Clinical trial results:
A randomized Phase II study of vemurafenib plus cobimetinib continuous versus intermittent, in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma.

Summary

EudraCT number	2014-005277-36
Trial protocol	ES
Global end of trial date	30 September 2019

Results information

Result version number	v1 (current)
This version publication date	17 December 2021
First version publication date	17 December 2021
Summary attachment (see zip file)	CSR Synopsis (GEM-01-15_CSR_Final v3.0_10Feb2021_Synopsis EN_Final.pdf)

Trial information

Trial identification

Sponsor protocol code	GEM-01-15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02583516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español Multidisciplinar de Melanoma (GEM)
Sponsor organisation address	C/ Secretari Coloma, nº 64-68. Escalera B, entresuelo 5ª, Barcelona, Spain, 08024
Public contact	Juan Berges (Clinical Operations), Pivotal, S.L., +34 91 7801250 , juan.berges@pivotalcr.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (in terms of PFS) of two schedules of administration of vemurafenib in combination with cobimetinib (continuous and intermittent) in previously untreated BRAFV600- mutation positive patients with unresectable locally advanced or metastatic melanoma.

Protection of trial subjects:

This study was conducted under standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
Principles of the World Medical Association Declaration of Helsinki (2004 revision)
ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use
Royal Decree 1090/2015, of December 4, which regulates clinical trials with drugs, the Research Ethics Committees with drugs and the Spanish Registry of Clinical Studies, and which fully incorporates the order of the Regulations (EU) No. 536/2014 of the European Parliament and the Council, of April 16, 2014, on clinical trials of medicinal products for human use.
Also applicable is Law 14/2007 on Biomedical Research and in Royal Decree 1716/2011, dated November 18, which establishes the minimum requirements for the authorization and operation of biobanks for biomedical research and treatment purposes. of biological samples of human origin. The investigator is aware when signing the protocol, to adhere to the instructions and procedures described in them and in this way, follow the principles of good clinical practices that they imply.
In compliance with Royal Decree 1090/2015, the sponsor will submit the relevant documentation to the IECs of its choice for its evolution and subsequent report.
The protocol, informed consent forms (ICF), and any appropriate related documents were submitted to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the principal investigator (PI) for approval. The investigator submitted periodic reports and informed the IRB or IEC of any reportable adverse events (AEs) as per International Conference on Harmonization (ICH) of Technical Requirement.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2015
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	Spain: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	46
From 65 to 84 years	23
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 27 months. Recruitment Status: Completed.
Date of the first enrolment: June 30th, 2015 (FPI). Date of last completed: September 30th, 2019 (LPO)
Follow-up period: 24 months from the inclusion of the last patient.
Date of completion of the study: September 2019. Territories: Spain.

Pre-assignment

Screening details:

There were 95 subjects screened for entry into the study. Of these subjects, 70 were randomized into the study and 25 subjects were identified as Screening Failure. There were 70 subjects randomized into the study, 35 subjects [50%] in the Group A - Continuous and 35 subjects [50%] in the Group B Intermittent.

Pre-assignment period milestones

Number of subjects started	70
Number of subjects completed	70

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (continuous administration)

Arm description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.

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

Dosage and administration details:

Experimental Group A - Continuous Administration: Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.

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

Dosage and administration details:

Experimental Group A - Continuous Administration:Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.

Arm title	Group B (intermittent administration)

Arm description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off).

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

Dosage and administration details:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off)

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off).

Number of subjects in period 1	Group A (continuous administration)	Group B (intermittent administration)
Started	35	35
Completed	6	5
Not completed	29	30
Consent withdrawn by subject	1	1
Physician decision	-	2
Adverse event, non-fatal	4	6
Death	3	2
Progressive Disease	21	19

Baseline characteristics

Reporting groups	
Reporting group title	Group A (continuous administration)
Reporting group description:	
Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.	
Reporting group title	Group B (intermittent administration)
Reporting group description:	
Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off).	

Reporting group values	Group A (continuous administration)	Group B (intermittent administration)	Total
Number of subjects	35	35	70
Age categorical			
Demography Age groups <65 years: 65.7%, >=65: 34.3%. Median age of 57.5 years (range: 29 to 85 years)			
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
<65 years	23	23	46
>=65	12	12	24
Age continuous			
Units: years			
median	58	56	
inter-quartile range (Q1-Q3)	49 to 69	49 to 67	-
Gender categorical			
Units: Subjects			
Female	11	22	33
Male	24	13	37

Subject analysis sets	
Subject analysis set title	Intention to treat Analyses
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All 70 randomized subjects were included in the ITT analysis set. In the ITT population defined as all randomized patients, 35 subjects [50%] in the Group A – Continuous and 35 subjects [50%] in the Group B – Intermittent were included. Patients were analyzed according to the treatment group to which	

they have been assigned, regardless of the treatment received. All randomized subjects were included in the analysis. Of these 70 subjects, 51 subjects did not have any major protocol deviation and met criteria for inclusion in the PP analysis set.

Reporting group values	Intention to treat Analyses		
Number of subjects	70		
Age categorical			
Demography Age groups <65 years: 65.7%, >=65: 34.3%. Median age of 57.5 years (range: 29 to 85 years)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	46		
From 65-84 years	23		
85 years and over	1		
<65 years	46		
>=65	24		
Age continuous			
Units: years			
median	57.5		
inter-quartile range (Q1-Q3)	49 to 67		
Gender categorical			
Units: Subjects			
Female	33		
Male	37		

End points

End points reporting groups

Reporting group title	Group A (continuous administration)

Reporting group description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.

Reporting group title	Group B (intermittent administration)

Reporting group description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off).

Subject analysis set title	Intention to treat Analyses
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All 70 randomized subjects were included in the ITT analysis set. In the ITT population defined as all randomized patients, 35 subjects [50%] in the Group A – Continuous and 35 subjects [50%] in the Group B – Intermittent were included. Patients were analyzed according to the treatment group to which they have been assigned, regardless of the treatment received. All randomized subjects were included in the analysis. Of these 70 subjects, 51 subjects did not have any major protocol deviation and met criteria for inclusion in the PP analysis set.

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

This study was designed to assess the efficacy, in terms of progression-free survival (PFS), of two regimens for the administration of the combination of vemurafenib and cobimetinib (continuous and intermittent), in the first-line treatment of patients with unresectable or metastatic advanced melanoma with the BRAF V600 mutation.
The main variable is the PFS, defined as the time elapsed between the random allocation and the first appearance of disease progression, or death from any cause, whichever comes first. If a patient has not progressed and is still alive on the cutoff date for data analysis, they were censored on the date of the last tumor evaluation performed. Those patients without documentation of progression before a loss of follow-up were censored for PFS on the date of the last tumor evaluation before the loss of follow-up.

End point type	Primary

End point timeframe:

Time elapsed between randomization and the first occurrence of disease progression, as determined by the investigator using the RECIST criteria, V1.1 , or death from any cause, whichever comes first.

End point values	Group A (continuous administration)	Group B (intermittent administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: months				
median (confidence interval 95%)	16.15 (9.54 to 24.11)	6.88 (5.20 to 9.28)		

Attachments (see zip file)	PFS By Study Group/Efficacy Analysis Fig.2.PNG

Statistical analyses

Statistical analysis title	Statistical Method

Statistical analysis description:

For an error α = 0.1 and an error β = 0.20, 34 evaluable pts recruited per group, using a Log-rank method (Tablecloth) Cox two-tailed . A power of 80% was obtained to detect a difference of 23% in the % PFS at 1 year (error α = 0.1) in the Kaplan-Meier curves, assuming 27 months of recruitment, 24 months of FU, a HR of 0.53 and a total of 61 events. A maximum loss of 10% of pts was estimated at follow-up and before progression, 38 pts per group, which gives an estimated total of 76 patients.

Comparison groups	Group A (continuous administration) v Group B (intermittent administration)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≥ 0.0823
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.642
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9384
upper limit	2.8731

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as the time elapsed between randomization and death from any cause. If a patient is still alive on the cut-off date for data analysis, they were censored on the date of the last tumor evaluation performed. Those patients without documentation of death before the loss of followup were censored for the OS on the date of the last evaluation before the loss of follow-up. However, all the details about the censoring dates for the OS were specified in the statistical analysis plan. It was described using the median survival, as well as the 1 and 2-year survival rate, estimated using the Kaplan-Meier curve, along with their confidence intervals. The analysis between the two treatment groups was carried out similarly to that described for the PFS, using the Log-rank test, calculating the HRs, and their corresponding confidence intervals, using the Cox proportional hazards method.

End point type	Secondary

End point timeframe:

Overall survival is defined as the time elapsed between randomization and death from any cause.

End point values	Group A (continuous administration)	Group B (intermittent administration)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: months				
median (confidence interval 95%)	23.59 (14.67 to 32)	27.53 (11.15 to 36.74)		

Attachments (see zip file)	OS By Study Group/Efficacy Analysis Fig.3.PNG

Statistical analyses

Statistical analysis title	Overall Survival Analysis

Statistical analysis description:

The comparison between both curves was made using the Log-rank test, calculating the HRs, and their corresponding confidence intervals, through the Cox proportional hazards method, between the two arms Group B - Intermittent vs Group A - Continuous,

Comparison groups	Group A (continuous administration) v Group B (intermittent administration)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	≥ 0.7345
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.1092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6094
upper limit	2.0188
Variability estimate	Standard deviation

Notes:

[1] - The comparison between both curves was made using the Log-rank test, calculating the HRs, and their corresponding confidence intervals, through the Cox proportional hazards method, between the two arms Group B - Intermittent vs Group A - Continuous,

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The objective responses were evaluated following the RECIST V1.1 criteria. An estimate was made of the percentage of overall objective responses (defined as the proportion of patients with CR and RP), with its 95% confidence interval. The comparison between the groups of these parameters was made through the chi-square test

End point type	Secondary

End point timeframe:

The objective responses were evaluated following the RECIST V1.1 criteria.

End point values	Group A (continuous administration)	Group B (intermittent administration)	Intention to treat Analyses	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	35	35	70	
Units: Percentage				
number (not applicable)	71.43	60.0	65.71	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients were closely monitored for safety and tolerability during all treatment cycles, at the end of study treatment visit and during the follow-up period.

Adverse event reporting additional description:

Patients were screened for AEs every 2 weeks for the first 12 weeks of treatment and thereafter each cycle. The biweekly evaluation of adverse events during cycles 2 and 3 of treatment may be carried out through an evolutionary telephone monitoring if it is duly documented in the patient's medical history.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Group A (continuous administration)

Reporting group description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle.

Reporting group title	Group B (intermittent administration)

Reporting group description:

Vemurafenib 960 mg orally twice daily on days 1-28 and cobimetinib 60 mg orally once a day on days 1-21 of each 28-day treatment cycle for 12 weeks. Then, both drugs were administered at the same doses previously indicated, but with an intermittent schedule: Vemurafenib days 1-28 followed by 14 days of rest (4 weeks on and 2 weeks off) and, Cobimetinib days 1-21 followed by 21 rest days. (3 weeks on and 3 weeks off).

Serious adverse events	Group A (continuous administration)	Group B (intermittent administration)	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 35 (48.57%)	17 / 35 (48.57%)	
number of deaths (all causes)	21	22	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Syncope			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
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	1 / 35 (2.86%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Chorioretinopathy			

subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctival disorder			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophagitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Pneumonia aspiration			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin toxicity			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin reaction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endocarditis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A (continuous administration)	Group B (intermittent administration)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 35 (60.00%)	19 / 35 (54.29%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Keratoacanthoma			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 35 (14.29%)	7 / 35 (20.00%)	
occurrences (all)	5	7	
Lymphoedema			

subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 35 (60.00%)	19 / 35 (54.29%)	
occurrences (all)	21	19	
Chest pain			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Discomfort			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Face oedema			
subjects affected / exposed	1 / 35 (2.86%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Gait disturbance			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
General physical health deterioration			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)	
occurrences (all)	4	2	
Oedema			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	6 / 35 (17.14%)	3 / 35 (8.57%)	
occurrences (all)	6	3	
Pyrexia			

subjects affected / exposed	12 / 35 (34.29%)	11 / 35 (31.43%)	
occurrences (all)	12	11	
Xerosis			
subjects affected / exposed	4 / 35 (11.43%)	0 / 35 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Nasal pruritus			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Depression			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Investigations			

Alanine aminotransferase increased				
subjects affected / exposed	3 / 35 (8.57%)	2 / 35 (5.71%)		
occurrences (all)	3	2		
Amylase increased				
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)		
occurrences (all)	2	0		
Aspartate aminotransferase increased				
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)		
occurrences (all)	2	1		
Blood alkaline phosphatase increased				
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)		
occurrences (all)	4	2		
Blood bilirubin increased				
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)		
occurrences (all)	2	0		
Blood cholesterol increased				
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)		
occurrences (all)	3	1		
Blood creatine phosphokinase increased				
subjects affected / exposed	6 / 35 (17.14%)	3 / 35 (8.57%)		
occurrences (all)	6	3		
Blood creatinine increased				
subjects affected / exposed	5 / 35 (14.29%)	0 / 35 (0.00%)		
occurrences (all)	5	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	2 / 35 (5.71%)	2 / 35 (5.71%)		
occurrences (all)	2	2		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)		
occurrences (all)	1	2		
Lipase increased				
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)		
occurrences (all)	2	0		
Transaminases increased				

subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Cardiac disorders			
Syncope			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Dysgeusia			
subjects affected / exposed	3 / 35 (8.57%)	4 / 35 (11.43%)	
occurrences (all)	3	4	
Headache			
subjects affected / exposed	3 / 35 (8.57%)	8 / 35 (22.86%)	
occurrences (all)	3	8	
Seizure			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 35 (22.86%)	4 / 35 (11.43%)	
occurrences (all)	8	4	
Neutropenia			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Leukopenia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	
occurrences (all)	3	0	
Eye disorders			
Blindness			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Chorioretinopathy			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Maculopathy			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Retinal detachment			
subjects affected / exposed	5 / 35 (14.29%)	3 / 35 (8.57%)	
occurrences (all)	5	3	
Uveitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Visual impairment			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	4 / 35 (11.43%)	4 / 35 (11.43%)	
occurrences (all)	39	24	
Diarrhoea			

subjects affected / exposed	17 / 35 (48.57%)	17 / 35 (48.57%)	
occurrences (all)	17	17	
Flatulence			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Gastric disorder			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	9 / 35 (25.71%)	8 / 35 (22.86%)	
occurrences (all)	29	24	
Odynophagia			
subjects affected / exposed	6 / 35 (17.14%)	0 / 35 (0.00%)	
occurrences (all)	29	24	
Stomatitis			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	10 / 35 (28.57%)	7 / 35 (20.00%)	
occurrences (all)	29	24	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Actinic keratosis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Alopecia			
subjects affected / exposed	5 / 35 (14.29%)	4 / 35 (11.43%)	
occurrences (all)	5	4	
Dermatitis acneiform			
subjects affected / exposed	0 / 35 (0.00%)	4 / 35 (11.43%)	
occurrences (all)	0	4	
Dry skin			
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)	
occurrences (all)	4	2	

Erythema			
subjects affected / exposed	7 / 35 (20.00%)	6 / 35 (17.14%)	
occurrences (all)	7	6	
Erythema multiforme			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Erythema nodosum			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Hyperkeratosis			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Palmoplantar keratoderma			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Panniculitis			
subjects affected / exposed	4 / 35 (11.43%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Photosensitivity reaction			
subjects affected / exposed	12 / 35 (34.29%)	6 / 35 (17.14%)	
occurrences (all)	12	6	
Pruritus			
subjects affected / exposed	10 / 35 (28.57%)	4 / 35 (11.43%)	
occurrences (all)	10	4	
Rash			
subjects affected / exposed	12 / 35 (34.29%)	12 / 35 (34.29%)	
occurrences (all)	12	12	
Rash maculo-papular			
subjects affected / exposed	2 / 35 (5.71%)	4 / 35 (11.43%)	
occurrences (all)	2	4	
Rash papular			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Skin exfoliation			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	

Skin lesion			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Skin toxicity			
subjects affected / exposed	7 / 35 (20.00%)	3 / 35 (8.57%)	
occurrences (all)	7	3	
Solar dermatitis			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Sunburn			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Dysuria			
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)	
occurrences (all)	4	2	
Renal failure			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 35 (28.57%)	12 / 35 (34.29%)	
occurrences (all)	10	12	
Back pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	

Groin pain			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Muscular weakness			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal discomfort			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			
subjects affected / exposed	4 / 35 (11.43%)	6 / 35 (17.14%)	
occurrences (all)	4	6	
Myalgia			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Cellulitis			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Conjunctivitis			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Cystitis			

subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Folliculitis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Gingivitis			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Influenza			
subjects affected / exposed	0 / 35 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Respiratory tract infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Tonsillitis			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 35 (17.14%)	7 / 35 (20.00%)	
occurrences (all)	6	7	
Hyperglycaemia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	
occurrences (all)	1	1	

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 35 (2.86%) 1	
Hyposideraemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 35 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2016	Due to the publication of a new version of the Investigator's Brochure for cobimetinib (Cotellic®), version 8 dated on January 2016, it has been decided to update the security information of this product, both in the study protocol and the patient information leaflet and informed consent form. On the other hand, and after a detailed review of the study protocol, it has been detected several inconsistencies that might lead to errors, or that should be updated. Because of the previous, this amendment has the following additional objectives: • To group cancer-related exclusion criteria and those based on ocular function to facilitate its reading and comprehension. Additionally, cardiac function related exclusion criteria are clarified. • Clarification of some protocol sections: randomization process, schedule of assessments and procedures (selection, treatment and follow up periods, dose adjustments based on adverse events), etc. • Update of the periods for conducting the clinical trial. • Adaptation of study documents to the new legislation (Spanish and European) in force on clinical investigation with medicinal products.
06 November 2018	Following the publication of the last three versions of the Cobimetinib (Cotellic®) Investigator's Brochure, version September 9, 2016, version September 10, 2017, and version September 11, 2018, as well as the update of the Technical Data Sheet of vemurafenib (Zelboraf®), we proceed to update the safety information of both drugs, both in the protocol and in the patient information sheet and informed consent of the study. Additionally, it is proposed to unlink the protocol and the list of adverse events of special interest (AESI) related to the study medication, due to the different update frequency of the latter. Regarding the patient information sheet, the confidentiality section is also updated according to Regulation (EU) 679/2016 of April 27, 2016 (GDPR). In addition, and due to the fact that the inclusion rate of patients since the beginning of the study has been slower than expected, the study recruitment period is extended by 9 additional months, making it necessary to update the terms of the study in consonance. For this same reason, some considerations of the planned statistical analysis are also modified by this amendment, thus adapting the sample size to the reality of the trial, and providing the corresponding justification in this regard, in terms of impact on safety and efficacy and risk balance. -benefit for the continuity of the study procedures in the patients already included. Finally, and due to the existing scientific competence in this field of research, the orientation of the planned analyzes is modified, in order to obtain data on the main variable (PFS), once the data in the clinical database is mature.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to limitations in patients' recruitment, the statistical method described by Brookmeyer R. et al has been used, for an error $\alpha = 0.1$ and an error $\beta = 0.20$.

Notes: