Eye disorders Vision blurred subjects affected / exposed occurrences (all) Chorioretinopathy subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 6 4 / 40 (10.00%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 13 / 40 (32.50%) 23 6 / 40 (15.00%) 7 5 / 40 (12.50%) 6		

Stomatitis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Abdominal pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 21		
Photosensitivity reaction subjects affected / exposed occurrences (all)	11 / 40 (27.50%) 13		
Rash maculo-papular subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 11		
Alopecia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Dermatitis acneiform subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 9		
Dry skin subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Palmar-plantar erythrodysaesthaesia syndrome subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Rash popular subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		
Erythema nodosum			

subjects affected / exposed occurrences (all) Pruritis subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 11 / 40 (27.50%) 14 4 / 40 (10.00%) 4 4 / 40 (10.00%) 4 4 / 40 (10.00%) 5 3 / 40 (7.50%) 4		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Rash pustular subjects affected / exposed occurrences (all)	 8 / 40 (20.00%) 11 6 / 40 (15.00%) 6 4 / 40 (10.00%) 4 2 / 40 (5.00%) 2		
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5		
Hypokalaemia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2016	Updates to eligibility criteria.
20 October 2016	Updates to safety information.
29 March 2017	Updated recruitment period and end of study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported