Clinical trial results:
A randomized, two-period, cross-over, Phase 2 study, comparing the pharmacokinetics, and assessing safety and tolerability of peripheral and central intravenous administration of melflufen in patients with relapsed and refractory multiple myeloma.

Summary

EudraCT number	2019-004127-21
Trial protocol	HU BG CZ
Global end of trial date	10 January 2022

Results information

Result version number	v1 (current)
This version publication date	09 March 2023
First version publication date	09 March 2023

Trial information

Trial identification

Sponsor protocol code	OP-109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04412707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oncopeptides AB
Sponsor organisation address	Västra Trädgårdsgatan 15 SE-111 53, Stockholm, Sweden,
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	14 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2022
Global end of trial reached?	Yes
Global end of trial date	10 January 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To evaluate and compare the pharmacokinetic (PK) variables Cmax, AUC(0-t) and AUC(0-∞) of melphalan after central and peripheral intravenous infusion of melflufen.
- To assess the local tolerability of peripheral intravenous administration of melflufen

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the ICH Harmonised Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), 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 (witnessed, where required by law or regulation), 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:

Dexamethasone was to be given PO at the standard dose of 40 mg weekly, at Days 1, 8, 15, and 22. Patients ≥75 years of age were to receive a dose of dexamethasone PO of 20 mg weekly.

Evidence for comparator:

not applicable

Actual start date of recruitment	22 June 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	Bulgaria: 7
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Ukraine: 5
Worldwide total number of subjects	27
EEA total number of subjects	22

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)	12
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient received their first dose of study drug on 04 August 2020. The last patient received their first dose of study drug on 05 April 2021.

Pre-assignment

Screening details:

Key inclusion criteria: age 18 or older; prior diagnosis of multiple myeloma; received at least 2 prior lines of therapy; measurable disease; adequate peripheral arm veins; life expectancy of at least 6 months; ECOG <=2; adequate organ function based on lab results; have had or be willing to get CVC and PVC.

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a PVC and Cycle 2 and onwards melflufen administered via a CVC.

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:

In Cycle 1, melflufen 40 mg was administered as a 30-minute infusion via PVC. From Cycle 2 onwards, melflufen was administered as a 30-minute infusion via CVC

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, at Days 1, 8, 15, and 22. Patients ≥75 years of age received a dose of dexamethasone PO of 20 mg weekly

Arm title	Arm B

Arm description:

Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a CVC and Cycle 2 administered via a PVC. From Cycle 3 and onwards melflufen administered via CVC.

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:

In Cycle 1, melflufen 40 mg was administered as a 30-minute infusion via CVC. At Cycle 2, melflufen was administered as a 30-minute infusion via PVC. From Cycle 3 onwards, melflufen was to be administered as a 30-minute infusion via a CVC.

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, at Days 1, 8, 15, and 22. Patients ≥75 years of age received a dose of dexamethasone PO of 20 mg weekly

Number of subjects in period 1	Arm A	Arm B
Started	14	13
Completed	0	0
Not completed	14	13
Adverse event, serious fatal	-	1
patient request	1	-
Adverse event, non-fatal	1	3
physician decision	-	1
study terminated by sponsor	3	2
disease progression	9	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a PVC and Cycle 2 and onwards melflufen administered via a CVC.	
Reporting group title	Arm B
Reporting group description:	
Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a CVC and Cycle 2 administered via a PVC. From Cycle 3 and onwards melflufen administered via CVC.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	14	13	27
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	4	12
From 65-84 years	6	9	15
85 years and over	0	0	0
Age continuous Units: years			
median	60.5	72.0	
full range (min-max)	44 to 76	47 to 80	-
Gender categorical Units: Subjects			
Female	7	7	14
Male	7	6	13
Race Units: Subjects			
Caucasian/White	14	13	27
Ethnicity Units: Subjects			
Not Hispanic or Latino	13	13	26
Not reported	1	0	1
Baseline ECOG Units: Subjects			
Score=0	4	4	8
Score=1	10	8	18
Score=2	0	1	1
Derived International Staging System (ISS) at study entry			

Units: Subjects			
Stage I	5	4	9
Stage II	6	6	12
Stage III	2	3	5
Missing	1	0	1
Derived Revised International Staging System (R-ISS) at study entry Units: Subjects			
R-I	2	2	4
R-II	10	9	19
R-III	0	1	1
Missing	2	1	3
Evidence of lytic bone disease at study entry Units: Subjects			
yes	14	12	26
no	0	1	1
Evidence of extramedullary disease at study entry Units: Subjects			
yes	2	0	2
no	12	13	25
Refractory status to the last prior systemic therapy Units: Subjects			
Refractory	12	13	25
Not refractory	1	0	1
Unknown	1	0	1
Prior autologous transplants Units: Subjects			
at least 1 prior autologous transplant	5	4	9
at least 2 prior autologous transplants	0	2	2
no prior autologous transplants	9	7	16
Number of prior systemic lines Units: Subjects			
2 prior lines of therapy	5	1	6
3 prior lines of therapy	2	2	4
4 prior lines of therapy	1	6	7
5 prior lines of therapy	1	1	2
6 prior lines of therapy	0	2	2
7 prior lines of therapy	2	1	3
8 prior lines of therapy	2	0	2
10 prior lines of therapy	1	0	1
Cytogenetic abnormalities identified by iFISH at study entry			
High risk based on interphase fluorescence in situ hybridization (iFISH) is defined in case the following abnormalities were found: deletion (17p), gain 1q (+1q), gain (1q21); t (4;14), t(4;14) (p16;q32), t (14;16), t (14;16) (q32;q23), t(14;20), t(14;20) (q32;q11). Standard-risk consisted of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk. Unknown: consists of patients for whom the iFISH procedure was not done or unevaluable.			
Units: Subjects			
High-risk	0	5	5

Standard-risk	4	0	4
Unknown	10	8	18

Baseline weight			
Units: kg			
median	80.6	72.0	
full range (min-max)	46.0 to 103.5	52.0 to 82.0	-
Baseline height			
Units: cm			
median	165.0	167.0	
full range (min-max)	156 to 188	150 to 190	-
Time since diagnosis			
Units: years			
median	3.49	5.65	
full range (min-max)	2.1 to 15.1	1.0 to 8.6	-
Time since most recent relapse/progression			
Units: months			
median	1.71	2.37	
full range (min-max)	0.5 to 4.3	0.5 to 5.5	-

Subject analysis sets

Subject analysis set title	PVC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Melflufen 40 mg iv Day 1 of each 28 day cycle. Dexamethasone 40 mg po Day 1,8, 15 and 22 of each 28 day cycle, if > 75 years of age 20 mg. Cycle 1 will be administered via a PVC and Cycle 2 will be administered via a CVC. From Cycle 3 and onwards melflufen will be administered via CVC.

Subject analysis set title	CVC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Melflufen 40 mg iv Day 1 of each 28 day cycle. Dexamethasone 40 mg po Day 1,8, 15 and 22 of each 28 day cycle, if > 75 years of age 20 mg. Cycle 1 will be administered via a Central Venous Catheter (CVC) and cycle 2 will be administered via a Peripheral Venous Catheter (PVC). From cycle 3 and onwards melflufen will be administered via CVC.

Reporting group values	PVC	CVC	
Number of subjects	14	13	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	4	
From 65-84 years	6	9	

85 years and over	0	0	

Age continuous Units: years			
median	60.5	72.0	
full range (min-max)	44 to 76	47 to 80	
Gender categorical Units: Subjects			
Female	7	7	
Male	7	6	
Race Units: Subjects			
Caucasian/White	14	13	
Ethnicity Units: Subjects			
Not Hispanic or Latino	13	13	
Not reported	1	0	
Baseline ECOG Units: Subjects			
Score=0	4	4	
Score=1	10	8	
Score=2	0	1	
Derived International Staging System (ISS) at study entry Units: Subjects			
Stage I	5	4	
Stage II	6	6	
Stage III	2	3	
Missing	1	0	
Derived Revised International Staging System (R-ISS) at study entry Units: Subjects			
R-I	2	2	
R-II	10	9	
R-III	0	1	
Missing	2	1	
Evidence of lytic bone disease at study entry Units: Subjects			
yes	14	12	
no	0	1	
Evidence of extramedullary disease at study entry Units: Subjects			
yes	2	0	
no	12	13	
Refractory status to the last prior systemic therapy Units: Subjects			
Refractory	12	13	
Not refractory	1	0	
Unknown	1	0	

Prior autologous transplants Units: Subjects			
at least 1 prior autologous transplant	5	4	
at least 2 prior autologous transplants	0	2	
no prior autologous transplants	9	7	
Number of prior systemic lines Units: Subjects			
2 prior lines of therapy	5	1	
3 prior lines of therapy	2	2	
4 prior lines of therapy	1	6	
5 prior lines of therapy	1	1	
6 prior lines of therapy	0	2	
7 prior lines of therapy	2	1	
8 prior lines of therapy	2	0	
10 prior lines of therapy	1	0	
Cytogenetic abnormalities identified by iFISH at study entry			
High risk based on interphase fluorescence in situ hybridization (iFISH) is defined in case the following abnormalities were found: deletion (17p), gain 1q (+1q), gain (1q21); t (4;14), t(4;14) (p16;q32), t (14;16), t (14;16) (q32;q23), t(14;20), t(14;20) (q32;q11). Standard-risk consisted of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk. Unknown: consists of patients for whom the iFISH procedure was not done or unevaluable.			
Units: Subjects			
High-risk	0	5	
Standard-risk	4	0	
Unknown	10	8	
Baseline weight Units: kg			
median	80.6	72.0	
full range (min-max)	46.0 to 103.5	52.0 to 82.0	
Baseline height Units: cm			
median	165.0	167.0	
full range (min-max)	156 to 188	150 to 190	
Time since diagnosis Units: years			
median	3.49	5.65	
full range (min-max)	2.1 to 15.1	1.0 to 8.6	
Time since most recent relapse/progression Units: months			
median	1.71	2.37	
full range (min-max)	0.5 to 4.3	0.5 to 5.5	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a PVC and Cycle 2 and onwards melflufen administered via a CVC.

Reporting group title	Arm B

Reporting group description:

Melflufen 40 mg iv Day 1 of each 28-day cycle. Dexamethasone 40 mg po Days 1,8,15 and 22 of each 28-day cycle (20 mg for patients 75 years or older). Cycle 1 administered via a CVC and Cycle 2 administered via a PVC. From Cycle 3 and onwards melflufen administered via CVC.

Subject analysis set title	PVC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Melflufen 40 mg iv Day 1 of each 28 day cycle. Dexamethasone 40 mg po Day 1,8, 15 and 22 of each 28 day cycle, if > 75 years of age 20 mg. Cycle 1 will be administered via a PVC
and Cycle 2 will be administered via a CVC. From Cycle 3 and onwards
melflufen will be administered via CVC.

Subject analysis set title	CVC
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Melflufen 40 mg iv Day 1 of each 28 day cycle. Dexamethasone 40 mg po Day 1,8, 15 and 22 of each 28 day cycle, if > 75 years of age 20 mg. Cycle 1 will be administered via a Central Venous Catheter (CVC) and cycle 2 will be administered via a Peripheral Venous Catheter (PVC). From cycle 3 and onwards melflufen will be administered via CVC.

Primary: Area Under the Plasma Concentration Versus Time Curve AUC(0-t) of Melphalan

End point title	Area Under the Plasma Concentration Versus Time Curve AUC(0-t) of Melphalan

End point description:

To evaluate and compare the pharmacokinetic (PK) variable AUC(0-t) of melphalan after central and peripheral intravenous infusion of melflufen.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[1]	13[2]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	49518.36 (± 23.71)	59543.2 (± 17.698)		
Cycle 2	60273.95 (± 30.037)	46173.13 (± 43.336)		

Notes:

[1] - 12 subjects in Cycle 1, 8 subjects in Cycle 2

[2] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for AUC(0-t) of melphalan

Statistical analysis description:

Based on a geometric mean ratio (GMR) peripheral vs. central of 0.95, a 90% confidence interval (CI) for the ratio of geometric means within bioequivalence limits of 0.8 and 1.25, and 80% power, a sample size of 20 patients (10 per sequence) was required assuming a within-patient variability for period differences (in log scale) of 0.29. Approximately 25 patients were to be enrolled to achieve 20 PK- and local tolerance-evaluable patients.

Comparison groups	PVC v CVC
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	adjusted GMR
Point estimate	0.952
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.861
upper limit	1.053

Notes:

[3] - The condition for similarity was if the 90% CI for the GMR was within the bioequivalence limits of 0.8 and 1.25.

Primary: Area Under the Plasma Concentration Versus Time Curve AUC(0-inf) of Melphalan

End point title	Area Under the Plasma Concentration Versus Time Curve AUC(0-inf) of Melphalan

End point description:

To evaluate and compare the pharmacokinetic (PK) variable AUC(0-inf) of melphalan after central and peripheral intravenous infusion of melflufen

End point type	Primary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[4]	13[5]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	54216.7 (± 23.794)	66835.47 (± 18.171)		

Cycle 2	67403.07 (± 30.149)	50835.59 (± 44.728)		

Notes:

[4] - 12 subjects in Cycle 1, 8 subjects in Cycle 2

[5] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

Statistical analysis title	GMR of AUC(0-inf) of melphalan
Comparison groups	PVC v CVC
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	geometric mean ratio
Point estimate	0.955
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.863
upper limit	1.058
Variability estimate	Standard deviation

Primary: Peak plasma concentration for melphalan

End point title	Peak plasma concentration for melphalan

End point description:

To evaluate and compare the pharmacokinetic (PK) variable Cmax of melphalan after central and peripheral intravenous infusion of melflufen.

End point type	Primary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[6]	13[7]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Geometric mean	486.1 (± 21.34)	530.1 (± 25.23)		
Cycle 2 geometric mean	546.3 (± 31.83)	449.2 (± 40.66)		

Notes:

[6] - 12 subjects in Cycle 1, 8 subjects in Cycle 2

[7] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

Statistical analysis title	GMR of maximum observed concentration of melphalan
Comparison groups	PVC v CVC
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	geometric mean ratio
Point estimate	0.946
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.849
upper limit	1.053
Variability estimate	Standard deviation

Secondary: Area under the plasma concentration vs time curve of melflufen (0-t)

End point title	Area under the plasma concentration vs time curve of melflufen (0-t)

End point description:

To evaluate and compare the pharmacokinetic (PK) variable AUC(0-t) of melflufen after central and peripheral intravenous infusion of melflufen

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[8]	8[9]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	3617.03 (± 52.244)	2828.69 (± 51.646)		
Cycle 2	3083.74 (± 80.639)	3078.21 (± 49.443)		

Notes:

[8] - 11 subjects in Cycle 1, 7 subjects in Cycle 2

[9] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration vs time curve of melflufen (0-inf)

End point title	Area under the plasma concentration vs time curve of melflufen (0-inf)

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[10]	8[11]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	3639.34 (± 52.379)	2841.23 (± 51.632)		
Cycle 2	3099.7 (± 80.708)	3093.96 (± 49.295)		

Notes:

[10] - 11 subjects in Cycle 1, 7 subjects in Cycle 2

[11] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Peak plasma concentration for melflufen

End point title	Peak plasma concentration for melflufen

End point description:

To evaluate and compare the pharmacokinetic (PK) variable Cmax of melflufen after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1 - 13 PK samples during and post infusion (28 days cycle). Samples were drawn 5-10 minutes after the end of infusion, 2-3 hours after the end of infusion, and 5-7 hours after the end of infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[12]	8[13]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	151.11 (± 59.74)	123.0 (± 47.498)		
Cycle 2	127.27 (± 75.872)	141.75 (± 47.921)		

Notes:

[12] - 11 subjects in Cycle 1, 7 subjects in Cycle 2

[13] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration vs time curve (0-t) of desethyl-melflufen

End point title	Area under the plasma concentration vs time curve (0-t) of desethyl-melflufen

End point description:

To evaluate and compare the pharmacokinetic (PK) variable AUC(0-t) of desethyl-melflufen after central and peripheral intravenous infusion of melflufen

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[14]	8[15]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	563.34 (± 42.086)	693.39 (± 34.053)		
Cycle 2	636.06 (± 51.627)	391.11 (± 49.458)		

Notes:

[14] - 11 subjects in Cycle 1, 8 subjects in Cycle 2

[15] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration vs time curve (0-inf) of desethyl-melflufen

End point title	Area under the plasma concentration vs time curve (0-inf) of desethyl-melflufen

End point description:

To evaluate and compare the PK variable AUC(0-inf) of desethyl-melflufen after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and

4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[16]	8[17]		
Units: min x ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	609.44 (± 40.778)	759.25 (± 34.619)		
Cycle 2	695.29 (± 51.722)	440.65 (± 43.547)		

Notes:

[16] - 11 subjects in Cycle 1, 8 subjects in Cycle 2

[17] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Peak plasma concentration for desethyl-melflufen

End point title	Peak plasma concentration for desethyl-melflufen

End point description:

To evaluate and compare the pharmacokinetic (PK) variable Cmax of desethyl-melflufen after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 & Cycle 2 Day 1-13 PK samples during & post infusion. Samples collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; & 5, 10, 15, & 30 minutes & 1, 2 & 4 hr after end of infusion

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[18]	8[19]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	16.721 (± 33.2618)	16.352 (± 25.4952)		
Cycle 2	16.801 (± 43.8965)	11.851 (± 41.3587)		

Notes:

[18] - 11 subjects in Cycle 1, 8 subjects in Cycle 2

[19] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life melphalan

End point title	Elimination half-life melphalan

End point description:

To evaluate elimination half-life (t½) for melphalan after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12[20]	8[21]		
Units: minutes				
geometric mean (geometric coefficient of variation)				
Cycle 1	72.51 (± 14.993)	80.09 (± 12.85)		
Cycle 2	78.09 (± 18.118)	72.97 (± 16.840)		

Notes:

[20] - 12 subjects in Cycle 1, 8 subjects in Cycle 2

[21] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life of melflufen

End point title	Elimination half-life of melflufen

End point description:

To evaluate elimination half-life (t½) for melflufen after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[22]	8[23]		
Units: minutes				
geometric mean (geometric coefficient of variation)				
Cycle 1	7.42 (± 106.832)	4.45 (± 90.634)		

Cycle 2	6.15 (± 81.278)	5.74 (± 80.837)		

Notes:

[22] - 11 subjects in Cycle 1, 7 subjects in Cycle 2

[23] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life of desethyl-melflufen

End point title	Elimination half-life of desethyl-melflufen

End point description:

To evaluate elimination half-life (t½) for desethyl-melflufen after central and peripheral intravenous infusion of melflufen.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and Cycle 2 Day 1. Samples were collected 5, 10, 15, 20, and 25 minutes after the start of the infusion; immediately before the end of the infusion; and 5, 10, 15, and 30 minutes and 1, 2, and 4 hours after the end of the infusion.

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[24]	8[25]		
Units: minutes				
geometric mean (geometric coefficient of variation)				
Cycle 1	18.44 (± 49.680)	23.49 (± 43.423)		
Cycle 2	25.04 (± 83.298)	17.43 (± 37.708)		

Notes:

[24] - 11 subjects in Cycle 1, 8 subjects in Cycle 2

[25] - 8 subjects in Cycle 1, 13 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Best response

End point title	Best response

End point description:

Two consecutive assessments with the same response result made at any time prior to new therapy initiation. (sCR, CR, VGPR, PR, MR, SD or PD) assessed by the investigator according to IMWG-URC.

End point type	Secondary

End point timeframe:

Patients were assessed for response after each cycle. After discontinuation of therapy, patients continued to be assessed until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: patients				
sCR	0	0		
CR	1	0		
VGPR	0	0		
PR	3	1		
MR	4	1		
SD	2	6		
PD	2	1		
Not available	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) and clinical benefit rate (CBR)

End point title	Overall response rate (ORR) and clinical benefit rate (CBR)

End point description:

The ORR is estimated as the proportion of patients who achieved a confirmed response (two consecutive assessments) of stringent sCR, CR, VGPR, or PR as their best response. CBR is the proportion of patients who achieved a confirmed response of sCR, CR, VGPR, PR and MR.

End point type	Secondary

End point timeframe:

Patients were assessed for response after each cycle. After discontinuation of therapy, patients continued to be assessed until documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: patients				
ORR	4	1		
CBR	8	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with local reactions including phlebitis at infusion site after peripheral intravenous administration

End point title	Number of participants with local reactions including phlebitis at infusion site after peripheral intravenous administration

End point description:

Assessment of the local tolerability of peripheral intravenous administration of melflufen using the Visual Infusion Phlebitis (VIP) scale. The VIP scale provides a score from 0 to 5, noting an ascending order of severity of inflammation. A score of 0 is the lowest possible score, meaning no inflammation detected, and 5 is the highest score, indicating the most severe reaction. Combined treatment ARM for all PVC administration from both Arm A & Arm B during Cycle 1 and 2.
Note: this was a primary endpoint; however, no statistical analysis is available since no patients experienced local infusion reactions.

End point type	Secondary

End point timeframe:

15 minutes and 4 hours after peripheral intravenous administration, pre- and post-infusion on Day 1 and Day 8

End point values	PVC	CVC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	27		
Units: patients				
Cycle 1 Day 1 pre-infusion	13	13		
VIP score=0	13	13		
Cycle 1 Day 1 post-infusion	13	13		
VIP score= 0	13	13		
Cycle 1 Day 8	10	10		
VIP score =0	10	10		
Cycle 2 Day 1 pre-infusion	8	8		
VIP score = 0	8	8		
Cycle 2 Day 1 post-infusion	8	8		
VIP score equals 0	8	8		
Cycle 2 Day 8	7	7		
VIP score is 0	7	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: collected from signing of the ICF until 30 days after last dose of study treatment or start of subsequent therapy. Non-serious AEs: collected from the start of study treatment until 30 days after the last dose or start of subsequent therapy

Adverse event reporting additional description:

Adverse events cannot be compared for Arm A versus Arm B. Due to the crossover design of the study, all patients had a different route of administration in Cycle 2 than Cycle 1; later AEs could be due to a cumulative effect of multiple treatment cycles. Thus, AEs occurring in Cycle 2 and beyond cannot be attributed to only 1 route of administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	
Reporting group title	Overall

Reporting group description: -

Serious adverse events	Arm A	Arm B	Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 14 (35.71%)	9 / 13 (69.23%)	14 / 27 (51.85%)
number of deaths (all causes)	1	6	7
number of deaths resulting from adverse events	1	1	2
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			

subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 14 (0.00%)	2 / 13 (15.38%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Asymptomatic COVID-19			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	3 / 13 (23.08%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia			

subjects affected / exposed	2 / 14 (14.29%)	2 / 13 (15.38%)	4 / 27 (14.81%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)	13 / 13 (100.00%)	26 / 27 (96.30%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Vascular pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)	2 / 13 (15.38%)	3 / 27 (11.11%)
occurrences (all)	2	2	4
General physical health deterioration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Pyrexia			

subjects affected / exposed	2 / 14 (14.29%)	3 / 13 (23.08%)	5 / 27 (18.52%)
occurrences (all)	2	3	5
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
C-reactive protein increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 14 (14.29%)	4 / 13 (30.77%)	6 / 27 (22.22%)
occurrences (all)	2	4	6
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Cognitive disorder			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 14 (64.29%)	7 / 13 (53.85%)	16 / 27 (59.26%)
occurrences (all)	16	12	28
Leukopenia			

subjects affected / exposed	2 / 14 (14.29%)	1 / 13 (7.69%)	3 / 27 (11.11%)
occurrences (all)	7	2	9
Lymphopenia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	2	3	5
Neutropenia			
subjects affected / exposed	9 / 14 (64.29%)	9 / 13 (69.23%)	18 / 27 (66.67%)
occurrences (all)	36	33	69
Thrombocytopenia			
subjects affected / exposed	10 / 14 (71.43%)	10 / 13 (76.92%)	20 / 27 (74.07%)
occurrences (all)	34	23	57
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Stomatitis			

subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 13 (15.38%)	3 / 27 (11.11%)
occurrences (all)	1	2	3
Back pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 13 (7.69%)	3 / 27 (11.11%)
occurrences (all)	2	1	3
Bone pain			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	2 / 27 (7.41%)
occurrences (all)	2	0	2
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	2	3
Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	2
Pharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1

Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	2	0	2
Respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 13 (0.00%)	2 / 27 (7.41%)
occurrences (all)	3	0	3
Rhinitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	1 / 13 (7.69%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	1 / 13 (7.69%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 13 (0.00%)	1 / 27 (3.70%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2020	Define PK parameters add QoL variables increase number of enrolled patients to approximately 25 and PK evaluable patients to 20 require enrolled patients to be refractory to IMid and PI add CRO Medical Monitor to DSMC define completion of the PK study define duration of treatment add R-ISS stage to MM history collect any SAEs considered related to melflufen or study participation beyond 30 days after the end of study treatment or initiation of subsequent therapy add myeloma response assessment to visits
23 December 2020	update the text in the synopsis with Melphalan flufenamide (hereinafter referred to as melflufen) update the study schema with correct number of patients in each study arm update and clarify the Schedule of Activities table update the section Melflufen preparation and Administration clarify the study procedures during End of Treatment visit and M protein Response assessment correct the section 8.10 Health outcome and Quality of Life measures on which study visit days the questionnaires are to be completed correct the section 9.4 Interim analyses and section 9.4.1 Data Safety Monitoring Committee clarify in Appendix 2 Clinical Laboratory Tests regarding M protein assessment at Local Lab update the reference list correct typographical and transcription errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 November 2021	The study was terminated early by the Sponsor following an FDA-requested partial clinical hold on the melflufen clinical study program.	-

Notes:

Limitations and caveats

None reported