



Clinical trial results:

A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/ Dexamethasone Compared with Pomalidomide/Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide

Summary

| | |
|--------------------------|---|
| EudraCT number | 2016-003517-95 |
| Trial protocol | HU ES CZ GB GR BE DK NL NO FR PL AT EE LT IT RO |
| Global end of trial date | 03 February 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 24 January 2024 |
| First version publication date | 24 January 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | OP-103 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03151811 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Oncopeptides AB |
| Sponsor organisation address | Luntmakargatan 46, Stockholm, Sweden, SE-111 37 |
| Public contact | Clinical Trials Information Desk, Oncopeptides AB, trials@oncopeptides.se |
| Scientific contact | Clinical Trials Information Desk, Oncopeptides AB, trials@oncopeptides.se |

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 | 03 February 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 February 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To compare the PFS of melflufen plus dexamethasone (Arm A) versus pomalidomide plus dexamethasone (Arm B) as assessed by the Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC).

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference of Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. Eligible patients were only to be included in the study after providing written, IEC-approved informed consent. The clinical study was designed based on well-established guidance for oncology studies including relapsed-refractory multiple myeloma (RRMM) management, response assessment, and National Comprehensive Cancer Network Guidelines.

Background therapy:

Dexamethasone 40 mg administered orally on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged <75 years

OR

Dexamethasone 20 mg administered orally on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged ≥75 years

Evidence for comparator:

Pomalidomide is a third-generation immunomodulatory drug approved in 2013 by the US FDA and the EMA in combination with low-dose dexamethasone for multiple myeloma (MM) patients who have received at least two prior therapies (including both lenalidomide and bortezomib) and whose disease progressed after the last treatment. An expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma noted that for patients who have exhausted lenalidomide- and bortezomib-based therapies, pomalidomide plus low-dose dexamethasone is an effective treatment option, and that evidence suggests that pomalidomide is equally effective in patients whose last therapy was lenalidomide or bortezomib.

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 3 |
| Country: Number of subjects enrolled | Norway: 33 |
| Country: Number of subjects enrolled | Poland: 47 |
| Country: Number of subjects enrolled | Romania: 20 |
| Country: Number of subjects enrolled | Spain: 42 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Austria: 3 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Czechia: 59 |
| Country: Number of subjects enrolled | Denmark: 1 |
| Country: Number of subjects enrolled | Estonia: 4 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Greece: 46 |
| Country: Number of subjects enrolled | Hungary: 31 |
| Country: Number of subjects enrolled | Italy: 30 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Country: Number of subjects enrolled | United States: 26 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Korea, Republic of: 15 |
| Country: Number of subjects enrolled | Russian Federation: 79 |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Worldwide total number of subjects | 495 |
| EEA total number of subjects | 346 |

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) | 181 |
| From 65 to 84 years | 309 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details:

The first patient initiated study treatment in OP-103 on 12 June 2017. A total of 495 patients were randomized in the study, 246 in the melflufen+dexamethasone group and 249 in the pomalidomide+dexamethasone group. Among the randomized patients, 21 were not treated (18 in the melflufen+dex group and 3 in the pomalidomide+dex group).

Pre-assignment

Screening details:

Key inclusion criteria: age \geq 18 years; prior diagnosis of multiple myeloma; received 2-4 prior lines of therapy, including lenalidomide and a protease inhibitor, either sequential or in the same line; and refractory to both the last line of therapy and to lenalidomide (\geq 10 mg) administered within 18 months prior to randomization.

Period 1

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

Blinding implementation details:

An Independent Review Committee (IRC) assessed all tumor responses and progression. The IRC members were blinded to all treatment data and performed their reviews.

Arms

| | |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A |

Arm description:

Melflufen 40 mg iv on Day 1 of each 28-day cycle via a central catheter. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for injection/infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Melflufen 40 mg was administered as a 30-minute infusion on Day 1 of each 28-day cycle via central catheter.

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

Dosage and administration details:

Dexamethasone was given po at the standard dose of 40 mg weekly, on Days 1, 8, 15, and 22 of each 28-day cycle. Patients \geq 75 years of age were given dexamethasone po 20 mg weekly. On the days that both melflufen and dexamethasone were given (i.e., Day 1 of each cycle), dexamethasone was to be taken before the administration of melflufen.

| | |
|------------------|-------|
| Arm title | Arm B |
|------------------|-------|

Arm description:

Pomalidomide 4 mg po on Days 1 to 21 of each 28-day cycle. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age).

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------|
| Investigational medicinal product name | Pomalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Pomalidomide 4 mg was administered orally on Days 1 to 28 of each 28-day cycle.

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

Dosage and administration details:

Dexamethasone was given po at the standard dose of 40 mg weekly, on Days 1, 8, 15, and 22 of each 28-day cycle. Patients \geq 75 years of age were given dexamethasone po 20 mg weekly. On the days that both pomalidomide and dexamethasone were given (i.e., Day 1 of each cycle), dexamethasone was to be taken before the administration of pomalidomide.

| Number of subjects in period 1 | Arm A | Arm B |
|---------------------------------------|-------|-------|
| Started | 246 | 249 |
| Treated | 228 | 246 |
| Completed | 0 | 0 |
| Not completed | 246 | 249 |
| Physician decision | 21 | 9 |
| Consent withdrawn by subject | 17 | 7 |
| Study terminated by Sponsor | 5 | 11 |
| Adverse event | 49 | 40 |
| Randomized But Not Treated | 18 | 3 |
| Progressive disease | 130 | 170 |
| Lost to follow-up | - | 1 |
| Lack of efficacy | 6 | 8 |

Baseline characteristics

Reporting groups

| | |
|---|-------|
| Reporting group title | Arm A |
| Reporting group description: Melflufen 40 mg iv on Day 1 of each 28-day cycle via a central catheter. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). | |
| Reporting group title | Arm B |
| Reporting group description: Pomalidomide 4 mg po on Days 1 to 21 of each 28-day cycle. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). | |

| Reporting group values | Arm A | Arm B | Total |
|------------------------------------|------------|------------|-------|
| Number of subjects | 246 | 249 | 495 |
| Age categorical | | | |
| Units: Subjects | | | |
| <65 years | 96 | 85 | 181 |
| 65 to <75 years | 113 | 125 | 238 |
| \geq 75 years | 37 | 39 | 76 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 66.1 | 66.5 | |
| standard deviation | \pm 8.98 | \pm 8.83 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 107 | 109 | 216 |
| Male | 139 | 140 | 279 |
| Race | | | |
| Units: Subjects | | | |
| Asian | 8 | 13 | 21 |
| Black or African American | 4 | 4 | 8 |
| White | 224 | 222 | 446 |
| Other | 1 | 0 | 1 |
| Unknown | 9 | 9 | 18 |
| Not reported | 0 | 1 | 1 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 8 | 5 | 13 |
| Not Hispanic or Latino | 232 | 237 | 469 |
| Not reported | 6 | 7 | 13 |
| Baseline ECOG Performance Status | | | |
| Units: Subjects | | | |
| Score = 0 | 90 | 92 | 182 |
| Score = 1 | 130 | 136 | 266 |
| Score = 2 | 26 | 21 | 47 |
| ISS stage at study entry | | | |
| ISS = International Staging System | | | |
| Units: Subjects | | | |
| Stage = I | 119 | 124 | 243 |

| | | | |
|--|---------|---------|-----|
| Stage = II | 94 | 94 | 188 |
| Stage = III | 33 | 31 | 64 |
| Bone lesions present at study entry Units: Subjects | | | |
| Yes | 184 | 206 | 390 |
| No | 62 | 43 | 105 |
| Extramedullary disease present at study entry Units: Subjects | | | |
| Yes | 31 | 31 | 62 |
| No | 215 | 218 | 433 |
| R-ISS stage of disease at study entry | | | |
| R-ISS = Revised-International Staging System | | | |
| Units: Subjects | | | |
| R-I | 69 | 69 | 138 |
| R-II | 129 | 138 | 267 |
| R-III | 24 | 17 | 41 |
| Unknown/missing | 24 | 25 | 49 |
| Cytogenic risk group based on FISH at study entry | | | |
| FISH = fluorescence in situ hybridization | | | |
| Units: Subjects | | | |
| High | 83 | 86 | 169 |
| Standard | 128 | 130 | 258 |
| Unknown | 35 | 33 | 68 |
| Baseline weight Units: kg | | | |
| arithmetic mean | 76.9 | 76.1 | |
| standard deviation | ± 14.71 | ± 14.38 | - |
| Time since initial diagnosis Units: years | | | |
| arithmetic mean | 4.88 | 4.82 | |
| standard deviation | ± 3.98 | ± 3.88 | - |

End points

End points reporting groups

| | |
|---|-------------------------|
| Reporting group title | Arm A |
| Reporting group description: Melflufen 40 mg iv on Day 1 of each 28-day cycle via a central catheter. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). | |
| Reporting group title | Arm B |
| Reporting group description: Pomalidomide 4 mg po on Days 1 to 21 of each 28-day cycle. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The FAS was defined as all subjects who were randomized. Subjects were analyzed according to the treatment assigned at randomization. | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The Safety Analysis Set was defined as all subjects who received at least one or partial dose of melflufen, pomalidomide, or dexamethasone. The Safety Analysis Set was the primary population for the summaries of all exposure and safety data. Subjects were summarized according to the treatment actually received. | |

Primary: Progression Free Survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression Free Survival (PFS) |
| End point description: To show the superiority of PFS in patients treated with melflufen+dexamethasone (Arm A) compared to pomalidomide+dexamethasone (Arm B) as assessed by the IRC. PFS was defined as the duration in months from the date of randomization to the date of first documentation of confirmed progressive disease or death due to any cause. | |
| End point type | Primary |
| End point timeframe: From date of randomization until confirmed disease progression or death due to any cause. Data cutoff date was 03 Feb 2021. | |

| End point values | Arm A | Arm B | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 ^[1] | 249 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.83 (4.96 to 8.54) | 4.93 (4.24 to 5.72) | | |

Notes:

[1] - Patients with events: 165
Patients censored: 81
Median follow-up: 15.47 months
[2] - Patients with events: 190
Patients censored: 59
Median follow-up: 16.26 months

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Statistical Analysis for PFS |
| Statistical analysis description: | |
| PFS analyzed using a log-rank test stratified by the randomization stratification factors to compare treatment group survival distributions based on the FAS. Kaplan-Meier (K-M) estimates of the survival distributions of the time-to-event based on log(-log[survival]) distribution were tabulated by treatment arm (including K-M estimates of medians and 95% CIs). Hazard ratio and 95% CIs were based on semiparametric Cox proportional hazards regression model stratified by randomization strata. | |
| Comparison groups | Arm A v Arm B |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.0319 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.792 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 0.981 |

Notes:

[3] - Superiority of melflufen+dexamethasone over pomalidomide+dexamethasone with respect to the primary endpoint was claimed if the 2-sided p-value was <0.05 favoring melflufen+dexamethasone. In addition to a significant p-value for the treatment comparison based on the log-rank test, the superiority of melflufen+dexamethasone versus pomalidomide+dexamethasone was demonstrated if the upper limit of the 95% CI for the hazard ratio was < 1.0.

[4] - Log-rank test stratified by randomization strata: age (<75, ≥75), number of lines of prior therapy (2, 3-4), and International Staging System (ISS) Score (1, ≥2).

Secondary: Overall Response Rate (ORR)

| | |
|---|-----------------------------|
| End point title | Overall Response Rate (ORR) |
| End point description: | |
| To assess and compare the ORR in Arm A versus Arm B, as assessed by the IRC. ORR was defined as the proportion of patients for whom the best overall confirmed response was stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). | |
| End point type | Secondary |

End point timeframe:

From randomization until best response achieved before confirmed disease progression or death due to any cause. Median time to best response was 2.1 and 2.0 months for Arm A and B, respectively. Data cutoff date was 03 Feb 2021.

| | | | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| End point values | Arm A | Arm B | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 ^[5] | 249 ^[6] | | |
| Units: Percent | | | | |
| number (confidence interval 95%) | 32.5 (26.71 to 38.76) | 26.9 (21.50 to 32.87) | | |

Notes:

[5] - Number of patients with best response ≥PR: 80

[6] - Number of patients with best response ≥PR: 67

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Statistical Analysis for ORR |
| Statistical analysis description: The treatment groups for the FAS population were compared using the Cochran Mantel Haenszel (CMH) chi square test. The two-sided 95% exact binomial CI for ORR was calculated for each treatment arm. | |
| Comparison groups | Arm A v Arm B |
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| P-value | = 0.1607 ^[8] |
| Method | Cochran-Mantel-Haenszel |

Notes:

[7] - Superiority testing of melflufen+dexamethasone over pomalidomide+dexamethasone with respect to the key secondary endpoints performed using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison was statistically significant at an alpha level of 0.05. In case of statistical superiority on the primary endpoint, then ORR was tested for statistical superiority.

[8] - P-value was calculated from a CMH test stratified by the following randomization strata: age (<75, ≥75), number of lines of prior therapy (2, 3-4), and International Staging System (ISS) Score (1, ≥2).

Secondary: Duration of Response (DOR)

| | |
|---|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: To assess and compare DOR in patients with ≥PR (sCR, CR, VGPR, PR) as best response in Arm A versus Arm B, as assessed by the IRC. DOR was defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. DOR was defined only for patients with a confirmed PR or better. | |
| End point type | Secondary |
| End point timeframe: From first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause. Data cutoff date was 03 Feb 2021. | |

| End point values | Arm A | Arm B | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 ^[9] | 249 ^[10] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.17 (8.48 to 17.48) | 11.07 (7.62 to 15.44) | | |

Notes:

[9] - Patients with best response ≥PR: 80 (42 with events / 38 censored)

Median follow-up: 15.84 months

[10] - Patients with best response ≥PR: 67 (38 with events / 29 censored)

Median follow-up: 16.76 months

Statistical analyses

| | |
|---|-----------------------------|
| Statistical analysis title | Statistical Analysis of DOR |
| Statistical analysis description: DOR analyzed using a log-rank test stratified by the randomization stratification factors to compare treatment group DOR distributions based on the FAS. K-M estimates of the DOR distributions of the time-to-event based on log(-log[survival]) distribution were tabulated by treatment arm (including K-M estimates of medians and 95% CIs). Hazard ratio and 95% CIs were based on semiparametric Cox proportional hazards regression model stratified by randomization strata. | |
| Comparison groups | Arm A v Arm B |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.061 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.651 |
| upper limit | 1.728 |

Notes:

[11] - DOR was not a key secondary endpoint. Therefore, it was not included in the multiplicity adjustment.

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

To assess and compare OS in Arm A versus Arm B. OS was defined as time (months) from date of randomization to death due to any cause. Patients who were still alive at end of study, or lost to follow up, were censored at the last day the patient was known to be alive.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until up to 24 months following confirmed disease progression or initiation of subsequent therapy. Data cutoff date was 03 Feb 2023.

| End point values | Arm A | Arm B | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 246 ^[12] | 249 ^[13] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 20.24 (15.84 to 24.15) | 23.98 (18.92 to 27.86) | | |

Notes:

[12] - Patients with events: 180 (73.2%)
Patients censored: 66 (26.8%)
Median follow-up: 40.31 months

[13] - Patients with events: 169 (67.9%)
Patients censored: 80 (32.1%)
Median follow-up: 38.08 months

Statistical analyses

| | |
|----------------------------|---------------------------------------|
| Statistical analysis title | Overall Survival Statistical Analysis |
|----------------------------|---------------------------------------|

Statistical analysis description:

OS analyzed using a log-rank test stratified by the randomization stratification factors to compare treatment group survival distributions based on the FAS. K-M estimates of the survival distributions of the time-to-event based on log(-log[survival]) distribution were tabulated by treatment arm (including K-M estimates of medians and 95% CIs). Hazard ratio and 95% CIs were based on a semiparametric Cox proportional hazards regression model stratified by randomization strata.

| | |
|-------------------|---------------|
| Comparison groups | Arm A v Arm B |
|-------------------|---------------|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 495 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.4088 ^[15] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.094 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.884 |
| upper limit | 1.352 |

Notes:

[14] - Superiority testing of melflufen+dexamethasone over pomalidomide+dexamethasone with respect to the key secondary endpoints performed using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison was statistically significant at an alpha level of 0.05. In case of statistical superiority on the primary endpoint then ORR was tested for superiority. In case of statistical superiority on ORR, then overall survival was tested for superiority.

[15] - Log-rank test was stratified by randomization strata: age (<75, ≥75), number of lines of prior therapy (2, 3-4), and ISS Score (1, ≥2).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs): from the start of study treatment until 30 days after the last dose of study drug or initiation of subsequent therapy. Serious AEs (SAEs): from signing of ICF until 30 days after the last dose of study drug. Data cutoff: 03 Feb 2023.

Adverse event reporting additional description:

SAEs reported in the SAE section are treatment-emergent SAEs. The frequency threshold for reporting treatment-emergent SAEs is 2%.

Non-serious AEs were not calculated in this study. The data reported in the non-serious AE section include all treatment-emergent AEs (non-serious AEs and SAEs).

Safety evaluations based on the Safety Analysis Set.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Melflufen 40 mg iv on Day 1 of each 28-day cycle via a central catheter. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). There were 228 patients in Arm A who received at least 1 dose of study treatment.

| | |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Pomalidomide 4 mg po on Days 1 to 21 of each 28-day cycle. Dexamethasone 40 mg po on Days 1, 8, 15 and 22 of each 28-day cycle (20 mg for patients \geq 75 years of age). There were 246 patients in Arm B who received at least 1 dose of study treatment.

| Serious adverse events | Arm A | Arm B | |
|---|-------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 99 / 228 (43.42%) | 124 / 246 (50.41%) | |
| number of deaths (all causes) | 168 | 167 | |
| number of deaths resulting from adverse events | 32 | 37 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 228 (2.19%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 228 (1.75%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 4 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 4 / 228 (1.75%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Chronic obstructive pulmonary disease | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 228 (0.44%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 228 (1.75%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 5 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 9 / 246 (3.66%) | |
| occurrences causally related to treatment / all | 0 / 1 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|-----------------|--|
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Nervous system disorders | | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 228 (3.51%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 9 / 11 | 11 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 11 / 228 (4.82%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 15 / 15 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 5 / 228 (2.19%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 5 / 6 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 228 (1.75%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 4 / 5 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal mass | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 14 / 228 (6.14%) | 23 / 246 (9.35%) | |
| occurrences causally related to treatment / all | 7 / 17 | 10 / 26 | |
| deaths causally related to treatment / all | 0 / 4 | 2 / 4 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 12 / 228 (5.26%) | 14 / 246 (5.69%) | |
| occurrences causally related to treatment / all | 0 / 13 | 1 / 14 | |
| deaths causally related to treatment / all | 0 / 8 | 1 / 5 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 11 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 228 (1.32%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 6 / 246 (2.44%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 5 / 246 (2.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Upper respiratory tract infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 228 (1.32%) | 1 / 246 (0.41%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 228 (0.44%) | 2 / 246 (0.81%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 3 / 246 (1.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Infection | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 0 / 246 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 228 (0.00%) | 4 / 246 (1.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A | Arm B | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 227 / 228 (99.56%) | 243 / 246 (98.78%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 30 / 228 (13.16%) | 28 / 246 (11.38%) | |
| occurrences (all) | 154 | 88 | |
| Platelet count decreased | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 40 / 228 (17.54%) 198 | 11 / 246 (4.47%) 25 | |
| SARS-CoV-2 test positive subjects affected / exposed occurrences (all) | 16 / 228 (7.02%) 17 | 22 / 246 (8.94%) 26 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 22 / 228 (9.65%) 86 | 6 / 246 (2.44%) 9 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 8 / 228 (3.51%) 9 | 16 / 246 (6.50%) 21 | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 137 / 228 (60.09%) 795 | 115 / 246 (46.75%) 421 | |
| Anaemia subjects affected / exposed occurrences (all) | 154 / 228 (67.54%) 487 | 97 / 246 (39.43%) 238 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 161 / 228 (70.61%) 918 | 50 / 246 (20.33%) 149 | |
| Leukopenia subjects affected / exposed occurrences (all) | 24 / 228 (10.53%) 89 | 11 / 246 (4.47%) 18 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 33 / 228 (14.47%) 52 | 44 / 246 (17.89%) 57 | |
| Asthenia subjects affected / exposed occurrences (all) | 33 / 228 (14.47%) 50 | 32 / 246 (13.01%) 47 | |
| Pyrexia subjects affected / exposed occurrences (all) | 33 / 228 (14.47%) 43 | 18 / 246 (7.32%) 25 | |
| Oedema peripheral | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 228 (5.26%) 17 | 24 / 246 (9.76%) 24 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 32 / 228 (14.04%) | 24 / 246 (9.76%) | |
| occurrences (all) | 46 | 32 | |
| Nausea | | | |
| subjects affected / exposed | 31 / 228 (13.60%) | 18 / 246 (7.32%) | |
| occurrences (all) | 44 | 20 | |
| Constipation | | | |
| subjects affected / exposed | 17 / 228 (7.46%) | 29 / 246 (11.79%) | |
| occurrences (all) | 19 | 33 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 22 / 228 (9.65%) | 27 / 246 (10.98%) | |
| occurrences (all) | 27 | 28 | |
| Cough | | | |
| subjects affected / exposed | 20 / 228 (8.77%) | 20 / 246 (8.13%) | |
| occurrences (all) | 24 | 30 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 21 / 228 (9.21%) | 21 / 246 (8.54%) | |
| occurrences (all) | 23 | 29 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 19 / 228 (8.33%) | 26 / 246 (10.57%) | |
| occurrences (all) | 20 | 33 | |
| Bone pain | | | |
| subjects affected / exposed | 16 / 228 (7.02%) | 13 / 246 (5.28%) | |
| occurrences (all) | 18 | 19 | |
| Arthralgia | | | |
| subjects affected / exposed | 16 / 228 (7.02%) | 8 / 246 (3.25%) | |
| occurrences (all) | 20 | 9 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 228 (0.88%) | 14 / 246 (5.69%) | |
| occurrences (all) | 2 | 15 | |

| | | | |
|---|--|---|--|
| Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) COVID-19 pneumonia subjects affected / exposed occurrences (all) | 21 / 228 (9.21%) 26 29 / 228 (12.72%) 33 13 / 228 (5.70%) 16 12 / 228 (5.26%) 17 8 / 228 (3.51%) 12 12 / 228 (5.26%) 15 | 36 / 246 (14.63%) 47 27 / 246 (10.98%) 43 29 / 246 (11.79%) 42 16 / 246 (6.50%) 24 20 / 246 (8.13%) 24 14 / 246 (5.69%) 16 | |
|---|--|---|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 29 June 2017 | <p>Protocol Amendment 2.0:</p> <ul style="list-style-type: none">- Consolidated all of the country-specific changes into a global amendment.- Clarified that IV dexamethasone was only an option for use in the USA.- Clarified that pregnancy tests must be medically supervised pregnancy test with a sensitivity consistent with the regional REMS or PPP program.- Excluded the use of live vaccines prior to, during and following treatment with study drug. Extended the duration of contraception required following treatment with melflufen.- Clarified the definition of abstinence.- Recommended that men consider cryopreservation of semen prior to initiation of therapy.- Added precautionary statements regarding the re-activation of HBV infection during treatment with pomalidomide.- Added precaution regarding the use of erythropoietic agents and other agents that may have increased the risk of thromboembolic events.- Added the precautionary statement regarding the risk of renal dysfunction with cyclosporine in combination with melflufen.- Added alpha interferon to the list of agents with possible therapeutic effect against MM.- Changed the dose modification guidelines for pomalidomide to be consistent with the SmPC.- Added the option of performing an additional CBC just prior to randomization.- Clarified the required disease assessments relative to the patient's disease characteristics and compliance with IMWG criteria.- Clarified the timing of response assessments at end of treatment and start of PFS assessments.- Provided clarification on the reference documents used to determine unexpected AE.- Informed patients regarding the availability of the study drug following study discontinuation. |
| 30 May 2018 | <p>Protocol Amendment 3.0:</p> <ul style="list-style-type: none">- Increased the number of sites to approximately 100 and added the Asia/Pacific region.- Changed entry criterion #4 to allow patients refractory to lenalidomide within 18 months of randomization, in addition to last line, to improve accrual in the study.- Allowed longer time for BMA and imaging studies done prior to randomization.- Allowed M-protein assessments to be performed locally during PFS-FU.- Permitted OS follow-up beyond 24 months. |

| | |
|---------------|--|
| 24 May 2019 | <p>Protocol Amendment 4.1:</p> <ul style="list-style-type: none"> - Changed the name of the Oncopeptides project physician. - Updated the summary of the now completed 012-M1 study. - Changed entry criteria # 4 to allow patients that received lenalidomide and a proteasome inhibitor during the first line of therapy and were refractory to lenalidomide in the first line to potentially enroll in the study to improve accrual. - Change the coagulation studies from required at every cycle day 1 to as clinically indicated. - Increased the time from signing consent from 21 days to 28 days prior to initiation of therapy. - Changed the instructions for preparation of melflufen solution for infusion to allow for dilution with saline, which increases the shelf-life of the solution. - Added patient reported outcomes as an exploratory study objective with the purpose of supporting European pricing and reimbursement activities. - Updated the references. - Added an exploratory objective to evaluate functional status and well-being based on PRO assessments and added a description of the endpoints to evaluate this objective. - Changed the drug preparation procedures to allow for the use of saline for the dilution of melflufen which increased the shelf life of the prepared solution. |
| 24 March 2020 | <p>Protocol Amendment 5.0:</p> <ul style="list-style-type: none"> - Implemented changes to reduce the number of on-site visits and thus the risk to patients following the COVID-19 pandemic as part of an urgent safety measure released in response to the COVID-19 pandemic. |
| 20 April 2021 | <p>Protocol Amendment 6.1:</p> <ul style="list-style-type: none"> - Consolidated all safety reporting to one vendor, hence new routine for SAE reporting was implemented. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported