Clinical trial results:
A Phase 2b, Open-Label, Single-Arm Study of Selinexor (KPT-330) Plus Low-Dose Dexamethasone (Sd) in Patients with Multiple Myeloma Previously Treated with Lenalidomide, Pomalidomide, Bortezomib, Carfilzomib, and Daratumumab, and Refractory to Prior Treatment with Glucocorticoids, an Immunomodulatory Agent, a Proteasome Inhibitor, and the anti-CD38 mAb Daratumumab

Summary

EudraCT number	2016-003094-18
Trial protocol	DE AT BE GR
Global end of trial date	26 July 2019

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021

Trial information

Trial identification

Sponsor protocol code	KCP-330-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02336815
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Karyopharm Therapeutics Inc.
Sponsor organisation address	85 Wells Avenue, Newton, MA, United States, 02459
Public contact	Clinical Trials Information, Karyopharm Therapeutic Inc., +1 617658 0600, clinicaltrials@karyopharm.com
Scientific contact	Clinical Trials Information, Karyopharm Therapeutic Inc., +1 617658 0600, clinicaltrials@karyopharm.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	26 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study is to evaluate the efficacy of selinexor 80 mg PO plus low-dose dexamethasone 20 mg PO (Sd) on Days 1 and 3 twice weekly in subjects with penta-exposed, triple-class-refractory MM enrolled in Part 2 of the study.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles originating in the Declaration of Helsinki in place at the time of study conduct. The study was conducted in compliance with the International Council on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP] guideline CPMP/ICH/135/95), United States Code of Federal Code of Regulations, and all applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2015
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	Austria: 1
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	United States: 163
Worldwide total number of subjects	202
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)	104
From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part 1 of the study was conducted at 32 sites in the United States and Part 2 of the study was conducted at 59 sites in France, Germany, Belgium, Greece, Austria and United States. Enrollment in both parts was between from 26 May 2015 (first subject first visit)) and 26 July 2019 (last subject last visit).

Pre-assignment

Screening details:

A total of 202 subjects were enrolled in the study, out of which 79 subjects were treated in Part 1 and 123 subjects were treated in Part 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1

Arm description:

Subjects with quad-exposed, double-class-refractory (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb) and penta-exposed, triple-class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, two dosing schedules (1) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly continuously in 4-week cycles; until disease progression, death, or unacceptable toxicity (maximum duration of approximately 13 months).

Arm type	Experimental
Investigational medicinal product name	Selinexor
Investigational medicinal product code	KPT-330
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received two dosing schedules (1) selinexor 80mg twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) selinexor 80mg twice-weekly continuously in 4-week cycles.

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

Dosage and administration details:

Subjects received two dosing schedules (1) low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) low-dose dexamethasone 20 mg (Sd) twice-weekly continuously in 4-week cycles.

Arm title	Part 2

Arm description:

Subjects who previously had received more than 3 anti-MM regimens and had penta-exposed, triple class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, selinexor 80 mg post oral (PO) plus low-dose dexamethasone 20 mg Sd twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity (maximum duration of approximately 17 months).

Arm type	Experimental
Investigational medicinal product name	Selinexor
Investigational medicinal product code	KPT-330
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received selinexor 80mg PO Sd twice-weekly on Days 1 and 3.

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

Dosage and administration details:

Subjects received low-dose dexamethasone 20 mg Sd twice-weekly on Days 1 and 3.

Number of subjects in period 1	Part 1	Part 2
Started	79	123
Completed	0	0
Not completed	79	123
Physician decision	11	4
Consent withdrawn by subject	3	2
Adverse event, non-fatal	18	39
Unspecified	1	5
Lost to follow-up	1	3
Disease Progression	45	70

Baseline characteristics

Reporting groups	
Reporting group title	Part 1
Reporting group description:	
Subjects with quad-exposed, double-class-refractory (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb) and penta-exposed, triple-class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, two dosing schedules (1) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly continuously in 4-week cycles; until disease progression, death, or unacceptable toxicity (maximum duration of approximately 13 months).	
Reporting group title	Part 2
Reporting group description:	
Subjects who previously had received more than 3 anti-MM regimens and had penta-exposed, triple class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, selinexor 80 mg post oral (PO) plus low-dose dexamethasone 20 mg Sd twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity (maximum duration of approximately 17 months).	

Reporting group values	Part 1	Part 2	Total
Number of subjects	79	123	202
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.9	64.5	
standard deviation	± 8.79	± 9.41	-
Gender categorical Units: Subjects			
Female	42	52	94
Male	37	71	108
Ethnicity Units: Subjects			
Hispanic or Latino	2	9	11
Not Hispanic or Latino	75	97	172
Unknown or Not Reported	2	17	19
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	2
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	14	21	35
White	62	86	148
More than one race	2	8	10
Unknown or Not Reported	1	5	6
Region of Enrollment Units: Subjects			

Austria	0	1	1
Belgium	0	7	7
France	0	14	14
Germany	0	10	10
Greece	0	7	7
United States	79	84	163

End points

End points reporting groups

Reporting group title	Part 1

Reporting group description:

Subjects with quad-exposed, double-class-refractory (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb) and penta-exposed, triple-class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, two dosing schedules (1) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) selinexor 80 mg plus low-dose dexamethasone 20 mg (Sd) twice-weekly continuously in 4-week cycles; until disease progression, death, or unacceptable toxicity (maximum duration of approximately 13 months).

Reporting group title	Part 2

Reporting group description:

Subjects who previously had received more than 3 anti-MM regimens and had penta-exposed, triple class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, selinexor 80 mg post oral (PO) plus low-dose dexamethasone 20 mg Sd twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity (maximum duration of approximately 17 months).

Primary: Part 2: Percentage of Subjects With Overall Response Rate (ORR) Per International Myeloma Working Group (IMWG) as Assessed by an Independent Review Committee (IRC)

End point title	Part 2: Percentage of Subjects With Overall Response Rate (ORR) Per International Myeloma Working Group (IMWG) as Assessed by an Independent Review Committee (IRC)[1][2]

End point description:

IRC assessed ORR per 2016 IMWG criteria: Percentage of subjects who experienced Partial response (PR): >=50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to lesser than (<) 200mg per 24 hours; Very good partial response (VGPR): Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100mg per 24 hours; Complete response (CR): Negative immunofixation on the serum, urine and disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow; or stringent complete response (sCR): CR as defined by Normal free light chain (FLC) ratio + Absence of clonal cells in bone marrow biopsy by immunohistochemistry). Modified intent-to-treat (mITT) population: Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Baseline until disease progression/discontinuation from the study, or death, whichever occurred first (maximum duration of 17 months)

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: Per protocol, only descriptive analyses was planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analyzed for Part 1.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Percentage of Subjects				
number (confidence interval 95%)	26.2 (18.7 to 35.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Duration of Response (DoR) Per IMWG as Assessed by IRC

End point title	Part 1: Duration of Response (DoR) Per IMWG as Assessed by IRC[3]

End point description:

IRC assessed DoR per 2016 IMWG criteria: time (in months) from the first documentation of objective response (confirmed CR or PR) to the date of first documentation of progressive disease (PD) or death due to any cause. PR: >50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg per 24 hours; CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow; PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1 g/dL if the lowest M-component was >=5g/dL; Urine M-protein (absolute increase must be >=200mg per 24 hours). Safety population: all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information. Here, "number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

First response subsequently confirmed to disease progression/discontinuation from the study, or death, whichever occurred first (maximum duration of 13 months)

Notes:

[3] - 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Months				
median (confidence interval 95%)	6.2 (3.6 to 9.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Duration of Response (DoR) Per IMWG as Assessed by an IRC

End point title	Part 2: Duration of Response (DoR) Per IMWG as Assessed by an IRC[4]

End point description:

IRC assessed DoR per 2016 IMWG criteria: time (in months) from the first documentation of objective response (confirmed CR or PR) to the date of first documentation of progressive disease (PD) or death

due to any cause. PR: >50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg per 24 hours; CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow; PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1 g/dL if the lowest M-component was >=5g/dL; Urine M-protein (absolute increase must be >=200mg per 24 hours). mITT population. Here, "number of subjects analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

First response subsequently confirmed to disease progression/discontinuation from the study, or death, whichever occurred first (maximum duration of 17 months)

Notes:

[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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Months				
median (confidence interval 95%)	4.4 (3.7 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Subjects With Clinical Benefit Rate (CBR)) Per IMWG as Assessed by IRC

End point title	Part 1: Percentage of Subjects With Clinical Benefit Rate (CBR)) Per IMWG as Assessed by IRC[5]

End point description:

IRC assessed CBR per 2016 IMWG criteria: Percentage of subjects with a confirmed minimal response (MR) or better (PR, VGPR, CR or sCR) before confirmed disease progression or initiating new MM treatment. MR: >=25% but <49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50-89%. PR: >=50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg per 24 hours; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours; CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <= 5% plasma cells in bone marrow; or sCR: CR as defined by Normal FLC ratio + Absence of clonal cells by immunohistochemistry). Safety population consisted of all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information.

End point type	Secondary

End point timeframe:

Baseline up to a maximum of 13 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage of Subjects				
number (confidence interval 95%)	31.6 (21.6 to 43.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects With Clinical Benefit Rate (CBR) Per IMWG as Assessed by IRC

End point title	Part 2: Percentage of Subjects With Clinical Benefit Rate (CBR) Per IMWG as Assessed by IRC[6]

End point description:

IRC assessed CBR per 2016 IMWG criteria: Percentage of subjects with a confirmed MR or better (PR, VGPR, CR or sCR) before confirmed disease progression or initiating new MM treatment. MR: >=25% but <49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50-89%. PR: >=50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to <200mg per 24 hours; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours; CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow; or sCR: CR as defined by Normal FLC ratio + Absence of clonal cells by immunohistochemistry). mITT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline up to a maximum of 17 months

Notes:

[6] - 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Percentage of Subjects				
number (confidence interval 95%)	39.3 (30.6 to 48.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Duration of Clinical Benefit Per IMWG as Assessed by IRC

End point title	Part 1: Duration of Clinical Benefit Per IMWG as Assessed by IRC[7]

End point description:

IRC assessed duration of clinical benefit per 2016 IMWG criteria: Duration from first response (at least MR) to time of IRC-determined PD or death due to disease progression, whichever occurs first. MR:

>=25% but <49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50-89%. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5 g/dL; Serum M-protein increase >=1 g/dL if the lowest M-component was >=5 g/dL; Urinary M-protein (absolute increase must be >= 200 mg per 24 hours). Safety population consisted of all subject, who had received at least 1 dose of study treatment and had any post-baseline safety information. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

First response subsequently confirmed to disease progression, or death, whichever occurred first (maximum duration of 13 months)

Notes:

[7] - 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Months				
median (confidence interval 95%)	5.6 (4.4 to 10.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Duration of Clinical Benefit Per IMWG as Assessed by IRC

End point title	Part 2: Duration of Clinical Benefit Per IMWG as Assessed by IRC[8]

End point description:

IRC assessed duration of clinical benefit per 2016 IMWG criteria: Duration from first response (at least MR) to time of IRC-determined PD or death due to disease progression, whichever occurs first. MR: >=25% but <49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50-89%. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1g/dL if the lowest M-component was >=5g/dL; Urinary M-protein (absolute increase must be >=200mg per 24 hours). Analysis was performed using Kaplan-Meier method. miTT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment. Here, "number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

First response subsequently confirmed to disease progression, or death, whichever occurred first (maximum duration of 17 months)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Months				
median (confidence interval 95%)	3.8 (3.2 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Disease Control Rate (DCR)

End point title	Part 2: Disease Control Rate (DCR)[9]

End point description:

DCR was defined as the percentage of subjects who achieved stable disease (SD) or better (MR, PR, VGPR, CR, sCR) for a minimum of 12 weeks. SD: Not recommended for use as an indicator of response; stability of disease was best described by providing the time to progression (TTP) estimates. MR: >=25% but <49% reduction of serum M-protein and reduction in 24-hour urinary M-protein by 50-89%. PR: >=50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg per 24 hours; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours; CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <=5% plasma cells in bone marrow; or sCR: CR as defined by Normal FLC ratio + Absence of clonal cells by immunohistochemistry). mITT population.

End point type	Secondary

End point timeframe:

Every 12 weeks until progressive disease or death due to any cause, up to 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: Data for this endpoint was not planned to be collected and analyzed for Part 1.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Percentage of subjects				
number (confidence interval 95%)	44.3 (35.3 to 53.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Progression Free Survival (PFS) Per IMWG as Assessed by IRC

End point title	Part 1: Progression Free Survival (PFS) Per IMWG as Assessed by IRC[10]

End point description:

IRC assessed PFS per 2016 IMWG criteria: Duration from start of study treatment until IRC-determined progressive disease (PD) or death from any cause, whichever occurred first. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1g/dL if the lowest M-component was >=5g/dL;

Urinary M-protein (absolute increase must be >=200mg/24 hours). Analysis was performed using Kaplan-Meier method. Safety population consisted of all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information.

End point type	Secondary

End point timeframe:

From start of study treatment to progression of disease or discontinuation from the study or death, whichever occurred first (maximum duration of 13 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	4.7 (3.3 to 7.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Progression Free Survival (PFS) Per IMWG as Assessed by IRC

End point title	Part 2: Progression Free Survival (PFS) Per IMWG as Assessed by IRC[11]

End point description:

IRC assessed PFS per 2016 IMWG criteria: Duration from start of study treatment until IRC-determined progressive disease (PD) or death from any cause, whichever occurred first. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1g/dL if the lowest M-component was >=5g/dL; Urinary M-protein (absolute increase must be >=200 mg/24 hours). Analysis was performed using Kaplan-Meier method. mITT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From start of study treatment to progression of disease or discontinuation from the study or death, whichever occurred first (maximum duration of 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Months				
median (confidence interval 95%)	3.7 (2.8 to 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Time to Progression (TTP) Per IMWG as Assessed by IRC

End point title	Part 1: Time to Progression (TTP) Per IMWG as Assessed by IRC[12]

End point description:

IRC assessed TTP per 2016 IMWG criteria: Duration from start of study treatment until PD or death due to PD (per IRC), whichever occurred first. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1g/dL if the lowest M-component was >=5g/dL; Urinary M-protein (absolute increase must be >=200mg/24 hours). Analysis was performed using Kaplan-Meier method. Safety population consisted of all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information.

End point type	Secondary

End point timeframe:

From start of study treatment to progression of disease or death, whichever occurred first (maximum duration of 13 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	5.5 (3.3 to 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to Progression (TTP) Per IMWG as Assessed by IRC

End point title	Part 2: Time to Progression (TTP) Per IMWG as Assessed by IRC[13]

End point description:

IRC assessed TTP per 2016 IMWG criteria: Duration from start of study treatment until PD or death due to PD (per IRC), whichever occurred first. PD: Increase of 25% from lowest confirmed response value in 1 or more of the following criteria: Serum M-protein with absolute increase of >=0.5g/dL; Serum M-protein increase >=1g/dL if the lowest M-component was >=5g/dL; Urinary M-protein (absolute increase must be >=200mg/24 hours). Analysis was performed using Kaplan-Meier method. mITT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From start of study treatment to progression of disease or death, whichever occurred first (maximum duration of 17 months)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Months				
median (confidence interval 95%)	4.1 (3.0 to 6.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Time to Next Treatment (TTNT)

End point title	Part 1: Time to Next Treatment (TTNT)[14]

End point description:

TTNT was defined as the duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurred first. Analysis was performed using Kaplan-Meier method. Safety population consisted of all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information.

End point type	Secondary

End point timeframe:

From start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first (maximum duration of 13 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	2.6 (1.8 to 4.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Time to Next Treatment (TTNT)

End point title	Part 2: Time to Next Treatment (TTNT)[15]

End point description:

TTNT was defined as the duration from start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurred first. Analysis was performed using Kaplan-Meier method. mITT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From start of study treatment to start of next anti-MM treatment or death due to disease progression, whichever occurs first (maximum duration of 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Months				
median (confidence interval 95%)	3.2 (2.6 to 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Overall Survival (OS)

End point title	Part 1: Overall Survival (OS)[16]

End point description:

OS was defined as the duration (in months) from start of study treatment to death from any cause. Subjects last known to be alive were censored at the date of discontinuation from the study, or database cut date, whichever was earlier. Analysis was performed using Kaplan-Meier method. Safety population consisted of all subjects, who had received at least 1 dose of study treatment and had any post-baseline safety information.

End point type	Secondary

End point timeframe:

From start of study treatment to death (maximum duration of 13 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	7.3 (5.8 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Overall Survival (OS)

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

End point description:

OS was defined as the duration (in months) from start of study treatment to death from any cause. Subjects last known to be alive were censored at the date of discontinuation from the study, or database cut date, whichever was earlier. Analysis was performed using Kaplan-Meier method. mITT population consisted of Part 2 subjects with penta-refractory MM who met all eligibility criteria and received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From start of study treatment to death (maximum duration of 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: Data for this endpoint was separately analysed for both the Part 1 and 2.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Months				
median (confidence interval 95%)	8.4 (6.2 to 11.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change From Baseline in Health-related Quality of Life (HRQL) Score Based on Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM) Questionnaire

End point title	Part 2: Change From Baseline in Health-related Quality of Life (HRQL) Score Based on Functional Assessment of Cancer Therapy - Multiple Myeloma (FACT-MM) Questionnaire[18]

End point description:

FACT-MM combines the general version of the FACT (FACT-G) with a MM-specific sub-scale (14 items). Sub-scales for the FACT-G are Physical Well-Being (7 items), Social/Family Well-Being (7 items), Emotional Well-Being (6 items), and Functional Well-Being (7 items). Trial outcomes index (TOI); total of (41 items) was the primary measurement of interest, comprised of the Physical and Functional sub-scales plus the MM-specific sub-scale. Each item is rated on a 5-point Likert scale, ranging from 0 ("Not at all") to 4 ("Very much"), therefore the TOI has a score ranging from 0-120. Higher scores indicated improvement in well being. mITT population. Here “number of subjects analysed” signifies those subjects who were evaluable for this endpoint and “n=number analysed” signifies those subjects who were evaluable at specified time points. Here, '99999' indicates standard deviation was not estimated due to single subject and '9999' indicates no subject was estimated at specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 2 to Cycle 20 (up to a maximum of 17 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: Data for this endpoint was not planned to be collected and analyzed for Part 1.

End point values	Part 2			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
TOI Score: Baseline (n=107)	67.5 (± 19.20)			
TOI Score: Change at C2D1 (n=76)	-6.1 (± 18.43)			
TOI Score: Change at C3D1 (n=50)	-8.5 (± 15.50)			
TOI Score: Change at C4D1 (n=31)	-9.1 (± 16.79)			
TOI Score: Change at C5D1 (n=26)	-6.9 (± 12.06)			
TOI Score: Change at C6D1 (n=19)	-8.3 (± 15.07)			
TOI Score: Change at C7D1 (n=13)	-7.5 (± 19.26)			
TOI Score: Change at C8D1 (n=5)	-15.4 (± 24.59)			
TOI Score: Change at C9D1 (n=3)	-4.7 (± 14.84)			
TOI Score: Change at C10D1 (n=3)	-4.0 (± 5.29)			
TOI Score: Change at C11D1 (n=1)	3.0 (± 99999)			
TOI Score: Change at C12D1 (n=1)	3.0 (± 99999)			
TOI Score: Change at C13D1 (n=1)	-23.0 (± 99999)			
TOI Score: Change at C14D1 (n=1)	14.0 (± 99999)			
TOI Score: Change at C15D1 (n=1)	1.0 (± 99999)			
TOI Score: Change at C16D1 (n=1)	4.0 (± 99999)			
TOI Score: Change at C17D1 (n=0)	9999 (± 9999)			
TOI Score: Change at C18D1 (n=0)	9999 (± 9999)			
TOI Score: Change at C19D1 (n=0)	9999 (± 9999)			
TOI Score: Change at C20D1 (n=0)	9999 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAE) of Grade 3/4, Graded Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAE) of Grade 3/4, Graded Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. As per NCI-CTCAE version 4.03, Grade 1: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self-care ADL; Grade 4: life-threatening consequence, urgent intervention indicated; Grade 5: death related to AE. TEAE are events between first dose of study drug and up to last dose of study treatment + 30 days (inclusive) that were absent before treatment or that worsened relative to pre-treatment state. Safety population set .

End point type	Secondary

End point timeframe:

Baseline to 30 days after last dose of study treatment (maximum duration of 18 months)

End point values	Part 1	Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	123		
Units: Subjects	75	115		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Treatment-Related Adverse Events (TEAEs) of Grade 3/4, Graded Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Treatment-Emergent Treatment-Related Adverse Events (TEAEs) of Grade 3/4, Graded Based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE), Version 4.03

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. As per NCI-CTCAE version 4.03, Grade 1: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self-care ADL; Grade 4: life-threatening consequence, urgent intervention indicated; Grade 5: death related to AE. A treatment related AE was any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event had a causal relationship with the treatment or usage. Safety population set.

End point type	Secondary

End point timeframe:

Baseline to 30 days after last dose of study treatment (maximum duration of 18 months)

End point values	Part 1	Part 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	123		
Units: Subjects	69	110		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Apparent Clearance (CL/F) of Selinexor in Plasma

End point title	Part 1: Apparent Clearance (CL/F) of Selinexor in Plasma[19]

End point description:

CL/F of selinexor in plasma was reported. Pharmacokinetic (PK) set included all subjects in Part 1 who received at least 1 dose of investigational product in this study.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1: Pre-dose, 1, 2 and 4 hours post-dose; Day 8 and 15: Pre-dose and 1 hour post-dose; Cycle 2: Day 1: Pre-dose, 1, 2 and 4 hours post-dose

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: Data for this endpoint was not planned to be collected and analyzed for Part 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Liters per Hour				
arithmetic mean (standard deviation)	16.6 (± 2.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Volume of Distribution (V/F) of Selinexor in Plasma

End point title	Part 1: Volume of Distribution (V/F) of Selinexor in Plasma[20]

End point description:

Vz/F of selinexor in plasma was reported. PK set included all subjects in Part 1 who received at least 1 dose of investigational product in this study.

End point type	Secondary

End point timeframe:

Cycle 1: Day 1: Pre-dose, 1, 2 and 4 hours post-dose; Day 8 and 15: Pre-dose and 1 hour post-dose; Cycle 2: Day 1: Pre-dose, 1, 2 and 4 hours post-dose

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for this endpoint was not planned to be collected and analyzed for Part 2.

End point values	Part 1			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Liter				
arithmetic mean (standard deviation)	145.6 (± 28.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to 30 days after last dose of study treatment (maximum duration of 18 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Part 1

Reporting group description:

Subjects with quad-exposed, double-class-refractory (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, but not an anti-CD38 mAb) and penta-exposed, triple-class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, two dosing schedules (1) Selinexor 80mg plus low-dose dexamethasone 20mg (Sd) twice-weekly on Days 1 and 3 for 3 weeks of each 4-week cycle; (2) Selinexor 80mg plus low-dose dexamethasone 20mg (Sd) twice-weekly continuously in 4-week cycles; until disease progression, death, or unacceptable toxicity (maximum duration of approximately 13 months).

Reporting group title	Part 2

Reporting group description:

Subjects who previously had received more than 3 anti-MM regimens and had penta-exposed, triple class-refractory MM (i.e. previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab, and refractory to prior treatment with glucocorticoids, an IMiD, a PI, and the anti-CD38 mAb daratumumab) received, Selinexor 80mg post oral (PO) plus low-dose dexamethasone 20mg Sd twice-weekly on Days 1 and 3 until disease progression, death, or unacceptable toxicity (maximum duration of approximately 17 months).

Serious adverse events	Part 1	Part 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 79 (56.96%)	78 / 123 (63.41%)	
number of deaths (all causes)	20	28	
number of deaths resulting from adverse events	8	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell leukaemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 8	0 / 12	
Vascular disorders			

Circulatory collapse			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 79 (2.53%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 79 (3.80%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 79 (1.27%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	0 / 79 (0.00%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 8	1 / 12	
Hyperthermia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 8	1 / 12	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 79 (3.80%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	1 / 8	0 / 12	
Epistaxis			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 8	1 / 12	
Respiratory failure			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 8	0 / 12	
Acute pulmonary oedema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 8	1 / 12	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 79 (5.06%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 79 (1.27%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			

subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus test positive			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 79 (2.53%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 79 (1.27%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	1 / 8	1 / 12	
Compression fracture			
subjects affected / exposed	2 / 79 (2.53%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical vertebral fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardio-respiratory arrest			
subjects affected / exposed	2 / 79 (2.53%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	2 / 8	0 / 12	
Cardiac disorder			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 12	
Cardiac failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 79 (1.27%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral neuropathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	5 / 79 (6.33%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 79 (2.53%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 79 (3.80%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 79 (3.80%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 79 (2.53%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 79 (2.53%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 79 (5.06%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vein thrombosis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 79 (2.53%)	14 / 123 (11.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 14	
deaths causally related to treatment / all	0 / 8	2 / 12	
Sepsis			
subjects affected / exposed	1 / 79 (1.27%)	12 / 123 (9.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 12	
deaths causally related to treatment / all	0 / 8	4 / 12	
Bacteraemia			
subjects affected / exposed	2 / 79 (2.53%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	4 / 79 (5.06%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	1 / 8	0 / 12	
Parainfluenzae virus infection			

subjects affected / exposed	1 / 79 (1.27%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 79 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 79 (1.27%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 79 (3.80%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 79 (2.53%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	4 / 79 (5.06%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	1 / 79 (1.27%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 79 (1.27%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 79 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1	Part 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 79 (100.00%)	123 / 123 (100.00%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 79 (69.62%)	77 / 123 (62.60%)	
occurrences (all)	55	77	
Pyrexia			
subjects affected / exposed	10 / 79 (12.66%)	18 / 123 (14.63%)	
occurrences (all)	10	18	
Asthenia			

subjects affected / exposed	5 / 79 (6.33%)	19 / 123 (15.45%)	
occurrences (all)	5	19	
Oedema peripheral			
subjects affected / exposed	5 / 79 (6.33%)	14 / 123 (11.38%)	
occurrences (all)	5	14	
Chills			
subjects affected / exposed	6 / 79 (7.59%)	4 / 123 (3.25%)	
occurrences (all)	6	4	
Malaise			
subjects affected / exposed	2 / 79 (2.53%)	8 / 123 (6.50%)	
occurrences (all)	2	8	
Gait disturbance			
subjects affected / exposed	0 / 79 (0.00%)	7 / 123 (5.69%)	
occurrences (all)	0	7	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	23 / 79 (29.11%)	28 / 123 (22.76%)	
occurrences (all)	23	28	
Cough			
subjects affected / exposed	12 / 79 (15.19%)	18 / 123 (14.63%)	
occurrences (all)	12	18	
Epistaxis			
subjects affected / exposed	11 / 79 (13.92%)	13 / 123 (10.57%)	
occurrences (all)	11	13	
Productive cough			
subjects affected / exposed	4 / 79 (5.06%)	3 / 123 (2.44%)	
occurrences (all)	4	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 79 (13.92%)	22 / 123 (17.89%)	
occurrences (all)	11	22	
Confusional state			
subjects affected / exposed	9 / 79 (11.39%)	11 / 123 (8.94%)	
occurrences (all)	9	11	
Anxiety			

subjects affected / exposed	4 / 79 (5.06%)	8 / 123 (6.50%)	
occurrences (all)	4	8	
Investigations			
Weight decreased			
subjects affected / exposed	39 / 79 (49.37%)	61 / 123 (49.59%)	
occurrences (all)	39	61	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 79 (7.59%)	13 / 123 (10.57%)	
occurrences (all)	6	13	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 79 (3.80%)	11 / 123 (8.94%)	
occurrences (all)	3	11	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 79 (5.06%)	13 / 123 (10.57%)	
occurrences (all)	4	13	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	9 / 79 (11.39%)	4 / 123 (3.25%)	
occurrences (all)	9	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 79 (15.19%)	19 / 123 (15.45%)	
occurrences (all)	12	19	
Headache			
subjects affected / exposed	10 / 79 (12.66%)	11 / 123 (8.94%)	
occurrences (all)	10	11	
Dysgeusia			
subjects affected / exposed	10 / 79 (12.66%)	10 / 123 (8.13%)	
occurrences (all)	10	10	
Peripheral neuropathy			
subjects affected / exposed	7 / 79 (8.86%)	8 / 123 (6.50%)	
occurrences (all)	7	8	
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	58 / 79 (73.42%)	91 / 123 (73.98%)	
occurrences (all)	58	91	
Anaemia			
subjects affected / exposed	37 / 79 (46.84%)	80 / 123 (65.04%)	
occurrences (all)	37	80	
Neutropenia			
subjects affected / exposed	23 / 79 (29.11%)	49 / 123 (39.84%)	
occurrences (all)	23	49	
Leukopenia			
subjects affected / exposed	20 / 79 (25.32%)	41 / 123 (33.33%)	
occurrences (all)	20	41	
Lymphopenia			
subjects affected / exposed	11 / 79 (13.92%)	20 / 123 (16.26%)	
occurrences (all)	11	20	
Eye disorders			
Vision blurred			
subjects affected / exposed	10 / 79 (12.66%)	13 / 123 (10.57%)	
occurrences (all)	10	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	60 / 79 (75.95%)	88 / 123 (71.54%)	
occurrences (all)	60	88	
Diarrhoea			
subjects affected / exposed	35 / 79 (44.30%)	57 / 123 (46.34%)	
occurrences (all)	35	57	
Vomiting			
subjects affected / exposed	37 / 79 (46.84%)	47 / 123 (38.21%)	
occurrences (all)	37	47	
Constipation			
subjects affected / exposed	21 / 79 (26.58%)	27 / 123 (21.95%)	
occurrences (all)	21	27	
Abdominal pain			
subjects affected / exposed	7 / 79 (8.86%)	12 / 123 (9.76%)	
occurrences (all)	7	12	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 123 (2.44%)	
occurrences (all)	4	3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 79 (11.39%)	10 / 123 (8.13%)	
occurrences (all)	9	10	
Bone pain			
subjects affected / exposed	7 / 79 (8.86%)	11 / 123 (8.94%)	
occurrences (all)	7	11	
Hypercreatinaemia			
subjects affected / exposed	9 / 79 (11.39%)	6 / 123 (4.88%)	
occurrences (all)	9	6	
Arthralgia			
subjects affected / exposed	6 / 79 (7.59%)	6 / 123 (4.88%)	
occurrences (all)	6	6	
Muscle spasms			
subjects affected / exposed	4 / 79 (5.06%)	8 / 123 (6.50%)	
occurrences (all)	4	8	
Muscular weakness			
subjects affected / exposed	6 / 79 (7.59%)	4 / 123 (3.25%)	
occurrences (all)	6	4	
Pain in extremity			
subjects affected / exposed	4 / 79 (5.06%)	4 / 123 (3.25%)	
occurrences (all)	4	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 79 (12.66%)	17 / 123 (13.82%)	
occurrences (all)	10	17	
Pneumonia			
subjects affected / exposed	3 / 79 (3.80%)	10 / 123 (8.13%)	
occurrences (all)	3	10	
Urinary tract infection			
subjects affected / exposed	6 / 79 (7.59%)	4 / 123 (3.25%)	
occurrences (all)	6	4	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	43 / 79 (54.43%)	68 / 123 (55.28%)	
occurrences (all)	43	68	
Hyponatraemia			
subjects affected / exposed	34 / 79 (43.04%)	45 / 123 (36.59%)	
occurrences (all)	34	45	
Hyperglycaemia			
subjects affected / exposed	16 / 79 (20.25%)	15 / 123 (12.20%)	
occurrences (all)	16	15	
Hypokalaemia			
subjects affected / exposed	5 / 79 (6.33%)	24 / 123 (19.51%)	
occurrences (all)	5	24	
Dehydration			
subjects affected / exposed	15 / 79 (18.99%)	10 / 123 (8.13%)	
occurrences (all)	15	10	
Hypocalcaemia			
subjects affected / exposed	7 / 79 (8.86%)	13 / 123 (10.57%)	
occurrences (all)	7	13	
Hypomagnesaemia			
subjects affected / exposed	10 / 79 (12.66%)	10 / 123 (8.13%)	
occurrences (all)	10	10	
Hypophosphataemia			
subjects affected / exposed	6 / 79 (7.59%)	8 / 123 (6.50%)	
occurrences (all)	6	8	
Hypercreatininaemia			
subjects affected / exposed	6 / 79 (7.59%)	6 / 123 (4.88%)	
occurrences (all)	6	6	
Hypercalcaemia			
subjects affected / exposed	6 / 79 (7.59%)	5 / 123 (4.07%)	
occurrences (all)	6	5	
Hyperkalaemia			
subjects affected / exposed	1 / 79 (1.27%)	10 / 123 (8.13%)	
occurrences (all)	1	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 February 2015	Protocol Amendment 1: - Extended the Screening Period from 14 days to 21 days prior to first dose. - Added resolution of hematologic toxicities from previous treatments to ≤ Grade 2 in response to a deficiency reported by the FDA. - Clarified that that PFS, QoL, and OS will not be tested for statistical significance, in response to comments from the FDA.
25 September 2015	Protocol Amendment 2: - Revised the study target subject population from quad-refractory to dualrefractory as shown in the following modified inclusion criteria: From: Subjects must have "MM refractory to lenalidomide, pomalidomide, bortezomib, and carfilzomib." To: "Subjects must have been previously exposed to lenalidomide, pomalidomide, bortezomib, and carfilzomib" and have "MM double refractory to previous treatment with both the PI and IMiD drug classes". - Changed the study treatment (selinexor plus dexamethasone) dose schedule from "twice-weekly for three weeks of every four-week cycle" to "twice weekly for every week of each four-week cycle." Changed the indication from Multiple myeloma quad-refractory to prior treatment with bortezomib, carfilzomib, lenalidomide, and pomalidomide to Multiple myeloma refractory to prior treatment with an IMiD and a PI. - Moved the following objective from exploratory objectives to secondary objectives: * Determine ORR, DOR, PFS, and OS in the subgroup of subjects with free light chain (FLC) MM" * Added MRD assessment for subjects who achieve sCR to Exploratory Objectives
11 August 2016	Protocol Amendment 3: - Expanded the population of subjects with penta-refractory MM by enrolling approximately 130 additional subjects. The overall study population increased to ~210 subjects. - Revised the study design to make the expansion population (Part 2) the mITT population for the primary efficacy analysis (using ORR); ORR for subjects enrolled in Part 1 became a secondary analysis. - Added that the secondary objectives DOR, PFS, DCR, CBR, TTP and OS will be analyzed separately in different subject sub-populations (i.e. Part 1 subjects with quad-refractory MM, Part 1 subjects with penta-refractory MM, and Part 2 subjects with penta-refractory MM). - Modified inclusion criteria 5 (now 4) to include either daratumumab or isatuximab Modified inclusion criteria 6 (now 5) to include subjects with MM refractory to previous treatment with one or more glucocorticoids, parenteral PI (i.e. bortezomib in and/or carfilzomib), IMiD (i.e. lenalidomide and/or pomalidomide), and anti-CD38 mAb (i.e. either daratumumab or isatuximab). - Modified inclusion criteria 7 (now 6) (multiple myeloma that is refractory to the subjects most recent anti-MM regimen). The new wording in 6 states that "documented severe intolerance to the subjects last therapy is allowed upon approval by the Medical Monitor." - Adjusted inclusion criterion 13 (now 12), requiring adequate platelet count of ≥50,000/mm3 (subjects in whom ≥50% of bone marrow nucleated cells are plasma cells) at baseline. - Added inclusion criteria13, regarding baseline hemoglobin level ≥8.5 g/dL.

28 April 2017	Protocol Amendment 4: - Removed blood draws for PDn and PK analysis as PK and PDn blood samples are no longer being collected. - Pregnancy Testing added, with the following text: "For females of childbearing potential, a negative serum human chorionic gonadotropin (hCG) pregnancy test must be obtained within 3 days before the first dose of study treatment. Test sensitivity for hCG must be ≥25 mIU/mL. Pregnancy testing (serum hCG or urine) is also required for females of childbearing potential prior to dosing on Day 1 of Cycles ≥2 during the study and at the EoT Visit (serum hCG). Pregnancy testing may also be performed as clinically indicated during the study." - Changed volume of Screening bone marrow aspirate from 1x6 mL to 2x10mL to provide sufficient material for PDn tests. Specified that karyotyping and FISH will be performed at a central laboratory.
13 December 2017	Protocol Amendment 5: - Updated definitions of Durations of CBR and DCR. - For consistency with Statistical Analysis Plan: updated the definition of mITT and PP populations; removed presentation of exploratory EE population (details to be provided SAP only). - Updated Sub-Group Efficacy Analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported