Clinical trial results:
A Phase 1/2 multicenter, open-label study to determine the recommended dose and regimen of Durvalumab (MEDI4736) in combination with Lenalidomide (LEN) with and without Dexamethasone (DEX)in subjects with newly diagnosed multiple myeloma (NDMM)

Summary

EudraCT number	2015-004831-11
Trial protocol	DE ES DK FI NL
Global end of trial date	06 September 2022

Results information

Result version number	v2 (current)
This version publication date	14 October 2023
First version publication date	17 September 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MEDI4736-MM-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	16 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the recommended dose and regimen of durvalumab in combination with LEN with and without DEX in subjects with newly diagnosed multiple myeloma (NDMM).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	56
EEA total number of subjects	39

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)	17
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 subjects treated

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	Cohort A: High risk, TNE

Arm description:

High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

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

Dosage and administration details:

25 mg/day on days 1 to 21 of each 28-day treatment cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	DEX
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg on day 1 of each 28-day cycle

Arm title	Cohort B: >=65 years old, TNE

Arm description:

>= 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg on day 1 of each 28-day cycle

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	DEX
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	LEN
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg/day on days 1 to 21 of each 28-day treatment cycle

Arm title	Cohort C: High risk, Post-transplant

Arm description:

High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.

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

Dosage and administration details:

10 mg/day on days 1 to 21 of each 28-day treatment cycle

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg on day 1 of each 28-day cycle

Number of subjects in period 1	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant
Started	25	10	21
Completed	0	0	0
Not completed	25	10	21
Consent withdrawn by subject	2	-	-
Adverse event, non-fatal	2	-	1
Progressive Disease	2	1	-
Full Clinical Hold by FDA	19	9	20

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: High risk, TNE
Reporting group description:	
High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.	
Reporting group title	Cohort B: >=65 years old, TNE
Reporting group description:	
>= 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.	
Reporting group title	Cohort C: High risk, Post-transplant
Reporting group description:	
High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.	

Reporting group values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant
Number of subjects	25	10	21
Age Categorical Units: participants			
<=75 years	12	7	20
>75 years	13	3	1
Age Continuous Units: years			
arithmetic mean	75.4	72.5	59.6
standard deviation	± 4.17	± 5.25	± 7.52
Sex: Female, Male Units: participants			
Female	15	0	4
Male	10	10	17
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	0
White	21	9	17
More than one race	0	0	0
Unknown or Not Reported	2	0	4

Reporting group values	Total		
Number of subjects	56		

Age Categorical Units: participants			
<=75 years	39		
>75 years	17		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: participants			
Female	19		
Male	37		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	47		
More than one race	0		
Unknown or Not Reported	6		

End points

End points reporting groups

Reporting group title	Cohort A: High risk, TNE

Reporting group description:

High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Reporting group title	Cohort B: >=65 years old, TNE

Reporting group description:

>= 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.

Reporting group title	Cohort C: High risk, Post-transplant

Reporting group description:

High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.

Primary: Participants with Dose-Limiting Toxicities (DLTs) During the Dose-Determining Timeframe (Day 1 – Day 28)

End point title	Participants with Dose-Limiting Toxicities (DLTs) During the Dose-Determining Timeframe (Day 1 – Day 28)[1]

End point description:

A Dose Review Team (DRT) evaluated DLTs to determine the recommended dose (RD) of Durvalumab to use in the Expansion Period. A DLT was defined as: a. Grade 4 neutropenia for >= 5 days. b. Grade 3 neutropenia associated with fever (≥ 38.5°C / 101.3°F) of any duration. c. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or platelets transfusion. d. Grade 4 hematologic toxicity that does not resolve to baseline level <=72 hours. e. Grade 4 anemia, unexplained by underlying disease. f. Any nonhematologic toxicity Grade ≥ 3 except for alopecia and nausea. g. Treatment interruption >= 2 weeks due to AE. If ≤ 1 of the 6 initial participants in each cohort experience a DLT during cycle 1, the RD was Durvalumab 1500 mg; If >=2 of the 6 initial participants in any cohort experience a DLT during cycle 1, the maximum tolerated dose (MTD) was exceeded and the dose level of Durvalumab was de-escalated to 750 mg

End point type	Primary

End point timeframe:

First treatment cycle: 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: Only summary analysis planned for this endpoint.

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	7	6	
Units: Count of participants	1	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Participants with Treatment Emergent Adverse Events (TEAE)

End point description:

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen during the course of a study. A TEAE includes AEs between the first dose date of either study drug and 90 days after the last dose of study drug. A serious AE is any AE occurring at any dose that: • Results in death; • Is life-threatening; • Requires or prolongs existing inpatient hospitalization; • Results in persistent or significant disability/incapacity; • Is a congenital anomaly/birth defect; • Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03): - Grade 1 = Mild - Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention required) - Grade 3 = Severe (limitation in activity; medical intervention required) - Grade 4 = Life-threatening - Grade 5 = Death 99999=NA

End point type	Secondary

End point timeframe:

Day 1 up to Week 84 (the longer of 90 days after discontinuing treatment with DURVA, or 28 days after the last dose of LEN or dex)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	10	21	
Units: Count of participants				
>= 1 TEAE	24	9	18	
>=1 treatment-related TEAE	22	8	17	
>=1 related to DURVA	16	4	15	
>=1 related to LEN	22	8	15	
>=1 related to dex	16	6	99999	
>=1 TEAE of severity grade 3 or 4	19	8	7	
>=1 severity 3/4, related to study drug	13	8	6	
>=1 severity 3/4, related to DURVA	7	4	4	
>=1 severity 3/4, related to LEN	11	8	4	
>=1 severity 3/4, related to dex	5	2	99999	
>=1 Grade 5 TEAE (Death)	1	0	1	
>=1 Grade 5 TEAE related to study drug	0	0	1	
>=1 Grade 5 TEAE related to DURVA	0	0	1	
>=1 Grade 5 TEAE related to LEN	0	0	0	
>=1 Grade 5 TEAE related to dex	0	0	99999	
>=1 Serious TEAE	12	6	4	
>=1 Serious TEAE related to study drug	8	4	4	
>=1 Serious TEAE related to DURVA	5	1	4	

>=1 Serious TEAE related to LEN	6	3	2	
>=1 Serious TEAE related to dex	5	1	99999	
>=1 TEAE leading to discontinuation of study drug	3	0	1	
>= TEAE leading to discontinuation of DURVA	2	0	1	
>= TEAE leading to discontinuation of LEN	3	0	0	
>= TEAE leading to discontinuation of dex	2	0	99999	
>=1 leading to delay/reduction/interruption drug	14	7	6	
>=1 leading to dose delay of DURVA	10	3	4	
>=1 leading to infusion interruption of DURVA	0	0	1	
>=1 leading to dose reduction of LEN	2	2	3	
>=1 leading to interruption of LEN	13	5	5	
>=1 leading to dose reduction of dex	1	3	99999	
>=1 leading to interruption of dex	9	3	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Response Improvement Rate (RIR) for Cohort C: Percentage of Participants Achieving a Response Improved from Cycle 1 Day 1 as Assessed by the Investigators Using the International Myeloma Working Group (IMWG) Uniform Response Criteria

End point title	Response Improvement Rate (RIR) for Cohort C: Percentage of Participants Achieving a Response Improved from Cycle 1 Day 1 as Assessed by the Investigators Using the International Myeloma Working Group (IMWG) Uniform Response Criteria

End point description:

Response Improvement Rate is defined as the percentage of participants who achieved a response from treatment as compared to the pre-autologous stem cell transplantation [ASCT] diseases measurement used as baseline for response assessment. IMWG response categories could be stable disease (SD), partial response (PR), very good partial response (VGPR), complete response (CR), or stringent complete response (sCR), as long as it represented an improvement compared to prior to transplant. 99999=NA

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1); Treatment: Day 1 of each cycle starting with Cycle 2 up to Cycle 15 plus one week for the end of treatment visit (Day 29 up to Week 61)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	21	
Units: percentage of participants				
number (confidence interval 80%)	(to)	(to)	0 (-99999 to 99999)	

Notes:

[2] - 0 subjects analyzed

[3] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) for Cohorts A and B: Percentage of Participants Who Achieved a Partial Response or Better According to the International Myeloma Working Group (IMWG) Uniform Response Criteria

End point title	Overall Response Rate (ORR) for Cohorts A and B: Percentage of Participants Who Achieved a Partial Response or Better According to the International Myeloma Working Group (IMWG) Uniform Response Criteria

End point description:

Tumor response, including progressive disease, was assessed by the investigators and captured the best assessment of response during the treatment period. ORR was defined as partial response (PR) or better which includes PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR). A PR required ≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours. If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas was also required. sCR required - a negative immunofixation of serum and urine and - disappearance of any soft tissue plasmacytomas and - ≤ 5% plasma cells in bone marrow and normal free light-chain (FLC) ratio and - absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry.

End point type	Secondary

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	10	0[4]	
Units: percentage of participants				
number (confidence interval 80%)	66.7 (51.6 to 79.5)	50.0 (26.7 to 73.3)	(to)	

Notes:

[4] - 0 subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (for Cohorts A and B)

End point title	Time to Response (for Cohorts A and B)

End point description:

Time to response (for responders only, per IMWG Uniform Response Criteria) is calculated as the time from the first date of dosing of study medication to the first date of documented response (PR or better).

End point type	Secondary

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	5	0[5]	
Units: weeks				
median (full range (min-max))	4.20 (3.9 to 23.1)	4.10 (4.0 to 13.0)	(to)	

Notes:

[5] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates for Duration of Response (for Cohort A and B)

End point title	Kaplan-Meier Estimates for Duration of Response (for Cohort A and B)

End point description:

Duration of response (for responders only) was defined as the time from earliest date of documented response (PR or better) to the earliest date of disease progression (DP) as determined by the investigator per IMWG Uniform Response criteria or death during study treatment, whichever occurred first. 99999=NA

End point type	Secondary

End point timeframe:

Day 1 of each cycle starting with Cycle 2 up to Cycle 17 plus one week for the end of treatment visit (Day 29 up to Week 73)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	5	0[6]	
Units: months				
median (confidence interval 80%)	10.3 (7.2 to 99999)	99999 (99999 to 99999)	(to)	

Notes:

[6] - 0 subjects analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum Pharmacokinetic (PK) Parameters in Cycle

1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point title	Durvalumab (DURVA) Serum Pharmacokinetic (PK) Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	10	20	
Units: day*µg/L				
geometric mean (geometric coefficient of variation)	3535033.014 (± 39.8)	3582905.960 (± 21.0)	4026520.655 (± 39.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	9	19	
Units: day*µg/L				
geometric mean (geometric coefficient of variation)	4944601.671 (± 60.9)	5532568.144 (± 62.5)	6531541.670 (± 36.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Maximum Observed Concentration (Cmax)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Maximum Observed Concentration (Cmax)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	10	20	
Units: µg/L				
geometric mean (geometric coefficient of variation)	449280.231 (± 36.7)	452827.419 (± 25.5)	482602.748 (± 39.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Time to Maximum Observed Concentration (Tmax)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Time to Maximum Observed Concentration (Tmax)

End point description:

Time to maximum observed concentration of Durvalumab (DURVA) after multiple doses on day 1 obtained from the observed concentration versus time data

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	10	20	
Units: day				
median (full range (min-max))	0.051 (0.04 to 0.22)	0.106 (0.04 to 0.22)	0.180 (0.04 to 0.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Clearance (CL)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Clearance (CL)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	9	19	
Units: L/day				
geometric mean (geometric coefficient of variation)	0.303 (± 60.9)	0.271 (± 62.5)	0.230 (± 36.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Terminal Elimination Half-life (t1/2)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Terminal Elimination Half-life (t1/2)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	9	19	
Units: day				
geometric mean (geometric coefficient of variation)	10.984 (± 52.1)	13.376 (± 90.9)	15.844 (± 29.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Maximum Observed Concentration (Cmax)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Maximum Observed Concentration (Cmax)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	10	21	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	395.774 (± 56.2)	354.018 (± 34.7)	161.372 (± 33.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Volume of Distribution (Vz)

End point title	Durvalumab (DURVA) Serum PK Parameters in Cycle 1: Volume of Distribution (Vz)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (Day 8), 336 hours (Day 15) and 504 hours (Day 22) after administration of DURVA on Day 1

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	9	19	
Units: liters				
geometric mean (geometric coefficient of variation)	4.244 (± 33.5)	4.582 (± 33.3)	4.563 (± 42.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	10	21	
Units: hour*ng/mL				
geometric mean (geometric coefficient of variation)	1468.102 (± 78.6)	1442.549 (± 29.9)	591.085 (± 22.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Area Under the Concentration-time Curve from Time Zero to Infinity (AUC0-inf)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	3	12	
Units: hour*ng/mL				
geometric mean (geometric coefficient of variation)	2534.684 (± 48.6)	2011.889 (± 26.8)	768.104 (± 33.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1

Day 1: Apparent Clearance (CL/F)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Clearance (CL/F)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	3	12	
Units: L/hour				
geometric mean (geometric coefficient of variation)	8.838 (± 52.7)	12.426 (± 26.8)	13.019 (± 33.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Time to Maximum Observed Concentration (Tmax)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Time to Maximum Observed Concentration (Tmax)

End point description:

Time to maximum observed concentration of Lenalidomide (LEN) after multiple doses on day 1 obtained from the observed concentration versus time data

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	10	21	
Units: hour				
median (full range (min-max))	1.050 (0.42 to 4.08)	1.925 (0.50 to 4.00)	1.150 (0.43 to 4.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Terminal Elimination Half-life (t1/2)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Terminal Elimination Half-life (t1/2)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	3	12	
Units: hour				
geometric mean (geometric coefficient of variation)	3.477 (± 61.3)	3.051 (± 16.8)	2.883 (± 29.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Volume of Distribution (Vz/F)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 1: Apparent Volume of Distribution (Vz/F)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	3	12	
Units: liters				
geometric mean (geometric coefficient of variation)	44.329 (± 25.4)	54.689 (± 29.7)	54.157 (± 22.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma PK parameters in Cycle 1 Day 15: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point title	Lenalidomide (LEN) Plasma PK parameters in Cycle 1 Day 15: Area Under the Concentration-time Curve from Time Zero to the Last Measured Time Point (AUC0-last)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	9	16	
Units: hour*ng/mL				
geometric mean (geometric coefficient of variation)	1911.739 (± 65.5)	1754.349 (± 34.3)	629.151 (± 16.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Maximum Observed Concentration (Cmax)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters

	in Cycle 1 Day 15: Maximum Observed Concentration (Cmax)

End point description:

Geometric mean was obtained by computing the arithmetic mean of the logarithm-transformed values of concentration/PK parameters and then using the exponentiation to return the computation to the original scales. Geometric CV% was calculated as follows: CV% = 100*SQRT(EXP(σ2)-1), where σ2 denotes the variance of the log-transformed values.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	9	16	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	409.764 (± 66.0)	452.850 (± 31.7)	171.235 (± 33.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Time to Maximum Observed Concentration (Tmax)

End point title	Lenalidomide (LEN) Plasma Pharmacokinetic (PK) Parameters in Cycle 1 Day 15: Time to Maximum Observed Concentration (Tmax)

End point description:

Time to maximum observed concentration of Lenalidomide (LEN) after multiple doses on day 15 obtained from the observed concentration versus time data

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: pre-dose, 0.5, 1, 2, 4, and 8 hours post LEN dose

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	9	16	
Units: hour				
median (full range (min-max))	2.000 (1.00 to 8.00)	1.000 (0.55 to 2.00)	1.042 (0.47 to 4.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Had Either Disease Progression or Death

End point title	Participants Who Had Either Disease Progression or Death

End point description:

This outcome was originally defined as a Kaplan-Meier estimate of progression-free survival (PFS) which estimated the time between first date of dosing of study medication and disease progression, as determined by the investigator using the IMWG Uniform Response Criteria, or death during study treatment, whichever occurred earlier. However due to the early study termination and limited follow-up time, the majority of participants were censored for PFS analysis. Data reported instead represent the number of participants who died during study treatment or had disease progression within 90 days of the last dose of durvalumab.

End point type	Secondary

End point timeframe:

Day 1 up to Week 84

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	10	21	
Units: Count of participants	4	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Developed Anti-drug Antibody Against Durvalumab

End point title	Participants Who Developed Anti-drug Antibody Against Durvalumab

End point description:

The number of participants who develop antidrug antibody against durvalumab at any of the sampling timepoints during the study.

End point type	Secondary

End point timeframe:

Pre-dose samples on Day 1 of cycles 1, 2, 4, 6, 10, and 14 (study days 1, 29, 85, 141, 253, 393)

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	10	21	
Units: Count of participants	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Who Died Up To Data Cut-off Date (15 December 2017)

End point title	Participants Who Died Up To Data Cut-off Date (15 December 2017)

End point description:

This outcome was originally defined as a Kaplan-Meier estimate of overall survival (OS) and was defined as the time between first date of dosing of study medication and death due to any cause. However due to the early study termination and limited follow-up time, the majority of participants were censored for OS analysis. Data reported instead represent the number of participants who died due to any cause from Day 1 up to data cut-off.

End point type	Secondary

End point timeframe:

Day 1 up to Week 87

End point values	Cohort A: High risk, TNE	Cohort B: >=65 years old, TNE	Cohort C: High risk, Post-transplant	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	10	21	
Units: Count of participants	2	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs assessed from first dose up to week 84 (the longer of 90 days after d/c treatment with DURVA, or 28 days after the last dose of LEN or DEX). Deaths (all-causes) assessed from first dose to study completion (Up to approximately 88 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort A: High Risk, TNE

Reporting group description:

High risk, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Reporting group title	Cohort B: >=65 Years Old, TNE

Reporting group description:

>= 65 years old, transplant non-eligible [TNE], newly diagnosed multiple myeloma (NDMM) participants who were not high risk were administered • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 25 mg/day (adjust per the creatinine clearance [CrCl] value) on Days 1 to 21 of each 28-day treatment cycle • Oral dexamethasone (dex) 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle, up to 12 cycles.

Reporting group title	Cohort C: High Risk, Post-transplant

Reporting group description:

High risk, post-transplant NDMM participants were administered the following as maintenance therapy: • Intravenous (IV) durvalumab at 1500 mg on Day 1 of each 28-day cycle • Oral lenalidomide (LEN) 10 mg/day on Days 1 to 21 of each 28-day treatment cycle.

Serious adverse events	Cohort A: High Risk, TNE	Cohort B: >=65 Years Old, TNE	Cohort C: High Risk, Post-transplant
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 25 (48.00%)	6 / 10 (60.00%)	4 / 21 (19.05%)
number of deaths (all causes)	9	3	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lung			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			

subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pubis fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (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
Hyperthyroidism			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (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
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			

subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cystitis klebsiella			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (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
Sepsis			

subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A: High Risk, TNE	Cohort B: >=65 Years Old, TNE	Cohort C: High Risk, Post-transplant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)	9 / 10 (90.00%)	18 / 21 (85.71%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Phlebitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 25 (16.00%)	3 / 10 (30.00%)	7 / 21 (33.33%)
occurrences (all)	4	3	8
Chills			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Asthenia			
subjects affected / exposed	7 / 25 (28.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	7	2	1
General physical health deterioration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	3 / 25 (12.00%)	4 / 10 (40.00%)	3 / 21 (14.29%)
occurrences (all)	4	5	3
Peripheral swelling			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Oedema peripheral			
subjects affected / exposed	8 / 25 (32.00%)	2 / 10 (20.00%)	0 / 21 (0.00%)
occurrences (all)	8	2	0
Non-cardiac chest pain			

subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 25 (12.00%)	2 / 10 (20.00%)	5 / 21 (23.81%)
occurrences (all)	3	2	5
Dysphonia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 10 (20.00%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	3 / 10 (30.00%)	0 / 21 (0.00%)
occurrences (all)	2	3	0
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	0	1	3
Productive cough			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	2	2	1
Respiratory tract congestion			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Rhinorrhoea			

subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Upper-airway cough syndrome			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 25 (16.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	4	0	2
Insomnia			
subjects affected / exposed	2 / 25 (8.00%)	4 / 10 (40.00%)	3 / 21 (14.29%)
occurrences (all)	2	4	3
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	3	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Amylase increased			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	2
Blood creatinine increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	3 / 25 (12.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	5	0	0
Prostatic specific antigen increased			

subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	5 / 25 (20.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	5	1	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Tooth fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	3
Infusion related reaction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Atrial flutter			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	4 / 25 (16.00%)	1 / 10 (10.00%)	3 / 21 (14.29%)
occurrences (all)	4	1	4
Dysgeusia			

subjects affected / exposed	3 / 25 (12.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	3	1	2
Headache			
subjects affected / exposed	1 / 25 (4.00%)	2 / 10 (20.00%)	1 / 21 (4.76%)
occurrences (all)	1	2	1
Paraesthesia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Tremor			
subjects affected / exposed	3 / 25 (12.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 25 (52.00%)	2 / 10 (20.00%)	3 / 21 (14.29%)
occurrences (all)	20	2	3
Leukopenia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	7	1	1
Thrombocytopenia			
subjects affected / exposed	8 / 25 (32.00%)	2 / 10 (20.00%)	4 / 21 (19.05%)
occurrences (all)	16	3	6
Neutropenia			
subjects affected / exposed	11 / 25 (44.00%)	5 / 10 (50.00%)	3 / 21 (14.29%)
occurrences (all)	21	11	6
Ear and labyrinth disorders			
Ear pruritus			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Vomiting			

subjects affected / exposed	5 / 25 (20.00%)	2 / 10 (20.00%)	2 / 21 (9.52%)
occurrences (all)	6	2	2
Nausea			
subjects affected / exposed	7 / 25 (28.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	11	0	3
Haemorrhoids			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Diarrhoea			
subjects affected / exposed	13 / 25 (52.00%)	2 / 10 (20.00%)	5 / 21 (23.81%)
occurrences (all)	19	3	5
Constipation			
subjects affected / exposed	9 / 25 (36.00%)	4 / 10 (40.00%)	4 / 21 (19.05%)
occurrences (all)	12	5	4
Anal fissure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	3 / 25 (12.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	3	1	0
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	5 / 21 (23.81%)
occurrences (all)	1	0	7
Erythema			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	3	0
Night sweats			
subjects affected / exposed	3 / 25 (12.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	4 / 25 (16.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	4	1	3
Rash			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Rash erythematous			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Rash generalised			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Solar dermatitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Haematuria			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Nocturia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0

Pollakiuria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Polyuria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Urethral stenosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Urine odour abnormal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	4 / 21 (19.05%)
occurrences (all)	2	0	4
Hyperthyroidism			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	6 / 21 (28.57%)
occurrences (all)	2	0	6
Adrenal insufficiency			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 10 (0.00%)	4 / 21 (19.05%)
occurrences (all)	3	0	4
Back pain			
subjects affected / exposed	6 / 25 (24.00%)	2 / 10 (20.00%)	2 / 21 (9.52%)
occurrences (all)	6	2	2
Bone pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Flank pain			

subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	1	1	0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Muscle contracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Musculoskeletal chest pain			
subjects affected / exposed	4 / 25 (16.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	4	1	1
Musculoskeletal pain			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Neck pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	3 / 25 (12.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	4	1	1
Pathological fracture			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0

Herpes simplex			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 25 (4.00%)	1 / 10 (10.00%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Nasopharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 10 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	7
Oral candidiasis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Pneumonia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 10 (10.00%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 10 (0.00%)	2 / 21 (9.52%)
occurrences (all)	2	0	4
Urinary tract infection			
subjects affected / exposed	5 / 25 (20.00%)	0 / 10 (0.00%)	0 / 21 (0.00%)
occurrences (all)	9	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 25 (16.00%)	3 / 10 (30.00%)	2 / 21 (9.52%)
occurrences (all)	4	3	2
Dehydration			
subjects affected / exposed	2 / 25 (8.00%)	0 / 10 (0.00%)	1 / 21 (4.76%)
occurrences (all)	4	0	1
Hypocalcaemia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 10 (10.00%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Hypokalaemia			

subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 7	1 / 10 (10.00%) 1	0 / 21 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2016	Table of Events Update
06 April 2017	Inclusion Criteria Update
05 December 2019	Clinical Hold on the Study Update

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was placed on full clinical hold by the US FDA on 05 Sep 2017. Study was closed for further enrollment and subjects were discontinued from all treatments. Subjects were followed for SPMs for 5 years after last subject was enrolled per protocol.

Notes: