Clinical trial results:
A Study of the Pharmacokinetics of Melphalan During Treatment with Melflufen and Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma and Impaired Renal Function

Summary

EudraCT number	2018-000478-31
Trial protocol	CZ PL GR
Global end of trial date	22 December 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	OP-107

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03639610
WHO universal trial number (UTN)	-
Other trial identifiers	Investigational New Drug Number: 116362

Notes:

Sponsors

Sponsor organisation name	Oncopeptides AB
Sponsor organisation address	Västra Trädgårdsgatan 15, Stockholm, Sweden, SE-111 53
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	22 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2021
Global end of trial reached?	Yes
Global end of trial date	22 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the relationship between renal function and the pharmacokinetic parameters for melphalan during treatment with melflufen
- To assess the safety and tolerability of melflufen in patients with moderate (Cohorts 1a and 1b) and severe (Cohorts 2a and 2b) renal impairment

Note: Cohort 2b was not enrolled as the study was terminated early.

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 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:

Not applicable

Actual start date of recruitment	28 August 2018
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	Poland: 10
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Greece: 16
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	10
From 65 to 84 years	24
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The first patient (in Cohort 1a) received their first dose of study drug on 17 September 2018. The last patient (in Cohort 2a) received their first dose of study drug on 29 June 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; life expectancy of at least 6 months; estimated glomerular filtration rate between ≥30 to <45 mL/min/1.73m² (Cohort 1) or between ≥15 to <30 mL/min/1.73m² (Cohort 2).

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1a

Arm description:

Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 40 mg

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 at a starting dose of 40 mg administered as a 30-minute intravenous infusion on Day 1 of every 28-day cycle via a central catheter. Melflufen was distributed in the EU as a powder for concentrate for solution for infusion; in the US, it was distributed as a powder for injection.

Arm title	Cohort 1b

Arm description:

Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 30 mg

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 at a starting dose of 30 mg administered as a 30-minute intravenous infusion on Day 1 of every 28-day cycle via a central catheter. Melflufen was distributed in the EU as a powder for concentrate for solution for infusion; in the US, it was distributed as a powder for injection.

Arm title	Cohort 2a

Arm description:

Patients with severe renal impairment (eGFR of ≥15 to <30 mL/min/1.73m²) and a starting dose of melflufen of 20 mg

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 at a starting dose of 20 mg administered as a 30-minute intravenous infusion on Day 1 of every 28-day cycle via a central catheter. Melflufen was distributed in the EU as a powder for concentrate for solution for infusion; in the US, it was distributed as a powder for injection.

Number of subjects in period 1	Cohort 1a	Cohort 1b	Cohort 2a
Started	21	10	4
Completed	0	0	0
Not completed	21	10	4
Physician decision	3	1	-
Disease progression	8	5	3
Adverse event	7	1	-
Study terminated by sponsor	2	1	1
Patient request to stop treatment	1	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1a
Reporting group description:	
Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 40 mg	
Reporting group title	Cohort 1b
Reporting group description:	
Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 30 mg	
Reporting group title	Cohort 2a
Reporting group description:	
Patients with severe renal impairment (eGFR of ≥15 to <30 mL/min/1.73m²) and a starting dose of melflufen of 20 mg	

Reporting group values	Cohort 1a	Cohort 1b	Cohort 2a
Number of subjects	21	10	4
Age categorical Units: Subjects			
<65 years	4	3	3
≥65 to ≤75 years	9	5	0
>75 years	8	2	1
Age continuous Units: years			
median	70.0	72.0	62.5
full range (min-max)	52 to 84	54 to 85	57 to 76
Gender categorical Units: Subjects			
Female	9	6	1
Male	12	4	3
Race Units: Subjects			
Caucasian/White	21	10	4
Ethnicity Units: Subjects			
Not Hispanic or Latino	21	10	4
Baseline Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
Score=0	11	3	3
Score=1	8	6	1
Score=2	2	1	0
International Staging System (ISS) stage at study entry Units: Subjects			
Stage I	2	0	0
Stage II	9	4	1
Stage III	9	6	3
Unknown	1	0	0

Evidence of lytic bone disease at study entry Units: Subjects			
Yes	16	9	4
No	5	1	0
Evidence of extramedullary disease at study entry Units: Subjects			
Yes	1	1	1
No	20	9	3
Disease status at study entry Units: Subjects			
Relapsed	13	3	2
Relapsed-refractory	8	7	2
Prior autologous transplants Units: Subjects			
At least 1 prior autologous transplant	9	1	1
No prior autologous transplant	12	9	3
Number of prior systemic therapy lines			
There was one patient who reported 2 prior line of therapies but only one of them was multiple myeloma therapy. However, this exception was not reflected in the database since a minimum of 2 lines were possible to report. Although this patient was enrolled into the study incorrectly, the patient was not excluded from analyses.			
Units: Subjects			
2 prior lines of therapy	5	6	2
3 prior lines of therapy	7	2	1
4 prior lines of therapy	9	2	1
Baseline estimated glomerular filtration rate (eGFR)			
Note that eligibility was based on eGFR measured at Screening, while Baseline measurements are from Cycle 1 Day 1. For some patients, the eGFR value was derived using CKD-EPI formula when eGFR was not reported but the corresponding visit serum creatinine value was available.			
Units: Subjects			
≥15 to <30 mL/min/1.73m²	0	2	4
≥30 to <45 mL/min/1.73m²	19	8	0
≥45 mL/min/1.73m²	2	0	0
Cytogenetics 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 based on iFISH consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk based on iFISH. The category of unknown consists of patients for whom the iFISH procedure was not done or unevaluable.			
Units: Subjects			
High-risk abnormalities	5	5	0
Standard-risk abnormalities	16	4	3
Unknown	0	0	1
Missing	0	1	0
Baseline height Units: cm			
median	165.0	169.0	172.5
full range (min-max)	147 to 181	155 to 189	167 to 180
Baseline weight Units: kg			

median	73.0	75.25	85.50
full range (min-max)	57.3 to 132.0	54.0 to 140.0	73.0 to 110.0
Time since diagnosis			
Units: years			
median	6.47	3.82	5.13
full range (min-max)	1.1 to 11.1	0.9 to 8.0	1.6 to 7.7
Time since most recent relapse/progression			
Units: months			
median	1.12	1.49	3.29
full range (min-max)	0.5 to 9.8	0.6 to 5.8	0.9 to 9.3

Reporting group values	Total		
Number of subjects	35		
Age categorical			
Units: Subjects			
<65 years	10		
≥65 to ≤75 years	14		
>75 years	11		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	16		
Male	19		
Race			
Units: Subjects			
Caucasian/White	35		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	35		
Baseline Eastern Cooperative Oncology Group (ECOG)			
Units: Subjects			
Score=0	17		
Score=1	15		
Score=2	3		
International Staging System (ISS) stage at study entry			
Units: Subjects			
Stage I	2		
Stage II	14		
Stage III	18		
Unknown	1		
Evidence of lytic bone disease at study entry			
Units: Subjects			
Yes	29		
No	6		
Evidence of extramedullary disease at study entry			

Units: Subjects			
Yes	3		
No	32		
Disease status at study entry Units: Subjects			
Relapsed	18		
Relapsed-refractory	17		
Prior autologous transplants Units: Subjects			
At least 1 prior autologous transplant	11		
No prior autologous transplant	24		
Number of prior systemic therapy lines			
There was one patient who reported 2 prior line of therapies but only one of them was multiple myeloma therapy. However, this exception was not reflected in the database since a minimum of 2 lines were possible to report. Although this patient was enrolled into the study incorrectly, the patient was not excluded from analyses.			
Units: Subjects			
2 prior lines of therapy	13		
3 prior lines of therapy	10		
4 prior lines of therapy	12		
Baseline estimated glomerular filtration rate (eGFR)			
Note that eligibility was based on eGFR measured at Screening, while Baseline measurements are from Cycle 1 Day 1. For some patients, the eGFR value was derived using CKD-EPI formula when eGFR was not reported but the corresponding visit serum creatinine value was available.			
Units: Subjects			
≥15 to <30 mL/min/1.73m²	6		
≥30 to <45 mL/min/1.73m²	27		
≥45 mL/min/1.73m²	2		
Cytogenetics 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 based on iFISH consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk based on iFISH. The category of unknown consists of patients for whom the iFISH procedure was not done or unevaluable.			
Units: Subjects			
High-risk abnormalities	10		
Standard-risk abnormalities	23		
Unknown	1		
Missing	1		
Baseline height Units: cm median full range (min-max)	- -		
Baseline weight Units: kg median full range (min-max)	- -		
Time since diagnosis Units: years median full range (min-max)	- -		

Time since most recent relapse/progression Units: months median full range (min-max)	- 		

Subject analysis sets

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set is defined as all patients who received at least 1 or partial dose of melflufen or dexamethasone.

Reporting group values	Safety Analysis Set		
Number of subjects	35		
Age categorical Units: Subjects			
<65 years	10		
≥65 to ≤75 years	14		
>75 years	11		
Age continuous Units: years			
median	70.0		
full range (min-max)	52 to 85		
Gender categorical Units: Subjects			
Female	16		
Male	19		
Race Units: Subjects			
Caucasian/White	35		
Ethnicity Units: Subjects			
Not Hispanic or Latino	35		
Baseline Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
Score=0	17		
Score=1	15		
Score=2	3		
International Staging System (ISS) stage at study entry Units: Subjects			
Stage I	2		
Stage II	14		
Stage III	18		
Unknown	1		
Evidence of lytic bone disease at study entry Units: Subjects			
Yes	29		
No	6		

Evidence of extramedullary disease at study entry Units: Subjects			
Yes	3		
No	32		
Disease status at study entry Units: Subjects			
Relapsed	18		
Relapsed-refractory	17		
Prior autologous transplants Units: Subjects			
At least 1 prior autologous transplant	11		
No prior autologous transplant	24		
Number of prior systemic therapy lines			
There was one patient who reported 2 prior line of therapies but only one of them was multiple myeloma therapy. However, this exception was not reflected in the database since a minimum of 2 lines were possible to report. Although this patient was enrolled into the study incorrectly, the patient was not excluded from analyses.			
Units: Subjects			
2 prior lines of therapy	13		
3 prior lines of therapy	10		
4 prior lines of therapy	12		
Baseline estimated glomerular filtration rate (eGFR)			
Note that eligibility was based on eGFR measured at Screening, while Baseline measurements are from Cycle 1 Day 1. For some patients, the eGFR value was derived using CKD-EPI formula when eGFR was not reported but the corresponding visit serum creatinine value was available.			
Units: Subjects			
≥15 to <30 mL/min/1.73m²	6		
≥30 to <45 mL/min/1.73m²	27		
≥45 mL/min/1.73m²	2		
Cytogenetics 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 based on iFISH consists of patients who have a genetic subtype recorded but none of the genetic subtypes categorized as high-risk based on iFISH. The category of unknown consists of patients for whom the iFISH procedure was not done or unevaluable.			
Units: Subjects			
High-risk abnormalities	10		
Standard-risk abnormalities	23		
Unknown	1		
Missing	1		
Baseline height Units: cm			
median	168.0		
full range (min-max)	147 to 189		
Baseline weight Units: kg			
median	74.00		
full range (min-max)	54.0 to 140.0		
Time since diagnosis Units: years			

median	4.78		
full range (min-max)	0.9 to 11.1		
Time since most recent relapse/progression Units: months			
median	1.25		
full range (min-max)	0.5 to 9.8		

End points

End points reporting groups

Reporting group title	Cohort 1a
Reporting group description:	
Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 40 mg	
Reporting group title	Cohort 1b
Reporting group description:	
Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 30 mg	
Reporting group title	Cohort 2a
Reporting group description:	
Patients with severe renal impairment (eGFR of ≥15 to <30 mL/min/1.73m²) and a starting dose of melflufen of 20 mg	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set is defined as all patients who received at least 1 or partial dose of melflufen or dexamethasone.	

Primary: Maximum observed concentration (Cmax) of melphalan

End point title	Maximum observed concentration (Cmax) of melphalan[1]
End point description:	
End point type	Primary
End point timeframe:	
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.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only results based on non-compartmental method are available. An updated population PK analysis, including subjects from this study together with PK data from other studies with melflufen, will be reported separately in a population PK report.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13[2]	6[3]	4[4]	22[5]
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1	550.1538 (± 170.024)	472.2000 (± 141.505)	181.2500 (± 76.098)	465.3636 (± 202.478)
Cycle 2	539.4444 (± 178.246)	469.5000 (± 177.340)	194.0000 (± 57.663)	458.5556 (± 201.121)

Notes:

[2] - 13 subjects in Cycle 1; 9 subjects in Cycle 2

[3] - 5 subjects in Cycle 1; 6 subjects in Cycle 2

[4] - 4 subjects in Cycle 1; 3 subjects in Cycle 2

[5] - 22 subjects in Cycle 1; 18 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Primary: Time of maximum observed concentration (Tmax) of melphalan

End point title	Time of maximum observed concentration (Tmax) of

End point description:

End point type	Primary

End point timeframe:

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.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only results based on non-compartmental method are available. An updated population PK analysis, including subjects from this study together with PK data from other studies with melflufen, will be reported separately in a population PK report.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13[7]	6[8]	4[9]	22[10]
Units: minutes				
median (full range (min-max))				
Cycle 1	38.0000 (35.0000 to 40.0000)	40.0000 (35.0000 to 45.0000)	37.0000 (36.0000 to 40.0000)	37.5000 (35.0000 to 45.0000)
Cycle 2	37.0000 (35.0000 to 40.0000)	40.0000 (38.0000 to 40.0000)	36.0000 (35.0000 to 37.0000)	38.5000 (35.0000 to 40.0000)

Notes:

[7] - 13 subjects in Cycle 1; 9 subjects in Cycle 2

[8] - 5 subjects in Cycle 1; 6 subjects in Cycle 2

[9] - 4 subjects in Cycle 1; 3 subjects in Cycle 2

[10] - 22 subjects in Cycle 1; 18 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Primary: Area under the curve (from 0 hours to the last measurable concentration) of melphalan

End point title	Area under the curve (from 0 hours to the last measurable concentration) of melphalan[11]

End point description:

AUC(0-t) is the area under the concentration-time curve from 0 hours to the last measurable concentration.

End point type	Primary

End point timeframe:

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.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only results based on non-compartmental method are available. An updated population PK analysis, including subjects from this study together with PK data from other studies with melflufen, will be reported separately in a population PK report.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13[12]	6[13]	4[14]	22[15]
Units: minutes*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1	78250.3462 (± 21391.384)	70303.4400 (± 16874.787)	27912.7125 (± 10385.219)	67291.9341 (± 26514.196)
Cycle 2	74415.5556 (± 21354.648)	67458.0000 (± 19241.040)	32146.0000 (± 5804.816)	65051.4444 (± 23811.614)

Notes:

[12] - 13 subjects in Cycle 1; 9 subjects in Cycle 2

[13] - 5 subjects in Cycle 1; 6 subjects in Cycle 2

[14] - 4 subjects in Cycle 1; 3 subjects in Cycle 2

[15] - 22 subjects in Cycle 1; 18 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Primary: Area under the curve (from 0 hours to infinity) of melphalan

End point title	Area under the curve (from 0 hours to infinity) of melphalan[16]

End point description:

AUCinf is the area under the concentration-time profile from 0 hours to infinity.

End point type	Primary

End point timeframe:

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.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only results based on non-compartmental method are available. An updated population PK analysis, including subjects from this study together with PK data from other studies with melflufen, will be reported separately in a population PK report.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13[17]	6[18]	4[19]	22[20]
Units: minutes*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1	85123.3635 (± 22765.646)	77173.0689 (± 15347.431)	31712.9042 (± 11597.404)	73605.4857 (± 27922.649)
Cycle 2	80365.5468 (± 22334.049)	72830.2410 (± 20632.358)	39685.8277 (± 6405.267)	71073.8250 (± 24195.476)

Notes:

[17] - 13 subjects in Cycle 1; 9 subjects in Cycle 2

[18] - 5 subjects in Cycle 1; 6 subjects in Cycle 2

[19] - 4 subjects in Cycle 1; 3 subjects in Cycle 2

[20] - 22 subjects in Cycle 1; 18 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Primary: Elimination half-life of melphalan

End point title	Elimination half-life of melphalan[21]

End point description:

End point type	Primary

End point timeframe:

Samples were collected 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.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only results based on non-compartmental method are available. An updated population PK analysis, including subjects from this study together with PK data from other studies with melflufen, will be reported separately in a population PK report.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13[22]	6[23]	4[24]	22[25]
Units: minutes				
arithmetic mean (standard deviation)				
Cycle 1	89.1390 (± 15.575)	98.3568 (± 27.249)	109.5502 (± 22.221)	94.9451 (± 20.368)
Cycle 2	87.5544 (± 15.860)	90.7844 (± 14.411)	136.2193 (± 13.679)	96.7419 (± 23.102)

Notes:

[22] - 13 subjects in Cycle 1; 9 subjects in Cycle 2

[23] - 5 subjects in Cycle 1; 6 subjects in Cycle 2

[24] - 4 subjects in Cycle 1; 3 subjects in Cycle 2

[25] - 22 subjects in Cycle 1; 18 subjects in Cycle 2

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate

End point title	Overall response rate

End point description:

Overall response rate (ORR) is the proportion of patients who achieved a confirmed response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as best response, as assessed by the Investigator.

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	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	21	10	4	35
Units: subjects	10	7	1	18

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate

End point title	Clinical benefit rate

End point description:

Clinical benefit rate (CBR) is the proportion of patients who achieved a confirmed minimal response (MR) or better (sCR [stringent complete response], CR [complete response], VGPR [very good partial response], PR [partial response], and MR [minimal response]) as their best response, as assessed by the Investigator.

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	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	21	10	4	35
Units: subjects	11	8	1	20

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-free survival (PFS) is defined as the time in months from initiation of therapy to the earlier of confirmed disease progression or death due to any cause. Patients were deemed 'progressed' in case of i) unconfirmed progressive disease (PD) as the final response assessment, ii) death after at least one response assessment or PD based on at least two consecutive response assessments at any time, or iii) death before the first response assessment. The distribution of PFS was summarized using the Kaplan-Meier (K-M) method. The median PFS was estimated from the 50th percentile of the corresponding K-M estimates. The 95% confidence interval for median PFS was constructed using the method of Brookmeyer (Brookmeyer, 1982).

(99999 = not estimable)

End point type	Secondary

End point timeframe:

Patients were assessed from the first dose of study drug until confirmed disease progression, initiation of subsequent therapy or death, whichever comes first.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	15	6	3	24
Units: months				
median (confidence interval 95%)	8.61 (4.30 to 14.52)	7.66 (6.24 to 99999)	3.43 (0.95 to 99999)	7.66 (4.73 to 14.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response (DOR) is defined as the time from the first evidence of confirmed assessment of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) to first confirmed disease progression, or to death due to any cause. The distribution of DOR was summarized using the Kaplan-Meier (K-M) method. The median DOR was estimated from the 50th percentile of the corresponding K-M estimates. The 95% confidence interval for median DOR was constructed using the method of Brookmeyer (Brookmeyer, 1982).

(99999 = not estimable)

End point type	Secondary

End point timeframe:

Patients were assessed for response from the first measure of a confirmed response (PR or better) until confirmed progression, death, or initiation of subsequent therapy.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	7	1	18
Units: months				
median (confidence interval 95%)	8.31 (5.82 to 23.49)	13.83 (4.63 to 99999)	99999 (99999 to 99999)	13.83 (5.78 to 23.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of clinical benefit

End point title	Duration of clinical benefit

End point description:

Duration of clinical benefit (DOCB) was calculated as time in months from the first evidence of confirmed assessment of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), or minimal response (MR) to first confirmed disease progression, or to death due to any cause. DOCB was defined only for patients with a confirmed MR or better. DOCB was summarized using the Kaplan-Meier (K-M) method. The median DOCB was estimated from the 50th percentile of the corresponding K-M estimates. The 95% confidence interval for median DOCB was constructed using the method of Brookmeyer (Brookmeyer, 1982).

(99999 = not estimable)

End point type	Secondary

End point timeframe:

Patients were assessed from the first measure of a confirmed MR or better until confirmed progression, death, or initiation of subsequent therapy.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	11	8	1	20
Units: months				
median (confidence interval 95%)	9.26 (5.82 to 23.49)	10.58 (4.63 to 99999)	99999 (99999 to 99999)	9.26 (5.78 to 23.49)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response

End point description:

Time from first dose of therapy to first documented confirmed response of partial response (PR) or better.

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	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	7	1	18
Units: months				
median (full range (min-max))	2.45 (1.0 to 11.3)	1.18 (0.9 to 7.6)	2.83 (2.83 to 2.83)	2.45 (0.9 to 11.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to clinical benefit

End point title	Time to clinical benefit

End point description:

Time to clinical benefit was defined as the time from first dose of therapy to first documented confirmed response of minimal response (MR) or better.

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	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	11	8	1	20
Units: months				
median (full range (min-max))	1.12 (1.0 to 8.7)	1.12 (0.9 to 5.9)	2.83 (2.83 to 2.83)	1.15 (0.9 to 8.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as the time in months from initiation of therapy to death due to any cause. Patients still alive at the end of the study, or lost to follow up, were censored at last day known alive. (99999 = not estimable)

End point type	Secondary

End point timeframe:

Patients were followed for overall survival until death or until the last patient in the study had documented progression (confirmed on 2 consecutive assessments) or initiation of subsequent therapy.

End point values	Cohort 1a	Cohort 1b	Cohort 2a	Safety Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	21	10	4	35
Units: months				
median (confidence interval 95%)	9.76 (5.06 to 15.38)	99999 (6.83 to 99999)	99999 (3.15 to 99999)	10.18 (6.31 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Best confirmed response

End point title	Best confirmed response

End point description:

Best confirmed response required 2 consecutive assessments with the same response result made at any time. In case at the second consecutive assessment (made at any time) the response is higher than the previous one, then confirmed response (linked to the first assessment visit) will be the first one (e.g., PR – VGPR consecutive pair will lead to a PR confirmed response at the first visit). In case the second consecutive response is lower than the first one, then confirmed response (linked to the first assessment visit) will be the second one (e.g. CR-VGPR consecutive pair will lead to a VGPR confirmed response at the first visit).

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	Cohort 1a	Cohort 1b	Cohort 2a	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	10	4	
Units: subjects				
Stringent complete response (sCR)	0	0	0	
Complete response (CR)	0	2	0	
Very good partial response (VGPR)	3	1	0	
Partial response (PR)	7	4	1	
Minimal response (MR)	1	1	0	
Stable disease (SD)	5	2	0	
Progressive disease (PD)	2	0	3	
Non-evaluable	3	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events (AEs) were reported from the first dose of study drug until 30 days after the last dose of study drug, or until the start of subsequent anticancer therapy (whichever occurred first).

Adverse event reporting additional description:

Serious adverse events (SAEs) were to be reported from when the patient signed informed consent until 30 days after the last administration of any study drug. SAEs considered by the investigator to be treatment-related were reported also if they occurred later than 30 days after the last administration of any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 1a

Reporting group description:

Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 40 mg

Reporting group title	Cohort 1b

Reporting group description:

Patients with moderate renal impairment (eGFR ≥30 to <45 mL/min/1.73m²) and a starting dose of melflufen of 30 mg

Reporting group title	Cohort 2a

Reporting group description:

Patients with severe renal impairment (eGFR of ≥15 to <30 mL/min/1.73m²) and a starting dose of melflufen of 20 mg

Serious adverse events	Cohort 1a	Cohort 1b	Cohort 2a
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 21 (42.86%)	5 / 10 (50.00%)	0 / 4 (0.00%)
number of deaths (all causes)	16	3	1
number of deaths resulting from adverse events	3	1	0
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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
Cardiac arrest			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Right ventricular failure			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Sinus node dysfunction			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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
Nervous system disorders			
Peripheral motor neuropathy			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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			
Catheter site haemorrhage			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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

Fatigue			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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
Sudden cardiac death			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	8 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Sepsis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Product issues			
Device issue			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (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

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

Non-serious adverse events	Cohort 1a	Cohort 1b	Cohort 2a
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)	10 / 10 (100.00%)	3 / 4 (75.00%)
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	4 / 21 (19.05%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Asthenia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 10 (20.00%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Oedema peripheral			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Oedema			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Investigations			
White blood cell count decreased			
subjects affected / exposed	3 / 21 (14.29%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	8	2	0
Blood creatinine increased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
C-reactive protein increased			

subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Paraesthesia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	14 / 21 (66.67%)	9 / 10 (90.00%)	2 / 4 (50.00%)
occurrences (all)	79	42	2
Neutropenia			
subjects affected / exposed	8 / 21 (38.10%)	5 / 10 (50.00%)	0 / 4 (0.00%)
occurrences (all)	42	17	0
Anaemia			
subjects affected / exposed	7 / 21 (33.33%)	4 / 10 (40.00%)	1 / 4 (25.00%)
occurrences (all)	31	14	1
Leukopenia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	5	4	0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 21 (19.05%)	1 / 10 (10.00%)	1 / 4 (25.00%)
occurrences (all)	4	1	1
Vomiting			
subjects affected / exposed	4 / 21 (19.05%)	1 / 10 (10.00%)	1 / 4 (25.00%)
occurrences (all)	5	1	1
Nausea			
subjects affected / exposed	1 / 21 (4.76%)	3 / 10 (30.00%)	0 / 4 (0.00%)
occurrences (all)	2	6	0
Oesophagitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Incontinence			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 21 (23.81%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	6	0	1
Arthralgia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Muscular weakness			
subjects affected / exposed	0 / 21 (0.00%)	2 / 10 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Spondyloarthropathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	4 / 10 (40.00%)	0 / 4 (0.00%)
occurrences (all)	2	6	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	2 / 4 (50.00%)
occurrences (all)	3	0	2
Lower respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	2 / 21 (9.52%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Myringitis			

subjects affected / exposed	0 / 21 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Otosalpingitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2018	* Addition of a potential Cohort 2 of at least 6 patients with severe renal impairment to further evaluate melflufen in this patient population * Change of the patient population to 2 - 4 prior lines of therapy * Change of the method of estimation of creatinine clearance (CrCl) * Addition of an alternate method of drug preparation of melflufen, to allow for dilution with saline to increase the time from drug reconstitution to start of infusion
26 September 2019	* The study will be divided into three cohorts; 1a, 1b and 2. To evaluate 30 mg of melflufen as starting dose in Cohort 1 (eGFR of ≥30 ml/min to <45 mL/min). There will be two groups of patients in Cohort 1; 1a that received 40 mg of melflufen as starting dose, and 1b that will receive 30 mg as starting dose. Cohort 1a will close for enrolment following approval of amendment 2. * The starting dose for Cohort 2 will be decided following evaluation of data from Cohort 1a and 1b and after recommendations by DSMC.
26 March 2020	* Reduced the number of patient visits to mitigate COVID-19-related patient risks. * Updated planned number of the subjects to be included. The rationale of this increase was a target of 25 PK-evaluable patients, and therefore 35-40 patients in total needed to be enrolled as not all patients are PK evaluable.
22 January 2021	*An interim analysis for an interim clinical study report (iCSR), to conclude the results from Cohort 1, has been included in the protocol. * Cohort 2 will consist of two groups (2a and 2b) and as more cohorts are added, the number of PK-evaluable patients have increased from 25 to approximately 35. * The DSMC-confirmed starting dose for Cohort 2a of 20 mg melflufen has been added, including dose reductions steps for this cohort. Furthermore Cohort 2b will only open if recommended by DSMC after evaluating data from Cohort 1a, 1b and Cohort 2a.
30 April 2021	The protocol has been updated with changes to inclusion criteria 3 and 10. The upper limits of allowed prior lines have been removed and a wider eGFR window allowed for patients to proceed from Screening 1 to Screening 2 has been updated in this version of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 July 2021	The head-to-head phase 3 OCEAN study evaluated the efficacy and safety of melflufen plus dexamethasone versus pomalidomide plus dexamethasone in patients with relapsed refractory multiple myeloma who have received 2 – 4 prior lines of therapy. Based on the observed large differences in overall survival in pre-specified subgroups in the OCEAN study, the US Food and Drug Administration requested a partial clinical hold of all clinical studies with melflufen.	-

Notes:

Limitations and caveats

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

Between-group comparisons were not performed in this study due the small number of patients in each cohort, as well as differences with regards to some baseline characteristics.

Notes: