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 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 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 Units: Subjects			
Female	2	4	2
Male	2	3	4
Race Units: Subjects			
Black or African American	1	1	0
Caucasian	3	6	6
Not collected as per local laws	0	0	0
Ethnicity 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 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 Units: Subjects			
Female	3	15	5
Male	3	30	8
Race Units: Subjects			
Black or African American	0	3	3
Caucasian	6	41	10

Not collected as per local laws	0	1	0
Ethnicity 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 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 Units: Subjects			
Female	29		
Male	46		
Race Units: Subjects			
Black or African American	8		
Caucasian	66		
Not collected as per local laws	1		
Ethnicity 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			

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			

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			

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			

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: