# Clinical trial results:
# An Open-Label Phase I/IIa Study of the Safety and Efficacy of Melphalan-flufenamide (Melflufen) and Dexamethasone Combination for Patients with Relapsed and/or Relapsed-Refractory Multiple Myeloma

## Summary

| | |
|---|---|
| EudraCT number | 2012-004315-31 |
| Trial protocol | SE NL IT DK |
| Global end of trial date | 29 October 2019 |

### Results information

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 17 October 2020 |
| First version publication date | 15 July 2020 |
| Version creation reason | • New data added to full data set<br>Overall Survival Data to be added to the results posting. |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | O-12-M1 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01897714 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Oncopeptides AB |
| Sponsor organisation address | Västra Trädgårdsgatan 15, Stockholm, Sweden, 111 53 |
| Public contact | Eva Nordström, Oncopeptides AB, +46 86152040, trials@oncopeptides.com |
| Scientific contact | Eva Nordström, Oncopeptides AB, +46 86152040, 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 | 29 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 November 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 October 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

Phase I: To determine the maximum tolerated dose (MTD) after 1 treatment cycle, of the combination of melflufen and dexamethasone in patients with relapsed and/or relapsed-refractory multiple myeloma (MM).

Phase IIa: To evaluate the overall response rate (ORR) (≥ partial response [PR] or better) and the clinical benefit rate (CBR) (≥ minimal response [MR] or better) of the combination of melflufen and dexamethasone, and of melflufen as a single-agent at the MTD determined in Phase I.

Protection of trial subjects:

The study was designed, implemented, and reported in accordance with International Council for Harmonisation Tripartite Guidelines for Good Clinical Practice, and with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21) and the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 04 July 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Sweden: 4 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Italy: 26 |
| Country: Number of subjects enrolled | United States: 28 |
| Worldwide total number of subjects | 75 |
| EEA total number of subjects | 47 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 34 |
| From 65 to 84 years | 41 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

This was an open-label, Phase I/IIa study conducted at 7 study centers in 5 countries in patients with relapsed and/or relapsed-refractory MM. Overall, 75 patients (23 during Phase I and 52 additional patients during Phase II) were enrolled in this study. Completed in subject disposition indicates patients who completed >=8 cycles of study drug.

### Pre-assignment

Screening details:

The study was conducted in 2 parts: Phase I (dose escalation) and Phase II (MTD). During Phase I, the standard 3 + 3 design was followed with 3 to 6 patients tested at each dose level, depending on the dose limiting toxicity (DLT) observed. During Phase II, patients were treated at the MTD determined in Phase I.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Phase I: Melflufen 15 mg + Dexamethasone |

Arm description:

Patients were treated with 15 milligram (mg) melflufen as intravenous (IV) infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 15 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 21-day treatment cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle.

| | |
|---|---|
| **Arm title** | Phase I: Melflufen 25 mg + Dexamethasone |

Arm description:

Patients were treated with 25 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 25 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 21-day treatment cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle.

| | |
|---|---|
| **Arm title** | Phase I: Melflufen 40 mg + Dexamethasone |

Arm description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 40 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 21-day treatment cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle.

| | |
|---|---|
| **Arm title** | Phase I: Melflufen 55 mg + Dexamethasone |

Arm description:

Patients were treated with 55 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 55 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 21-day treatment

cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle.

| **Arm title** | Phase I + II: Melflufen 40 mg + Dexamethasone |
|---|---|

Arm description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day or 28-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator. In Protocol amendment 4, the cycle of melflufen was increased from 21 to 28 days. For any patients on the 28-day treatment schedule, an additional dose of 40 mg dexamethasone was administered on Day 22 of each cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 40 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 21-day or 28-day treatment cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle and an additional dose of 40 mg dexamethasone was administered on Day 22 of each 28-day treatment cycle.

| **Arm title** | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|

Arm description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 of each 28-day treatment cycle. Dexamethasone was not administered as an antitumor compound. However, all patients were treated with 8 mg dexamethasone as an antiemetic on Days 1 and 2, and an optional 4 mg dexamethasone as an antiemetic on Days 3 and 4 of the same 28-day cycle, unless the Investigator decided to switch a patient to a combination regimen. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Melflufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A dose of 40 mg melflufen administered as a 30-minute IV infusion on Day 1 of each 28-day treatment cycle.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Solution for infusion |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

A dose of 8 mg dexamethasone oral tablet or IV infusion on Days 1, 2, and an optional 4 mg on Days 3 and 4 of each 28-day treatment cycle.

| **Number of subjects in period 1** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|---|---|
| Started | 4 | 7 | 6 |
| Completed | 1 | 0 | 1 |
| Not completed | 3 | 7 | 5 |
| Consent withdrawn by subject | - | - | - |
| Disease progression | 3 | 5 | 1 |
| Study terminated with patient alive | - | - | - |
| Adverse event, non-fatal | - | 1 | 4 |
| Death | - | - | - |
| Unspecified | - | 1 | - |
| Lost to follow-up | - | - | - |
| Joined | 0 | 0 | 0 |
| Transferred in from Phase I: Melflufen 40 mg group | - | - | - |

| **Number of subjects in period 1** | Phase I: Melflufen 55 mg + Dexamethasone | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|---|---|
| Started | 6 | 39 | 13 |
| Completed | 0 | 15 | 2 |
| Not completed | 6 | 30 | 11 |
| Consent withdrawn by subject | - | - | 1 |
| Disease progression | 3 | - | - |
| Study terminated with patient alive | - | 1 | - |
| Adverse event, non-fatal | 3 | - | - |
| Death | - | 25 | 10 |
| Unspecified | - | 3 | - |
| Lost to follow-up | - | 1 | - |
| Joined | 0 | 6 | 0 |
| Transferred in from Phase I: Melflufen 40 mg group | - | 6 | - |

## Baseline characteristics

| Reporting groups[1] | |
|---|---|
| Reporting group title | Phase I: Melflufen 15 mg + Dexamethasone |

Reporting group description:

Patients were treated with 15 milligram (mg) melflufen as intravenous (IV) infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 25 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 25 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 55 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I + II: Melflufen 40 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day or 28-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator. In Protocol amendment 4, the cycle of melflufen was increased from 21 to 28 days. For any patients on the 28-day treatment schedule, an additional dose of 40 mg dexamethasone was administered on Day 22 of each cycle.

| Reporting group title | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 of each 28-day treatment cycle. Dexamethasone was not administered as an antitumor compound. However, all patients were treated with 8 mg dexamethasone as an antiemetic on Days 1 and 2, and an optional 4 mg dexamethasone as an antiemetic on Days 3 and 4 of the same 28-day cycle, unless the Investigator decided to switch a patient to a combination regimen. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: 6 patients in the Phase I: Melflufen 40 mg + Dexamethasone reporting group were included in the analysis of the Phase IIa part of the study. So, these 6 patients were also included in the Phase I + II: Melflufen 40 mg + Dexamethasone reporting group.

| Reporting group values | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|---|---|
| Number of subjects | 4 | 7 | 6 |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 1 | 3 | 3 |
| From 65-84 years | 3 | 4 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 4 | 2 |
| Male | 2 | 3 | 4 |
| Race<br>Units: Subjects | | | |
| Black or African American | 1 | 1 | 0 |
| Caucasian | 3 | 6 | 6 |
| Not collected as per local laws | 0 | 0 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 0 |
| Not Hispanic or Latino | 4 | 6 | 5 |
| Not collected as per local laws | 0 | 0 | 1 |

| **Reporting group values** | Phase I: Melflufen 55 mg + Dexamethasone | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|---|---|
| Number of subjects | 6 | 45 | 13 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 2 | 20 | 8 |
| From 65-84 years | 4 | 25 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 15 | 5 |
| Male | 3 | 30 | 8 |
| Race<br>Units: Subjects | | | |
| Black or African American | 0 | 3 | 3 |
| Caucasian | 6 | 41 | 10 |

| | | | |
|---|---|---|---|
| Not collected as per local laws | 0 | 1 | 0 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 0 | 1 | 0 |
| Not Hispanic or Latino | 5 | 37 | 12 |
| Not collected as per local laws | 1 | 7 | 1 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 75 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 34 | | |
| From 65-84 years | 41 | | |
| 85 years and over | 0 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 29 | | |
| Male | 46 | | |
| Race<br>Units: Subjects | | | |
| Black or African American | 8 | | |
| Caucasian | 66 | | |
| Not collected as per local laws | 1 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 2 | | |
| Not Hispanic or Latino | 64 | | |
| Not collected as per local laws | 9 | | |

## End points

### End points reporting groups

| Reporting group title | Phase I: Melflufen 15 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 15 milligram (mg) melflufen as intravenous (IV) infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 25 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 25 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 55 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| Reporting group title | Phase I + II: Melflufen 40 mg + Dexamethasone |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day or 28-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator. In Protocol amendment 4, the cycle of melflufen was increased from 21 to 28 days. For any patients on the 28-day treatment schedule, an additional dose of 40 mg dexamethasone was administered on Day 22 of each cycle.

| Reporting group title | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 of each 28-day treatment cycle. Dexamethasone was not administered as an antitumor compound. However, all patients were treated with 8 mg dexamethasone as an antiemetic on Days 1 and 2, and an optional 4 mg dexamethasone as an antiemetic on Days 3 and 4 of the same 28-day cycle, unless the Investigator decided to switch a patient to a combination regimen. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

### Primary: Percentage of Patients Who Achieved Best Overall Disease Response

| End point title | Percentage of Patients Who Achieved Best Overall Disease Response[1] |
|---|---|

End point description:

The best overall disease response on treatment including stringent complete response (sCR), complete response (CR), very good partial response (VGPR), PR, MR, stable disease (SD) or progressive disease (PD) were evaluated. Starting on completion of Cycle 2, response was assessed according to

International Myeloma Working Group (IMWG) criteria based on Investigator's assessment for all patients at every cycle during treatment period. PD was defined as increase of ≥25% from lowest response value in any 1 of the following: serum M-component (absolute increase must be ≥0.5 gram/deciliter) and/or urine M-component (absolute increase must be ≥200 mg/24 hr); development of new bone lesions or soft tissue plasmacytomas or increase in size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia that could be attributed solely to plasma cell proliferative disorder. SD was defined as not meeting criteria for CR, VGPR, PR or PD.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline (Cycle 1 Day 1) and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until end of trial (EOT) date of 29 October 2019; up to a maximum of approximately 76 months.

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 descriptive statistical analysis was performed for this endpoint.

| **End point values** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4[2] | 7[3] | 6[4] | 6[5] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | | | | |
| sCR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 0.0 (0.0 to 45.9) | 0.0 (0.0 to 45.9) |
| CR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 0.0 (0.0 to 45.9) | 0.0 (0.0 to 45.9) |
| VGPR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 16.7 (0.4 to 64.1) | 16.7 (0.4 to 64.1) |
| PR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 50.0 (11.8 to 88.2) | 0.0 (0.0 to 45.9) |
| MR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 0.0 (0.0 to 45.9) | 0.0 (0.0 to 45.9) |
| SD | 75.0 (19.4 to 99.4) | 42.9 (9.9 to 81.6) | 16.7 (0.4 to 64.1) | 66.7 (22.3 to 95.7) |
| PD | 25.0 (0.6 to 80.6) | 57.1 (18.4 to 90.1) | 16.7 (0.4 to 64.1) | 16.7 (0.4 to 64.1) |
| Missing | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 0.0 (0.0 to 45.9) | 0.0 (0.0 to 45.9) |
| sCR + CR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 0.0 (0.0 to 45.9) | 0.0 (0.0 to 45.9) |
| sCR + CR + VGPR | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 16.7 (0.4 to 64.1) | 16.7 (0.4 to 64.1) |

Notes:

[2] - Safety Analysis Set.

[3] - Safety Analysis Set.

[4] - Safety Analysis Set.

[5] - Safety Analysis Set.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45[6] | 13[7] | | |
| Units: percentage of patients | | | | |

| number (confidence interval 95%) | | | | |
|---|---|---|---|---|
| sCR | 0.0 (0.0 to 7.9) | 0.0 (0.0 to 24.7) | | |
| CR | 0.0 (0.0 to 7.9) | 0.0 (0.0 to 24.7) | | |
| VGPR | 11.1 (3.7 to 24.1) | 0.0 (0.0 to 24.7) | | |
| PR | 20.0 (9.6 to 34.6) | 7.7 (0.2 to 36.0) | | |
| MR | 17.8 (8.0 to 32.1) | 15.4 (1.9 to 45.4) | | |
| SD | 26.7 (14.6 to 41.9) | 69.2 (38.6 to 90.9) | | |
| PD | 15.6 (6.5 to 29.5) | 7.7 (0.2 to 36.0) | | |
| Missing | 8.9 (2.5 to 21.2) | 0.0 (0.0 to 24.7) | | |
| sCR + CR | 0.0 (0.0 to 7.9) | 0.0 (0.0 to 24.7) | | |
| sCR + CR + VGPR | 11.1 (3.7 to 24.1) | 0.0 (0.0 to 24.7) | | |

Notes:

[6] - Modified Intent-to-Treat (mITT) Analysis Set.

[7] - mITT Analysis Set.

### Statistical analyses

No statistical analyses for this end point

### Primary: Overall Response Rate

| End point title | Overall Response Rate[8] |
|---|---|

End point description:

ORR was defined as percentage of patients with an overall response (OR), defined as first occurrence of confirmed disease response including PR or better (i.e, PR, VGPR, CR or sCR). Starting on completion of Cycle 2, response was assessed according to IMWG criteria based on Investigator's assessment for all patients at every cycle during treatment period. VGPR was defined as serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum plus urine M-protein level <100 mg/24hr and >90% decrease in difference between involved and uninvolved free light chain (FLC) levels (only in FLC diseased patients). CR was defined as negative immunofixation on serum and urine, loss of any soft tissue plasmacytomas, <5% plasma cells in bone marrow and normal FLC ratio of 0.26 to 1.65 (only in FLC diseased patients). sCR was defined as CR plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or 2 to 4 color flow cytometry.

| End point type | Primary |
|---|---|

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[8] - 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 descriptive statistical analysis was performed for this endpoint.

| **End point values** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4[9] | 7[10] | 6[11] | 6[12] |
| Units: percentage of patients | | | | |

| | | | | |
|---|---|---|---|---|
| number (confidence interval 95%) | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 66.7 (22.3 to 95.7) | 16.7 (0.4 to 64.1) |

Notes:

[9] - Safety Analysis Set.

[10] - Safety Analysis Set.

[11] - Safety Analysis Set.

[12] - Safety Analysis Set.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45[13] | 13[14] | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 31.1 (18.2 to 46.6) | 7.7 (0.2 to 36.0) | | |

Notes:

[13] - mITT Analysis Set.

[14] - mITT Analysis Set.

### Statistical analyses

No statistical analyses for this end point

## Primary: Clinical Benefit Response Rate (CBRR)

| | |
|---|---|
| End point title | Clinical Benefit Response Rate (CBRR)[15] |

End point description:

The CBRR was defined as the percentage of patients with a CBR, defined as the first occurrence of confirmed disease response including MR or better (i.e, MR, PR, VGPR, CR, or sCR). Starting on completion of Cycle 2, response was assessed according to the IMWG criteria based on the Investigator's assessment for all patients at every cycle during the treatment period. MR was defined as ≥25% but <49% reduction of serum M-protein and reduction in 24 hour urine M-protein by 50 to 89%, which still exceeds 200 mg/24 hours. In addition to above; if present at baseline, 25 to 49% reduction in the size of soft tissue plasmacytomas is also required. No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response). PR was defined as 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥90% or to <200 mg/24 hour.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[15] - 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 descriptive statistical analysis was performed for this endpoint.

| **End point values** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4[16] | 7[17] | 6[18] | 6[19] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 60.2) | 0.0 (0.0 to 41.0) | 66.7 (22.3 to 95.7) | 16.7 (0.4 to 64.1) |

Notes:

[16] - Safety Analysis Set.

[17] - Safety Analysis Set.

[18] - Safety Analysis Set.

[19] - Safety Analysis Set.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45[20] | 13[21] | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 48.9 (33.7 to 64.2) | 23.1 (5.0 to 53.8) | | |

Notes:

[20] - mITT Analysis Set.

[21] - mITT Analysis Set.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Disease Response (DOR)

| End point title | Duration of Disease Response (DOR)[22] |
|---|---|

End point description:

The DOR to treatment was defined as time from first response (PR or better) to disease progression or death, or date of last evaluable disease response assessment for those who had not progressed or died. DOR was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Only patients who had achieved at least PR were evaluated. -9999 and 9999 = confidence interval could not be determined as only 1 patient was analysed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the maximum tolerated dose (MTD) were analysed for this endpoint.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 1 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.4 (4.6 to 11.1) | 7.2 (-9999 to 9999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Disease Response in Patients Who Achieved OR and CBR

| End point title | Time to Disease Response in Patients Who Achieved OR and CBR[23] |
|---|---|

End point description:

Time to first OR was defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of PR or better (first of 2 consecutive assessments-confirmed response). Time to first CBR was defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of MR or better (first of 2 consecutive assessments-confirmed response). Time to disease response was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Here, 'n' was defined as patients who had achieved OR and CBR for each respective time to response parameter; -9999 and 9999 = confidence interval could not be determined as only 1 patient was analysed.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the MTD were analysed for this endpoint.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | | | | |
| OR (n= 14, 1) | 2.8 (1.6 to 4.7) | 6.7 (-9999 to 9999) | | |
| CBR (n= 22, 3) | 2.4 (1.4 to 3.0) | 2.8 (2.8 to 6.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Disease Progression

| End point title | Time to Disease Progression[24] |
|---|---|

End point description:

Time to disease progression was defined as the time from the date of the first dose of study drug (overall reference start date) to the date of the first occurrence of evaluable PD. Time to disease progression was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Only patients who had experienced disease progression at the time of EOT (29 October 2019) were reported.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT

date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the MTD were analysed for this endpoint.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.5 (3.7 to 9.3) | 4.4 (2.8 to 12.2) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Progression-Free Survival (PFS)

| End point title | Median Progression-Free Survival (PFS)[25] |
|---|---|

End point description:

The PFS was defined as the time from the date of the first dose of melflufen (overall reference start date) to the date of the first occurrence of any disease response assessment available for PD or death. The PFS was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Only patients who had information about PFS at the time of EOT (29 October 2019) were reported.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline and every cycle from Cycle 2 onwards until confirmed disease progression. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the MTD were analysed for this endpoint.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.7 (3.7 to 9.2) | 4.4 (2.8 to 7.6) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Median Overall Survival (OS)

| End point title | Median Overall Survival (OS)[26] |
|---|---|

End point description:

The OS was defined as the time from the date of the first dose of melflufen (overall reference start date) to death. The OS was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Only patients who had information about OS at the time of EOT (29 October 2019) were reported.

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline until death. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the MTD were analysed for this endpoint.

| **End point values** | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 20.7 (11.8 to 41.3) | 15.5 (4.9 to 23.4) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to First Subsequent Treatment

| End point title | Time to First Subsequent Treatment[27] |
|---|---|

End point description:

Time to first subsequent treatment start was defined as the time from the date of the actual end of treatment to the date of the first subsequent treatment. Time to first subsequent treatment was estimated using Kaplan-Meier statistics. The mITT Analysis Set included all patients considered to be valid for the Safety Analysis Set and who received at least 1 dose of study drug at the MTD as the initial dose. Only patients who had information about first subsequent treatment at the time of EOT (29 October 2019) were reported. 9999 = upper limit of confidence could not be calculated as it was not reached.

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline until start of first subsequent treatment. Assessed until EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients who were treated at the MTD were analysed for this endpoint.

| End point values | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.5 (7.9 to 12.2) | 10.7 (5.3 to 9999) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Patients With Treatment Emergent Adverse Events (TEAEs)

| End point title | Number of Patients With Treatment Emergent Adverse Events (TEAEs) |
|---|---|

End point description:

An adverse event (AE) was any untoward medical occurrence in a study patient administered an investigational product and that does not necessarily have a causal relationship with this treatment. A serious adverse event (SAE) was defined as any AE, occurring at any dose, that met any 1 or more of the following criteria: fatal or immediately life-threatening; persistent or significant disability/incapacity; congenital anomaly/birth defect; medically significant; requires inpatient hospitalization or prolongation of existing hospitalization; or other important medical event. TEAEs were defined as AEs that started or worsened on or after first dose of study drug (overall reference start date) up to and including actual EOT date. The Safety Analysis Set included all patients who received at least 1 dose, or part thereof, of study drug. TESAEs = Treatment emergent serious adverse events. 99999 = not applicable.

| End point type | Secondary |
|---|---|

End point timeframe:

From the first dose of study drug up to and including the actual EOT date of 29 October 2019; up to a maximum of approximately 76 months.

| End point values | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone | Phase I: Melflufen 55 mg + Dexamethasone |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 7 | 6 | 6 |
| Units: participants | | | | |
| TEAEs | 4 | 7 | 6 | 6 |
| TEAEs leading to death | 0 | 1 | 0 | 0 |
| TESAEs | 3 | 4 | 2 | 4 |
| DLT TEAEs | 0 | 0 | 0 | 4 |
| TEAEs related to melflufen and/or dexamethasone | 4 | 7 | 6 | 6 |
| TESAEs related to melflufen and/or dexamethasone | 3 | 4 | 2 | 4 |

| End point values | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 13 | | |
| Units: participants | | | | |
| TEAEs | 45 | 13 | | |
| TEAEs leading to death | 3 | 0 | | |
| TESAEs | 17 | 9 | | |
| DLT TEAEs | 99999 | 99999 | | |
| TEAEs related to melflufen and/or dexamethasone | 45 | 13 | | |
| TESAEs related to melflufen and/or dexamethasone | 17 | 9 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to and including the actual EOT date of 29 October 2019; up to a maximum of approximately 76 months.

Adverse event reporting additional description:

The Safety Analysis Set included all patients who received at least 1 dose, or part thereof, of study.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Phase I: Melflufen 15 mg + Dexamethasone |

Reporting group description:

Patients were treated with 15 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Reporting group title | Phase I: Melflufen 25 mg + Dexamethasone |

Reporting group description:

Patients were treated with 25 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Reporting group title | Phase I: Melflufen 40 mg + Dexamethasone |

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Reporting group title | Phase I: Melflufen 55 mg + Dexamethasone |

Reporting group description:

Patients were treated with 55 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator.

| | |
|---|---|
| Reporting group title | Phase I + II: Melflufen 40 mg + Dexamethasone |

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 and 40 mg dexamethasone oral tablet or IV infusion on Days 1, 8 and 15 of each 21-day or 28-day treatment cycle. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug was discontinued at the discretion of the Investigator. In Protocol amendment 4, the cycle of melflufen was increased from 21 to 28 days. For any patients on the 28-day treatment schedule, an additional dose of 40 mg dexamethasone was administered on Day 22 of each cycle.

| | |
|---|---|
| Reporting group title | Phase II: Melflufen 40 mg (Single Agent) |

Reporting group description:

Patients were treated with 40 mg melflufen as IV infusion on Day 1 of each 28-day treatment cycle. Dexamethasone was not administered as an antitumor compound. However, all patients were treated with 8 mg dexamethasone as an antiemetic on Days 1 and 2, and an optional 4 mg dexamethasone as an antiemetic on Days 3 and 4 of the same 28-day cycle, unless the Investigator decided to switch a patient to a combination regimen. Patients could continue receiving treatment for up to 8 cycles or until they experienced unacceptable toxicity, disease progression, withdrew consent, and/or the study drug

| **Serious adverse events** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 4 / 7 (57.14%) | 2 / 6 (33.33%) |
| number of deaths (all causes) | 3 | 5 | 2 |
| number of deaths resulting from adverse events | 0 | 1 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (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 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 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 | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone lesion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (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 |
| Spinal disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (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 |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (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 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (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 |

| **Serious adverse events** | Phase I: Melflufen 55 mg + Dexamethasone | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 17 / 45 (37.78%) | 9 / 13 (69.23%) |
| number of deaths (all causes) | 5 | 30 | 10 |
| number of deaths resulting from adverse events | 0 | 3 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasmacytoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (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 |
| Investigations | | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (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 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 2 / 45 (4.44%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 2 / 13 (15.38%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 10 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (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 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (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 |
| Bone lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Cystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (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 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Parainfluenzae virus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (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 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (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 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (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 |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 45 (11.11%) | 1 / 13 (7.69%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 5 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (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 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 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** | Phase I: Melflufen 15 mg + Dexamethasone | Phase I: Melflufen 25 mg + Dexamethasone | Phase I: Melflufen 40 mg + Dexamethasone |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 4 (100.00%) | 7 / 7 (100.00%) | 6 / 6 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Application site erosion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 3 / 7 (42.86%) | 3 / 6 (50.00%) |
| occurrences (all) | 1 | 5 | 7 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Influenza like illness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Mucous membrane disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 0 / 7 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 2 | 0 | 2 |
| Immune system disorders | | | |
| Immune system disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Erectile Dysfunction | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 1 | 0 | 2 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Mood altered | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervousness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Restlessness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 7 (42.86%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CD4 lymphocytes decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Fibrin d dimer increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin B12 decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Humerus fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Mitral valve disease mixed | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Neuropathy peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 4 (75.00%) | 4 / 7 (57.14%) | 2 / 6 (33.33%) |
| occurrences (all) | 3 | 5 | 4 |
| Anaemia vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 1 | 1 |

| | | | |
|---|---|---|---|
| Neutropenia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 3 / 7 (42.86%) | 3 / 6 (50.00%) |
| occurrences (all) | 1 | 7 | 12 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 6 / 7 (85.71%) | 4 / 6 (66.67%) |
| occurrences (all) | 2 | 9 | 26 |
| Ear and labyrinth disorders | | | |
| Ear haemorrhage | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 4 (50.00%) | 3 / 7 (42.86%) | 1 / 6 (16.67%) |
| occurrences (all) | 2 | 3 | 1 |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 3 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 4 / 6 (66.67%) |
| occurrences (all) | 1 | 0 | 6 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Blood blister | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Back pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 3 / 7 (42.86%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Bone pain | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Bursitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 1 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Synovial cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Acarodermatitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Administration site infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Candida infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctivitis bacterial | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Gingivitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Oral herpes | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 1 / 6 (16.67%) |
| occurrences (all) | 0 | 1 | 2 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 2 / 6 (33.33%) |
| occurrences (all) | 0 | 1 | 4 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperuricaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 1 / 7 (14.29%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 4 (0.00%) | 0 / 7 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Phase I: Melflufen 55 mg + Dexamethasone | Phase I + II: Melflufen 40 mg + Dexamethasone | Phase II: Melflufen 40 mg (Single Agent) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 45 / 45 (100.00%) | 12 / 13 (92.31%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasmacytoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematoma | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Application site erosion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 14 / 45 (31.11%) | 0 / 13 (0.00%) |
| occurrences (all) | 3 | 46 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 13 / 45 (28.89%) | 4 / 13 (30.77%) |
| occurrences (all) | 2 | 20 | 4 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Influenza like illness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 45 (13.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Mucous membrane disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 16 / 45 (35.56%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 19 | 0 |
| Immune system disorders | | | |
| Immune system disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Erectile Dysfunction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 8 / 45 (17.78%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 11 | 0 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 6 (33.33%) | 6 / 45 (13.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 6 | 1 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 45 (13.33%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 8 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depression | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 6 / 45 (13.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 8 | 0 |
| Mood altered | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervousness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Restlessness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sleep disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| CD4 lymphocytes decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fibrin d dimer increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Protein total increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Red blood cell count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin B12 decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Weight increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 45 (8.89%) | 3 / 13 (23.08%) |
| occurrences (all) | 1 | 4 | 3 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Humerus fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Mitral valve disease mixed | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 45 (13.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 8 | 0 |
| Neuropathy peripheral | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 29 / 45 (64.44%) | 5 / 13 (38.46%) |
| occurrences (all) | 6 | 96 | 14 |
| Anaemia vitamin B12 deficiency | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Increased tendency to bruise | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 3 | 3 |

| | | | |
|---|---|---|---|
| Neutropenia | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 31 / 45 (68.89%) | 9 / 13 (69.23%) |
| occurrences (all) | 26 | 115 | 25 |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 6 (83.33%) | 33 / 45 (73.33%) | 9 / 13 (69.23%) |
| occurrences (all) | 35 | 154 | 30 |
| Ear and labyrinth disorders | | | |
| Ear haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 7 / 45 (15.56%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 8 | 1 |
| Diarrhoea | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 6 (66.67%) | 9 / 45 (20.00%) | 2 / 13 (15.38%) |
| occurrences (all) | 5 | 10 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Gastric disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 12 / 45 (26.67%) | 2 / 13 (15.38%) |
| occurrences (all) | 5 | 14 | 3 |
| Oral pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 5 / 45 (11.11%) | 1 / 13 (7.69%) |
| occurrences (all) | 2 | 5 | 1 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Blood blister | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Erythema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 45 (11.11%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 45 (13.33%) | 2 / 13 (15.38%) |
| occurrences (all) | 1 | 9 | 2 |
| Bone pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 6 / 45 (13.33%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 8 | 0 |
| Bursitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 45 (11.11%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Osteoporosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Synovial cyst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Acarodermatitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Administration site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctivitis bacterial | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Enterococcal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Furuncle | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Gingivitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lung infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral fungal infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Oral herpes | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 2 | 1 |
| Periodontitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 3 | 1 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 5 / 45 (11.11%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 45 (6.67%) | 1 / 13 (7.69%) |
| occurrences (all) | 1 | 5 | 1 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 45 (8.89%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 13 | 0 |
| Hyperuricaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 1 / 13 (7.69%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 45 (4.44%) | 0 / 13 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 45 (0.00%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 45 (6.67%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 45 (2.22%) | 0 / 13 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 October 2013 | MR was included in the OR assessment for evaluable patients. Lymphopenia was excluded from the definition of DLT. Criteria for assessment of renal function was clarified. Clarified the acceptable infusion devices permitted for melflufen infusion and that initially a patient would receive a screening number and treatment assignment would be communicated via email and/or fax. To be evaluable for response, patients were to have received at least 2 cycles of therapy defined as at least 2 doses of melflufen. Study drug would not be modified based on QTcF evaluations collected by the Holter Monitor. A typographical error for the duration of Holter monitoring was corrected from 210 minutes to 120 minutes. Instruction was added for preparing the study drug to shake the vial to disintegrate the freeze dried powder cake to a powder before adding the glucose solution. Table of assessments was updated to distinguish which evaluations of bone marrow aspirate would be conducted by the contract research organization and which would be performed locally. Also, results of the local laboratory could be used for entry criteria and treatment decisions while the central laboratory results were awaited. Serum sample for correlative testing was removed. Reporting timelines for AEs and SAEs were clarified. |
| 07 May 2014 | Platelet transfusion in absence of clinically significant bleeding or an urgent need to prevent bleeding (Grade 4 that required a platelet transfusion) was not considered DLT. Platelet transfusion within 7 days of registration was allowed (which previously was 14 days). To facilitate retreatment, use of growth factors was allowed in Cycle 1. To begin the treatment, Cycle 1, Day 1 values were required within the guidelines of entry criteria. Retreatment of patients with a platelet count of 50,000 per cube millimeter regardless of level of plasma cell infiltration in the bone marrow at baseline was allowed. Following Cycle 2 Day 1, clinic visits were made optional at the Investigator's discretion as long as the complete blood count and toxicity were reviewed by the Investigator on Days 8 and 15 of the cycle (that is, local laboratory could be used by the patients). Patients continuing beyond Cycle 8 were to follow the same schedule of assessments as required from Cycle 2 to Cycle 8. The additional dose level of 70 mg of melflufen was added to the Phase I in the study. In case a 70 mg dose would be needed, it would be prepared from 2 boxes of 40 mg (volume would be calculated to ensure correct dose is given). The term 'patient registration' was changed to 'initiation of therapy'. The study timeline was extended and 1 more site for pharmacokinetic sampling was added. |
| 27 January 2015 | For the Phase IIa, patient sample size was increased to 55. The response analysis was changed to assume an ORR of 50%. Disease assessment was added to Cycle 1 Day 1. The difference between ORR (≥ PR) and CBR (≥ MR) was clarified. Inclusion criteria that prior therapy must include both lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of therapy was added. |
| 20 June 2015 | The cycle of melflufen was increased from 21 to 28 days. The dose of dexamethasone was reduced from 40 mg weekly to a maximum of 24 mg per cycle in a single agent cohort. |
| 06 July 2016 | In addition to the vials available, a 20 mg vial was introduced in the ongoing study. It was clarified that the Data Safety Monitoring Committee was continuously reviewing the data and could make recommendations at any time to continue to treat patients with single agent melflufen or recommend that melflufen be given in combination with 40 mg dexamethasone weekly. |
| 02 November 2018 | The follow up period was extended beyond 24 months to allow an additional assessment of OS. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

Study is terminated and long-term follow-up ended due to Sponsor decision.

Notes: