Clinical trial results:
A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation Study of MGC018 (Anti–B7-H3 Antibody Drug Conjugate) Alone and in Combination with MGA012 (Anti–PD-1 Antibody) in Patients with Advanced Solid Tumors

Summary

EudraCT number	2018-003555-38
Trial protocol	PL ES
Global end of trial date	18 March 2023

Results information

Result version number	v1 (current)
This version publication date	07 December 2024
First version publication date	07 December 2024

Trial information

Trial identification

Sponsor protocol code	CP-MGC018-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03729596
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MacroGenics, Inc.
Sponsor organisation address	9704 Medical Center Drive, Rockville, MD, United States, 20850
Public contact	Global Trial Manager, MacroGenics, Inc., +1 3012515172, info@macrogenics.com
Scientific contact	Global Trial Manager, MacroGenics, Inc., +1 3012515172, info@macrogenics.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	08 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 March 2023
Global end of trial reached?	Yes
Global end of trial date	18 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD) (if no MTD is defined) for MGC018 administered as monotherapy or in combination with MGA012, each administered intravenously (IV), in participants who have relapsed/refractory, unresectable locally advanced or metastatic solid tumors.

Protection of trial subjects:

This study was conducted under United States Investigational New Drug application, in compliance with Good Clinical Practice, as well as all applicable local and national laws and regulations of countries in which the trial was performed. At each trial site, an institutional review board (IRB) or independent ethics committee (IEC) reviewed and approved the clinical trial protocol, the current and previous versions of the Investigator's Brochure, and informed consent form(s), as applicable. The IRB/IEC subsequently approved protocol amendments and revisions. Investigators were responsible for obtaining and documenting written informed consent from each participant or legal representative. Written informed consent was obtained for all participants before any protocol-specific procedures or interventions were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	143
EEA total number of subjects	48

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)	66
From 65 to 84 years	76
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 19 investigational sites in 4 countries.

Pre-assignment

Screening details:

Adult patients with metastatic or advanced solid tumors for who no approved therapy with demonstrated clinical benefit was available.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: 0.5 mg/kg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	vobramitamab duocarmazine
Investigational medicinal product code	
Other name	MGC018-01
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of 0.5 mg/kg every 3 weeks.

Arm title	Cohort 2: 1.0 mg/kg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	vobramitamab duocarmazine
Investigational medicinal product code	
Other name	MGC018-01
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of 1.0 mg/kg every 3 weeks.

Arm title	Cohort 3: 2.0 mg/kg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	vobramitamab duocarmazine
Investigational medicinal product code	
Other name	MGC018-01
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of 2.0 mg/kg every 3 weeks.

Arm title	Cohort 4: 3.0 mg/kg

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	vobramitamab duocarmazine
Investigational medicinal product code	
Other name	MGC018-01
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of 3.0 mg/kg every 3 weeks.

Arm title	Cohort 5: 4.0 mg/kg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	vobramitamab duocarmazine
Investigational medicinal product code	
Other name	MGC018-01
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion of 4.0 mg/kg every 3 weeks.

Number of subjects in period 1	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg
Started	3	6	7
Completed	0	0	0
Not completed	3	6	7
Consent withdrawn by subject	-	-	-
Death	3	5	4
Protocol amendment	-	1	3
Study terminated by sponsor	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Cohort 4: 3.0 mg/kg	Cohort 5: 4.0 mg/kg
Started	121	6
Completed	0	0
Not completed	121	6
Consent withdrawn by subject	4	1
Death	95	-
Protocol amendment	6	5
Study terminated by sponsor	14	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: 0.5 mg/kg
Reporting group description: -	
Reporting group title	Cohort 2: 1.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 3: 2.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 4: 3.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 5: 4.0 mg/kg
Reporting group description: -	

Reporting group values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg
Number of subjects	3	6	7
Age categorical Units: Subjects			
Adults (18-64 years)	3	4	3
From 65-84 years	0	2	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.3	56.5	64.0
standard deviation	± 12.42	± 11.98	± 11.72
Gender categorical Units: Subjects			
Female	1	4	2
Male	2	2	5

Reporting group values	Cohort 4: 3.0 mg/kg	Cohort 5: 4.0 mg/kg	Total
Number of subjects	121	6	143
Age categorical Units: Subjects			
Adults (18-64 years)	54	2	66
From 65-84 years	66	4	76
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	62.9	65.3	
standard deviation	± 12.22	± 8.09	-
Gender categorical Units: Subjects			
Female	40	1	48
Male	81	5	95

Subject analysis sets	
Subject analysis set title	Response Evaluable Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants who received at least 1 dose of study drug, had baseline measurable disease, and had at least one post-baseline radiographic tumor assessment.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received at least 1 dose of study drug.	
Subject analysis set title	Metastatic prostate cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with a diagnosis of metastatic prostate cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Non-small cell lung cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of non-small lung cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Triple negative breast cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of triple negative breast cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Melanoma population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of melanoma who have received at least 1 dose of MGC018.	
Subject analysis set title	Squamous cell carcinoma of the head and neck population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of squamous cell carcinoma of the head and neck who received at least 1 dose of MGC018.	

Reporting group values	Response Evaluable Population	Safety population	Metastatic prostate cancer population
Number of subjects	139	143	41
Age categorical Units: Subjects			
Adults (18-64 years)	63	66	8
From 65-84 years	75	76	33
85 years and over	1	1	0
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	45	48	0
Male	94	95	41

Reporting group values	Non-small cell lung cancer population	Triple negative breast cancer population	Melanoma population

Number of subjects	20	16	21
Age categorical Units: Subjects			
Adults (18-64 years)	11	14	8
From 65-84 years	9	2	12
85 years and over	0	0	1
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	11	16	5
Male	9	0	16

Reporting group values	Squamous cell carcinoma of the head and neck population		
Number of subjects	13		
Age categorical Units: Subjects			
Adults (18-64 years)	6		
From 65-84 years	7		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female	4		
Male	9		

End points

End points reporting groups

Reporting group title	Cohort 1: 0.5 mg/kg
Reporting group description: -	
Reporting group title	Cohort 2: 1.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 3: 2.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 4: 3.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 5: 4.0 mg/kg
Reporting group description: -	
Subject analysis set title	Response Evaluable Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All participants who received at least 1 dose of study drug, had baseline measurable disease, and had at least one post-baseline radiographic tumor assessment.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who received at least 1 dose of study drug.	
Subject analysis set title	Metastatic prostate cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with a diagnosis of metastatic prostate cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Non-small cell lung cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of non-small lung cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Triple negative breast cancer population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of triple negative breast cancer who have received at least 1 dose of MGC018.	
Subject analysis set title	Melanoma population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of melanoma who have received at least 1 dose of MGC018.	
Subject analysis set title	Squamous cell carcinoma of the head and neck population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with the diagnosis of squamous cell carcinoma of the head and neck who received at least 1 dose of MGC018.	

Primary: Type and number of adverse events

End point title	Type and number of adverse events[1]
End point description:	
End point type	Primary

End point timeframe:

Adverse events are recorded from the time of informed consent signature through 30 days of the last dose of study treatment.

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: Data displays were summary tables with the number and percent of participants who experience a given event. There is no active control or comparator to allow for statistical inferences.

End point values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg	Cohort 4: 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	7	121
Units: participants with adverse events				
Study treatment related adverse event	3	5	6	120
Severe adverse event	3	4	7	105
Severe treatment related adverse event	2	2	6	79
Study treatment related serious adverse event	1	1	2	40
Fatal adverse event	1	0	0	4

End point values	Cohort 5: 4.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants with adverse events				
Study treatment related adverse event	6			
Severe adverse event	5			
Severe treatment related adverse event	4			
Study treatment related serious adverse event	2			
Fatal adverse event	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

The percentage of patients who have a complete or partial response to study treatment.

End point type	Secondary

End point timeframe:

From the first dose of study treatment throughout the study

End point values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg	Cohort 4: 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	7	118
Units: percentage				
number (not applicable)	0	0	0	5.9

End point values	Cohort 5: 4.0 mg/kg	Response Evaluable Population	Metastatic prostate cancer population	Non-small cell lung cancer population
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	139		
Units: percentage				
number (not applicable)	20	5.8	4.9	15.0

End point values	Triple negative breast cancer population	Melanoma population	Squamous cell carcinoma of the head and neck population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed				
Units: percentage				
number (not applicable)	0	4.8	7.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic progression free survival in prostate cancer

End point title	Radiographic progression free survival in prostate cancer

End point description:

End point type	Secondary

End point timeframe:

From the first date of study treatment until first documented disease progression or death, whichever is earlier.

End point values	Metastatic prostate cancer population			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Months				
median (confidence interval 95%)	5.5 (2.92 to 8.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate specific antigen response rate

End point title	Prostate specific antigen response rate

End point description:

The number of patients with metastatic prostate cancer who have greater than or equal to a 50% decline in PSA, with confirmation of the decline at least 3 weeks later.

End point type	Secondary

End point timeframe:

From the date of first dose throughout the study.

End point values	Metastatic prostate cancer population			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: patients with PSA response	18			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of PSA response

End point title	Duration of PSA response

End point description:

End point type	Secondary

End point timeframe:

Throughout the study

End point values	Metastatic prostate cancer population			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: Months				
median (confidence interval 95%)	6.2 (3.22 to 9.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total exposure

End point title	Total exposure

End point description:

Data were obtained from 143 study subjects, with , doses of 0.5, 1, 2, 3, and 4 mg/kg were administered to, respectively, 3, 6, 8, 120, and 6 subjects

End point type	Secondary

End point timeframe:

Throughout the study from baseline through treatment discontinuation.

End point values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg	Cohort 4: 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	7	120
Units: mcg/mL*day				
arithmetic mean (standard deviation)				
Antibody drug conjugate	10.6 (± 6.54)	51.5 (± 19.2)	119 (± 48.7)	140 (± 34.9)
Duocarmycin	0.0448 (± 0.023)	0.101 (± 0.0668)	0.0512 (± 0.0454)	0.0657 (± 0.0349)

End point values	Cohort 5: 4.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mcg/mL*day				
arithmetic mean (standard deviation)				
Antibody drug conjugate	227 (± 105)			
Duocarmycin	0.268 (± 0.061)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: peak and trough concentrations

End point title	PK parameters: peak and trough concentrations

End point description:

End point type	Secondary

End point timeframe:

Throughout the study from baseline through treatment discontinuation.

End point values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg	Cohort 4: 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	7	121
Units: mcg/mL				
arithmetic mean (standard deviation)				
ADC maximum concentration	7.69 (± 1.98)	23.4 (± 0.0408)	43.4 (± 14)	59 (± 11)
ADC trough concentration	0.00928 (± 0.0129)	0.0415 (± 0.0415)	0.123 (± 0.652)	0.157 (± 0.119)
Duocarmycin maximum concentration	0.0243 (± 0.0225)	0.0274 (± 0.016)	0.0512 (± 0.0454)	0.657 (± 0.0349)
Duocarmycin trough concentration	0.000243 (± 0.000107)	0.00074 (± 0.000532)	0.00226 (± 0.00244)	0.00185 (± 0.000658)

End point values	Cohort 5: 4.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: mcg/mL				
arithmetic mean (standard deviation)				
ADC maximum concentration	78.6 (± 22.4)			
ADC trough concentration	0.313 (± 0.323)			
Duocarmycin maximum concentration	0.0571 (± 0.00757)			
Duocarmycin trough concentration	0.00194 (± 0.000973)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

End point type	Secondary

End point timeframe:

The time from the first documented complete or partial response to the first documented disease progression or death, whichever comes first.

End point values	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg	Cohort 4: 3.0 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	7
Units: Months				
number (not applicable)				
Minimum duration				1.41
Maximum duration				17.61

Notes:

[2] - There were no responses in this group.

[3] - There were no responses in this group.

[4] - There were no responses in this group.

End point values	Cohort 5: 4.0 mg/kg	Metastatic prostate cancer population	Non-small cell lung cancer population	Triple negative breast cancer population
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	41	20	0[5]
Units: Months				
number (not applicable)				
Minimum duration	5.32	4.27	1.14	
Maximum duration	5.32	6.28	17.61	

Notes:

[5] - There were no clinical responses in this group.

End point values	Melanoma population	Squamous cell carcinoma of the head and neck population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	13		
Units: Months				
number (not applicable)				
Minimum duration	10.28	2.10		
Maximum duration	10.28	2.10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of first dose through 30 days after the last dose, average 6 months. All-cause mortality was collected from the first dose until the primary completion date, average 2 years.

Adverse event reporting additional description:

AEs are based on physical exam, patient reports, and significant abnormal laboratory values. AEs were not collected in survival follow up. Only SAEs were collected in survival follow up if related to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Cohort 1: 0.5 mg/kg
Reporting group description: -	
Reporting group title	Cohort 2: 1.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 3: 2.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 4: 3.0 mg/kg
Reporting group description: -	
Reporting group title	Cohort 5: 4.0 mg/kg

Reporting group description: -

Serious adverse events	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	3 / 7 (42.86%)
number of deaths (all causes)	3	5	4
number of deaths resulting from adverse events	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Face oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Dyspnoea exertional			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Neutrophil count decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Fall			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Cardiac arrest			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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

Angina pectoris			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Supraventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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

Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Pancytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Duodenal ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Enterovesical fistula			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 inflammation			

subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
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			
Hepatic failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Haematinuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
COVID-19			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 bacterial			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 7 (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
Sepsis pasteurella			
subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Arthritis infective			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Catheter site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Coronavirus infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 simplex			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 aspiration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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 tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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
Subdural haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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			
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (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	Cohort 4: 3.0 mg/kg	Cohort 5: 4.0 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 121 (42.98%)	2 / 6 (33.33%)	
number of deaths (all causes)	95	0	
number of deaths resulting from adverse events	4	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 121 (3.31%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 121 (4.13%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	4 / 121 (3.31%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Supraventricular extrasystoles			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 121 (4.13%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 121 (2.48%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 121 (3.31%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 121 (2.48%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 121 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 121 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 121 (2.48%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematinuria			
subjects affected / exposed	1 / 121 (0.83%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 121 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis pasteurella			
subjects affected / exposed	0 / 121 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 121 (2.48%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 121 (1.65%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 121 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 121 (0.83%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: 0.5 mg/kg	Cohort 2: 1.0 mg/kg	Cohort 3: 2.0 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	6 / 6 (100.00%)	7 / 7 (100.00%)
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	3 / 6 (50.00%)	2 / 7 (28.57%)
occurrences (all)	0	4	2
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	1	2	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Pyrexia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	3	3
Platelet count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	3

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	3 / 6 (50.00%)	2 / 7 (28.57%)
occurrences (all)	1	4	2
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	3 / 7 (42.86%)
occurrences (all)	0	0	3
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Skin hyperpigmentation			

subjects affected / exposed	0 / 3 (0.00%)	3 / 6 (50.00%)	1 / 7 (14.29%)
occurrences (all)	0	3	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 3 (66.67%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Dehydration			
subjects affected / exposed	2 / 3 (66.67%)	3 / 6 (50.00%)	0 / 7 (0.00%)
occurrences (all)	3	3	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	1	1

Non-serious adverse events	Cohort 4: 3.0 mg/kg	Cohort 5: 4.0 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 121 (100.00%)	6 / 6 (100.00%)	

General disorders and administration site conditions			
Nausea			
subjects affected / exposed	42 / 121 (34.71%)	3 / 6 (50.00%)	
occurrences (all)	50	4	
Asthenia			
subjects affected / exposed	20 / 121 (16.53%)	0 / 6 (0.00%)	
occurrences (all)	30	0	
Chills			
subjects affected / exposed	7 / 121 (5.79%)	2 / 6 (33.33%)	
occurrences (all)	7	2	
Fatigue			
subjects affected / exposed	61 / 121 (50.41%)	3 / 6 (50.00%)	
occurrences (all)	75	4	
Non-cardiac chest pain			
subjects affected / exposed	9 / 121 (7.44%)	1 / 6 (16.67%)	
occurrences (all)	9	1	
Oedema peripheral			
subjects affected / exposed	35 / 121 (28.93%)	0 / 6 (0.00%)	
occurrences (all)	47	0	
Pyrexia			
subjects affected / exposed	12 / 121 (9.92%)	4 / 6 (66.67%)	
occurrences (all)	12	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 121 (14.05%)	0 / 6 (0.00%)	
occurrences (all)	17	0	
Dyspnoea			
subjects affected / exposed	25 / 121 (20.66%)	1 / 6 (16.67%)	
occurrences (all)	25	3	
Pleural effusion			
subjects affected / exposed	35 / 121 (28.93%)	1 / 6 (16.67%)	
occurrences (all)	38	1	
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	9 / 121 (7.44%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Lymphocyte count decreased			
subjects affected / exposed	17 / 121 (14.05%)	0 / 6 (0.00%)	
occurrences (all)	22	0	
Neutrophil count decreased			
subjects affected / exposed	25 / 121 (20.66%)	0 / 6 (0.00%)	
occurrences (all)	44	0	
Platelet count decreased			
subjects affected / exposed	16 / 121 (13.22%)	1 / 6 (16.67%)	
occurrences (all)	22	1	
Weight decreased			
subjects affected / exposed	19 / 121 (15.70%)	1 / 6 (16.67%)	
occurrences (all)	19	1	
White blood cell count decreased			
subjects affected / exposed	16 / 121 (13.22%)	1 / 6 (16.67%)	
occurrences (all)	18	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	17 / 121 (14.05%)	2 / 6 (33.33%)	
occurrences (all)	29	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 121 (4.96%)	1 / 6 (16.67%)	
occurrences (all)	9	1	
Pericardial effusion			
subjects affected / exposed	15 / 121 (12.40%)	1 / 6 (16.67%)	
occurrences (all)	15	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	8 / 121 (6.61%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Headache			
subjects affected / exposed	25 / 121 (20.66%)	1 / 6 (16.67%)	
occurrences (all)	29	1	
Neuropathy peripheral			

subjects affected / exposed	8 / 121 (6.61%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	37 / 121 (30.58%)	2 / 6 (33.33%)	
occurrences (all)	48	2	
Neutropenia			
subjects affected / exposed	43 / 121 (35.54%)	3 / 6 (50.00%)	
occurrences (all)	69	3	
Thrombocytopenia			
subjects affected / exposed	17 / 121 (14.05%)	1 / 6 (16.67%)	
occurrences (all)	25	1	
Leukopenia			
subjects affected / exposed	8 / 121 (6.61%)	2 / 6 (33.33%)	
occurrences (all)	10	2	
Lymphopenia			
subjects affected / exposed	9 / 121 (7.44%)	1 / 6 (16.67%)	
occurrences (all)	9	1	
Eye disorders			
Dry eye			
subjects affected / exposed	12 / 121 (9.92%)	1 / 6 (16.67%)	
occurrences (all)	13	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 121 (4.96%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Abdominal pain upper			
subjects affected / exposed	5 / 121 (4.13%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Constipation			
subjects affected / exposed	22 / 121 (18.18%)	1 / 6 (16.67%)	
occurrences (all)	22	1	
Diarrhoea			
subjects affected / exposed	17 / 121 (14.05%)	3 / 6 (50.00%)	
occurrences (all)	21	3	
Dysphagia			

subjects affected / exposed	8 / 121 (6.61%)	0 / 6 (0.00%)	
occurrences (all)	12	0	
Stomatitis			
subjects affected / exposed	19 / 121 (15.70%)	1 / 6 (16.67%)	
occurrences (all)	21	1	
Vomiting			
subjects affected / exposed	19 / 121 (15.70%)	0 / 6 (0.00%)	
occurrences (all)	22	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 121 (9.92%)	0 / 6 (0.00%)	
occurrences (all)	12	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	50 / 121 (41.32%)	2 / 6 (33.33%)	
occurrences (all)	64	2	
Pruritus			
subjects affected / exposed	19 / 121 (15.70%)	0 / 6 (0.00%)	
occurrences (all)	25	0	
Rash			
subjects affected / exposed	20 / 121 (16.53%)	0 / 6 (0.00%)	
occurrences (all)	22	0	
Skin hyperpigmentation			
subjects affected / exposed	28 / 121 (23.14%)	2 / 6 (33.33%)	
occurrences (all)	28	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 121 (7.44%)	1 / 6 (16.67%)	
occurrences (all)	10	1	
Back pain			
subjects affected / exposed	10 / 121 (8.26%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Myalgia			
subjects affected / exposed	8 / 121 (6.61%)	2 / 6 (33.33%)	
occurrences (all)	8	3	
Pain in extremity			

subjects affected / exposed	6 / 121 (4.96%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	10 / 121 (8.26%)	0 / 6 (0.00%)	
occurrences (all)	12	0	
Urinary tract infection			
subjects affected / exposed	8 / 121 (6.61%)	1 / 6 (16.67%)	
occurrences (all)	9	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 121 (33.06%)	1 / 6 (16.67%)	
occurrences (all)	44	1	
Dehydration			
subjects affected / exposed	5 / 121 (4.13%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Hypokalaemia			
subjects affected / exposed	7 / 121 (5.79%)	2 / 6 (33.33%)	
occurrences (all)	9	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2018	Added safety measures: sentinel dosing for first 2 dose levels, Independent Safety Monitor oversight, revised definition of non-hematologic dose limiting toxicity, revised inclusion criteria, added cardiac monitoring, added ophthalmological examinations, and amylase and lipase monitoring.
26 February 2019	Modified entry criteria to require metastatic castration-resistant prostate cancer, and PSA testing for all participants with prostate cancer.
31 July 2020	Added tumor types to expansion cohorts: metastatic castration-resistant prostate cancer, non-small cell lung cancer, and triple negative breast cancer. Relevant sections of the protocol were updated accordingly, including study design, sample size, objectives, eligibility, and medical history requirements. Added secondary objectives to describe the radiographic progression free survival, PSA response rate and best PSA percent change from baseline. Added exploratory objective for patient reported outcome using the brief pain inventory short form and symptomatic skeletal events . Provided guidance of study procedures during the COVID-19 pandemic. Revised toxicity management guidelines.
17 March 2021	Updated the study design to include additional expansion cohorts of squamous cell cancer of the head and neck and melanoma. Relevant sections of the protocol were updated accordingly, including study design, sample size, objectives, eligibility, and medical history requirements. Updated toxicity management guidelines
26 July 2021	Revised toxicity management guidelines.
16 August 2021	Revised toxicity management guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported