Clinical trial results:
A Phase 1/2, Open-Label, Multiple Ascending Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN2034 in Patients With Metastatic or Locally Advanced Solid Tumors, With Expansion to Second-Line Cervical Cancer

Summary

EudraCT number	2017-000556-26
Trial protocol	FR EE ES BE LT PL
Global end of trial date	15 June 2022

Results information

Result version number	v1 (current)
This version publication date	30 June 2023
First version publication date	30 June 2023

Trial information

Trial identification

Sponsor protocol code	C-700-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03104699
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Agenus, Inc.
Sponsor organisation address	3 Forbes Road, Lexington, MA, United States, 02421
Public contact	Amy Cohen, Agenus, Inc., 1 781.674.4615, AGEN2034@agenusbio.com
Scientific contact	Amy Cohen, Agenus, Inc., 1 781.674.4615, AGEN2034@agenusbio.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	15 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to assess the safety and tolerability of balstilimab (AGEN2034), determine the maximum tolerated dose of balstilimab in participants with metastatic or locally advanced solid tumours (Phase 1 safety cohort), and to assess the best overall response (BOR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in participants with recurrent, unresectable, or metastatic cervical cancer that had progressed after a platinum doublet administered for treatment of advanced disease (Phase 2 efficacy expansion cohort).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 65
Country: Number of subjects enrolled	Brazil: 21
Country: Number of subjects enrolled	Chile: 19
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 81
Worldwide total number of subjects	211
EEA total number of subjects	102

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)	154
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

For Phase 1 results, at the time of data cut off, 2 participants who completed 24 months of treatment were ongoing in follow up. Phase 1 subject disposition will be updated as soon as data becomes available.

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	Phase 1: Dose 1

Arm description:

Participants received 1 milligram/kilogram every 2 weeks balstilimab for up to 24 months.

Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.

Arm title	Phase 1: Dose 2

Arm description:

Participants received 3 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.

Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.

Arm title	Phase 1: Dose 3

Arm description:

Participants received 6 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.

Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.

Arm title	Phase 1: Dose 4
Arm description:	
Participants received 10 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.	
Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.	

Arm title	Phase 1: Dose 5
Arm description:	
Participants received 10 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.	
Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.	

Arm title	Phase 2: Recommended Phase 2 Dose
Arm description:	
Participants received 3 milligrams/kilogram every 2 weeks balstilimab for a maximum of 24 months or until progression, unacceptable toxicity, stopping the study drug, or withdrawal from the study.	
Arm type	Experimental
Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Balstilimab infusions were administered within 60 minutes (-10/+20 minutes) using an infusion pump.	

Number of subjects in period 1	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3
Started	10	10	10
Received at Least 1 Dose of Study Drug	10	10	10
Completed	0	0	0
Not completed	10	10	10
Consent withdrawn by subject	2	2	4
Physician decision	-	-	2
Death	6	3	-
Participant left to participate in another trial	-	-	-
Administrative study closure	-	-	-

Completed Follow Up	2	2	1
Lost to follow-up	-	1	1
Progressive disease	-	-	-
Still in study	-	-	2
Disease Progression	-	2	-
Protocol deviation	-	-	-

Number of subjects in period 1	Phase 1: Dose 4	Phase 1: Dose 5	Phase 2: Recommended Phase 2 Dose
Started	10	10	161
Received at Least 1 Dose of Study Drug	10	10	161
Completed	0	0	28
Not completed	10	10	133
Consent withdrawn by subject	8	4	6
Physician decision	1	-	-
Death	1	1	107
Participant left to participate in another trial	-	-	1
Administrative study closure	-	-	13
Completed Follow Up	-	2	-
Lost to follow-up	-	-	5
Progressive disease	-	1	1
Still in study	-	-	-
Disease Progression	-	-	-
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1: Dose 1
Reporting group description:	
Participants received 1 milligram/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 2
Reporting group description:	
Participants received 3 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 3
Reporting group description:	
Participants received 6 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 4
Reporting group description:	
Participants received 10 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 5
Reporting group description:	
Participants received 10 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 2: Recommended Phase 2 Dose
Reporting group description:	
Participants received 3 milligrams/kilogram every 2 weeks balstilimab for a maximum of 24 months or until progression, unacceptable toxicity, stopping the study drug, or withdrawal from the study.	

Reporting group values	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3
Number of subjects	10	10	10
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)	7	9	6
From 65-84 years	3	1	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	8	9
Male	2	2	1
Race Units: Subjects			
Asian	0	3	1
Black or African American	2	1	0
White	8	6	9
Not Reported (France)	0	0	0
Romanian	0	0	0
Mixed	0	0	0

Brown	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	9	10	8
Unknown	0	0	0
Not Reported	0	0	0

Reporting group values	Phase 1: Dose 4	Phase 1: Dose 5	Phase 2: Recommended Phase 2 Dose
Number of subjects	10	10	161
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)	7	6	119
From 65-84 years	3	4	42
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	9	8	161
Male	1	2	0
Race Units: Subjects			
Asian	1	1	1
Black or African American	0	0	2
White	9	9	72
Not Reported (France)	0	0	81
Romanian	0	0	1
Mixed	0	0	3
Brown	0	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	38
Not Hispanic or Latino	9	9	39
Unknown	0	0	82
Not Reported	0	0	2

Reporting group values	Total		
Number of subjects	211		
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)	154		
From 65-84 years	57		
85 years and over	0		
Gender categorical Units: Subjects			
Female	203		
Male	8		
Race Units: Subjects			
Asian	7		
Black or African American	5		
White	113		
Not Reported (France)	81		
Romanian	1		
Mixed	3		
Brown	1		
Ethnicity Units: Subjects			
Hispanic or Latino	43		
Not Hispanic or Latino	84		
Unknown	82		
Not Reported	2		

End points

End points reporting groups

Reporting group title	Phase 1: Dose 1
Reporting group description:	
Participants received 1 milligram/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 2
Reporting group description:	
Participants received 3 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 3
Reporting group description:	
Participants received 6 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 4
Reporting group description:	
Participants received 10 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 1: Dose 5
Reporting group description:	
Participants received 10 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.	
Reporting group title	Phase 2: Recommended Phase 2 Dose
Reporting group description:	
Participants received 3 milligrams/kilogram every 2 weeks balstilimab for a maximum of 24 months or until progression, unacceptable toxicity, stopping the study drug, or withdrawal from the study.	
Subject analysis set title	Phase 1: All
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants that received balstilimab for up to 24 months during Phase 1.	
Subject analysis set title	Intent-to-treat Efficacy Analysis Set (ITT EAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All participants who received ≥1 dose of study treatment, with measurable disease at baseline (per Independent Endpoint Review Committee [IERC]).	
Subject analysis set title	Dose-limiting Toxicity (DLT) Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who were enrolled for DLT evaluation (excluding participants enrolled to backfill cohorts) and either received all study treatment administrations or stopped treatment due to a DLT during the DLT evaluation period.	
Subject analysis set title	Receptor Occupancy Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who completed ≥1 infusion of study drug, with adequate measurements of programmed cell death protien-1 (PD-1) receptor occupancy on circulating T cells.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received ≥1 dose of study treatment.	
Subject analysis set title	Pharmacokinetic (PK) Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All participants who completed ≥1 infusion of study drug and who had sufficient evaluable drug concentration measurements prior to and after treatment.	

Primary: Phase 1: Number of Participants Experiencing DLTs for Balstilimab

End point title	Phase 1: Number of Participants Experiencing DLTs for Balstilimab[1]

End point description:

A DLT was defined as any treatment-related toxicity that was National Cancer Institute Common Terminology Criteria for Adverse Event Grade ≥3, confirmed by the safety monitoring committee to be relevant for the study drug treatment, and that occurred during the first 3 weeks of balstilimab treatment in the dose escalation portion of the study (DLT evaluation period).

End point type	Primary

End point timeframe:

21 Days

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: Only the number of participants is reported for this end point.

End point values	Dose-limiting Toxicity (DLT) Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Number of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)

End point title	Phase 1: Number of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)[2]

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product, which did not necessarily have a causal relationship with the treatment. TEAEs were AEs with onset dates during the on-treatment period, or the worsening of an event during the on-treatment period.

End point type	Primary

End point timeframe:

From the time of the first dose to the end of follow-up (up to 2 years after the last dose)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only the number of participants is reported for this end point.

End point values	Phase 1: All			
Subject group type	Subject analysis set			
Number of subjects analysed	50[3]			
Units: Participants	50			

Notes:

[3] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Objective Response Rate (ORR)

End point title	Phase 2: Objective Response Rate (ORR)[4][5]

End point description:

ORR was defined as proportion of participants with a BOR of complete response (CR) or partial response (PR), as determined by an IERC per RECIST 1.1.

End point type	Primary

End point timeframe:

Up to 4 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only percentage and confidence interval are reported for this end point.

[5] - 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: Only percentage and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[6]			
Units: Percentage of participants				
number (confidence interval 95%)	15.6 (10.8 to 22.0)			

Notes:

[6] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Receptor Occupancy of Circulating T Cells

End point title	Phase 1: Receptor Occupancy of Circulating T Cells

End point description:

The percentage of PD-1 receptor occupancy on circulating T cells was measured as an indication of target engagement.

End point type	Secondary

End point timeframe:

4 hours after the first dose (Cycle 1 Day 1) and immediately prior to the second dose (Cycle 2 Day 1)

End point values	Receptor Occupancy Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	18[7]			
Units: Percent occupancy				
arithmetic mean (standard deviation)				

Cycle 1 Day 1	72.7 (± 9.48)			
Cycle 2 Day 1	67.4 (± 13.89)			

Notes:

[7] - Cycle 1 Day 1 (N=18); Cycle 2 Day 1 (N=16)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Maximum Drug Concentration Observed Postdose (Cmax)

End point title	Phase 1: Maximum Drug Concentration Observed Postdose (Cmax)[8]

End point description:

Blood samples were collected for serum balstilimab concentration determinations. Results are reported as micrograms/millilitre (ug/mL).

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[8] - 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: Only the geometric mean and coefficient of variation are reported for the participants in Phase 1.

End point values	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3	Phase 1: Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[9]	9[10]	10[11]	10[12]
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	18.1 (± 34.3)	71.9 (± 19.5)	153 (± 23.7)	236 (± 26.6)
Cycle 2 Day 1	20.3 (± 47.0)	86.3 (± 30.0)	161 (± 27.5)	239 (± 28.2)

Notes:

[9] - PK Analysis Set

[10] - PK Analysis Set

[11] - PK Analysis Set; Cycle 1 Day 1 (N=10); Cycle 2 Day 1 (N=8)

[12] - PK Analysis Set; Cycle 1 Day 1 (N=9); Cycle 2 Day 1 (N=10)

End point values	Phase 1: Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	10[13]			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	282 (± 28.4)			
Cycle 2 Day 1	315 (± 25.5)			

Notes:

[13] - PK Analysis Set; Cycle 1 Day 1 (N=10); Cycle 2 Day 1 (N=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Area Under the Drug Concentration-time Curve from Time Zero to the Last Quantifiable Concentration (AUC0-last)

End point title	Phase 1: Area Under the Drug Concentration-time Curve from Time Zero to the Last Quantifiable Concentration (AUC0-last)[14]

End point description:

Blood samples were collected for serum balstilimab concentration determinations. Results are reported as hours*micrograms/millilitre (h*µg/mL).

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

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: Only the geometric mean and coefficient of variation are reported for the participants in Phase 1.

End point values	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3	Phase 1: Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[15]	9[16]	10[17]	10[18]
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	1265 (± 47.4)	6470 (± 34.6)	12632 (± 51.5)	22294 (± 47.5)
Cycle 2 Day 1	1477 (± 73.7)	7725 (± 40.2)	17479 (± 49.4)	21298 (± 47.1)

Notes:

[15] - PK Analysis Set

[16] - PK Analysis Set

[17] - PK Analysis Set; Cycle 1 Day 1 (N=10); Cycle 2 Day 1 (N=8)

[18] - PK Analysis Set; Cycle 1 Day 1 (N=9); Cycle 2 Day 1 (N=10)

End point values	Phase 1: Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	10[19]			
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	30751 (± 50.4)			
Cycle 2 Day 1	42266 (± 41.0)			

Notes:

[19] - PK Analysis Set; Cycle 1 Day 1 (N=10); Cycle 2 Day 1 (N=7)

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Number of Participants with Serum Anti-drug Antibodies (ADAs) for Balstilimab

End point title	Part 1: Number of Participants with Serum Anti-drug Antibodies (ADAs) for Balstilimab[20]

End point description:

Blood samples were collected for serum balstilimab ADA determination.

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

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: Only the number of participants is reported for the participants in Phase 1.

End point values	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3	Phase 1: Dose 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[21]	10[22]	10[23]	10[24]
Units: Participant	2	0	0	0

Notes:

[21] - Safety Analysis Set

[22] - Safety Analysis Set

[23] - Safety Analysis Set

[24] - Safety Analysis Set

End point values	Phase 1: Dose 5			
Subject group type	Reporting group			
Number of subjects analysed	10[25]			
Units: Participant	0			

Notes:

[25] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants Experiencing TEAEs

End point title	Phase 2: Number of Participants Experiencing TEAEs[26]

End point description:

An AE was any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product, which did not necessarily have a causal relationship with the treatment. TEAEs were AEs with onset dates during the on-treatment period, or the worsening of an event during the on-treatment period.

End point type	Secondary

End point timeframe:

From the time of the first dose to the end of follow-up (up to 2 years after the last dose)

Notes:

[26] - 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: Only the number of participants is reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	161[27]			
Units: Participant	161			

Notes:

[27] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Maximum Drug Concentration Observed Postdose (Cmax)

End point title	Phase 2: Maximum Drug Concentration Observed Postdose (Cmax)[28]

End point description:

Blood samples were collected for serum balstilimab concentration determinations. Results are reported in µg/mL.

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[28] - 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: Only the geometric mean and coefficient of variation are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	124[29]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	55.4 (± 42.8)			
Cycle 2 Day 1	56.6 (± 23.9)			

Notes:

[29] - Cycle 1 Day 1 (N=124); Cycle 2 Day 1 (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Area Under the Drug Concentration-time Curve from Time Zero to the Last Quantifiable Concentration (AUC0-last)

End point title	Phase 2: Area Under the Drug Concentration-time Curve from Time Zero to the Last Quantifiable Concentration (AUC0-last)[30]

End point description:

Blood samples were collected for serum balstilimab concentration determinations. Results are reported in day*µg/mL.

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[30] - 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: Only the geometric mean and coefficient of variation are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	124[31]			
Units: day*µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	174 (± 46.3)			
Cycle 2 Day 1	184 (± 59.7)			

Notes:

[31] - Cycle 1 Day 1 (N=124); Cycle 2 Day 1 (N=28)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants with Serum ADAs for Balstilimab

End point title	Phase 2: Number of Participants with Serum ADAs for Balstilimab[32]

End point description:

Blood samples were collected for serum balstilimab ADA determination.

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[32] - 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: Only the number of participants is reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	161[33]			
Units: Participant	8			

Notes:

[33] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: ORR

End point title	Phase 2: ORR[34]

End point description:

ORR was defined as proportion of participants with a BOR of CR or PR, as determined by an IERC per RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[34] - 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: Only percentage and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[35]			
Units: Percentage of participants				
number (confidence interval 95%)	14.4 (9.8 to 20.6)			

Notes:

[35] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR)[36]

End point description:

DOR was defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumour assessment), per RECIST 1.1 and as determined by an IERC and the investigator. Participants without an event at analysis cutoff date were censored on date of last tumour assessment. Percentile (25th) is reported with 95% confidence interval.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[36] - 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: Only the 25th percentile and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[37]			
Units: Month				
number (confidence interval 95%)	6.9 (2.8 to 11.0)			

Notes:

[37] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Disease Control Rate (DCR)

End point title	Phase 2: Disease Control Rate (DCR)[38]

End point description:

DCR was defined as the proportion of participants with CR, PR, or stable disease (SD) for at least 12 weeks.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[38] - 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: Only percentage and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[39]			
Units: Percentage of participants				
number (confidence interval 95%)	50.6 (43.0 to 58.3)			

Notes:

[39] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Tumour Control Rate (TCR)

End point title	Phase 2: Tumour Control Rate (TCR)[40]

End point description:

TCR was defined as proportion of participants who had a BOR of either SD or a confirmed objective response (CR or PR).

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[40] - 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: Only percentage and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[41]			
Units: Percentage of participants				
number (confidence interval 95%)	52.5 (44.8 to 60.1)			

Notes:

[41] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Response (TTR)

End point title	Phase 2: Time to Response (TTR)[42]

End point description:

TTR was defined as the time from the first dose date to first observation of confirmed response.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[42] - 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: Only the mean and standard deviation are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	25[43]			
Units: Day				
arithmetic mean (standard deviation)	84.4 (± 58.03)			

Notes:

[43] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS)[44]

End point description:

PFS was defined as time from first treatment administration to first observation of documented disease progression (or death within 12 weeks after last tumour assessment), per RECIST 1.1, as determined by an IERC and investigator. Participants without an event at analysis cutoff date were censored on date of last tumour assessment.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[44] - 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: Only the median and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	160[45]			
Units: Month				
median (confidence interval 95%)	2.8 (2.4 to 3.9)			

Notes:

[45] - ITT EAS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)[46]

End point description:

OS was defined as time from start of treatment to death. For participants who were still alive at the time of data cutoff for trial analysis or who were lost to follow-up, survival was censored at the last recorded date that the participant was known to have been alive as of the cutoff date for analysis.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[46] - 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: Only the median and confidence interval are reported for the participants in Phase 2.

End point values	Phase 2: Recommended Phase 2 Dose			
Subject group type	Reporting group			
Number of subjects analysed	161[47]			
Units: Month				
median (confidence interval 95%)	11.2 (9.6 to 14.6)			

Notes:

[47] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 years

Adverse event reporting additional description:

Phase 1 Non-serious Adverse Events: The number '0' is used strictly as a placeholder as the comprehensive Phase 1 data for non-serious adverse events are currently unavailable. The Phase 1 non-serious adverse events will be updated accordingly as soon as the data become available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Phase 1: Dose 1

Reporting group description:

Participants received 1 milligram/kilogram every 2 weeks balstilimab for up to 24 months.

Reporting group title	Phase 1: Dose 2

Reporting group description:

Participants received 3 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.

Reporting group title	Phase 1: Dose 3

Reporting group description:

Participants received 6 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.

Reporting group title	Phase 1: Dose 4

Reporting group description:

Participants received 10 milligrams/kilogram every 2 weeks balstilimab for up to 24 months.

Reporting group title	Phase 1: Dose 5

Reporting group description:

Participants received 10 milligrams/kilogram every 3 weeks balstilimab for up to 24 months.

Reporting group title	Phase 2: Recommended Phase 2 Dose

Reporting group description:

Participants received 3 milligrams/kilogram every 2 weeks balstilimab for a maximum of 24 months or until progression, unacceptable toxicity, stopping the study drug, or withdrawal from the study.

Serious adverse events	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	3 / 10 (30.00%)	5 / 10 (50.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to spine			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypertensive crisis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed[1]	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed[2]	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix haemorrhage uterine			
subjects affected / exposed[3]	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Aortic injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cystitis radiation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 10 (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
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 10 (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

Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper GI haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 10 (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	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
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%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	0 / 10 (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
Hepatitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Biliary dilatation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated nephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital fistula			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia of malignancy			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 10 (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
Corona virus infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arboviral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia pyelonephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 1: Dose 4	Phase 1: Dose 5	Phase 2: Recommended Phase 2 Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	2 / 10 (20.00%)	90 / 161 (55.90%)
number of deaths (all causes)	0	0	15
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 161 (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
Tumour associated fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	5 / 161 (3.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed[1]	0 / 9 (0.00%)	0 / 8 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed[2]	0 / 9 (0.00%)	0 / 8 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Cervix haemorrhage uterine			
subjects affected / exposed[3]	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	0 / 161 (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
Acute respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 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%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical condition abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Aortic injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis radiation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper GI haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	7 / 161 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	5 / 161 (3.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intra-abdominal haemorrhage			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 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 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dilatation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	6 / 161 (3.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated nephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postrenal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oliguria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urogenital fistula			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impetigo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 161 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	4 / 161 (2.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	3 / 161 (1.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arboviral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia pyelonephritis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	2 / 161 (1.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	1 / 161 (0.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This serious adverse event only affected female participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This serious adverse event only affected female participants.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This serious adverse event only affected female participants.

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

Non-serious adverse events	Phase 1: Dose 1	Phase 1: Dose 2	Phase 1: Dose 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed[4]	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed[5]	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immune-mediated hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase 1: Dose 4	Phase 1: Dose 5	Phase 2: Recommended Phase 2 Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	160 / 161 (99.38%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	11
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	56 / 161 (34.78%)
occurrences (all)	0	0	105
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	37 / 161 (22.98%)
occurrences (all)	0	0	70
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	35 / 161 (21.74%)
occurrences (all)	0	0	48
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	21 / 161 (13.04%)
occurrences (all)	0	0	28
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed[4]	0 / 9 (0.00%)	0 / 8 (0.00%)	25 / 161 (15.53%)
occurrences (all)	0	0	30
Vaginal haemorrhage			

subjects affected / exposed[5]	0 / 9 (0.00%)	0 / 8 (0.00%)	16 / 161 (9.94%)
occurrences (all)	0	0	19
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	31 / 161 (19.25%)
occurrences (all)	0	0	38
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	23 / 161 (14.29%)
occurrences (all)	0	0	27
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	16 / 161 (9.94%)
occurrences (all)	0	0	18
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	15 / 161 (9.32%)
occurrences (all)	0	0	17
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	17 / 161 (10.56%)
occurrences (all)	0	0	30
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	17 / 161 (10.56%)
occurrences (all)	0	0	26
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	17 / 161 (10.56%)
occurrences (all)	0	0	22
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	16 / 161 (9.94%)
occurrences (all)	0	0	29
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	16 / 161 (9.94%)
occurrences (all)	0	0	18
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	13 / 161 (8.07%)
occurrences (all)	0	0	19

Lipase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	12
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	26 / 161 (16.15%)
occurrences (all)	0	0	35
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	80 / 161 (49.69%)
occurrences (all)	0	0	230
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	13 / 161 (8.07%)
occurrences (all)	0	0	23
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	47 / 161 (29.19%)
occurrences (all)	0	0	65
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	45 / 161 (27.95%)
occurrences (all)	0	0	63
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	41 / 161 (25.47%)
occurrences (all)	0	0	66
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	38 / 161 (23.60%)
occurrences (all)	0	0	50
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	35 / 161 (21.74%)
occurrences (all)	0	0	57
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	11 / 161 (6.83%)
occurrences (all)	0	0	13
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	30 / 161 (18.63%)
occurrences (all)	0	0	46

Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	10 / 161 (6.21%)
occurrences (all)	0	0	11
Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	14
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	10 / 161 (6.21%)
occurrences (all)	0	0	11
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	16
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	11
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	11 / 161 (6.83%)
occurrences (all)	0	0	12
Immune-mediated hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	13
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	36 / 161 (22.36%)
occurrences (all)	0	0	48
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	22 / 161 (13.66%)
occurrences (all)	0	0	32
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	19 / 161 (11.80%)
occurrences (all)	0	0	22
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	14 / 161 (8.70%)
occurrences (all)	0	0	16

Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	12 / 161 (7.45%)
occurrences (all)	0	0	21
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	9 / 161 (5.59%)
occurrences (all)	0	0	10
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	35 / 161 (21.74%)
occurrences (all)	0	0	52
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	34 / 161 (21.12%)
occurrences (all)	0	0	40
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	19 / 161 (11.80%)
occurrences (all)	0	0	34
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	15 / 161 (9.32%)
occurrences (all)	0	0	15
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	13 / 161 (8.07%)
occurrences (all)	0	0	16
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 10 (0.00%)	10 / 161 (6.21%)
occurrences (all)	0	0	19

Notes:

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This non-serious adverse event only affected female participants.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This non-serious adverse event only affected female participants.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2017	- Addition of an expansion cohort in which approximately 40 participants with American Joint Committee on Cancer Stage IV cutaneous squamous cell carcinoma (cSCC) not curable by radiation therapy were to be enrolled. - Addition of an IDMC to monitor the cervical cancer and cSCC expansion cohorts. - Addition of a futility analysis (at >50% information fraction) to expansion cohorts in response to the request from Institutional Review Boards for futility analysis for cervical cancer cohort. - Removed assessment of immune-related RECIST as secondary endpoint. Assessment of tumour response was according to RECIST 1.1. - Removed continuation of treatment after a relapse following CR. - Requirement that participants enrolled in Phase 2 need to provide archival tumour tissue sample. - Added allowance for treatment beyond disease progression. - Added criteria for treatment delay and criteria to resume treatment. - Added specification for palliative radiation therapy as permitted for a single lesion provided it is not to a target lesion and treatment was not administered for tumour control.
24 January 2019	- Removed the Phase 2 expansion cohort for cSCC. This cohort was removed based on a company strategic decision to focus on the indication of cervical cancer based on the experience in the escalation phase data to date. No participants with cSCC were enrolled. - Reorganized and refined the study objectives and endpoints for Phase 1 versus Phase 2, to (1) be consistent with terminology and definitions for endpoints (for example best overall response versus objective response rate) based on Food and Drug Administration (FDA) guidelines, (2) clearly identify the objectives for Phase 1 versus Phase 2 of the study, and (3) clearly show which endpoints are associated with each objective. - Removed the futility analysis for efficacy endpoints in Phase 2 expansion cohorts. This change was made because the Phase 2 portion of the study was to include a full interim analysis by an IDMC to assess all available data and make a recommendation to the Sponsor, instead of having just a predefined study stop cut-off. - Added expanded electrocardiogram evaluation in Phase 2. This change was made in alignment with PK timepoints to enable an assessment of the effects of study drug on cardiac conduction. - Changed Study Title from “Expansion to Select Solid Tumors” to “Expansion to Cervical Cancer”. - Changed dose delay interval that resulted in treatment withdraw from more than 10 weeks to more than 6 weeks. - Changed timing of initial tumour imaging from within 18 days before first dose to within 21 days. - Added tumour PD-L1 expression was to be assessed using an FDA-approved test.
27 September 2019	- Phase 2 population increase, and post-interim analysis enrollment language clarified. - Statistical calculation changes based on population increase. - Clinical progression criteria defined to accommodate absence of radiologic progression on basis of RECIST 1.1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Comprehensive Phase 1 data for subject disposition and non-serious adverse events are currently unavailable. Both will be updated accordingly as soon as the data become available.

Notes: