



## 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
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##### 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
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<b>Arm title</b>	Part 1: Cohort A
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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

<b>Arm title</b>	Part 1: Cohort B
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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	
<b>Arm title</b>	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

<b>Number of subjects in period 1</b>	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 <sup>[1][2]</sup>
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 <sup>[3][4]</sup>
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) <sup>[5]</sup>
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.

<b>End point values</b>	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 <sup>[6]</sup>			
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.

<b>End point values</b>	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 <sup>[7]</sup>	0 <sup>[8]</sup>	0 <sup>[9]</sup>	
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 <sup>[10]</sup>			
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.

<b>End point values</b>	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 <sup>[11]</sup>
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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<sup>[12]</sup>

End point description:

Area under the plasma concentration-time curve from time 0 to 24 hrs (AUC[0-24]), maximum observed concentration (C<sub>max</sub>), t<sub>max</sub>, and concentration at 24 hours (C<sub>24</sub>) 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))				
AUC <sub>0-24h</sub> (h*ng/mL): Week 4	999 (999 to 999)			
C <sub>max</sub> (ng/mL): Week 4	48300 (10500 to 78900)			
T <sub>max</sub> (h) : Week 4	3 (1.83 to 6.02)			
AUC <sub>last</sub> (h*ng/mL) Week 4	846000 (185000 to 1520000)			
C <sub>trough</sub> (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<sup>[13]</sup>

End point description:

Area under the plasma concentration-time curve from time 0 to 24 hrs (AUC[0-24]), maximum observed concentration C<sub>max</sub>, t<sub>max</sub>, and concentration at 24 hours (C<sub>24</sub>) of pazopanib; Pre-dose (trough) concentration at the end of the dosing interval/AUC<sub>last</sub>

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.

<b>End point values</b>	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) <sup>[14]</sup>
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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
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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.

<b>End point values</b>	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) <sup>[15]</sup>
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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
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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.

<b>End point values</b>	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) <sup>[16]</sup>
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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
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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) <sup>[17]</sup>
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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
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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.

<b>End point values</b>	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) <sup>[18]</sup>
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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
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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.

<b>End point values</b>	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)
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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
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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) <sup>[20]</sup>
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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
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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.

<b>End point values</b>	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) <sup>[21]</sup>
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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
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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.

<b>End point values</b>	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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	Cohort A
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Reporting group description:

Cohort A

Reporting group title	Cohort B
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Reporting group description:

Cohort B

Reporting group title	Cohort C
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Reporting group description:

Cohort C

<b>Serious adverse events</b>	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
<b>Nausea</b>			
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
<b>Vomiting</b>			
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
<b>Hepatobiliary disorders</b>			
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
<b>Respiratory, thoracic and mediastinal disorders</b>			
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
<b>Psychiatric disorders</b>			
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
<b>Renal and urinary disorders</b>			
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
<b>Musculoskeletal and connective tissue disorders</b>			
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
<b>Metabolism and nutrition disorders</b>			
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 %

<b>Non-serious adverse events</b>	Cohort A	Cohort B	Cohort C
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	21 / 21 (100.00%)
<b>Vascular disorders</b>			
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 occurrences (all)	3 / 10 (30.00%) 4	8 / 10 (80.00%) 11	10 / 21 (47.62%) 14
General disorders and administration site conditions			
Chills			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 10 (30.00%) 3	3 / 21 (14.29%) 4
Fatigue			
subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 4	6 / 10 (60.00%) 8	12 / 21 (57.14%) 14
Feeling jittery			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Ill-defined disorder			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Influenza like illness			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
Malaise			
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	1 / 21 (4.76%) 1
Mucosal inflammation			
subjects affected / exposed occurrences (all)	4 / 10 (40.00%) 6	1 / 10 (10.00%) 1	2 / 21 (9.52%) 2
Non-cardiac chest pain			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
Oedema			
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
Oedema peripheral			
subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 10 (10.00%) 1	2 / 21 (9.52%) 2
Pain			

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

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	2 / 21 (9.52%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	1 / 10 (10.00%) 1	1 / 21 (4.76%) 2
Paranasal sinus hypersecretion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Pneumonitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	2 / 21 (9.52%) 3
Productive cough subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	1 / 21 (4.76%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Sinus congestion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	1 / 21 (4.76%) 1
Psychiatric disorders			
Confusional state subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 10 (20.00%) 2	1 / 21 (4.76%) 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 occurrences (all)	6 / 10 (60.00%) 13	4 / 10 (40.00%) 7	5 / 21 (23.81%) 5
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 10 (0.00%) 0	2 / 21 (9.52%) 2
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 10 (0.00%) 0	2 / 21 (9.52%) 3
<b>Injury, poisoning and procedural complications</b>			
Contusion subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 10 (20.00%) 2	0 / 21 (0.00%) 0
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
<b>Nervous system disorders</b>			
Aphasia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Balance disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 10 (20.00%) 2	2 / 21 (9.52%) 2
Dysgeusia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	3 / 10 (30.00%) 3	9 / 21 (42.86%) 10
Headache			

subjects affected / exposed occurrences (all)	6 / 10 (60.00%) 6	4 / 10 (40.00%) 6	5 / 21 (23.81%) 5
Lethargy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 10 (0.00%) 0	3 / 21 (14.29%) 3
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	1 / 21 (4.76%) 3
Sciatica subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Sinus headache subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Speech disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	0 / 21 (0.00%) 0
Spinal cord compression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	1 / 21 (4.76%) 2
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 10 (0.00%) 0	3 / 21 (14.29%) 3
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 10 (0.00%) 0	0 / 21 (0.00%) 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 occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	5 / 10 (50.00%) 8	1 / 10 (10.00%) 3	9 / 21 (42.86%) 9
<b>Skin and subcutaneous tissue disorders</b>			
Actinic keratosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Alopecia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
Dermatitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Dry skin subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 10 (30.00%) 3	0 / 21 (0.00%) 0
Erythema subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	1 / 21 (4.76%) 1
Hair colour changes subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	4 / 10 (40.00%) 4	4 / 21 (19.05%) 4
Night sweats subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	3 / 21 (14.29%) 3
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	3 / 21 (14.29%) 4
Photosensitivity reaction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0
Pruritus			

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

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

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

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported