Clinical trial results:
A Randomized, Controlled, Open-Label Phase 3 Study of Melflufen in combination with Daratumumab Compared with Daratumumab in Patients with Relapsed or Relapsed-Refractory Multiple Myeloma

Summary

EudraCT number	2019-002161-36
Trial protocol	CZ NO HU FI SK BG PL GR ES
Global end of trial date	07 February 2022

Results information

Result version number	v1 (current)
This version publication date	07 April 2023
First version publication date	07 April 2023

Trial information

Trial identification

Sponsor protocol code	OP-108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04649060
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oncopeptides AB
Sponsor organisation address	Luntmakargatan 46, Stockholm, Sweden, SE-117 37
Public contact	Clinical Trials Information Desk, Oncopeptides AB, trials@oncopeptides.com
Scientific contact	Clinical Trials Information Desk, Oncopeptides AB, trials@oncopeptides.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	07 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2022
Global end of trial reached?	Yes
Global end of trial date	07 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To show superiority of progression free-survival (PFS) in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

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 RRMM management, response assessment, and National Comprehensive Cancer Network Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2020
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	Norway: 6
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czechia: 18
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	Serbia: 7
Country: Number of subjects enrolled	Ukraine: 6
Worldwide total number of subjects	54
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	20
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 54 patients were enrolled in the Study, 27 in Arm A and 27 in Arm B. Among the enrolled patients, 22 in Arm A and 26 in Arm B received at least one dose of study drug.

Pre-assignment

Screening details:

Key inclusion criteria: age ≥ 18 years; prior diagnosis of multiple myeloma; double refractory to an immunomodulatory drug and a proteasome Inhibitor or received at least 3 prior lines of therapy; measurable disease; life expectancy of ≥ 6 months; ECOG performance ≤ 2; QT interval ≤470 msec; adequate organ function based on lab results.

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:

Independent Review Committee was planned to be blinded to treatment assignment. Due to the early termination, the response assessments were only done by Investigators, not by an Independent Review Committee (IRC). No IRC meeting had yet been held.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients in Arm A received treatment with melflufen, dexamethasone, and daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment.

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

Dosage and administration details:

In each 28-day cycle, melflufen 30 mg was given as a 30-minute intravenous infusion on Day 1.

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

Dosage and administration details:

In each 28-day cycle, dexamethasone 40 mg was given per oral weekly. For patients ≥ 75 years, dexamethasone 20 mg was given per oral weekly.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	Darzalex FASPRO
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Daratumumab 1800 mg was given subcutaneously on Days 1, 8, 15, and 22 in Cycles 1 and 2, on Days 1 and 15 in Cycles 3 to 6, and on Day 1 from Cycle 7.

Arm title	Arm B

Arm description:

Patients in Arm B received treatment with daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment. Patients in Arm B with a confirmed disease progression had the option to cross over and receive the same treatment as in Arm A. There were 2 patients in Arm B that crossed over and received the same treatment as in Arm A after a confirmed disease progression and received at least one dose of treatment. For the 2 crossover patients, 1 was discontinued due to adverse events, and 1 was lost to follow-up.

Arm type	Active comparator
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	Darzalex FASPRO
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Daratumumab 1800 mg was given subcutaneously on Days 1, 8, 15, and 22 in Cycles 1 and 2, on Days 1 and 15 in Cycles 3 to 6, and on Day 1 from Cycle 7.

Number of subjects in period 1	Arm A	Arm B
Started	27	27
Treated	22	26
Completed	0	0
Not completed	27	27
Physician decision	1	1
Patient request	1	-
Unknown	1	-
Study terminated by sponsor	17	10
Adverse event	-	3
Progressive disease	3	12
Failed criteria for treatment initiation	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Patients in Arm A received treatment with melflufen, dexamethasone, and daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment.	
Reporting group title	Arm B
Reporting group description:	
Patients in Arm B received treatment with daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment. Patients in Arm B with a confirmed disease progression had the option to cross over and receive the same treatment as in Arm A. There were 2 patients in Arm B that crossed over and received the same treatment as in Arm A after a confirmed disease progression and received at least one dose of treatment. For the 2 crossover patients, 1 was discontinued due to adverse events, and 1 was lost to follow-up.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	27	27	54
Age categorical Units: Subjects			
Adults (18-64 years)	12	8	20
From 65-75 years	13	16	29
Over 75 years	2	3	5
Age continuous Units: years			
median	65	68	
full range (min-max)	43 to 80	50 to 83	-
Gender categorical Units: Subjects			
Female	11	10	21
Male	16	17	33
Race Units: Subjects			
White	27	27	54
Ethnicity Units: Subjects			
Not Hispanic or Latino	27	27	54
Baseline Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
score = 0	8	6	14
score = 1	18	15	33
score = 2	1	6	7
Weight Units: kg			
median	78.0	76.0	
full range (min-max)	61.0 to 103.8	56.3 to 107.6	-
Height Units: cm			

median	168	167	
full range (min-max)	151 to 195	150 to 188	-

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients in Arm A received treatment with melflufen, dexamethasone, and daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment.

Reporting group title	Arm B

Reporting group description:

Patients in Arm B received treatment with daratumumab in 28-day cycles until disease progression, unacceptable toxicity, patient withdrawal of consent, or the treating physician determined it was no longer in the patient's best interest to continue the treatment. Patients in Arm B with a confirmed disease progression had the option to cross over and receive the same treatment as in Arm A. There were 2 patients in Arm B that crossed over and received the same treatment as in Arm A after a confirmed disease progression and received at least one dose of treatment. For the 2 crossover patients, 1 was discontinued due to adverse events, and 1 was lost to follow-up.

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 and dexamethasone in combination with daratumumab compared to daratumumab alone. PFS is 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 the date of randomization until the end of study.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[1]	27[2]		
Units: Events (disease progression/death)	3	13		

Notes:

[1] - Disease progression/death was reported in 3 patients. The median PFS was not reached in Arm A.

[2] - Disease progression/death was reported in 13 patients. The median PFS was 4.9 months in Arm B.

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS

Statistical analysis description:

The primary statistical analysis of PFS was performed using a Log-rank test. The Cox proportional hazard was used to estimate the hazard ratio for melflufen+dexamethasone+daratumumab versus daratumumab and its 95% confidence interval.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.65

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

To evaluate and compare ORR in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone. ORR is the proportion of patients who achieve a best-confirmed response of stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), or Partial Response (PR).

End point type	Secondary

End point timeframe:

From the date of randomization until the end of study.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: percent				
number (confidence interval 95%)	59.3 (38.8 to 77.6)	29.6 (13.8 to 50.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR

Statistical analysis description:

ORR was presented together with two-sided 95% exact binomial confidence intervals based on the Clopper-Pearson method. The treatment groups were compared using the Cochran-Mantel-Haenszel test.

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Cochran-Mantel-Haenszel

Secondary: Best Response

End point title	Best Response

End point description:

To evaluate the best response in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone.

End point type	Secondary

End point timeframe:

From the date of randomization until the end of study.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: number of patient				
Complete Response (CR)	1	0		
Very Good Partial Response (VGPR)	4	3		
Partial Response (PR)	11	5		
Minimal Response (MR)	3	5		
Stable Disease (SD)	3	5		
Progressive Disease (PD)	1	5		
Not Evaluable (NE)	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

To evaluate the OS in patients treated with melflufen and dexamethasone in combination with daratumumab compared to daratumumab alone. OS is defined as time in months from the date of randomization to death due to any cause.

End point type	Secondary

End point timeframe:

From the date of randomization until the end of study.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[3]	27[4]		
Units: death	2	4		

Notes:

[3] - The median OS was 11.0 months in Arm A.

[4] - The 4 deaths include 1 death in the crossover group. The median OS was not reached in Arm B.

Statistical analyses

Statistical analysis title	Statistical Analysis for OS

Statistical analysis description:

OS was performed using Kaplan-Meier method. The median time to event was estimated for each treatment arm from the 50th percentile of the corresponding Kaplan-Meier estimates. 95% confidence intervals were based on the log(-log(survival)) distribution.

Comparison groups	Arm B v Arm A
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	2.57

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: from the start of study treatment until 30 days after the last dose of study drug or initiation of subsequent therapy. SAEs: from signing of the ICF until 30 days after the last dose of study drug or initiation of subsequent therapy.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Safety was evaluated based on the safety analysis set, which included all patients that had received at least 1 dose of melflufen, dexamethasone, or daratumumab. There were 22 patients in Arm A who received at least 1 dose of study treatment.

Reporting group title	Arm B

Reporting group description:

Safety was evaluated based on the safety analysis set, which included all patients that had received at least 1 dose of melflufen, dexamethasone, or daratumumab. There were 26 patients in Arm B who received at least 1 dose of study treatment.

Reporting group title	Crossover

Reporting group description:

Safety was evaluated based on the safety analysis set, which included all patients that had received at least 1 dose of melflufen, dexamethasone, or daratumumab. There were 2 patients who crossed over from Arm B to receive the same treatment as in Arm A after a confirmed disease progression and received at least 1 dose of study treatment.

Serious adverse events	Arm A	Arm B	Crossover
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	12 / 26 (46.15%)	1 / 2 (50.00%)
number of deaths (all causes)	2	3	1
number of deaths resulting from adverse events	0	1	1
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 26 (11.54%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Disease progression			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 22 (4.55%)	0 / 26 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asymptomatic COVID-19			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Crossover
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)	22 / 26 (84.62%)	2 / 2 (100.00%)
Investigations			
Neutrophil count decreased			
subjects affected / exposed	3 / 22 (13.64%)	0 / 26 (0.00%)	0 / 2 (0.00%)
occurrences (all)	7	0	0
Platelet count decreased			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences (all)	9	1	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 22 (0.00%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	13 / 22 (59.09%)	8 / 26 (30.77%)	1 / 2 (50.00%)
occurrences (all)	78	14	8
Anaemia			
subjects affected / exposed	12 / 22 (54.55%)	7 / 26 (26.92%)	1 / 2 (50.00%)
occurrences (all)	37	23	5
Thrombocytopenia			

subjects affected / exposed	12 / 22 (54.55%)	4 / 26 (15.38%)	0 / 2 (0.00%)
occurrences (all)	65	15	0
Lymphopenia			
subjects affected / exposed	1 / 22 (4.55%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences (all)	10	4	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 26 (11.54%)	0 / 2 (0.00%)
occurrences (all)	2	3	0
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences (all)	4	1	0
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	0 / 26 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 26 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 22 (9.09%)	3 / 26 (11.54%)	1 / 2 (50.00%)
occurrences (all)	2	3	1
Infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 26 (7.69%)	0 / 2 (0.00%)
occurrences (all)	4	2	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	1 / 26 (3.85%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 26 (0.00%) 0	0 / 2 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2020	The overall rationale for Amendment 1 was an update of the study design to 1:1 randomization and increased sample size to 240 patients with 90% power at the request of Competent Authorities. Also, a crossover opportunity was added to allow patients with documented disease progression in Arm B to receive melflufen, dexamethasone, and daratumumab treatment. In addition, exclusion criteria related to infections were updated with information about COVID-19. Information that the subcutaneous formulation of daratumumab used in the study has been approved by FDA in the US, EMA in Europe, and MHRA in UK during 2020 was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 July 2021	The study was prematurely terminated as a consequence of the financial situation of the Sponsor following the partial clinical hold put on the melflufen program by the FDA. Enrollment was stopped on 08-Jul-2021, and the decision to prematurely close the Study was taken on 04-Nov-2021.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated prematurely with limited data available, and data cleaning was not done according to the original plan. Due to the early termination, the response assessments were only done by Investigators. No IRC meeting had yet been held.

Notes: