# 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 |

**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/m^2 once weekly to KRd 27 mg/m^2 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/m^2 on Days 1 and 2 of Cycle 1 and 27 mg/m^2 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/m^2 on Days 1 and 2 of Cycle 1 and 27 mg/m^2 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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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 |
| 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/m^2 on Days 1 and 2 of Cycle 1 and 27 mg/m^2 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 |
| 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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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<br>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<br>Units: years | | | |
| arithmetic mean | 64.0 | 63.7 | |
| standard deviation | ± 8.2 | ± 8.4 | - |
| Gender Categorical<br>Units: participants | | | |
| Female | 100 | 118 | 218 |
| Male | 126 | 110 | 236 |
| Race/Ethnicity, Customized<br>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)<br>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<br>Units: Subjects | | | |
| Yes | 79 | 85 | 164 |
| No | 147 | 143 | 290 |
| Prior Proteasome Inhibitor Treatment<br>Units: Subjects | | | |
| Yes | 218 | 214 | 432 |
| No | 8 | 14 | 22 |
| Prior Anti-CD38 Treatment<br>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 reporting groups

| Reporting group title | Twice-weekly KRd 20/27 mg/m^2 |
|---|---|

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/m^2 on Days 1 and 2 of Cycle 1 and 27 mg/m^2 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 |
|---|---|

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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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 |
|---|---|
| Subject analysis set type | Safety analysis |

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/m^2 on Days 1 and 2 of Cycle 1 and 27 mg/m^2 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 |
|---|---|
| Subject analysis set type | Safety analysis |

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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 |

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 |
|---|---|

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 |
|---|---|

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 | 1.049 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.653 |
| upper limit | 1.683 |

| Secondary: Time to Response (TTR) | |
|---|---|
| End point title | Time to Response (TTR) |

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 (± 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 |

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 |

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:<br>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:<br>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:<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

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

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/m^2 on Days 1 and 2 of cycle 1 and 27 mg/m^2 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 |

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/m^2 on Day 1 of Cycle 1 and 56 mg/m^2 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 | |
| Polyarthritis | | | |
| 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 | 13 / 231 (5.63%) | 26 / 223 (11.66%) | |
| occurrences (all) | 26 | 37 | |
| Fatigue | | | |
| subjects affected / exposed | 29 / 231 (12.55%) | 24 / 223 (10.76%) | |
| occurrences (all) | 39 | 32 | |
| Pyrexia | | | |
| subjects affected / exposed | 27 / 231 (11.69%) | 23 / 223 (10.31%) | |
| occurrences (all) | 28 | 27 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 17 / 231 (7.36%) | 23 / 223 (10.31%) | |
| occurrences (all) | 20 | 26 | |
| Diarrhoea | | | |
| subjects affected / exposed | 43 / 231 (18.61%) | 42 / 223 (18.83%) | |
| occurrences (all) | 58 | 58 | |
| Nausea | | | |
| subjects affected / exposed | 15 / 231 (6.49%) | 19 / 223 (8.52%) | |
| occurrences (all) | 17 | 38 | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 8 / 231 (3.46%) | 12 / 223 (5.38%) | |
| occurrences (all) | 11 | 15 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 20 / 231 (8.66%) | 13 / 223 (5.83%) | |
| occurrences (all) | 32 | 27 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 16 / 231 (6.93%) | 21 / 223 (9.42%) | |
| occurrences (all) | 21 | 23 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 16 / 231 (6.93%) | 21 / 223 (9.42%) | |
| occurrences (all) | 17 | 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 | - Added overall survival at 1 year as secondary endpoint.<br>- 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 | - Added duration to secondary objectives.<br>- Deleted early success from interim analysis. |
| 12 August 2021 | - Updated primary endpoint to overall response (removed "rate").<br>- Updated inclusion criteria.<br>- Updated exclusion criteria.<br>- Clarified administration of dexamethasone.<br>- Updated planned analysis and methods of analysis. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported