



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/1.73m ²) 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/1.73m ²) 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/1.73m ²) 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/1.73m ² | 0 | 2 | 4 |
| ≥30 to <45 mL/min/1.73m ² | 19 | 8 | 0 |
| ≥45 mL/min/1.73m ² | 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 full range (min-max) | 73.0 57.3 to 132.0 | 75.25 54.0 to 140.0 | 85.50 73.0 to 110.0 |
| Time since diagnosis Units: years | | | |
| median full range (min-max) | 6.47 1.1 to 11.1 | 3.82 0.9 to 8.0 | 5.13 1.6 to 7.7 |
| Time since most recent relapse/progression Units: months | | | |
| median full range (min-max) | 1.12 0.5 to 9.8 | 1.49 0.6 to 5.8 | 3.29 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/1.73m ² | 6 | | |
| ≥30 to <45 mL/min/1.73m ² | 27 | | |
| ≥45 mL/min/1.73m ² | 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/1.73m ² | 6 | | |
| ≥30 to <45 mL/min/1.73m ² | 27 | | |
| ≥45 mL/min/1.73m ² | 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/1.73m ²) 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/1.73m ²) 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/1.73m ²) 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 (\pm 170.024) | 472.2000 (\pm 141.505) | 181.2500 (\pm 76.098) | 465.3636 (\pm 202.478) |
| Cycle 2 | 539.4444 (\pm 178.246) | 469.5000 (\pm 177.340) | 194.0000 (\pm 57.663) | 458.5556 (\pm 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 melphalan, 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 melphalan, 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 occurrences (all) | 4 / 21 (19.05%) 6 | 0 / 10 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Asthenia subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 1 / 10 (10.00%) 1 | 0 / 4 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 10 (20.00%) 2 | 1 / 4 (25.00%) 1 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 4 (25.00%) 1 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 4 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 10 (10.00%) 1 | 0 / 4 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 4 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 10 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Investigations White blood cell count decreased subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 8 | 1 / 10 (10.00%) 2 | 0 / 4 (0.00%) 0 |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 10 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 3 | 0 / 10 (0.00%) 0 | 0 / 4 (0.00%) 0 |
| C-reactive protein increased | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 19 November 2018 | <ul style="list-style-type: none">* 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 | <ul style="list-style-type: none">* 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 | <ul style="list-style-type: none">* 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 | <ul style="list-style-type: none">* 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: