Clinical trial results:
A Phase I/II, open-label, dose escalation trial to evaluate the safety, pharmacokinetics, and pharmacodynamics of RAF265 (CHIR-265) administered orally to patients with locally advanced or metastatic melanoma

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2007-005367-10
Trial protocol	NL
Global end of trial date	30 November 2013
Results information	
Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification	
Sponsor protocol code	CRAF265A2101
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00304525
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RPTD), dose limiting toxicities (DLTs), and the safety profile of RAF265 when administered orally to patients with locally advanced or metastatic melanoma; to determine the plasma pharmacokinetics (PK) of orally administered RAF265; and to evaluate potential pharmacodynamic effects of RAF265 using tumor/nevus biopsies, peripheral blood samples, and imaging.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 97
Country: Number of subjects enrolled	Switzerland: 7
Worldwide total number of subjects	104
EEA total number of subjects	0

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)	70
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened over a period of 28 days.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1 - PK Run-in/Dose escalation

Arm description:

Subjects received a run-in dose then daily and weekly doses of RAF265 for at least one 28-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	RAF265
Investigational medicinal product code	
Other name	CHIR-265
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Subjects were administered a run-in dose of 10 mg of a 50mg/ml solution, then received the same dose daily for 11 days, followed by a dose of 10 mg weekly after a hold. One subject had the run-in dose then proceeded to 10 mg/week after the hold. Subjects mixed RAF265 with 20 or 40 mL of juice, and were requested to consume no more than 8 oz. of additional liquid for the next 2 hours.

Arm title	Arm 2 - PK Run-in/Dose escalation

Arm description:

Seven cohorts of subjects received run-in, loading, and daily doses of RAF265 for at least one 28-day cycles; the last (eighth) cohort did not receive a run-in dose. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	RAF265
Investigational medicinal product code	
Other name	CHIR-265
Pharmaceutical forms	Oral liquid, Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohorts 1-7.1 received RAF265 as a single oral dose of a 50 mg/ml solution on Day 1 of the PK run-in period (cohorts 1-7 only) followed 7 to 10 days later by one loading dose on cycle 1 day 1, and then by lower once daily doses starting on cycle 1 day 2; until progression or toxicity. Run-in doses were 10-403 mg; loading doses were 8-322 mg; daily doses were 2-67 mg. Four subjects transitioned from oral solution to tablets. The dose was based on the tablet equivalent to the subject’s current liquid dose rounded to the nearest 10 mg by using 10 and 50 mg tablets. For the oral solution, subjects mixed RAF265 with 20 or 40 mL of juice, and were requested to consume no more than 8 oz. of additional liquid for the next 2 hours. For tablets, subjects were instructed to take their daily dosing at approximately the same time each day with a glass of water and to consume it over as short a time as possible. Subjects were also instructed to ingest RAF265 at least 2 hours before or after a meal.

Arm title	Arm 3 - Dose escalation

Arm description:

Four cohorts of subjects received RAF265 weekly for at least one 28-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	RAF265
Investigational medicinal product code	
Other name	CHIR-265
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Four cohorts received a weekly dose of RAF265 from Cycle 1 until disease progression or unacceptable toxicity required discontinuation of treatment. Doses for all cycles were 10 to 40 mg of a 50 mg/ml solution. Subjects mixed RAF265 with 20 or 40 mL of juice, and were requested to consume no more than 8 oz. of additional liquid for the next 2 hours.

Arm title	Arm 4 - Bioequivalence

Arm description:

Arm 4 was added to establish the bioequivalency of the oral liquid formulation to the tablet, but was later closed. Bioavailability was instead assessed in a separate study. While three subjects underwent prescreening, none were treated in this arm. For two subjects, no data were entered into the case report form (CRF) due to withdrawal of consent or failure of prescreening. The remaining subject was recruited into Arm 5.

Arm type	Bioequivalence
No investigational medicinal product assigned in this arm	
Arm title	Arm 5 - Dose escalation

Arm description:

Two cohorts of subjects received RAF265 daily for 2 weeks with a 1-week dose holiday, for at least one 21-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	RAF265
Investigational medicinal product code	
Other name	CHIR-265
Pharmaceutical forms	Oral liquid, Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohorts 1 and 2 received a daily dose of RAF265 for 14 days of each 21-day cycle, from Cycle 1 until disease progression or unacceptable toxicity required discontinuation of treatment. Doses for all cycles were 67 or 94 mg of a 50 mg/ml solution. Three subjects were transitioned from oral solution to tablets. The dose was based on the tablet equivalent to the subject's current liquid dose rounded to the nearest 10 mg by using 10 and 50 mg tablets. For the oral solution, subjects mixed RAF265 with 20 or 40 mL of juice, and were requested to consume no more than 8 oz. of additional liquid for the next 2 hours. For tablets, subjects were instructed to take their daily dosing at approximately the same time each day with a glass of water and to consume it over as short a time as possible. Subjects were also instructed to ingest RAF265 at least 2 hours before or after a meal.

Number of subjects in period 1	Arm 1 - PK Run-in/Dose escalation	Arm 2 - PK Run-in/Dose escalation	Arm 3 - Dose escalation
Started	2	77	16
Completed	0	0	0
Not completed	2	77	16
Adverse event, serious fatal	-	6	2
Subject withdrew consent	-	2	-

Disease progression	2	56	14
Adverse event, non-fatal	-	9	-
Protocol violation	-	2	-
Transferred to other arm/group	-	-	-
Follow-up completed as per protocol	-	-	-
Administrative problems	-	1	-
Lost to follow-up	-	1	-
Joined	0	0	0
Transferred in from other group/arm	-	-	-

Number of subjects in period 1	Arm 4 - Bioequivalence	Arm 5 - Dose escalation
Started	1	8
Completed	0	0
Not completed	1	9
Adverse event, serious fatal	-	-
Subject withdrew consent	-	2
Disease progression	-	3
Adverse event, non-fatal	-	-
Protocol violation	-	-
Transferred to other arm/group	1	-
Follow-up completed as per protocol	-	3
Administrative problems	-	-
Lost to follow-up	-	1
Joined	0	1
Transferred in from other group/arm	-	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall study
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Arm 4 was added to establish the bioequivalency of the oral liquid formulation to the tablet, but was later closed. One subject was recruited into Arm 5.

Reporting group values	Overall study	Total	
Number of subjects	104	104	
Age categorical Units: Subjects			
Adults (18-64 years)	70	70	
From 65-84 years	34	34	
Gender categorical Units: Subjects			
Female	44	44	
Male	60	60	

End points

End points reporting groups

Reporting group title	Arm 1 - PK Run-in/Dose escalation

Reporting group description:

Subjects received a run-in dose then daily and weekly doses of RAF265 for at least one 28-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Reporting group title	Arm 2 - PK Run-in/Dose escalation

Reporting group description:

Seven cohorts of subjects received run-in, loading, and daily doses of RAF265 for at least one 28-day cycles; the last (eighth) cohort did not receive a run-in dose. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Reporting group title	Arm 3 - Dose escalation

Reporting group description:

Four cohorts of subjects received RAF265 weekly for at least one 28-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Reporting group title	Arm 4 - Bioequivalence

Reporting group description:

Arm 4 was added to establish the bioequivalency of the oral liquid formulation to the tablet, but was later closed. Bioavailability was instead assessed in a separate study. While three subjects underwent prescreening, none were treated in this arm. For two subjects, no data were entered into the case report form (CRF) due to withdrawal of consent or failure of prescreening. The remaining subject was recruited into Arm 5.

Reporting group title	Arm 5 - Dose escalation

Reporting group description:

Two cohorts of subjects received RAF265 daily for 2 weeks with a 1-week dose holiday, for at least one 21-day cycle. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 10 mg (run-in), 8 mg (loading dose), and 2 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 20 mg (run-in), 16 mg (loading dose), and 3 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 30-36 mg (run-in), 24-29 mg (loading dose), and 4-6 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 40-72 mg (run-in), 32-58 mg (loading dose), and 5-12 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 50-144 mg (run-in), 40-115 mg (loading dose), and 6-24 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 6
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 60-288 mg (run-in), 48-230 mg (loading dose), and 7-48 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 7
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 70-403 mg (run-in), 56-322 mg (loading dose), and 8-67 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Level 7.1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 288 mg (loading dose split into 3 doses of 96 mg each) and 67 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 3 Dose Level 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 10 mg of RAF265 each week. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 3 Dose Level 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 20 mg of RAF265 each week. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 3 Dose Level 3
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 30 mg of RAF265 each week. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 3 Dose Level 4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject received 40 mg of RAF265 each week. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 5 Dose Level 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 67 mg of RAF265 daily for 14 days followed by a 1-week dose holiday. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 5 Dose Level 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 94 mg of RAF265 daily for 14 days followed by a 1-week dose holiday. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Levels 1-4
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 10-72 mg (run-in), 8-58 mg (loading dose), and 2-12 mg (daily maintenance dose) of

RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Subject analysis set title	Arm 2 Dose Levels 7-7.1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received no run-in or 70-403 mg (run-in), 56-322 mg (loading dose), and 8-67 mg (daily maintenance dose) of RAF265. Subjects entered the assigned dose level and continued until disease progression or unacceptable toxicity.

Primary: Observed Maximum Plasma Concentration (Cmax) of RAF265 After a Run-in Dose-Arm 2

End point title	Observed Maximum Plasma Concentration (Cmax) of RAF265 After a Run-in Dose-Arm 2[1]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, 6, 8, 24,48, 72, and 96 hours post-dose

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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	10
Units: ug/mL				
arithmetic mean (standard deviation)	0.136 (± 0.0523)	0.149 (± 0.0554)	0.263 (± 0.0829)	0.54 (± 0.177)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	22	9	
Units: ug/mL				
arithmetic mean (standard deviation)	1.06 (± 0.308)	2.31 (± 0.916)	2.68 (± 1.04)	

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum (Tmax), Last Quantifiable (Tlast), And Half-Life (T1/2) Concentration of CRAF265 After a Run-in Dose-Arm 2

End point title	Time to Maximum (Tmax), Last Quantifiable (Tlast), And Half-Life (T1/2) Concentration of CRAF265 After a Run-in Dose-Arm

	2[2]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, 8, 24, 48, 72, and 96 hours post dose

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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3[3]	3[4]	4[5]	10[6]
Units: hours				
median (full range (min-max))				
Tmax	3 (2 to 3)	2 (2 to 3)	2.52 (2 to 3)	2.01 (2 to 4)
Tlast	168 (166 to 169)	168 (168 to 215)	168 (168 to 168)	167 (165 to 167)
T1/2	287 (163 to 412)	209 (209 to 209)	127 (122 to 133)	174 (151 to 259)

Notes:

[3] - n's were: Tmax, 3; Tlast, 3; T1/2, 2

[4] - n's were: Tmax, 3; Tlast, 3, T1/2, 1

[5] - n's were: Tmax, 4; Tlast, 4; T1/2, 2

[6] - n's were: Tmax, 10; Tlast, 7; T1/2, 5

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15[7]	23[8]	9[9]	
Units: hours				
median (full range (min-max))				
Tmax	2.15 (1.05 to 4)	3 (1.98 to 8)	3 (2 to 3.02)	
Tlast	167 (165 to 192)	167 (164 to 216)	168 (120 to 189)	
T1/2	182 (73.4 to 813)	183 (22.6 to 3850)	294 (98.3 to 409)	

Notes:

[7] - n's were: Tmax, 15; Tlast, 15; T1/2, 11

[8] - n's were: Tmax, 22; Tlast, 20; T1/2, 13

[9] - n's were: Tmax, 9; Tlast, 9; T1/2, 4

Statistical analyses

No statistical analyses for this end point

Primary: Area Under The Plasma Concentration-time Curve From Time Zero to The Time of The Last Quantifiable Measurement (AUC0-tlast) of CRAF265 After a Run-in

Dose-Arm 2

End point title	Area Under The Plasma Concentration-time Curve From Time Zero to The Time of The Last Quantifiable Measurement (AUC0-tlast) of CRAF265 After a Run-in Dose-Arm 2[10]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, 8, 24, 48, 72, and 96 hours post dose

Notes:

[10] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	7
Units: h*ug/mL				
arithmetic mean (standard deviation)	6.2 (± 1.53)	8.77 (± 4.37)	12.1 (± 4.01)	22.6 (± 8.81)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	19	9	
Units: h*ug/mL				
arithmetic mean (standard deviation)	51.8 (± 14.3)	99.8 (± 43.2)	137 (± 53.5)	

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of RAF265 on Day 1 of Cycle 1-All Arms

End point title	Cmax of RAF265 on Day 1 of Cycle 1-All Arms[11]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, 6 (all arms), and 8 (Arms 3 and 5 only) hours post-dose

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: No statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	10
Units: ug/mL				
arithmetic mean (standard deviation)	0.141 (± 0.0636)	0.168 (± 0.0201)	0.276 (± 0.0695)	0.498 (± 0.135)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	22	9	10
Units: ug/mL				
arithmetic mean (standard deviation)	1.07 (± 0.273)	2.25 (± 1.15)	2.72 (± 0.694)	1.13 (± 0.232)

End point values	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3	Arm 3 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	7	5	1
Units: ug/mL				
arithmetic mean (standard deviation)	0.147 (± 0.0639)	0.234 (± 0.087)	0.23 (± 0.0557)	0.33 (± 0)

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	6		
Units: ug/mL				
arithmetic mean (standard deviation)	0.56 (± 0.145)	0.677 (± 0.185)		

Statistical analyses

No statistical analyses for this end point

Primary: Tmax and Tlast of RAF265 on Day 1 of Cycle 1-All Arms

End point title	Tmax and Tlast of RAF265 on Day 1 of Cycle 1-All Arms[12]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265

plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, 6 (all arms), and 8 (Arms 3 and 5 only) hours post-dose

Notes:

[12] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3[13]	3[14]	4[15]	10[16]
Units: hours				
median (full range (min-max))				
Tmax	4 (2 to 4)	3 (2 to 3.08)	3.53 (1.92 to 6.08)	3 (2 to 6)
Tlast	25 (21.5 to 27.1)	22.9 (21.5 to 24.4)	23.8 (23.3 to 24.3)	24.4 (23.4 to 26)

Notes:

[13] - n's were: Tmax, 3; Tlast, 3

[14] - n's were: Tmax, 3; Tlast, 3

[15] - n's were: Tmax, 4; Tlast, 4

[16] - n's were: Tmax, 10; Tlast, 9

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15[17]	23[18]	9[19]	10[20]
Units: hours				
median (full range (min-max))				
Tmax	2 (0 to 4)	2.58 (1 to 4)	3 (1 to 4.02)	22.3 (2 to 25.5)
Tlast	24 (23 to 26.3)	24.1 (21.1 to 24.6)	24 (23.1 to 25.6)	23.8 (21.5 to 25.2)

Notes:

[17] - n's were: Tmax, 15; Tlast, 14

[18] - n's were: Tmax, 22; Tlast, 21

[19] - n's were: Tmax, 9; Tlast, 8

[20] - n's were: Tmax, 10; Tlast, 10

End point values	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3	Arm 3 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3[21]	7[22]	5[23]	1[24]
Units: hours				
median (full range (min-max))				
Tmax	2 (2 to 3)	2.02 (1 to 4.07)	4.03 (2 to 6)	4 (4 to 4)
Tlast	166 (166 to 167)	167 (164 to 171)	166 (165 to 191)	169 (169 to 169)

Notes:

[21] - n's were: Tmax, 3; Tlast, 2

[22] - n's were: Tmax, 7; Tlast, 7

[23] - n's were: Tmax, 5; Tlast, 5

[24] - n's were: Tmax, 1; Tlast, 1

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[25]	6[26]		
Units: hours				
median (full range (min-max))				
Tmax	3 (2.08 to 4.07)	3 (2.07 to 21.3)		
Tlast	24.1 (22.3 to 24.4)	23.8 (21.3 to 24.2)		

Notes:

[25] - n's were: Tmax, 3; Tlast, 3

[26] - n's were: Tmax, 6; Tlast, 5

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tlast of RAF265 on Day 1 of Cycle 1-All Arms

End point title	AUC0-tlast of RAF265 on Day 1 of Cycle 1-All Arms[27]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, 6 (all arms), and 8 (Arms 3 and 5 only) hours post-dose

Notes:

[27] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	9
Units: h*ug/mL				
arithmetic mean (standard deviation)	2.08 (± 0.612)	2.65 (± 0.408)	3.93 (± 0.678)	7.28 (± 1.67)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	21	8	10
Units: h*ug/mL				

arithmetic mean (standard deviation)	15.7 (± 4.01)	28.1 (± 11.6)	39 (± 10.1)	18.4 (± 3.7)

End point values	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3	Arm 3 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	7	5	1
Units: h*ug/mL				
arithmetic mean (standard deviation)	5.79 (± 3.24)	9.67 (± 4.13)	14.3 (± 3.41)	16.9 (± 0)

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: h*ug/mL				
arithmetic mean (standard deviation)	7.44 (± 1.8)	9.5 (± 3.46)		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of RAF265 on Day 15 of Cycle 1-Arm 2

End point title	Cmax of RAF265 on Day 15 of Cycle 1-Arm 2[28]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, and 6 hours post-dose

Notes:

[28] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	8
Units: ug/mL				
arithmetic mean (standard deviation)	0.133 (± 0.0434)	0.119 (± 0.0343)	0.199 (± 0.0233)	0.423 (± 0.157)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	19	9	9
Units: ug/mL				
arithmetic mean (standard deviation)	0.845 (± 0.23)	1.65 (± 0.625)	2.65 (± 1.1)	1.83 (± 0.652)

Statistical analyses

No statistical analyses for this end point

Primary: Tmax and Tlast of RAF265 on Day 15 of Cycle 1-Arm 2

End point title	Tmax and Tlast of RAF265 on Day 15 of Cycle 1-Arm 2[29]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, and 6 hours post-dose

Notes:

[29] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3[30]	3[31]	4[32]	10[33]
Units: hours				
median (full range (min-max))				
Tmax	3 (2.58 to 4)	3.07 (2.12 to 4)	2.52 (1 to 4)	5.13 (2 to 25)
Tlast	25.3 (22.9 to 28)	22.5 (22.4 to 23.5)	24.1 (23.4 to 24.8)	24 (22.8 to 25.4)

Notes:

[30] - n's were: Tmax, 3; Tlast, 3

[31] - n's were: Tmax, 3; Tlast, 3

[32] - n's were: Tmax, 4; Tlast, 4

[33] - n's were: Tmax, 8; Tlast, 7

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15[34]	23[35]	9[36]	10[37]
Units: hours				

median (full range (min-max))				
Tmax	2.75 (0.967 to 4.5)	3.93 (1 to 6.08)	4 (0 to 22.1)	3 (1 to 23.3)
Tlast	24 (18.9 to 28.9)	23.7 (18.3 to 25.3)	23.4 (19.8 to 24.1)	23.8 (21.6 to 24.2)

Notes:

[34] - n's were: Tmax, 15; Tlast, 14

[35] - n's were: Tmax, 19; Tlast, 16

[36] - n's were: Tmax, 9; Tlast, 9

[37] - n's were: Tmax, 9; Tlast, 9

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tlast of RAF265 on Day 15 of Cycle 1-Arm 2

End point title	AUC0-tlast of RAF265 on Day 15 of Cycle 1-Arm 2[38]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, 4, and 6 hours post-dose

Notes:

[38] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	7
Units: h*ug/mL				
arithmetic mean (standard deviation)	2.67 (± 0.591)	2.3 (± 0.777)	4.15 (± 0.342)	8.59 (± 3.4)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	16	9	9
Units: h*ug/mL				
arithmetic mean (standard deviation)	16.1 (± 5)	28.5 (± 11.7)	46.8 (± 23)	35.4 (± 13.7)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of RAF265 on Day 14 of Cycles 1 and 2-Arm 5

End point title	Cmax of RAF265 on Day 14 of Cycles 1 and 2-Arm 5[39]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, and 8 hours post-dose

Notes:

[39] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[40]	5[41]		
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1	1.18 (± 0.2)	1.33 (± 0.452)		
Cycle 2	1.55 (± 0.264)	1.79 (± 0.7)		

Notes:

[40] - n's were: Cycle 1, 3; Cycle 2, 3

[41] - n's were: Cycle 1, 5; Cycle 2, 5

Statistical analyses

No statistical analyses for this end point

Primary: Tmax of RAF265 on Day 14 of Cycles 1 and 2-Arm 5

End point title	Tmax of RAF265 on Day 14 of Cycles 1 and 2-Arm 5[42]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, and 8 hours post-dose

Notes:

[42] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[43]	5[44]		
Units: hours				
median (full range (min-max))				
Cycle 1	3 (2.03 to 8)	3 (1.93 to 30.3)		
Cycle 2	3 (1.13 to 3.07)	3 (2 to 3.05)		

Notes:

[43] - n's were: Cycle 1, 3; Cycle 2, 3

[44] - n's were: Cycle 1, 5; Cycle 2, 5

Statistical analyses

No statistical analyses for this end point

Primary: Tlast of RAF265 on Day 14 of Cycles 1 and 2-Arm 5

End point title	Tlast of RAF265 on Day 14 of Cycles 1 and 2-Arm 5[45]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, and 8 hours post-dose

Notes:

[45] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[46]	5[47]		
Units: hours				
median (full range (min-max))				
Cycle 1	192 (191 to 194)	192 (190 to 197)		
Cycle 2	193 (193 to 193)	192 (167 to 196)		

Notes:

[46] - n's were: Cycle 1, 2; Cycle 2; 2

[47] - n's were: Cycle 1, 4; Cycle 2, 5

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tlast of RAF265 on Day 14 of Cycles 1 and 2-Arm 5

End point title	AUC0-tlast of RAF265 on Day 14 of Cycles 1 and 2-Arm 5[48]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Pre-dose and 1, 2, 3, and 8 hours post-dose

Notes:

[48] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3[49]	5[50]		
Units: h*ug/mL				
arithmetic mean (standard deviation)				
Cycle 1	106 (± 1.88)	180 (± 40.3)		
Cycle 2	167 (± 29.7)	217 (± 92)		

Notes:

[49] - n's were: Cycle 1, 2; Cycle 2, 2

[50] - n's were: Cycle 1, 4; Cycle 2, 5

Statistical analyses

No statistical analyses for this end point

Primary: Observed Mimimum Plasma Concentration (Cmin) of RAF265 at Steady State-Arms 2, 3, and 5

End point title	Observed Mimimum Plasma Concentration (Cmin) of RAF265 at Steady State-Arms 2, 3, and 5[51]

End point description:

Four mls of blood were collected to determine the concentration of RAF265 in plasma. Unbound RAF265 plasma concentration vs. time data were used to determine RAF265 pharmacokinetic (PK) parameters. PK analysis was performed by non-compartmental methods.
This endpoint analyzed the PK Analysis Set, defined as all subjects who had sufficient and interpretable PK assessments (sufficient samples collected for calculating noncompartmental or compartmental PK parameters, as appropriate) treated in the study (Arms 2, 3 and 5).

End point type	Primary

End point timeframe:

Day 1 pre-dose of Cycle 2 and all subsequent cycles

Notes:

[51] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	3	6
Units: ug/mL				
arithmetic mean (standard deviation)	1.23 (± 0.217)	1.51 (± 0.82)	1.82 (± 0.282)	4.31 (± 1.22)

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	18	6	8
Units: ug/mL				
arithmetic mean (standard deviation)	7.31 (± 1.99)	13.1 (± 5.57)	21.8 (± 3.76)	15.5 (± 7.47)

End point values	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3	Arm 3 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	6	4	1
Units: ug/mL				
arithmetic mean (standard deviation)	0.49 (± 0.156)	1.03 (± 0.372)	0.942 (± 0.391)	1.92 (± 0)

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: ug/mL				
arithmetic mean (standard deviation)	6.12 (± 1.87)	6.58 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline of Tissue Biomarker Expression (H-score) and Response Evaluation Criteria in Solid Tumors (RECIST) Tumor Response at Day 8 of Cycle 2-Arm 2

End point title	Percent Change From Baseline of Tissue Biomarker Expression (H-score) and Response Evaluation Criteria in Solid Tumors (RECIST) Tumor Response at Day 8 of Cycle 2-Arm 2[52][53]

End point description:

By using established immunohistochemical methods, tumor tissue (and nevi, if available), were assessed for baseline levels and, in instances of paired pre- and on-treatment biopsies, relative changes in the levels of core pharmacodynamic and response markers. A negative value indicates less expression. pMEK = phosphorylated MAPK/ERK kinase, pERK = phosphorylated extracellar signal-regulated kinase,

Ki67 = proliferation-associated antigen Ki-67, BIM= a pro-apoptotic member of the BCL-2 family, PARP = Poly(ADP-ribose)polymerase, Cyclin D1 = cell cycle gene, MITF = microphthalmia-associated transcription factor, CKIT=c-KIT, P53= Tumor Protein 53/TP53, PAKT473= Phospho Akt S 473, PS6=Phosphoserine 240-S6 ribosomal protein, PTEN=Phosphatase and Tensin homolog.
This endpoint analyzed the Full Analysis Set (FAS), defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

Day 8 of Cycle 2

Notes:

[52] - 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 statistical analysis was planned for this primary outcome measure.

[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: Data for this endpoint were not collected from subjects in Arms 1, 4 and 5; data for Arms 2 and 3 are reported in separate endpoints.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Levels 1-4
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77[54]	15[55]	23[56]	20[57]
Units: scores on a scale				
arithmetic mean (standard deviation)				
pMEK-cytoplasmic	-4.28 (± 31.959)	0 (± 0)	-16.09 (± 17.341)	0.78 (± 44.403)
pERK-cytoplasmic	-3.62 (± 48.61)	27.08 (± 55.979)	-27.03 (± 40.914)	52.55 (± 79.967)
BIM-cytoplasmic	-17 (± 54.518)	-1000 (± 0)	-7.13 (± 11.13)	-17.97 (± 65.11)
CKIT-cytoplasmic	-30 (± 61.412)	999999 (± 999999)	0 (± 0)	-60 (± 80)
PAKT473-cytoplasmic	1.19 (± 105.359)	-4.55 (± 0)	-48.35 (± 55.894)	20.05 (± 132.918)
PS6-cytoplasmic	6.92 (± 70.82)	255.56 (± 0)	-20.61 (± 29.141)	-16.77 (± 20.858)
PTEN-cytoplasmic	-3.16 (± 32.443)	0 (± 0)	-9.43 (± 27.022)	-4.98 (± 44.095)
pERK-nuclear	-2.04 (± 51.626)	18.17 (± 35.795)	-41.8 (± 47.963)	21.11 (± 52.132)
Ki67-nuclear	-13.46 (± 49.923)	0 (± 0)	-47.93 (± 40.786)	0.21 (± 59.628)
PARP-nuclear	89.13 (± 172.278)	99999 (± 99999)	20 (± 121.244)	65.14 (± 180.498)
CyclinD1-nuclear	0.19 (± 93.705)	56.79 (± 125.591)	-49.12 (± 30.716)	-4.53 (± 94.955)
MITF-nuclear	197.33 (± 856.877)	11.79 (± 23.739)	20.13 (± 111.294)	400.58 (± 1312.529)
P27-nuclear	86.34 (± 251.868)	-40 (± 56.569)	156.35 (± 312.151)	-2.15 (± 44.004)
P53-nuclear	42.14 (± 195.033)	82.35 (± 190.533)	49.32 (± 123.273)	-27.3 (± 49.484)

Notes:

[54] - n's were: 23, 13, 14, 8, 19, 19, 18, 21, 23, 14, 23, 21, 20, 20

[55] - n's were: 2, 2, 1, 0, 1, 1, 2, 2, 2, 0, 3, 2, 2, 2,

[56] - n's were: 6, 5, 2, 1, 4, 6, 5, 5, 6, 3, 5, 6, 5, 4

[57] - n's were: 11, 2, 8, 4, 11, 8, 8, 10, 11, 8, 10, 9, 9, 10

End point values	Arm 2 Dose Levels 7-7.1			
Subject group type	Subject analysis set			
Number of subjects analysed	19[58]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
pMEK-cytoplasmic	-2.63 (± 5.263)			
pERK-cytoplasmic	-17.78 (± 11.466)			
BIM-cytoplasmic	6.67 (± 5.774)			
CKIT-cytoplasmic	0 (± 0)			
PAKT473-cytoplasmic	0 (± 0)			
PS6-cytoplasmic	33.44 (± 55.725)			
PTEN-cytoplasmic	10 (± 17.321)			
pERK-nuclear	-20.32 (± 31.333)			
Ki67-nuclear	-6.08 (± 19.959)			
PARP-nuclear	222.22 (± 167.774)			
CyclinD1-nuclear	25 (± 113.614)			
MITF-nuclear	98.61 (± 239.7)			
P27-nuclear	261.11 (± 427.309)			
P53-nuclear	188.47 (± 400.618)			

Notes:

[58] - n's were: 4, 4, 3, 3, 3, 4, 3, 4, 4, 3, 5, 4, 4, 4

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline of Tissue Biomarker Expression (H-score) and RECIST Tumor Response at Day 28 of Cycle 2-Arm 3

End point title	Percent Change From Baseline of Tissue Biomarker Expression (H-score) and RECIST Tumor Response at Day 28 of Cycle 2-Arm 3[59][60]

End point description:

By using established immunohistochemical methods, tumor tissue (and nevi, if available), were assessed for baseline levels and, in instances of paired pre- and on-treatment biopsies, relative changes in the levels of core pharmacodynamic and response markers. A negative value indicates less expression. Abbreviations: pMEK = phosphorylated MAPK/ERK kinase, pERK = phosphorylated extracellar signal-regulated kinase, Ki67 = proliferation-associated antigen Ki-67, BIM= a pro-apoptotic member of the BCL-2 family, PARP = Poly(ADP-ribose)polymerase, Cyclin D1 = cell cycle gene, MITF = microphthalmia-associated transcription factor, CKIT=c-KIT, P53= Tumor Protein 53/TP53, PAKT473= Phospho Akt S 473, PS6=Phosphoserine 240-S6 ribosomal protein, PTEN=Phosphatase and Tensin homolog.
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

Day 28 of Cycle 2

Notes:

[59] - 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 statistical analysis was planned for this primary outcome measure.

[60] - 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: Data for this endpoint were not collected from subjects in Arms 1, 4 and 5; data for Arms 2 and 3 are reported in separate endpoints.

End point values	Arm 3 - Dose escalation	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16[61]	3[62]	7[63]	6[64]
Units: scores on a scale				
arithmetic mean (standard deviation)				
pMEK-cytoplasmic	54.4 (± 145.981)	-20.73 (± 15.682)	36.76 (± 133.079)	125 (± 182.498)
BIM-cytoplasmic	-12.21 (± 65.49)	-33.33 (± 115.47)	-34.33 (± 39.409)	22.58 (± 46.781)
CKIT-cytoplasmic	-45.83 (± 29.463)	-25 (± 0)	-66.67 (± 0)	99999 (± 99999)
PAKT473-cytoplasmic	20.22 (± 67.063)	29.2 (± 101.618)	12.66 (± 35.145)	33.47 (± 95.211)
PS6-cytoplasmic	-4.1 (± 21.769)	3.21 (± 18.526)	-1.32 (± 32.691)	-6.92 (± 9.496)
PTEN-cytoplasmic	-27.26 (± 42.416)	99999 (± 99999)	-29.84 (± 37.677)	-39.12 (± 45.917)
pERK-nuclear	-23.09 (± 28.677)	-17.11 (± 7.977)	-41.11 (± 28.682)	-0.23 (± 18.648)
Ki67-nuclear	-2.04 (± 20.707)	8.33 (± 7.217)	-7.14 (± 17.539)	2.55 (± 27.392)
PARP-nuclear	160.97 (± 385.895)	637.5 (± 866.206)	25.88 (± 94.003)	158.32 (± 418.183)
Cyclin D1-nuclear	14.48 (± 74.548)	61.27 (± 88.147)	-25.45 (± 45.93)	41.46 (± 91.893)
MITF-nuclear	41.36 (± 188.614)	159.31 (± 246.101)	-38.63 (± 18.835)	79.3 (± 256.125)
P27-nuclear	-23.07 (± 27.344)	3.82 (± 21.115)	-28.89 (± 26.555)	-21.47 (± 28.987)
P53-nuclear	28.31 (± 150.05)	207.78 (± 287.254)	-23.89 (± 10.864)	-8.41 (± 29.285)

Notes:

[61] - , n's were: 15, 13, 2, 16, 16, 11, 17, 17, 15, 16, 14, 14, 14

[62] - n's were: 3, 3, 1, 3, 3, 0, 3, 3, 2, 3, 2, 2, 3

[63] - n's were: 5, 5, 1, 7, 6, 6, 7, 7, 7, 7, 5, 6, 6,

[64] - n's were: 6, 5, 0, 5, 6, 4, 6, 6, 5, 5, 6, 5, 4

End point values	Arm 3 Dose Level 4			
Subject group type	Subject analysis set			
Number of subjects analysed	1[65]			
Units: scores on a scale				
arithmetic mean (standard deviation)				
pMEK-cytoplasmic	-55.56 (± 0)			
BIM-cytoplasmic	99999 (± 99999)			
CKIT-cytoplasmic	99999 (± 99999)			

PAKT473-cytoplasmic	-20 (± 0)			
PS6-cytoplasmic	-25.81 (± 0)			
PTEN-cytoplasmic	35.71 (± 0)			
pERK-nuclear	-52.08 (± 0)			
Ki67-nuclear	-25 (± 0)			
PARP-nuclear	166.67 (± 0)			
Cyclin D1-nuclear	18.75 (± 0)			
MITF-nuclear	-22.22 (± 0)			
P27-nuclear	-50 (± 0)			
P53-nuclear	-50 (± 0)			

Notes:

[65] - n's were: 1, 0, 0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in The Concentrations of Soluble Markers at Day 15 of Cycle 1-Arm 2

End point title	Percent Change From Baseline in The Concentrations of Soluble Markers at Day 15 of Cycle 1-Arm 2[66][67]

End point description:

Plasma samples were analyzed by ELISA for changes in the circulating levels of soluble vascular endothelial growth factor (VEGF), soluble VEGF receptor type 1 (sVEGFR-1), soluble VEGF receptor type 2 (sVEGFR-2), basic fibroblast growth factor (bFGF), placental growth factor (PLGF), and melanoma inhibitory activity protein (MIA).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

Pre-dose serum and plasma samples of subjects in the dose escalation phase were collected on the first day of the PK run-in and on Day 15 of Cycle 1

Notes:

[66] - 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 statistical analysis was planned for this primary outcome measure.

[67] - 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: Data for this endpoint were not collected from subjects in Arms 1, 4 and 5; data for Arms 2 and 3 are reported in separate endpoints.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Levels 1-4
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77[68]	15[69]	23[70]	20[71]
Units: pg/mL				
arithmetic mean (standard deviation)				
VEGF	37.58 (± 65.009)	11.32 (± 23.161)	47.32 (± 74.377)	-8.41 (± 32.521)
sVEGFR-1	2.26 (± 30.501)	-4.92 (± 30.085)	-7.27 (± 16.894)	-4.73 (± 30.605)
sVEGFR-2	-11.3 (± 16.166)	-2.26 (± 16.527)	-13.72 (± 12.383)	-5.71 (± 16.924)
bFGF	4.88 (± 102.744)	-14 (± 31.477)	11.62 (± 95.093)	25.74 (± 164.101)

PLGF	35.19 (± 47.693)	13.52 (± 26.976)	33.24 (± 37.622)	4.01 (± 22.871)
MIA	-9770 (± 22133)	-4320 (± 20111)	-7740 (± 28643)	2530 (± 1967)
cKIT	4.38 (± 16.438)	2.85 (± 10.522)	6.52 (± 19.458)	-0.86 (± 15.471)

Notes:

[68] - n's were: 68, 68, 68, 68, 68, 50, 68

[69] - n's were: 13, 13, 13, 13, 13, 12, 13

[70] - n's were: 19, 19, 19, 19, 19, 18, 19

[71] - n's were: 19, 19, 19, 19, 19, 2, 19

End point values	Arm 2 Dose Levels 7-7.1			
Subject group type	Subject analysis set			
Number of subjects analysed	19[72]			
Units: pg/mL				
arithmetic mean (standard deviation)				
VEGF	98.17 (± 52.878)			
sVEGFR-1	26.19 (± 32.026)			
sVEGFR-2	-21.76 (± 12.965)			
bFGF	-11.54 (± 42.971)			
PLGF	88.8 (± 46.939)			
MIA	-16810 (± 15297)			
cKIT	9 (± 17.227)			

Notes:

[72] - n's were: 17, 17, 17, 17, 17, 18, 17

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in The Concentrations of Soluble Markers at Day 15 of Cycle 1-Arm 3

End point title	Percent Change From Baseline in The Concentrations of Soluble Markers at Day 15 of Cycle 1-Arm 3[73][74]

End point description:

Plasma samples were analyzed by ELISA for changes in the circulating levels of soluble vascular endothelial growth factor (VEGF), soluble VEGF receptor type 1 (sVEGFR-1), soluble VEGF receptor type 2 (sVEGFR-2), basic fibroblast growth factor (bFGF), placental growth factor (PLGF), and melanoma inhibitory activity protein (MIA).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

Pre-dose serum and plasma samples of subjects in the dose escalation phase were collected on the first day of the PK run-in and on Day 15 of Cycle 1

Notes:

[73] - 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 statistical analysis was planned for this primary outcome measure.

[74] - 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: Data for this endpoint were not collected from subjects in Arms 1, 4 and 5; data for Arms 2 and 3 are reported in separate endpoints.

End point values	Arm 3 - Dose escalation	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16[75]	3[76]	7[77]	5[78]
Units: pg/mL				
arithmetic mean (standard deviation)				
VEGF	22.26 (± 76.58)	-24.51 (± 68.006)	82.65 (± 77.753)	-21.57 (± 33.789)
sVEGFR-1	-12.4 (± 43.877)	-44.92 (± 87.439)	-0.35 (± 36.439)	-11.89 (± 10.735)
sVEGFR-2	3.62 (± 12.638)	5.64 (± 14.023)	9.54 (± 13.702)	-3.79 (± 9.816)
bFGF	113.79 (± 202.359)	271.04 (± 316.226)	133.11 (± 201.438)	-10.18 (± 63.444)
PLGF	-0.94 (± 19.605)	-11.29 (± 24.747)	7.74 (± 24.123)	-2.39 (± 8.225)
MIA	-10410 (± 3384)	99999 (± 99999)	-8020 (± 0)	99999 (± 99999)
cKIT	5.57 (± 10.776)	-2.83 (± 8.978)	13.39 (± 11.255)	3.22 (± 5.652)

Notes:
[75] - n's were: 15, 15, 15, 15, 15, 2, 15
[76] - n's were: 3, 3, 3, 3, 3, 0, 3
[77] - n's were: 6, 6, 6, 6, 6, 1, 6
[78] - n's were: 5, 5, 5, 5, 5, 0, 5

End point values	Arm 3 Dose Level 4			
Subject group type	Subject analysis set			
Number of subjects analysed	1[79]			
Units: pg/mL				
arithmetic mean (standard deviation)				
VEGF	19.28 (± 0)			
sVEGFR-1	10.32 (± 0)			
sVEGFR-2	-1.01 (± 0)			
bFGF	145.98 (± 0)			
PLGF	-14.79 (± 0)			
MIA	-12800 (± 0)			
cKIT	-4.3 (± 0)			

Notes:
[79] - n's were: 1, 1, 1, 1, 1, 1, 1,

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Metabolic Response as Assayed by 18[F}-Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)-Arm 2

End point title	Number of Subjects With Metabolic Response as Assayed by 18[F}-Fluorodeoxyglucose-Positron Emission Tomography

	PET)-Arm 2[80][81]

End point description:

Metabolic response was defined as either complete metabolic response (CMR; complete resolution of tumor FDG-PET uptake so the maximum standardized uptake value [SUVmax] is the same as background) or partial metabolic response (PMR; a decrease in tumor sSUVmax of >=25% from the baseline scan). Scans were preferably obtained 3 to 8 hours after RAF265 oral administration, but not later than 48 hours after dosing.
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

FDG-PET scans were done at baseline (within 14 days prior to treatment), Cycle 1 Day 8, Cycle 1 Day 15 (± 2 days), Cycle 1 Day 28 (± 2 days), and the end of treatment

Notes:

[80] - 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 statistical analysis was planned for this primary outcome measure.

[81] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Levels 1-4
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	15	23	20
Units: subjects				
Cycle 1 Day 8	1	0	0	1
Cycle 1 Day 15	11	1	3	2
Cycle 1 Day 28	12	2	4	2
End of treatment	0	0	0	0

End point values	Arm 2 Dose Levels 7-7.1			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: subjects				
Cycle 1 Day 8	0			
Cycle 1 Day 15	5			
Cycle 1 Day 28	4			
End of treatment	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Metabolic Response as Assayed by FDG-PET-Arm 3

End point title	Number of Subjects With Metabolic Response as Assayed by

	FDG-PET-Arm 3[82][83]

End point description:

Metabolic response was defined as either complete metabolic response (CMR; complete resolution of tumor FDG-PET uptake so the maximum standardized uptake value [SUVmax] is the same as background) or partial metabolic response (PMR; a decrease in tumor sSUVmax of >=25% from the baseline scan). Scans were preferably obtained 3 to 8 hours after RAF265 oral administration, but not later than 48 hours after dosing.
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

FDG-PET scans were done at baseline (within 14 days prior to treatment), Cycle 1 Day 8 and the end of treatment

Notes:

[82] - 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 statistical analysis was planned for this primary outcome measure.

[83] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 3 - Dose escalation	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	3	7	5
Units: subjects				
Cycle 1 Day 8 End of treatment	0	0	0	0

End point values	Arm 3 Dose Level 4			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: subjects				
Cycle 1 Day 8 End of treatment	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Metabolic Response as Assayed by FDG-PET-Arm 5

End point title	Number of Subjects With Metabolic Response as Assayed by FDG-PET-Arm 5[84][85]

End point description:

Metabolic response was defined as either complete metabolic response (CMR; complete resolution of tumor FDG-PET uptake so the maximum standardized uptake value [SUVmax] is the same as background) or partial metabolic response (PMR; a decrease in tumor sSUVmax of >=25% from the baseline scan). Scans were preferably obtained 3 to 8 hours after RAF265 oral administration, but not

later than 48 hours after dosing.
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

FDG-PET scans were done at baseline (within 14 days prior to treatment), Cycles 1 and 2 Day 14 and the end of treatment

Notes:

[84] - 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 statistical analysis was planned for this primary outcome measure.

[85] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 5 - Dose escalation	Arm 5 Dose Level 1	Arm 5 Dose Level 2	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	6	
Units: subjects				
Cycle 1 Day 14	0	0	0	
Cycle 2 Day 14	2	0	2	
End of treatment	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Both Metabolic Response as Assayed by FDG-PET And Response as Defined by RECIST-Arms 2, 3, and 5

End point title	Number of Subjects With Both Metabolic Response as Assayed by FDG-PET And Response as Defined by RECIST-Arms 2, 3, and 5[86][87]

End point description:

Metabolic response was defined as either complete metabolic response (CMR; complete resolution of tumor FDG-PET uptake so the maximum standardized uptake value [SUVmax] is the same as background) or partial metabolic response (PMR; a decrease in tumor sSUVmax of >=25% from the baseline scan).
RECIST Response was defined as partial response (PR) or complete response (CR). PR and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). PR was defined as a decrease of at least 30% from baseline in the sum of the longest diameter (LD) of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Primary

End point timeframe:

Through Cycle 2

Notes:

[86] - 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 statistical analysis was planned for this primary outcome measure.

[87] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 3 - Dose escalation	Arm 5 - Dose escalation	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	16	9	
Units: subjects	2	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With a Dose-Limiting Toxicity (DLT) During The First 28 Days of Treatment--Arms 2, 3, and 5

End point title	Number of Subjects With a Dose-Limiting Toxicity (DLT) During The First 28 Days of Treatment--Arms 2, 3, and 5[88]

End point description:

A DLT was defined as any adverse event or abnormality judged by the investigator to be related to RAF265, and not related to an intercurrent illness, disease progression, other medication or procedure. Grading of laboratory abnormalities was done according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP; Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events 2003).
This endpoint analyzed the Dose Determining Set (DDS), defined as subjects who received at least 75% (21 days in Arm 2 and 5 or 3 doses in Arm 3) of the scheduled doses in the first cycle for Arm 2 and 3, first 28 days for Arm 5 (with or without DLT) or had experienced a DLT any time in the first cycle for Arm 2 and 3, first 28 days for Arm 5.

End point type	Primary

End point timeframe:

Up to 28 days after the start of treatment

Notes:

[88] - 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 statistical analysis was planned for this primary outcome measure.

End point values	Arm 2 Dose Level 1	Arm 2 Dose Level 2	Arm 2 Dose Level 3	Arm 2 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	3	4	8
Units: subjects	0	0	0	0

End point values	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Level 7	Arm 2 Dose Level 7.1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	20	7	10
Units: subjects	0	2	2	2

End point values	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3	Arm 3 Dose Level 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	6	5	1
Units: subjects	0	0	0	0

End point values	Arm 5 Dose Level 1	Arm 5 Dose Level 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	6		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 2

End point title	Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 2[89]

End point description:

Response was defined as partial response (PR) or complete response (CR). PR and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). PR was defined as a decrease of at least 30% from baseline in the sum of the longest diameter (LD) of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

Day 28 of every two cycles of treatment and end of study

Notes:

[89] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Levels 1-4
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	15	23	20
Units: subjects				
BRAF mutation	2	0	0	2
BRAF wild-type	1	0	1	0
BRAF unspecified/unknown	1	0	0	0

End point values	Arm 2 Dose Levels 7-7.1			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: subjects				
BRAF mutation	0			
BRAF wild-type	0			
BRAF unspecified/unknown	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 3

End point title	Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 3[90]

End point description:

Response was defined as partial response (PR) or complete response (CR). PR and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). PR was defined as a decrease of at least 30% from baseline in the sum of the LD of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

Day 28 of every two cycles of treatment and end of study

Notes:

[90] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 3 - Dose escalation	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	3	7	5
Units: subjects				
BRAF mutation	0	0	0	0
BRAF wild-type	0	0	0	0
BRAF unspecified/unknown	0	0	0	0

End point values	Arm 3 Dose Level 4			

Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: subjects				
BRAF mutation	0			
BRAF wild-type	0			
BRAF unspecified/unknown	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 5

End point title	Number of Subjects With Response as Assayed by Central Radiology by Mutations Status of The BRAF Gene-Arm 5[91]

End point description:

Response was defined as partial response (PR) or complete response (CR). PR and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). PR was defined as a decrease of at least 30% from baseline in the sum of the LD of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

Day 28 of every two cycles of treatment and end of study

Notes:

[91] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 5 - Dose escalation	Arm 5 Dose Level 1	Arm 5 Dose Level 2	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	6	
Units: subjects				
BRAF mutation	0	0	0	
BRAF wild-type	0	0	0	
BRAF unspecified/unknown	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 2

End point title	Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 2[92]

End point description:

Stable disease (SD) or better was defined as SD, partial response (PR), or complete response (CR). SD, PR, and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). SD was defined as neither sufficient decrease to meet the definition of PR nor sufficient increase to meet the definition of progressive disease (PD); PR as a decrease of at least 30% from baseline in the sum of the longest diameter of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

12 months after the start of treatment

Notes:

[92] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 2 - PK Run-in/Dose escalation	Arm 2 Dose Level 5	Arm 2 Dose Level 6	Arm 2 Dose Levels 1-4
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	15	23	20
Units: percent of subjects				
number (confidence interval 95%)	6.5 (1 to 12)	0 (0 to 0)	8.7 (0 to 20.2)	15 (0 to 30.6)

End point values	Arm 2 Dose Levels 7-7.1			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent of subjects				
number (confidence interval 95%)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 3

End point title	Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 3[93]

End point description:

Stable disease (SD) or better was defined as SD, partial response (PR), or complete response (CR). SD, PR, and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). SD was defined as neither sufficient decrease to meet the definition of PR nor sufficient increase to meet the definition of progressive disease (PD); PR as a decrease of at least 30% from baseline in the sum of the longest diameter of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

12 months after the start of treatment

Notes:

[93] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 3 - Dose escalation	Arm 3 Dose Level 1	Arm 3 Dose Level 2	Arm 3 Dose Level 3
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	16	3	7	5
Units: percent of subjects				
number (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

End point values	Arm 3 Dose Level 4			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: percent of subjects				
number (confidence interval 95%)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 5

End point title	Percent of Subjects With Stable Disease or Better After 12 Months as Assayed by Central Radiology-Arm 5[94]

End point description:

Stable disease (SD) or better was defined as SD, partial response (PR), or complete response (CR). SD, PR, and CR were defined by using Response Evaluation Criteria in Solid Tumors (RECIST criteria). SD was defined as neither sufficient decrease to meet the definition of PR nor sufficient increase to meet the definition of progressive disease (PD); PR as a decrease of at least 30% from baseline in the sum of the longest diameter of target lesions, and CR as disappearance of all target lesions. An additional confirmatory computed tomography scan was required > 28 days after initial response (partial response or complete response).
This endpoint analyzed the FAS, defined as all subjects who received at least one full or partial dose of RAF265.

End point type	Secondary

End point timeframe:

12 months after the start of treatment

Notes:

[94] - 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: Data for this endpoint were not collected from subjects in Arms 1 and 4; data for Arms 2, 3 and 5 are reported in separate endpoints.

End point values	Arm 5 - Dose escalation	Arm 5 Dose Level 1	Arm 5 Dose Level 2	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	9	3	6	
Units: percent of subjects				
number (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Arm 2
Reporting group description:	
Arm 2	
Reporting group title	Arm 5
Reporting group description:	
Arm 5	
Reporting group title	Arm 3
Reporting group description:	
Arm 3	

Serious adverse events	Arm 2	Arm 5	Arm 3
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 77 (38.96%)	2 / 9 (22.22%)	6 / 16 (37.50%)
number of deaths (all causes)	5	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hypergammaglobulinaemia benign monoclonal			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Squamous cell carcinoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subgaleal haematoma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 77 (6.49%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	3 / 77 (3.90%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinopathy			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm 2	Arm 5	Arm 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 77 (96.10%)	9 / 9 (100.00%)	16 / 16 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1

Tumour haemorrhage			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Tumour pain			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Tumour ulceration			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Haematoma			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	13 / 77 (16.88%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	18	1	0
Hypotension			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 77 (6.49%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Axillary pain			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Disease progression			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Fatigue			

subjects affected / exposed	48 / 77 (62.34%)	5 / 9 (55.56%)	7 / 16 (43.75%)
occurrences (all)	59	6	11
Influenza like illness			
subjects affected / exposed	4 / 77 (5.19%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Local swelling			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	2	1	1
Non-cardiac chest pain			
subjects affected / exposed	4 / 77 (5.19%)	2 / 9 (22.22%)	1 / 16 (6.25%)
occurrences (all)	4	2	1
Oedema			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	10 / 77 (12.99%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	11	1	1
Pyrexia			
subjects affected / exposed	5 / 77 (6.49%)	2 / 9 (22.22%)	3 / 16 (18.75%)
occurrences (all)	6	2	3
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 77 (16.88%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	15	0	2
Dry throat			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dysphonia			

subjects affected / exposed	2 / 77 (2.60%)	2 / 9 (22.22%)	0 / 16 (0.00%)
occurrences (all)	3	5	0
Dyspnoea			
subjects affected / exposed	10 / 77 (12.99%)	1 / 9 (11.11%)	2 / 16 (12.50%)
occurrences (all)	11	1	2
Epistaxis			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Hiccups			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Increased upper airway secretion			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	1	0	2
Oropharyngeal pain			
subjects affected / exposed	4 / 77 (5.19%)	2 / 9 (22.22%)	0 / 16 (0.00%)
occurrences (all)	4	3	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	4	0	5
Delirium			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	6 / 77 (7.79%)	1 / 9 (11.11%)	3 / 16 (18.75%)
occurrences (all)	8	1	3
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	9 / 77 (11.69%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	12	0	0
Amylase increased			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 77 (9.09%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	10	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Eosinophil count increased			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Haematocrit decreased			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Haemoglobin decreased			
subjects affected / exposed	8 / 77 (10.39%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	10	1	0
Lipase increased			
subjects affected / exposed	9 / 77 (11.69%)	3 / 9 (33.33%)	1 / 16 (6.25%)
occurrences (all)	11	3	1
Weight decreased			
subjects affected / exposed	32 / 77 (41.56%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	34	1	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Toxicity to various agents			

subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Dizziness			
subjects affected / exposed	9 / 77 (11.69%)	4 / 9 (44.44%)	0 / 16 (0.00%)
occurrences (all)	11	6	0
Dysgeusia			
subjects affected / exposed	19 / 77 (24.68%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	19	1	0
Headache			
subjects affected / exposed	13 / 77 (16.88%)	2 / 9 (22.22%)	1 / 16 (6.25%)
occurrences (all)	15	2	1
Hypoaesthesia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	2
Neuropathy peripheral			
subjects affected / exposed	3 / 77 (3.90%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	6	0	1
Paraesthesia			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Somnolence			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	2
Lymphopenia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Neutropenia			
subjects affected / exposed	5 / 77 (6.49%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	6	0	0
Thrombocytopenia			
subjects affected / exposed	18 / 77 (23.38%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	24	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	5	0	0
Photopsia			
subjects affected / exposed	19 / 77 (24.68%)	2 / 9 (22.22%)	0 / 16 (0.00%)
occurrences (all)	23	2	0
Vision blurred			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Visual impairment			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Vitreous floaters			
subjects affected / exposed	21 / 77 (27.27%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	22	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	1	1	2
Abdominal distension			

subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Abdominal pain			
subjects affected / exposed	16 / 77 (20.78%)	2 / 9 (22.22%)	2 / 16 (12.50%)
occurrences (all)	18	3	2
Abdominal pain upper			
subjects affected / exposed	4 / 77 (5.19%)	1 / 9 (11.11%)	2 / 16 (12.50%)
occurrences (all)	4	1	2
Constipation			
subjects affected / exposed	11 / 77 (14.29%)	2 / 9 (22.22%)	4 / 16 (25.00%)
occurrences (all)	11	2	4
Diarrhoea			
subjects affected / exposed	34 / 77 (44.16%)	5 / 9 (55.56%)	2 / 16 (12.50%)
occurrences (all)	52	8	2
Dry mouth			
subjects affected / exposed	7 / 77 (9.09%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	7	0	1
Flatulence			
subjects affected / exposed	3 / 77 (3.90%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	3	0	1
Gastrointestinal inflammation			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	3 / 16 (18.75%)
occurrences (all)	2	1	4
Nausea			
subjects affected / exposed	26 / 77 (33.77%)	4 / 9 (44.44%)	6 / 16 (37.50%)
occurrences (all)	38	5	10
Oral pain			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pancreatitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Stomatitis			

subjects affected / exposed	1 / 77 (1.30%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	21 / 77 (27.27%)	2 / 9 (22.22%)	3 / 16 (18.75%)
occurrences (all)	30	4	3
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 77 (6.49%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	5	1	0
Dermatomyositis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Erythema			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	3	1	1
Night sweats			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Pruritus			
subjects affected / exposed	4 / 77 (5.19%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	4	1	1
Rash			
subjects affected / exposed	11 / 77 (14.29%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	13	1	0
Rash papular			

subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 77 (15.58%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	14	0	2
Back pain			
subjects affected / exposed	11 / 77 (14.29%)	3 / 9 (33.33%)	6 / 16 (37.50%)
occurrences (all)	11	3	6
Flank pain			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Groin pain			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	2	1	0
Limb discomfort			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	17 / 77 (22.08%)	2 / 9 (22.22%)	0 / 16 (0.00%)
occurrences (all)	23	2	0
Muscular weakness			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	4	0	1
Musculoskeletal chest pain			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	2 / 16 (12.50%)
occurrences (all)	3	1	2
Musculoskeletal pain			
subjects affected / exposed	10 / 77 (12.99%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	11	1	1
Musculoskeletal stiffness			

subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	2 / 16 (12.50%)
occurrences (all)	2	0	2
Myalgia			
subjects affected / exposed	8 / 77 (10.39%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	9	0	1
Pain in extremity			
subjects affected / exposed	12 / 77 (15.58%)	4 / 9 (44.44%)	3 / 16 (18.75%)
occurrences (all)	13	4	3
Infections and infestations			
Candida infection			
subjects affected / exposed	1 / 77 (1.30%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	1	1	0
Cellulitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Laryngitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Tinea infection			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 77 (3.90%)	1 / 9 (11.11%)	2 / 16 (12.50%)
occurrences (all)	3	2	2
Urinary tract infection			
subjects affected / exposed	5 / 77 (6.49%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	6	1	1
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	24 / 77 (31.17%)	0 / 9 (0.00%)	5 / 16 (31.25%)
occurrences (all)	24	0	5
Dehydration			
subjects affected / exposed	6 / 77 (7.79%)	2 / 9 (22.22%)	1 / 16 (6.25%)
occurrences (all)	10	2	1
Fluid overload			
subjects affected / exposed	0 / 77 (0.00%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	2 / 77 (2.60%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Hypoalbuminaemia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	4	1	0
Hypocalcaemia			
subjects affected / exposed	2 / 77 (2.60%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	2	1	2
Hypokalaemia			
subjects affected / exposed	4 / 77 (5.19%)	1 / 9 (11.11%)	1 / 16 (6.25%)
occurrences (all)	6	1	1
Hyponatraemia			
subjects affected / exposed	4 / 77 (5.19%)	0 / 9 (0.00%)	0 / 16 (0.00%)
occurrences (all)	4	0	0
Hypophosphataemia			
subjects affected / exposed	5 / 77 (6.49%)	0 / 9 (0.00%)	1 / 16 (6.25%)
occurrences (all)	5	0	1
Hypoproteinaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 9 (11.11%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2006	This amendment introduced the following changes: -Added blood pressure (BP) assessment Cycle 2 Day 8 (C2D8) -Added serum lipase required safety lab -Reworded exclusion criteria 3 (mutation status) and clarified consent and destruction of patient samples -Adjusted PK/Pharmacodynamic timepoints and clarified collection of PK/Pharmacodynamic only through Cycle 6 -Additional text added to clarify original intent of protocol and tables adjusted accordingly
03 August 2006	This amendment introduced the following changes: - Changed Chiron Corporation to Novartis Pharmaceuticals due to acquisition of Chiron - Added RAF265 compound name and protocol name - Changed to Novartis (NVS) SAE reporting process - Changed "subject" to "patient" throughout protocol - Updated window period for tumor biopsy on C1D15 to day of dosing - Added treatment Arm 2 (PK runin/ loading dose/daily maintenance dose) and Arm 3 (once a week dosing) and increased total number of patient enrolled -Added the Multinomial Two-Stage Design to be used in the statistical analysis for the MTD dose expansion segment of the study, and added two clinical study reports to be written: one for the dose escalation segment as soon as the MTD has been determined on both arms 2 and 3, and a final clinical study report at the end of the study. - Added biomarkers to Arm 2 and 3 in dose escalation and expansion - Removed urine PK - Added multinomial two-stage design for stats analysis for MTD dose expansion; two CSRs planned (dose escalation as soon as MTD reached in both Arm 2 and 3; and final CSR at end of study)

19 July 2007	This amendment made the following changes: -Clarified single "PK run-in" dose given in Arm 2 and its relationship to the targeted and actual loading doses given on C1D1 - Allow option of expanding either the MTD or an "optimal biologic dose" (OBD). - Changes were made to dose escalation: 1. The dose of RAF265 was doubled from one cohort of patients to the next until two or more patients experience grade 2 drug-related toxicity, or until any 1 patient experiences grade 3 or higher toxicity. Thereafter increases in dose can be no greater than 40% from one cohort of patients to the next. 2. Bayesian logistic regression analysis with overdose control was implemented in Arm 2 (daily dosing regimen). 3. The observation period before new patients are enrolled at the next highest dose level of RAF265 was changed from 8 weeks to 4 weeks. - Changes to simplify procedures and better assess the pharmacodynamics of RAF265 1. Include DCE- Magnetic resonance imaging (MRI) and FDG-PET to assess RAF265's potential effects on tumor tissue 2. Added collection of plasma and serum samples for exploratory studies including circulating tumor DNA 3. Added optional collection of peripheral blood mononuclear cells (pre- and post-treatment) in separately consented individuals during the expansion phase for HLA typing, kinase studies and immunological studies 4. Sites may collect fine needle aspirate (FNA) biopsies during the dose expansion phase of the study to permit enrollment of patients whose tumor cannot be accessed by core, punch or excisional biopsy at the first timepoint. Only after consultation with NVS clinical team. 5. Modified the number and frequency of certain procedures in both Arm 2 and Arm 3 6. Inclusion criteria were modified
06 February 2008	This amendment introduced the following changes: - Added Arm 4 (tablet formulation); 12 patients to be treated exclusively with tablet formulation at a dose calculated to produce the same average steady state plasma concentration as the liquid formulation MTD - If needed, the PK run-in dose (in Arm 2) and the loading dose (in Arms 2 and 4) can be split evenly into 2-3 doses, given 8-12 hours apart. If this strategy is adopted, the PK sampling scheme will be altered accordingly. - Changed the requirement of pre- and post-treatment biopsies; a minimum of 6 patients treated at the MTD will have pre- and on-treatment biopsies. NVS reserved option to conduct pre- and ontreatment paired tumor biopsies at any dose if needed to choose the optimaldose for phase II or other studies. Mutational status from archival tumor tissue for all other patients. If no archival tumor tissue can be obtained, mutation status must be determined from a pre-treatment biopsy of tumor tissue. - A window of 3 days allowed for the performance of all study procedures except for PK sampling or unless otherwise specified in the protocol.
15 May 2009	This amendment introduced the following changes: - Addition of complete eye exam including: visual acuity testing, visual field testing, color vision testing, IOP, split lamp exam of anterior eye segment, dilated funduscopy at baseline, C2D1, then every 3 cycles, and EOT. Additionally, eye exams should be done as soon as patient complains of visual disturbance and repeated as clinically indicated - Added eligibility criteria to exclude patents with history or current evidence of retinal disease as confirmed by eye exam - Updated dose limiting toxicity table to include visual toxicity and adjusted dose modification criteria for visual toxicity - Eliminated loading dose in expansion phase of study - Allowed for 12 additional patients to be enrolled in Arm 4 if initial data indicates new/different correction factor for tablets is required for cancer patients - Updated PK timepoints for Arm 2 and Arm 4

11 December 2009	This amendment introduced the following changes: -Eliminated PK run-in - Loading dose established at 288mg administered into 3 doses (96mg every 8 hours); only daily maintenance dose will be escalated - Addition of Treatment Arm 5 alternate dosing schedule: 2 weeks continuous dosing followed by 1 week off (21 day cycle) without loading dose starting at 67mg daily maintenance dose - Allow only patients with documented BRAF mutations in phase II; 30 evaluable patients with BRAF mutation, including at least 20 V600E will be enrolled in the phase II expansion portion of this study
11 November 2011	This amendment introduced the following changes: - Protocol synopsis updated. Figures and tables were updated to reflect tablet transition and continued drug access for ongoing patients. - References to Arm 4 were removed to reflect closure of this study arm in the Ethics section. - Exploratory biomarkers and Arm 4 objective were removed from study objectives, Investigation Plan, was updated to reflect closure of treatment arms after Phase I of study, removal of dose expansion (Phase II) portions of study, and addition of tablet transition and drug access for ongoing patients. - Exploratory biomarker studies were removed. Table 5-10 in the protocol was updated to reflect removal of expansion portions of the study, and DCE-MRI was removed as it only pertained to the removed expansion arms. - Tumor response section was updated to reflect continued drug access. - Safety section was updated to reflect continued drug access. - Removal of Patients from treatment or assessment was updated to reflect continued drug access. - Treatments administered section, was updated to reflect removal of expansion portion of the study. - Directions for administration, was updated to reflect tablet transition and continued drug access. - Exploratory biomarker variables were removed from the Efficacy and safety section. - Statistical and analytical plans section was updated to indicate that the final analysis of data will be done after every patient has been followed for at least 6 cycles or has discontinued from study due to disease progression or death; data collected from patients receiving continued drug access after study enrollment is closed will not be summarized but will be listed in an addendum to the CSR. Removed the expansion (Phase II) portion of the study and sample size considerations for the dose expansion section. - Removed sample size considerations for DCEMRI section. -RECIST quick reference was updated to correct definition of progressive disease.

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 EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: