



Clinical trial results:

A Randomized, Open-label, Phase 3 Study Comparing Once-weekly vs Twice-weekly Carfilzomib in Combination With Lenalidomide and Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma (A.R.R.O.W.2)

Summary

EudraCT number	2018-000665-36
Trial protocol	SE DE NL ES CZ FR BG SK FI LT AT RO
Global end of trial date	31 March 2023

Results information

Result version number	v1 (current)
This version publication date	10 April 2024
First version publication date	10 April 2024

Trial information

Trial identification

Sponsor protocol code	20180015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03859427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	31 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to compare the efficacy of carfilzomib, lenalidomide, and dexamethasone (KRd) 56 mg/m² once weekly to KRd 27 mg/m² twice weekly in participants with relapsed or refractory multiple myeloma (RRMM) with 1 to 3 prior lines of therapy.

Protection of trial subjects:

The study was conducted in accordance with International Council for Harmonisation Good Clinical Practice regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 May 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
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	Bulgaria: 12
Country: Number of subjects enrolled	Czechia: 71
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 90
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Romania: 58
Country: Number of subjects enrolled	Russian Federation: 44
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Sweden: 20
Country: Number of subjects enrolled	Türkiye: 35
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	United States: 4

Worldwide total number of subjects	454
EEA total number of subjects	350

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)	223
From 65 to 84 years	230
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 80 study centers in Europe, Japan, and the United States, and participated from 08 May 2019 to 31 March 2023.

Pre-assignment

Screening details:

Participants with RRMM were randomized in a 1:1 ratio to receive once-weekly or twice-weekly carfilzomib, stratified by original International Staging System (ISS) stage at the time of study entry (stage 1 or 2 vs stage 3), prior lenalidomide treatment (yes vs no), proteasome inhibitor treatment (yes vs no), and anti-CD38 exposure (yes vs no).

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	Twice-weekly KRd 20/27 mg/m ²

Arm description:

Carfilzomib was administered twice-weekly intravenously as a 10 ± 5 minute infusion using an infusion pump on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of Cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Twice-weekly IV infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of Cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter.

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

Dosage and administration details:

Dexamethasone 40 mg weekly by IV infusion.

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

Dosage and administration details:

Dexamethasone 40 mg weekly orally.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Lenalidomide 25 mg daily orally on Days 1 to 21 of each 28-day cycle	
Arm title	Once-weekly KRd 20/56 mg/m ²

Arm description:

Carfilzomib was administered once-weekly intravenously as a 30 ± 5 minute infusion using an infusion pump on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Once-weekly IV infusion on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter.

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

Dosage and administration details:

Dexamethasone 40 mg weekly by IV infusion.

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

Dosage and administration details:

Dexamethasone 40 mg weekly orally.

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

Dosage and administration details:

Lenalidomide 25 mg daily orally on Days 1 to 21 of each 28-day cycle

Number of subjects in period 1	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²
Started	226	228
Received carfilzomib	226	228
Completed 12 cycles of carfilzomib	152 ^[1]	150 ^[2]
Received lenalidomide	226	228
Received dexamethasone	226	228
Completed	197	191
Not completed	29	37
Adverse event, serious fatal	22	25
Consent withdrawn by subject	4	7
Lost to follow-up	3	2
Decision by sponsor	-	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestone represents the numbers of participants in each treatment arm completing 12 cycles of carfilzomib.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestone represents the numbers of participants in each treatment arm completing 12 cycles of carfilzomib.

Baseline characteristics

Reporting groups

Reporting group title	Twice-weekly KRd 20/27 mg/m ²
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Reporting group description:

Carfilzomib was administered twice-weekly intravenously as a 10 ± 5 minute infusion using an infusion pump on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of Cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Reporting group title	Once-weekly KRd 20/56 mg/m ²
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Reporting group description:

Carfilzomib was administered once-weekly intravenously as a 30 ± 5 minute infusion using an infusion pump on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Reporting group values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²	Total
Number of subjects	226	228	454
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	107	116	223
From 65-84 years	118	112	230
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	64.0	63.7	
standard deviation	± 8.2	± 8.4	-
Gender Categorical Units: participants			
Female	100	118	218
Male	126	110	236
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	12	21
Black or African American	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	209	209	418
Other	7	6	13
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	8	8	16
Not Hispanic or Latino	213	215	428
Unknown or Not Reported	5	5	10
Prior Lenalidomide Treatment Units: Subjects			
Yes	79	85	164
No	147	143	290
Prior Proteasome Inhibitor Treatment Units: Subjects			
Yes	218	214	432
No	8	14	22
Prior Anti-CD38 Treatment Units: Subjects			
Yes	17	21	38
No	209	207	416
Original ISS Stage at Study Entry			
ISS stage classification at study entry per interactive voice/web response system for randomization. Stage 1: serum beta-2 microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL; Stage 2: serum beta-2 microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL or serum beta-2 microglobulin 3.5 - < 5.5 mg/L irrespective of the serum albumin; Stage 3: serum beta-2 microglobulin ≥ 5.5 mg/L.			
Units: Subjects			
Stage 1 or 2	201	201	402
Stage 3	25	27	52

End points

End points reporting groups

Reporting group title	Twice-weekly KRd 20/27 mg/m ²
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Reporting group description:

Carfilzomib was administered twice-weekly intravenously as a 10 ± 5 minute infusion using an infusion pump on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of Cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Reporting group title	Once-weekly KRd 20/56 mg/m ²
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Reporting group description:

Carfilzomib was administered once-weekly intravenously as a 30 ± 5 minute infusion using an infusion pump on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Subject analysis set title	Twice-weekly KRd 20/27 mg/m ² : Safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants in the safety population were analyzed according to the treatment arm corresponding to the actual treatment received. Carfilzomib was administered twice-weekly intravenously as a 10 ± 5 minute infusion using an infusion pump on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of Cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Subject analysis set title	Once-weekly KRd 20/56 mg/m ² : Safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Participants in the safety population were analyzed according to the treatment arm corresponding to the actual treatment received. Carfilzomib was administered once-weekly intravenously as a 30 ± 5 minute infusion using an infusion pump on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Primary: Overall Response Rate (ORR) per International Myeloma Working Group Uniform Response Criteria (IMWG-URC)

End point title	Overall Response Rate (ORR) per International Myeloma Working Group Uniform Response Criteria (IMWG-URC)
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End point description:

ORR was defined as the percentage of participants with a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) per IMWG-URC. CR: negative immunofixation on serum and urine, soft tissue plasmacytomas disappearance, < 5% plasma cells in bone marrow (BM). sCR: CR and normal serum free light chain ratio and no clonal cells in BM by immunohistochemistry. VGPR: Serum and urine M-protein detectable by immunofixation or ≥ 90% reduction in serum M-protein (urine M-protein level < 100 mg/24-hours). PR: ≥ 50% reduction of serum M-protein and reduction in 24-hours urinary M-protein by ≥ 90% or to < 200 mg/24-hours. The ORR 95% confidence intervals (CIs) were estimated using the Clopper-Pearson method.

The intent-to-treat (ITT) population included all randomized participants.

End point type	Primary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: percentage of participants				
number (confidence interval 95%)	86.3 (81.1 to 90.5)	82.5 (76.9 to 87.2)		

Statistical analyses

Statistical analysis title	Risk Ratio
Statistical analysis description:	
Risk ratio and 95% CIs were estimated by a stratified analysis using the Cochran-Mantel-Haenszel method. The non-inferiority margin was 0.87 for the estimated ORR risk ratio.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0666
Method	Synthesis approach
Parameter estimate	Risk ratio (RR)
Point estimate	0.954
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.882
upper limit	1.032

Secondary: Kaplan-Meier Estimate of Progression-free Survival (PFS) Rate at 12 Months

End point title	Kaplan-Meier Estimate of Progression-free Survival (PFS) Rate at 12 Months
End point description:	
PFS rate was defined as the percentage of participants without disease progression or death due to any cause at 12 months. The PFS rate at 12 months was estimated using the Kaplan-Meier method by Klein and Moeschberger (1997). 95% CIs were estimated using the method by Kalbfleisch and Prentice (1980). PFS data was censored for participants who met any one of the following: 1. no baseline/no post-baseline disease assessments; 2. starting new anti-myeloma therapy before documentation of progressive disease (PD) or death; 3. PD or death immediately after more than 1 consecutively missed disease assessment visit (PD or death immediately after > 63 days without disease assessment visit); 4. alive without documentation of PD; 5. lost to follow-up or withdrawn consent. The ITT analysis set included all randomized participants.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: percentage of participants				
number (confidence interval 95%)	79.7 (73.6 to 84.6)	80.7 (74.7 to 85.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical study participant irrespective of a causal relationship with the study treatment. TEAEs were AEs starting on or after the first dose of any study drug, and up to 30 days of the last dose of any study drug, excluding AEs reported after End of Study date.

The safety population included all randomized participants who received at least 1 dose of any study treatment (carfilzomib, lenalidomide, or dexamethasone). Participants were analyzed according to the treatment arm corresponding to the actual treatment received.

End point type	Secondary
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End point timeframe:

Day 1 Cycle 1 up to end of Cycle 12 + 30 days, where each cycle was 28 days; median treatment duration (any study treatment) was 47.00 weeks in the twice-weekly KRd group and 47.14 weeks in the once-weekly KRd group

End point values	Twice-weekly KRd 20/27 mg/m ² : Safety population	Once-weekly KRd 20/56 mg/m ² : Safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	231	223		
Units: participants	219	209		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Reported Convenience as Measured by

the Patient-reported Convenience with Carfilzomib-dosing Schedule Question

End point title	Percentage of Participants who Reported Convenience as Measured by the Patient-reported Convenience with Carfilzomib-dosing Schedule Question
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End point description:

Patient-reported convenience was measured by the Patient-reported Convenience with Carfilzomib-dosing Schedule Question. The items in the questionnaire were categorized as 'Convenient', which included responses of 'Very Convenient' and 'Convenient', and 'Inconvenient' which included responses of 'Inconvenient' and 'Very Inconvenient'. The 95% CIs were estimated using the Clopper-Pearson method.

The ITT population included all randomized participants.

End point type	Secondary
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End point timeframe:

Day 28 of Cycle 4

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: percentage of participants				
number (confidence interval 95%)	80.5 (74.8 to 85.5)	81.6 (75.9 to 86.4)		

Statistical analyses

Statistical analysis title	Odds Ratio
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Statistical analysis description:

Odds ratio and 95% CIs were estimated by a stratified analysis using the Cochran-Mantel-Haenszel method.

Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
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Number of subjects included in analysis	454
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Analysis specification	Pre-specified
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Analysis type	other
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Parameter estimate	Odds ratio (OR)
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Point estimate	1.049
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.653
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upper limit	1.683
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Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)
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End point description:

TTR was defined as the time from randomization to the earliest date when confirmed sCR, CR, VGPR, or

PR per IMWG-URC was first achieved.

The ITT population included all randomized participants. Data is presented for participants in the ITT population who achieved a confirmed response of PR or better.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	188		
Units: months				
median (full range (min-max))	1.0 (1 to 12)	1.0 (1 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Duration of Response (DOR)

End point title	Kaplan-Meier Estimate of Duration of Response (DOR)
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End point description:

For participants who achieved a PR or better, i.e., sCR, CR, VGPR, or PR per IMWG-URC, the DOR was defined as the time from the earliest date when a PR or better was first achieved, and confirmed, to the earliest date of confirmed PD or death due to any cause. Median DOR was estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. For those alive and who had not experienced PD by analysis time, DOR was censored for participants who met any one of the following: 1. no baseline/no post-baseline disease assessments; 2. starting new anti-myeloma therapy before documentation of PD or death; 3. PD or death immediately after more than 1 consecutively missed disease assessment visit (PD or death immediately after > 63 days without disease assessment visit); 4. alive without documentation of PD; 5. lost to follow-up or withdrawn consent. 99999=median and 95% CIs could not be estimated due to too few events.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	188		
Units: months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival (OS)

End point title	Kaplan-Meier Estimate of Overall Survival (OS)
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End point description:

OS was defined as the time from randomization to the date of death due to any cause. Median OS was estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. Participants still alive or lost to follow-up or withdrawn consent from study by the analysis time were censored at the date on which the participant was last known to be alive. The ITT population included all randomized participants. 99999 = median and 95% CIs could not be estimated due to too few events.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Time to Progression (TTP)

End point title	Kaplan-Meier Estimate of Time to Progression (TTP)
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End point description:

TTP was defined as the duration from randomization for the first documented disease progression per IMWG-UCR. Median TTP was estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger (1997) with log-log transformation. TTP was censored for participants who had no confirmed PD at the last non non-evaluable (non-NE), post-baseline disease assessment or the earlier of the following, where applicable: 1. the last non-NE, post-baseline disease assessment prior to start of a new anti-myeloma treatment, or 2. the last non-NE, post-baseline assessment followed > 63 days later by disease progression; otherwise, at randomization. The ITT population included all randomized participants. 99999=median and 95% CIs could not be estimated due to too few events.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved Minimal Residual Disease Negative Complete Response (MRD[-]CR) by Independent Review Committee (IRC) per IMWG-URC

End point title	Percentage of Participants who Achieved Minimal Residual Disease Negative Complete Response (MRD[-]CR) by Independent Review Committee (IRC) per IMWG-URC
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End point description:

MRD[-]CR was defined as achievement of CR or better by IRC per IMWG-URC and achievement of MRD negativity as assessed by next generation sequencing method at a 10⁻⁵ threshold over the duration of the study. The 95% CIs for proportions were estimated using the Clopper-Pearson method. The ITT population included all randomized participants.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 up to approximately 12 months (cycle = 28 days); median treatment duration for the twice-weekly arm was 47.00 weeks and for the once-weekly arm was 47.14 weeks.

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: percentage of participants				
number (confidence interval 95%)	18.1 (13.3 to 23.8)	21.5 (16.3 to 27.4)		

Statistical analyses

Statistical analysis title	Odds Ratio
Statistical analysis description: Odds ratio and 95% CIs were estimated by a stratified analysis using the Cochran-Mantel-Haenszel method.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.775
upper limit	1.97

Secondary: Percentage of Participants with Minimal Residual Disease Negativity (MRD[-]) by IRC per IMWG-URC at 12 Months

End point title	Percentage of Participants with Minimal Residual Disease Negativity (MRD[-]) by IRC per IMWG-URC at 12 Months
End point description: The percentage of participants with achievement of MRD[-] at 12 months (\pm 4 weeks) from randomization, as assessed by next generation sequencing method at a 10^{-5} threshold. MRD negativity results from BM samples obtained at 8 to 13 months from randomization and prior to new anti-myeloma therapy or disease progression were considered in the calculation. The 95% CIs for proportions were estimated using the Clopper-Pearson method. The ITT population included all randomized participants.	
End point type	Secondary
End point timeframe: Cycle 1 Day 1 up to 12 months (cycle = 28 days)	

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: percentage of participants				
number (confidence interval 95%)	18.1 (13.3 to 23.8)	18.9 (14.0 to 24.6)		

Statistical analyses

Statistical analysis title	Odds Ratio
Statistical analysis description: Odds ratio and 95% CIs were estimated by a stratified analysis using the Cochran-Mantel-Haenszel method.	

Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.657
upper limit	1.711

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-Core 30 (C30) Physical Functioning Scale

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-Core 30 (C30) Physical Functioning Scale
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End point description:

The QLQ-C30 physical function score ranges from 0-100 points, with 100 points indicating the best possible functioning. A positive change from baseline indicated an improvement in functioning. The ITT population included all randomized participants. Participants with data available at each time point are presented.

End point type	Secondary
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End point timeframe:

Baseline (Cycle 1 Day 1), Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1, Cycle 12 Day 1, and safety follow-up (30 days after last dose)

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (N=186, 182)	-2.76 (± 16.84)	-0.77 (± 14.95)		
Cycle 5 Day 1 (N=181, 177)	-2.65 (± 15.76)	0.26 (± 15.59)		
Cycle 7 Day 1 (N=162, 161)	-0.82 (± 16.59)	0.17 (± 14.62)		
Cycle 9 Day 1 (N=152, 148)	-1.05 (± 15.59)	2.03 (± 14.75)		
Cycle 12 Day 1 (N=134, 132)	-1.89 (± 15.15)	1.06 (± 15.63)		
Safety Follow-up (N=146, 145)	-1.55 (± 16.32)	2.11 (± 18.27)		

Statistical analyses

Statistical analysis title	Least Squares (LS) Mean Treatment Difference
Statistical analysis description:	
Analysis was based on repeated measures analysis of covariance (ANCOVA) model, including arm, baseline scale score, randomization stratification factors and visit as repeated measure.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	2.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	4.69

Secondary: Change from Baseline in EORTC QLQ C30 Role Functioning Scale

End point title	Change from Baseline in EORTC QLQ C30 Role Functioning Scale
End point description:	
The QLQ-C30 role function score ranges from 0-100 points, with 100 points indicating the best possible functioning. A positive change from baseline indicated an improvement in functioning. The ITT population included all randomized participants. Participants with data available at each time point are presented.	
End point type	Secondary
End point timeframe:	
Baseline (Cycle 1 Day 1), Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1, Cycle 12 Day 1, and safety follow-up (30 days after last dose)	

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	228		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (N=186, 182)	-4.30 (± 26.16)	-2.47 (± 24.81)		
Cycle 5 Day 1 (N=181, 177)	-2.67 (± 25.77)	-3.11 (± 24.32)		
Cycle 7 Day 1 (N=162, 161)	-3.29 (± 26.19)	1.76 (± 24.34)		
Cycle 9 Day 1 (N=152, 148)	-0.88 (± 23.24)	2.70 (± 24.90)		
Cycle 12 Day 1 (N=134, 132)	-0.25 (± 23.21)	1.64 (± 28.97)		
Safety Follow-up (N=146, 145)	-2.28 (± 24.73)	3.68 (± 26.24)		

Statistical analyses

Statistical analysis title	LS Mean Treatment Difference
Statistical analysis description: Analysis was based on ANCOVA model, including arm, baseline scale score, randomization stratification factors and visit as repeated measure.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	4.72

Secondary: Patient-reported Treatment Satisfaction as Measured by the Cancer Therapy Satisfaction Questionnaire (CTSQ)

End point title	Patient-reported Treatment Satisfaction as Measured by the Cancer Therapy Satisfaction Questionnaire (CTSQ)
End point description: The CTSQ measures treatment satisfaction in individuals with cancer and includes a domain for satisfaction with therapy. The satisfaction with therapy scores ranges from 0 to 100 points, with 100 points indicating greatest satisfaction. Analysis was based on ANCOVA model. The dependent variable of the models were the scale scores measured at each visit. The model included effects of intercept, scale score measured at cycle 2 day 1 visit, treatment arm, and randomization stratification factors. The ITT population included all randomized participants. Participants with data available at each time point are presented.	
End point type	Secondary
End point timeframe: Day 1 Cycle 5, Day 1 Cycle 12, and safety follow-up (30 days after last dose)	

End point values	Twice-weekly KRd 20/27 mg/m ²	Once-weekly KRd 20/56 mg/m ²		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	165		
Units: score on a scale				
least squares mean (standard error)				
Cycle 5 Day 1 (N=169, 165)	75.73 (± 1.78)	75.47 (± 1.76)		

Cycle 12 Day 1 (N=128, 122)	78.39 (± 2.40)	77.91 (± 2.40)		
Safety follow-up (N=138, 134)	74.55 (± 2.58)	75.99 (± 2.49)		

Statistical analyses

Statistical analysis title	Treatment Difference at Cycle 5
Statistical analysis description: LS mean treatment difference at Cycle 5.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	2.03
Variability estimate	Standard error of the mean
Dispersion value	1.16

Statistical analysis title	Treatment Difference at Safety Follow-up
Statistical analysis description: LS mean treatment difference at safety follow-up.	
Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	4.58
Variability estimate	Standard error of the mean
Dispersion value	1.59

Statistical analysis title	Treatment Difference at Cycle 12
Statistical analysis description: LS mean treatment difference at Cycle 12.	

Comparison groups	Twice-weekly KRd 20/27 mg/m ² v Once-weekly KRd 20/56 mg/m ²
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	2.28
Variability estimate	Standard error of the mean
Dispersion value	1.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from first dose of study drug to last dose of study drug + 30 days; median treatment duration (any study treatment) was 11.8 months.

Adverse event reporting additional description:

Serious AEs and other AEs were collected for all participants in the safety population who received at least one dose of study drug. Participants in the safety population were analyzed according to the treatment arm corresponding to the actual treatment received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Twice-weekly KRd 20/27 mg/m ² : Safety population
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Reporting group description:

Participants in the safety population were analyzed according to the treatment arm corresponding to the actual treatment received. Carfilzomib was administered twice-weekly intravenously as a 10 ± 5 minute infusion using an infusion pump on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The dose was 20 mg/m² on Days 1 and 2 of cycle 1 and 27 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Reporting group title	Once-weekly KRd 20/56 mg/m ² : Safety population
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Reporting group description:

Participants in the safety population were analyzed according to the treatment arm corresponding to the actual treatment received. Carfilzomib was administered once-weekly intravenously as a 30 ± 5 minute infusion using an infusion pump on Days 1, 8, and 15 of each 28-day cycle. The dose was 20 mg/m² on Day 1 of Cycle 1 and 56 mg/m² beginning on Day 8 of Cycle 1 and thereafter. Participants also received lenalidomide 25 mg daily orally on Days 1 to 21 of each cycle and dexamethasone 40 mg weekly orally or intravenously. Participants were treated for up to 12 28-day cycles.

Serious adverse events	Twice-weekly KRd 20/27 mg/m ² : Safety population	Once-weekly KRd 20/56 mg/m ² : Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 231 (32.47%)	84 / 223 (37.67%)	
number of deaths (all causes)	24	24	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryoglobulinaemia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 231 (1.30%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor venous access			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia	subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
	occurrences causally related to treatment / all	0 / 0	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Death	subjects affected / exposed	0 / 231 (0.00%)	3 / 223 (1.35%)	
	occurrences causally related to treatment / all	0 / 0	0 / 3	
	deaths causally related to treatment / all	0 / 0	0 / 3	
General physical health deterioration	subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
	occurrences causally related to treatment / all	0 / 1	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome	subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia	subjects affected / exposed	2 / 231 (0.87%)	2 / 223 (0.90%)	
	occurrences causally related to treatment / all	0 / 2	0 / 2	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure	subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
	occurrences causally related to treatment / all	0 / 1	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
	occurrences causally related to treatment / all	0 / 2	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
	occurrences causally related to treatment / all	0 / 0	1 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 231 (2.60%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	3 / 7	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
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			
Cervical vertebral fracture			

subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (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 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	2 / 231 (0.87%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autonomic nervous system imbalance			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intensive care unit acquired weakness			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 231 (0.87%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (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	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 231 (0.43%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 231 (1.30%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Amplified musculoskeletal pain syndrome			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthrititis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 231 (0.87%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	11 / 231 (4.76%)	8 / 223 (3.59%)	
occurrences causally related to treatment / all	0 / 12	1 / 11	
deaths causally related to treatment / all	0 / 1	0 / 4	
COVID-19			

subjects affected / exposed	3 / 231 (1.30%)	6 / 223 (2.69%)	
occurrences causally related to treatment / all	1 / 4	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 231 (0.43%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	9 / 231 (3.90%)	12 / 223 (5.38%)	
occurrences causally related to treatment / all	0 / 10	9 / 14	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 231 (0.87%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 231 (0.87%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinobronchitis			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 231 (0.43%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 231 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypocalcaemia			
subjects affected / exposed	1 / 231 (0.43%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	0 / 231 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 231 (0.43%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Twice-weekly KRd 20/27 mg/m ² : Safety population	Once-weekly KRd 20/56 mg/m ² : Safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 231 (82.25%)	182 / 223 (81.61%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	56 / 231 (24.24%)	48 / 223 (21.52%)	
occurrences (all)	92	66	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 231 (5.19%)	9 / 223 (4.04%)	
occurrences (all)	13	12	
Neuropathy peripheral			
subjects affected / exposed	11 / 231 (4.76%)	22 / 223 (9.87%)	
occurrences (all)	16	26	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	55 / 231 (23.81%)	56 / 223 (25.11%)	
occurrences (all)	71	88	
Neutropenia			
subjects affected / exposed	73 / 231 (31.60%)	65 / 223 (29.15%)	
occurrences (all)	207	147	
Thrombocytopenia			
subjects affected / exposed	31 / 231 (13.42%)	46 / 223 (20.63%)	
occurrences (all)	80	105	
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	13 / 231 (5.63%) 26	26 / 223 (11.66%) 37	
Fatigue subjects affected / exposed occurrences (all)	29 / 231 (12.55%) 39	24 / 223 (10.76%) 32	
Pyrexia subjects affected / exposed occurrences (all)	27 / 231 (11.69%) 28	23 / 223 (10.31%) 27	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	17 / 231 (7.36%) 20	23 / 223 (10.31%) 26	
Diarrhoea subjects affected / exposed occurrences (all)	43 / 231 (18.61%) 58	42 / 223 (18.83%) 58	
Nausea subjects affected / exposed occurrences (all)	15 / 231 (6.49%) 17	19 / 223 (8.52%) 38	
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	8 / 231 (3.46%) 11	12 / 223 (5.38%) 15	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	20 / 231 (8.66%) 32	13 / 223 (5.83%) 27	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	16 / 231 (6.93%) 21	21 / 223 (9.42%) 23	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	16 / 231 (6.93%) 17	21 / 223 (9.42%) 22	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 231 (5.63%)	8 / 223 (3.59%)	
occurrences (all)	16	8	
Muscle spasms			
subjects affected / exposed	21 / 231 (9.09%)	12 / 223 (5.38%)	
occurrences (all)	27	17	
Back pain			
subjects affected / exposed	19 / 231 (8.23%)	17 / 223 (7.62%)	
occurrences (all)	20	20	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	33 / 231 (14.29%)	32 / 223 (14.35%)	
occurrences (all)	44	47	
Nasopharyngitis			
subjects affected / exposed	16 / 231 (6.93%)	16 / 223 (7.17%)	
occurrences (all)	21	18	
COVID-19			
subjects affected / exposed	14 / 231 (6.06%)	22 / 223 (9.87%)	
occurrences (all)	14	23	
Bronchitis			
subjects affected / exposed	15 / 231 (6.49%)	11 / 223 (4.93%)	
occurrences (all)	20	12	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	18 / 231 (7.79%)	10 / 223 (4.48%)	
occurrences (all)	22	21	
Hypocalcaemia			
subjects affected / exposed	13 / 231 (5.63%)	10 / 223 (4.48%)	
occurrences (all)	13	11	
Hyperglycaemia			
subjects affected / exposed	17 / 231 (7.36%)	9 / 223 (4.04%)	
occurrences (all)	22	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2019	<ul style="list-style-type: none">- Added overall survival at 1 year as secondary endpoint.- Added a long-term follow-up period with a duration of 12 months after randomization to separate this period from the safety follow-up period after cessation of treatment.
24 August 2020	<ul style="list-style-type: none">- Added duration to secondary objectives.- Deleted early success from interim analysis.
12 August 2021	<ul style="list-style-type: none">- Updated primary endpoint to overall response (removed "rate").- Updated inclusion criteria.- Updated exclusion criteria.- Clarified administration of dexamethasone.- Updated planned analysis and methods of analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported