Clinical trial results:
A Phase 1/2 study to evaluate safety, pharmacokinetics and efficacy of isatuximab in combination with cemiplimab in patients with relapsed/refractory multiple myeloma

Summary

EudraCT number	2017-001431-39
Trial protocol	HU CZ ES GR IT
Global end of trial date	05 April 2023

Results information

Result version number	v1
This version publication date	19 April 2024
First version publication date	19 April 2024

Trial information

Trial identification

Sponsor protocol code	TCD14906

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03194867
WHO universal trial number (UTN)	U1111-1189-4706

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	23 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the safety and tolerability of the combination of isatuximab and cemiplimab.
- Phase 2 only: To compare the overall response rate (ORR), defined as complete response (CR) + very good partial response (VGPR) + partial response (PR) of the combination of isatuximab and cemiplimab versus isatuximab alone in subjects with relapsed/refractory multiple myeloma (RRMM) based on International Myeloma Working Group (IMWG) criteria.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency.
Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 February 2018
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	Australia: 7
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	109
EEA total number of subjects	58

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)	47
From 65 to 84 years	61
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were screened at 30 sites. The study was conducted i.e. subjects were randomised at 29 sites in 10 countries. A total of 3 subjects in Phase 1 and 106 subjects in Phase 2 were enrolled (Phase 1)/randomised (Phase 2) from 21 Feb 2018 to 20 Mar 2019.

Pre-assignment

Screening details:

The study consisted of 2 phases: Phase 1 confirmed the feasibility of isatuximab/cemiplimab combination and Phase 2 further evaluated safety, efficacy and pharmacokinetics (PK) of combination versus isatuximab monotherapy. Subjects in Phase 2 were randomised in a 1:1:1 ratio to receive either isatuximab monotherapy or combination therapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)

Arm description:

Subjects received isatuximab 10 milligram/ kilogram (mg/kg) intravenous (IV) infusion once weekly for 4 weeks (QWx4) followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable adverse events (AEs), consent withdrawal, or any other reason.

Arm type	Experimental
Investigational medicinal product name	Isatuximab
Investigational medicinal product code	SAR650984
Other name	Sarclisa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Isatuximab 10 mg/kg IV infusion was administered QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Investigational medicinal product name	Cemiplimab
Investigational medicinal product code	REGN2810
Other name	Libtayo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 250 mg was administered as an IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Arm title	Phase 2: Isatuximab

Arm description:

Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.

Arm type	Experimental

Investigational medicinal product name	Isatuximab
Investigational medicinal product code	SAR650984
Other name	Sarclisa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Isatuximab 10 mg/kg IV infusion was administered QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Arm title	Phase 2: Isatuximab + CemiplimabQ2W

Arm description:

Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.

Arm type	Experimental
Investigational medicinal product name	Isatuximab
Investigational medicinal product code	SAR650984
Other name	Sarclisa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Isatuximab 10 mg/kg IV infusion was administered QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Investigational medicinal product name	Cemiplimab
Investigational medicinal product code	REGN2810
Other name	Libtayo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 250 mg was administered as an IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Arm title	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)

Arm description:

Subjects isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q4W (on Day 1 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.

Arm type	Experimental
Investigational medicinal product name	Isatuximab
Investigational medicinal product code	SAR650984
Other name	Sarclisa
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Isatuximab 10 mg/kg IV infusion was administered QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Investigational medicinal product name	Cemiplimab
Investigational medicinal product code	REGN2810
Other name	Libtayo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 250 mg was administered as an IV infusion Q4W (on Days 1 and 15 every cycle of a 28-day cycle) until protocol-defined discontinuation criteria were met.

Number of subjects in period 1	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W
Started	3	34	36
Completed	3	34	35
Not completed	0	0	1
Incorrect completion of end of study form	-	-	1

Number of subjects in period 1	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)
Started	36
Completed	36
Not completed	0
Incorrect completion of end of study form	-

Baseline characteristics

Reporting groups

Reporting group title	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)
Reporting group description:	
Subjects received isatuximab 10 milligram/ kilogram (mg/kg) intravenous (IV) infusion once weekly for 4 weeks (QWx4) followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable adverse events (AEs), consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab
Reporting group description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab + CemiplimabQ2W
Reporting group description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)
Reporting group description:	
Subjects isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q4W (on Day 1 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	

Reporting group values	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W
Number of subjects	3	34	36
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.7	66.1	63.7
standard deviation	± 2.9	± 9.3	± 10.0
Gender categorical Units: Subjects			
Female	1	16	14
Male	2	18	22
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	3
White	3	29	30
More than one race	0	0	0
Unknown or Not Reported	0	3	3

Reporting group values	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	Total	
Number of subjects	36	109	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.4		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	16	47	
Male	20	62	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	8	
White	29	91	
More than one race	0	0	
Unknown or Not Reported	3	9	

End points reporting groups

Reporting group title	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)
Reporting group description:	
Subjects received isatuximab 10 milligram/ kilogram (mg/kg) intravenous (IV) infusion once weekly for 4 weeks (QWx4) followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable adverse events (AEs), consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab
Reporting group description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab + CemiplimabQ2W
Reporting group description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Reporting group title	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)
Reporting group description:	
Subjects isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q4W (on Day 1 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Subject analysis set title	Phase 2: Isatuximab: Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Subject analysis set title	Phase 2: Isatuximab + CemiplimabQ2W: Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Subject analysis set title	Phase 2: Isatuximab + CemiplimabQ4W: Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q4W (on Day 1 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Subject analysis set title	Phase 2: Isatuximab: PK
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.	
Subject analysis set title	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who received isatuximab in combination with cemiplimab were included in this arm.

Subject analysis set title	Phase 1 and 2: Isatuximab + CemiplimabQ2W: ADA
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects received isatuximab 10 mg/kg IV infusion QWx4 followed by Q2W (on Days 1, 8, 15 and 22 in Cycle 1, and on Days 1 and 15 in Cycle 2 and beyond of a 28-day cycle) and cemiplimab 250 mg IV infusion Q2W (on Days 1 and 15 every cycle of a 28-day cycle) until disease progression, unacceptable AEs, consent withdrawal, or any other reason.

Primary: Phase 1: Number of Subjects With Dose-Limiting Toxicities (DLTs)

End point title	Phase 1: Number of Subjects With Dose-Limiting Toxicities (DLTs)[1][2]

End point description:

Potential DLTs: Occurrence of any of following adverse reactions at first treatment cycle, unless due to disease progression or obviously unrelated cause: Hematological (hem) DLTs: Grade(G) 4 neutropenia (N) for more than 7 consecutive days,G3 to G4 N with fever (temperature >= 38.5 degree Celsius on more than 1 occasion) or microbiologically/radiographically documented infection,G3 to G4 thrombocytopenia with clinically significant bleeding requiring clinical intervention or Non-hem DLTs:G4 non-hem AE,G>=2 uveitis,G3 non-hem AE lasting >3 days despite optimal care support, delay in initiation of Cycle 2 >14 days due to Rx related laboratory abnormalities/AE or any other AE that investigator/study committee deemed to be DL. The DLT evaluable population: Phase 1 subjects who received planned doses of isatuximab and cemiplimab during Cycle 1 and completed DLT observation period of Cycle 1 after first study Rx administration, unless they discontinued study treatment (s) due to DLT.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 to Day 28

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: As the endpoint is descriptive in nature, no statistical analysis is provided.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 1 subjects are included in this analysis.

End point values	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1 and Phase 2: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Phase 1 and Phase 2: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)[3][4]

End point description:

An AE: Any untoward medical occurrence in subject or clinical investigation subject administered with pharmaceutical product, did not necessarily have causal relationship with study treatment. SAEs: Any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was congenital anomaly/birth defect, was medically important event. TEAEs: An AE which occurred after first dose of study treatment administration up to 30 days after last dose of study treatment administration. DLT observation period was 1 cycle (28 days). However, all AEs during treatment, unless due to disease progression or an obviously unrelated cause,were taken into consideration by Study Committee for determination of maximum tolerated dose and recommended Phase 2 dose. Safety population tabulated according to treatment actually received [as treated].

End point type	Primary

End point timeframe:

TEAEs were collected from the first dose up to 30 days after the last dose of study treatment, approximately 50 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Safety population is tabulated according to treatment actually received [as treated]). 2 subjects randomised in isatuximab and isatuximab+cemiplimabQ4W respectively took another treatment.

End point values	Phase 1: Isatuximab + Cemiplimab Once Every 2 Weeks (Q2W)	Phase 2: Isatuximab: Safety	Phase 2: Isatuximab + CemiplimabQ2 W: Safety	Phase 2: Isatuximab + CemiplimabQ4 W: Safety
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	33[5]	37	35[6]
Units: subjects				
number (not applicable)				
TEAEs	3	33	36	33
TESAEs	1	17	17	21

Notes:

[5] - 1 subject randomised in original arm took another treatment.

[6] - 1 subject randomised in original arm took another treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Percentage of Subjects With ORR

End point title	Phase 2: Percentage of Subjects With ORR[7][8]

End point description:

ORR by Investigator using IMWG response criteria: percentage of subjects with CR (including stringent CR [sCR], VGPR and PR). CR: negative immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas, less than (<)5% plasma cells in bone marrow (BM) aspirates and normal free light chain (FLC)ratio (0.26-1.65).sCR: CR plus no clonal cells in BM biopsy. VGPR: serum and urine M-protein detectable by immunofixation, not electrophoresis;>=90% reduction in serum M-protein plus urine M-protein level<100mg/24hour(h);FLC only:>=90% decrease in difference between involved and uninvolved FLC levels.PR:>=50% reduction of serum M-protein and reduction in 24h urine M-protein by >=90% or <200mg/24h.In addition to above, if present at baseline,>=50% reduction in size (sum of products of maximal perpendicular diameters of measured lesions [SPD]) of soft tissue plasmacytomas required. The Randomised population.

End point type	Primary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[7] - 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: As the endpoint is descriptive in nature, no statistical analysis is provided.

[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 Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	36	
Units: percentage of subjects				
number (confidence interval 95%)	11.8 (3.30 to 27.45)	25.0 (12.12 to 42.20)	22.2 (10.12 to 39.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Subjects With Clinical Benefit Rate (CBR)

End point title	Phase 2: Percentage of Subjects With Clinical Benefit Rate (CBR)[9]

End point description:

CBR by Investigator using IMWG response criteria: percentage of subjects with CR (including sCR), VGPR, PR (all defined in previous endpoint) or MR. MR was defined as >= 25% but <= 49% reduction in serum M-protein and reduction in 24h urine M-protein by 50-89%, which still exceeded 200 mg/24h; if present at baseline, >=50% reduction in size (SPD) of soft tissue plasmacytomas was also required. The Randomised population consisted of all subjects from Phase 2 who gave their informed consent and were assigned a randomisation number by the interactive response technology (IRT), regardless of whether subjects received any study treatment or received a different study treatment from which they were randomised.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[9] - 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 Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	36	
Units: percentage of subjects				
number (confidence interval 95%)	23.5 (10.75 to	36.1 (20.82 to	38.9 (23.14 to	

41.17)	53.78)	56.54)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Follow-up

End point title	Phase 2: Duration of Follow-up[10]

End point description:

Duration of follow-up was defined as the time from randomisation to last disease assessment before start of other therapy or cut-off date or death, whichever came first. Median duration of follow-up is reported. The Randomised population consisted of all subjects from Phase 2 who gave their informed consent and were assigned a randomisation number by the IRT, regardless of whether subjects received any study treatment or received a different study treatment from which they were randomised.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	36	
Units: months				
median (confidence interval 95%)	10.28 (8.739 to 11.368)	8.84 (8.016 to 11.072)	9.03 (8.016 to 10.875)	

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)[11]

End point description:

DOR:Time from date of first response(>=PR) that was subsequently confirmed to date of first documented progressive disease (PD) or death.DOR was determined only for subjects who achieved a response of PR or better.If progression/death not observed, subject was censored at date of last valid disease assessment not showing disease progression performed prior to initiating further anticancer treatment and analysis cut-off date.PD(IMWG criteria):increase of >=25% from lowest confirmed value in any 1:serum M-protein(absolute increase>=0.5 gram/decilitre[g/dL]),serum M-protein increase>=1g/dL if lowest M component >=5g/dL;urine M-component(absolute increase >=200mg/24h),appearance of new lesion(s),>=50% increase from nadir in SPD of >1 lesion or >=50%

increase in longest diameter of previous lesion >1cm in short axis,>=50% increase in circulating plasma cells(minimum 200 cells/microlitre[c/mcL]) if that was the only measure of disease.PR: as defined in endpoint 3.The Randomised population.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[12]	9[13]	8[14]	
Units: months				
median (confidence interval 95%)	5.6 (4 to 7)	4.7 (3 to 12)	5.7 (2 to 12)	

Notes:

[12] - Only responders were included in the analysis.

[13] - Only responders were included in the analysis.

[14] - Only responders were included in the analysis.

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)[15]

End point description:

TTR was defined as the time from randomisation to first response (PR or better) that was subsequently confirmed. PR as per IMWG criteria was defined as >=50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >=90% or to <200 mg/24 hours. In addition to the above listed criteria, if present at baseline, a >=50% reduction in the size SPD of soft tissue plasmacytomas was also required. The Randomised population consisted of all subjects from Phase 2 who gave their informed consent and were assigned a randomisation number by the IRT, regardless of whether subjects received any study treatment or received a different study treatment from which they were randomised. Only responders were included in the analysis.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	9	8	
Units: months				
median (full range (min-max))	1.5 (1 to 2)	1.0 (1 to 3)	1.0 (1 to 4)	

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)[16]

End point description:

PFS: Time interval from randomisation date to date of first documented disease progression that was subsequently confirmed or the date of death due to any cause, whichever came first. If progression or death was not observed, subject was censored at date of last valid disease assessment not showing disease progression performed prior to initiation of a further anticancer treatment or the analysis cut-off date. Analysis was performed by Kaplan-Meier method. PD (IMWG) criteria:increase of >=25% from lowest confirmed value in any 1:serum M-protein (absolute increase >=0.5g/dL), serum M-protein increase >=1g/dL if lowest M component was >=5g/dL; urine M-component (absolute increase >=200mg/24h), appearance of new lesion(s),>=50% increase from nadir in SPD of >1 lesion or >=50% increase in the longest diameter of a previous lesion >1 cm in short axis or >=50% increase in circulating plasma cells (minimum of 200 c/mcL) if that was the only measure of disease. The Randomised population.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	36	
Units: months				
median (confidence interval 95%)	2.89 (1.971 to 3.811)	3.75 (1.971 to 5.881)	3.02 (2.793 to 5.158)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)[17]

End point description:

OS was defined as the time interval from the date of randomisation to death from any cause. Subjects without death prior to the analysis cut-off date were censored at the last date the subject was known to be alive or the cut-off date, whichever came first. The results provided below corresponds to descriptive OS information at the time of primary analysis completion date of 09 October 2019. The Randomised population consisted of all subjects from Phase 2 who gave their informed consent and were assigned a randomisation number by the IRT, regardless of whether subjects received any study treatment or received a different study treatment from which they were randomised. 99999 = Due to the limited follow-up time, most of subjects were still alive, so the parameter was not reached.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 17 months

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase 2 subjects are included in this analysis.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + CemiplimabQ2W	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	36	36	
Units: months				
median (confidence interval 95%)	99999 (7.622 to 99999)	99999 (6.801 to 99999)	12.78 (7.392 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Plasma Concentration Observed at the End of IV Infusion (Ceoi) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: Plasma Concentration Observed at the End of IV Infusion (Ceoi) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

Plasma samples were collected at specified timepoints and those non-impacted by the bioanalytical issue were used for evaluation of Ceoi. It was calculated using non-compartmental analysis (NCA) after the first administration in Cycle 1. The Pharmacokinetic (PK) population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the all-treated (AT) population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. "Isatuximab + Cemiplimab” arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At end of infusion (EOI) on Cycle 1 Day 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: microgram (mcg)/mL				
arithmetic mean (standard deviation)	255 (± 72.1)	239 (± 67.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Maximum Observed Concentration (Cmax) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: Maximum Observed Concentration (Cmax) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

Plasma samples were collected at specified timepoints and those non-impacted by the bioanalytical issue were used for evaluation of Cmax. It was calculated using NCA after the first administration in Cycle 1. The PK was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. "Isatuximab + Cemiplimab" arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At start of infusion (SOI), EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: mcg/mL				
arithmetic mean (standard deviation)	264 (± 68.0)	247 (± 65.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Time to Reach Cmax (Tmax) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: Time to Reach Cmax (Tmax) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

Plasma samples were collected at specified timepoints and those non-impacted by the bioanalytical issue were used for evaluation of tmax. It was calculated using NCA after the first administration in Cycle 1. The PK population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. “Isatuximab + Cemiplimab” arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At SOI, EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: hour				
median (full range (min-max))	5.56 (3.25 to 10.50)	4.85 (2.58 to 13.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Last Concentration Observed Above the Lower Limit of Quantitation (Clast) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: Last Concentration Observed Above the Lower Limit of Quantitation (Clast) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

Plasma samples were collected at specified timepoints and those non-impacted by the bioanalytical issue were used for evaluation of Clast. It was calculated using NCA after the first administration in Cycle 1. The PK population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. "Isatuximab + Cemiplimab” arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At SOI, EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: mcg/mL				
arithmetic mean (standard deviation)	85.7 (± 44.9)	64.1 (± 32.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Time of Clast (Tlast) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: Time of Clast (Tlast) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

Plasma samples were collected at specified timepoints and those non-impacted by the bioanalytical issue were used for evaluation of tlast. It was calculated using NCA after the first administration in Cycle 1. The PK population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. “Isatuximab + Cemiplimab” arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At SOI, EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: hour				
median (full range (min-max))	155.00 (72.40 to 169.00)	165.00 (70.20 to 239.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Area Under the Concentration Versus Time Curve (AUC) From Time Zero to Tlast (AUClast) of Isatuximab Alone and in Combination With

Cemiplimab

End point title	Phase 1 and 2: Area Under the Concentration Versus Time Curve (AUC) From Time Zero to Tlast (AUClast) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

AUClast was defined as the area under the plasma concentration versus time curve from time 0 to real time tlast calculated using the trapezoidal method over the dosing interval after the first administration in Cycle 1. The PK population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. "Isatuximab + Cemiplimab" arm includes 3 and 27 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

At SOI, EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	30		
Units: (mcg*h)/mL				
arithmetic mean (standard deviation)	21000 (± 7220)	20200 (± 6590)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: AUC From Time 0 to Week 1 (AUC1week) of Isatuximab Alone and in Combination With Cemiplimab

End point title	Phase 1 and 2: AUC From Time 0 to Week 1 (AUC1week) of Isatuximab Alone and in Combination With Cemiplimab

End point description:

AUC1week was defined as the area under the plasma concentration versus time curve from time 0 to 1 week post dose calculated using the trapezoidal method over the dosing interval after the first administration in Cycle 1. The PK population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 available concentration post-baseline (whatever the cycle and even if dosing was incomplete) with adequate documentation of dosing and sampling dates and times. Only those subjects with data available were analysed. "Isatuximab + Cemiplimab" arm includes 3 and 27 subjects from phase 1 and phase 2, respectively. Only those subjects with data available were analysed.

End point type	Secondary

End point timeframe:

At SOI, EOI, EOI+4 hours, 72 hours and 168 hours on Day 1 of Cycle 1

End point values	Phase 2: Isatuximab: PK	Phase 1 and 2: Combination Arm: Isatuximab + Cemiplimab: PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	29		
Units: (mcg*h)/mL				
arithmetic mean (standard deviation)	23000 (± 7250)	21100 (± 6450)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Number of Subjects With Anti-Drug Antibodies (ADA) to Isatuximab

End point title	Phase 1 and 2: Number of Subjects With Anti-Drug Antibodies (ADA) to Isatuximab[18]

End point description:

ADA responses were categorised as treatment-induced ADA and treatment boosted ADA. Pre-existing ADA was defined as ADA that were present in samples drawn during the pre-treatment period. Treatment-induced ADA was defined as ADA that developed at any time during the ADA on-study observation period in subjects without pre-existing ADA. Treatment boosted ADA was defined as pre-existing ADAs with a significant increase in the ADA titer during the study compared to the Baseline titer. The ADA evaluable population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 ADA result (negative, positive, or inconclusive) post-baseline. "Isatuximab + CemiplimabQ2W" arm includes 3 and 36 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 20 months

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "Isatuximab + CemiplimabQ2W" arm in ADA includes 3 and 36 subjects from phase 1 and phase 2, respectively.

End point values	Phase 2: Isatuximab	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	Phase 1 and 2: Isatuximab + CemiplimabQ2W: ADA	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	32	34	39	
Units: subjects				
number (not applicable)				
Pre-existing ADA	0	0	1	
Treatment-induced	0	0	0	
Treatment boosted	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1 and 2: Number of Subjects With ADA to Cemiplimab

End point title	Phase 1 and 2: Number of Subjects With ADA to Cemiplimab[19]

End point description:

ADA responses were categorised as treatment-induced ADA and treatment boosted ADA. Pre-existing ADA was defined as ADA that were present in samples drawn during the pre-treatment period. Treatment-induced ADA was defined as ADA that developed at any time during the ADA on-study observation period in subjects without pre-existing ADA. Treatment boosted ADA was defined as pre-existing ADAs with a significant increase in the ADA titer during the study compared to the Baseline titer. The ADA evaluable population was defined independently for isatuximab and cemiplimab and consisted of all subjects from the AT population with at least 1 ADA result (negative, positive, or inconclusive) post-baseline. "Isatuximab + CemiplimabQ2W" arm includes 3 and 36 subjects from phase 1 and phase 2, respectively.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to primary analysis completion date of 9 Oct 2019 i.e., up to approximately 20 months

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: "Isatuximab + CemiplimabQ2W" arm in ADA includes 3 and 36 subjects from phase 1 and phase 2, respectively.

End point values	Phase 2: Isatuximab + Cemiplimab Once Every 4 Weeks (Q4W)	Phase 1 and 2: Isatuximab + CemiplimabQ2W: ADA		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34	39		
Units: subjects				
number (not applicable)				
Pre-existing ADA	0	1		
Treatment-induced	0	2		
Treatment boosted	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from the first dose up to 30 days after the last dose of study treatment, approximately 50 months. Number of deaths (all causes) was reported for the whole study duration, approximately 62 months

Adverse event reporting additional description:

Analysis was performed on the Safety population (tabulated according to treatment actually received [as treated]). There were 2 subjects randomised in group isatuximab and isatuximab + cemiplimabQ4W respectively and who took another treatment/schedule.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Phase 1 Isa+CemQ2W
Reporting group description: -	
Reporting group title	Phase 2 Isa+CemQ4W
Reporting group description: -	
Reporting group title	Phase 2 Isa+CemQ2W
Reporting group description: -	
Reporting group title	Phase 2 Isa
Reporting group description: -	

Serious adverse events	Phase 1 Isa+CemQ2W	Phase 2 Isa+CemQ4W	Phase 2 Isa+CemQ2W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	21 / 35 (60.00%)	17 / 37 (45.95%)
number of deaths (all causes)	1	22	23
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine Carcinoma Of The Skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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
Colon Neoplasm			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Cancer Pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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
Surgical and medical procedures			
Euthanasia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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			
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
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 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Pulmonary Embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet Count Decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Nervous system disorders			
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Spinal Cord Compression			

subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Radicular Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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			
Hyperviscosity Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Anal Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 Abdomen			

subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction Gastric			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fanconi Syndrome Acquired			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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
Urinary Tract Obstruction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 3 (33.33%)	1 / 35 (2.86%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Lesion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Musculoskeletal Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Pathological Fracture			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Infections and infestations			

Covid-19 Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalomyelitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Encephalitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Catheter Site Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae Virus Infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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
Osteomyelitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (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
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 Disseminated			

subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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 / 35 (0.00%)	0 / 37 (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 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonia Staphylococcal			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			

subjects affected / exposed	0 / 3 (0.00%)	5 / 35 (14.29%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (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			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase 2 Isa		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 33 (51.52%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroendocrine Carcinoma Of The Skin			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colon Neoplasm			

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cancer Pain				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Euthanasia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease Progression				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple Organ Dysfunction Syndrome				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac Chest Pain				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Epistaxis				

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural Effusion			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet Count Decreased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Failure Congestive			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Psychomotor Hyperactivity			

subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Compression				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radicular Pain				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Hyperviscosity Syndrome				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal Haemorrhage				

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute Abdomen				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction Gastric				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small Intestinal Obstruction				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute Kidney Injury				
subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Fanconi Syndrome Acquired				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				

subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Obstruction				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back Pain				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone Lesion				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone Pain				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal Pain				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological Fracture				

subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalomyelitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter Site Infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae Virus Infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			

subjects affected / exposed	3 / 33 (9.09%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Herpes Zoster Disseminated				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia Bacteraemia				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salmonellosis				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	1 / 33 (3.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Sepsis				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia Staphylococcal				
subjects affected / exposed	0 / 33 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1 Isa+CemQ2W	Phase 2 Isa+CemQ4W	Phase 2 Isa+CemQ2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	27 / 35 (77.14%)	34 / 37 (91.89%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	3 / 37 (8.11%)
occurrences (all)	0	2	3

General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	5 / 35 (14.29%)	8 / 37 (21.62%)
occurrences (all)	0	5	12
Disease Progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	5 / 37 (13.51%)
occurrences (all)	0	2	5
Oedema Peripheral			
subjects affected / exposed	1 / 3 (33.33%)	3 / 35 (8.57%)	1 / 37 (2.70%)
occurrences (all)	1	4	1
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	6 / 37 (16.22%)
occurrences (all)	0	3	10
Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	5 / 37 (13.51%)
occurrences (all)	1	2	7
Dysphonia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 35 (2.86%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			

subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Dyspnoea Exertional			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Productive Cough			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Confusional State			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Investigations			
Weight Decreased			
subjects affected / exposed	0 / 3 (0.00%)	4 / 35 (11.43%)	1 / 37 (2.70%)
occurrences (all)	0	4	1
Injury, poisoning and procedural complications			
Infusion Related Reaction			
subjects affected / exposed	2 / 3 (66.67%)	15 / 35 (42.86%)	15 / 37 (40.54%)
occurrences (all)	2	15	15
Fall			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Peripheral Sensory Neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Neuralgia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Lethargy			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 3 (0.00%)	4 / 35 (11.43%)	3 / 37 (8.11%)
occurrences (all)	0	4	5
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	4 / 37 (10.81%)
occurrences (all)	0	3	6
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	1 / 37 (2.70%)
occurrences (all)	0	8	1
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Abdominal Pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	4	1
Constipation			

subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	7 / 35 (20.00%)	7 / 37 (18.92%)
occurrences (all)	1	10	10
Dyspepsia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	6 / 35 (17.14%)	1 / 37 (2.70%)
occurrences (all)	1	6	1
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Oral Papule			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	5 / 35 (14.29%)	5 / 37 (13.51%)
occurrences (all)	1	6	7
Lip Oedema			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Gingival Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2

Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Muscular Weakness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Muscle Spasms			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	2	3
Groin Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	1	0	2
Bone Pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	3 / 37 (8.11%)
occurrences (all)	0	3	3
Musculoskeletal Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	3 / 37 (8.11%)
occurrences (all)	0	1	5
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	4 / 37 (10.81%)
occurrences (all)	0	3	6
Back Pain			
subjects affected / exposed	1 / 3 (33.33%)	3 / 35 (8.57%)	7 / 37 (18.92%)
occurrences (all)	1	3	9
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	4 / 37 (10.81%)
occurrences (all)	0	1	4
Neck Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Pain In Extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 35 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 3 (0.00%)	5 / 35 (14.29%)	3 / 37 (8.11%)
occurrences (all)	0	5	3
Labyrinthitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	1 / 37 (2.70%)
occurrences (all)	0	4	1
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	7 / 35 (20.00%)	4 / 37 (10.81%)
occurrences (all)	2	13	9
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 35 (0.00%)	3 / 37 (8.11%)
occurrences (all)	1	0	3
Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	2 / 37 (5.41%)
occurrences (all)	1	2	2
Oral Candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	2 / 35 (5.71%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Urinary Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	3 / 35 (8.57%)	2 / 37 (5.41%)
occurrences (all)	0	3	3
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 35 (2.86%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 3 (33.33%)	2 / 35 (5.71%)	4 / 37 (10.81%)
occurrences (all)	1	3	4

Non-serious adverse events	Phase 2 Isa		

Total subjects affected by non-serious adverse events subjects affected / exposed	31 / 33 (93.94%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4		
General disorders and administration site conditions Influenza Like Illness subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Disease Progression subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Oedema Peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2 3 / 33 (9.09%) 3 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 3 / 33 (9.09%) 6 2 / 33 (6.06%) 2 4 / 33 (12.12%) 7 0 / 33 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia	5 / 33 (15.15%) 6		

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dyspnoea Exertional			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Productive Cough			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Anxiety			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Confusional State			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Investigations			
Weight Decreased			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Infusion Related Reaction subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	 18 / 33 (54.55%) 22 3 / 33 (9.09%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 2 / 33 (6.06%) 2 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 3 / 33 (9.09%) 3		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 1 / 33 (3.03%) 1		
Gastrointestinal disorders			

Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2			
Constipation subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Diarrhoea subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 8			
Dyspepsia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Vomiting subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 4			
Stomatitis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1			
Oral Papule subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Nausea subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5			
Lip Oedema subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Gingival Pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0			
Skin and subcutaneous tissue disorders Eczema				

subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Muscular Weakness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscle Spasms			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Groin Pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Bone Pain			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Back Pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Myalgia			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Neck Pain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pain In Extremity			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Labyrinthitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Respiratory Tract Infection			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Oral Candidiasis			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Urinary Tract Infection			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		

Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2017	Changed DLT definition. Added physical examinations, haematology, biochemistry and urinalysis lab tests at visits 60 and 90 days after last dose of study treatment.
17 November 2017	Revised Phase 1 and Phase 2 study design. Body weight-based dose was changed to flat dose. Added a data monitoring committee (DMC). Added an exclusion criterion: Subjects who have previously been treated with idelalisib (a PI3K inhibitor). Added additional safety guidance language added for the management of subjects developing stomatitis or mucositis. An adverse event of special interest (AESI) was added to the list of AESIs: an immune related AE of any grade in a subject previously treated with a PI3K inhibitor and additional safety guidance language added for the management of subjects developing stomatitis or mucositis. Clarify plasmacytoma assessment at screening: in subjects with known or suspected extramedullary disease. Changed REGN2810 to cemiplimab.
06 August 2018	Added an anti-CD38 refractory cohort in Phase 2. Added assessment of humoral and cellular immune responses to myeloma-related tumor antigens in blood and their correlation with clinical response. Updated PK/Pharmacodynamic flowcharts. Added an appendix of contraceptive guidance and collection of pregnancy information and provided reference in exclusion criteria No.18. Extended OS follow-up period to 24 months after last subject first dose, best of response for post anticancer therapy was collected during this study follow-up period. Changed DMC review for every 4 months to every 3 months. Updated cemiplimab clinical information. Added an instruction for prophylaxis of opportunistic infections. Added additional exclusion criterion.
11 June 2019	Updated contraceptive measures and pregnancy counseling.
14 August 2020	Based on updated analysis of primary endpoint (overall response rate [ORR]) planned six months after last subject in (LSI) and other secondary endpoints (including overall survival [OS]) performed at the planned cutoff date 1 year after LPI, the addition to cemiplimab to SAR650984 only resulted in marginal additive efficacy. No safety concerns were observed during periodic Data Monitoring Committee (DMC) review. No further efficacy data collection at longer follow-up was performed. Per DMC recommendation, the final OS analysis planned at 24 months after LPI was not performed and the follow-up stopped after the extended safety period of 90 days after last study treatment dose. Subjects under treatment continued to be treated as long as they benefited from it. A risk of hepatitis reactivation had been identified in the SAR650984 Investigator's Brochure Edition 11 (30-Apr-2020).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported