Clinical trial results:
A Phase I/II study to assess the safety and efficacy of pazopanib and MK-3475 in patients with advanced renal cell carcinoma

Summary

EudraCT number	2013-003785-14
Trial protocol	GB
Global end of trial date	17 February 2019

Results information

Result version number	v1 (current)
This version publication date	11 March 2020
First version publication date	11 March 2020

Trial information

Trial identification

Sponsor protocol code	CPZP034A2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02014636
WHO universal trial number (UTN)	-
Other trial identifiers	GSK: 200249, Merck: KEYNOTE-018

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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the safety, tolerability, maximum tolerated regimen (MTR), and recommended Phase II dose (RP2D) of pazopanib in combination with MK-3475 in treatment naïve subjects with advanced renal cell carcinoma (RCC). Following an Urgent Safety Measure (USM) released on February 09, 2017, the phase II (Part 2) portion of this study did not commence. Hence, this is only a Phase 1 study.

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	30 December 2013
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 Kingdom: 21
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	42
EEA total number of subjects	21

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)	28

From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study was conducted in 6 centers across 2 countries (4 centers in the USA and 2 centers in the UK). In one of the 4 centers in the USA, no subjects were treated. 42 subjects were enrolled originally, however, in Cohort C, one subject did not receive treatment, as the patient was not clinically suitable to be treated, and withdrew consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Cohort A

Arm description:

10 subjects were enrolled and treated (6 subjects from the dose escalation period, and 4 subjects newly enrolled). All received treatment with pazopanib (800 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	PZP034
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg once daily

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg iv Q3W

Arm title	Part 1: Cohort B

Arm description:

10 new subjects were enrolled and treated with pazopanib (600 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	PZP034
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg once daily

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Q3W

Arm title	Part 1: Cohort C

Arm description:

Run-in period only: 9 pts. received pazopanib monotherapy starting dose of 800 mg oral daily for 9 weeks but did not continue after the run-in period. Run-in and post run-in periods: 12 pts. treated w/pazopanib in run-in, and post run-in pts. 6 pts. treated with combination therapy, 4 treated with pembrolizumab monotherapy, and 4 treated with pazopanib monotherapy

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	PZP034
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg daily for 9 weeks

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	KEYTRUDA
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Q3W

Number of subjects in period 1	Part 1: Cohort A	Part 1: Cohort B	Part 1: Cohort C
Started	10	10	22
Completed	3	4	6
Not completed	7	6	16
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	3	2	6
Physician decision	-	3	9
Lost to follow-up	4	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Cohort A
Reporting group description:	
10 subjects were enrolled and treated (6 subjects from the dose escalation period, and 4 subjects newly enrolled). All received treatment with pazopanib (800 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)	
Reporting group title	Part 1: Cohort B
Reporting group description:	
10 new subjects were enrolled and treated with pazopanib (600 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)	
Reporting group title	Part 1: Cohort C
Reporting group description:	
Run-in period only: 9 pts. received pazopanib monotherapy starting dose of 800 mg oral daily for 9 weeks but did not continue after the run-in period. Run-in and post run-in periods: 12 pts. treated w/pazopanib in run-in, and post run-in pts. 6 pts. treated with combination therapy, 4 treated with pembrolizumab monotherapy, and 4 treated with pazopanib monotherapy	

Reporting group values	Part 1: Cohort A	Part 1: Cohort B	Part 1: Cohort C
Number of subjects	10	10	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	9	14
From 65-84 years	4	1	8
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	3	6
Male	5	7	16

Reporting group values	Total		
Number of subjects	42		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	29		

From 65-84 years	13		
85 years and over	0		

Gender categorical Units: Subjects			
Female	14		
Male	28		

End points

End points reporting groups

Reporting group title	Part 1: Cohort A
Reporting group description:	
10 subjects were enrolled and treated (6 subjects from the dose escalation period, and 4 subjects newly enrolled). All received treatment with pazopanib (800 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)	
Reporting group title	Part 1: Cohort B
Reporting group description:	
10 new subjects were enrolled and treated with pazopanib (600 mg oral once daily) + pembrolizumab (2 mg/kg iv Q3W)	
Reporting group title	Part 1: Cohort C
Reporting group description:	
Run-in period only: 9 pts. received pazopanib monotherapy starting dose of 800 mg oral daily for 9 weeks but did not continue after the run-in period. Run-in and post run-in periods: 12 pts. treated w/pazopanib in run-in, and post run-in pts. 6 pts. treated with combination therapy, 4 treated with pembrolizumab monotherapy, and 4 treated with pazopanib monotherapy	

Primary: Summary of Adverse Events/Serious Adverse Events for Cohort A and B

End point title	Summary of Adverse Events/Serious Adverse Events for Cohort A and B[1][2]
End point description:	
Any sign or symptom that occurs during the study treatment plus the post treatment follow-up period	
End point type	Primary
End point timeframe:	
From the start of study treatment (first dose) until the post-treatment follow-up visit (at least 30 days after the last dose of investigational product) for AEs, and until 90 days after last dose for SAEs	

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: Statistical analysis not performed for this primary endpoint.

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

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number of Subjects				
Incidence of any AE	6	6		
Severity of Adverse Events by Grade 3/4	9	9		
Incidence of any SAE	6	6		

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Adverse Events/Serious Adverse Events for Cohort C

End point title	Summary of Adverse Events/Serious Adverse Events for Cohort C[3][4]

End point description:

Any sign or symptom that occurs during the study treatment plus the post treatment follow-up period

End point type	Primary

End point timeframe:

From the start of study treatment (first dose) until the post-treatment follow-up visit (at least 30 days after the last dose of investigational product) for AEs, and until 90 days after last dose for SAEs

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not performed for this endpoint.

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Number of Subjects				
Incidence of any AE - Pazo + Pembro (N=6)	6			
Incidence of any AE- Pembrolizumab (N=4)	4			
Incidence of any AE- Pazopanib (N=11)	11			
Severity of AEs Grade 3/4: Pazo + Pembro (N=6)	6			
Severity of AEs by Grade 3/4:Pembrolizumab (N=4)	2			
Severity of AEs Grade 3/4 :Pazo + Pembro (N=6)	6			
Incidence of any SAE Pazo + Pembro (N=6	3			
Incidence of any SAE Pembrolizumab (N=4)	1			
Incidence of any SAE Pazopanib (N=11)	3			

Statistical analyses

No statistical analyses for this end point

Primary: Dose limiting toxicities (DLT) and maximum tolerated regimen (MTR)

End point title	Dose limiting toxicities (DLT) and maximum tolerated regimen (MTR)[5]

End point description:

MTR is defined as the highest dose of pazopanib in combination with the highest dose of MK 3475 at which no more than 1 of 6 subjects experiences a DLT after a minimum of 8 weeks of treatment. DLT is defined as a drug-related AE starting in the first 8 weeks of treatment

End point type	Primary

End point timeframe:

8 weeks

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not performed for this endpoint.

End point values	Part 1: Cohort A	Part 1: Cohort B	Part 1: Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	22	
Units: Number of Subjects				
Summary of Dose Limiting Toxicities	2	5	1	

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Anti-Drug Antibody Positivity (Mk-3475) for Cohorts A, B, C

End point title	Incidence of Anti-Drug Antibody Positivity (Mk-3475) for Cohorts A, B, C[6]

End point description:

Subjects were monitored for anti-MK 3475 antibodies throughout the study

End point type	Primary

End point timeframe:

24 months

Notes:

[6] - 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: Statistical analysis not performed for this endpoint.

End point values	Part 1: Cohort A	Part 1: Cohort B	Part 1: Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: Number				

Notes:

[7] - Dataset has negative results for all analyzed subjects, hence no positive results.

[8] - Dataset has negative results for all analyzed subjects, hence no positive results.

[9] - Dataset has negative results for all analyzed subjects, hence no positive results.

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pembrolizumab (MK-3475) PK Concentration-time data (Cmax and Ctrough) for Cohort A Dose Escalation

End point title	Summary of Pembrolizumab (MK-3475) PK Concentration-time data (Cmax and Ctrough) for Cohort A Dose Escalation[10]

End point description:

Analysis of plasma and serum concentrations in blood samples collected from subjects

End point type	Secondary

End point timeframe:

MK-3475: Until 6 months after the last dose of MK-3475

Notes:

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

Justification: Statistical analysis not performed for this endpoint.

End point values	Part 1: Cohort A			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ug/ML				
median (full range (min-max))				
Cmax- Cycle 1 (N=5)	65.8 (53.4 to 71.4)			
Ctrough- Cycle 1 (N=5)	999 (999 to 999)			
Cmax-Cycle 2 (N=5)	69 (64.3 to 94.7)			
Ctrough- Cycle 2 (N=5)	15.8 (0.00 to 18.1)			
Cmax- Cycle 4 (N=2)	999 (999 to 999)			
Ctrough- Cycle 4 (N=2)	38 (37.2 to 38.8)			
Cmax- Cycle 7 (N=4)	999 (999 to 999)			
Ctrough- Cycle 7 (N=4)	45.2 (28.4 to 57.2)			
Cmax-Cycle 13 (N=4)	999 (999 to 999)			
Ctrough-Cycle 13 (N=4)	49.9 (23.6 to 66.4)			
Cmax- Cycle 19 (N=4)	999 (999 to 999)			
Ctrough- Cycle 19 (N=4)	47.9 (33.2 to 61)			
Cmax- Cycle 25 (N=3)	999 (999 to 999)			
Ctrough- Cycle 25 (N=3)	45.8 (39.3 to 63.2)			
Cmax- Cycle 31 (N=4)	999 (999 to 999)			
Ctrough- Cycle 31 (N=4)	52.6 (38.8 to 76.8)			
Cmax- Cycle 37 (N=2)	999 (999 to 999)			
Ctrough- Cycle 37 (N=2)	50.5 (45.7 to 55.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pembrolizumab (MK-3475) PK Concentration-time Data (Cmax and Ctrough) for Cohort B

End point title	Summary of Pembrolizumab (MK-3475) PK Concentration-time Data (Cmax and Ctrough) for Cohort B[11]

End point description:

Analysis of plasma and serum concentrations for MK-3475 collected in subjects

End point type	Secondary

End point timeframe:

MK-3475: until 6 months after the last dose of MK-3475

Notes:

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

End point values	Part 1: Cohort B			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ug/mL				
median (full range (min-max))				
Cmax -Cycle 1 (N=6)	41.9 (33.4 to 52.4)			
Ctrough-Cycle 1 (N=6)	999 (999 to 999)			
Cmax -Cycle 4 (N=3)	67.6 (66.5 to 75.9)			
Ctrough-Cycle 4 (N=3)	23.5 (19.3 to 26.4)			
Cmax -Cycle 7 (N=5)	999 (999 to 999)			
Ctrough-Cycle 7 (N=5)	25.4 (22.4 to 32.7)			
Cmax -Cycle 13 (N=5)	999 (999 to 999)			
Ctrough-Cycle 13 (N=5)	39.1 (33.1 to 43.5)			
Cmax -Cycle 19 (N=4)	999 (999 to 999)			
Ctrough-Cycle 19 (N=4)	44.4 (35.7 to 46.2)			
Cmax -Cycle 25 (N=3)	999 (999 to 999)			
Ctrough-Cycle 25 (N=3)	36.4 (35.4 to 39.8)			
Cmax-Cycle 31 (N=3)	999 (999 to 999)			
Ctrough- Cycle (N=3)	41 (38.6 to 44.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pazopanib Pharmacokinetic (PK) parameters for Cohort C (Run-in Period) in Expansion cohort

End point title	Summary of Pazopanib Pharmacokinetic (PK) parameters for Cohort C (Run-in Period) in Expansion cohort[12]

End point description:

Area under the plasma concentration-time curve from time 0 to 24 hrs (AUC[0-24], maximum observed concentration (Cmax), tmax, and concentration at 24 hours (C24) of pazopanib; Pre-dose (trough) concentration at the end of the dosing interval

End point type	Secondary

End point timeframe:

For Pazopanib: before and after the 1st and 2nd dose of MK-3475.

Notes:

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/ML, h, h*ng/ML,				
median (full range (min-max))				
AUC0-24h (h*ng/ML): Week 4	999 (999 to 999)			
Cmax (ng/ML): Week 4	48300 (10500 to 78900)			
Tmax (h) : Week 4	3 (1.83 to 6.02)			
AUClast (h*ng/ML) Week 4	846000 (185000 to 1520000)			
Ctrough (ng/ML) Week 4	29900 (6250 to 54100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Pazopanib and Pazopanib+Pembrolizumab Pharmacokinetic (PK) parameters for Cohort C (Post Run-in Period) in Expansion cohort

End point title	Summary of Pazopanib and Pazopanib+Pembrolizumab Pharmacokinetic (PK) parameters for Cohort C (Post Run-in Period) in Expansion cohort[13]

End point description:

Area under the plasma concentration-time curve from time 0 to 24 hrs (AUC[0-24], maximum observed concentration Cmax, tmax, and concentration at 24 hours (C24) of pazopanib; Pre-dose (trough) concentration at the end of the dosing interval/AUClast

End point type	Secondary

End point timeframe:

For Pazopanib: Before and after the 1st and 2nd dose of MK-3475. For MK-3475: Until 6 months after the last dose of MK-3475

Notes:

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: h*ng/mL, ng/mL, h				
median (full range (min-max))				
AUC0-24h (h*ng/mL) Pazopanib (Week 19, N=1)	999 (999 to 999)			
Cmax (ng/mL) Pazopanib (Week 19, N=1)	18600 (18600 to 18600)			
Tmax (h) Pazopanib (Week 19, N=1)	0.967 (0.967 to 0.967)			
AUC0-24h (h*ng/mL) Pazo + Pembro (Week 10, N=6)	999 (999 to 999)			
Cmax (ng/mL) Pazo + Pembro (Week 10, N=6)	43000 (31300 to 65900)			
Tmax (h) Pazo + Pembro (Week 10, N=6)	2 (1 to 4.03)			
AUC0-24h (h*ng/mL) Pazo + Pembro (Week 19, N=2)	999 (999 to 999)			
Cmax (ng/mL) Pazo + Pembro (Week 19, N=2)	40200 (37800 to 42700)			
Tmax (h) Pazo + Pembro (Week 19, N=2)	2.5 (2 to 3)			
AUClast (h*ng/mL) Pazopanib (Week 19, N=1)	281000 (281000 to 281000)			
Ctrough (ng/mL) Pazopanib (Week 19, N=1)	8790 (8790 to 8790)			
AUClast (h*ng/mL) Pazo + Pembro (Week 10, N=6)	880000 (163000 to 1300000)			
Ctrough (ng/mL) Pazo + Pembro (Week 10, N=6)	32100 (24900 to 43200)			
AUClast (h*ng/mL) Pazo + Pembro (Week 19, N=2)	747000 (682000 to 812000)			
Ctrough (ng/mL) Pazo + Pembro (Week 19, N=2)	26600 (25800 to 27400)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Investigator-Assessed Best Confirmed Response for Cohort A and B (RECIST 1.1 Criteria) Overall Response Rate (ORR)

End point title	Summary of Investigator-Assessed Best Confirmed Response for Cohort A and B (RECIST 1.1 Criteria) Overall Response Rate (ORR)[14]

End point description:

Overall response rate is defined as the percentage of subjects, who achieved either a confirmed complete response (CR) or partial response (PR) by RECIST v1.1 and modified RECIST

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

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

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number				
Complete Response	2	1		
Partial response	4	1		
Stable disease	4	7		
Progressive disease	0	1		
Not evaluable	0	0		
ORR=Complete Response (CR) + Partial Response (PR)	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Investigator-Assessed Best Confirmed Response for Cohort A and B (RECIST 1.1 Criteria): Clinical Benefit Rate (CBR)

End point title	Summary of Investigator-Assessed Best Confirmed Response for Cohort A and B (RECIST 1.1 Criteria): Clinical Benefit Rate (CBR)[15]

End point description:

Clinical benefit rate is defined as a confirmed response of Complete Response (CR) or Partial Response (PR) or at least 6-months Stable Disease (SD) by RECIST v1.1 and modified RECIST.

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

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

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number				
CBR: CR or PR with at least 6 months of SD	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Progression-free survival rate at 18 months (PFSR18) for Cohorts A and B (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)

End point title	Summary of Progression-free survival rate at 18 months (PFSR18) for Cohorts A and B (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)[16]

End point description:

Duration of response is defined for all subjects with confirmed Complete Response or Partial Response (as the time from the first documented evidence of CR or PR until time of first documented disease progression or death due to any causes, whichever is first) by RECIST1.1 and modified RECIST 1.1 Criteria

End point type	Secondary

End point timeframe:

18 months

Notes:

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

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number				
median (full range (min-max))				
18 months PFS rate : RECIST 1.1 Criteria	0.56 (0.22 to 0.96)	0.88 (0.28 to 0.99)		
18 months PFS rate: modified RECIST 1.1 Criteria	0.56 (0.22 to 0.96)	0.88 (0.28 to 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Progression-free survival rate at 18 months (PFSR18) for Cohort C (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)

End point title	Summary of Progression-free survival rate at 18 months (PFSR18) for Cohort C (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)[17]

End point description:

Duration of response is defined for all subjects with confirmed Complete Response or Partial Response (as the time from the first documented evidence of CR or PR until time of first documented disease progression or death due to any causes, whichever is first) by RECIST1.1 and modified RECIST 1.1 Criteria

End point type	Secondary

End point timeframe:

18 months

Notes:

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Number				
median (full range (min-max))				
Pazo + Pembro (N=6) RECIST 1.1 criteria	0.20 (0.01 to 0.72)			
Pembrolizumab (N=4) RECIST 1.1 criteria	0.50 (0.16 to 1.00)			
Pazopanib (N=11) RECIST 1.1 criteria	1.00 (0.72 to 1.00)			
Pazo + Pembro (N=6) modified RECIST 1.1 criteria	0.20 (0.01 to 0.72)			
Pembrolizumab (N=4)modified RECIST 1.1 criteria	0.50 (0.16 to 1.00)			
Pazopanib (N=11) modified RECIST 1.1 criteria	1.00 (0.72 to 1.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response in Months for Cohorts A and B (RECIST 1.1 Criteria)

End point title	Time to response in Months for Cohorts A and B (RECIST 1.1 Criteria)[18]

End point description:

Time to response is defined for all subjects with a confirmed Complete Response (CR) or Partial Response (PR) as per RECIST v1.1v as the time from randomization until the first documented evidence of CR or PR (whichever status is recorded first)

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

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

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number				
median (full range (min-max))	2.8 (2.6 to 2.8)	2.7 (2.6 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response in Months for Cohort C (RECIST 1.1 Criteria)

End point title	Time to Response in Months for Cohort C (RECIST 1.1

End point description:

Time to response is defined for all subjects with a confirmed Complete Response (CR) or Partial Response (PR) as per RECIST v1.1v as the time from randomization until the first documented evidence of CR or PR (whichever status is recorded first)

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number				
median (full range (min-max))				
Pazo + Pembro (n=2)	1.6 (1.6 to 1.6)			
Pembrolizumab (n=1)	1.6 (1.6 to 1.6)			
Pazopanib (n=0)	0.0 (0.0 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response in months for Cohorts A and B (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)

End point title	Duration of response in months for Cohorts A and B (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)[20]

End point description:

Duration of response is defined for all subjects with confirmed Complete Response (CR) or Partial Response (PR) as the time from the first documented evidence of CR or PR until time of first documented disease progression or death due to any causes, whichever is first by RECIST v1.1 and modified RECIST

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis not performed for this endpoint.

End point values	Part 1: Cohort A	Part 1: Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	2		
Units: Number				
median (full range (min-max))	20.6 (10.8 to 26.3)	29.3 (19.6 to 38.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Months for Cohort C (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)

End point title	Duration of Response in Months for Cohort C (RECIST 1.1 Criteria/modified RECIST 1.1 Criteria)[21]

End point description:

Duration of response is defined for all subjects with confirmed Complete Response (CR) or Partial Response (PR) as the time from the first documented evidence of CR or PR until time of first documented disease progression or death due to any causes, whichever is first by RECIST v1.1 and modified RECIST

End point type	Secondary

End point timeframe:

Average of 4 years

Notes:

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

End point values	Part 1: Cohort C			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number				
median (full range (min-max))				
Pazo + Pembro (n=2)	19.5 (14.5 to 24.4)			
Pembrolizumab (n=1)	28.4 (28.4 to 28.4)			
Pazopanib (n=0)	0.0 (0.0 to 0.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to approximately maximum duration of 5 years, 2 months.

Adverse event reporting additional description:

Any sign or symptom that occurs during the study treatment plus the 30 days post treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Cohort A

Reporting group description:

Cohort A

Reporting group title	Cohort B

Reporting group description:

Cohort B

Reporting group title	Cohort C

Reporting group description:

Cohort C

Serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	6 / 10 (60.00%)	7 / 21 (33.33%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 10 (30.00%)	4 / 10 (40.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	3 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (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
Lipase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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
Liver function test increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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 failure congestive			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Tubulointerstitial nephritis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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			
Flank pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (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	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (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

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

Non-serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	21 / 21 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Hot flush			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Hypertension			

subjects affected / exposed	3 / 10 (30.00%)	8 / 10 (80.00%)	10 / 21 (47.62%)
occurrences (all)	4	11	14
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	3 / 21 (14.29%)
occurrences (all)	0	3	4
Fatigue			
subjects affected / exposed	4 / 10 (40.00%)	6 / 10 (60.00%)	12 / 21 (57.14%)
occurrences (all)	4	8	14
Feeling jittery			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Ill-defined disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Mucosal inflammation			
subjects affected / exposed	4 / 10 (40.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	6	1	2
Non-cardiac chest pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Pain			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	3 / 21 (14.29%)
occurrences (all)	0	4	3
Temperature intolerance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pelvic discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	5 / 21 (23.81%)
occurrences (all)	4	4	6
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	5 / 21 (23.81%)
occurrences (all)	3	2	6
Dyspnoea exertional			
subjects affected / exposed	4 / 10 (40.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	4	1	0
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Nasal congestion			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Oropharyngeal pain			
subjects affected / exposed	3 / 10 (30.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	3	1	2
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pneumonitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	3
Productive cough			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	6 / 10 (60.00%)	7 / 10 (70.00%)	10 / 21 (47.62%)
occurrences (all)	10	10	13
Amylase increased			
subjects affected / exposed	3 / 10 (30.00%)	2 / 10 (20.00%)	3 / 21 (14.29%)
occurrences (all)	4	3	5
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 10 (70.00%)	7 / 10 (70.00%)	9 / 21 (42.86%)
occurrences (all)	11	11	12
Bilirubin conjugated increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 10 (30.00%)	1 / 10 (10.00%)	9 / 21 (42.86%)
occurrences (all)	3	1	9
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Blood phosphorus decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Body temperature increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Haemoglobin decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Lipase increased			

subjects affected / exposed	6 / 10 (60.00%)	4 / 10 (40.00%)	5 / 21 (23.81%)
occurrences (all)	13	7	5
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Rib fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Balance disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	2 / 21 (9.52%)
occurrences (all)	1	2	2
Dysgeusia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	9 / 21 (42.86%)
occurrences (all)	2	3	10
Headache			

subjects affected / exposed	6 / 10 (60.00%)	4 / 10 (40.00%)	5 / 21 (23.81%)
occurrences (all)	6	6	5
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Neuropathy peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	3
Sciatica			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Speech disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Spinal cord compression			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Eye disorders			

Eye pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Ocular discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Photopsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Vitreous floaters			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Abdominal distension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	2 / 21 (9.52%)
occurrences (all)	2	3	2
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	4 / 21 (19.05%)
occurrences (all)	2	5	4
Diarrhoea			
subjects affected / exposed	6 / 10 (60.00%)	8 / 10 (80.00%)	16 / 21 (76.19%)
occurrences (all)	10	11	26
Dry mouth			

subjects affected / exposed	0 / 10 (0.00%)	4 / 10 (40.00%)	3 / 21 (14.29%)
occurrences (all)	0	4	3
Dyspepsia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Flatulence			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	1	1	3
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	3
Haemorrhoids			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Mouth ulceration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	6 / 10 (60.00%)	3 / 10 (30.00%)	12 / 21 (57.14%)
occurrences (all)	7	4	17
Oral pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Pancreatitis acute			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	0	1	4
Toothache			

subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	1 / 10 (10.00%)	9 / 21 (42.86%)
occurrences (all)	8	3	9
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	0 / 21 (0.00%)
occurrences (all)	1	3	0
Erythema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Hair colour changes			
subjects affected / exposed	1 / 10 (10.00%)	4 / 10 (40.00%)	4 / 21 (19.05%)
occurrences (all)	1	4	4
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	0	1	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	4
Photosensitivity reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pruritus			

subjects affected / exposed	4 / 10 (40.00%)	4 / 10 (40.00%)	3 / 21 (14.29%)
occurrences (all)	5	5	4
Pruritus generalised			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 10 (20.00%)	5 / 10 (50.00%)	3 / 21 (14.29%)
occurrences (all)	2	7	3
Rash macular			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	1 / 21 (4.76%)
occurrences (all)	0	3	1
Skin depigmentation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Skin hypopigmentation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Hypothyroidism			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	3 / 21 (14.29%)
occurrences (all)	3	4	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 10 (60.00%)	4 / 10 (40.00%)	2 / 21 (9.52%)
occurrences (all)	6	6	3
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	3 / 21 (14.29%)
occurrences (all)	0	2	3
Bone pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	2
Limb discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Musculoskeletal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Myalgia			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Osteonecrosis of jaw			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	4 / 10 (40.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	6	2	2
Plantar fasciitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Diverticulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Oral candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Sinusitis			
subjects affected / exposed	3 / 10 (30.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Tooth infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Upper respiratory tract infection			
subjects affected / exposed	4 / 10 (40.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	8	4	2
Urinary tract infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	2	1	3
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	8 / 21 (38.10%)
occurrences (all)	0	3	9
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	3
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 10 (20.00%)	2 / 21 (9.52%)
occurrences (all)	3	2	2
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	4
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Hypophosphataemia			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2018	Final Protocol Amendment 6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported