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 ≥ 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 (≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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
≥75 years	37	39	76
Age continuous Units: years			
arithmetic mean	66.1	66.5	
standard deviation	± 8.98	± 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 ≥ 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 ≥ 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+dexamthasone 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 ≥ 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 ≥ 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	40 / 228 (17.54%)	11 / 246 (4.47%)	
occurrences (all)	198	25	
SARS-CoV-2 test positive			
subjects affected / exposed	16 / 228 (7.02%)	22 / 246 (8.94%)	
occurrences (all)	17	26	
White blood cell count decreased			
subjects affected / exposed	22 / 228 (9.65%)	6 / 246 (2.44%)	
occurrences (all)	86	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 228 (3.51%)	16 / 246 (6.50%)	
occurrences (all)	9	21	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	137 / 228 (60.09%)	115 / 246 (46.75%)	
occurrences (all)	795	421	
Anaemia			
subjects affected / exposed	154 / 228 (67.54%)	97 / 246 (39.43%)	
occurrences (all)	487	238	
Thrombocytopenia			
subjects affected / exposed	161 / 228 (70.61%)	50 / 246 (20.33%)	
occurrences (all)	918	149	
Leukopenia			
subjects affected / exposed	24 / 228 (10.53%)	11 / 246 (4.47%)	
occurrences (all)	89	18	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	33 / 228 (14.47%)	44 / 246 (17.89%)	
occurrences (all)	52	57	
Asthenia			
subjects affected / exposed	33 / 228 (14.47%)	32 / 246 (13.01%)	
occurrences (all)	50	47	
Pyrexia			
subjects affected / exposed	33 / 228 (14.47%)	18 / 246 (7.32%)	
occurrences (all)	43	25	
Oedema peripheral			

subjects affected / exposed	12 / 228 (5.26%)	24 / 246 (9.76%)	
occurrences (all)	17	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	21 / 228 (9.21%)	36 / 246 (14.63%)	
occurrences (all)	26	47	
Upper respiratory tract infection			
subjects affected / exposed	29 / 228 (12.72%)	27 / 246 (10.98%)	
occurrences (all)	33	43	
Bronchitis			
subjects affected / exposed	13 / 228 (5.70%)	29 / 246 (11.79%)	
occurrences (all)	16	42	
Urinary tract infection			
subjects affected / exposed	12 / 228 (5.26%)	16 / 246 (6.50%)	
occurrences (all)	17	24	
Respiratory tract infection			
subjects affected / exposed	8 / 228 (3.51%)	20 / 246 (8.13%)	
occurrences (all)	12	24	
COVID-19 pneumonia			
subjects affected / exposed	12 / 228 (5.26%)	14 / 246 (5.69%)	
occurrences (all)	15	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2017	Protocol Amendment 2.0: - 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	Protocol Amendment 3.0: - 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	Protocol Amendment 4.1: - 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	Protocol Amendment 5.0: - 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	Protocol Amendment 6.1: - 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